Supplementary Materials for

Decarboxylative borylation

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Decarboxylative Borylation

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General Information

Tetrahydrofuran (THF), N,N-dimethylformamide (DMF), acetonitrile (CH$_3$CN) and dichloromethane (CH$_2$Cl$_2$) were obtained by passing the previously degassed solvents through activated alumina columns. Purity and source of reagents were listed on Page S19. Reagents were used as received without further purification, unless otherwise stated. Yields refer to chromatographically and spectroscopically (1H NMR) homogeneous material, unless otherwise stated. Reactions were monitored by GC/MS, LC/MS, and thin layer chromatography (TLC). TLC was performed using 0.25 mm E. Merck silica plates (60F-254), using short-wave UV light as visualizing agent, as well as potassium permanganate (KMnO$_4$) or ceric ammonium molybdate (CAM) and heat as developing agents. NMR spectra were recorded on Bruker DRX-600, DRX-500, or DPX-400 instruments and were calibrated using residual undeuterated solvent (1H: δ 7.26 for CDCl$_3$, δ 3.31 for MeOH-d$_4$, δ 3.58, 1.73 for THF-d$_8$, δ 2.50 for DMSO-d$_6$, δ 2.05 for acetone-d$_6$; 13C: δ 77.16 for CDCl$_3$, δ 49.0 for MeOH-d$_4$, δ 67.6, 25.5 for THF-d$_8$, δ 39.50 for DMSO-d$_6$, δ 29.84 for acetone-d$_6$). The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Column chromatography was performed using E. Merck silica gel (60, particle size 0.043-0.063 mm), and preparative TLC was performed on 0.25 mm E. Merck silica plates (60F-254). High resolution mass spectra (HRMS) were recorded on an Agilent LC/MSD TOF mass spectrometer by electrospray ionization time of flight reflectron experiments. Preparative high performance liquid chromatography (HPLC) was performed using an Agilent SD-1 prepstar system equipped with Phenomenex Gemini 10 μm C18 column with dimension 200 × 50 mm. Melting points were recorded on a Fisher-Johns 12-144 melting point apparatus and are uncorrected. All X-ray diffraction data were collected and analyzed by the UCSD small molecule X-ray facility. The deactivated silica gel (35 wt% H$_2$O) was prepared by mixing silica gel and deionized water, followed by vigorous shaking until a fluffy powder was observed.
## Purity and Source of Reagents

<table>
<thead>
<tr>
<th>Reagents (Purity)</th>
<th>Sources</th>
<th>Catalog Numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>NiCl₂•6H₂O ((ReagentPlus^\text{®}, &gt;99%))</td>
<td>Sigma-Aldrich^\text{®}</td>
<td>223387</td>
</tr>
<tr>
<td>MeLi in Et₂O ((1.6 \text{ M}))</td>
<td>Sigma-Aldrich^\text{®}</td>
<td>197343</td>
</tr>
<tr>
<td>MgBr₂•OEt₂ ((99%))</td>
<td>Sigma-Aldrich^\text{®}</td>
<td>225959</td>
</tr>
<tr>
<td>B₂pin₂ ((99%))</td>
<td>Oakwood Chemical^\text{®}</td>
<td>019250</td>
</tr>
<tr>
<td>4,4′-di-\text{tert}-butyl-2,2′-dipyridine ((\text{di-}t\text{Bubipy, 98%)})</td>
<td>Sigma-Aldrich^\text{®}</td>
<td>515477</td>
</tr>
<tr>
<td>4,4′-dimethoxy-2,2′-bipyridine ((\text{di-MeObipy, 97%)})</td>
<td>Sigma-Aldrich^\text{®}</td>
<td>536040</td>
</tr>
<tr>
<td>\text{N}-hydroxyphthalimide ((&gt;98%)})</td>
<td>Alfa Aesar^\text{®}</td>
<td>A13862</td>
</tr>
<tr>
<td>\text{N,N′}-diisopropylcarbodiimide ((\text{DIC, &gt;99%)})</td>
<td>Oakwood Chemical^\text{®}</td>
<td>M02889</td>
</tr>
<tr>
<td>4-dimethylaminopyridine ((\text{DMAP, 99%)})</td>
<td>Acros Organics^\text{®}</td>
<td>148275000</td>
</tr>
</tbody>
</table>
General Procedure for the Synthesis of Redox-active Esters (RAEs) (General Procedure A)

A round bottom flask was charged with carboxylic acid (1.0 equiv.), N-hydroxyphthalimide (NHPI, 1.0 equiv.) or tetrachloro-N-hydroxyphthalimide (TCNHPI, 1.0 equiv.), and DMAP (0.1 equiv.). CH₂Cl₂ (0.2 M) was added, followed by N,N'-diisopropylcarbodiimide (DIC, 1.1 equiv.), both at room temperature (RT). The mixture was allowed to stir until all the acid was consumed (as indicated by TLC). The resulting mixture was quickly filtered and the solid residue was rinsed with more CH₂Cl₂. The filtrate was concentrated in vacuo and purified by flash column chromatography to afford the corresponding redox-active ester (RAE), which was used without further purification unless otherwise noted.

Note: Some RAEs that are prone to hydrolysis on silica gel during column chromatography were purified by recrystallization or column chromatography using deactivated silica gel (35 wt% H₂O).
Optimization Details

All reactions were screened based on 0.1 mmol scale.

The optimization started with S1. TCNHPI esters were used in the initial screening since earlier conditions indicated better performance than NHPI esters (NHPI esters were used in the optimized conditions in the end, vide infra):

Table S1. Comparison of NHPI and TCNHPI esters.

<table>
<thead>
<tr>
<th>RAES</th>
<th>Yield*</th>
</tr>
</thead>
<tbody>
<tr>
<td>X = H</td>
<td>31%</td>
</tr>
<tr>
<td>X = Cl</td>
<td>45%</td>
</tr>
</tbody>
</table>

*Yields determined by GC-FID with dodecane as internal standard.

Table S2. Screening of bases.

<table>
<thead>
<tr>
<th>Base</th>
<th>Yield*</th>
</tr>
</thead>
<tbody>
<tr>
<td>w/o base</td>
<td>0</td>
</tr>
<tr>
<td>MeLi</td>
<td>58% (54%)</td>
</tr>
<tr>
<td>MeLi-LiBr</td>
<td>58%</td>
</tr>
<tr>
<td>nBuLi</td>
<td>45%</td>
</tr>
<tr>
<td>fBuLi</td>
<td>36%</td>
</tr>
<tr>
<td>MeMgBr</td>
<td>11%</td>
</tr>
<tr>
<td>MeMgBr (w/o MgBr₂)</td>
<td>7%</td>
</tr>
<tr>
<td>EtMgBr</td>
<td>10%</td>
</tr>
<tr>
<td>EtOK</td>
<td>0</td>
</tr>
<tr>
<td>fBuOK</td>
<td>0</td>
</tr>
<tr>
<td>MeOLi</td>
<td>0</td>
</tr>
<tr>
<td>NaHMDS</td>
<td>0</td>
</tr>
<tr>
<td>KHMDS</td>
<td>0</td>
</tr>
<tr>
<td>LiHMDS</td>
<td>0</td>
</tr>
<tr>
<td>KF</td>
<td>0</td>
</tr>
<tr>
<td>CsF</td>
<td>0</td>
</tr>
</tbody>
</table>

*Yields determined by GC-FID with dodecane as internal standard. †Isolated yield.
Table S3. Screening of additives.

<table>
<thead>
<tr>
<th>Additive (equiv.)</th>
<th>Yield*</th>
</tr>
</thead>
<tbody>
<tr>
<td>w/o</td>
<td>4%</td>
</tr>
<tr>
<td>Mg(OAc)$_2$ (1.5 equiv.)</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>Mg(acac)$_2$ (1.5 equiv.)</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>MgCl$_2$ (1.5 equiv.)</td>
<td>13%</td>
</tr>
<tr>
<td>MgSO$_4$ (1.5 equiv.)</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>LiBr (3.0 equiv.)</td>
<td>34%</td>
</tr>
<tr>
<td>ZnCl$_2$ (1.5 equiv.)</td>
<td>14%</td>
</tr>
<tr>
<td>MgBr$_2$·OE$_2$ (0.2 equiv.)</td>
<td>23%</td>
</tr>
<tr>
<td>MgBr$_2$·OE$_2$ (0.6 equiv.)</td>
<td>53%</td>
</tr>
<tr>
<td>MgBr$_2$·OE$_2$ (1.0 equiv.)</td>
<td>64%</td>
</tr>
<tr>
<td>MgBr$_2$·OE$_2$ (1.5 equiv.)</td>
<td><strong>67% (53%†)</strong></td>
</tr>
<tr>
<td>MgBr$_2$·OE$_2$ (2.0 equiv.)</td>
<td>66%</td>
</tr>
<tr>
<td>MgBr$_2$·OE$_2$ (2.5 equiv.)</td>
<td>57%</td>
</tr>
</tbody>
</table>

*Yields determined by GC-FID with dodecane as internal standard. †Isolated yield.

Table S4. Screening of nickel catalysts.

<table>
<thead>
<tr>
<th>Nickel source</th>
<th>Yield*</th>
</tr>
</thead>
<tbody>
<tr>
<td>NiCl$_2$·6H$_2$O</td>
<td><strong>67% (63%†)</strong></td>
</tr>
<tr>
<td>NiCl$_2$ (glyme)</td>
<td>58%</td>
</tr>
<tr>
<td>NiBr$_2$ (glyme)</td>
<td>63%</td>
</tr>
<tr>
<td>NiI$_2$</td>
<td>14%</td>
</tr>
<tr>
<td>Ni(acac)$_2$ 2H$_2$O</td>
<td>17%</td>
</tr>
<tr>
<td>Ni(CIO$_4$)$_2$</td>
<td>3%</td>
</tr>
<tr>
<td>Ni(PCy)$_3$Cl$_2$</td>
<td>4%</td>
</tr>
<tr>
<td>w/o nickel</td>
<td>0%</td>
</tr>
</tbody>
</table>

*Yields determined by GC-FID with dodecane as internal standard. †Isolated yield.
Table S5. Screening of ligands.

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Yield*</th>
</tr>
</thead>
<tbody>
<tr>
<td>L2 (20 mol%)</td>
<td>67% (63%)</td>
</tr>
<tr>
<td>L2</td>
<td>57%</td>
</tr>
<tr>
<td>L1</td>
<td>51%</td>
</tr>
<tr>
<td>L3</td>
<td>23%</td>
</tr>
<tr>
<td>L4</td>
<td>26%</td>
</tr>
<tr>
<td>L5</td>
<td>4%</td>
</tr>
<tr>
<td>L6</td>
<td>0</td>
</tr>
<tr>
<td>L7</td>
<td>13%</td>
</tr>
<tr>
<td>L8</td>
<td>11%</td>
</tr>
<tr>
<td>L9</td>
<td>17%</td>
</tr>
<tr>
<td>L10</td>
<td>0</td>
</tr>
<tr>
<td>L11</td>
<td>0</td>
</tr>
<tr>
<td>L12</td>
<td>1%</td>
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<tr>
<td>L13</td>
<td>1%</td>
</tr>
<tr>
<td>L14</td>
<td>0</td>
</tr>
<tr>
<td>L15</td>
<td>1%</td>
</tr>
<tr>
<td>L16</td>
<td>1%</td>
</tr>
<tr>
<td>w/o ligand</td>
<td>0</td>
</tr>
</tbody>
</table>

*Yields determined by GC-FID with dodecane as internal standard. †Isolated yield.
Table S6. Optimization of $[\text{B}_2\text{pin}_2\text{Me}]\text{Li}$ complexation.

<table>
<thead>
<tr>
<th>$\text{B}_2\text{pin}_2$ (equiv.), MeLi (equiv.)</th>
<th>Yield*</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{B}_2\text{pin}_2$ (2.2 equiv.), MeLi (2.0 equiv.)</td>
<td>51%</td>
</tr>
<tr>
<td>$\text{B}_2\text{pin}_2$ (2.75 equiv.), MeLi (2.5 equiv.)</td>
<td>65%</td>
</tr>
<tr>
<td>$\text{B}_2\text{pin}_2$ (3.3 equiv.), MeLi (3.0 equiv.)</td>
<td>67% (63%†)</td>
</tr>
<tr>
<td>$\text{B}_2\text{pin}_2$ (3.85 equiv.), MeLi (3.5 equiv.)</td>
<td>60%</td>
</tr>
<tr>
<td>$\text{B}_2\text{pin}_2$ (4.4 equiv.), MeLi (4.0 equiv.)</td>
<td>57%</td>
</tr>
</tbody>
</table>

*Yields determined by GC-FID with dodecane as internal standard. †Isolated yield.

Table S7. Screening of reaction concentration.

<table>
<thead>
<tr>
<th>Concentration</th>
<th>Yield*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.025 M</td>
<td>44%</td>
</tr>
<tr>
<td>0.033 M</td>
<td>58%</td>
</tr>
<tr>
<td>0.05 M</td>
<td>67%</td>
</tr>
<tr>
<td>0.10 M</td>
<td>67% (63%†)</td>
</tr>
<tr>
<td>0.15 M</td>
<td>65%</td>
</tr>
</tbody>
</table>

*Yields determined by GC-FID with dodecane as internal standard. †Isolated yield.
However, under the aforementioned optimized conditions for $S_1$, decarboxylative borylation of $S_{2a}$ proceeded in lower yield than the NHPI ester of $S_2$.

Table S8. Comparison of NHPI and TCNHPI esters of a primary acid.

<table>
<thead>
<tr>
<th>RAES</th>
<th>Yield*</th>
</tr>
</thead>
<tbody>
<tr>
<td>$X = H$</td>
<td>39%</td>
</tr>
<tr>
<td>$X = Cl$</td>
<td>28%</td>
</tr>
</tbody>
</table>

*Yields determined by GC-FID with dodecane as internal standard.

In order to identify a more general set of conditions, further optimization efforts were undertaken on the NHPI ester $S_2$.

Table S9. Screening of nickel catalysts.

<table>
<thead>
<tr>
<th>Nickel/ligand</th>
<th>Yield*</th>
</tr>
</thead>
<tbody>
<tr>
<td>NiCl$_2$•6H$_2$O/L1</td>
<td>67% (65%)$^1$</td>
</tr>
<tr>
<td>NiCl$_2$•6H$_2$O/L2</td>
<td>28%</td>
</tr>
<tr>
<td>NiCl$_2$•6H$_2$O/L4</td>
<td>32%</td>
</tr>
<tr>
<td>NiCl$_2$•6H$_2$O/L5</td>
<td>55%</td>
</tr>
<tr>
<td>NiCl$_2$•glyme/L1</td>
<td>53%</td>
</tr>
<tr>
<td>NiBr$_2$•glyme/L1</td>
<td>64%</td>
</tr>
<tr>
<td>Ni(OAc)$_2$•4H$_2$O/L1</td>
<td>61%</td>
</tr>
<tr>
<td>Ni(acac)$_2$/L1</td>
<td>46%</td>
</tr>
<tr>
<td>Ni(NO$_3$)$_2$•6H$_2$O/L1</td>
<td>58%</td>
</tr>
</tbody>
</table>

*Yields determined by GC-FID with dodecane as internal standard. $^1$Isolated yield.
Table S10. Screening of solvents.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Yield*</th>
</tr>
</thead>
<tbody>
<tr>
<td>THF (0.4 mL)</td>
<td>54%</td>
</tr>
<tr>
<td>DMF (0.4 mL)</td>
<td>44%</td>
</tr>
<tr>
<td><strong>THF/DMF (0.2/0.2 mL)</strong></td>
<td><strong>67%</strong></td>
</tr>
<tr>
<td><strong>THF/DMF (0.4/0.2 mL)</strong></td>
<td><strong>67%</strong> (65%&lt;sup&gt;†&lt;/sup&gt;)</td>
</tr>
<tr>
<td>THF/DMF (0.6/0.2 mL)</td>
<td>67%</td>
</tr>
<tr>
<td>THF/DMF (1.0/0.2 mL)</td>
<td>62%</td>
</tr>
<tr>
<td>THF/DMF (1.4/0.2 mL)</td>
<td>57%</td>
</tr>
<tr>
<td>dioxane/DMF (0.4/0.2 mL)</td>
<td>41%</td>
</tr>
<tr>
<td>glyme/DMF (0.4/0.2 mL)</td>
<td>49%</td>
</tr>
<tr>
<td>diglyme/DMF (0.4/0.2 mL)</td>
<td>43%</td>
</tr>
<tr>
<td>Et&lt;sub&gt;2&lt;/sub&gt;O/DMF (0.4/0.2 mL)</td>
<td>38%</td>
</tr>
<tr>
<td>THF/DMA (0.4/0.2 mL)</td>
<td>39%</td>
</tr>
<tr>
<td>THF/CH&lt;sub&gt;3&lt;/sub&gt;CN (0.4/0.2 mL)</td>
<td>8%</td>
</tr>
<tr>
<td>THF/HMPA (0.4/0.2 mL)</td>
<td>63%</td>
</tr>
<tr>
<td>THF/DMPU (0.4/0.2 mL)</td>
<td>45%</td>
</tr>
<tr>
<td>THF/DMSO (0.4/0.2 mL)</td>
<td>10%</td>
</tr>
<tr>
<td>THF/NMP (0.4/0.2 mL)</td>
<td>45%</td>
</tr>
</tbody>
</table>

*Yields determined by GC-FID with dodecane as internal standard. †Isolated yield.

This optimized set of condition for the decarboxylative borylation of S2 (1º RAE) was more general, and was also suitable for 2 (2º RAE).
Further screening indicated that employing THF as sole solvent gave the best yield for tertiary carboxylic acids (3° RAEs).

**Table S11. Optimization on tertiary RAEs.**

<table>
<thead>
<tr>
<th>X</th>
<th>Ligand</th>
<th>Solvent</th>
<th>Yield*</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>L2</td>
<td>THF (0.4 mL)</td>
<td>26%</td>
</tr>
<tr>
<td>H</td>
<td>L1</td>
<td><strong>THF (0.4 mL)</strong></td>
<td><strong>74% (68%†)</strong></td>
</tr>
<tr>
<td>H</td>
<td>L1</td>
<td>THF/DMF (0.4/0.2 mL)</td>
<td>66%</td>
</tr>
<tr>
<td>H</td>
<td>L5</td>
<td>THF (0.4 mL)</td>
<td>62%</td>
</tr>
<tr>
<td>Cl</td>
<td>L2</td>
<td>THF (0.4 mL)</td>
<td>70%</td>
</tr>
<tr>
<td>Cl</td>
<td>L1</td>
<td>THF (0.4 mL)</td>
<td>52%</td>
</tr>
</tbody>
</table>

*Yields determined by GC-FID with dodecane as internal standard. †Isolated yield.
General Procedure for Nickel Catalyzed Decarboxylative Borylation

Part I. Preparation of NiCl₄•6H₂O/Ligand Stock Solution or Suspension

(1) Suspension A: NiCl₂•6H₂O/di-MeObipy (L₁) in THF (0.025 M).
A screw-capped culture tube charged with NiCl₂•6H₂O (23.8 mg, 0.1 mmol) and 4,4’-dimethoxy-2,2’-bipyridine (L₁, 28.1 mg, 0.13 mmol) was evacuated and backfilled with argon for three times. THF (4.0 mL) was added and the resulting mixture was stirred at room temperature overnight (or until no granular NiCl₂•6H₂O was observed) to afford a pale green suspension.

(2) Suspension B: NiCl₂•6H₂O/di-MeObipy (L₁) in DMF (0.05 M).
A screw-capped culture tube charged with NiCl₂•6H₂O (23.8 mg, 0.1 mmol) and 4,4’-dimethoxy-2,2’-bipyridine (L₁, 28.1 mg, 0.13 mmol) was evacuated and backfilled with argon for three times. DMF (2.0 mL) was added and the resulting mixture was stirred at room temperature overnight to afford a pale green suspension.

(3) Suspension C: NiCl₂•6H₂O/di-tBubipy (L₂) in THF (0.025 M).
A screw-capped culture tube charged with NiCl₂•6H₂O (23.8 mg, 0.1 mmol) and 4,4’-di-tert-butyl-2,2’-bipyridine (L₂, 34.8 mg, 0.13 mmol) was evacuated and backfilled with argon for three times. THF (4.0 mL) was added and the resulting mixture was stirred at room temperature overnight (or until no granular NiCl₂•6H₂O was observed) to afford a pale green suspension.

(4) Solution D: NiCl₂•6H₂O/di-tBubipy (L₂) in DMF (0.05 M).
A screw-capped culture tube charged with NiCl₂•6H₂O (23.8 mg, 0.1 mmol) and 4,4’-di-tert-butyl-2,2’-bipyridine (L₂, 34.8 mg, 0.13 mmol) was evacuated and backfilled with argon for three times. DMF (2.0 mL) was added and the resulting mixture was stirred at room temperature for 2 h to afford a green solution.

Note: All the solutions or suspensions kept under argon can be used for two weeks without appreciable deterioration in reaction yields.
Part II. Preparation of [B₂pin₂Me]Li Complex

To a solution of B₂pin₂ (168 mg, 0.66 mmol) in THF (0.6 mL) was added MeLi (0.38 mL, 1.6 M in Et₂O, 0.6 mmol) at 0 °C under argon. The reaction mixture was warmed to room temperature and stirred for 1 h to afford a suspension (sometimes a clear solution was observed).

Note: The resulting mixture can be stored under constant stirring for 12 hours without appreciable deterioration.

Part III. Nickel Catalyzed Decarboxylative Borylation

General Procedure B

A screw-capped culture tube charged with redox-active ester (0.2 mmol, 1.0 equiv.) and MgBr₂•OEt₂ (77 mg, 0.3 mmol, 1.5 equiv.) was evacuated and backfilled with argon for three times. THF (0.8 mL) was added, and the mixture was stirred until no granular MgBr₂•OEt₂ was observed (ca. 10 min, sonication could promote this process) before suspension B [0.4 mL, NiCl₂•6H₂O (10 mol%)/di-MeObipy (13 mol%) in DMF], or solution D [0.4 mL, NiCl₂•6H₂O (10 mol%)/di-tBubipy (13 mol%) in DMF] was added via a syringe. The resulting mixture was stirred vigorously until no visible solid was observed on the bottom of the reaction vessel (ca. 10 min, sonication could promote this process). This mixture was cooled to 0 °C before a suspension of [B₂pin₂Me]Li in THF (3.0 equiv., 1.1 mL) was added in one portion (note: do not add it dropwise! ). After stirring for 1 h at 0 °C, the reaction was warmed to room temperature and stirred for another 1 h before quenching with 0.1 N HCl (10 mL). The resulting mixture was extracted with Et₂O or EtOAc (3 mL×2). The combined organic layers were concentrated in vacuo, and the crude product was purified by flash column chromatography. For acid labile substrates, the reaction was alternatively quenched with saturated aqueous NH₄Cl (10 mL).
**General Procedure C**

A screw-capped culture tube charged with redox-active ester (0.2 mmol, 1.0 equiv.) and MgBr$_2$•OEt$_2$ (77 mg, 0.3 mmol, 1.5 equiv.) was evacuated and backfilled with argon for three times. Suspension A [0.8 mL, NiCl$_2$•6H$_2$O (10 mol%)/di-MeObipy (13 mol%) in THF] or C [0.8 mL, NiCl$_2$•6H$_2$O (10 mol%)/di-tBubipy (13 mol%) in THF] was added via a syringe. The mixture was stirred vigorously at room temperature until no granular MgBr$_2$•OEt$_2$ was observed (*ca.* 10 min, sonication could promote this process). This suspension was cooled to 0 °C before a suspension of [B$_2$pin$_2$Me]Li was added in one portion (*note: do not add it dropwise!*). After stirring for 1 h at 0 °C, the reaction was warmed to room temperature and stirred for another 1 h. The reaction mixture was diluted with Et$_2$O (10 mL), filtered through a short pad of silica gel and celite (top layer: celite, bottom layer: silica gel, v/v celite:silica gel = 1:1), and washed with Et$_2$O (50 mL). The filtrate was concentrated, and the crude product was purified by flash column chromatography.

For polar substrates, such as peptides, the reaction was quenched either with 0.1 N HCl (10 mL) or saturated aqueous NH$_4$Cl (10 mL) followed by extraction with EtOAc (3 mL×2). The combined organic layers were dried over anhydrous Na$_2$SO$_4$, concentrated *in vacuo* and purified by flash column chromatography.

**Note:**

1. *Addition of THF to solid MgBr$_2$•OEt$_2$ is exothermic.*

2. *Addition of [B$_2$pin$_2$Me]Li to the reaction mixture is exothermic.*
Guide for Selecting Reaction Conditions

Based on the substrates examined, a flow chart is presented herein to guide the selection of optimal conditions for each substrate:

1. Selection of redox-active ester (RAE)

2. Selection of catalyst system

- NHPI ester or TCNHPi ester
  - NiCl₂·6H₂O (10 mol%), L1 or L2 (13 mol%) in THF or DMF (suspension A, B, C or solution D)
  - [Me₃P̃]₂Ni₃Li in THF (3 equiv.)

- 1° benzylc RAEs and a few 2° RAEs

- 1° benzylc RAEs, 3° RAEs and most of 2° RAEs

- 2° RAEs on cyclopropane
  - NiCl₂·6H₂O (10 mol%), L2 (13 mol%) in THF (suspension C)

- 1° RAEs and some 2° RAEs
  - NiCl₂·6H₂O (10 mol%), L1 (13 mol%) in DMF (suspension B)

- Some 2° RAEs and 3° benzylc RAEs, and RAEs derived from amino acids and peptides
  - NiCl₂·6H₂O (10 mol%), L2 (13 mol%) in THF (suspension C)

- 3° RAEs and 2° benzylc RAEs
  - NiCl₂·6H₂O (10 mol%), L1 (13 mol%) in THF (suspension A)
Graphical Supporting Information for Nickel Catalyzed Decarboxylative Borylation

Part I. NiCl₂•6H₂O/Ligand Stock Solution or Suspension

Figure S1. (Left) NiCl₂•6H₂O/ligand stock solution and suspensions: (a) NiCl₂•6H₂O/di-tBubipy in DMF (0.05 M), (b) NiCl₂•6H₂O/di-MeObipy in DMF (0.05 M), (c) NiCl₂•6H₂O/di-tBubipy in THF (0.025 M), (d) NiCl₂•6H₂O/di-MeObipy in THF (0.025M). (Right) The suspensions were used under stirring.
Part II. Preparation of [B$_2$pin$_2$Me]Li Complex

Figure S2. (Above) MeLi (1.6 M in Et$_2$O) and B$_2$pin$_2$

Figure S3. (Left) A flask containing B$_2$pin$_2$ was evacuated. (Center) The flask was backfilled with argon. (Right) THF was added.

Figure S4. (Left) After addition of THF, the mixture was stirred until all B$_2$pin$_2$ dissolved. (Center) The solution was cooled to 0 °C. (Right) MeLi (1.6 M in Et$_2$O) was added dropwise.
After addition of MeLi, a white suspension was obtained. (Center) The suspension was warmed to room temperature. (Right) After stirring for 1 h at room temperature.

Figure S5. (Left) After addition of MeLi, a white suspension was obtained. (Center) The suspension was warmed to room temperature. (Right) After stirring for 1 h at room temperature.
Part III. Nickel Catalyzed Decarboxylative Borylation (General Procedure B)

**Figure S6. (Left)** MgBr₂•OEt₂ was added to a screw-capped culture tube containing NHPI ester (S2, 0.2 mmol), and the tube was evacuated. **(Center)** The tube was backfilled with argon. **(Right)** THF was added.

**Figure S7. (Left)** The mixture was stirred at room temperature until no granular MgBr₂•OEt₂ was observed (ca. 10 min). **(Center)** Sonication could accelerate this process (this was optional). **(Right)** No solid was observed at the bottom of the tube.
Figure S8. (Left) The suspension of NiCl₂•6H₂O/di-MeObipy in DMF (0.05 M) was added. (Center) The mixture was stirred at room temperature until no granular MgBr₂•OEt₂ was observed (ca. 10 min). (Right) Sonication could accelerate this process (this is optional).

Figure S9. (Left) No solid was observed at the bottom of the culture tube. (Center) The resulting mixture was cooled to 0 °C. (Right) [B₂pin₂Me]Li complex was added at 0 °C.
Figure S10. (Left) After addition of $[\text{B}_2\text{pin}_2\text{Me}]\text{Li}$, the resulting mixture was stirred at 0 °C for 1 h. (Center) The reaction mixture was warmed to room temperature and stirred for another 1 h. (Right) After 1 h stirring at room temperature.

Figure S11. (Left) The reaction was quenched with 0.1 N HCl. (Center) After the addition of HCl. (Right) Et$_2$O was added.
Figure S12. (Left) After the addition of Et₂O, the tube was capped and shaken. (Center) First extraction. (Right) Second extraction.

Figure S13. (Left) The combined organic layers were dried over anhydrous Na₂SO₄. (Right) TLC of the reaction mixture (1:20 EtOAc:hexanes). Lane 1: starting material; Lane 2: co-spot of starting material and reaction mixture; Lane 3: reaction mixture (the top spot was the desired product).
Part IV. Nickel Catalyzed Decarboxylative Borylation (General Procedure C)

Figure S14. (Left) MgBr$_2$•OEt$_2$ was added to a screw-capped culture tube containing NHPI ester (S7, 0.2 mmol), and the tube was evacuated. (Center) The tube was backfilled with argon. (Right) The suspension of NiCl$_2$•6H$_2$O/di-tBubipy in THF (0.025 M) was added.

Figure S15. (Left) After addition of NiCl$_2$•6H$_2$O/di-tBubipy in THF. (Center) The mixture was stirred at room temperature until no granular MgBr$_2$•OEt$_2$ was observed (ca. 10 min). (Right) The resulting mixture was cooled to 0 °C.
Figure S16. (Left) [B$_2$pin$_2$Me]Li complex was added at 0 °C. (Center) After the addition of [B$_2$pin$_2$Me]Li, the resulting mixture was stirred at 0 °C for 1 h. (Right) The reaction mixture was warmed to room temperature and stirred for another 1 h.

Figure S17. (Left) After 1 h stirring at room temperature. (Center) The reaction mixture was diluted with Et$_2$O. (Right) A short pad of silica gel and celite (top layer: celite, middle layer: silica gel, bottom layer: sand).
Figure S18. (Left) The diluted mixture was filtered through a short pad of silica gel and celite. (Center) The filtrate. (Right) TLC of the reaction mixture (1:20 EtOAc:hexanes). Lane 1: starting material; Lane 2: co-spot of starting material and reaction mixture; Lane 3: reaction mixture (the top spot was the desired product).

For polar substrates, such as peptides, the reaction was quenched either with 0.1 N HCl (10 mL) or saturated aqueous NH₄Cl (10 mL) followed by extraction with EtOAc (3 mL×2). The combined organic layers were dried over anhydrous Na₂SO₄, concentrated in vacuo and purified by flash column chromatography.
General Procedure for Gram Scale Nickel Catalyzed Decarboxylative Borylation (Ibuprofen)

The gram scale procedure was adapted from General Procedure C. A flame-dried round bottom flask charged with B₂pin₂ (2.57 g, 10.1 mmol, 3.3 equiv.) was evacuated and backfilled with argon for three times. THF (9.2 mL) was added, and the clear solution was cooled to 0 °C when MeLi (5.8 mL, 1.6 M in Et₂O, 9.3 mmol, 3.0 equiv.) was added dropwise. The reaction mixture was then warmed to room temperature and stirred for 1 h.

The NHPI redox-active ester of ibuprofen S16 (1.08 g, 3.07 mmol, 1.0 equiv.) and MgBr₂•OEt₂ (792 mg, 3.07 mmol, 1.0 equiv.) were sequentially added to another flame-dried round-bottom flask. This flask was evacuated and backfilled with argon for three times and was cooled to 0 °C. THF (12 mL) was added, followed by a suspension of NiCl₂•6H₂O (73 mg, 0.31 mmol, 10 mol%) and di-MeObipy (L1, 86 mg, 0.40 mmol, 13 mol%) in THF (12 mL). The resulting mixture was sonicated until there was no visible solid on the bottom of the flask. The mixture was then cooled to 0 °C before a suspension of [B₂pin₂Me]Li in THF was added in one portion. After stirring for 1 h at 0 °C, the reaction mixture was warmed to room temperature and stirred for another 1 h.

The reaction mixture was then poured into Et₂O (100 mL), and the flask was rinsed with additional Et₂O (100 mL). The resulting mixture was filtered through a plug of silica gel and celite (top layer: celite, bottom layer: silica gel, v/v celite:silica gel = 1:1), the solid residue was washed with Et₂O (350 mL), and the filtrate was concentrated in vacuo. Purification by flash column chromatography (silica gel, hexanes to 1:30 Et₂O: hexanes) furnished the product (709 mg, 80%) as a colorless oil.

Note:
1. Addition of THF to solid MgBr₂•OEt₂ is exothermic.
2. Addition of [B₂pin₂Me]Li to the reaction mixture is exothermic.
Graphical Supporting Information for Gram Scale Nickel Catalyzed Decarboxylative Borylation (Ibuprofen)

**Figure S19. (Left)** A flask containing NHPI ester of ibuprofen and MgBr₂•OEt₂ powder was evacuated and backfilled with argon. **(Center)** THF was added at 0 °C. **(Right)** The suspension of NiCl₂•6H₂O and di-MeObipy in THF was added, and the reaction mixture was sonicated until no granular MgBr₂•Et₂O was observed.

**Figure S20. (Left)** The reaction mixture was sonicated until no solid left on the bottom, and was then cooled to 0 °C. **(Right)** The [B₂pin₂Me]Li complex in THF was added.
Figure S21. (Left) After addition of [B$_2$pin$_2$Me]Li complex. (Center) The resulting mixture was stirred at 0 °C for 1 h and at room temperature for another 1 h. (Right) The reaction mixture was poured onto Et$_2$O.

Figure S22. (Left) The diluted mixture was filtered through a pad of silica gel and celite, washed with Et$_2$O. (Center) After filtration. (Right) TLC of the reaction mixture (1:9 EtOAc:hexanes) under UV. (Lane 1: starting material; Lane 2: co-spot of starting material and reaction mixture; Lane 3: reaction mixture).
Figure S23. (Left) After concentration. (Center) The residue was purified by flash column chromatography. (Right) The desired product.
General Procedure for \emph{in situ} Nickel Catalyzed Decarboxylative Borylation of Alkyl Carboxylic Acids (General Procedure D)

A screw-capped culture tube equipped with a stir bar was charged with alkyl carboxylic acid (0.2 mmol, 1.0 equiv.), \textit{N}-hydroxypythalimide or tetrachloro-\textit{N}-hydroxypythalimide (0.2 mmol, 1.0 equiv.) and \textit{N},\textit{N}’-dicyclohexylcarbodiimide (0.2 mmol, 1.0 equiv.). The tube was then evacuated and backfilled with argon for three times. \textit{CH}_2\textit{Cl}_2 (2.0 mL) was added and the resulting mixture was stirred at room temperature for 2 h before the volatiles were removed \emph{in vacuo}. MgBr\textsubscript{2}•OEt\textsubscript{2} (77 mg, 0.3 mmol, 1.5 equiv.) was added. The tube was evacuated and backfilled with argon for three times. Suspension A [0.8 mL, NiCl\textsubscript{2}•6H\textsubscript{2}O (10 mol\%)\textsubscript{/}L\textsubscript{1} (13 mol\%) in THF] or suspension C [0.8 mL, NiCl\textsubscript{2}•6H\textsubscript{2}O (10 mol\%)\textsubscript{/}L\textsubscript{2} (13 mol\%) in THF] was added. The mixture was stirred vigorously at room temperature for 10 min (or until no granular MgBr\textsubscript{2}•OEt\textsubscript{2} was observed) and was subsequently cooled to 0 °C before a suspension of [B\textsubscript{2}pin\textsubscript{2}Me]Li in THF (1.1 mL) was added in one portion (\textit{note: do not add it dropwise!}). After stirring at that temperature for 1 h, the reaction was warmed to room temperature and stirred for another 1 h. The reaction mixture was then quenched with 0.1 N HCl (10 mL) and extracted with Et\textsubscript{2}O (5 mL×2). The combined organic layers were dried over anhydrous Na\textsubscript{2}SO\textsubscript{4}, concentrated \emph{in vacuo} and purified by column chromatography to afford the desired product.
Graphical Supporting Information for *in situ* Nickel Catalyzed Decarboxylative Borylation of Alkyl Carboxylic Acids (General Procedure D)

**Figure S24.** (Left) A screw-capped culture tube equipped with a stir bar was charged with 2-methyl-4-phenylbutanoic acid (0.2 mmol, 1.0 equiv.), tetrachloro-N-hydroxyphthalimide (0.2 mmol, 1.0 equiv.), and N,N'-dicyclohexylcarbodiimide (0.2 mmol, 1.0 equiv.). (Center) The tube was evacuated and backfilled with argon for three times. (Right) CH$_2$Cl$_2$ was added.

**Figure S25.** (Left) After addition of CH$_2$Cl$_2$. (Center) After stirring at room temperature for 2 h. (Right) The reaction mixture was concentrated to dryness *in vacuo*. 
Figure S26. (Left) MgBr₂•OEt₂. (Center) MgBr₂•OEt₂ was added to the crude TCNHP ester. (Right) The tube was evacuated and backfilled with argon for three times.

Figure S27. (Left) Suspension C [0.8 mL, NiCl₂•6H₂O (10 mol%)/L₂ (13 mol%) in THF] was added. (Center) The mixture was stirred vigorously at room temperature until no granular MgBr₂•OEt₂ was observed (ca. 10 min). (Right) [B₂pin₂Me]Li complex was added in one portion at 0 °C.
Figure S28. (Left) After addition of [B_{2}pin_{2}Me]Li complex, the mixture was stirred at 0 °C for 1 h. (Center) The mixture was stirred at room temperature for another 1 h. (Right) The reaction mixture was quenched with 0.1 N HCl (10 mL) and extracted with Et_{2}O (5 mL×2).

Figure S29. (Left) TLC of the reaction mixture (1:9 EtOAc:hexanes). Lane 1: reaction mixture; Lane 2: co-spot of reaction mixture and pure product; Lane 3: pure product. (Right) The same TLC after staining with CAM.
Examples of *in situ* Nickel Catalyzed Decarboxylative Borylation of Alkyl Carboxylic Acids

This *in situ* procedure was demonstrated on seven alkyl carboxylic acids following *General Procedure D*.

![Chemical Reaction Diagram](attachment:image.png)

**Figure S30.** Examples of *in situ* nickel catalyzed decarboxylative borylation. *X = Cl, L = di-**B**ubipy (L2). †X = H, L = di-MeObipy (L1).

*Note: General Procedure D is less effective for primary carboxylic acids (typically ~ 20% yield).*
General Procedure for Nickel Catalyzed Decarboxylative Borylation with 2.5 mol% Nickel Catalyst.

Part I. Preparation of NiCl₂•6H₂O/Ligand Stock Solution or Suspension

(1) Suspension E: NiCl₂•6H₂O/di-MeObipy (L1) in THF (6.25 mM).

A screw-capped culture tube charged with NiCl₂•6H₂O (23.8 mg, 0.1 mmol) and 4,4′-dimethoxy-2,2′-bipyridine (L1, 28.1 mg, 0.13 mmol) was evacuated and backfilled with argon for three times. THF (16.0 mL) was added and the resulting mixture was stirred at room temperature overnight (or until no granular NiCl₂•6H₂O was observed) to afford a pale green suspension.

(2) Solution F: NiCl₂•6H₂O/di-MeObipy (L1) in DMF (12.5 mM).

A screw-capped culture tube charged with NiCl₂•6H₂O (23.8 mg, 0.1 mmol) and 4,4′-dimethoxy-2,2′-bipyridine (L1, 28.1 mg, 0.13 mmol) was evacuated and backfilled with argon for three times. DMF (8.0 mL) was added and the resulting mixture was stirred at room temperature overnight to afford a light green solution.

(3) Suspension G: NiCl₂•6H₂O/di-tBubipy (L2) in THF (6.25 mM).

A screw-capped culture tube charged with NiCl₂•6H₂O (23.8 mg, 0.1 mmol) and 4,4′-di-tert-butyl-2,2′-bipyridine (L2, 34.8 mg, 0.13 mmol) was evacuated and backfilled with argon for three times. THF (16.0 mL) was added and the resulting mixture was stirred at room temperature overnight (or until no granular NiCl₂•6H₂O was observed) to afford a pale green suspension.

Note: All the solutions or suspensions kept under argon can be used for two weeks without appreciable deterioration in reaction yields.
Part II. Nickel Catalyzed Decarboxlyative Borylation

Decarboxylative borylation of redox-active esters with 2.5 mol% nickel loading followed General Procedure B/C with Suspension E/Solution F/Suspension G.
Examples of Nickel Catalyzed Decarboxylative Borylation with 2.5 mol% Nickel

Figure S31. Examples of nickel catalyzed decarboxylative borylation with 2.5 mol% nickel. *Using THF as solvent. †Using L2 (di-tBubipy) as ligand and THF as solvent. ‡Using TCNHPI redox-active ester.
Troubleshooting and Frequently Asked Questions (FAQs):

Part I. Redox-active Ester Synthesis

Question 1:
Some polar redox-active esters (RAEs), such as those derived from amino acids or peptides, are very prone to hydrolysis on silica gel. How can I isolate them?

Answer:
Purification by flash column chromatography using deactivated silica gel (35 wt% H₂O) is recommended.

Question 2:
How does the retention factor of the products change when using deactivated silica gel (35 wt. % H₂O)?

Answer:
The adsorption capacity of deactivated silica gel (35 wt% H₂O) is lower than the normal silica gel. Thus, a less polar eluent should be used compared to normal.

Part II. Preparation of NiCl₂•6H₂O/Ligand Stock Solution or Suspension

Question 1:
NiCl₂•6H₂O has very low solubility in THF in the presence of di-MeObipyl (L₁) or di-tBubipyl (L₂). How do I proceed?

Answer:
The complexes of NiCl₂•6H₂O/L₁ and NiCl₂•6H₂O/L₂ do not dissolve well in THF. However, a very good suspension of such complexes can be afforded after vigorous stirring overnight. **Tips:** It is much easier to get good suspensions (4 – 6 h), if the culture tube was placed at the edge of a stir plate (with a stirring rate of 500 – 800 rpm) instead of the center (see below).
Question 2:
How can I make sure that I have added the precise amount of NiCl₂•6H₂O/L₁ or NiCl₂•6H₂O/L₂ as these complexes do not fully dissolve in THF?
Answer:
The precise amount of catalyst complexes can be drawn out from a “homogeneous” suspension under vigorous stirring.

Question 3:
If there are precipitates in catalyst suspensions A, B, or C, can I still use them?
Answer:
Yes, they can be still used after stirring.

Part III. Preparation of [B₂pin₂Me]Li Complex

Question 1:
Do I have to use 3.0 equiv. of [B₂pin₂Me]Li?
Answer:
2.5 equiv. of [B₂pin₂Me]Li also works fine for most of the substrates. Addition of more than 3.0 equiv. of [B₂pin₂Me]Li, nevertheless, does not help the borylation reaction.
**Question 2:**
How can I monitor the $[\text{B}_2\text{pin}_2\text{Me}]\text{Li}$ complex formation?

**Answer:**
It is very hard to monitor the formation of $[\text{B}_2\text{pin}_2\text{Me}]\text{Li}$ complex, but we have determined that the reaction between MeLi and $\text{B}_2\text{pin}_2$ is completed in 1 h. If the reaction is run for less than 30 min, unreacted MeLi could destroy some base sensitive substrates (such as Fmoc protected amino acids), leading to lower yields.

**Question 3:**
If I get a clear solution of $[\text{B}_2\text{pin}_2\text{Me}]\text{Li}$ instead of a white suspension after stirring for 1 h, what can I do?

**Answer:**
In a few cases, we have also obtained a clear solution after stirring for 1 h. It was found that both clear solution and white suspension worked fine for the borylation reaction.

**Question 4:**
How long can I keep the suspension of $[\text{B}_2\text{pin}_2\text{Me}]\text{Li}$ in THF?

**Answer:**
The suspension of $[\text{B}_2\text{pin}_2\text{Me}]\text{Li}$ in THF can be kept at room temperature for 12 h under stirring. A lower yield was observed if the suspension was left for more than 12 h. This complex is not very stable under air and should thus be kept under an inert atmosphere.

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**Part IV. Nickel Catalyzed Decarboxylative Borylation**

**Question 1:**
If I only have a small amount of carboxylic acid material, which condition would you suggest to try first?

**Answer:**
A flow chart is provided on page S32 to guide the selection of optimal conditions for
different structural classes of substrates.

**Question 2:**
Have you tried any other magnesium salts for this reaction?

**Answer:**
During our initial screening, we examined several magnesium salts, such as MgCl$_2$, Mg(OAc)$_2$, Mg(acac)$_2$, MgSO$_4$, etc., among which MgBr$_2$•OEt$_2$ gave the best yield.

**Question 3:**
Can I change the amount of MgBr$_2$•OEt$_2$ to increase the yield?

**Answer:**
Generally, more than 2.0 equiv. or less than 1.2 equiv. of MgBr$_2$•OEt$_2$ led to diminished yields. However, for the 2° benzylic RAEs, 1.0 equiv. proved to be sufficient for the borylation reaction.

**Question 4:**
Can I use granular MgBr$_2$•OEt$_2$ in this reaction?

**Answer:**
Granular MgBr$_2$•OEt$_2$ can be used in this reaction, but longer stirring time (until no granular MgBr$_2$•OEt$_2$ was observed) was required before the addition of [B$_2$pin$_2$Me]Li complex. MgBr$_2$•OEt$_2$ powder is therefore highly recommended.

**Question 5:**
If there is granular MgBr$_2$•OEt$_2$ left after stirring for 15 min, what can I do?

**Answer:**
Sonicate the mixture or stir for longer periods of time.

**Question 6:**
Can I add the [B$_2$pin$_2$Me]Li complex at room temperature?
Answer:
This borylation reaction is *exothermic*. The reaction temperature would increase a lot if [B₂pin₂Me]Li complex was added at room temperature, leading to lower yields.

**Question 7:**
How do you monitor the reaction?

**Answer:**
We monitor the reaction by TLC (UV visualization or staining based on redox-active esters). Reactions on all substrates examined herein (> 40 examples) were completed in 1 h at 0 °C and another 1 h at room temperature. Longer reaction time generally lead to lower yield. Shorter reaction time is recommended for substrates that are conceivably unstable under the reaction conditions.

**Question 8:**
How can I detect the pinacol alkylboronate esters (alkyl-Bpin) on TLC?

**Answer:**
Most of the pinacol alkylboronate esters are sensitive to ceric ammonium molybdate (CAM, Hanessian's stain) and potassium permanganate (KMnO₄). You can also detect the product *via* UV visualization if your product is UV active. GC/MS and LC/MS are also recommended.

**Question 9:**
What other possible byproduct were observed in this reaction?

**Answer:**
We occasionally observed hydrodecarboxylation, decarboxylative dimerization or the hydrolysis (to carboxylic acids) of RAEs.
**Question 10:**
Is there any indicative color change during the reaction?

**Answer:**
The color of the coupling reaction varies for different substrates. Normally, we observed a color change from green to yellow, brown, or black after addition of the [B₂pin₂Me]Li complex.

**Question 11:**
Can I purify the pinacol alkylboronate esters (alkyl-Bpin) on preparative TLC?

**Answer:**
The pinacol alkylboronate esters are not very stable on preparative TLC due to possible oxidation of C–B bond or hydrolytic cleavage of pinacol esters. Usually, we purify the products using flash column chromatography with gradient elution. Some pinacol α-aminoboronate esters were purified by flash column chromatography with gradient elution using deactivated silica gel (35 wt% H₂O).

**Question 12:**
Are the pinacol alkylboronate esters bench-stable?

**Answer:**
Most of the pinacol alkylboronate esters we made can be stored under air at room temperature for two weeks without appreciable decomposition. Normally, we store them under argon at –20 °C.

**Question 13:**
If the desired product was contaminated with some phthlimide after column, what can I do to remove it and get the pure product?

**Answer:**
Most of the pinacol alkylboronate esters can be dissolved in hexanes, but phthlimide
can not. Thus one can dissolve the product in hexanes and filter it through celite to remove the phthlimide.

**Question 14:**
Although I am able to obtain some product, the yield is not satisfactory for my purposes. How should I optimize the reaction?

**Answer:**
For further optimization, we recommend the following:
1. Screen the four nickel catalytic systems first (suspension A, B, C and solution D).
2. If NHPI ester does not work well, try TCNHPI redox-active ester.
3. Try a higher loading of nickel precatalyst.
4. If suspension B or solution D work better than suspension A or C, one can also try to use DMA instead of DMF.

**Part V Nickel Catalyzed in situ Decarboxlyative Borylation of Alkyl Carboxylic Acids**

**Question 1**
Can I use DIC instead of DCC as coupling reagent in this *in situ* coupling reaction?

**Answer:**
We have tried both of them and found that DCC gave better yield than DIC.

**Question 2**
When is the *in situ* protocol applicable?

**Answer:**
The protocol is suitable for secondary and tertiary carboxylic acids. Lower yields were obtained for primary substrates. Also, the quality of DCC was found to be critical.
Part VI. Deprotection of Pinacol Alkylboronate Esters

Question 1
Are the alkyl boronic acids stable?

Answer:
1. Alkyl boronic acids on tertiary carbon are prone to oxidation. We only obtained the corresponding alcohols instead of desired boronic acids after column chromatography or preparative TLC.
2. Alkyl boronic acids on primary and secondary carbon are relatively stable and can survive quick purifications.
3. α-Amino boronic acids containing electron-withdrawing protecting group on amine are relatively stable.
4. Alkyl boronic acids are prone to dimerization and trimerization, but they can generally be stabilized through addition of water.
Experimental Procedures and Characterization Data for Redox-active Esters

**Compound 2**

![Compound 2](image)

1,3-dioisoindolin-2-yl 2-methyl-4-phenylbutanoate (2)

On 8.75 mmol scale, General Procedure A was followed with 2-methyl-4-phenylbutanoic acid. Purification by flash column chromatography (silica gel, 1:9 EtOAc:hexanes) afforded 2 (2.31 g, 82%).

**Physical state:** colorless oil;

$R_f = 0.60$ (silica gel, 3:7 EtOAc:hexanes);

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.92 – 7.88 (m, 2H), 7.81 – 7.78 (m, 2H), 7.32 – 7.29 (m, 2H), 7.27 – 7.25 (m, 2H), 7.22 – 7.20 (m, 1H), 2.90 – 2.74 (m, 3H), 2.20 – 2.14 (m, 1H), 1.96 – 1.90 (m, 1H), 1.40 (d, $J = 7.2$ Hz, 3H) ppm;

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 172.7, 162.2, 141.3, 134.9, 129.2, 128.7, 128.6, 126.2, 124.1, 36.7, 35.7, 33.1, 17.2 ppm;

HRMS (ESI-TOF, m/z): Calcd for C$_{19}$H$_{18}$NO$_4$ [M+H]$^+$ 324.1230; found 324.1230.

**Compound S1**

![Compound S1](image)

4,5,6,7-tetrachloro-1,3-dioisoindolin-2-yl 2-methyl-4-phenylbutanoate (S1)

On 13.0 mmol scale, General Procedure A was followed with 2-methyl-4-phenylbutanoic acid. Purification by flash column chromatography (silica gel, 1:10 EtOAc:hexanes) afforded a yellow solid which was recrystallized from CH$_2$Cl$_2$/MeOH.
to afford S1 (4.12 g, 69 %).

**Physical state:** white solid;

**m.p.** = 80 – 81 ºC;

**Rf** = 0.63 (silica gel, 1:4 EtOAc:hexanes);

**1H NMR (600 MHz, CDCl3):** δ 7.32 – 7.28 (m, 2H), 7.26 – 7.19 (m, 3H), 2.89 – 2.72 (m, 3H), 2.20 – 2.13 (m, 1H), 1.95 – 1.88 (m, 1H), 1.39 (d, *J* = 8.4 Hz, 3H) ppm;

**13C NMR (151 MHz, CDCl3):** δ 172.3, 157.8, 141.1, 141.0, 130.6, 128.6, 126.3, 124.9, 36.6, 35.5, 33.1, 17.3 ppm;

**HRMS (ESI-TOF, m/z):** Calcd for C19H14Cl4NO4 [M+H]+ 459.9671; found 459.9659.

**Compound S3**

![Compound S3](image)

**1,3-dioxoisoadolin-2-yl 3-(2-bromophenyl)propanoate (S3)**

On 5.0 mmol scale, General Procedure A was followed with 3-(2-bromophenyl)propanoic acid. Purification by flash column chromatography (silica gel, 1:9 EtOAc:hexanes) afforded S3 (1.63 g, 87 %).

**Physical state:** white solid;

**m.p.** = 158 – 160 ºC;

**Rf** = 0.36 (silica gel, 1:4 EtOAc:hexanes);

**1H NMR (600 MHz, CDCl3):** δ 7.90 – 7.87 (m, 2H), 7.80 – 7.77 (m, 2H), 7.56 (dd, *J* = 1.2 Hz, 7.8 Hz, 1H), 7.34 (dd, *J* = 7.8 Hz, 1.8 Hz, 1H), 7.28 (dt, *J* = 7.8 Hz, 1.2 Hz, 1H), 7.12 (dt, *J* = 7.8 Hz, 1.8 Hz, 1H), 3.21 (t, *J* = 7.2 Hz, 2H), 3.02 (t, *J* = 7.2 Hz, 2H) ppm;

**13C NMR (151 MHz, CDCl3):** δ 168.8, 162.0, 138.5, 134.9, 133.1, 130.1, 129.0, 128.7, 127.9, 124.4, 124.1, 31.2, 31.0 ppm;

**HRMS (ESI-TOF, m/z):** Calcd for C17H13BrNO4 [M+H]+ 374.0022; found 374.0022.
Compound S4

1,3-dioisoindolin-2-yl 6-bromohexanoate (S4)
On 5.0 mmol scale, General Procedure A was followed with 6-bromohexanoic acid. Purification by flash column chromatography (silica gel, 1:10 EtOAc:hexanes) afforded S4 (1.52 g, 89%).
Physical state: white solid;
m.p. = 60 – 62 °C;
$R_f = 0.45$ (silica gel, 1:4 EtOAc:hexanes);
$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.89 – 7.86 (m, 2H), 7.79 – 7.77 (m, 2H), 3.42 (t, $J = 7.2$ Hz, 2H), 2.68 (t, $J = 7.2$ Hz, 2H), 1.94 – 1.89 (m, 2H), 1.84 – 1.79 (m, 2H), 1.63 – 1.57 (m, 2H) ppm;
$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 169.4, 162.0, 134.9, 129.0, 124.1, 33.3, 32.3, 30.9, 27.5, 24.0 ppm;
HRMS (ESI-TOF, m/z): Calcd for C$_{14}$H$_{15}$BrNO$_4$ [M+H]$^+$ 340.0179; found 340.0178.

Compound S5

1-(tert-butyl) 5-(1,3-dioisoindolin-2-yl) (((9H-fluoren-9-yl)methoxy)carbonyl)-L-glutamate (S5)
On 3.0 mmol scale, General Procedure A was followed with Fmoc-Glu-OtBu. Purification by flash column chromatography (silica gel, 1:3 EtOAc:hexanes) afforded S5 (1.53 g, 89%).
Physical state: white foam;
$R_f = 0.49$ (silica gel, 1:4 EtOAc:hexanes);
$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.90 – 7.86 (m, 2H), 7.80 – 7.76 (m, 4H), 7.67 – 7.61 (m, 2H), 7.42 – 7.38 (m, 2H), 7.31 (dt, $J = 7.2$ Hz, 1.2 Hz, 2H), 5.52 (br d, $J = 7.8$ Hz, 1H), 4.50 (dd, $J = 10.8$ Hz, 7.2 Hz, 1H), 4.39 – 4.36 (m, 2H), 4.23 (t, $J = 7.2$ Hz, 1H), 2.82 – 2.77 (m, 1H), 2.73 – 2.67 (m, 1H), 2.40 – 2.34 (m, 1H), 2.15 – 2.09 (m, 1H), 1.50 (s, 9H) ppm;  

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 170.6, 169.1, 162.0, 156.2, 141.5, 134.9, 129.0, 127.9, 127.2, 125.4, 125.2, 124.2, 120.1, 83.1, 67.2, 53.7, 47.4, 28.1, 28.0, 27.6 ppm;  

HRMS (ESI-TOF, m/z): Calcd for C$_{32}$H$_{30}$N$_2$NaO$_8$ [M+Na]$^+$ 593.1894; found 593.1895;  

[a]$_D^{20} = +5.4$ (c 1.0, CHCl$_3$).  

**Compound S6**  

![Image of S6 compound](image)  

4,5,6,7-tetrachloro-1,3-dioxoisindolin-2-yl 2-(4-bromophenyl)acetate (S6)  

On 5.0 mmol scale, General Procedure A was followed with 2-(4-bromophenyl)acetic acid. After completion of the reaction, reaction mixture was filtered through a short pad of silica gel and washed with EtOAc/hexanes (1:8). The filtrate was concentrated, and S6 was obtained after recrystallization with CH$_2$Cl$_2$/MeOH (1.52 g, 61%).  

**Physical state:** pale yellow solid;  

**m.p.** = 212 – 213 °C;  

$R_f = 0.57$ (silica gel, 1:4 EtOAc:hexanes);  

$^1$H NMR (600 MHz, DMSO-$d_6$): $\delta$ 7.61 – 7.59 (m, 2H), 7.37 – 7.35 (m, 2H), 4.25 (s, 2H) ppm;  

$^{13}$C NMR (151 MHz, DMSO-$d_6$): $\delta$ 167.7, 157.5, 139.3, 131.7, 131.6, 131.6, 129.0, 125.2, 120.9, 35.8 ppm;  

HRMS (ESI-TOF, m/z): Calcd for C$_{16}$H$_7$BrCl$_4$NO$_4$ [M+H]$^+$ 495.8307; found 495.8323.
Compound S7

4,5,6,7-tetrachloro-1,3-dioxoisindolin-2-yl 2-methyl-3-phenylpropanoate (S7)

On 5.0 mmol scale, General Procedure A was followed with 2-methyl-3-phenylpropanoic acid. Purification by flash column chromatography (silica gel, 1:10 EtOAc:hexanes) afforded a yellow solid which was recrystallized from CH₂Cl₂/MeOH to afford S7 (1.45 g, 65%).

Physical state: pale yellow solid;

m.p. = 127 – 128 °C

R_f = 0.63 (silica gel, 1:4 EtOAc:hexanes);

^1H NMR (600 MHz, CDCl₃): δ 7.35 – 7.32 (m, 2H), 7.28 – 7.23 (m, 3H), 3.25 (dd, J = 13.8 Hz, 6.6 Hz, 1H), 3.14 – 3.08 (m, 1H), 2.82 (dd, J = 13.8 Hz, 7.8 Hz, 1H), 1.34 (d, J = 7.2 Hz, 3H) ppm;

^13C NMR (151 MHz, CDCl₃): δ 171.9, 157.7, 141.2, 137.8, 130.6, 129.2, 128.8, 127.0, 124.9, 39.3, 39.0, 16.6 ppm;

HRMS (ESI-TOF, m/z): Calcd for C_{18}H_{12}Cl₄NO₄ [M+H]^+ 445.9515; found 445.9516.

Compound S8

1,3-dioxoisindolin-2-yl 2-phenylpropanoate (S8)

On 5.0 mmol scale, General Procedure A was followed with 2-phenylpropanoic acid. Purification by flash column chromatography (silica gel, 1:10 EtOAc:hexanes) afforded S8 (1.19 g, 81%).

Physical state: colorless oil;
$R_f = 0.21$ (silica gel, 1:4 EtOAc:hexanes);

$^1$H NMR (600 MHz, CDCl$_3$): δ 7.87 – 7.85 (m, 2H), 7.79 – 7.76 (m, 2H), 7.43 – 7.39 (m, 4H), 7.34 – 7.31 (m, 1H), 4.13 (q, $J = 7.2$ Hz, 1H), 1.68 (d, $J = 7.2$ Hz, 3H) ppm;

$^{13}$C NMR (151 MHz, CDCl$_3$): δ 170.9, 162.0, 138.5, 134.9, 129.1, 129.1, 127.9, 127.7, 124.1, 43.1, 19.1 ppm;

HRMS (ESI-TOF, m/z): Calcd for C$_{17}$H$_{14}$NO$_4$ [M+H]$^+$ 296.0917; found 296.0920.

**Compound S9**

![Diagram of compound S9](image)

1,3-dioxoisoindolin-2-yl 2,2-diphenylacetate (S9)

On 1.5 mmol scale, General Procedure A was followed with diphenylacetic acid. Purification by flash column chromatography (silica gel, 1:4 EtOAc:hexanes) afforded S9 (0.46 g, 86%).

**Physical state:** white solid;

**m.p.** = 135 – 137 °C;

$R_f = 0.33$ (silica gel, 1:4 EtOAc:hexanes)

$^1$H NMR (600 MHz, CDCl$_3$): δ 7.89 – 7.86 (m, 2H), 7.80 – 7.77 (m, 2H), 7.42 – 7.37 (m, 8H), 7.34 – 7.31 (m, 2H), 5.42 (s, 1H) ppm;

$^{13}$C NMR (151 MHz, CDCl$_3$): δ 169.2, 162.0, 136.9, 134.9, 129.1, 129.1, 127.9, 127.7, 124.1, 54.2 ppm;

HRMS (ESI-TOF, m/z): Calcd for C$_{22}$H$_{16}$NO$_4$ [M+H]$^+$ 358.1074; found 358.1078.
Compound S10

1,3-dioxoisooindolin-2-yl-bicyclo[2.2.1]heptane-2-carboxylate (S10)

On 3.0 mmol scale, General Procedure A was followed with bicyclo[2.2.1]heptane-2-carboxylic acid (mixture of exo/endo isomers). Purification by flash column chromatography (silica gel, 1:19 to 1:9 EtOAc:hexanes) afforded S10 (0.75 g, 88%) as mixture of exo/endo isomers.

**Physical state:** white solid;

$R_f = 0.41$ (silica gel, 1:4 EtOAc:hexanes);

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.90 – 7.86 (m, 2H), 7.80 – 7.77 (m, 2H), 3.15 – 3.11 (m, 0.82H), 2.81 (br s, 0.82H), 2.77 (br d, $J = 4.2$ Hz, 0.18 H), 2.70 (dd, $J = 9.6$ Hz, 6.0 Hz, 0.18H), 2.38 (br t, $J = 4.2$ Hz, 0.18 H), 2.35 – 2.33 (br, m, 0.82H), 2.00 – 1.96 (m, 0.18H), 1.86 – 1.81 (m, 0.82H), 1.74 – 1.70 (m, 0.82H), 1.63 – 1.67 (m, 3.28H), 1.51 – 1.44 (m, 1.64H), 1.38 – 1.25 (m, 1.26H) ppm;

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 171.5, 162.3, 134.8, 129.2, 124.0, 43.4, 41.0, 40.5, 37.0, 32.7, 29.0, 24.9 ppm (major isomer); 172.3, 162.3, 134.8, 129.2, 124.0, 43.7, 41.7, 36.7, 36.2, 34.6, 29.5, 28.6 ppm (minor isomer).

**HRMS (ESI-TOF, m/z):** Calcd for C$_{16}$H$_{16}$NO$_4$ [M+H]$^+$ 286.1074; found 286.1071.

Compound S11

4,5,6,7-tetrachloro-1,3-dioxoisooindolin-2-yl trans-2-phenylcyclopropane-1-carboxylate (S11)

On 3.0 mmol scale, General Procedure A was followed with trans-2-
phenylcyclopropane-1-carboxylic acid. Upon complete consumption of starting material as indicated by TLC, the reaction mixture was filtered through celite, washed with CH$_2$Cl$_2$ (100 mL), and concentrated under reduced pressure. The crude product was purified by crystallization (CH$_2$Cl$_2$/MeOH) to afford S11 (949 mg, 71%).

**Physical state:** pale yellow needles;

**m.p.** = 203 – 205 °C;

**$R_f$** = 0.48 (silica gel, 1:9 EtOAc:hexanes);

**$^1$H NMR (600 MHz, CDCl$_3$):** δ 7.34 – 7.31 (m, 2H), 7.28 – 7.25 (m, 1H), 7.18 – 7.16 (m, 2H), 2.80 – 2.77 (m, 1H), 2.22 – 2.19 (m, 1H), 1.84 (dt, $J$ = 10.2 Hz, 5.4 Hz, 1H), 1.69 – 1.66 (m, 1H) ppm;

**$^{13}$C NMR (151 MHz, CDCl$_3$):** δ 169.4, 157.7, 141.2, 138.3, 130.6, 128.8, 127.4, 126.5, 124.8, 28.8, 21.0, 18.6 ppm;

**HRMS (ESI-TOF, $m/z$):** Calcd for C$_{18}$H$_{10}$Cl$_4$NO$_4$ [M+H]$^+$ 443.9358; found 443.9356.

**Compound S12**

![Compound S12](image)

1,3-dioxoisooindolin-2-yl 2,2-dimethyl-3-phenylpropanoate (S12)

On 5.0 mmol scale, General Procedure A was followed with 2, 2-dimethyl-3-phenylpropanoic acid. Purification by flash column chromatography (silica gel, 1:10 EtOAc:hexanes) afforded S12 (1.36 g, 84%).

**Physical state:** white solid;

**m.p.** = 70 – 72 °C;

**$R_f$** = 0.45 (silica gel, 1:4 EtOAc:hexanes);

**$^1$H NMR (600 MHz, CDCl$_3$):** δ 7.92 – 7.88 (m, 2H), 7.81 – 7.78 (m, 2H), 7.36 – 7.31 (m, 4H), 7.29 – 7.26 (m, 1H), 3.10 (s, 2H), 1.40 (s, 6H) ppm;

**$^{13}$C NMR (151 MHz, CDCl$_3$):** δ 173.7, 162.2, 136.5, 134.8, 130.6, 129.1, 128.3, 127.0,
HRMS (ESI-TOF, \(m/z\)): Calcd for $\text{C}_{19}\text{H}_{18}\text{NO}_4 [\text{M+H}]^+$ 324.1230; found 324.1232.

Compound S13

1,3-dioxoisindolin-2-yl 1-phenylcyclohexane-1-carboxylate (S13)

On 5.0 mmol scale, General Procedure A was followed with 2-phenylpropanoic acid. Purification by flash column chromatography (silica gel, 1:9 EtOAc:hexanes) afforded S13 (1.64 g, 81%).

**Physical state:** white solid;

**m.p.** = 108 – 109 °C;

$R_f$ = 0.39 (silica gel, 1:4 EtOAc:hexanes);

$^1\text{H NMR (600 MHz, CDCl}_3\text{)}$: $\delta$ 7.87 – 7.84 (m, 2H), 7.78 – 7.75 (m, 2H), 7.54 – 7.52 (m, 2H), 7.44 – 7.41 (m, 2H), 7.34 – 7.31 (m, 1H), 2.64 (br d, $J$ = 13.2 Hz, 2H), 1.89 – 1.73 (m, 7H), 1.37 – 1.30 (m, 1H) ppm;

$^{13}\text{C NMR (151 MHz, CDCl}_3\text{)}$: $\delta$ 171.8, 162.2, 142.3, 134.8, 129.2, 128.9, 127.7, 126.1, 124.0, 51.3, 35.5, 25.6, 23.6 ppm;

HRMS (ESI-TOF, \(m/z\)): Calcd for $\text{C}_{21}\text{H}_{20}\text{NO}_4 [\text{M+H}]^+$ 350.1387; found 350.1387.

Compound S14

1,3-dioxoisindolin-2-yl 2-methyl-2-phenylpropanoate (S14)

On 5.0 mmol scale, General Procedure A was followed with 2-methyl-2-phenylpropanoic acid. Purification by flash column chromatography (silica gel, 1:8
EtOAc:hexanes afforded **S14** (1.32 g, 85%).

**Physical state:** white solid;

**m.p.** = 73 – 74 °C;

**Rf** = 0.36 (silica gel, 1:4 EtOAc:hexanes);

**1H NMR (600 MHz, CDCl₃):** δ 7.88 – 7.85 (m, 2H), 7.79 – 7.75 (m, 2H), 7.51 – 7.49 (m, 2H), 7.44 – 7.41 (m, 2H), 7.34 – 7.31 (m, 1H), 1.79 (s, 6H) ppm;

**13C NMR (151 MHz, CDCl₃):** δ 173.4, 162.1, 142.7, 134.8, 129.1, 128.8, 127.5, 125.9, 124.0 46.5, 27.0 ppm;

**HRMS (ESI-TOF, m/z):** Calcd for C₁₈H₁₆NO₄ [M+H]⁺ 310.1074; found 310.1082.

**Compound S15**

![Compound S15](image)

1,3-dioxisoindolin-2-yl-2-(1-(((tert-butoxycarbonyl)amino)methyl)cyclohexyl) acetate (S15)

On 0.44 mmol scale, General Procedure A was followed with N-Boc-gabapentin. Purification by flash column chromatography (silica gel, 1:5 EtOAc:hexanes) afforded **S15** (165 mg, 85%).

**Physical state:** white solid;

**m.p.** = 76 – 79 °C;

**Rf** = 0.32 (silica gel, 1:5 EtOAc:hexanes);

**1H NMR (600 MHz, CDCl₃):** δ 7.90 – 7.87 (m, 2H), 7.82 – 7.77 (m, 2H), 4.95 (br t, J = 7.2 Hz, 1H), 3.38 (d, J = 6.6 Hz, 2H), 2.63 (s, 2H), 1.65 – 1.43 (m, 10H), 1.44 (s, 9H) ppm;

**13C NMR (151 MHz, CDCl₃):** δ 168.3, 162.1, 156.6, 135.0, 129.0, 124.2, 79.3, 46.9, 39.1, 37.8, 33.9, 28.5, 26.0, 21.6 ppm;

**HRMS (ESI-TOF, m/z):** Calcd for C₂₂H₂₉N₂O₆ [M+H]⁺ 417.2020; found 417.2022.
Compound S16

1,3-dioxoisindolin-2-yl-2-(4-isobutylphenyl)propanoate (S16)

On 5.0 mmol scale, General Procedure A was followed with ibuprofen. Purification by flash column chromatography (silica gel, 1:9 EtOAc:hexanes) afforded S16 (1.48 g, 84%).

Physical state: colorless solid;

m.p. = 67 – 68 °C;

$R_f$ = 0.42 (silica gel, 1:4 EtOAc:hexanes);

$^1$H NMR (600 MHz, CDCl$_3$): δ 7.87 – 7.85 (m, 2H), 7.79 – 7.76 (m, 2H), 7.31 (d, $J$ = 8.4 Hz, 2H), 7.17 (d, $J$ = 8.4 Hz, 2H), 4.10 (q, $J$ = 7.2 Hz, 1H), 2.48 (d, $J$ = 7.2 Hz, 2H), 1.91 – 1.84 (m, 1H), 1.67 (d, $J$ = 7.2 Hz, 3H), 0.91 (d, $J$ = 6.6 Hz, 6H) ppm;

$^{13}$C NMR (151 MHz, CDCl$_3$): δ 171.1, 162.0, 141.4, 135.7, 134.8, 129.8, 129.1, 127.4, 124.0, 45.2, 42.7, 30.3, 22.5, 19.2 ppm;

HRMS (ESI-TOF, m/z): Calcd for C$_{21}$H$_{22}$NO$_4$ [M+H]$^+$ 352.1543; found 352.1544.

Compound S17

1,3-dioxoisindolin-2-yl 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoate (S17)

On 1.0 mmol scale, General Procedure A was followed with gemfibrozil. Purification by flash column chromatography (silica gel, 1:25 EtOAc:hexanes) afforded S17 (0.33 g, 84%).

Physical state: white solid;
m.p. = 65 – 67 °C;

$R_f = 0.50$ (silica gel, 1:4 EtOAc:hexanes);

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.90 – 7.87 (m, 2H), 7.80 – 7.77 (m, 2H), 7.01 (d, $J = 7.8$ Hz, 1H), 6.67 (d, $J = 7.8$ Hz, 1H), 6.66 (s, 1H), 4.02 (t, $J = 6.0$ Hz, 2H), 2.32 (s, 3H), 2.20 (s, 3H), 1.95 – 2.00 (m, 4H), 1.46 (s, 6H) ppm;

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 173.9, 162.2, 157.1, 136.6, 134.8, 130.4, 129.2, 124.0, 123.8, 120.8, 112.1, 67.9, 42.1, 37.5, 31.7, 25.3, 25.1, 21.5, 15.9 ppm;

HRMS (ESI-TOF, m/z): Calcd for C$_{23}$H$_{26}$NO$_5$ [M+H]$^+$ 396.1805; found 396.1803.

**Compound S18**

![Compound S18](image)

1,3-dioisoindolin-2-yl 2-(6-methoxynaphthalen-2-yl)propanoate (S18)

On 5.0 mmol scale, General Procedure A was followed with naproxen. Purification by flash column chromatography (silica gel, 1:7 EtOAc:hexanes) afforded S18 (1.65 g, 88%).

**Physical state:** white solid;

m.p. = 110 – 111 °C;

$R_f = 0.53$ (silica gel, 2:3 EtOAc:hexanes);

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.86 (br s, 2H), 7.80 – 7.75 (m, 5H), 7.49 (dd, $J = 8.4$ Hz, 1.8 Hz, 1H), 7.17 (dd, $J = 8.4$ Hz, 2.4 Hz, 1H), 7.14 (d, $J = 2.4$ Hz, 1H), 4.26 (q, $J = 7.2$ Hz, 1H), 3.92 (s, 3H), 1.75 (d, $J = 7.2$ Hz, 3H) ppm;

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 171.1, 162.0, 157.1, 134.9, 134.1, 133.6, 129.6, 129.1, 127.7, 126.5, 126.0, 124.1, 119.3, 105.8, 55.5, 43.1, 19.2 ppm;

HRMS (ESI-TOF, m/z): Calcd for C$_{23}$H$_{18}$NO$_5$ [M+H]$^+$ 376.1179; found 376.1183.
Compound S19

bis(1,3-dioxoisooindolin-2-yl) nonanedioate (S19)

On 5.0 mmol scale, General Procedure A was followed with azelaic acid (5.0 mmol, 1.0 equiv.), NHPI (10 mmol, 2.0 equiv.), DIC (11 mmol, 2.2 equiv.) and DMAP (1 mmol, 0.2 equiv.). Purification by flash column chromatography (silica gel, 1:10 EtOAc:CH₂Cl₂) afforded S19 (1.52 g, 64%).

Physical state: white solid;
m.p. = 103 – 105 °C;
R_f = 0.55 (silica gel, 1:1 EtOAc:hexanes);

^1H NMR (600 MHz, CDCl₃): δ 7.90 – 7.87 (m, 4H), 7.81 – 7.78 (m, 4H), 2.69 (t, J = 4.8 Hz, 4H), 1.85 – 1.80 (m, 4H), 1.53 – 1.48 (m, 4H), 1.45 – 1.42 (m, 2H) ppm;

^13C NMR (151 MHz, CDCl₃): δ 169.1, 161.5, 134.3, 128.5, 123.5, 30.5, 28.1, 28.0, 24.1 ppm;

HRMS (ESI-TOF, m/z): Calcd for C₂₅H₂₃N₂O₈[M+H]^+ 479.1449; found 479.1451.

Compound S20

1,3-dioxoisooindolin-2-yl 4-(4-(bis(2-chloroethyl)amino)phenyl)butanoate (S20)

On 1.0 mmol scale, General Procedure A was followed with chlorambucil. Purification by flash column chromatography (silica gel, 1:4 EtOAc:hexanes) afforded S20 (431 mg, 96%).

Physical state: yellow oil;
R_f = 0.23 (silica gel, 1:4 EtOAc:hexanes);
$^{1}$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.91 – 7.87 (m, 2H), 7.81 – 7.77 (m, 2H), 7.12 (d, $J = 8.5$ Hz, 2H), 6.65 (d, $J = 9.0$ Hz, 2H), 3.66 (AB t, $J = 6.7$ Hz, 4H), 3.63 (BA t, $J = 6.7$ Hz, 4H), 2.67 (dt, $J = 7.5$ Hz, 16 Hz, 4H), 2.09 – 2.02 (m, 2H) ppm;

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 169.6, 162.1, 144.7, 134.9, 130.0, 129.9, 129.1, 124.1, 112.4, 53.8, 40.7, 33.6, 30.3, 26.6 ppm;

HRMS (ESI-TOF, $m/z$): Calcd for C$_{22}$H$_{23}$Cl$_2$N$_2$O$_4$ [M+H]$^+$ 449.1029; found 449.1009.

Compound S21

![Chemical Structure of S21]

1,3-dioxoisoindolin-2-yl 2-(3-benzoylphenyl)propanoate (S21)

On 5.0 mmol scale, General Procedure A was followed with ketoprofen. Purification by flash column chromatography (silica gel, 1:3 EtOAc:hexanes) afforded S21 (1.91 g, 96%).

Physical state: white solid;

m.p. = 118 – 120 °C;

$R_f = 0.45$ (silica gel, 1:2 EtOAc:hexanes);

$^{1}$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.88 (dd, $J = 5.5$ Hz, 3.1 Hz, 2H), 7.86 – 7.83 (m, 3H), 7.80 – 7.76 (m, 3H), 7.68 – 7.65 (m, 1H), 7.60 (ddt, $J = 8.7$ Hz, 7.0 Hz, 1.3 Hz, 1H), 7.53 (t, $J = 7.7$ Hz, 1H), 7.52 – 7.48 (m, 2H), 4.20 (q, $J = 7.2$ Hz, 1H), 1.71 (d, $J = 7.2$ Hz, 3H) ppm;

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 196.4, 170.6, 161.9, 138.7, 138.4, 137.5, 134.9, 132.7, 131.7, 130.3, 129.8, 129.5, 129.1, 129.1, 128.5, 124.1, 43.0, 19.0 ppm;

HRMS (ESI-TOF, $m/z$): Calcd for C$_{24}$H$_{18}$NO$_5$ [M+H]$^+$ 400.1179; found 400.1181.
Compound S22

![Compound S22](image)

1,3-dioxoisindolin-2-yl 2-(3-phenoxyphenyl)propanoate (S22)

On 5.0 mmol scale, General Procedure A was followed with fenoprofen. Purification by flash column chromatography (silica gel, 1:8 EtOAc:hexanes) afforded S22 (1.83 g, 94%).

**Physical state:** colorless oil;

$R_f = 0.50$ (silica gel, 1:4 EtOAc:hexanes);

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.89 – 7.85 (m, 2H), 7.79 – 7.76 (m, 2H), 7.37 – 7.33 (m, 3H), 7.16 (dt, $J = 7.8$ Hz, 1.2 Hz, 1H), 7.13 – 7.10 (m, 1H), 7.09 (t, $J = 2.4$ Hz, 1H), 7.07 – 7.04 (m, 2H), 6.95 (ddd, $J = 7.8$ Hz, 2.4 Hz, 0.6 Hz, 1H), 4.09 (q, $J = 7.2$ Hz, 1H). 1.67 (d, $J = 7.2$ Hz, 3H) ppm;

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 170.6, 161.9, 157.8, 157.1, 140.3, 134.9, 130.3, 129.9, 129.1, 124.1, 123.5, 122.5, 119.2, 118.4, 118.2, 42.9, 19.0 ppm;

HRMS (ESI-TOF, $m/z$): Caled for C$_{23}$H$_{18}$NO$_5$ [M+H]$^+$ 388.1179; found 388.1178.

Compound S23

![Compound S23](image)

1,3-dioxoisindolin-2-yl 2-((4R,6R)-6-(2-(2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1H-pyrrol-1-yl)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (S23)

On 0.5 mmol scale, General Procedure A was followed with acetone ketal of
atorvastatin (Lipitor). Purification by flash column chromatography (silica gel, 1:2 EtOAc:hexanes) afforded S23 (0.35 g, 95%).

**Physical state:** yellow foam;

$R_f = 0.35$ (silica gel, 1:2 EtOAc:hexanes);

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.90 – 7.87 (m, 2H), 7.81 – 7.77 (m, 2H), 7.21 – 7.15 (m, 9H), 7.08 (d, $J = 8.4$ Hz, 2H), 7.02 – 6.97 (m, 3H), 6.88 (br s, 1H), 4.33 – 4.28 (m, 1H), 4.14 – 4.07 (m, 1H), 3.89 – 3.84 (m, 1H), 3.75 – 3.71 (m, 1H), 3.61 – 3.56 (m, 1H), 2.85 (dd, $J = 15.6$ Hz, 6.6 Hz, 1H), 2.69 (dd, $J = 15.0$ Hz, 6.6 Hz, 1H), 1.76 – 1.70 (m, 2H), 1.55 – 1.53 (m, 7H), 1.40 (s, 3H), 1.35 (s, 3H), 1.18 (dd, $J = 12.0$ Hz, 5.4 Hz, 1H) ppm;

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 166.9, 164.9, 162.4 (d, $J = 247.8$ Hz), 161.9, 141.6, 138.5, 134.9, 134.8, 133.3 (d, $J = 8.0$ Hz), 130.6, 129.0, 128.9, 128.8, 128.4, 128.3 (d, $J = 3.6$ Hz), 126.7, 124.1, 123.6, 121.9, 119.7, 115.5 (d, $J = 21.3$ Hz), 99.2, 66.4, 65.6, 40.9, 38.4, 38.1, 35.8, 29.9, 26.2, 21.9, 21.7, 19.7 ppm;

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –113.9 ppm;

HRMS (ESI-TOF, m/z): Calcd for C$_{44}$H$_{43}$FN$_3$O$_7$ [M+H]$^+$ 744.3080; found 744.3061. 

$[\alpha]_D^{20} = +25.1$ (c 1.0, CHCl$_3$).

**Compound S24**

![Compound S24](image)

1,3-dioxoisoindolin-2-yl (2S,4aS,6aS,6bR,8aR,10S,12aS,12bR,14bR)-10-acetoxy-2,4a,6a,6b,9,9,12a-heptamethyl-13-oxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-icosahydropicene-2-carboxylate (S24)

On 1.0 mmol scale, General Procedure A was followed with acetyl enoxolone.
Purification by flash column chromatography (silica gel, 1:5 EtOAc:hexanes) afforded S24 (0.49 g, 75%).

**Physical State:** white solid;

m.p. = 264 °C;

$R_f$ = 0.57 (silica gel, 2:3 EtOAc:hexanes);

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.89 – 7.86 (m, 2H), 7.80 – 7.77 (m, 2H), 5.76 (s, 1H), 4.51 (dd, $J = 11.8$ Hz, 4.6 Hz, 1H), 2.79 (dt, $J = 13.7$ Hz, 3.7 Hz, 1H), 2.45 (ddd, $J = 13.7$ Hz, 4.3 Hz, 1.7 Hz, 1H), 2.35 (s, 1H), 2.15 – 2.11 (m, 1H), 2.11 – 2.00 (m, 2H), 2.04 (s, 3H), 1.86 (td, $J = 13.7$ Hz, 4.7 Hz, 1H), 1.79 (t, $J = 13.7$ Hz, 1H), 1.74 – 1.55 (m, 4H), 1.51 – 1.40 (m, 4H), 1.43 (s, 3H), 1.37 (s, 3H), 1.20 (ddd, $J = 13.8$ Hz, 4.6 Hz, 2.4 Hz, 1H), 1.15 (s, 3H), 1.14 (s, 3H), 1.10 – 1.01 (m, 3H), 0.90 (s, 3H), 0.87 (s, 6H), 0.80 (dd, $J = 11.9$ Hz, 1.8 Hz, 1H) ppm;

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 200.0, 172.7, 171.1, 168.5, 162.2, 134.8, 129.2, 129.0, 124.0, 80.8, 61.9, 55.2, 47.9, 45.5, 44.0, 43.3, 41.3, 38.9, 38.2, 37.4, 37.1, 32.9, 32.0, 31.6, 28.5, 28.2, 28.1, 26.6, 26.6, 23.7, 23.4, 21.5, 18.8, 17.5, 16.8, 16.6 ppm;

HRMS (ESI-TOF, m/z): Calcd for C$_{40}$H$_{52}$NO$_7$ [M+H]$^+$ 658.3738; found 658.3736; $[\alpha]_{D}^{20} = +191.0$ (c 1.0, CHCl$_3$).

**Compound S25**

1,3-dioxoisindolin-2-yl $^{(E)}$-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methylhex-4-enoate (S25)

On 1.0 mmol scale, General Procedure A was followed with mycophenolic acid. Purification by flash column chromatography (silica gel, 1:4 EtOAc:hexanes) afforded S25 (0.36 g, 78%).

**Physical state:** white solid;
m.p. = 126 – 128 °C;

$R_f = 0.40$ (silica gel, 1:3 EtOAc:hexanes);

$^1$H NMR (600 MHz, CDCl₃): δ 7.88 – 7.85 (m, 2H), 7.79 – 7.77 (m, 2H), 7.68 (s, 1H), 5.34 (t, $J = 7.2$ Hz, 1H), 5.19 (s, 2H), 3.77 (s, 3H), 3.42 (d, $J = 6.6$ Hz, 2H), 2.76 (t, $J = 7.8$ Hz, 2H), 2.45 (t, $J = 7.8$ Hz, 2H), 2.15 (s, 3H), 1.85 (s, 3H) ppm;

$^{13}$C NMR (151 MHz, CDCl₃): δ 173.0, 169.3, 163.8, 162.0, 153.8, 144.2, 134.9, 133.1, 129.0, 124.1, 123.9, 122.0, 116.8, 106.5, 70.2, 61.2, 34.1, 29.9, 22.8, 16.2, 11.7 ppm;

HRMS (ESI-TOF, m/z): Calcd for C$_{25}$H$_{24}$NO$_8$ [M+H]$^+$ 466.1496; found 466.1499.
The preparation and spectral data of the following RAEs have been reported (22-26).

Figure S32. Structures of S2, S26-S39.
Experimental Procedure and Characterization Data for Borylation Products

**Compound 3**

![Structure of Compound 3](image)

**4,4,5,5-tetramethyl-2-(4-phenylbutan-2-yl)-1,3,2-dioxaborolane (3)**

On 0.2 mmol scale, General Procedure B was followed with NHPI ester (2) and suspension B (NiCl₂•6H₂O/di-MeObipy in DMF). Purification by flash column chromatography (silica gel, hexanes to 1:35 Et₂O:hexanes) afforded 3 (32.7 mg, 63%).

**Physical state:** colorless oil;

$R_f = 0.49$ (silica gel, 1:12 EtOAc:hexanes);

$^1$H NMR (600 MHz, CDCl₃): $\delta$ 7.28 – 7.25 (m, 2H), 7.20 – 7.14 (m, 3H), 2.66 – 2.58 (m, 2H), 1.82 – 1.76 (m, 1H), 1.62 – 1.57 (m, 1H), 1.25 (s, 12H), 1.10 – 1.05 (m, 1H), 1.02 (d, $J = 7.2$ Hz, 3H) ppm;

$^{13}$C NMR (151 MHz, CDCl₃): $\delta$ 143.2, 128.6, 128.3, 125.6, 83.0, 35.5, 35.4, 25.0, 24.9, 15.7 ppm;

Spectroscopic data matches that reported in the literature (10).

**Compound 4**

![Structure of Compound 4](image)

**4,4,5,5-tetramethyl-2-(4-phenylbutyl)-1,3,2-dioxaborolane (4)**

On 0.2 mmol scale, General Procedure B was followed with NHPI ester (S2) and solution B (NiCl₂•6H₂O/di-MeObipy in DMF). Purification by flash column chromatography (silica gel, hexanes to 1:30 Et₂O:hexanes) afforded 4 (34.0 mg, 65%).
Physical state: colorless oil;

$R_f = 0.50$ (silica gel, 1:12 EtOAc: Hexane);

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.28 – 7.25 (m, 2H), 7.18 – 7.15 (m, 3H), 2.61 (t, $J = 7.8$ Hz, 2H), 1.66 – 1.61 (m, 2H), 1.50 – 1.45 (m, 2H), 1.24 (s, 12H), 0.82 (t, $J = 7.8$ Hz, 2H) ppm;

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 143.1, 128.5, 128.3, 125.6, 83.0, 35.9, 34.3, 25.0, 23.9 ppm;

Spectroscopic data matches that reported in the literature (55).

**Compound 5**

Methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentanoate (5)

On 0.2 mmol scale, General Procedure B was followed with NHPI ester (S26) and solution B (NiCl$_2$$\cdot$6H$_2$O/di-MeObipy in DMF). Purification by flash column chromatography (silica gel, hexanes to 1:100 CH$_2$Cl$_2$:hexanes) afforded 5 (25.2 mg, 52%).

Physical state: colorless oil;

$R_f = 0.55$ (silica gel, 1:6 EtOAc:hexanes);

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 3.64 (s, 3H), 2.29 (t, $J = 7.2$ Hz, 2H), 1.64 – 1.59 (m, 2H), 1.45 – 1.40 (m, 2H), 1.23 (s, 12H), 0.78 (t, $J = 7.8$ Hz, 2H) ppm;

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 174.4, 83.1, 51.6, 34.1, 27.7, 25.0, 23.8 ppm;

HRMS (ESI-TOF, $m/z$): Calcd for C$_{12}$H$_{24}$BO$_4$ [M+H]$^+$ 243.1762; found 243.1765.
Compound 6

2-(2-bromophenethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6)

On 0.2 mmol scale, General Procedure B was followed with NHPI ester (S3) and solution B (NiCl₂•6H₂O/di-MeObipy in DMF). Purification by flash column chromatography (silica gel, hexanes to 1:30 Et₂O:hexanes) afforded 6 (34.3 mg, 55%).

Physical state: colorless oil;

\( R_f = 0.55 \) (silica gel, 1:12 EtOAc:hexanes);

\(^1\text{H NMR (600 MHz, CDCl}_3\):} \ δ 7.50 (d, \( J = 7.8 \text{ Hz, 1H} \)), 7.27 (d, \( J = 7.8 \text{ Hz, 1H} \)), 7.21 (t, \( J = 7.8 \text{ Hz, 1H} \)), 7.02 (t, \( J = 7.8 \text{ Hz, 2H} \)), 2.84 (t, \( J = 7.8 \text{ Hz, 2H} \)), 1.24 (s, 12H), 1.15 (t, \( J = 7.8 \text{ Hz, 2H} \)) ppm;

\(^{13}\text{C NMR (151 MHz, CDCl}_3\):} \ δ 143.7, 132.8, 129.9, 127.4, 127.4, 124.5, 83.3, 30.6, 25.0 ppm;

HRMS (ESI-TOF, \( m/z \)): Calcd for C₁₄H₂₁BBrO₂ [M+H]^+ 313.0798; found 313.0799.

Compound 7

2-(5-bromopentyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (7)

On 0.2 mmol scale, General Procedure B was followed with NHPI ester (S4) and solution B (NiCl₂•6H₂O/di-MeObipy in DMF). Purification by flash column chromatography (silica gel, hexanes to 1:30 Et₂O:hexanes) afforded 7 (36.0 mg, 65%).

Physical state: colorless oil;

\( R_f = 0.55 \) (silica gel, 1:12 EtOAc:hexanes)

\(^1\text{H NMR (600 MHz, CDCl}_3\):} \ δ 3.40 (t, \( J = 7.2 \text{ Hz, 2H} \)), 1.88 – 1.83 (m, 2H), 1.45 – 1.42 (m, 4H), 1.24 (s, 12H), 0.80 – 0.77 (m, 2H) ppm;
$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 83.1, 34.2, 32.8, 31.0, 25.0, 23.4 ppm;

HRMS (ESI-TOF, $m$/z): Calcd for C$_{11}$H$_{23}$BBrO$_2$ [M+H]$^+$ 277.0969; found 277.0968.

**Compound 8**

![Chemical Structure](Image)

*tert*-butyl 2-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate (8)

On 0.2 mmol scale, General Procedure B was followed with NHPI ester (S5) and solution B (NiCl$_2$•6H$_2$O/di-MeObipy in DMF). Purification by flash column chromatography (silica gel, 1:12 EtOAc:hexanes to 1:6 EtOAc:hexanes to 1:4 EtOAc:hexanes) afforded 8 (37.6 mg, 37%).

**Physical state:** colorless oil;

$R_f$ = 0.40 (silica gel, 1:4 EtOAc:hexanes)

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.76 (d, $J = 7.2$ Hz, 2H), 7.61 (d, $J = 7.2$ Hz, 2H), 7.41 – 7.38 (m, 2H), 7.33 – 7.30 (m, 2H), 5.53 (d, $J = 8.4$ Hz, 1H), 4.34 – 4.24 (m, 2H), 4.23 – 4.19 (m, 2H), 1.97 – 1.91 (m, 1H), 1.84 – 1.78 (m, 1H), 1.47 (s, 9H), 1.23 (s, 12H), 0.89 – 0.78 (m, 2H) ppm;

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 171.8, 156.2, 144.2, 144.1, 141.4, 127.8, 127.2, 125.3, 120.1, 83.5, 81.9, 67.0, 56.1, 47.4, 28.2, 27.0, 25.0, 24.9 ppm;

HRMS (ESI-TOF, $m$/z): Calcd for C$_{29}$H$_{38}$BNNaO$_6$ [M+Na]$^+$ 530.2684; found 530.2685;

$[\alpha]_D^{20} = +2.3$ (c 0.35, CHCl$_3$).
Compound 9

\[
\begin{align*}
\text{Br} & \quad \text{B} \quad \text{O} \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\end{align*}
\]

\text{2-(4-bromobenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (9)}

On 0.2 mmol scale, General Procedure C was followed with TCNHPI ester (S6) and suspension C (NiCl\textsubscript{2}•6H\textsubscript{2}O/di-\textit{t}Bubipy in THF). Purification by flash column chromatography (silica gel, 1:40 to 1:20 Et\textsubscript{2}O:hexanes) afforded 9 (30.5 mg, 51%).

**Physical State**: colorless oil;

\(R_f = 0.30\) (silica gel, 1:19 EtOAc:hexanes);

\(^1\text{H NMR (600 MHz, CDCl}_3\)): \(\delta 7.35 – 7.33\) (m, 2H), \(7.06 – 7.04\) (m, 2H), 2.23 (s, 2H), 1.23 (s, 12H) ppm;

\(^{13}\text{C NMR (151 MHz, CDCl}_3\)): \(\delta 137.8, 131.4, 130.9, 118.7, 83.7, 24.9\) ppm;

Spectroscopic data matches that reported in the literature (13).

Compound 10

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\end{align*}
\]

\text{4,4,5,5-tetramethyl-2-(1-phenylpropan-2-yl)-1,3,2-dioxaborolane (10)}

On 0.2 mmol scale, General Procedure C was followed with TCNHPI ester (S7) and suspension C (NiCl\textsubscript{2}•6H\textsubscript{2}O/di-\textit{t}Bubipy in THF). Purification by flash column chromatography (silica gel, hexanes to 1:35 Et\textsubscript{2}O:hexanes) afforded 10 (33.1 mg, 67%).

**Physical state**: colorless oil;

\(R_f = 0.53\) (silica gel, 1:12 EtOAc:hexanes);

\(^1\text{H NMR (600 MHz, CDCl}_3\)): \(\delta 7.26 – 7.13\) (m, 5H), 2.81 (dd, \(J = 13.8\) Hz, 7.8 Hz, 1H), 2.54 (dd, \(J = 13.8\) Hz, 7.8 Hz, 1H), 1.41 – 1.34 (m, 1H), 1.19 (s, 6H), 1.18 (s, 6H), 0.97 (d, \(J = 7.8\) Hz, 3H) ppm;
\(^{13}\)C NMR (151 MHz, CDCl\(_3\)): \(\delta\) 142.5, 129.0, 128.1, 125.7, 83.1, 39.1, 24.9, 15.3 ppm; Spectroscopic data matches that reported in the literature (56).

**Compound 11**

\[
\begin{align*}
\text{4,4,5,5-tetramethyl-2-(1-phenylethyl)-1,3,2-dioxaborolane (11)}
\end{align*}
\]

On 0.2 mmol scale, General Procedure C was followed with NHPI ester (S8) and suspension A (NiCl\(_2\)•6H\(_2\)O/di-MeObipy in THF). 1.0 equiv. of MgBr\(_2\)•OEt\(_2\) was used in this case. Purification by flash column chromatography (silica gel, hexanes to 1:30 Et\(_2\)O:hexanes) afforded 11 (33.8 mg, 73%).

**Physical State:** colorless oil;

\(R_f = 0.33\) (silica gel, 1:19 EtOAc:hexanes);

\(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta\) 7.27 – 7.21 (m, 4H), 7.15 – 7.12 (m, 1H), 2.44 (q, \(J = 7.8\) Hz, 1H), 1.33 (d, \(J = 7.8\) Hz, 3H), 1.21 (s, 6H), 1.20 (s, 6H) ppm;

\(^{13}\)C NMR (151 MHz, CDCl\(_3\)): \(\delta\) 145.1, 128.4, 127.9, 125.2, 83.4, 24.8, 24.7, 17.2 ppm; Spectroscopic data matches that reported in the literature (70).

**Compound 12**

\[
\begin{align*}
\text{2-benzhydryl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (12)}
\end{align*}
\]

On 0.2 mmol scale, General Procedure C was followed with NHPI ester (S9) and suspension A (NiCl\(_2\)•6H\(_2\)O/di-MeObipy in THF). Purification by flash column
chromatography (silica gel, hexanes to 1:30 Et<sub>2</sub>O:hexanes) afforded 12 (41.0 mg, 70%).

**Physical State:** colorless oil;

\[ R_f = 0.41 \] (silica gel, 1:9 EtOAc:hexanes);

\(^1\)H NMR (600 MHz, CDCl<sub>3</sub>): \( \delta 7.30 - 7.25 \) (m, 8H), \( 7.19 - 7.15 \) (m, 2H), 3.88 (s, 1H), 1.24 (s, 12H) ppm;

\(^13\)C NMR (151 MHz, CDCl<sub>3</sub>): \( \delta 142.2, 129.2, 128.5, 125.7, 83.9, 24.7 \) ppm;

Spectroscopic data matches that reported in the literature (57).

**Compound 13**

![Image](image1.png)

2-(4,4-difluorocyclohexyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (13)

On 0.2 mmol scale, General Procedure C was followed with TCNHP1 ester (S28) and suspension C (NiCl<sub>2</sub>·6H<sub>2</sub>O/di-tBuBipy in THF). Purification by flash column chromatography (silica gel, hexanes to 1:45 Et<sub>2</sub>O:hexanes) afforded 13 (23.0 mg, 47%).

**Physical state:** colorless oil;

\[ R_f = 0.45 \] (silica gel, 1:9 EtOAc:hexanes);

\(^1\)H NMR (600 MHz, CDCl<sub>3</sub>): \( \delta 2.02 - 1.95 \) (m, 2H), 1.82-1.78 (m, 2H), 1.75 – 1.58 (m, 4H), 1.23 (s, 12H), 1.00 – 0.96 (m, 1H) ppm;

\(^13\)C NMR (151 MHz, CDCl<sub>3</sub>): \( \delta 123.9 \) (t, \( J = 239.9 \) Hz), 83.4, 34.5 (t, \( J = 23.3 \) Hz), 24.9, 24.4 (t, \( J = 4.6 \) Hz) ppm;

**HRMS (ESI-TOF, m/z):** High-resolution mass spectra data could not be obtained for this compound.
**Compound 14**

![Structure of Compound 14](image)

2-(heptan-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (14)

On 0.2 mmol scale, General Procedure C was followed with TCNHP ester (S27) and suspension C (NiCl₂•6H₂O/di-tBubipy in THF). Purification by flash column chromatography (silica gel, hexanes to 1:40 Et₂O:hexanes) afforded 14 (25.6 mg, 57%).

**Physical state:** colorless oil;

\[ R_f = 0.42 \] (silica gel, 1:19 EtOAc:hexanes);

**¹H NMR (600 MHz, CDCl₃):** δ 1.45 – 1.22 (m, 20H), 0.90 – 0.86 (m, 7H) ppm;

**¹³C NMR (151 MHz, CDCl₃):** δ 82.9, 31.7, 30.8, 25.0, 24.4, 23.1, 14.3, 13.9 ppm;

Spectroscopic data matches that reported in the literature (58).

**Compound 15**

![Structure of Compound 15](image)

**tert-Butyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolidine-1-carboxylate (15)**

On 0.2 mmol scale, General Procedure C was followed with NHPI ester (S30) and suspension C (NiCl₂•6H₂O/di-tBubipy in THF). Purification by flash column chromatography (first flash column chromatography: deactivated silica gel, hexanes to 1:9 EtOAc:hexanes; second flash column chromatography: deactivated silica gel, CH₂Cl₂) afforded 15 (39.2 mg, 66%).

**Physical State:** colorless oil;

\[ R_f = 0.45 \] (silica gel, 1:4 EtOAc:hexanes);

**¹H NMR (600 MHz, CDCl₃):** δ 3.42 – 2.99 (m, 3H), 2.09 – 1.65 (m, 4H), 1.43 (s, 9H),...
1.26 – 1.22 (m, 12H) ppm;

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 155.1, 83.6, 79.1, 46.1, 28.7, 27.9, 27.3 25.2, 25.0, 24.6 ppm;

HRMS (ESI-TOF, m/z): Calcd for C$_{15}$H$_{29}$BNO$_4$ [M+H]$^+$ 298.2184; found 298.2179; $\alpha$D$^20$ = 0 (c 0.3, CHCl$_3$).

**Compound 16**

![Diagram of Compound 16](image)

2-(Bicyclo[2.2.1]heptan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (16)

On 0.2 mmol scale, General Procedure B was followed with NHPI ester (S10, mixture of endo/exo) and solution B (NiCl$_2$•6H$_2$O/di-MeOBipy in DMF). Purification by flash column chromatography (silica gel, hexanes to 1:40 Et$_2$O:hexanes to 1:20 Et$_2$O:hexanes) afforded 16 (24.4 mg, 55%, exo/endo = 10:1).

**Physical state:** colorless oil;

$R_f$ = 0.38 (silica gel, 1:19 EtOAc:hexanes);

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 2.28 – 2.27 (m, 1H), 2.22 – 2.21 (m, 1H), 1.56 – 1.44 (m, 3H), 1.37 – 1.33 (m, 1H), 1.26 – 1.21 (m, 14H), 1.20 – 1.14 (m, 2H), 0.89 – 0.86 (m, 1H) ppm;

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 82.9, 38.9, 38.3, 36.8, 32.4, 32.3, 29.4, 24.9 ppm (exo); 83.0, 41.1, 39.1, 37.2, 32.3, 30.0, 28.0, 25.1, 25.0 ppm (endo);

Spectroscopic data matches that reported in the literature (11).
Compound 17

2-Adamantan-2-yl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (17)

On 0.2 mmol scale, General Procedure C was followed with NHPI ester (S29) and suspension A (NiCl₂•6H₂O/di-MeObipy in THF). Purification by flash column chromatography (silica gel, hexanes to 1:30 Et₂O:hexanes) afforded 17 (30.9 mg, 59%).

Physical state: colorless oil;

\[ R_f = 0.55 \] (silica gel, 1:9 EtOAc:hexanes);

\(^1\)H NMR (600 MHz, CDCl₃): \( \delta 2.06 – 2.04 \) (m, 2H), 1.90 – 1.67 (m, 12H), 1.37 – 1.35 (m, 1H), 1.25 (s, 12H) ppm;

\(^{13}\)C NMR (151 MHz, CDCl₃): \( \delta 82.9, 39.5, 37.9, 36.4, 29.5, 28.4, 28.3, 25.0 \) ppm;

Spectroscopic data matches that reported in the literature (10).

Compound 18

trans-4,4,5,5-tetramethyl-2-(2-phenylecyclopropyl)-1,3,2-dioxaborolane (18)

On 0.2 mmol scale, General Procedure B was followed with TCNHPI ester (S11) and solution D (NiCl₂•6H₂O/di-tBuobipy in DMF). Purification by flash column chromatography (silica gel, hexanes to 1:30 Et₂O:hexanes) afforded 18 (11.3 mg, 23%, d.r. > 20:1).

Physical State: colorless oil;

\[ R_f = 0.48 \] (silica gel, 1:9 EtOAc:hexanes);

\(^1\)H NMR (600 MHz, CDCl₃): \( \delta 7.25 – 7.22 \) (m, 2H), 7.15 – 7.11 (m, 1H), 7.09 – 7.06
(m, 2H), 2.10 (dt, J = 7.8 Hz, 5.4 Hz, 1H), 1.25 (s, 6H), 1.24 (s, 6H), 1.17 – 1.14 (m, 1H), 1.02 – 0.99 (m, 1H), 0.32 – 0.29 (m, 1H) ppm;

$^{13}$C NMR (151 MHz, CDCl$_3$): δ 143.5, 128.4, 125.8, 125.7, 83.3, 24.9, 24.8, 22.0, 15.2 ppm;

HRMS (ESI-TOF, $m$/z): Calcd for C$_{15}$H$_{22}$BO$_2$ [M+H]$^+$ 245.1707; found 245.1714.

**Compound 19**

![Structure of Compound 19](image)

4,4,5,5-tetramethyl-2-(2-methyl-1-phenylpropan-2-yl)-1,3,2-dioxaborolane (19)

On 0.2 mmol scale, General Procedure C was followed with NHPI ester (S12) and suspension A (NiCl$_2$•6H$_2$O/di-MeObipy in THF). Purification by flash column chromatography (silica gel, hexanes to 1:30 Et$_2$O:hexanes) afforded 19 (35.3 mg, 68%).

**Physical State**: colorless solid;

m.p. = 36 – 37 °C;

$R_f$ = 0.50 (silica gel, 1:12 EtOAc:hexanes);

$^1$H NMR (600 MHz, CDCl$_3$): δ 7.24 – 7.19 (m, 4H), 7.17 – 7.14 (m, 1H), 2.61 (s, 2H), 1.21 (s, 12H), 0.94 (s, 6H) ppm;

$^{13}$C NMR (151 MHz, CDCl$_3$): δ 140.6, 130.3, 127.8,125.8, 83.24, 46.5, 24.9 ppm.

Spectroscopic data matches that reported in the literature (10).

**Compound 20**

![Structure of Compound 20](image)

2-Adamantan-1-yl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (20)

On 0.2 mmol scale, General Procedure C was followed with NHPI ester (S32) and
suspension C (NiCl$_2$•6H$_2$O/di-tBubipy in THF). Purification by flash column chromatography (silica gel, 1:60 Et$_2$O:hexanes to 1:40 Et$_2$O:hexanes) afforded 20 (29.2 mg, 56%).

**Physical State:** white amorphous solid;

$R_f = 0.60$ (silica gel, 1:9 EtOAc:hexanes);

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 1.84 (br s, 3H), 1.75 (br t, $J = 3.6$ Hz, 12H), 1.20 (s, 12H) ppm;

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 82.7, 38.1, 37.6, 27.7, 24.8 ppm;

Spectroscopic data matches that reported in the literature (10).

**Compound 21**

Methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cubane-1-carboxylate (21)

On 0.2 mmol scale, General Procedure C was followed with NHPI ester (S33) and suspension A (NiCl$_2$•6H$_2$O/di-MeObipy in THF). Purification by flash column chromatography (silica gel, hexanes to 1:15:15 Et$_2$O:CH$_2$Cl$_2$:hexanes) afforded 21 (26.2 mg, 45%).

**Physical State:** white solid;

m.p. = 152 – 155 °C;

$R_f = 0.45$ (silica gel, 1:6 EtOAc:hexanes);

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 4.30 – 4.28 (m, 3H), 4.03 – 4.01 (m, 3H), 3.70 (s, 3H), 1.26 (s, 12H);

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 172.8, 83.4, 55.4, 51.6, 50.0, 45.2, 24.9 ppm;

**HRMS (ESI-TOF, m/z):** Calcd for C$_{16}$H$_{22}$BO$_4$ [M+H]$^+$ 289.1606; found 289.1607.
Compound 22

Methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)bicyclo[2.2.2]octane-1-carboxylate (22)

On 0.2 mmol scale, General Procedure C was followed with NHPI ester (S34) and suspension C (NiCl$_2$•6H$_2$O/di-tBu-bipy in THF). Purification by flash column chromatography (silica gel, hexanes to 1:9 Et$_2$O:hexanes) afforded 22 (31.1 mg, 53%).

**Physical State:** colorless solid;
Sublimation at 100 $^\circ$C;
$R_f$ = 0.39 (silica gel, 1:5 EtOAc:hexanes);

$^1$H NMR (600 MHz, CDCl$_3$): δ 3.62 (s, 3H), 1.72 – 1.65 (m, 6H), 1.62 – 1.54 (m, 6H), 1.19 (s, 12H) ppm;

$^{13}$C NMR (151 MHz, CDCl$_3$): δ 179.0, 83.0, 51.7, 38.6, 27.9, 26.7, 24.8 ppm;

HRMS (ESI-TOF, m/z): Calcd for C$_{16}$H$_{28}$BO$_4$ [M+H]$^+$ 295.2075; found 295.2077.

Compound 23

4,4,5,5-tetramethyl-2-(1-methylcyclohexyl)-1,3,2-dioxaborolane (23)

On 0.2 mmol scale, General Procedure C was followed with NHPI ester (S35) and suspension A (NiCl$_2$•6H$_2$O/di-MeObipy in THF). Purification by flash column chromatography (silica gel, hexanes to 1:30 Et$_2$O:hexanes) afforded 23 (27.8 mg, 62%).

**Physical State:** colorless oil;
$R_f$ = 0.50 (silica gel, 1:12 EtOAc:hexanes);

$^1$H NMR (600 MHz, CDCl$_3$): δ 1.84 – 1.80 (m, 2H), 1.64 – 1.57 (m, 3H), 1.29 – 1.21
(m, 14H), 1.16 – 1.08 (m, 1H), 0.92 – 0.87 (m, 5H) ppm;

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 82.9, 37.2, 26.6, 26.0, 25.7, 24.8 ppm;

Spectroscopic data matches that reported in the literature (10).

**Compound 24**

![Diagram of Compound 24]

4,4,5,5-tetramethyl-2-(1-phenylcyclohexyl)-1,3,2-dioxaborolane (24)

On 0.2 mmol scale, General Procedure C was followed with NHPI ester (S13) and suspension C (NiCl$_2$•6H$_2$O/di-tBu-bipy in THF). Purification by flash column chromatography (silica gel, hexanes to 1:30 Et$_2$O:hexanes) afforded 24 (28.5 mg, 50%).

**Physical State:** white solid;

m.p. = 87 – 88 °C;

$R_f$ = 0.60 (silica gel, 1:9 EtOAc:hexanes);

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.36 – 7.34 (m, 2H), 7.29 – 7.26 (m, 2H), 7.13 – 7.11 (m, 1H), 2.36 – 2.32 (m, 2H), 1.82 – 1.78 (m, 2H), 1.70 – 1.66 (m, 1H), 1.49 – 1.38 (m, 4H), 1.21 – 1.14 (m, 1H), 1.17 (s, 12H) ppm;

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 147.6, 128.2, 126.3, 125.1, 83.4, 35.0, 26.4, 25.9, 25.7 ppm;

HRMS (ESI-TOF, m/z): Calcd for C$_{18}$H$_{28}$BO$_2$ [M+H]$^+$ 287.2177; found 287.2184.

**Compound 25**

![Diagram of Compound 25]

*tert*-butyldimethyl(2-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-
(2-phenylpropoxy)silane (25)

On 0.2 mmol scale, General Procedure C was followed with NHPI ester (S31) and suspension A (NiCl₂•6H₂O/di-MeObipy in THF). Purification by flash column chromatography (silica gel, hexanes to 1:30 Et₂O:hexanes) afforded 25 (41.2 mg, 66%).

Physical State: colorless oil;

R_f = 0.40 (silica gel, 1:12 EtOAc:hexanes);

^1H NMR (600 MHz, CDCl₃): δ 3.39 (s, 2H), 1.22 (s, 12H), 0.90 (s, 6H), 0.88 (s, 9H), 0.01 (s, 6H) ppm;

^13C NMR (151 MHz, CDCl₃): δ 83.0, 72.0, 26.1, 24.9, 21.4, 18.5, –5.34 ppm;

HRMS (ESI-TOF, m/z): Calcd for C₁₆H₃₆B₂O₃Si [M+H]^+ 315.2521; found 315.2523.

Compound 26

4,4,5,5-tetramethyl-2-(2-phenylpropan-2-yl)-1,3,2-dioxaborolane (26)

On 0.2 mmol scale, General Procedure C was followed with NHPI ester (S14) and suspension C (NiCl₂•6H₂O/di-tBuOpy in THF). Purification by flash column chromatography (silica gel, hexanes to 1:30 Et₂O:hexanes) afforded 26 (23.3 mg, 47%).

Physical State: colorless oil;

R_f = 0.51 (silica gel, 1:9 EtOAc:hexanes);

^1H NMR (600 MHz, CDCl₃): δ 7.33 – 7.27 (m, 4H), 7.15 – 7.12 (m, 1H), 1.35 (s, 6H), 1.20 (s, 12H) ppm;

^13C NMR (151 MHz, CDCl₃): δ 148.8, 128.2, 126.4, 125.1, 83.4, 25.7, 24.7 ppm;

Spectroscopic data matches that reported in the literature (59).
Compound 27

2-(1-(4-chlorophenyl)cyclopropyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (27)

On 0.2 mmol scale, General Procedure C was followed with NHPI ester (S36) and suspension A (NiCl₂•6H₂O/di-MeObipy in THF). Purification by flash column chromatography (silica gel, hexanes to 1:30 Et₂O:hexanes) afforded 27 (32.9 mg, 59%).

**Physical State**: white solid;  
**m.p.** = 83 – 85 °C;  
**Rf** = 0.37 (silica gel, 1:19 EtOAc:hexanes);  
**¹H NMR (600 MHz, CDCl₃)**: δ 7.19 (s, 4H), 1.21 (s, 12H), 1.11 (dd, J = 6.0 Hz, 3.6 Hz, 2H), 0.87 (dd, J = 6.0 Hz, 3.6 Hz, 2H) ppm;  
**¹³C NMR (151 MHz, CDCl₃)**: δ 143.5, 131.0, 130.5, 128.2, 83.6, 24.7, 13.6 ppm;  
**HRMS (ESI-TOF, m/z)**: Calcd for C₁₅H₂₁BClO₂ [M+H]⁺ 279.1318; found 279.1319.

Compound 28

**tert-butyl ((1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)cyclohexyl)methyl)carbamate (28)**

On 0.1 mmol scale, General Procedure B was followed with NHPI ester (S15) and solution B (NiCl₂•6H₂O/di-MeObipy in DMF). Purification by flash column chromatography (silica gel, 1:20 EtOAc:hexanes) afforded 28 (22.5 mg, 64%).

**Physical State**: white solid;  
**m.p.** = 92 – 96 °C;  
**Rf** = 0.28 (silica gel, 1:20 EtOAc:hexanes);
$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 5.32 (br s, 1H), 3.08 (d, $J = 6.0$ Hz, 2H), 1.52 – 1.41 (m, 4H), 1.43 (s, 9H), 1.38 – 1.31 (m, 6H), 1.25 (s, 12H), 0.81 (s, 2H) ppm;

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 156.5, 83.4, 78.7, 50.0, 36.7, 36.3, 28.6, 26.4, 25.0, 21.9 ppm;

HRMS (ESI-TOF, $m/z$): Calcd for C$_{19}$H$_{37}$BNO$_4$ [M+H]$^+$ 354.2810; found 354.2809.

**Compound 29**

![Compound 29](image)

2-(1-(4-isobutylphenyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (29)

On 0.2 mmol scale, General Procedure C was followed with NHPI ester (S16) and suspension A (NiCl$_2$•6H$_2$O/di-MeObpy in THF, 1.0 equiv. of MgBr$_2$•OEt$_2$ was used in this case). Purification by flash column chromatography (silica gel, hexanes to 1:30 Et$_2$O:hexanes) afforded 29 (43.0 mg, 75%).

**Physical State:** colorless oil;

$R_f$ = 0.59 (silica gel, 1:9 EtOAc:hexanes);

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.12 – 7.10 (m, 2H), 7.04 – 7.02 (m, 2H), 2.42 (d, $J = 7.2$ Hz, 2H), 2.40 (q, $J = 7.2$ Hz, 1H), 1.79 – 1.88 (m, 1H), 1.31 (d, $J = 7.2$ Hz, 3H), 1.21 (s, 6H), 1.20 (s, 6H), 0.89 (d, $J = 6.6$ Hz, 6H) ppm;

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 142.1, 138.4, 129.2, 127.6, 83.4, 45.2, 30.4, 24.8, 24.7, 22.6, 17.2 ppm;

Spectroscopic data matches that reported in the literature (60).
Compound 30

2-(5-(2,5-dimethylphenoxy)-2-methylpentan-2-yl)-4,4,5,5-tetramethyl-1,3,2-
dioxaborolane (30)

On 0.2 mmol scale, General Procedure C was followed with NHPI ester (S17) and suspension A (NiCl₂•6H₂O/di-MeObipy in THF). Purification by flash column chromatography (silica gel, hexanes to 1:30 Et₂O:hexanes) afforded 30 (36.3 mg, 55%).

Physical State: colorless solid;

m.p. = 59 – 61 °C;

$R_f$ = 0.60 (silica gel, 1:12 EtOAc:hexanes);

$^1$H NMR (600 MHz, CDCl₃): $\delta$ 6.99 (d, $J = 7.8$ Hz, 1H), 6.64 (d, $J = 7.2$ Hz, 1H), 6.62 (s, 1H), 3.92 (t, $J = 6.6$ Hz, 2H), 2.30 (s, 3H), 2.18 (s, 3H), 1.78 – 1.73 (m, 2H), 1.41 – 1.44 (m, 2H), 1.23 (s, 12H), 0.96 (s, 6H) ppm;

$^{13}$C NMR (151 MHz, CDCl₃): $\delta$ 157.3, 136.5, 130.4, 123.8, 120.6, 112.2, 83.1, 68.8, 37.4, 26.6, 25.0, 24.9, 21.6, 16.0 ppm;

HRMS (ESI-TOF, m/z): Calcd for C₂₀H₃₄BO₃ [M+H]$^+$ 333.2595; found 333.2598.

Compound 31

2-(1-(6-methoxynaphthalen-2-yl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (31)

On 0.2 mmol scale, General Procedure C was followed with NHPI ester (S18) and
suspension A (NiCl$_2$$\cdot$6H$_2$O/di-MeObipy in THF, 1.0 equiv. of MgBr$_2$$\cdot$OEt$_2$ was used in this case). Purification by flash column chromatography (silica gel, hexanes to 1:25 Et$_2$O:hexanes) afforded 31 (50.0 mg, 80%).

**Physical State**: white solid;

m.p. = 82 – 84 °C;

$R_f = 0.62$ (silica gel, 1:4 EtOAc:hexanes);

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.64 – 7.67 (m, 2H), 7.57 (s, 1H), 7.35 (dd, $J = 8.4$, 1.8 Hz, 1H), 7.09 – 7.11 (m, 2H), 3.90 (s, 3H), 2.57 (q, $J = 7.2$ Hz, 1H), 1.41 (d, $J = 7.2$ Hz, 3H), 1.21 (s, 6H), 1.20 (s, 6H) ppm;

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 157.1, 140.3, 132.8, 129.5, 129.1, 127.8, 126.7, 125.3, 118.5, 105.8, 83.5, 55.4, 24.8, 24.8, 17.1 ppm;

HRMS (ESI-TOF, $m/z$): Calcd for C$_{19}$H$_{26}$BO$_3$ [M+H]$^+$ 313.1969; found 313.1970.

**Compound 32**

![Compound 32](image)

1,7-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)heptane (32)

On 0.2 mmol scale, General Procedure B was followed with NHPI ester (S19) and solution B [NiCl$_2$$\cdot$6H$_2$O (20 mol%)/di-MeObipy (26 mol%) in DMF]. Purification by flash column chromatography (silica gel, hexanes to 1:20 Et$_2$O:hexanes) afforded 32 (26.5 mg, 38%).

**Physical State**: colorless oil;

$R_f = 0.45$ (silica gel, 1:8 EtOAc:hexanes);

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 1.41 – 1.36 (m, 4H), 1.29 – 1.24 (m, 6H), 1.24 (s, 24H), 0.75 (t, $J = 7.8$ Hz, 4H) ppm;

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 83.0, 32.5, 29.4, 25.0, 24.2 ppm;

HRMS (ESI-TOF, $m/z$): Calcd for C$_{19}$H$_{39}$B$_2$O$_4$ [M+H]$^+$ 353.3029; found 353.3030.
**Compound 33**

\[
\text{N,N-bis(2-chloroethyl)-4-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl)aniline (33)}
\]

On 0.2 mmol scale, General Procedure C was followed with NHPI ester (S20) and suspension A (NiCl\(_2\)•6H\(_2\)O/di-MeObipy in THF). Purification by flash column chromatography (silica gel, hexanes to 1:19 EtOAc:hexanes) afforded 33 (20.7 mg, 27%).

**Physical State**: yellow oil;

\[R_f = 0.36\text{ (silica gel, 1:9 EtOAc:hexanes)};\]

\(^1\text{H NMR (600 MHz, CDCl}_3\):}\ δ 7.09 – 7.04 (m, 2H), 6.63 – 6.59 (m, 2H), 3.69 (t, \(J =\) 7.1 Hz, 4H), 3.61 (t, \(J = 7.1\text{ Hz, 4H})\), 2.54 – 2.48 (t, \(J = 7.8\text{ Hz, 2H})\), 1.68 (p, \(J = 7.8\text{ Hz, 2H})\), 1.24 (s, 12H), 0.81 (t, \(J = 7.8\text{ Hz, 2H})\) ppm;

\(^{13}\text{C NMR (151 MHz, CDCl}_3\):}\ δ 144.2, 132.2, 129.9, 112.2, 83.1, 53.8, 40.7, 37.6, 26.5, 25.0 ppm;

**HRMS (ESI-TOF, m/z)**: Calcd for C\(_{19}\)H\(_{31}\)BCl\(_2\)NO\(_2\) [M+H]\(^+\) 386.1819; found 386.1815.

**Compound 34**

\[
\text{phenyl (3-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)phenyl) methanone (34)}
\]

On 0.2 mmol scale, General Procedure C was followed with NHPI ester (S21) and suspension A (NiCl\(_2\)•6H\(_2\)O/di-MeObipy in THF, 1.0 equiv. of MgBr\(_2\)•OEt\(_2\) was used in
this case). Purification by flash column chromatography (silica gel, hexanes to 1:15 EtOAc:hexanes) afforded 34 (51.9 mg, 77%).

**Physical State:** colorless oil;

\( R_f \) = 0.45 (silica gel, 1:6 EtOAc:hexanes);

\(^1\)H NMR (600 MHz, CDCl\(_3\)): \( \delta \) 7.81 (dd, \( J = 8.2 \) Hz, 1.4 Hz, 2H), 7.66 (t, \( J = 1.8 \) Hz, 1H), 7.58 (tt, \( J = 7.2 \) Hz, 1.4 Hz, 2H), 7.50 – 7.44 (m, 3H), 7.37 (t, \( J = 7.6 \) Hz, 1H), 2.51 (q, \( J = 7.8 \) Hz, 1H), 1.35 (d, \( J = 7.8 \) Hz, 3H), 1.21 (s, 6H), 1.21 (s, 6H) ppm;

\(^{13}\)C NMR (151 MHz, CDCl\(_3\)): \( \delta \) 197.2, 145.4, 138.0, 137.7, 132.4, 132.2, 130.3, 129.7, 128.4, 128.3, 127.2, 83.6, 24.8, 24.8, 17.1 ppm;

**HRMS (ESI-TOF, \( m/z \)):** Calcd for \( C_{21}H_{26}BO_3 \) [M+H]^+ 337.1969; found 337.1971.

**Compound 35**

![Compound 35](image)

4,4,5,5-tetramethyl-2-(1-(3-phenoxyphenyl)ethyl)-1,3,2-dioxaborolane (35)

On 0.2 mmol scale, General Procedure C was followed with NHPI ester (S22) and suspension A (NiCl\(_2\)•6H\(_2\)O/di-MeObipy in THF, 1.0 equiv. of MgBr\(_2\)•OEt\(_2\) was used in this case). Purification by flash column chromatography (silica gel, hexanes to 1:30 Et\(_2\)O:hexanes) afforded 35 (52.6 mg, 81%).

**Physical State:** colorless oil;

\( R_f \) = 0.50 (silica gel, 1:12 EtOAc:hexanes);

\(^1\)H NMR (600 MHz, CDCl\(_3\)): \( \delta \) 7.32 (t, \( J = 7.8 \) Hz, 2H), 7.22 (t, \( J = 7.8 \) Hz, 1H), 7.07 (t, \( J = 7.8 \) Hz, 1H), 7.01 (d, \( J = 7.2 \) Hz, 2H), 6.97 (d, \( J = 7.2 \) Hz, 1H), 6.91 (t, \( J = 1.8 \) Hz, 1H), 6.79 (dd, \( J = 7.8 \) Hz, 2.4 Hz, 1H), 2.42 (q, \( J = 7.8 \) Hz, 1H), 1.31 (d, \( J = 7.8 \) Hz, 3H), 1.20 (s, 6H), 1.19 (s, 6H) ppm;

\(^{13}\)C NMR (151 MHz, CDCl\(_3\)): \( \delta \) 157.7, 157.2, 147.3, 129.7, 129.6, 123.0, 123.0, 118.8, 118.7, 115.9, 83.5, 24.8, 24.7, 17.0 ppm;
HRMS (ESI-TOF, m/z): Calcd for C_{20}H_{26}BO_{3} [M+H]^+ 325.1969; found 325.1970.

Compound 36

![Compound 36](image)

1-(2-((4R,6S)-2,2-dimethyl-6-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)-1,3-dioxan-4-yl)ethyl)-5-(4-fluorophenyl)-2-isopropyl-N,4-diphenyl-1H-pyrrole-3-carboxamide (36)

On 0.2 mmol scale, General Procedure B was followed with NHPI ester (S23) and solution B (NiCl₂•6H₂O/di-MeObipy in DMF). Purification by flash column chromatography (silica gel, hexanes to 1:9 EtOAc:hexanes) afforded 36 (77.4 mg, 57%).

Physical State: white foam;

$R_f = 0.52$ (silica gel, 1:4 EtOAc:hexanes);

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.21 – 7.14 (m, 9H), 7.07 (br d, $J = 8.4$ Hz, 2H), 7.00 – 6.97 (m, 3H), 6.85 (br s, 1H), 4.08 – 4.03 (m, 1H), 4.00 – 3.96 (m, 1H), 3.85 – 3.80 (m, 1H), 3.69 – 3.65 (m, 1H), 3.60 – 3.55 (m, 1H), 1.68 – 1.64 (m, 2H), 1.55 (d, $J = 1.8$ Hz, 3H), 1.53 (d, $J = 1.8$ Hz, 3H), 1.34 (dt, $J = 13.2$ Hz, 1.2 Hz, 1H), 1.34 (s, 3H), 1.30 (s, 3H), 1.23 (s, 12H), 1.08 – 1.03 (m, 2H), 0.98 – 0.94 (m, 1H) ppm;

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 165.0, 162.4 (d, $J = 247.6$ Hz), 141.7, 138.6, 134.8, 134.5, 133.3 (d, $J = 8.2$ Hz), 130.7, 128.9, 128.8, 128.5, 128.4 (d, $J = 3.8$ Hz), 126.7, 123.8, 123.6, 121.8, 119.7, 115.4 (d, $J = 21.3$ Hz), 98.6, 83.3, 66.7, 66.7, 41.0, 38.4, 38.3, 30.3, 26.2, 24.9, 24.9, 21.9, 21.7, 20.0 ppm;

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –114.1 ppm;

HRMS (ESI-TOF, m/z): Calcd for C_{41}H_{51}BFN_{2}O_{5} [M+H]^+ 681.3870; found 681.3870; $\alpha_D^{20} = +4.0$ (c 0.68, CHCl$_3$).

S103
Compound 37

(4-chlorophenyl)(5-methoxy-2-methyl-3-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)-1H-indol-1-yl)methanone (37)

On 0.1 mmol scale, General Procedure C was followed with NHPI ester (S37) and suspension A (NiCl₂•6H₂O/di-MeObipy in THF). Purification by flash column chromatography (silica gel, hexanes to 1:17 EtOAc:hexanes) afforded 37 (22.1 mg, 50%).

Physical State: yellow oil;

$R_f = 0.5$ (silica gel, 1:4 EtOAc:hexanes);

$^1$H NMR (600 MHz, CDCl₃): $\delta$ 7.64 (dt, $J = 9.0$ Hz, 1.8 Hz, 2H), 7.45 (m, dt, $J = 8.4$ Hz, 1.8 Hz, 2H), 6.96 – 6.93 (m, 2H), 6.64 (dd, $J = 9.0$ Hz, 2.6 Hz, 1H), 3.84 (s, 3H), 2.29 (s, 3H), 2.18 (s, 2H), 1.23 (s, 12H) ppm;

$^{13}$C NMR (151 MHz, CDCl₃): $\delta$ 168.3, 156.0, 138.8, 134.7, 133.2, 132.0, 131.2, 131.1, 129.1, 116.7, 115.0, 111.3, 101.7, 83.7, 55.8, 29.9, 25.0, 13.9 ppm;

HRMS (ESI-TOF, m/z): Calcd for C₂₄H₂₈BClNO₄ [M+H]$^+$ 440.1794; found 440.1794.

Compound 38

(5S,8R,9S,10S,13R,14S,17R)-10,13-dimethyl-17-((R)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2-yl)dodecahydro-3H-cyclopenta[a]phenanthrene-
3,7,12(2H,4H)-trione (38)
On 0.2 mmol scale, General Procedure B was followed with NHPI ester (S38) and solution B (NiCl₂•6H₂O/di-MeObipy in DMF). Purification by flash column chromatography (silica gel, hexanes to 1:5 EtOAc:hexanes) afforded 38 (63.0 mg, 65%).

Physical State: white solid;
$R_f = 0.40$ (silica gel, 1:3 EtOAc:hexanes);

m.p. = 230 – 232 °C;

$^1$H NMR (600 MHz, CDCl₃): $\delta$ 2.92 – 2.82 (m, 3H), 2.35 – 2.19 (m, 6H), 2.14 – 2.09 (m, 2H), 2.05 – 1.94 (m, 4H), 1.80 – 1.85 (m, 1H), 1.56 – 1.63 (m, 2H), 1.39 (s, 3H), 1.35 – 1.12 (m, 16 H), 1.06 (s, 3H), 0.87 – 0.81 (m, 4H), 0.68 – 0.62 (m, 1H) ppm;

$^{13}$C NMR (151 MHz, CDCl₃): $\delta$ 212.1, 209.2, 208.9, 83.0, 57.1, 51.9, 49.2, 47.0, 45.8, 45.7, 45.1, 42.9, 38.8, 38.2, 36.6, 36.1, 35.4, 29.4, 27.8, 25.4, 25.0, 24.9, 22.1, 18.6, 12.0 ppm;

HRMS (ESI-TOF, m/z): Caled for C$_{29}$H$_{45}$BO$_{5}$ [M+H]$^+$ 485.3433; found 485.3435.

$[^{\alpha}]D_{20}^{20} = +16.9$ (c 0.62, CHCl$_3$).
Compound 39

(3S,4aR,6aR,6bS,8aR,11S,12aR,14aR,14bS)-4,4,6a,6b,8a,11,14b-heptamethyl-14-oxo-11-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12a,14,14a,14b-icosahydropicen-3-yl acetate (39)

On 0.2 mmol scale, General Procedure C was followed with NHPI ester (S24) and suspension A (NiCl₂•6H₂O/di-MeObipy in THF). Purification by flash column chromatography (silica gel, 1:12:3 EtOAc:hexanes:CH₂Cl₂) afforded 39 (82.0 mg, 69%, d.r. = 11.8:1).

Physical State: colorless film;

\( R_f = 0.34 \) (silica gel, 1:5 EtOAc:hexanes);

\(^1\text{H NMR (600 MHz, CDCl}_3\): } Major isomer \( \delta \) 5.57 (s, 1H), 4.51 (dd, \( J = 11.8 \) Hz, 4.7 Hz, 1H), 2.79 (dt, \( J = 13.7 \) Hz, 3.6 Hz, 1H), 2.35 (s, 1H), 2.20 (ddd, \( J = 13.3 \) Hz, 4.4 Hz, 1.7 Hz, 1H), 2.12 (td, \( J = 13.7 \) Hz, 4.6 Hz, 1H), 2.04 (s, 3H), 1.96 (t, \( J = 13.6 \) Hz, 1H), 1.80 (td, \( J = 13.7 \) Hz, 4.6 Hz, 1H), 1.75 – 1.38 (m, 7H), 1.37 (s, 3H), 1.27 – 1.13 (m, 5H), 1.20 (d, \( J = 1.8 \) Hz, 12H), 1.15 (s, 3H), 1.12 (s, 3H), 1.02 (td, \( J = 13.5 \) Hz, 3.6 Hz, 1H), 0.99 (s, 3H), 0.94 (ddt, \( J = 13.7 \) Hz, 4.5 Hz, 2.2 Hz, 1H), 0.87 (s, 6H), 0.84 (s, 3H), 0.81 – 0.76 (m, 1H) ppm;

\(^{13}\text{C NMR (151 MHz, CDCl}_3\): } Major isomer \( \delta \) 200.1, 171.14, 171.12, 128.3, 83.0, 80.8, 61.8, 55.2, 45.5, 45.3, 43.6, 38.9, 38.5, 38.2, 37.1, 34.2, 32.9, 32.7, 29.1, 28.2, 27.8, 26.7, 26.6, 24.8, 24.7, 23.7, 23.4, 21.5, 18.9, 17.7, 17.6, 16.8, 16.6 ppm;

HRMS (ESI-TOF, m/z): Caled for C\(_{37}\)H\(_{60}\)BO\(_3\) [M+H]\(^+\) 595.4528; found 595.4520; 
[\( \alpha \)]\(_D\)\(^{20} \) = +65.8 (c 1.0, CHCl\(_3\)).
Compound 40

(2S,4aR,6aS,6bR,8aR,10S,12aS,12bR,14bR)-10-hydroxy-2,4a,6a,6b,9,9,12a-heptamethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12a,12b,14b-octadecahydropicen-13(2H)-one (40)

On 0.2 mmol scale, General Procedure C was followed with NHPI ester (S39) and suspension A (NiCl$_2$$\cdot$6H$_2$O/di-MeObipy in THF). Purification by flash column chromatography (silica gel, first flash column chromatography: 1:5.7 to 1:4 EtOAc:hexanes; second flash column chromatography, 1:6:3 to 2:6:3 EtOAc:hexanes:CH$_2$Cl$_2$) afforded 40 (72.1 mg, 65%, d.r. = 11.3:1).

**Physical State:** colorless film; $R_f = 0.46$ (silica gel, 3:7 EtOAc:hexanes);

$^1$H NMR (600 MHz, CDCl$_3$): Major isomer $\delta$ 5.59 (s, 1H), 3.27 – 3.18 (m, 1H), 2.81 (dt, $J = 13.5$ Hz, 3.6 Hz, 1H), 2.36 (s, 1H), 2.22 (ddd, $J = 13.5$ Hz, 4.5 Hz, 1.7 Hz, 1H), 2.14 (td, $J = 13.7$ Hz, 4.6 Hz, 1H), 1.99 (t, $J = 13.6$ Hz, 1H), 1.83 (td, $J = 13.7$ Hz, 4.7 Hz, 1H), 1.74 – 1.58 (m, 4H), 1.55 (td, $J = 13.8$ Hz, 4.0 Hz, 1H), 1.51 – 1.35 (m, 2H), 1.41 (s, 3H), 1.33 – 1.15 (m, 7H), 1.22 (s, 6H), 1.22 (s, 6H), 1.15 (s, 3H), 1.15 (s, 3H), 1.02 (s, 3H), 1.01 (s, 3H), 1.00 – 0.94 (m, 1H), 0.86 (s, 3H), 0.82 (s, 3H), 0.71 (dd, $J = 11.8$ Hz, 1.9 Hz, 1H) ppm;

$^{13}$C NMR (151 MHz, CDCl$_3$): Major isomer $\delta$ 200.3, 171.1, 128.3, 83.0, 79.0, 61.9, 55.2, 45.5, 45.3, 43.6, 39.31, 39.27, 38.5, 37.2, 34.2, 33.0, 32.7, 29.1, 28.3, 27.8, 27.5, 26.7, 26.6, 24.8, 24.7, 23.5, 18.9, 17.7, 16.5, 15.7 ppm;

HRMS (ESI-TOF, m/z): Calcd for C$_{35}$H$_{58}$BO$_4$ [M+H]$^+$ 553.4422; found 553.4423;

S107
$[\alpha]D^{20} = +73.4$ (c 1.0, CHCl$_3$).

**Compound 40a**

![Compound 40a](image)

$(3S,4aR,6aR,6bS,8aR,11S,12aR,14aR,14bS)-4,4,6a,6b,8a,11,14b$-heptamethyl-14-oxo-11-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yi)-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12a,14,14a,14b$-icosahydropicen-3-yl 3,5-dinitrobenzoate (40a)

A culture tube charged with 40 (30 mg, 0.054 mmol, 1.0 equiv.), 3,5-dinitrobenzoyl chloride (50 mg, 0.22 mmol, 4.1 equiv.), and DMAP (1.3 mg, 0.011 mmol, 0.2 equiv.). CH$_2$Cl$_2$ (0.3 mL) and Et$_3$N (30 μL, 0.22 mmol, 4.1 equiv.) were added, and the resulting mixture was stirred for 1 h at room temperature. The mixture was loaded directly onto a silica gel column for purification by flash column chromatography (1:11 EtOAc:hexanes) to afford 40a (39.0 mg, 96%, $d.r. = 11.3:1$). The pure product was crystallized from hexanes/CH$_2$Cl$_2$.

**Physical State:** pale yellow solid (major isomer is a white solid);

**m.p.** decompose at 295 °C;

$R_f = 0.45$ (silica gel, 1:5.7 EtOAc:hexanes);

$^1$H NMR (600 MHz, CDCl$_3$): **Major isomer** $\delta$ 9.22 (t, $J = 2.2$ Hz, 1H), 9.13 (d, $J = 2.2$ Hz, 2H), 5.60 (s, 1H), 4.88 (dd, $J = 11.9$ Hz, 4.7 Hz, 1H), 2.92 (dt, $J = 13.7$ Hz, 3.6 Hz, 1H), 2.40 (s, 1H), 2.26 – 2.19 (m, 1H), 2.13 (td, $J = 13.7$ Hz, 4.5 Hz, 1H), 1.98 (t, $J = 13.6$ Hz, 1H), 1.95 – 1.87 (m, 1H), 1.87 – 1.75 (m, 2H), 1.74 – 1.59 (m, 3H), 1.56 – 1.48 (m, 2H), 1.45 (dt, $J = 12.8$ Hz, 3.1 Hz, 1H), 1.40 (s, 3H), 1.30 – 1.09 (m, 5H), 1.23 (s, 3H), 1.21 (s, 6H), 1.21 (s, 6H), 1.16 (s, 3H), 1.08 (s, 3H), 1.00 (s, 3H), 0.97 (s, 3H), 0.92 (s, 3H).
0.97 – 0.94 (m, 1H), 0.89 (dd, \(J = 11.8\) Hz, 1.9 Hz, 1H), 0.86 (s, 3H) ppm;

\(^{13}\)C NMR (151 MHz, CDCl\(_3\)): *Major isomer* \(\delta\) 199.9, 171.4, 162.3, 148.8, 134.8, 129.5, 128.3, 122.4, 84.3, 83.1, 61.7, 55.3, 45.6, 45.3, 43.6, 38.9, 38.6, 38.5, 37.1, 34.2, 32.8, 32.7, 29.2, 28.5, 27.8, 26.7, 26.6, 24.8, 24.7, 23.8, 23.4, 18.9, 17.7, 17.6, 17.2, 16.6 ppm;

HRMS (ESI-TOF, \(m/z\)): Calcd for C\(_{42}\)H\(_{60}\)BN\(_2\)O\(_9\) [M+H]\(^+\) 747.4386; found 747.4385; 

[\(\alpha\)]\(_D\)^20 = +60.5 (c 1.0, CHCl\(_3\)).

**Compound 41**

![Image of compound 41]

*(E)-7-hydroxy-5-methoxy-4-methyl-6-(3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-2-en-1-yl)isobenzofuran-1(3H)-one (41)*

On 0.2 mmol scale, General Procedure B was followed with NHPI ester (S25) and solution B (NiCl\(_2\)•6H\(_2\)O/di-MeObipy in DMF). Purification by flash column chromatography (silica gel, hexanes to 1:6:6 EtOAc:hexanes:CH\(_2\)Cl\(_2\)) afforded 41 (37.0 mg, 46%).

**Physical State:** white solid;

**m.p.** = 122 – 124 °C;

\(R_f\) = 0.40 (silica gel, 1:2 EtOAc:hexanes);

\(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta\) 7.64 (s, 1H), 5.21 – 5.18 (m, 3H), 3.75 (s, 3H), 3.37 (d, \(J = 6.6\) Hz, 2H), 2.13 (s, 3H), 2.08 (t, \(J = 7.8\) Hz, 2H), 1.77 (s, 3H), 1.17 (s, 12H), 0.86 (t, \(J = 7.8\) Hz, 2H) ppm;

\(^{13}\)C NMR (151 MHz, CDCl\(_3\)): \(\delta\) 173.1, 163.9, 153.8, 143.9, 137.8, 122.8, 120.6, 116.8, 106.4, 83.0, 70.1, 61.1, 33.6, 24.9, 22.7, 16.3, 11.7 ppm;

HRMS (ESI-TOF, \(m/z\)): Calcd for C\(_{22}\)H\(_{32}\)BO\(_6\) [M+H]\(^+\) 403.2286; found 403.2289.
Experimental Procedure and Characterization Data for Boronic Acids

Compound 4a

(4-phenylbutyl)boronic acid (4a)

Pinacol boronate ester 4 (70 mg, 0.27 mmol) was dissolved in CH₂Cl₂ (5 mL) under argon and the solution was cooled to −78 °C in a dry ice/acetone bath. BCl₃ (0.81 mL, 1.0 M in CH₂Cl₂, 3.0 equiv.) was added dropwise, after which the mixture was stirred for 1 h at −78 °C. The mixture was then allowed to warm up to room temperature, and the volatiles were removed in vacuo. Anhydrous methanol (5 mL) was added and the resulting mixture was stirred for 10 minutes when methanol was removed in vacuo. An additional portion of methanol (5 mL) was added; the mixture was stirred for 10 minutes before it was concentrated in vacuo. This process was repeated for another three times. The resulting crude product was then purified with preparative TLC to afford 4a as a white solid (41.8 mg, 87%).

¹H NMR (600 MHz, DMSO-d₆/D₂O 100/1): δ 7.28 – 7.22 (m, 2H), 7.15 (ddt, J = 13.9 Hz, 6.9 Hz, 1.5 Hz, 3H), 2.56 – 2.51 (m, 2H), 1.51 (tt, J = 7.8, 6.7 Hz, 2H), 1.38 – 1.28 (m, 2H), 0.60 (t, J = 7.9 Hz, 2H);

¹³C NMR (151 MHz, DMSO-d₆/D₂O 100/1): δ 142.6, 128.3, 128.3, 125.6, 35.3, 34.2, 24.0, 15.3 (br);

HRMS (ESI-TOF) Calcd for C₁₀H₁₆BO₂ [M+H]⁺ 179.1238; found 179.1236.
Compound 3a

(4-phenylbutan-2-yl)boronic acid (3a)

Pinacol boronate ester 3 (30 mg, 0.12 mmol) was dissolved in CH2Cl2 (2 mL) under argon and the solution was cooled to −78 °C in a dry ice/acetone bath. BCl3 (0.36 mL, 1.0 M in CH2Cl2, 3.0 equiv.) was added dropwise, after which the mixture was stirred for 1 h at −78 °C. The mixture was then allowed to warm up to room temperature, and the volatiles were removed in vacuo. Anhydrous methanol (5 mL) was added and the resulting mixture was stirred for 10 minutes before methanol was removed in vacuo. An additional portion of methanol (5 mL) was added; the mixture was stirred for 10 minutes before it was concentrated in vacuo. This process was repeated for another three times. The resulting crude product was then purified with preparative TLC to afford 4a as a white solid (15.4 mg, 75%).

1H NMR (600 MHz, DMSO-d6/D2O 100/1): δ 7.24 (t, J = 7.6 Hz, 2H), 7.18 – 7.10 (m, 3H), 2.53 – 2.48 (m, 2H), 1.74 – 1.63 (m, 1H), 1.42 (ddt, J = 13.0 Hz, 9.9 Hz, 6.5 Hz, 1H), 0.90 (d, J = 7.2 Hz, 3H), 0.89 – 0.81 (m, 1H) ppm;

13C NMR (151 MHz, DMSO-d6/D2O 100/1): δ 143.0, 128.3, 125.6, 35.7, 35.1, 20.3 (br), 16.4 ppm;

HRMS (ESI-TOF) Calcd for C10H16BO2 [M+H]+ 179.1238; found 179.1232.
Compound 33a

(3-(4-(bis(2-chloroethyl)amino)phenyl)propyl)boronic acid (33a)

Pinacol boronate ester 33 (7.62 mg, 0.2 mmol) was dissolved in CH₂Cl₂ (1 mL) under argon and the solution was cooled to −78 °C in a dry ice/acetone bath. BCl₃ (0.79 mL, 1.0 M in CH₂Cl₂, 4.0 equiv.) was added dropwise, after which the mixture was stirred for 1 h at −78 °C. The mixture was then allowed to warm up to room temperature, and the volatiles were removed in vacuo. Anhydrous methanol (2 mL) was added and the resulting mixture was stirred for 10 minutes when methanol was removed in vacuo. An additional portion of methanol (2 mL) was added; the mixture was stirred for 10 minutes before it was concentrated in vacuo. This process was repeated for another three times. Purification of the resulting residue by preparative reverse-phase HPLC (20 − 80% CH₃CN/H₂O over 30 min, both CH₃CN and H₂O containing 0.1% TFA) afforded 33a (27 mg, 50%) as a colorless oil.

¹H NMR (600 MHz, DMSO-d₆/D₂O 10/1): δ 7.00 (d, J = 12.6 Hz, 2H), 6.65 (d, J = 12.6 Hz, 2H), 3.71 − 3.65 (m, 8H), 2.39 (t, J = 7.8 Hz, 2H), 1.58 − 1.53 (m, 2H), 0.59 (t, J = 8.4 Hz, 2H) ppm;

¹³C NMR (151 MHz, DMSO-d₆/D₂O 10/1): δ 144.2, 130.9, 129.3, 111.8, 52.3, 41.2, 37.2, 26.6 ppm;

HRMS (ESI-TOF) Calcd for C₁₃H₂₁BCl₂NO₂ [M+H]⁺ 304.1037; found 304.1030.
Synthesis of Ixazomib (Ninlaro)

**Figure S33. Synthesis of ixazomib (Ninlaro).**

**Compound S41**

(2,5-dichlorobenzoyl)glycyleucine (S41)

*Removal of Boc:* To a solution of Boc-Gly-Leu-OMe (61) (S40, 3.1 g, 10.36 mmol) in CH₂Cl₂ (30 mL) was added TFA (15 mL) at room temperature, the reaction mixture was stirred for 1 h before concentration *in vacuo*. The residue was used directly in the next step.

*Amide bond formation:* To a solution 2,5-dichlorobenonic acid (2.94 g, 15.4 mmol) in THF (70 mL) was added 4-methylmorpholine (4.0 mL, 35.9 mmol) at −15 °C, the reaction mixture was stirred for 10 min at that temperature. To the resulting white
suspension was added isobutyl chloroformate (2.0 mL, 15.4 mmol) dropwise and the mixture was stirred for another 30 min at –15 °C. The crude TFA salt (from the deprotection step) in THF (35 mL) was added slowly at the same temperature. The reaction mixture was warmed up to room temperature and stirred for 6 h. The resulting mixture was diluted with EtOAc (100 mL), washed with water (100 mL), sat. aqueous NaHCO₃ (100 mL), and brine (100 mL). The combined organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated. Purification by flash column chromatography (silica, 3:2 Hexane/EtOAc) afforded the desired ester which was directly used in next step without further purification.

*Hydrolysis of methyl ester:* To a solution of the aforementioned ester in THF (50 mL) was added aqueous LiOH (1 M, 50 mL). The reaction mixture was stirred at room temperature for 2 h and was then washed with EtOAc (60 mL). The aqueous layer was acidified with 1 N HCl (65 mL) and extracted with EtOAc (100 mL). The organic layer was washed with brine (100 mL) whereby the aqueous layers were back-extracted with EtOAc (100 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo.* To the residue was added CH₂Cl₂ (30 mL) when the desired product S41 precipitated out and was collected by filtration (2.31 g, 63% over 3 steps).

**m.p.** = 137 – 138 °C;

**¹H NMR (600 MHz, MeOH-d₄):** δ 7.63 (dd, J = 1.8 Hz, 0.6 Hz, 1H), 7.45 – 7.48 (m, 2H), 4.50 (dd, J = 9.6 Hz, 5.4 Hz, 1H), 4.08 (dd, J = 37.8 Hz, 16.8 Hz, 2H), 1.79 – 1.72 (m, 1H), 1.70 – 1.62 (m, 2H), 0.98 (d, J = 6.6 Hz, 3H), 0.95 (d, J = 6.6 Hz, 3H) ppm;

**¹³C NMR (151 MHz, MeOH-d₄):** δ 175.8, 170.9, 168.7, 138.4, 134.0, 132.6, 132.3, 130.6, 130.2, 52.1, 43.6, 41.9, 26.0, 23.4, 21.9 ppm;

**HRMS (ESI-TOF) Calcd** for C₁₅H₁₉Cl₂N₂O₄ [M+H]⁺ 361.0716; found 361.0706;

[α]D²⁰ = −14.0 (c 1.0, MeOH).
Compound S42

1,3-dioxoisodolin-2-yl (2,5-dichlorobenzoyl)glycylleucinate (S42)

On 2.0 mmol scale, General Procedure A was followed with S37. Purification by flash column chromatography (deactivated silica gel, 3:7 EtOAc:hexanes) afforded S42 (940 mg, 79%).

Physical state: white solid;

m.p. = 164 °C;

R_f = 0.55 (silica gel, 3:2 EtOAc:hexanes);

^1^H NMR (600 MHz, THF-d_8): δ 8.05 (br s, 1H), 7.99 – 7.97 (m, 1H), 7.91 – 7.89 (m, 2H), 7.87 – 7.85 (m, 2H), 7.58 (dd, J = 2.4 Hz, 0.5 Hz, 1H), 7.42 – 7.38 (m, 2H), 5.10 – 5.06 (m, 1H), 4.14 (dd, J = 16.8 Hz, 6.0 Hz, 1H), 3.99 (dd, J = 16.8 Hz, 6.0 Hz, 1H), 1.92 – 1.83 (m, 2H), 1.80 – 1.75 (m, 1H), 1.02 (d, J = 6.0 Hz, 3H), 1.00 (d, J = 6.0 Hz, 3H) ppm;

^13^C NMR (151 MHz, THF-d_8): δ 170.5, 169.4, 166.0, 162.4, 139.2, 135.9, 133.5, 132.3, 131.5, 130.7, 130.5, 130.2, 124.7, 49.7, 43.6, 42.3, 25.8, 23.4, 22.1 ppm;

HRMS (ESI-TOF) Calcd for C_{23}H_{22}Cl_2N_3O_6\ [M+H]^+ 506.0880; found 506.0875;

[α]_D^{20} = -1.0 (c 1.0, THF).
On 0.2 mmol scale, General Procedure C was followed using suspension C (NiCl₂•6H₂O/di-μBubipy in THF) with S42. Flash column chromatography (silica gel, hexanes to 2:3 EtOAc:hexanes to 4:1 EtOAc:hexanes) afforded pinacol aminoboronate ester S43 which was directly used in the next step without further purification.

The pinacol aminoboronate ester S43 was dissolved in CH₂Cl₂ (5 mL) under argon and the solution was cooled to -78 °C in a dry ice/acetone bath. BCl₃ (0.6 mL, 1.0 M in CH₂Cl₂, 3.0 equiv.) was added dropwise, after which the mixture was stirred for 1 h at -78 °C. The mixture was then allowed to warm up to room temperature, and the volatiles were removed in vacuo. Anhydrous methanol (5 mL) was added and the mixture was stirred for 10 minutes when the methanol was removed in vacuo. An additional portion of methanol (5 mL) was added; the mixture was stirred for 10 minutes before it was concentrated in vacuo. This process was repeated for another three times. The resulting residue was then purified by preparative reverse-phase HPLC (10 – 60% CH₃CN/H₂O over 35 min, both CH₃CN and H₂O containing 0.1% TFA) to afford ixazomib (Ninlaro) (1, 23.0 mg, 32% over 2 steps).

**¹H NMR (600 MHz, MeOH-d₄):** \( \delta 7.60 \) (br t, J = 1.5 Hz, 1H), 7.49 – 7.47 (m, 2H), 4.24 (s, 2H), 2.79 (t, J = 7.6 Hz, 1H), 1.68 (ddt, J = 14.7 Hz, 13.0 Hz, 6.4 Hz, 1H), 1.38 (tdd, J = 13.8 Hz, 10.4 Hz, 5.9 Hz, 2H), 0.94 (d, J = 6.6 Hz, 3H), 0.93 (d, J = 6.6 Hz, 3H);

**¹³C NMR (151 MHz, MeOH-d₄):** \( \delta 175.6, 168.8, 138.0, 134.0, 132.7, 132.5, 130.7, 130.2, 44.7 \) (br, \( \alpha \) to boron), 40.9, 40.2, 27.1, 23.7, 22.4.

**HRMS (ESI-TOF, m/z):** Calcd for C₁₄H₁₈BCl₂N₂O₃ [M–H₂O+H]⁺ 343.0782; found
343.0779;

\([\alpha]_D^{20} = -0.6 \ (c \ 1.0, \text{MeOH})\).
Decarboxylative Borylation Enabled Late-stage Diversification of Lipitor

**Compound 36a**

![Chemical Structure of Compound 36a](image)

**tert-butyl (((4R,6R)-6-(2-(2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1H-pyrrol-1-yl)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)carbamate (36a)**

A solution of *O*-methylhydroxylamine (63 μL, 2.8 M in THF, 6.0 equiv.) was diluted with THF (1 mL). *n*BuLi (72 μL, 2.45 M in hexanes, 6.0 equiv.) was added at –78 °C, and the resulting mixture was stirred for 1 h at that temperature. A solution of pinacol boronate 36 (20 mg, 0.03 mmol, 1.0 equiv.) in THF (1 mL) was added dropwise at –78 °C. After warming up to room temperature, the reaction mixture was heated to 65 °C and stirred for 36 h. Upon cooling to room temperature, Boc₂O (66 mg, 10.0 equiv.) was added. The resulting mixture was stirred at room temperature for 1 h before the volatiles were removed *in vacuo*. Purification of the resulting residue by preparative TLC (silica gel, 15:1 CH₂Cl₂:Et₂O) afforded 36a (10.7 mg, 54%) as colorless oil.

**Physical state:** colorless oil;

\[ R_f = 0.40 \] (silica gel, 3:1 EtOAc:hexanes);

\[ ^1H \text{ NMR (600 MHz, CDCl}_3\]: } \delta 7.24 – 7.09 (m, 9H), 7.07 (d, \( J = 8.0 \) Hz, 2H), 7.04 – 6.94 (m, 3H), 6.86 (s, 1H), 4.84 (s, 1H), 4.07 (ddd, \( J = 15.3 \) Hz, 10.7 Hz, 5.1 Hz, 1H), 3.82 (ddt, \( J = 15.1 \) Hz, 10.3 Hz, 6.5 Hz, 2H), 3.66 (tt, \( J = 8.2 \) Hz, 3.6 Hz, 1H), 3.57 (p, \( J = 7.2 \) Hz, 1H), 3.24 (d, \( J = 8.7 \) Hz, 1H), 2.98 (ddd, \( J = 13.8 \) Hz, 6.8 Hz, 5.1 Hz, 1H), 1.70-1.63 (m, 2H), 1.53 (d, \( J = 7.1 \) Hz, 6H), 1.44 (s, 9H), 1.34 (s, 3H), 1.31 (s, 3H), 1.27 – 1.20 (m, 1H), 1.07 (q, \( J = 12.0 \) Hz, 1H) ppm;
$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 164.9, 162.4 (d, $J = 247.9$ Hz), 156.2, 141.6, 138.5, 134.8, 133.3 (d, $J = 8.1$ Hz), 130.6, 128.9, 128.8, 128.5, 128.4 (d, $J = 3.5$ Hz), 126.7, 123.6, 121.9, 119.7, 115.5 (d, $J = 21.3$ Hz), 98.8, 79.6, 68.2, 66.3, 45.4, 41.0, 38.3, 33.4, 30.5, 30.0, 28.5, 26.2, 21.9, 21.7, 20.0 ppm; 

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ -113.9 ppm; 

HRMS (ESI-TOF, m/z): Calcd for C$_{40}$H$_{49}$FN$_3$O$_5$ [M+H]$^+$ 670.3651; found 670.3646; 

$[\alpha]_D^{20} = -2.0$ (c 0.74, CHCl$_3$).

**Compound 36b**

![Chemical Structure](attachment:image)

5-(4-fluorophenyl)-1-(2-((4R,6R)-6-(hydroxymethyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethyl)-2-isopropyl-N,4-diphenyl-1H-pyrrole-3-carboxamide (36b)

To a solution of 36 (50 mg, 0.073 mmol, 1.0 equiv.) in THF/H$_2$O (1:1, 0.73 mL) at room temperature open to air was added NaBO$_3$·4H$_2$O (56 mg, 0.37 mmol, 5.1 equiv.). The mixture was stirred vigorously for 3 h before H$_2$O (10 mL) was added. The resulting mixture was extracted with EtOAc (10 mL × 3). The combined organic extracts were dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, 2:3 EtOAc:hexanes) afforded 36b (40 mg, 86%).

**m.p.** = 166 - 170 °C; 

$R_f = 0.27$ (silica gel, 2:3 EtOAc:hexanes); 

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.21 – 7.15 (m, 9H), 7.07 (d, $J = 8.0$ Hz, 2H), 7.02 – 6.96 (m, 3H), 6.86 (s, 1H), 4.13 – 4.05 (m, 1H), 3.92 – 3.81 (m, 2H), 3.73 – 3.66 (m,
1H), 3.61 – 3.52 (m, 2H), 3.45 (dd, J = 11.4 Hz, 6.1 Hz, 1H), 1.74 – 1.61 (m, 2H), 1.54 (s, 3H), 1.53 (s, 3H), 1.37 (s, 3H), 1.34 (s, 3H), 1.74 – 1.61 (m, 2H) ppm;

\(^{13}\text{C NMR (151 MHz, CDCl}_3\): \(\delta\) 164.9, 162.4 (d, \(J = 247.6\) Hz), 141.7, 138.5, 134.8, 133.3 (d, \(J = 8.0\) Hz), 130.6, 128.9, 128.8, 128.5, 128.4 (d, \(J = 3.5\) Hz), 126.7, 123.6, 121.9, 119.7, 115.5 (d, \(J = 21.4\) Hz), 98.9, 69.4, 66.2, 66.0, 41.0, 38.3, 31.9, 30.0, 26.2, 21.9, 21.7, 20.0 ppm;

\(^{19}\text{F NMR (376 MHz, acetone-\(d_6\): \(\delta\) –114.0 ppm;}

HRMS (ESI-TOF, \(m/z\)): Calcd for C\(_{35}\)H\(_{40}\)FN\(_2\)O\(_4\) [M+H]\(^+\) 571.2966; found 571.2963; \([\alpha]\)\(_{D}^{20}\) = –4.6 (c 1.0, CHCl\(_3\)).

**Compound 36c**

![Image of compound 36c](image_url)

1-(2-((4R,6R)-2,2-dimethyl-6-(thiophen-2-ylmethyl)-1,3-dioxan-4-yl)ethyl)-5-(4-fluorophenyl)-2-isopropyl-N,4-diphenyl-1\(H\)-pyrrole-3-carboxamide (36c)

To a solution of thiophene (23 μL, 0.29 mmol) in THF (1.0 mL) was added \(n\)BuLi (0.1 mL, 2.5 M in hexanes, 0.25 mmol) at –78 °C. The resulting mixture was warmed to room temperature and stirred for 1 h when 0.33 mL (4.1 equiv.) of the resulting yellow solution was transferred to a reaction tube. A solution of 36 (12.4 mg, 0.018 mmol, 1.0 equiv.) in THF (0.3 mL) was added dropwise at –78 °C. The resulting mixture was stirred at the same temperature for 1.5 h when a solution of \(N\)-bromosuccinimide (14.4 mg, 0.081 mmol, 4.5 equiv.) in THF (0.3 mL) was added. After stirring for 1 h at the same temperature, the reaction was quenched with sat. aqueous Na\(_2\)S\(_2\)O\(_3\) (1 mL) before warming up to room temperature. The resulting mixture was extracted with EtOAc (1 mL × 3). The combined organic layers were dried over anhydrous Na\(_2\)SO\(_4\) and
concentrated *in vacuo*. Purification by flash column chromatography (silica gel, 1:9 
EtOAc:hexanes) followed by preparative TLC (silica gel, 1:6 EtOAc:hexanes) afforded 
36c (6.5 mg, 56%).

**Physical state:** white foam;

\[ R_f = 0.61 \text{ (silica gel, 2:3 EtOAc:hexanes);} \]

**$^{1}$H NMR (600 MHz, acetone-$d_6$):** $\delta$ 8.29 (br s, 1H), 7.45 (d, $J$ =7.8 Hz, 2H), 7.30 – 7.27 (m, 2H), 7.24 (dd, $J$ = 5.4 Hz, 1.2 Hz, 1H), 7.20 (t, $J$ = 7.8 Hz, 2H), 7.13 – 7.09 (m, 6H), 7.08 – 7.05 (m, 1H), 6.99 – 6.96 (m, 1H), 6.92 (dd, $J$ = 5.4 Hz, 3.6 Hz, 1H), 6.85 – 6.84 (m, 1H), 4.11 – 4.06 (m, 1H), 4.05 – 4.00 (m, 1H), 3.91 – 3.86 (m, 1H), 3.85 – 3.81 (m, 1H), 3.43 – 3.39 (m, 1H), 2.93 – 2.90 (m, 1H), 2.87 – 2.83 (m, 1H), 1.75 – 1.63 (m, 2H), 1.47 (d, $J$ = 1.2 Hz, 3H), 1.45 (d, $J$ = 1.2 Hz, 3H), 1.36 (dt, $J$ = 12.6 Hz, 3.0 Hz, 1H), 1.36 (s, 3H), 1.28 (s, 3H) 1.05 – 0.99 (m, 1H) ppm;

**$^{13}$C NMR (151 MHz, acetone-$d_6$):** $\delta$ 166.4, 163.1 (d, $J$ = 245.6 Hz), 140.9, 140.6, 139.4, 136.1, 134.5 (d, $J$ = 8.2 Hz), 130.8, 129.9 (d, $J$ = 3.3 Hz), 129.3, 128.9, 128.6, 127.3, 126.70, 126.65, 124.9, 123.8, 122.4, 120.2, 118.0, 116.0 (d, $J$ = 21.6 Hz), 99.2, 70.2, 67.3, 41.3, 39.1, 37.3, 36.5, 30.5, 26.9 22.4, 22.3, 20.1 ppm;

**$^{19}$F NMR (376 MHz, acetone-$d_6$):** $\delta$ –114.9 ppm;

**HRMS (ESI-TOF) Calcd** for C$_{39}$H$_{42}$FN$_{2}$O$_{3}$S [M+H]$^+$ 637.2895; found 637.2892;

$[\alpha]$$^D_{20}$ = + 19.2 (c 0.5, CHCl$_3$).

**Compound 36d**

![Compound 36d](image_url)

1-(2-(((4R,6R)-6-(benzofuran-2-ylmethyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethyl)-5-(4-fluorophenyl)-2-isopropyl-N,4-diphenyl-1H-pyrrole-3-carboxamide (36d)
To a solution of 2,3-benzofuran (30 μL, 0.27 mmol) in THF (1.0 mL) was added nBuLi (0.1 mL, 2.5 M in hexanes, 0.25 mmol) at –78 °C. The resulting mixture was warmed to room temperature and stirred for 1 h when 0.33 mL (4.1 equiv.) of the resulting yellow solution was transferred to a reaction tube. A solution of 36 (12.0 mg, 0.018 mmol, 1.0 equiv.) in THF (0.3 mL) was added dropwise at –78 °C. The resulting mixture was stirred at the same temperature for 1 h when a solution of N-bromosuccinimide (14.4 mg, 0.081 mmol, 4.5 equiv.) in THF (0.3 mL) was added. After stirring for 1 h at the same temperature, the reaction was quenched with sat. aqueous Na2S2O3 (1 mL) before warming up to room temperature. The resulting mixture was extracted with EtOAc (1 mL × 3). The combined organic layers were dried over anhydrous Na2SO4 and concentrated in vacuo. Purification by flash column chromatography (silica gel, 1:9 EtOAc:hexanes) followed by preparative TLC (silica gel, 1:9 EtOAc:hexanes) afforded 36d (6.1 mg, 52%).

Physical state: colorless oil;

\[ R_f = 0.64 \] (silica gel, 2:3 EtOAc:hexanes);

\( ^1H \text{ NMR (600 MHz, acetone-}\text{d}_6\):} \delta 8.29 (br s, 1H), 7.54 – 7.52 (m, 1H), 7.44 (d, \( J = 7.8 \text{ Hz} \), 2H), 7.45 – 7.42 (m, 1H), 7.31 – 7.27 (m, 2H), 7.24 – 7.17 (m, 4H), 7.13 – 7.05 (m, 7H), 6.99 – 6.96 (m, 1H), 6.58 (dd, \( J = 1.2 \text{ Hz} \), 0.6 Hz, 1H), 4.29 – 4.24 (m, 1H), 4.11 – 4.06 (m, 1H), 3.91 – 3.85 (m, 2H), 3.44 – 3.37 (m, 1H), 2.93 (dd, \( J = 15.6 \text{ Hz} \), 6.6 Hz, 1H), 2.79 (dd, \( J = 15.6 \text{ Hz} \), 6.6 Hz, 1H), 1.76 – 1.65 (m, 2H), 1.46 (s, 3H), 1.45 (s, 3H), 1.51 – 1.46 (m, 1H), 1.39 (d, \( J = 0.6 \text{ Hz} \), 3H), 1.27 (d, \( J = 0.6 \text{ Hz} \), 3H), 1.14 – 1.08 (m, 1H) ppm;

\( ^{13}C \text{ NMR (151 MHz, acetone-}\text{d}_6\):} \delta 166.4, 163.1 (d, \( J = 245.7 \text{ Hz} \)), 156.5, 155.5, 140.6, 139.4, 136.1, 134.5 (d, \( J = 8.3 \text{ Hz} \)), 130.8, 129.9 (d, \( J = 3.3 \text{ Hz} \)), 129.9, 129.3, 128.9, 128.6, 126.7, 124.2, 123.8, 123.4, 122.4, 121.3, 120.2, 120.1, 118.0, 116.0 (d, \( J = 21.6 \text{ Hz} \)), 111.4, 104.6, 99.3, 68.1, 67.3, 41.3, 39.1, 37.0, 36.2, 30.4, 26.9, 22.4, 22.3, 20.1 ppm;

\( ^{19}F \text{ NMR (376 MHz, acetone-}\text{d}_6\):} \delta –115.0 ppm;
HRMS (ESI-TOF) Calcd for C_{43}H_{44}FN_{2}O_{4} [M+H]^+ 671.3280; found 671.3274; [α]_{D}^{20} = +28.5 (c 0.5, CHCl₃).

**Compound 36e**

1-(2-((4R,6S)-6-((3-chloropyridin-2-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethyl)-5-(4-fluorophenyl)-2-isopropyl-N,4-diphenyl-1H-pyrrole-3-carboxamide (36e)

To a screw-capped culture tube was added Pd₂(dba)₃ (1.9 mg, 0.0022 mmol, 0.1 equiv.), p-anisyl diphenylphosphine (3.7 mg, 0.0132 mmol, 0.6 equiv.), 2,3-dichloropyridine (32.6 mg, 0.22 mmol, 10 equiv.), and K₃PO₄ (47 mg, 0.22 mmol, 10 equiv.). This tube was then evacuated and backfilled with argon for three times. 1,4-dioxane (0.4 mL) was then added via a syringe and the resulting mixture was stirred at room temperature for 5 minutes. A deoxygenated solution of 36 (15.0 mg, 0.022 mmol, 1.0 equiv.) in dioxane (0.6 mL) was added followed by degassed deionic water (0.5 mL). The reaction mixture was heated at 100 °C for 15 h, after which it was cooled to room temperature and treated with brine (4 mL). The resulting mixture was extracted with EtOAc (2 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated in vacuo. Purification by flash column chromatography (silica gel, 1:6 to 3:7 EtOAc:hexanes) and preparative TLC (silica gel, 1:3 EtOAc:hexanes) afforded 36e (7.9 mg, 54%).

**Physical state:** colorless oil;

R₇ = 0.38 (silica gel, 3:7 EtOAc:hexanes);

¹H NMR (600 MHz, acetone-d₆): δ 8.45 (dd, J = 4.8 Hz, 1.8 Hz, 1H), 8.30 (br s, 1H), 7.79 (dd, J = 8.4 Hz, 1.8 Hz, 1H), 7.45 (d, J = 7.8 Hz, 2H), 7.30 – 7.25 (m, 3H), 7.20
(t, J = 7.8 Hz, 2H), 7.12 – 7.05 (m, 7H), 6.99 – 6.96 (m, 1H), 4.46 – 4.41 (m, 1H), 4.11 – 4.06 (m, 1H), 3.91 – 3.86 (m, 1H), 3.85 – 3.81 (m, 1H), 3.44 – 3.39 (m, 1H), 3.13 (dd, J = 14.4 Hz, 6.6 Hz, 1H), 2.88 (dd, J = 14.4 Hz, 7.2 Hz, 1H), 1.76 – 1.64 (m, 2H), 1.47 (d, J = 0.6 Hz, 3H), 1.45 (d, J = 0.6 Hz, 3H), 1.38 (dt, J = 12.6 Hz, 2.4 Hz, 1H), 1.34 (s, 3H), 1.24 (s, 3H), 1.16 – 1.10 (m, 1H) ppm;

$^{13}$C NMR (151 MHz, acetone-$d_6$): δ 166.4, 163.1 (d, J = 245.5 Hz), 156.2, 148.3, 140.6, 139.3, 137.6, 136.2, 134.5 (d, J = 8.3 Hz), 132.2, 130.8, 129.9 (d, J = 3.3 Hz), 129.3, 128.9, 128.6, 126.7, 123.8, 123.8, 122.4, 120.2, 118.0, 116.0 (d, J = 21.6 Hz), 99.2, 68.7, 67.3, 42.3, 41.3, 39.2, 37.0, 30.5, 26.9, 22.4, 22.3, 20.1 ppm;

$^{19}$F NMR (376 MHz, acetone-$d_6$): δ -114.9 ppm;

HRMS (ESI-TOF) Calcd for C$_{40}$H$_{42}$ClF$_3$N$_3$O$_3$ [M+H]$^+$ 666.2893; found 666.2884; 
$[\alpha]$$^D_{20}$ = +26.2 (c 0.5, CHCl$_3$).

**Compound 36f**

![Chemical Structure](image)

1-(2-((4R,6S)-2,2-dimethyl-6-(4-nitrobenzyl)-1,3-dioxan-4-yl)ethyl)-5-(4-fluorophenyl)-2-isopropyl-N,4-diphenyl-1H-pyrrole-3-carboxamide (36f)

To a screw-capped culture tube was added Pd$_2$(dba)$_3$ (1.9 mg, 0.0022 mmol, 0.1 equiv.), $p$-anisyldiphenylphosphine (3.7 mg, 0.0132 mmol, 0.6 equiv.), 1-chloro-4-nitrobenzene (35 mg, 0.22 mmol, 10 equiv.), and K$_3$PO$_4$ (47 mg, 0.22 mmol, 10 equiv.). This tube was evacuated and backfilled with argon for three times. 1,4-dioxane (0.4 mL) was added via a syringe and the resulting mixture was stirred at room temperature for 5 minutes. A deoxygenated solution of 36 (15.0 mg, 0.022 mmol, 1.0 equiv.) in dioxane (0.6 mL) was added followed by degassed deionic water (0.5 mL). The reaction mixture
was heated to 100 °C for 15 h after which it was cooled to room temperature and treated with brine (4 mL). The resulting mixture was extracted with EtOAc (2 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated in vacuo. Purification by flash column chromatography (silica gel, 1:9 to 1:3 EtOAc:hexanes) followed by preparative TLC (silica gel, 1:4 EtOAc:hexanes) afforded 36f (10.5 mg, 72%).

**Physical state:** yellow oil;

**R_f = 0.45** (silica gel, 3:7 EtOAc:hexanes);

**1H NMR (600 MHz, acetone-d₆):** δ 8.28 (br s, 1H), 8.15 (dt, J = 9.0 Hz, 1.8 Hz, 2H), 7.51 (dt, J = 9.0 Hz, 1.8 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 7.30 – 7.27 (m, 2H), 7.20 (t, J = 7.8 Hz, 2H), 7.14 – 7.10 (m, 6H), 7.09 – 7.05 (m, 1H), 6.99 – 6.96 (m, 1H), 4.17 – 4.13 (m, 1H), 4.11 – 4.06 (m, 1H), 3.92 – 3.87 (m, 1H), 3.85 – 3.81 (m, 1H), 3.44 – 3.37 (m, 1H), 2.87 (dd, J = 13.8 Hz, 7.2 Hz, 1H), 2.81 (dd, J = 13.8 Hz, 7.2 Hz, 1H), 1.73 – 1.65 (m, 2H), 1.46 (d, J = 0.6 Hz, 3H), 1.45 (d, J = 0.6 Hz, 3H), 1.36 (dt, J = 12.6 Hz, 2.4 Hz, 1H), 1.32 (s, 3H), 1.25 (s, 3H), 1.09 – 1.03 (m, 1H) ppm;

**13C NMR (151 MHz, acetone-d₆):** δ 166.4, 163.1 (d, J = 245.5 Hz), 147.6, 147.5, 140.5, 139.4, 136.1, 134.5 (d, J = 8.3 Hz), 131.4, 130.8, 129.9 (d, J = 3.8 Hz), 129.3, 128.9, 128.7, 126.7, 123.9, 123.8, 122.4, 120.2, 118.0, 116.0 (d, J = 21.4 Hz), 99.2, 69.8, 67.3, 42.9, 41.2, 39.1, 36.7, 30.4, 26.9, 22.4, 22.3, 20.1 ppm;

**19F NMR (376 MHz, acetone-d₆):** δ −114.9 ppm;

**HRMS (ESI-TOF) Calcd for C₄₁H₄₆FN₃O₅ [M+H]+ 676.3181; found 676.3182;**

[α]D²⁰ = + 10.8 (c 0.5, CHCl₃).
Synthesis of Borono-vancomycin Analog

Figure S34. Synthesis of 42, 43 and 44.
Compound S45

To S44 [synthesized according to literature report (38, 62)] (600 mg, 0.43 mmol, 1.0 equiv.) in CH₃CN (5.1 mL) was added N-tert-butylidemethylsilyl-N-methyltrifluoroacetamide (MTBSTFA, 2.4 mL, 10.2 mmol, 23.7 equiv.), the resulting mixture was heated to 50 °C. After 30 h, the reaction mixture was poured onto a mixture of sat. aqueous citric acid (50 mL)/EtOAc (20 mL) and stirred vigorously at room temperature for 12 h. The organic layer was separated and washed with sat. aqueous NaHCO₃ (50 mL) and brine (50 mL). The aqueous layers were then back-extracted with EtOAc (20 mL × 2). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated in vacuo. Purification by flash column chromatography (silica gel, 1:1 to 4:1 EtOAc:hexanes) and preparative TLC (7:93 MeOH/CH₂Cl₂) afforded the desired product S45 (440 mg, 63%).

Physical state: white film;

*RF* = 0.31 (silica gel, 7:93 MeOH/CH₂Cl₂);

¹H NMR (600 MHz, acetone-*d₆*): δ 9.43 (br s, 1H), 7.94 (d, *J* = 6.5 Hz, 1H), 7.57 (dd, *J* = 8.3 Hz, 1.9 Hz, 1H), 7.53 (br s, 3H), 7.49 (s, 1H), 7.46 (s, 1H), 7.45 (s, 1H), 7.43 – 7.33 (m, 4H), 7.26 (d, *J* = 8.3 Hz, 1H), 7.19 (d, *J* = 8.3 Hz, 1H), 7.08 (s, 1H), 7.03 (d, *J* = 8.7 Hz, 1H), 6.77 (d, *J* = 9.9 Hz, 1H), 6.73 (s, 1H), 6.67 (d, *J* = 2.3 Hz, 1H), 6.45 (br s, 1H), 6.31 (d, *J* = 2.3 Hz, 1H), 5.94 (br s, 1H), 5.85 (s, 1H), 5.58 (d, *J* = 4.9 Hz, 1H), 5.54 (s, 1H), 5.51(s, 1H), 5.39 (d, *J* = 12.3 Hz, 1H), 5.23 (d, *J* = 12.3 Hz, 1H), 5.20 (br s, 1H), 5.10 (br s, 1H), 4.96 (d, *J* = 6.5 Hz, 1H), 4.67 (d, *J* = 5.2 Hz, 1H), 4.63 (t, *J* = 7.2 Hz, 1H), 4.42 (d, *J* = 11.7 Hz, 1H), 4.18 (s, 3H), 3.68 (s, 3H), 3.67 (s, 3H), 3.59 (s,
3H), 2.83 (s, 3H), 2.59 (d, $J = 16.5$ Hz, 1H), 2.42 (d, $J = 16.3$ Hz, 1H), 2.09 (s, 1H), 1.66 – 1.57 (m, 2H), 1.53 (s, 9H), 1.54 – 1.48 (m, 2H), 1.00 (s, 9H), 0.92 (s, 9H), 0.92 (d, $J = 6.5$ Hz, 3H) 0.86 (d, $J = 6.5$ Hz, 3H), 0.17 (s, 6H), 0.13 (s, 3H), 0.12 (s, 3H) ppm;

$^{13}$C NMR (151 MHz, acetone-$d_6$): δ 172.3, 171.7, 171.34, 171.31, 171.1, 170.8, 168.9, 168.0, 161.1, 159.9, 158.1, 156.9, 154.5, 153.0, 151.54, 151.51, 141.5, 140.0, 138.4, 137.0, 136.9, 136.2, 135.7, 130.0, 129.34, 129.30, 129.0, 128.3, 127.9, 127.6, 126.1, 125.4, 124.7, 124.1, 122.1, 113.8, 106.5, 106.1, 105.4, 99.6, 80.3, 74.6, 74.0, 67.2, 64.3, 61.5, 60.0, 57.5, 56.5, 56.2, 56.1, 55.7, 55.4, 55.2, 52.0, 38.1, 37.2, 28.9, 28.6, 26.5, 26.3, 25.7, 23.7, 23.3, 22.8, 19.15, 19.13, –4.4, –4.6, –4.71, –4.78.

HRMS (ESI-TOF, m/z): Calcd for C$_{81}$H$_{103}$Cl$_2$N$_8$O$_{19}$Si$_2$ [M+H]$^+$ 1617.6249; found 1617.6248.

Note: The loading amount of material for preparative TLC is crucial for separation [no more than 15 mg per PTLC plate (20 cm × 20 cm, 0.5 mm)].

Compound 42

![Compound 42](image)

To a solution of S45 (600 mg, 0.37 mmol) in EtOH/EtOAc (4/1, 50 mL) was added Pd/C (240 mg, 5% Pd/C, 50% wetted powder); the resulting black suspension was stirred under a hydrogen atmosphere at room temperature for 12 h. The reaction mixture was then filtered through celite and washed with EtOH/EtOAc (4:1, 150 mL). The filtrate was concentrated under reduced pressure. The resulting residue was purified by
preparative reverse-phase HPLC (85%–100% CH₃CN/H₂O over 30 min, 100% CH₃CN for 30 min, both CH₃CN and H₂O containing 0.1% TFA) to afford 42 (450 mg, 79%) as a TFA salt.

Note: The Boc group was found to have cleaved during the purification process.

Physical state: pale yellow film;

¹H NMR (600 MHz, methanol-d₄): δ 8.68 (d, J = 5.4 Hz, 1H), 7.60 (dd, J = 8.4 Hz, 2.4 Hz, 1H), 7.48 (br s, 1H), 7.42 (br s, 1H), 7.37 (d, J = 8.4 Hz, 1H) 7.40 – 7.35 (br m, 1H), 7.10 (d, J = 9.0 Hz, 1H), 7.04 – 7.02 (m, 2H), 6.68 (d, J = 2.4 Hz, 1H), 6.58 (d, J = 2.4 Hz, 1H), 6.39 (br s, 2H), 5.77 (d, J = 1.2 Hz, 1H), 5.65 (br s, 1H), 5.46 (s, 1H), 5.37 (s, 1H), 5.30 (br s, 1H), 4.80 (s, 1H), 4.60 (d, J = 3.4 Hz, 1H), 4.23 (s, 3H), 4.10 (br s, 1H), 3.93 – 3.90 (m, 1H), 3.87 (s, 3H), 3.73 (s, 3H), 3.67 (s, 3H), 2.83 (s, 3H), 2.83 – 2.78 (m, 1H), 2.42 (dd, J = 16.8 Hz, 5.4 Hz, 1H), 1.89 – 1.82 (m, 1H), 1.79 – 1.74 (m, 2H), 0.98 – 0.93 (m, 24H), 0.15 (s, 3H), 0.15 (s, 3H), 0.13 (s, 3H), 0.12 (s, 3H) ppm;

¹³C NMR (600 MHz, methanol-d₄): δ 175.3, 174.0, 172.3, 171.9, 171.8, 171.4, 170.4, 169.4, 169.2, 162.0, 160.4, 159.0, 155.2, 154.2, 153.3, 152.1, 142.2, 140.0, 139.4, 137.3, 136.8, 135.4, 130.6, 129.2, 128.46, 128.52, 128.0, 127.2, 126.1, 125.2, 124.9, 122.5, 114.1, 107.3, 106.7, 106.4, 99.4, 74.9, 65.0, 62.5, 62.4, 61.1, 58.2, 56.6, 56.1, 56.0, 55.6, 52.4, 40.8, 37.0, 33.2, 26.8, 26.5, 25.3, 23.7, 22.0, 19.7, 19.5, −4.3, −4.5, −4.65, −4.68 ppm;

¹⁹F NMR (376 MHz, methanol-d₄): δ −77.2 ppm;

HRMS (ESI-TOF, m/z): Calcd for C₆₉H₈₉Cl₂N₈O₁₇Si₂ [M+H]⁺ 1427.5256; found 1427.5258.
To a solution of 42 (15.0 mg, 0.0097 mmol, 1.0 equiv.) in CH$_3$CN (1.5 mL) was added a solution of tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) in DMF (120 μL, 1.0 M, 12.4 equiv.). The resulting mixture was stirred at room temperature for 1.5 h before it was concentrated to a final volume of ca. 0.1 mL under reduced pressure. This residue was purified by preparative reverse-phase HPLC (30%–45% CH$_3$CN/H$_2$O over 40 min, both CH$_3$CN and H$_2$O containing 0.1% TFA) to afford 43 (9.3 mg, 73%) as a TFA salt.

**Physical state:** white film;

$^1$H NMR (600 MHz, methanol-d$_4$) δ 9.01 (d, $J = 6.4$ Hz, 0.6H), 8.73 (d, $J = 5.8$ Hz, 0.4H), 7.86 (d, $J = 8.8$ Hz, 1H), 7.75 (d, $J = 2.1$ Hz, 1H), 7.65 (d, $J = 8.5$ Hz, 1H), 7.64 (d, $J = 2.1$ Hz, 1H) 7.61 (ddd, $J = 8.5$ Hz, 2.2 Hz, 0.9 Hz, 1H), 7.21 (d, $J = 8.5$ Hz, 1H), 7.09 (d, $J = 2.3$ Hz, 1H), 6.85 (d, $J = 8.8$ Hz, 1H), 6.78 (d, $J = 8.2$ Hz, 1H), 6.68 (d, $J = 2.3$ Hz, 1H), 6.51 (d, $J = 2.2$ Hz, 1H), 6.13 (br s, 1H), 6.06 (s, 1H), 5.87 (s, 1H), 5.40 (dd, $J = 2.2$ Hz, 1.0 Hz, 1H), 5.37 (s, 1H), 5.27 (d, $J = 3.5$ Hz, 1H), 4.78 (s, 1H), 4.65 (s, 1H), 4.27 (dd, $J = 9.6$ Hz, 1.9 Hz, 1H), 4.18 (s, 1H), 4.11 (s, 3H), 4.02 (t, $J = 7.2$ Hz, 1H), 3.86 (s, 3H), 3.66 (s, 3H), 3.63 (s, 3H), 3.03 (d, $J = 15.7$ Hz, 1H), 2.76 (s, 3H), 2.03 (dd, $J = 15.7$ Hz, 10.4 Hz, 1H), 1.90 (dt, $J = 14.0$ Hz, 7.2 Hz, 1H), 1.69 – 1.57 (m, 2H), 0.88 (d, $J = 6.4$ Hz, 3H), 0.85 (d, $J = 6.4$ Hz, 3H).

$^{13}$C NMR (600 MHz, methanol-d$_4$): δ 175.8, 174.6, 172.8, 171.7, 170.0, 169.9, 169.4, 169.0, 161.9, 160.4, 158.7, 154.2, 153.0, 152.3, 151.1, 142.7, 141.7, 138.1, 136.8, 136.7, 136.6, 130.2, 129.01, 128.95, 128.9, 128.5, 127.6, 127.3, 125.33, 125.27, 124.8, 122.4,
113.8, 109.8, 106.7, 106.3, 99.2, 74.3, 73.4, 63.9, 62.1, 61.9, 59.5, 58.5, 56.6, 56.3, 56.2, 56.0, 55.2, 53.0, 52.9, 40.2, 38.7, 36.4, 33.0, 25.5, 23.2, 22.8 ppm;

$^{19}$F NMR (376 MHz, methanol-$d_4$): $\delta$ –76.9 ppm;

HRMS (ESI-TOF, m/z): Calcd for $\text{C}_{57}\text{H}_{61}\text{Cl}_2\text{N}_8\text{O}_{17}$ [M+H]$^+$ 1199.3526; found 1199.3521.

**Compound S46**

To a suspension of 42 (45 mg, 0.029 mmol, 1.0 equiv.), $N$-hydroxyphthalimide (26 mg, 0.16 mmol, 5.5 equiv.), and $N,N$-dimethylpyridin-4-amine (0.4 mg, 0.0033 mmol, 0.11 equiv.) in $\text{CH}_2\text{Cl}_2$ (0.5 mL) was added $N,N'$-diisopropylcarbodiimide (25 $\mu$L, 0.16 mmol, 5.5 equiv.). The reaction mixture was stirred at room temperature for 1 h before AcOH (10 $\mu$L) was added. The resulting mixture was stirred for another 2 h and was subjected to flash column chromatography directly [silica gel, column: $d$ 1.6 cm $\times$ l 7.5 cm, 3:2 EtOAc:hexanes (200 mL) to 1:19 MeOH:$\text{CH}_2\text{Cl}_2$ (120 mL)]. The combined fractions eluted with MeOH-$\text{CH}_2\text{Cl}_2$ were concentrated under reduced pressure, and the residue (31 mg) was used in next step without further purification.

**Note:**

1. LC/MS indicated that the desired redox-active ester (S46) only eluted with MeOH/$\text{CH}_2\text{Cl}_2$. Nonpolar impurities, such as 1,3-diisopropylurea, were found to elute with EtOAc/hexanes.

2. Additional amounts of DMAP or longer reaction time have deleterious effects on
the reaction yield.

(3) This redox-active ester (S46) was rather unstable and should be used in next step within 3 h after purification. Alternatively, it can be stored at –20 °C.

**Compound S47**

![Chemical Structure of S47](image)

A screw-capped culture tube containing S46 (31 mg), MgBr$_2$•OEt$_2$ powder (38 mg, 0.15 mmol) was evacuated and backfilled with argon for three times. Suspension C (0.4 mL, NiCl$_2$•6H$_2$O/di-tBubipy in THF) was added next and the mixture was stirred vigorously at room temperature for 15 min (or sonicated until no granular MgBr$_2$•OEt$_2$ was observed). The resulting suspension was cooled to 0 °C, and the suspension of [B$_2$pin$_2$Me]Li in THF (0.55 mL) was added in one portion. After stirring for 1 h, the reaction mixture was diluted with CH$_2$Cl$_2$ (5 mL), filtered through a short pad of silica gel and celite, washed with 5% MeOH/CH$_2$Cl$_2$ (50 mL). The filtrate was concentrated under reduced pressure, and the residue was subjected to flash column chromatography directly [silica gel, column: d 1.6 cm × l 7.5 cm, 1:1 EtOAc:hexanes (200 mL) to 1:19 MeOH:CH$_2$Cl$_2$ (120 mL)]. The MeOH/CH$_2$Cl$_2$ elution was concentrated under reduced pressure, and the residue (16 mg) was used in next step without further purification.

**Note:**

(1) The pinacol ester was found to hydrolyze during the reaction based on LC/MS analysis.

(2) LC/MS indicated that S47 only eluted with MeOH/CH$_2$Cl$_2$ based on LC/MS analysis.
Nonpolar impurities, such as \( {B_2}pin_2 \), were found to elute with EtOAc/hexanes. 

(3) Not all impurities can be removed through flash chromatography in this step; instead the unpure materials were carried forward to the next step.

**Compound 44**

To a solution of \( S_47 \) (16 mg) in \( CH_3CN \) (1.3 mL) was added a solution of tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) in DMF (120 μL, 1.0 M). The mixture was stirred at room temperature for 1.5 h and was concentrated to a final volume of ca. 0.3 mL under reduced pressure. The residue was purified by preparative reverse-phase HPLC (20%–50% \( CH_3CN/H_2O \) over 30 min, both \( CH_3CN \) and \( H_2O \) containing 0.1% TFA) to afford 44 (4.1 mg, 11% over 3 steps) as a TFA salt.

*Note: This compound was not stable in neat condition due to its propensity toward polymerization. Therefore, the purified compound was dissolved immediately. Solutions in MeOH were used for HRMS; solutions in MeOH-\( d_4 \) were used for NMR study; solutions in DMSO were used for biological studies.*

**Physical state:** white film;

\(^1H\) NMR (600 MHz, methanol-\( d_4 \)): \( \delta \) 9.05 (d, \( J = 6.6 \) Hz, 1H), 7.65 – 7.58 (m, 4H), 7.31 (d, \( J = 9.0 \) Hz, 1H), 7.30 (d, \( J = 9.6 \) Hz, 1H), 7.15 (dd, \( J = 9.0 \) Hz, 1.8 Hz, 1H), 6.97 – 6.91 (m, 2H), 6.81 (s, 1H), 6.52 (d, \( J = 2.4 \) Hz, 1H), 5.81 (d, \( J = 5.4 \) Hz, 1H), 5.69 (s, 1H), 5.65 (s, 1H), 5.54 (s, 1H), 5.35 (d, \( J = 3.6 \) Hz, 1H), 5.07 (br s, 1H), 5.04
(d, \(J = 6.6 \text{ Hz} \), 1H), 4.43 (s, 1H), 4.32 (d, \(J = 5.4 \text{ Hz} \), 1H), 4.14 (s, 3H), 4.03 (t, \(J = 7.2 \text{ Hz} \), 1H), 3.87 (s, 3H), 3.68 (s, 3H), 3.65 (s, 3H), 2.96 (d, \(J = 15.6 \), 1H), 2.77 (s, 3H), 2.34 (dd, \(J = 16.2 \text{ Hz} \), 9.0 Hz, 1H), 1.86 – 1.82 (m, 1H), 1.79 – 1.73 (m, 1H), 1.86 – 1.71 (m, 1H), 1.01 (d, \(J = 6.0 \text{ Hz} \), 3H), 0.98 (d, \(J = 6.0 \text{ Hz} \), 3H) ppm;

\[^{11}B\text{NMR (500 MHz, methanol-}d_4\]): \(\delta \sim 0.87 \) (s) ppm;

**HRMS (ESI-TOF, \(m/z\)):** Calcd for \(C_{56}H_{62}BCl_2N_8O_{17} \ [M+H]^+ \) 1199.3698; found 1199.3698.

Antibiotic susceptibilities were determined using the Clinical and Laboratory Standards Institute broth microdilution method (63). Briefly, antibiotics were prepared as 2-fold dilutions in 96-well plates containing cation-adjusted Mueller-Hinton broth (S. aureus strains) or brain-heart infusion broth (Enterococcus strains). Stock solutions of antibiotics were made in dimethyl sulfoxide (DMSO). Wells were inoculated from a fresh plate scrape diluted to a final concentration of $5 \times 10^5$ CFU/mL and incubated at 37 °C. Growth observed visually at 20 h. All MICs are an average of at least three independent determinations.

Table S12. Antibacterial evaluation of a boronic acid vancomycin analog.

<table>
<thead>
<tr>
<th>Compd.</th>
<th>S. aureus</th>
<th>MRSA</th>
<th>E. faecium</th>
<th>E. faecalis</th>
<th>E. faecalis</th>
</tr>
</thead>
<tbody>
<tr>
<td>vancomycin</td>
<td>0.5</td>
<td>0.5</td>
<td>&gt;64</td>
<td>&gt;64</td>
<td>16</td>
</tr>
<tr>
<td>vancomycin aglycon</td>
<td>1</td>
<td>1</td>
<td>&gt;64</td>
<td>&gt;64</td>
<td>32</td>
</tr>
<tr>
<td>43</td>
<td>2</td>
<td>2</td>
<td>&gt;64</td>
<td>&gt;64</td>
<td>8</td>
</tr>
<tr>
<td>44</td>
<td>16</td>
<td>16</td>
<td>&gt;64</td>
<td>&gt;64</td>
<td>16</td>
</tr>
</tbody>
</table>

* Staphylococcus aureus (ATCC 25923)

† Staphylococcus aureus (methicillin resistant, ATCC 43300)

‡ Enterococcus faecium (Van A, ATCC BAA-2317)

§ Enterococcus faecalis (VanA, BM4166)

¶ Enterococcus faecalis (VanB, ATCC 51299)

Note: compound 44 was not very stable in H$_2$O at 37 °C under air. Under such conditions, ca. 20% of 44 was found to have decomposed after 24 h as indicated by LC/MS analysis (254 nM UV detector).
Probing the Stereoselectivity on Peptide Substrates

**Compound S48**

![Compound S48](image)

**1,3-dioxoisindolin-2-yl (tert-butoxycarbonyl)-L-alanyl-L-valinate (S48)**

N-(3-Dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (EDC, 422 mg, 2.2 mmol, 1.1 equiv.) was added into a solution of Boc-L-Ala-L-Val-OH (2.0 mmol, 1.0 equiv.) and NHPI (359 mg, 2.2 mmol, 1.1 equiv.) in CH$_2$Cl$_2$ (30 mL) at −10 °C. After stirring for 1 h at room temperature, the mixture was washed with water and the aqueous phase was extracted with CH$_2$Cl$_2$ for three times. The combined organic phases were dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo. Purification by flash column chromatography (silica gel, 3:7 EtOAc:hexanes) afforded S48 (591 mg, 62%).

**Physical state:** white foam;

$R_f$ = 0.36 (silica gel, 2:3 EtOAc:hexanes);

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.88 (dd, $J = 5.5$ Hz, 3.1 Hz, 2H), 7.79 (dd, $J = 5.5$ Hz, 3.1 Hz, 2H), 6.93 – 6.79 (br, 1H), 5.02 – 4.88 (m, 2H), 4.28 – 4.14 (br, s, 1H), 2.48 – 2.32 (m, 1H), 1.44 (s, 9H), 1.38 (d, $J = 7.0$ Hz, 3H), 1.10 (d, $J = 6.9$ Hz, 3H), 1.08 (d, $J = 6.9$ Hz, 3H) ppm;

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 172.6, 168.4, 161.6, 155.9, 135.0, 129.0, 124.2, 80.5, 55.6, 50.0, 31.8, 28.4, 18.9, 17.5 ppm;

**HRMS (ESI-TOF, m/z):** Calcd for C$_{21}$H$_{28}$N$_3$O$_7$ [M+H]$^+$ 434.1922; found 434.1930.
Compound 45

**tert-butyl ((2S)-1-((2-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl)amino)-1-oxopropan-2-yl)carbamate (45)**

On 0.2 mmol scale, General Procedure C was followed with suspension C (NiCl$_2$•6H$_2$O/di-$r$Bubipy in THF). Flash column chromatography (silica gel, 3:7 EtOAc:hexanes) afforded 45 as a mixture of inseparable diastereomers (50 mg, $d.r.$ = 1:1, 67%)

**Physical state:** colorless oil;

$R_f$ = 0.22 (silica gel, 3:7 EtOAc:hexanes);

$^1$H NMR (600 MHz, C$_6$D$_6$): $\delta$ 6.77 (s, 1H), 6.73 (s, 1H), 5.56 (s, 1H), 5.37 (s, 1H), 4.23 (s, 1H), 4.11 (s, 1H), 3.05 (s, 2H), 2.10 – 2.04 (m, 2H), 1.41 (s, 9H), 1.40 (s, 9H), 1.25 – 0.92 (m, 42H) ppm;

$^{13}$C NMR (151 MHz, C$_6$D$_6$): $\delta$ 174.7, 174.2, 156.0, 155.9, 82.8, 82.6, 79.4, 74.7, 49.1, 49.0, 37.0, 30.3, 28.4, 25.3, 25.3, 25.2, 25.0, 20.73, 20.68, 20.0, 19.9, 17.9, 17.7 ppm;

**HRMS (ESI-TOF, m/z):** Calcd for C$_{18}$H$_{36}$BN$_2$O$_5$ [M+H]$^+$ 371.2712; found 371.2710.
On a 2.0 mmol scale, General Procedure A was followed with Boc-L-Val-L-Val-OH (S49). Purification by flash column chromatography (silica gel, 1:3 EtOAc:hexanes) afforded S50a (187 mg, 20%) and S50b (395 mg, 43%).

Compound S50a

1,3-dioxoisindolin-2-yl (tert-butoxycarbonyl)-L-valyl-L-valinate (S50a)

Physical state: white foam;

$R_f = 0.40$ (silica gel, 1:2 EtOAc:hexanes);

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.90 – 7.88 (m, 2H), 7.81 – 7.79 (m, 2H), 6.48 (br d, $J = 8.8$ Hz, 1H), 5.09 (br d, $J = 8.4$ Hz, 1H), 4.98 (dd, $J = 8.8$ Hz, 5.1 Hz, 1H), 3.91 (dd, $J = 8.7$ Hz, 6.8 Hz, 1H), 2.43-2.38 (m, 1H), 2.14 (br s, 1H), 1.43 (s, 9H), 1.11 (t, $J = 6.3$ Hz, 6H), 0.97 (dd, $J = 16.5$ Hz, 6.8 Hz, 6H) ppm;

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 171.9, 168.4, 161.6, 156.1, 135.0, 129.0, 124.2, 80.2, 60.4, 55.6, 31.7, 30.6, 28.4, 19.4, 18.9, 18.2, 17.7 ppm;

HRMS (ESI-TOF, m/z): Calcd for C$_{18}$H$_{24}$N$_3$O$_5$ [M-Boc+H]$^+$ 362.1710; found
362.1705;
\[\alpha\]_D^20 = -31.8 (c 0.96, CHCl₃).

**Compound S50b**

![Structure of S50b](image)

1,3-dioxoisindolin-2-yl (\textit{tert}-butoxycarbonyl)-\textit{L}-valyl-\textit{L}-valinate (S50b)

**Physical state:** white foam;

\(R_f = 0.4\) (silica gel, 1:2 EtOAc:hexanes);

\(^1\H\) NMR (600 MHz, CDCl₃): \(\delta 7.87 - 7.85\) (m, 2H), \(7.79 - 7.77\) (m, 2H), 6.60 (br d, \(J = 8.8\) Hz, 1H), 5.15 (d, \(J = 8.9\) Hz, 1H), 4.96 (dd, \(J = 8.8\) Hz, 5.2 Hz, 1H), 3.92 (dd, \(J = 8.8\) Hz, 6.8 Hz, 1H), 2.41 – 2.36 (m, 1H), 2.10 (br s, 1H), 1.42 (s, 9H), 1.09 (dd, \(J = 6.9\) Hz, 4.6 Hz, 6H), 0.97 (d, \(J = 6.8\) Hz, 3H), 0.94 (d, \(J = 6.8\) Hz, 3H) ppm;

\(^13\C\) NMR (151 MHz, CDCl₃): \(\delta 172.0, 168.4, 161.6, 156.1, 134.9, 128.9, 124.1, 80.1, 60.3, 55.6, 31.6, 30.6, 28.4, 19.4, 18.9, 18.2, 17.7\) ppm;

**HRMS (ESI-TOF, \textit{m/z}):** Calcd for C\(_{18}\)H\(_{24}\)N\(_3\)O\(_5\) [M-Boc+H]\(^+\) 362.1710; found 362.1714;

\[\alpha\]_D^20 = -31.2 (c 1.0, CHCl₃).

**Compound 46**

![Structure of 46](image)

\textit{tert}-butyl (\((S)\)-3-methyl-1-(((\((S)\)-2-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborol-2-y)propyl)amino)-1-oxobutan-2-yl)carbamate (46)
From **S50a**:  
On 0.2 mmol scale, General Procedure C was followed with suspension C (NiCl₂•6H₂O/di-tBubipy in THF) from **S50a** (1.0 equiv. of MgBr₂•Et₂O was used in this case). Purification by flash column chromatography (silica gel, 1:3 EtOAc:hexanes) afforded 46 as a mixture of inseparable diastereomers (37.1 mg, d.r. = 1.7 : 1, 47%).

From **S50b**:  
On 0.2 mmol scale, General Procedure C was followed with suspension C (NiCl₂•6H₂O/di-tBubipy in THF) from **S50b** (1.0 equiv. of MgBr₂•Et₂O was used in this case). Purification by flash column chromatography (silica gel, 1:3 EtOAc: hexanes) afforded 46 as a mixture of inseparable diastereomers (36.5 mg, d.r. = 1.7 : 1, 46%).

**Physical state**: colorless oil; 
\[ R_f \] = 0.30 (silica gel, 1:2 EtOAc:hexanes);

\(^1\)H NMR (600 MHz, CDCl₃): \( \delta \) 6.30 (br d, \( J = 5.5 \) Hz, 0.78H), 6.22 (br s, 0.22H), 5.10 (br d, \( J = 8.7 \) Hz, 1H), 3.92 – 3.86 (m, 1H), 3.03 (br s, 1H), 2.10 (br s, 1H), 1.96 – 1.90 (m, 1H), 1.42 (s, 9H), 1.28 – 1.16 (m, 12H), 0.95 (d, \( J = 6.7 \) Hz, 3H), 0.93 (d, \( J = 6.7 \) Hz, 3H), 0.92 (d, \( J = 6.7 \) Hz, 6H) ppm;

\(^{13}\)C NMR (151 MHz, CDCl₃): \( \delta \) 172.48 (minor), 172.46, 155.92, 83.37, 79.91, 59.57 (minor), 59.25, 44.96 (br), 31.10, 31.02 (minor), 30.01, 29.91 (minor), 28.51, 28.44, 25.18, 25.12, 25.10 (minor), 25.03 (minor), 24.97, 20.42, 20.37 (minor), 20.12, 20.03, 19.35, 19.21 (minor), 18.13 (minor), 17.90 ppm;

HRMS (ESI-TOF, \( m/z \)): Calcd for C₂₀H₄₀BN₂O₅ \([\text{M+H}]^+\) 399.3025; found 399.3028.

**Compound S51**
**tert-butyl (R)-2-(((S)-1-((1,3-dioxoisindolin-2-yl)oxy)-3-methyl-1-oxobutan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (S51)**

On 1.0 mmol scale (based on Boc-\(L\)-Pro-\(L\)-Leu-OH), the same procedure as in the synthesis of S48 was used. Purification by flash column chromatography (silica gel, 1:2 EtOAc:hexanes) afforded S51 (308 mg, 67%).

**Physical state:** white foam;

\(R_f = 0.4\) (silica gel, 1:1 EtOAc:hexanes);

\(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta 7.88 – 7.85\) (m, 2H), 7.87 (br s, 0.6H), 7.79 – 7.77 (m, 2H), 6.63 (s, 0.4H), 4.99 – 4.88 (m, 1H), 4.37 – 4.30 (m, 1H), 3.61 – 3.21 (m, 2H), 2.47 (br s, 0.4H), 2.43 – 2.37 (m, 1H), 2.16 (br s, 0.6H), 2.03 – 1.76 (m, 3H), 1.51 – 1.39 (m, 9H), 1.12 – 1.03 (m, 6H); (complex spectrum was observed due to mixture of rotamers);

\(^{13}\)C NMR (151 MHz, CDCl\(_3\)): \(\delta 172.7, 172.0, 168.4, 161.6, 156.3, 154.9, 140.9, 137.2, 134.9, 130.1, 129.0, 124.1, 115.6, 110.4, 81.4, 80.7, 61.3, 59.5, 55.7, 55.1, 47.0, 31.5, 28.5, 27.1, 24.8, 19.0, 17.5; (complex spectrum was observed due to mixture of rotamers);

HRMS (ESI-TOF, \(m/z\)): Calcd for \(C_{18}H_{22}N_3O_5\) [M-Boc+H]\(^+\) 360.1554; found 360.1554.

**Compound 47**

\(\text{tert-butyl } 2-(((S)-2-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl)\)

**carbamoyl)pyrrolidine-1-carboxylate (47)**

On 0.28 mmol scale, General Procedure C was followed with S51 and suspension C (NiCl\(_2\)•6H\(_2\)O/di-iBubipy in THF). Purification by flash column chromatography (silica gel, 2:1 EtOAc:hexanes) afforded 47 as a mixture of diastereomers (70.5 mg, \(d.r. =\)
2.6:1, 63%). Diastereomeric ratio was determined by $^1$H NMR and NOESY in DMSO-$d_6$ at 65 °C.

**Physical state:** colorless oil;

$R_f = 0.30$ (silica gel, 2:1 EtOAc:hexanes);

$^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 8.37 (s, 0.72H), 8.28 (s, 0.28H), 4.25 (dd, $J = 8.5$, 2.8 Hz, 1H), 3.44 – 3.35 (m, 1H), 3.34 – 3.27 (m, 1H), 2.46 (t, $J = 5.3$ Hz, 0.28H), 2.40 (t, $J = 4.7$ Hz, 0.72H), 2.19 – 2.05 (m, 1H), 1.89 – 1.74 (m, 4H), 1.39 (s, 9H), 1.13 (s, 3.36H), 1.12 (s, 8.64H), 0.93 – 0.85 (m, 6H) ppm;

$^{13}$C NMR (126 MHz, DMSO-$d_6$): $\delta$ 174.9, 153.0, 80.6 (minor), 80.4, 78.5, 57.5 (minor), 57.3, 46.2, 28.9 (minor), 28.7, 27.8, 27.7, 24.9 (minor), 24.8, 24.7, 20.1, 20.0 (minor), 19.2 ppm;

HRMS (ESI-TOF, m/z): Calcd for C$_{20}$H$_{38}$BN$_2$O$_5$ [M+H]$^+$ 397.2868; found 397.2864.
Figure S36. Synthesis of bortezomib (Velcade).

Compound S53

1,3-dioisoindolin-2-yl (tert-butoxycarbonyl)-L-phenylalanyl-leucinate (S53)

On 3.0 mmol scale, General Procedure A was followed with Boc-L-Phe-L-Leu-OH (64) (S62). Purification by flash column chromatography (deactivated silica gel, 1:5.6 EtOAc:hexanes) afforded S53 as a mixture of inseparable diastereomers (1.42 g, d.r. = 3:2, 90%). Diastereomeric ratio was determined by $^1$H NMR and NOESY.

Physical state: White foam;

$R_f = 0.50$ (silica gel, 2:3 EtOAc:hexanes);
\(^1\)H NMR (600 MHz, methanol-\(d_4\)): Minor isomer: \(\delta \) 7.94 – 7.89 (m, 4H), 7.29 – 7.15 (m, 5H), 4.78 (dd, \(J = 9.5\) Hz, 5.8 Hz, 1H), 4.39 – 4.35 (m, 1H), 3.05 (dd, \(J = 13.7\) Hz, 7.2 Hz, 1H), 2.90 (dd, \(J = 13.6\) Hz, 8.1 Hz, 1H), 1.76 – 1.70 (m, 2H), 1.54 – 1.50 (m, 1H), 1.38 (s, 9H), 0.94 (d, \(J = 6.6\) Hz, 3H), 0.89 (d, \(J = 6.6\) Hz, 3H) ppm; Major isomer: \(\delta \) 7.94 – 7.89 (m, 4H), 7.29 – 7.15 (m, 5H), 4.92 (dd, \(J = 9.6\) Hz, 6.0 Hz, 1H), 4.39 – 4.35 (m, 1H), 3.13 (dd, \(J = 14.4\) Hz, 5.4 Hz, 1H), 2.84 (dd, \(J = 13.8\) Hz, 9.0 Hz, 1H), 1.89 – 1.83 (m, 3H), 1.37 (s, 9H), 1.02 (d, \(J = 6.0\) Hz, 3H), 0.99 (d, \(J = 6.0\) Hz, 3H) ppm; 

\(^{13}\)C NMR (151 MHz, methanol-\(d_4\)): Minor isomer: \(\delta \) 174.4, 170.4, 163.1, 157.3, 138.3, 136.3, 135.5, 130.4, 130.1, 129.5, 127.7, 124.9, 124.0, 80.7, 57.4, 50.2, 41.2, 39.6, 28.6, 28.4, 25.7, 25.5, 23.2, 21.7 ppm; Major isomer: \(\delta \) 174.6, 170.4, 163.1, 157.6, 138.4, 136.4, 135.5, 130.4, 130.1, 129.4, 127.6, 124.9, 124.0, 80.6, 57.1, 50.2, 41.5, 39.1, 28.6, 28.4, 25.7, 25.5, 23.2, 21.8 ppm; 

HRMS (ESI-TOF, \(m/z\)): Calcd for C\(_{23}\)H\(_{26}\)N\(_3\)O\(_5\) [M-Boc+H]\(^+\) 424.1867; found 424.1871.

**Compound 48**

\[
\text{tert-butyl (}(S)-1-(((R)-3-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (48)}
\]

On 0.6 mmol scale, General Procedure C was followed with suspension C (NiCl\(_2\)•6H\(_2\)O/di-rBubipy in THF) and S53. The reaction was started from \(-15^\circ\)C and warmed to room temperature over 3 h. Flash column chromatography (silica gel, 1:9 EtOAc:hexanes to 1:4 EtOAc:hexanes) afforded 48, which was dissolved in hexanes.
and filtered through celite. The filtrate was concentrated \textit{in vacuo} to afford 48 as a mixture of inseparable diastereomers (151 mg, \textit{d.r.} = 5.1 : 1, 55%).

\textbf{Physical state:} Pale yellow oil;

\(R_f = 0.50\) (silica gel, 2:3 EtOAc:hexanes);

\textit{\textbf{1H NMR (600 MHz, CDCl$_3$):} Major isomer:} \(\delta\) 7.31 – 7.26 (m, 2H), 7.24 – 7.21 (m, 3H), 6.19 (br s, 1H), 5.00 (br s, 1H), 4.35 (q, \(J = 7.3\) Hz, 1H), 3.10 – 3.02 (m, 2H), 2.98 (ddd, \(J = 8.8\) Hz, 6.3 Hz, 4.4 Hz, 1H), 1.49 – 1.42 (m, 1H), 1.39 (s, 9H), 1.37 – 1.35 (m, 2H), 1.24 (s, 6H), 1.23 (s, 6H), 0.86 (d, \(J = 6.6\) Hz, 3H), 0.84 (d, \(J = 6.6\) Hz, 3H) ppm;

\textit{\textbf{13C NMR (151 MHz, CDCl$_3$):} Major isomer:} \(\delta\) 172.6, 155.5, 134.4, 129.6, 128.8, 127.1, 83.0, 80.3, 54.8, 39.9, 38.3, 28.4, 25.6, 25.1, 25.0, 23.3, 22.0 ppm;

\textit{\textbf{HRMS (ESI-TOF, m/z):}} Calcd for C$_{25}$H$_{42}$BN$_2$O$_5$ [M+H]$^+$ 461.3181; found 461.3179.

\textbf{Compound 49}

\begin{center}
\includegraphics[width=0.5\textwidth]{compound49.png}
\end{center}

\textit{(3-methyl-1-\textit{((S)}-3-phenyl-2-(pyrazine-2-carboxamido)propanamido)butyl)boronic acid (49)}

Bortezomib (49) was synthesized from 48 using the literature procedure (19) with slight modifications.

\textit{Boc deprotection:} To a screw-capped culture tube charged with 48 (151 mg, 0.33 mmol) was added HCl in EtOAc (14 wt\%) at 0 °C, and the reaction mixture was stirred at 0 °C for 3 h and room temperature for an additional 1 h. The reaction mixture was concentrated to dryness and the resulting solid was washed with hexanes. The desired product was afforded as a white solid and was used in next step without further purification.
Esterification: CH₂Cl₂ (1.2 mL, 0.5 M) was added to a screw-capped culture tube containing the hydrochloride salt obtained from the previous step. The mixture was cooled to 0 °C. Diisopropylethylamine (0.15 mL, 0.86 mmol) was added dropwise, and the reaction mixture was stirred for 5 min. 2-Pyrazine carboxylic acid (56 mg, 0.45 mmol) was then added to the solution in one portion. o-(Benzotriazol-1-yl)-N,N',N'-tetramethyluronium tetrafluoroborate (TBTU, 118 mg, 0.37 mmol) was then added to the reaction mixture which was stirred at 0 °C for 2 h and room temperature for additional 1 h. The reaction mixture was then concentrated in vacuo. The crude residue was dissolved in EtOAc (10 mL) and transferred to a separatory funnel. The organic layer was washed with deionic H₂O (2 × 10 mL), 1% phosphoric acid (2 × 10 mL), 2% K₂CO₃ (2 × 10 mL), and brine (2 × 10 mL) successively. Each aqueous layer was back-extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The resulting pale yellow foam was carried on to the next step without further purification.

Boronate ester exchange: Pentane (0.8 mL) and MeOH (0.8 mL) were added to a screw-capped culture tube containing the pinacol boronate obtained from the previous step. 2-Methylpropaneboronic acid (125 mg, 1.2 mmol) was then added to the solution. 1 N aq. HCl (0.6 mL) was added to the reaction mixture, and the resulting biphasic solution was stirred vigorously for 16 h. Stirring was then stopped and the biphasic mixture was allowed to separate. The aqueous layer was washed with pentane (2 × 10 mL) and was then concentrated in vacuo. The resulting film was partitioned between CH₂Cl₂ and 1 N aq. NaOH (10 mL). The aqueous layer was washed with CH₂Cl₂ (3 × 10 mL) and the organic phase was back-extracted with 1 N aq. NaOH (2 × 10 mL). 1 N aq. HCl was added to the combined aqueous layers until the pH = 6 when the desired product was extracted into the organic layer with CH₂Cl₂ (3 × 10 mL). The combined organic phase was dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo. The resulting residue was dissolved in EtOAc (2 mL), and the solution was subsequently concentrated
in vacuo. To the residue was then added hexanes (2 mL), and the suspension was concentrated in vacuo to afford the product 49 (64 mg, d.r. = 5.1 :1, 51% over 3 steps).

Physical state: white solid;

1H NMR (600 MHz, CD₃CN:D₂O = 4:1): Major isomer: δ 9.10 (d, J = 1.8 Hz, 1H), 8.74 (d, J = 2.4 Hz, 1H)), 8.61 (dd, J = 2.4 Hz, 1.8 Hz, 1H), 7.26 – 7.22 (m, 4H), 7.20 – 7.17 (m, 1H), 4.78 (dd, J = 8.4 Hz, 6.0 Hz, 1H), 3.19 (dd, J = 13.8 Hz, 6.0 Hz, 1H), 3.07 (dd, J = 13.8 Hz, 8.2 Hz, 1H), 2.93 (dd, J = 10.2 Hz, 5.4 Hz, 1H), 1.44 – 1.33 (m, 2H), 1.26 – 1.21 (m, 1H), 0.80 (d, J = 6.6 Hz, 3H), 0.78 (d, J = 6.6 Hz, 3H) ppm;

13C NMR (151 MHz, CD₃CN:D₂O = 4:1): Major isomer: 172.4, 164.5, 148.7, 145.0, 144.7, 144.4, 137.7, 130.4, 129.5, 127.8, 54.9, 40.2, 40.2 (br s), 38.5, 25.9, 23.6, 22.0 ppm;

Synthesis of Elastase Inhibitor 50

**Figure S37.** Synthesis of 50 and 50a.

**Compound 50a**

(methoxycarbonyl)-L-valyl-L-prolyl-L-valine (50a)

_Cbz deprotection:_ A 100 mL flask equipped with a stirrer bar was charged with Z-L-Pro-L-Val-OrBu (65) (S54, 2.55 g, 6.3 mmol), 10% Pd/C (128 mg, 5 wt%), and MeOH (30 mL). The flask was then evacuated and backfilled with H₂ from a balloon for three times. The mixture was stirred at room temperature for 6 h and was filtered through a short pad of celite which was then rinsed with MeOH (10 mL). The filtrate was concentrated _in vacuo_ to give the corresponding amine as colorless oil.
Amide bond formation: The aforementioned amine was treated successively with S55 (1.1 g, 6.3 mmol, 1.0 equiv.), HOBt•H₂O (96 mg, 0.07 mmol, 0.11 equiv.), and CH₂Cl₂ (25 mL). The resulting solution was cooled to 0 °C before DCC (1.43 g, 6.9 mmol, 1.1 equiv.) was added. The reaction mixture was allowed to stir at 0 °C for 30 min and then at room temperature overnight. The reaction mixture was filtered through a pad of celite; the filtrate was redissolved in EtOAc and washed with 0.1 N aq. HCl, 0.1 M aq. NH₄OH, and brine successively. The organic layer was dried over anhydrous Na₂SO₄ and concentrated in vacuo to give S56 (2.2 g) as colorless oil, which was used in the next step without further purification.

tBu deprotection: In a 25 mL flask equipped with a stirrer bar, S56 (428 mg, 1.0 mmol) was dissolved in CH₂Cl₂ (3 mL). TFA (3 mL) was added and the resulting solution was allowed to stir at room temperature for 5 h. After the volatiles were removed in vacuo, the crude mixture was purified by flash column chromatography (silica gel, 2:1 EtOAc:hexanes) to furnish 50a (359 mg, 80% over 3 steps).

Physical state: white foam;

R_f = 0.35 (silica gel, 1:2 hexanes: EtOAc);

^1H NMR (600 MHz, CDCl₃): δ 7.43 (br d, J = 8.4 Hz, 2H), 6.17 (d, J = 9.0 Hz, 1H), 4.64 (dd, J = 7.8 Hz, 3.0 Hz, 1H), 4.48 (dd, J = 8.4 Hz, 4.0 Hz, 1H), 4.29 (t, J = 8.4 Hz, 1H), 3.84 (dd, J = 16.8 Hz, 8.4 Hz, 1H), 3.69 – 3.63 (m, 4H), 2.33 – 2.29 (m, 1H), 2.20 – 2.10 (m, 2H), 2.03 – 1.92 (m, 3H), 0.97 (d, J = 6.6 Hz, 3H), 0.95 (d, J = 6.6 Hz, 3H), 0.91 (d, J = 7.2 Hz, 3H), 0.89 (d, J = 7.2 Hz, 3H) ppm;

^13C NMR (151 MHz, CDCl₃): δ 174.5, 173.5, 171.1, 157.8, 60.6, 58.1, 57.8, 52.5, 48.3, 31.4, 31.2, 27.7, 25.2, 19.4, 19.0, 18.1, 17.8 ppm;

HRMS (ESI-TOF, m/z): Calcld for C_{17}H_{30}N_{3}O_{6} [M+H]^+ 372.2129; found 372.2126; [α]D^{20} = -62.9 (c 0.79, CHCl₃)
Compound S57

1,3-dioxoisoinolin-2-yl (methoxycarbonyl)-L-valyl-L-prolylvalinate (S57)

On 2.34 mmol scale, General Procedure A was followed with (methoxycarbonyl)-L-valyl-L-prolyl-L-valine. Purification by flash column chromatography (silica gel, 1:1 EtOAc:hexanes) furnished S57 (640 mg, 53%).

Physical state: white foam;

$R_f = 0.40$ (silica gel, 1:2 hexanes: EtOAc);

$^1$H NMR (600 MHz, CDCl$_3$) δ 7.88 – 7.84 (m, 2H), 7.78 – 7.75 (m, 2H), 7.50 (d, $J = 8.4$ Hz, 1H), 5.61 (d, $J = 9.2$ Hz, 1H), 4.84 (dd, $J = 8.5$ Hz, 5.0 Hz, 1H), 4.61 (dd, $J = 8.1$ Hz, 3.0 Hz, 1H), 4.29 (dd, $J = 9.3$ Hz, 6.9 Hz, 1H), 3.79 – 3.72 (m, 1H), 3.63 (s, 3H), 3.64 – 3.61 (m, 1H), 2.41 – 2.30 (m, 2H), 2.17 (dt, $J = 12.3$ Hz, 9.1 Hz, 1H), 2.01 – 1.96 (m, 2H), 1.95 – 1.89 (m, 1H), 1.07 (d, $J = 7.2$ Hz, 3H), 1.06 (d, $J = 6.6$ Hz, 3H), 0.97 (d, $J = 6.7$ Hz, 3H), 0.93 (d, $J = 6.7$ Hz, 3H) ppm;

$^{13}$C NMR (151 MHz, CDCl$_3$) δ 172.5, 171.2, 168.4, 161.7, 157.3, 134.9, 129.0, 124.1, 60.0, 57.7, 56.0, 52.4, 48.0, 31.6, 31.4, 27.4, 25.3, 19.5, 18.8, 17.8, 17.7 ppm;

HRMS (ESI-TOF, m/z): Calcd for C$_{25}$H$_{33}$N$_4$O$_8$ [M+H]$^+$ 517.2293; found 517.2289;

$[\alpha]_D^{20} = -61.0$ (c 1.0, CHCl$_3$).
**Compound S58**

![Chemical structure of S58]

methyl ((S)-3-methyl-1-((S)-2-(((R)-2-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl)carbamoyl)pyrrolidin-1-yl)-1-oxobutan-2yl)-carbamate (S58)

On 0.33 mmol scale, General Procedure C was followed with suspension C (NiCl₂•6H₂O/di-iBubipy in THF). MgBr₂•Et₂O (1.0 equiv.) was used in this case. Purification by flash column chromatography (silica gel, 2:3 EtOAc:hexanes to 20:1 CH₂Cl₂:MeOH) furnished S58 (72 mg, 48%) as slightly yellow oil.

**Compound 50**

![Chemical structure of 50]

((R)-1-((S)-1-((methoxycarbonyl)-L-valyl)pyrrolidine-2-carboxamido)-2-methylpropyl)boronic acid (50)

Aminoboronate ester S58 (24 mg, 0.053 mmol) was dissolved in CH₂Cl₂ (2 mL) under argon; the solution was cooled to −78 °C with a dry ice/acetone bath when BCl₃ (0.16 mL, 1.0 M in CH₂Cl₂, 3.0 equiv.) was added dropwise, after which the mixture was stirred for 1 h at −78 °C. The reaction was then allowed to warm up to room temperature, and the volatiles were removed in vacuo. Anhydrous methanol (4 mL) was added and the resulting mixture was stirred for 10 minutes prior to concentration in vacuo. The
resulting residue was treated with methanol (4 mL) for 10 minutes and was concentrated 
in vacuo. This process was repeated for three times. The resulting crude product was 
then purified by preparative reverse-phase HPLC (10–40% CH$_3$CN/H$_2$O over 25 min, 
both CH$_3$CN and H$_2$O containing 0.1% TFA) and lyophilized to afford 50 as a white 
floppy powder (15.0 mg, 76%).

**Physical state:** white powder;

$^1$H NMR (600 MHz, methanol-$d_4$): $\delta$ 4.61 (dd, $J = 8.4$ Hz, 6.0 Hz, 1H), 4.17 (d, $J = 
7.8$ Hz, 1H), 3.97–3.93 (m, 1H), 3.75–3.71 (m, 1H), 3.64 (s, 3H), 2.33–2.24 (m, 2H), 
2.19–2.13 (m, 1H), 2.08–1.98 (m, 3H), 1.80–1.74 (m, 1H), 1.05 (d, $J = 6.6$ Hz, 3H), 
1.00 (d, $J = 6.6$ Hz, 3H), 0.96 (d, $J = 6.6$ Hz, 3H), 0.92 (d, $J = 6.6$ Hz, 3H) ppm;

$^{13}$C NMR (151 MHz, methanol-$d_4$): $\delta$ 179.3, 173.5, 159.4, 59.7, 57.9, 52.7, 31.7, 31.0, 
29.8, 26.2, 21.4, 21.2, 19.6, 18.8 ppm;

HRMS (ESI-TOF, m/z): Calcd for C$_{16}$H$_{26}$BN$_3$O$_5$ [M–H$_2$O+H]$^+$ 354.2195; found 
354.2189;

$\left[\alpha\right]_D^{20} = -81.1$ (c 0.44, MeOH).
Synthesis of Elastase Inhibitors 51 and 52

Figure S38. Synthesis of 51 and 52.
(tert-butoxycarbonyl)-L-valyl-L-prolyl-L-valine (S60)

Cbz deprotection: A 100 mL flask equipped with a stirrer bar was charged with Z-L-Pro-L-Val-OMe (66) (S59, 1.95 g, 5.4 mmol), 10% Pd/C (98 mg, 5 wt%), and MeOH (25 mL). This flask was then evacuated and backfilled with H₂ from a balloon for three times. The reaction mixture was stirred at room temperature for 6 h and was filtered through a thin pad of celite which was then rinsed with MeOH (10 mL). The filtrate was concentrated in vacuo to give the corresponding amine as colorless oil.

Amide bond formation: The aforementioned amine was treated sequentially with Boc-L-Valine (1.17 g, 5.4 mmol, 1.0 equiv.), HOBt•H₂O (83 mg, 0.61 mmol, 0.11 equiv.), and CH₂Cl₂ (25 mL). The resulting solution was cooled to 0 °C before DCC (1.23 g, 6.0 mmol, 1.1 equiv.) was added. The reaction mixture was allowed to stir at 0 °C for 30 min and then at room temperature overnight. The resulting mixture was filtered through a pad of celite; the filtrate was concentrated in vacuo, redissolved in EtOAc, and washed with 0.1N aq. HCl, 0.1 M aq. NH₄OH, and brine successively. The organic layer was dried over anhydrous Na₂SO₄, concentrated in vacuo, and purified by flash column chromatography (silica gel, 2:1 EtOAc:hexanes) to give Boc-L-Val-L-Pro-L-Val-OMe (1.32 g) as a colorless oil.

Hydrolysis of ester: A 25 mL flask equipped with a stirrer bar was charged with Boc-L-Val-L-Pro-L-Val-OMe (1.32 g) and THF (3 mL). LiOH (4 mL, 1 M aqueous solution) was added and the resulting solution was allowed to stir vigorously at room temperature...
for 12 h. 1 N HCl was added to the reaction mixture until pH = 2–3 and the mixture was extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated in vacuo to give S60 (1.24 g, 53% over 3 steps) as a white foam, which was used in the next step without further purification.

**Compound S61**

1,3-dioxoisooindolin-2-yl (tert-butoxycarbonyl)-L-valyl-L-prolylvalinate (S61)

On 10.0 mmol scale, General Procedure A was followed with Boc-L-valyl-L-prolyl-L-valine (S60). Purification by flash column chromatography (silica gel, 1:1 EtOAc:hexanes) furnished S61 (4.7 g, 84%).

**Physical state:** white foam;

\[ R_f = 0.50 \] (silica gel, 1:2 hexane: EtOAc);

\[ ^1H \text{ NMR (600 MHz, CDCl}_3\):} \delta 7.88 – 7.85 (m, 2H), 7.79 – 7.76 (m, 2H), 7.50 (d, J = 8.4 Hz, 1H), 5.28 (d, J = 9.6 Hz, 1H), 4.84 (dd, J = 8.4 Hz, 4.8 Hz, 1H), 4.62 (dd, J = 7.8 Hz, 3.0 Hz, 1H), 4.28 (dd, J = 9.6 Hz, 6.6 Hz, 1H), 3.71 – 3.77 (m, 1H), 3.60 (dt, J = 8.4 Hz, 3.6 Hz, 1H), 2.43 – 2.39 (m, 1H), 2.37 – 2.31 (m, 1H), 2.11 – 2.19 (m, 1H), 1.88 – 2.02 (m, 3H), 1.41 (s, 9H), 1.08 (d, J = 6.6 Hz, 3H), 1.07 (d, J = 6.6 Hz, 3H), 0.98 (d, J = 7.2 Hz, 3H), 0.92 (d, J = 7.2 Hz, 3H) ppm;

\[ ^{13}C \text{ NMR (151 MHz, CDCl}_3\):} \delta 172.9, 171.1, 168.3, 161.7, 156.0, 134.9, 129.0, 124.1, 79.7, 60.0, 57.0, 56.1, 47.9, 31.60, 31.56, 28.5, 27.1, 25.4, 19.7, 18.9, 17.8, 17.6 ppm;

**HRMS (ESI-TOF, m/z):** Calcd for C₂₈H₃₉N₄O₈ [M+H]^+ 559.2762; found 559.2757.

\[ [\alpha]^{20}_D = -86.2 \] (c 1.0, CHCl₃).
Compound S62

\[
\text{tert-butyl } ((S)-3\text{-methyl-1-}((S)-2-((R)-2\text{-methyl-1-}(4,4,5,5\text{-tetramethyl-1,3,2-dioxaborolan-2-yl})propyl)carbamoyl)pyrrolidin-1-yl)-1\text{-oxobutan-2-yl})\text{carbamate (S62)}
\]

On 1.1 mmol scale, General Procedure C was followed with S61 and suspension C (NiCl\(_2\)•6H\(_2\)O/di-rBubipy in THF), 1.0 equiv. of MgBr\(_2\)•Et\(_2\)O was used in this case. Purification by flash column chromatography (silica gel, 2:3 EtOAc:hexanes to 3:1 EtOAc:hexanes) furnished S62 (257 mg, 47%).

**Physical state:** slight yellow oil;  
\(R_f = 0.65\) (silica gel, 1:2 hexanes: EtOAc);

\(^1\text{H NMR (600 MHz, CDCl}_3\)):\(\delta 7.08\) (br s, 1H), 5.22 (d, \(J = 9.3\) Hz, 1H), 4.66 (dd, \(J = 8.2\) Hz, 2.6 Hz, 1H), 4.28 (dd, \(J = 9.3\) Hz, 6.0 Hz, 1H), 3.70 (q, \(J = 8.7\) Hz, 1H), 3.56 (ddd, \(J = 9.7\) Hz, 8.1 Hz, 3.7 Hz, 1H), 2.97 – 2.86 (m, 1H), 2.41 – 2.38 (m, 1H), 2.19 – 2.11 (m, 1H), 2.01 – 1.94 (m, 2H), 1.94 – 1.80 (m, 2H), 1.43 (s, 9H), 1.25 (d, \(J = 5.4\) Hz, 12H), 0.97 (d, \(J = 6.8\) Hz, 3H), 0.95 (d, \(J = 6.8\) Hz, 3H), 0.93 (d, \(J = 6.8\) Hz, 3H), 0.91 (d, \(J = 6.7\) Hz, 3H) ppm;

\(^{13}\text{C NMR (151 MHz, CDCl}_3\)):\(\delta 172.8, 171.8, 156.0, 83.3, 79.8, 59.0, 56.9, 47.7, 31.6, 29.8, 28.5, 27.0, 25.3, 25.2, 25.1, 20.6, 20.3, 19.7, 17.5\) ppm;

**HRMS (ESI-TOF, m/z):** Calcd for C\(_{25}\)H\(_{47}\)BN\(_3\)O\(_6\) [M+H]\(^+\) 496.3552; found 496.3550.  
\([\alpha]_D^{20} = -73.6\) (c 1.0, CHCl\(_3\)).
Compound 51

(1-((S)-1-((4-(((4-chlorophenyl)sulfonyl)carbamoyl)benzoyl)-L-valyl)pyrrolidine-2-carboxamido)-2-methylpropyl)boronic acid (51)

**Boc deprotection:** In a screw-capped culture tube equipped with a stir bar, S62 (55 mg, 0.11 mmol) was dissolved in CH₂Cl₂ (1 mL). TFA (1 mL) was added at 0 °C and the resulting solution was allowed to stir at 0 °C for 2 h. The volatiles were removed *in vacuo* using a rotary evaporator (water bath temperature < 25 °C), and the residue was used in next step without purification.

**Esterification:** Benzoic acid S63 (45 mg, 0.13 mmol, 1.2 equiv.) and PyBOP (69 mg, 0.13 mmol, 1.2 equiv.) were then added and the mixture was dissolved in DMF (2.0 mL). N-methyl morpholine (49 μL, 0.45 mmol, 4.0 equiv.) was added and the reaction was allowed to stir at room temperature for 3 h. The mixture was then diluted with EtOAc, washed with brine, dried over anhydrous Na₂SO₄, concentrated *in vacuo*, and purified by flash column chromatography (silica gel, 10:1 CH₂Cl₂:MeOH) to give the pinacol boronate of 51 (69 mg) contaminated with some tripyrrolidinophosphine oxide. This mixture was used in the next step without further purification.

**Boronic ester exchange:** In a screw-capped culture tube equipped with a stir bar, the aforementioned mixture (53 mg) and PhB(OH)₂ (14 mg) was dissolved in Et₂O (3 mL). 2 N HCl (3 mL) was added and the resulting biphasic mixture was allowed to stir vigorously at room temperature for 36 h when it was extracted with EtOAc (5 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄, concentrated *in vacuo.*
The resulting residue was purified by preparative reverse-phase HPLC (20–80% CH$_3$CN/H$_2$O over 35 min, both CH$_3$CN and H$_2$O containing 0.1% TFA) and lyophilized to afford 51 (14.0 mg, 26% for 3 steps).

**Physical state:** white powder;

$^1$H NMR (600 MHz, methanol-$d_4$): $\delta$ 8.10 (d, $J = 8.4$ Hz, 2H), 7.94 – 7.90 (m, 4H), 7.66 (d, $J = 9.0$ Hz, 2H), 4.64 (dd, $J = 8.4$ Hz, 3.6 Hz, 1H), 4.61 (d, $J = 9.6$ Hz, 1H), 4.12 (dt, $J = 9.6$ Hz, 6.6 Hz, 1H), 3.82 (dt, $J = 9.6$ Hz, 6.6 Hz, 1H), 2.38 – 2.31 (m, 2H), 2.25-2.19 (m, 2H), 2.14 – 2.02 (m, 2H), 1.82 – 1.77 (m, 1H), 1.16 (d, $J = 6.6$ Hz, 3H), 1.10 (d, $J = 7.2$ Hz, 3H), 0.98 (d, $J = 6.6$ Hz, 3H), 0.94 (d, $J = 6.6$ Hz, 3H) ppm;

$^{13}$C NMR (151 MHz, methanol-$d_4$): $\delta$ 179.2, 173.0, 169.1, 166.9, 141.3, 139.5, 139.4, 135.9, 131.2, 130.3, 129.5, 128.9, 59.0, 57.9, 31.8, 31.1, 29.8, 26.3, 21.4, 21.2, 19.6, 19.5 ppm;

**HRMS (ESI-TOF, m/z):** Calcd for C$_{28}$H$_{35}$BClN$_4$O$_7$S [M-H$_2$O+H]$^+$ 617.2003; found 617.2002.

$[\alpha]_D^{20} = -72.2$ (c 0.36, MeOH).
Compound 52

\[
\text{HO} \quad \begin{array}{c}
\text{Me} \\
\text{Me} \\
\text{Me}
\end{array} \\
\text{B} \quad \begin{array}{c}
\text{HO} \\
\text{Me}
\end{array} \\
\text{HN} \quad \begin{array}{c}
\text{O} \\
\text{NH}
\end{array} \\
\text{O}
\]

(4-(((2S)-1-((2S)-2-((1-borono-2-methylpropyl)carbamoyl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl)carbamoyl)benzoyl)glycine (52)

Boc deprotection: In a screw-capped culture tube equipped with a stir bar, S62 (55 mg, 0.11 mmol) was dissolved in CH₂Cl₂ (1 mL). TFA (1 mL) was added at 0 °C and the resulting solution was allowed to stir at 0 °C for 2 h. The volatiles were removed in vacuo using a rotary evaporator (water bath temperature < 25 °C), and the residue was used in next step without purification.

Esterification: Benzoic acid S64 (37 mg, 0.13 mmol, 1.2 equiv.) and PyBOP (69 mg, 0.13 mmol, 1.2 equiv.) were then added and the mixture was dissolved in DMF (2.0 mL). N-methyl morpholine (49 μL, 0.45 mmol, 4.0 equiv.) was added and the reaction was allowed to stir at room temperature for 3 h. The mixture was then diluted with EtOAc, washed with brine, dried over anhydrous Na₂SO₄, concentrated in vacuo and purified by flash column chromatography (silica gel, 10:1 CH₂Cl₂: MeOH) to give the pinacol boronate (63 mg) which was used in the next step without further purification.

Global deprotection: In a culture tube equipped with a stir bar, the aforementioned pinacol boronic ester (32 mg) was dissolved in CH₂Cl₂ (1 mL). TFA (1 mL) was added at 0 °C and the resulting solution was allowed to stir at room temperature overnight. The volatiles were removed in vacuo using a rotary evaporator (water bath temperature < 25 °C), and the residue was purified by preparative reverse-phase HPLC (20–80% CH₃CN/H₂O over 40 min, both CH₃CN and H₂O containing 0.1% TFA) and lyophilized.
to afford 52 (13.0 mg, 52% over 3 steps).

**Physical state:** white powder;

\(^1\text{H NMR (600 MHz, methanol-\text{d}4)}: \delta 7.96 – 7.90 (m, 4H), 4.66 – 4.59 (m, 2H), 4.16 – 4.07 (m, 3H), 3.83 (dt, \(J = 10.1\) Hz, 6.8 Hz, 1H), 2.40 – 2.29 (m, 2H), 2.26 – 2.16 (m, 2H), 2.14 – 2.02 (m, 2H), 1.82 – 1.72 (m, 1H), 1.17 (d, \(J = 6.7\) Hz, 3H), 1.12 (d, \(J = 6.7\) Hz, 3H), 0.98 (d, \(J = 6.6\) Hz, 3H), 0.95 (d, \(J = 6.6\) Hz, 3H) ppm;.

\(^{13}\text{C NMR (151 MHz, methanol-\text{d}4)}: \delta 179.3, 173.1, 173.0, 169.50, 169.48, 138.1, 138.0, 128.8, 128.6, 59.0, 58.0, 42.3, 31.8, 31.1, 29.8, 26.3, 21.4, 21.2, 19.6, 19.5 ppm;

**HRMS (ESI-TOF, \(m/z\)):** Calcd for C\(_{24}\)H\(_{34}\)BN\(_4\)O\(_7\) [M-H\(_2\)O+H\(^+\)]\(^+\) 501.2515; found 501.2516;

\([\alpha]_D^{20} = -97.3\) (c 0.26, MeOH).
The pinacol $\alpha$-amino boronate S66a/S66b was prepared using the literature procedure (67) with slight modifications.

**Compound S66a**

(R)-2-methyl-N-((R)-2-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl)propane-2-sulfinamide (S66a)

A culture tube equipped with a stir bar was charged sequentially with PCy$_3$•HBF$_4$ (12 mg, 0.033 mmol, 1.2 mol%) , toluene (0.55 mL), aqueous CuSO$_4$ (1.1 mL, 0.03 M, 1.2 mol%) and benzylamine (15.3 $\mu$L, 0.14 mmol, 5 mol%). The mixture was stirred for 10 min at the room temperature when a solution of aldimine S65 (480 mg, 2.74 mmol, 1.0 equiv.) in toluene (5.0 mL) was added, followed by B$_2$pin$_2$ (1.39 g, 5.5 mmol, 2.0 equiv.). The mixture was stirred vigorously for 14 h, diluted with EtOAc and filtered.
through a silica gel plug eluting with EtOAc. The filtrate was concentrated and purified by flash column chromatography (silica gel, 1:3 EtOAc:hexanes) to give S66a (1.07 g, d.r. > 20:1) that was contaminated with impurities originating from B2pin2 which could be removed in the next step.

**Compound S66b**

(R)-2-methyl-N-((S)-2-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl)propane-2-sulfinamide (S66b)

To a culture tube equipped with a stir bar were added a solution of P(Ph)3 (0.33 mL, 0.1 M in toluene, 1.2 mol%), aqueous CuSO4 (1.1 mL, 0.03 M, 1.2 mol%), and benzylamine (15.3 μL, 0.14 mmol, 5 mol%) sequentially. The mixture was stirred for 10 min, after which a solution of aldimine S65 (480 mg, 2.74 mmol, 1.0 equiv.) in toluene (5.0 mL) and B2pin2 (1.39 g, 5.5 mmol, 2.0 equiv.) were added sequentially. The mixture was stirred vigorously for 14 h, diluted with EtOAc, and filtered through a silica gel plug eluting with EtOAc. The filtrate was concentrated in vacuo, and purified by flash column chromatography (silica gel, 1:3 EtOAc:hexanes) to give S66b (857 mg, d.r. = 6.1:1) contaminated with impurities originating from B2pin2 which could be removed in the next step.
The α-boronic amine hydrochloride S67a/S67b was prepared using the literature procedure (19).

**Compound S67a**

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{NH}_3\text{Cl} & \\
\text{B} & \quad \text{O} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\end{align*}
\]

(R)-2-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-amine hydrochloride (S67a)

S66a (190 mg, contaminated with B2pin2 impurities) was dissolved in 1,4-dioxane (1.2 mL) and methanol (0.1 mL) under argon. HCl (80 µL, 4.0 M in 1,4-dioxane) was added at room temperature and the resulting mixture was stirred at the same temperature before the volatiles were removed in vacuo. The resulting solid was triturated with a 2:1 mixture of hexanes and Et2O to give S67a (48 mg, 42 % over 2 steps).

**Physical state:** white solid;

\[\text{^1H NMR (600 MHz, CDCl}_3\text{)} \delta 8.23 (s, 3H), 2.79 (br s, 1H), 2.26 (pd, J = 6.9 Hz, 4.8 Hz, 1H), 1.28 (br s, 12H), 1.11 (d, J = 7.0 Hz, 3H), 1.10 (d, J = 7.0 Hz, 3H).\]

\[\text{^13C NMR (151 MHz, CDCl}_3\text{)} \delta 85.2, 44.4 (br), 29.3, 25.2, 24.8, 20.4, 19.9.\]

**HRMS (ESI-TOF, m/z):** Calcd for C16H23BNO2 [M+H]⁺ 200.1816; found 200.1812. \(\alpha\)\(\beta\) = -3.0 (c 1.0, CHCl3).

**Compound S67b**

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{NH}_3\text{Cl} & \\
\text{B} & \quad \text{O} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\end{align*}
\]

(S)-2-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-amine hydrochloride (S67b)
S66b (350 mg, contaminated with Bpin impurities) was dissolved in 1,4-dioxane (2.4 mL) and methanol (0.2 mL) under argon. HCl (0.16 mL, 4.0 M in 1,4-dioxane) was added at room temperature and the resulting mixture was stirred at the same temperature before the volatiles were removed in vacuo. The resulting solid was triturated with a 2:1 mixture of hexanes and Et₂O to give S67b (94 mg, 37% over 2 steps).

**Physical state:** white solid;

**¹H NMR (600 MHz, CDCl₃)** δ 8.25 (s, 3H), 2.80 (q, J = 5.6 Hz, 1H), 2.26 (pd, J = 6.9 Hz, 4.9 Hz, 1H), 1.28 (br s, 12H), 1.12 (d, J = 7.2 Hz, 3H), 1.11 (d, J = 7.2 Hz, 3H);

**¹³C NMR (151 MHz, CDCl₃)** δ 85.2, 44.5 (br), 29.3, 25.2, 24.8, 20.4, 19.9;

**HRMS (ESI-TOF, m/z):** Calcd for C₁₀H₂₃BNO₂ [M+H]+ 200.1816; found 200.1817;

[α]D²⁰ = +2.7 (c 1.0, CHCl₃).

**Compound S62a**

![Compound S62a](image)

To a culture tube charged with Boc-L-Val-L-Pro-OH (S68, 34 mg, 0.11 mmol, 1.2 equiv.) and 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU, 44 mg, 0.12 mmol, 1.3 equiv.) was added DMF (0.5 mL), followed by diisopropylethylamine (45 μL, 0.26 mmol, 2.9 equiv.). S67a (21 mg, 0.089 mmol) in DMF (1.0 mL) was added dropwise at 0 °C. After the completion of addition, the reaction was kept stirring at room temperature for 1 h. The mixture was diluted with Et₂O, washed with brine, dried over anhydrous Na₂SO₄, concentrated in vacuo. The resulting residue was purified by flash column chromatography (silica gel, 1:1 EtOAc:hexanes to 3:1 EtOAc:hexanes) to give S62a (32.3 mg, 73%) as a colorless
The NMR spectra of \textbf{S62a} are in agreements with those of \textbf{S62} prepared via decarboxylative borylation. This confirms the configuration of the stereocenter \( \alpha \) to boron in \textbf{S62} to be \( R \).

\textbf{Compound S62b}

To a culture tube charged with Boc-\textit{L}-Val-\textit{L}-Pro-OH (\textbf{S68}, 26 mg, 0.083 mmol, 1.2 equiv.) and 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-\textit{b}]pyridinium 3-oxid hexafluorophosphate (HATU, 34 mg, 0.089 mmol, 1.3 equiv.) was added DMF (0.5 mL), followed by diisopropylethylamine (35 \( \mu \)L, 0.2 mmol, 2.9 equiv.). \textbf{S67b} (16 mg, 0.068 mmol, 1.0 equiv.) in DMF (1.0 mL) was added dropwise at 0 \(^\circ\)C. After the completion of addition, the reaction was kept stirring at room temperature for 1 h. The mixture was diluted with \( \text{Et}_2\text{O} \), washed with brine, dried over anhydrous \( \text{Na}_2\text{SO}_4 \), concentrated \textit{in vacuo}, and purified by flash column chromatography (silica gel, 1:1 \( \text{EtOAc:hexanes} \) to \( \text{EtOAc} \)) to give \textbf{S62b} (22 mg, 65\%) as a colorless oil.

\textbf{Physical state}: colorless oil;

\( R_f = 0.60 \) (silica gel, 1:2 \( \text{EtOAc:hexanes} \));

\[ ^1\text{H NMR (600 MHz, CDCl}_3\] \( \delta \) 7.08 (br s, 1H), 5.21 (d, \( J = 9.3 \) Hz, 1H), 4.65 (dd, \( J = 8.2 \) Hz, 2.3 Hz, 1H), 4.28 (dd, \( J = 9.4 \) Hz, 6.1 Hz, 1H), 3.70 (td, \( J = 9.4 \) Hz, 7.1 Hz, 1H), 3.56 (ddd, \( J = 9.6 \) Hz, 8.1 Hz, 3.4 Hz, 1H), 2.94 (td, \( J = 5.7 \) Hz, 2.6 Hz, 1H), 2.39 (ddd, \( J = 12.8 \) Hz, 6.1 Hz, 2.6 Hz, 1H), 2.14 – 2.05 (m, 1H), 1.98 (dtd, \( J = 12.3 \) Hz, 6.8 Hz, 3.5 Hz, 2H), 1.88 (tdd, \( J = 11.3 \) Hz, 9.0 Hz, 5.8 Hz, 2H), 1.42 (s, 9H), 1.21 (d, \( J = 6.3 \) Hz, 3H).
Hz, 12H), 1.00 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H), 0.91 (d, J = 6.8 Hz, 6H) ppm;

\textsuperscript{13}C NMR (151 MHz, CDCl\textsubscript{3}) \(\delta\) 172.9, 171.8, 156.0, 83.1, 79.8, 59.0, 56.9, 47.7, 45.5, 31.6, 29.8, 28.5, 27.2, 25.2, 25.12, 25.10, 20.4, 20.3, 19.9, 17.7 ppm.

The NMR spectra of \textit{S62b} differ from those of \textit{S62}.
Elastase Inhibition Assay

Figure S40. Structures of selected elastase inhibitors.

Materials and methods:

Compounds 50–58, 50a, 50b, and 51a were subjected to this assay.

Serially diluted compounds in DMSO were dispensed into a 384-well black opaque plate by Echo dispenser. 0.1 μg/mL human neutrophil elastase (EPC, Catalog# SE563, Owensville, MS) or human sputum diluted with assay buffer (100 mM HEPES, 500 mM NaCl, 0.02% Tween 20) was added into the 384-well plate, and was incubated with different compounds at different concentrations for 30 minutes at room temperature. The final concentration of DMSO in the reaction was 0.1%. Elastase substrate MeOSuc-AAPV-AMC (Bachem, Catalog # I-1270, Torrance, CA) of 100 μM final concentration was then added into the reaction system just before enzyme kinetics were read on PheraSTAR plate reader at excitation of 380 nm and emission of 460 nm with a 3-minutes interval for 30 minutes in total. Slope of fluorescence intensity vs. time representing the V_max of enzyme activity was calculated with MARS software. %relative inhibition was calculated as:

$$\frac{Slope_{DMSO} - Slope_{inhibitor}}{Slope_{DMSO}} \times 100\%$$

IC_{50} was calculated based on the % relative inhibition curve using log(agonist) vs.
response (three parameters) method with Prism software. All experiments were performed in triplicate for at least three independent times. The IC\textsubscript{50} results of all experiments are shown as the average of triplicates with error bar indicating standard deviation as indicated in individual figures. For compounds 51, 52, and 58, the assay above was repeated with 2.5, 25, 50 and 100 μM of elastase substrate (MeOSuc-AAPV-AMC) and Ki/nM values were calculated based on these results using the mixed model (68).

**Quantification of elastase concentration in human sputum:**

Human sputum was purchased from Discovery Life Sciences (Los Osos, CA). Human sputum was diluted 1:10 in volume with assay buffer (100 mM HEPES, 500 mM NaCl, 0.02% Tween 20) followed by vigorous vortexing. The 1:10 diluted human sputum was further diluted into 1:30, 1:90, 1:270, 1:810, and 1:2430. The elastase concentration was determined by elastase inhibition assay as described above. Specifically, a series of standards of human neutrophil elastase (starting at 2 μg/mL and further diluted 1:2 in volume) were prepared in the assay buffer. The samples and standards were plated in a 384-well black solid bottom plate; the substrate MeOSuc-AAPV-AMC of 100 μM final concentration was then added into the reaction system just before enzyme kinetics were read on PheraSTAR plate reader as mentioned above. The slope of enzymatic kinetic reading was calculated by MARS software. The elastase levels of the human sputum were calculated based on the standard curve.
**Table S13.** IC\textsubscript{50} and LipE of selected elastase inhibitors.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Purified NHE</th>
<th>CF sputum</th>
<th>COPD sputum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IC\textsubscript{50}/nM</td>
<td>LipE</td>
<td>IC\textsubscript{50}/nM</td>
</tr>
<tr>
<td>50–B(OH)\textsubscript{2}</td>
<td>0.27±0.02</td>
<td>8.37</td>
<td>0.51±0.04</td>
</tr>
<tr>
<td>50a–C(O)CF\textsubscript{3}</td>
<td>134.9±12.2</td>
<td>4.57</td>
<td>358.3±54.5</td>
</tr>
<tr>
<td>50b–CO\textsubscript{2}H</td>
<td>Not Active</td>
<td>N.A.</td>
<td>N.A.</td>
</tr>
<tr>
<td>51–B(OH)\textsubscript{2}</td>
<td>0.030±0.002</td>
<td>7.33</td>
<td>0.096±0.002</td>
</tr>
<tr>
<td>51a–C(O)CF\textsubscript{3}</td>
<td>289.8±32.1</td>
<td>1.95</td>
<td>833.4±220.5</td>
</tr>
<tr>
<td>52–B(OH)\textsubscript{2}</td>
<td>0.015±0.001</td>
<td>10.1</td>
<td>0.043±0.002</td>
</tr>
<tr>
<td>53</td>
<td>2.62±0.39</td>
<td>7.32</td>
<td>4.08±0.39</td>
</tr>
<tr>
<td>54</td>
<td>0.031±0.002</td>
<td>6.76</td>
<td>0.40±0.04</td>
</tr>
<tr>
<td>55</td>
<td>0.093±0.008</td>
<td>18.6</td>
<td>0.48±0.03</td>
</tr>
<tr>
<td>56</td>
<td>1.34±0.13</td>
<td>4.59</td>
<td>2.68±0.04</td>
</tr>
<tr>
<td>57</td>
<td>0.99±0.13</td>
<td>9.46</td>
<td>2.04±0.08</td>
</tr>
<tr>
<td>58</td>
<td>0.0111±0.0002</td>
<td>5.04</td>
<td>202.8±31.2</td>
</tr>
</tbody>
</table>

Note: (1) Average ± SD, n=3 plotted, representative of 3 independent, triplicate experiments. A non-linear, 3-parameter log inhibitor curve was used to calculate the IC\textsubscript{50} values. Curve fit statistics: purified HNE, \(R^2 \geq 0.95\), CF patient sputum, \(R^2 \geq 0.93\), COPD patient sputum, \(R^2 \geq 0.93\).

(2) LipE value is calculated based on the formula LipE=pIC\textsubscript{50}–logP where pIC\textsubscript{50}=–logIC\textsubscript{50} and logP is calculated using SEURAT software (69).
**Figure S41.** Inhibitory activity of selected elastase inhibitors.

**Table S14.** Ki values of 51, 52 and 53.

<table>
<thead>
<tr>
<th>Compound</th>
<th>51</th>
<th>52</th>
<th>58</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ki/nM</td>
<td>0.034</td>
<td>0.0037</td>
<td>0.0027</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>0.002</td>
<td>0.0005</td>
<td>0.0029</td>
</tr>
</tbody>
</table>

*Note: Measurements were performed in 3 replicates and average values were reported.*
Time Dependence of Elastase Inhibition

Method:
The procedure for the elastase inhibition assay (Page S164-166) was followed with slight modifications. 0.1 μg/mL human neutrophil elastase was incubated with a range of concentrations of inhibitors for 5, 15, 30 and 60 minutes before substrate MeOSuc-AAPV-AMC of 100 μM final concentration was added. Enzyme kinetics were read on PheraSTAR plate reader and IC\textsubscript{50} was calculated with the method described above.

Table S15. Result of time dependence experiment.

<table>
<thead>
<tr>
<th>Compound</th>
<th>51</th>
<th>52</th>
<th>58</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IC\textsubscript{50}/nM</td>
<td>Standard deviation</td>
<td>IC\textsubscript{50}/nM</td>
</tr>
<tr>
<td>5 min</td>
<td>0.027</td>
<td>0.002</td>
<td>0.0040</td>
</tr>
<tr>
<td>15 min</td>
<td>0.030</td>
<td>0.007</td>
<td>0.0047</td>
</tr>
<tr>
<td>30 min</td>
<td>0.037</td>
<td>0.005</td>
<td>0.0042</td>
</tr>
<tr>
<td>60 min</td>
<td>0.026</td>
<td>0.010</td>
<td>0.0042</td>
</tr>
</tbody>
</table>

Note: Measurements were performed in 3 replicates and average values were reported.

Figure S42. Time dependence curves of 51, 52 and 58.
Plasma Stability Assay

Materials:

1) Compounds 50, 50a, 51, 51a and 52 were tested. Propantheline was used as the reference compound in this assay; all stock solutions were stored at −40°C before use.

2) Test system: CD-1 Mouse Plasma from a minimum of 20 male individuals were obtained from BioreclamationIVT (Catalog #: MSEPLEDTA2-M; Batch #: MSE244515). EDTA-K2 was used as the anticoagulant.

Procedure:
The frozen plasma was thawed in a water bath at 37 °C prior to the experiments. The plasma was centrifuged at 4000 rpm for 5 min and the clots were removed if necessary. The pH was adjusted to 7.4 ± 0.1 as necessary. An intermediate solution (1 mM) was prepared and a 100 μM dosing solution was prepared by diluting 10 μL of the intermediate solution with 90 μL 45% MeOH/H₂O. Duplicate of test samples were made by mixing 98 μL of blank plasma with 2 μL of dosing solution (100 μM) to achieve the final concentration of 2 μM. Samples were incubated at 37 °C. At each time point (0, 10, 30, 60, and 120 min), 400 μL of stop solution (consisting of 200 ng/mL tolbutamide and 20 ng/mL buspirone in 50% MeOH/CH₃CN) was added to precipitate protein under thorough mixing. The sample plates were then centrifuged at 4,000 rpm for 10 min. An aliquot of supernatant (100 μL) was transferred from each well and mixed with 200 of μL ultrapure water. The samples were shaken at 800 rpm for about 10 min before LC-MS/MS analysis.
**Data analysis**: The % remaining of test compound after incubation in plasma was calculated using following equation:

\[
% \text{ Remaining} = 100 \times \frac{P_{AR \ at \ T_n}}{P_{AR \ at \ T_0}}
\]

where \( P_{AR} \) is the peak area ratio of analyte versus internal standard (IS) and the appointed incubation time points are \( T_0 \) (0 min), \( T_n \) (n=0, 10, 30, 60, 120 min).

**LC-MS/MS condition**: Each compound was analyzed by LC/MS using an ACE 5-phenyl 50×2.1 mm column (Part No. ACE-125-0502) with 0.1% formic acid in water and 0.1% formic acid in acetonitrile as the mobile phases. Tobultamide was used as the internal standard. Data collected were processed by Analyst 1.6.2 software and MultiQuant 3.0.2 software.
Table S16. Result of plasma stability assay.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Species / Matrix</th>
<th>Time Point (min)</th>
<th>% Remaining (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>CD-1 Mouse Plasma</td>
<td>0</td>
<td>100.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>100.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30</td>
<td>105.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60</td>
<td>88.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>120</td>
<td>76.7</td>
</tr>
<tr>
<td>50a</td>
<td>CD-1 Mouse Plasma</td>
<td>0</td>
<td>100.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>101.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30</td>
<td>98.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60</td>
<td>100.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>120</td>
<td>92.5</td>
</tr>
<tr>
<td>51</td>
<td>CD-1 Mouse Plasma</td>
<td>0</td>
<td>100.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>90.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30</td>
<td>79.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60</td>
<td>84.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>120</td>
<td>90.3</td>
</tr>
<tr>
<td>51a</td>
<td>CD-1 Mouse Plasma</td>
<td>0</td>
<td>100.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>99.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30</td>
<td>109.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60</td>
<td>99.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>120</td>
<td>106.6</td>
</tr>
<tr>
<td>52</td>
<td>CD-1 Mouse Plasma</td>
<td>0</td>
<td>100.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>116.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30</td>
<td>104.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60</td>
<td>96.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>120</td>
<td>79.2</td>
</tr>
<tr>
<td>Propantheline</td>
<td>CD-1 Mouse Plasma</td>
<td>0</td>
<td>100.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>76.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30</td>
<td>39.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60</td>
<td>21.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>120</td>
<td>7.7</td>
</tr>
</tbody>
</table>
Mouse Liver Microsomal Metabolic Stability Assay

Materials:
1) Compounds 50, 50a, 51, 51a, and 52 were tested in this assay. Testosterone, Dichlofenac, and Propafenone were used as control.

2) **Buffers:**
   1. 100 mM potassium phosphate buffer, pH 7.4.
   2. 10 mM MgCl₂

3) **Compound Dilution:**
   Intermediate solution was prepared by diluting 5 μL of compound or control stock solution (10 mM in DMSO) with DMSO (45 μL) and 1:1 methanol/water (450 μL) (concentration=100 μM, 45% MeOH). Working solution was prepared by diluting 50 μL of the intermediate solution with 450 μL of 100 mM potassium phosphate buffer, pH=7.4 (centration= 10 μM, 4.5%MeOH).

4) **NADPH regenerating system** (final Isocitric dehydrogenase concentration = 1 unit/mL at incubation) comprised:
   β-Nicotinamide adenine dinucleotide phosphate acquired from Sigma (Catalog # N0505), isocitric acid from Sigma (Cat. No. I1252) and isocitric dehydrogenase from Sigma (Catalog # I2002).

5) **Liver microsome solution** (final concentration of 0.5 mg protein/mL) was prepared using Mouse liver microsomes from Xenotech (Catalog # M1000, Lot # 1310028).

6) **Stop solution**: Cold acetonitrile containing 100 ng/mL Tolbutamide and 100 ng/mL Labetalol as internal standards (IS)
Procedure:

10 µL/well of compound working solution or control working solution was added to all plates (T0, T5, T10, T20, T30, T60, NCF60) except the matrix blank. 80 µL/well of microsome solution was added to every plate. The mixtures of microsome solution and compound were incubated at 37 °C for about 10 min. 10 µL/well of NADPH regenerating system (pre-warmed to 37 °C) was then added to every plate to start the reaction. The plates were incubated for the durations indicated (matrix blank: 1 h; T60: 1 h; T30: 31 min; T20: 40 min; T10 50min; T5: 55min). For NCF60 (abbreviation of no co-factor) no NADPH regenerating system was added, but was replaced by 10 µL/well of potassium phosphate buffer (100 mM, pH 7.4); the resulting mixture was incubated at 37 °C for 1 h.

The reactions were then terminated with the stop solution (cold at 4 °C) containing 100 ng/mL Tolbutamide and 100 ng/mL Labetalol (300 µL/well). The sampling plates were shaken for approximately 10 minutes, then were centrifuged at 4000 rpm for 20 min at 4 °C. While centrifuging, 8 new 96 well plates were loaded with 300 µL of HPLC grade water. 100 µL of supernatant was finally added to 300 µL of HPLC grade water and mixed for LC/MS/MS analysis.

Apricott pipetting robot was used for all additions, mixing, and transformations described above in 96-well plate format.

Data Analysis

The equation of first order kinetics was used to calculate $T_{1/2}$ and $\text{CL}_{\text{int(mic)}}$:

$$C_t = C_o \cdot e^{-k_e \cdot t}$$

when $C_t = \frac{1}{2} C_o$, $T_{1/2} = \frac{\ln 2}{k_e} = 0.693/k_e$

$$\text{CL}_{\text{int(mic)}} = \frac{0.693}{\text{in vitro } T_{1/2}} \cdot \left( \frac{1}{mg/mL \text{ microsomal protein in reaction system}} \right)$$

$$\text{CL}_{\text{int(liver)}} = \text{CL}_{\text{int(mic)}} \cdot \left( \frac{mg \text{ microsomes}}{g \text{ liver}} \right) \cdot \left( \frac{g \text{ liver}}{Kg \text{ body weight}} \right)$$
Table S17. Result of mouse liver microsomal metabolic stability assay.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>MLM 0.5</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>Remaining (T=60min)</th>
<th>Remaining (*NCF=60min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R²</td>
<td>T½ (min)</td>
<td>CL\text{(mic)} (μL/min/mg)</td>
<td>CL\text{(liver)} (mL/min/kg)</td>
<td>Extraction ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>0.8919</td>
<td>&gt; 145</td>
<td>&lt; 9.6</td>
<td>&lt; 38.0</td>
<td>&lt; 0.3</td>
<td>78.5%</td>
<td>99.0%</td>
</tr>
<tr>
<td>50a</td>
<td>0.6722</td>
<td>&gt; 145</td>
<td>&lt; 9.6</td>
<td>&lt; 38.0</td>
<td>&lt; 0.3</td>
<td>92.9%</td>
<td>82.3%</td>
</tr>
<tr>
<td>51</td>
<td>0.2713</td>
<td>&gt; 145</td>
<td>&lt; 9.6</td>
<td>&lt; 38.0</td>
<td>&lt; 0.3</td>
<td>85.8%</td>
<td>95.0%</td>
</tr>
<tr>
<td>51a</td>
<td>0.9190</td>
<td>71.6</td>
<td>19.4</td>
<td>76.6</td>
<td>0.5</td>
<td>52.2%</td>
<td>91.7%</td>
</tr>
<tr>
<td>52</td>
<td>0.4436</td>
<td>&gt; 145</td>
<td>&lt; 9.6</td>
<td>&lt; 38.0</td>
<td>&lt; 0.3</td>
<td>78.9%</td>
<td>103.6%</td>
</tr>
<tr>
<td>Testosterone</td>
<td>0.9992</td>
<td>2.3</td>
<td>597.4</td>
<td>2365.5</td>
<td>1.0</td>
<td>0.0%</td>
<td>70.3%</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>0.9820</td>
<td>51.0</td>
<td>27.2</td>
<td>107.6</td>
<td>0.5</td>
<td>43.0%</td>
<td>88.0%</td>
</tr>
<tr>
<td>Propafenone</td>
<td>0.9858</td>
<td>1.3</td>
<td>1.3</td>
<td>4188.4</td>
<td>1.0</td>
<td>0.2%</td>
<td>84.3%</td>
</tr>
</tbody>
</table>

Notes: 1) * NCF: the abbreviation of no co-factor. No NADPH regenerating system was added into NCF samples (replaced by buffer) during the 60 min-incubation, if the NCF remaining is less than 60%, then Non-NADPH dependent occurs.
2) R² is the correlation coefficient of the linear regression for the determination of kinetic constant.
3) T½ is half-life and CL\text{(mic)} is the intrinsic clearance.
4) \( \frac{mg \text{ microsomes}}{g \text{ liver}} = 45mg/g \) for five species.
5) \( \frac{g \text{ liver weight}}{Kg \text{ body weight}} = 88g/Kg \) for mouse.
6) Hepatic blood clearance (CLH) = \( \frac{CL\text{(liver)}\times Qh}{CL\text{(liver)}+Qh} \)

Hepatic extraction ratio (EH) = \( \frac{CLH}{QH} = \frac{CL\text{(liver)}}{CL\text{(liver)}+Qh} \)

Whereby Qh(mL/min/Kg liver) = 90.0 mL/min/Kg for mouse liver
Kinetic Solubility Test

Materials:
Compounds 50, 50a, 51, 51a, and 52 were tested.

Procedure:
The stock solution of each compound (10 µL; 10 mM in DMSO) was diluted with phosphate buffer solution (490 µL; 50 mM, pH 6.8). The resulting mixture was shaken for 24 h. Samples were then filtered. Kinetic solubility was then determined by UV spectroscopy [calibrated by a standard curve (1, 20, and 200 µM)].

Table S18. Result of kinetic solubility test.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Kinetic Solubility pH=6.8 (µg/mL)</th>
<th>Kinetic Solubility pH=6.8 (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>&gt;74.25</td>
<td>&gt;200.00</td>
</tr>
<tr>
<td>50a</td>
<td>&gt;84.69</td>
<td>&gt;200.00</td>
</tr>
<tr>
<td>51</td>
<td>&gt;126.99</td>
<td>&gt;200.00</td>
</tr>
<tr>
<td>51a</td>
<td>119.75</td>
<td>174.28</td>
</tr>
<tr>
<td>52</td>
<td>&gt;103.67</td>
<td>&gt;200.00</td>
</tr>
</tbody>
</table>
**Caco-2 Permeability Assay**

**Materials:**

1) **Caco-2 culture:** Caco-2 cells purchased from ATCC were seeded onto polyethylene membranes (PET) in 96-well BD Insert plates at 1 x 10^5 cells/cm², and refreshed medium every 4~5 days until to the 21st to 28th day for confluent cell monolayer formation.

2) **Compound information:** compounds 51 and 51a were subjected to the assay. Digoxin, fenoterol, and propranolol were used as standards respectively.

**Transport method:**
The transport buffer used in the study was HBSS with 10 mM HEPES at pH 7.40±0.05. Compounds were tested at 2 μM bi-directionally in duplicates. Digoxin was tested at 10 μM bi-directionally in a duplicate, while fenoterol and propranolol were tested at 2 μM in A(apical) to B (basolateral) direction in duplicates. The final DMSO concentration was adjusted to less than 1%. The plate was incubated for 2 hours in a CO₂ incubator at 37±1°C, with 5% CO₂ at saturated humidity without shaking. All samples, after mixing with acetonitrile containing internal standard, were centrifuged at 4000 rpm for 20 min. Subsequently,100 μL supernatant solution was diluted with 100 μL distilled water for LC/MS/MS analysis. Concentrations of test and control compounds in starting solution, donor solution, and receiver solution were quantified by LC/MS/MS methodologies, using peak area ratio of analyte/internal standard. After transport assay, lucifer yellow rejection assay was applied to determine the Caco-2 cell monolayer integrity. All data presented herein have passed this test.

**Data analysis:** The apparent permeability coefficient Papp (cm/s) was calculated using the equation:
\[ P_{app} = \left( \frac{dC_r}{dt} \right) \cdot \frac{V_r}{(A \cdot C_0)} \]

Where \( \frac{dC_r}{dt} \) is the cumulative concentration of compound in the receiver chamber as a function of time (µM/s); \( V_r \) is the solution volume in the receiver chamber (0.075 mL on the apical side, 0.25 mL on the basolateral side); \( A \) is the surface area for the transport, \( i.e. \) 0.0804 cm\(^2\) for the area of the monolayer; \( C_0 \) is the initial concentration in the donor chamber (µM).

The efflux ratio was calculated using the equation:

\[ \text{Efflux ratio} = \frac{P_{app}(BA)}{P_{app}(AB)} \]

Percent recovery was calculated using the equation:

\[ \% \text{ Recovery} = 100 \times \left[ (V_r \cdot C_r) + (V_d \cdot C_d) \right] / (V_d \cdot C_0) \]

Where \( V_d \) is the volume in the donor chambers (0.075 mL on the apical side, 0.25 mL on the basolateral side); \( C_d \) and \( C_r \) are the final concentrations of transport compound in donor and receiver chambers, respectively.

**LC/MS conditions**: Each compound was analyzed by LC/MS using an ACE 5-phenyl 50×2.1 mm column (Part No. ACE-125-0502) with 0.1% formic acid in water and 0.1% formic acid in acetonitrile as the mobile phases. Tobultamide was used as the internal standard. Data collected were processed by Analyst 1.6.2 software and MultiQuant 3.0.2 software.
Table S19. Result of Caco-2 permeability assay.

<table>
<thead>
<tr>
<th>Compound ID</th>
<th>Mean $P_{\text{app}}$ (10$^{-6}$ cm/s)</th>
<th>Efflux Ratio</th>
<th>Mean Recovery %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A to B</td>
<td>B to A</td>
<td>A to B</td>
</tr>
<tr>
<td>Fenoterol</td>
<td>0.24</td>
<td>ND</td>
<td>–</td>
</tr>
<tr>
<td>Propranolol</td>
<td>19.76</td>
<td>ND</td>
<td>–</td>
</tr>
<tr>
<td>Digoxin</td>
<td>&lt;0.02</td>
<td>8.50</td>
<td>&gt;364.02</td>
</tr>
<tr>
<td>51</td>
<td>&lt;0.16</td>
<td>0.61</td>
<td>&gt;3.91</td>
</tr>
<tr>
<td>51a</td>
<td>&lt;0.08</td>
<td>&lt;0.12</td>
<td>NA</td>
</tr>
</tbody>
</table>

Note:

1) For digoxin and test compound, the signal responses in receiver samples were lower than the limit of quantification. For the convenience of calculating $P_{\text{app}}$ values, 50 was used as the peak area of analyte in receiver samples instead.

2) The permeation was assessed over a 120-minute incubation at 37±1°C and 5% CO$_2$ with saturated humidity.
X-ray Crystallographic Data for Compound 28

Table S20. Crystal data and structure refinement for 28.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification code</td>
<td>CCDC 1525341</td>
</tr>
<tr>
<td>Empirical formula</td>
<td>C19 H36 B N O4</td>
</tr>
<tr>
<td>Molecular formula</td>
<td>C19 H36 B N O4</td>
</tr>
<tr>
<td>Formula weight</td>
<td>353.30</td>
</tr>
<tr>
<td>Temperature</td>
<td>100.0 K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P 1 21/c 1</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 10.7315(3) Å  β= 90°.</td>
</tr>
<tr>
<td></td>
<td>b = 17.6585(4) Å</td>
</tr>
<tr>
<td></td>
<td>c = 11.5200(3) Å</td>
</tr>
<tr>
<td></td>
<td>α= 90°.</td>
</tr>
<tr>
<td>Volume</td>
<td>2087.69(9) Å</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.124 Mg/m³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.076 mm⁻¹</td>
</tr>
<tr>
<td>F(000)</td>
<td>776</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.271 x 0.235 x 0.096 mm³</td>
</tr>
<tr>
<td>Crystal color, habit</td>
<td>Colorless Block</td>
</tr>
<tr>
<td>Theta range for data collection</td>
<td>1.984 to 26.372°</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-13&lt;=h&lt;=13, -21&lt;=k&lt;=22, -13&lt;=l&lt;=11</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>12673</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>4204 [R(int) = 0.0267, R(sigma) = 0.0283]</td>
</tr>
<tr>
<td>Completeness to theta = 25.000°</td>
<td>99.2 %</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>Semi-empirical from equivalents</td>
</tr>
<tr>
<td>Max. and min. transmission</td>
<td>0.2602 and 0.2254</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
</tr>
</tbody>
</table>
Data / restraints / parameters 4204 / 1 / 237
Goodness-of-fit on F^2 1.037
Final R indices [I>2sigma(I)] R1 = 0.0370, wR2 = 0.0864
R indices (all data) R1 = 0.0481, wR2 = 0.0930
Extinction coefficient n/a
Largest diff. peak and hole 0.237 and -0.182 e.Å^-3

Table S21. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for 28. U(eq) is defined as one third of the trace of the orthogonalized U^ij tensor.

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U(eq)</th>
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X-ray Crystallographic Data for Compound 38

Table S22. Crystal data and structure refinement for 38.

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<td>Max. and min. transmission</td>
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<td>Refinement method</td>
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<td>Data / restraints / parameters</td>
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Goodness-of-fit on $F^2$: $1.075$

Final $R$ indices [$|\sigma(I)|$]: $R1 = 0.0564$, $wR2 = 0.1220$

$R$ indices (all data): $R1 = 0.0679$, $wR2 = 0.1268$

Absolute structure parameter: $0.01(13)$

Extinction coefficient: n/a

Largest diff. peak and hole: 0.248 and -0.234 e.Å$^{-3}$

Table S23. Atomic coordinates (x 10$^4$) and equivalent isotropic displacement parameters (Å$^2$ x 10$^3$) for compound 38. $U_{eq}$ is defined as one third of the trace of the orthogonalized $U_{ij}$ tensor.

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X-ray Crystallographic Data for compound 40a

![Image](image.png)

**Table S24.** Crystal data and structure refinement for 40a.

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S187
Independent reflections  7157 [R(int) = 0.0968, R(sigma) = 0.0578]
Completeness to theta = 68.000°  99.0 %
Absorption correction  Semi-empirical from equivalents
Max. and min. transmission  0.3201 and 0.2131
Refinement method  Full-matrix least-squares on F^2
Data / restraints / parameters  7157 / 0 / 499
Goodness-of-fit on F^2  1.019
Final R indices [I>2sigma(I)]  R1 = 0.0400, wR2 = 0.0828
R indices (all data)  R1 = 0.0580, wR2 = 0.0872
Absolute structure parameter  0.18(11)
Extinction coefficient  0.00055(9)
Largest diff. peak and hole  0.261 and -0.179 e.Å^-3

Table S25. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for 40a. U(eq) is defined as one third of the trace of the orthogonalized U^ij tensor.

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NMR Spectra

Compound 2 $^1$H NMR
Compound 2 $^{13}$C NMR
Compound S1 $^1$H NMR
Compound S1 $^{13}$C NMR
Compound S3 $^1$H NMR
Compound S3 $^{13}$C NMR
Compound S4 $^1$H NMR
Compound S4 $^{13}$C NMR
Compound S5 $^1$H NMR
Compound S5 $^{13}$C NMR
Compound S6 $^1$H NMR

S200
Compound S6 $^{13}$C NMR
Compound S7 $^1$H NMR

![Compound S7 NMR spectrum](image)
Compound S7 $^{13}$C NMR
Compound S8 $^1$H NMR
Compound S8 $^{13}$C NMR
Compound S9 $^1$H NMR
Compound S9 $^{13}$C NMR
Compound S10 $^1$H NMR

S10, mixture of exo and endo

S208
Compound S10 $^{13}$C NMR

S10, mixture of exo and endo
Compound S11 $^1$H NMR

S210
Compound S11 $^{13}$C NMR
Compound S12 $^1$H NMR

![Chemical structure of S12](attachment:chemical_diagram.png)
Compound S12 $^{13}$C NMR
Compound S13 $^1$H NMR
Compound S13 $^{13}$C NMR
Compound S14 $^1$H NMR
Compound S14 $^{13}$C NMR
Compound S15 $^1$H NMR
Compound S15 $^{13}$C NMR
Compound S16 $^1$H NMR
Compound S16 $^{13}$C NMR
Compound S17 $^1$H NMR
Compound S17 $^{13}$C NMR
Compound S18 $^1$H NMR
Compound S18 $^{13}$C NMR
Compound S19 $^1\text{H}$ NMR
Compound S19 $^{13}$C NMR
Compound S20 $^1$H NMR

![Chemical Structure of S20]

![NMR Spectrum of S20]
Compound S20 $^{13}$C NMR
Compound S21 $^1$H NMR
Compound S21 $^{13}$C NMR

![Compound S21 $^{13}$C NMR spectrum](image-url)
Compound S22 $^1$H NMR
Compound S22 $^{13}$C NMR
Compound S23 $^1$H NMR
Compound S23 $^{13}$C NMR
Compound S23 $^{19}$F NMR
Compound S24 $^1$H NMR
Compound S24 $^{13}$C NMR
Compound S25 $^1$H NMR
Compound S25 $^{13}$C NMR
Compound 3 $^1$H NMR
Compound 3 $^{13}$C NMR
Compound 4 $^1$H NMR
Compound 4 $^{13}$C NMR
Compound 5 $^1$H NMR

![Compound 5 $^1$H NMR](image-url)
Compound 5 $^{13}$C NMR
Compound 6 $^1$H NMR

S247
Compound 6 $^{13}$C NMR
Compound 7 $^1$H NMR
Compound 7 $^{13}$C NMR
Compound 8 $^1$H NMR
Compound 8 $^{13}$C NMR
Compound 9 $^1$H NMR
Compound 9 $^{13}$C NMR
Compound 10 $^1$H NMR
Compound 10 $^{13}$C NMR
Compound 11 $^1$H NMR
Compound 11 $^{13}$C NMR
Compound 12 $^1$H NMR
Compound 12 $^{13}$C NMR
Compound 13 $^1$H NMR
Compound 13 $^{13}\text{C}$ NMR
Compound 14 $^1$H NMR
Compound 14 $^{13}$C NMR
Compound 15 $^1$H NMR
Compound 15 $^{13}$C NMR
Compound 16 $^1$H NMR

16, exo:endo = 10:1
Compound 16 $^{13}$C NMR

16, exo:endo = 10:1
Compound 17 $^1$H NMR
Compound 17 $^{13}$C NMR
Compound 18 $^1$H NMR

![Compound 18 $^1$H NMR spectrum](image-url)
Compound 18 $^{13}$C NMR

![Chemical Structure]
Compound 18 2D NOESY
Compound 19 $^1$H NMR
Compound 19 $^{13}$C NMR
 Compound 20 $^1$H NMR
Compound 20 $^{13}$C NMR
Compound 21 $^1$H NMR
Compound 21 $^{13}$C NMR
Compound 22 $^1$H NMR
Compound 22 $^{13}$C NMR
Compound 23 $^1$H NMR
Compound 23 $^{13}$C NMR
Compound 24 $^1$H NMR

![Compound 24 $^1$H NMR diagram]
Compound 24 $^{13}$C NMR

![Compound 24 $^{13}$C NMR spectrum](image-url)
Compound 25 \(^1\)H NMR
Compound 25 $^{13}$C NMR
Compound 26 $^1$H NMR
Compound 26 $^{13}$C NMR
Compound 27 $^1$H NMR
Compound 27 $^{13}$C NMR
Compound 28 $^1$H NMR
Compound 28 $^{13}$C NMR
Compound 29 $^1$H NMR
Compound 29 $^{13}$C NMR
Compound 30 $^1$H NMR
Compound 30 $^{13}$C NMR
Compound 31 $^1$H NMR
Compound 31 $^{13}$C NMR
Compound 32 $^1$H NMR

S301
Compound 32 $^{13}$C NMR
Compound 33 $^1$H NMR
Compound 33 $^{13}$C NMR
Compound 34 $^1$H NMR
Compound 34 $^{13}$C NMR
Compound 35 $^1$H NMR
Compound 35 $^{13}$C NMR
Compound 36 $^1$H NMR
Compound 36 $^{13}$C NMR
Compound 36 $^{19}$F NMR
Compound 37 $^1$H NMR
Compound 37 $^{13}$C NMR
Compound 38 $^1$H NMR

![NMR spectrum of Compound 38]
Compound 38 $^{13}$C NMR
Compound 39 \(^1\)H NMR

39, d.r. = 11.8:1
Compound 39 $^{13}$C NMR

39, d.r. = 11.8:1
Compound 40 $^1$H NMR
Compound 40 $^{13}$C NMR

40, d.r. = 11.3:1
Compound 40a $^1$H NMR
Compound 40a $^{13}$C NMR

40a, d.r. = 11.3:1
Compound 40a (crystal) $^1$H NMR
Compound 40a (crystal) $^{13}$C NMR
Compound 41 $^1$H NMR
Compound 41 $^{13}$C NMR
Compound 4a $^1$H NMR
Compound 4a $^{13}$C NMR
Compound 3a $^1$H NMR
Compound 3a $^{13}$C NMR
Compound 33a $^1$H NMR

33a, DMSO-$d_6$:D$_2$O = 10:1
Compound 33a $^{13}$C NMR

33a, DMSO-$d_6$/$d_2$O = 10:1
Compound S41 $^1$H NMR
Compound S41 $^{13}$C NMR
Compound S42 $^1$H NMR
Compound S42 $^{13}$C NMR
Compound 1 $^1$H NMR
Compound 1 $^{13}$C NMR
Compound 36a $^1$H NMR
Compound 36a $^{13}$C NMR
Compound 36a $^{19}$F NMR
Compound 36b $^1$H NMR
Compound 36b $^{13}$C NMR
Compound 36b $^{19}$F NMR
Compound 36c $^1$H NMR
Compound 36c $^{13}$C NMR
Compound 36c $^{19}$F NMR
Compound 36d $^1$H NMR
Compound 36d $^{13}$C NMR
Compound 36 $^{19}$F NMR
Compound 36e $^1$H NMR
Compound 36e $^{13}$C NMR
Compound 36e $^{19}$F NMR
Compound 36f $^1$H NMR
Compound 36f $^{13}$C NMR
Compound 36f $^{19}$F NMR
Compound S45 $^1$H NMR

![NMR Spectrum of Compound S45]
Compound S45 $^{13}$C NMR
Compound 42 (TFA salt) $^1$H NMR
Compound 42 (TFA salt) $^{13}$C NMR
Compound 42 (TFA salt) $^{19}$F NMR
Compound 43 (TFA salt) $^1$H NMR
Compound 43 (TFA salt) $^{13}$C NMR
Compound 43 (TFA salt) $^{19}$F NMR
Compound 44 (TFA salt) $^1$H NMR
Compound 44 (TFA salt) $^1$B NMR
Compound 44 $^{11}$B NMR-background
Compound S48 $^1$H NMR
Compound S48 $^{13}$C NMR
Compound 45 $^1$H NMR
Compound 45 $^{13}$C NMR

45, d.r. = 1:1
Compound 45 2D NOESY

45, d.r. = 1:1

S372
Compound S50a $^1$H NMR
Compound S50a $^{13}$C NMR
Compound S50b $^1$H NMR
Compound S50b $^{13}$C NMR

S50b, Boc-L-Val-D-Val-ONHPI
Compound 46 $^1$H NMR

46, d.r. = 1.7:1
Compound 46 $^{13}$C NMR

$\text{BocHN}$

46, $d.r. = 1.7:1$
Compound S51 $^1$H NMR
Compound S51 $^1$H NMR

S51, rotamers
Compound 47 $^1$H NMR

$47, \text{ d.r.} = 2.6:1$
DMSO-$d_6$, 65 °C

S381
Compound 47 $^{13}$C NMR

47, s.r. = 2.6:1
DMSO-$d_6$, 65 °C
Compound 47 2D NOESY

47, d.r. = 2.6:1
DMSO-δ6, 65 °C
Compound S53 $^1$H NMR

S53, d.r. = 3:2
Compound S53 $^{13}$C NMR

$\text{S53, } d.r. = 3:2$
Compound S53 2D NOESY

S53, d.r. = 3:2
Compound 48 $^1$H NMR

$48, d.r. = 5:1:1$
Compound 48 $^{13}$C NMR

48, d.r. = 5.1:1
Compound 49 $^1$H NMR

bortezomib (Velcade); 49
d.r. = 5.1:1
Compound 49 $^{13}$C NMR

bortezomib (Velcade); 49
d.r. = 5:1:1
Compound 50a $^1$H NMR
Compound 50a $^{13}$C NMR
Compound S57 $^1$H NMR
Compound S57 $^{13}$C NMR
Compound 50 $^1$H NMR
Compound 50 $^{13}$C NMR
Compound S61 $^1$H NMR
Compound S61 $^{13}$C NMR
Compound S62 $^{13}$C NMR
Compound 51 $^1$H NMR
Compound 51 $^{13}$C NMR

![Carbon-13 NMR spectrum of compound 51](image_url)
Compound 52 $^1$H NMR

[Chemical structure diagram]

S403
Compound 52 $^{13}$C NMR
Compound S67a $^1$H NMR
Compound S67a $^{13}$C NMR

\[ \text{S67a} \]
Compound S67b $^1$H NMR
Compound S67b $^{13}$C NMR
Compound S62b $^1$H NMR

S62b, d.r. = 6:1
Compound S62b $^{13}$C NMR

S62b, d.r. = 6:1
References


