Predictive Multivariate Linear Regression Analysis Guides Successful Catalytic Enantioselective Minisci Reactions of Diazones

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General information:

**NMR spectra:** $^1$H NMR spectra were recorded on a 600 MHz Bruker Avance DRX-600 spectrometer, a 400 MHz Bruker Avance III spectrometer or 400 MHz Bruker Neo Prodigy Cryoprobe. Chemical shifts are reported in parts per million (ppm) and the spectra are calibrated to the resonance resulting from incomplete deuteration of the solvent (CDCl$_3$: 7.26 ppm, (CD$_3$)$_2$CO: 2.05 ppm). $^{13}$C NMR spectra were recorded with the same spectrometer with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($^{13}$CDCl$_3$: 77.16 ppm, t; (CD$_3$)$_2$CO: 2.05). Data are reported as follows: chemical shift δ/ppm, integration ($^1$H only), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, oct = octet, br = broad, m = multiplet) or combinations thereof; $^{13}$C signals are singlets unless otherwise stated), coupling constants $J$ in Hz, assignment. $^1$H-COSY, DEPT-135, HMQC, HMBC and NOESY were used where appropriate to facilitate structural determination of regioisomers. $^{31}$P NMR spectra were recorded on a 400 MHz Bruker Avance III HD Spectrometer.

**High Resolution Mass Spectrometry (HRMS):** Some were recorded on a Waters Micromass LCT Premier spectrometer using a positive electrospray ionization (ESI+). Others were measured at the EPSRC Mass Spectrometry Service at the University of Swansea. Measured values are reported to 4 decimal places are within ±5 ppm of the calculated value. The calculated values are based on the most abundant isotope.

**Chromatography:** Analytical thin layer chromatography was performed using precoated Merck glass backed silica gel plates (Silicagel 60 F254). Visualisation was by ultraviolet fluorescence (λ = 254 nm) and/or staining with Dragendorff’s reagent, cerium ammonium molybdate (CAM) or potassium permanganate (KMnO$_4$). Flash column chromatography was performed using silica gel 60 (0.040-0.063 μm) from Material Harvest. Deactivated silica gel was prepared according to Cahnmann.¹

**Optical rotations** were measured in CHCl$_3$ on a Perkin Elmer 343 Polarimeter using a sodium lamp (λ 589 nm, D-line). [α]. D values are reported at a given temperature (° C) in degrees cm$^2$ g$^{-1}$ with concentration in mg mL$^{-1}$.¹

**Chiral HPLC analysis** was performed either: On a Shimadzu XR-LC apparatus with Chiralpak (IC and AD-H) in a mixed solvent system of n-hexane and iso-propanol or a Waters Acquity UPC² with Chiralpak (IG and IE) or YMC CHIRAL ART (SB and SC) columns in a mixed solvent system of supercritical carbon dioxide and methanol.

**X-ray crystallography** was performed on a Nonius Kappa CCD diffractometer or a Bruker D8- QUEST PHOTON-100 dиффрактометр using CuKa radiation (lambda = 1.5418 Å) at the Cambridge University Chemistry X-Ray Laboratory.

**Reagents**, unless otherwise stated, were used as supplied from commercial sources without further purification. Anhydrous Dioxane was purchased from Acros Organics and sparged with argon for 30 mins before us. CH$_2$Cl$_2$ and THF were purified by distillation on site under inert atmosphere via the following processes: THF was were pre-dried over sodium wire then distilled from calcium hydride and lithium aluminium hydride. CH$_2$Cl$_2$ and n-hexane were distilled from calcium hydride. TRIP (CPA-4) was prepared as described by List & co-workers² and (R)-TCYP (CPA-9) prepared as described by Toste co-workers.³ [Ir(dF(CF$_3$)ppy)$_2$(dtbpy)]PF$_6$ was prepared as described in the literature.⁴ Redox-active esters were stored at -20 °C in vials under an argon atmosphere.
General Procedures:

General Procedure A for asymmetric Minisci-type reaction of heteroarenes

Sequentially, $N$-heteroarene (0.20 mmol, 1.0 equiv.), redox-active ester (0.24 mmol, 1.2 equiv.), $\text{Ir}[dF(CF_3)pp{(p)}y)]_2(dtbp{y})PF_6$ (2.2 mg, 0.0020 mmol, 0.01 equiv.), and ($R$)-TRIP (7.5 mg, 0.010 mmol, 0.05 equiv.) were added to a 4 mL crimp top vial containing a stirrer bar. The vial was sealed with a crimp seal, evacuated and refilled with argon three times. Anhydrous, freshly argon-sparged 1,4- dioxane (2.0 mL) was then added via syringe. The reaction mixture was stirred under irradiation with 14.4 W 470 nm Farnell LED strips for 14 hours. The apparatus was maintained at approximately room temperature by use of a desk fan close to the vials. The reaction was quenched with a few drops of sat. Na$_2$CO$_3$ (aq.) and solvent was removed under a stream of compressed air and the crude residue was purified via flash column chromatography on silica gel.

General Procedure B for asymmetric Minisci-type reaction of heteroarenes

Sequentially, $N$-heteroarene (0.30 mmol, 1.5 equiv.), redox-active ester (0.20 mmol, 1.0 equiv.), $\text{Ir}[dF(CF_3)pp{(p)}y)]_2(dtbp{y})PF_6$ (2.2 mg, 0.0020 mmol, 0.01 equiv.), and 5 mol% ($R$)-TRIP (7.5 mg, 0.010 mmol, 0.05 equiv.) were added to a 4 mL crimp top vial containing a stirrer bar. The vial was sealed with a crimp seal, evacuated and refilled with argon three times. Anhydrous, freshly argon-sparged 1,4- dioxane (2.0 mL) was then added via syringe. The reaction mixture was stirred under irradiation with blue LEDs for 14 hours. The apparatus was maintained at approximately room temperature by use of a desk fan close to the vials. The reaction was quenched with a few drops of sat. Na$_2$CO$_3$ (aq.) and solvent was removed under a stream of compressed air and the crude residue was purified via flash column chromatography on silica gel.

General Procedure C for asymmetric Minisci-type reaction of heteroarenes

Sequentially, $N$-heteroarene (0.30 mmol, 1.5 equiv.), 1,3-dioxoisindolin-2-yl acetylphenylalaninate (70.5 mg, 0.20 mmol, 1.0 equiv.), $\text{Ir}[dF(CF_3)pp{(p)}y)]_2(dtbp{y})PF_6$ (2.2 mg, 0.0020 mmol, 0.01 equiv.), and 10 mol% ($R$)-TRIP (15.1 mg, 0.020 mmol, 0.05 equiv.) were added to a 4 mL crimp top vial containing a stirrer bar. The vial was sealed with a crimp seal, evacuated
and refilled with argon three times. Anhydrous, freshly argon-sparged 1,4- dioxane (2.0 mL) was then added via syringe. The reaction mixture was stirred under irradiation with blue LEDs for 48 hours. The apparatus was maintained at approximately room temperature by use of a desk fan close to the vials. The reaction was quenched with a few drops of sat. Na₂CO₃ (aq.) and solvent was removed under a stream of compressed air and the crude residue was purified via flash column chromatography on silica gel.
Synthesis of catalysts

The syntheses for catalysts CPA-1, CPA-2, CPA-3, CPA-5, CPA-6, CPA-7, CPA-8, CPA-11 and CPA-13 are reported.5–13 CPA-10 and CPA-14 are commercially available.

\[
(R)-3,3'-\text{bis}(2,6\text{-dimethylphenyl})-1,1'-\text{binaphthol} \ (19)
\]

A 40 mL microwave vial was charged with 3,3'-diiodo-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (500 mg, 0.80 mmol, 1 equiv.), (2,6-dimethylphenyl)boronic acid (480 mg, 0.32 mmol, 4 equiv.), tetrakis(triphenylphosphine)palladium (185 mg, 0.16 mmol, 0.2 equiv.) and barium hydroxide (548, 3.20 mmol, 4 equiv.) and set under Argon. Subsequently a 5:1 mixture of 1,2-dimethoxyethane/H₂O (12 ml) was added and the reaction mixture was heated at 95 °C for 96 h. The resulting mixture was heated at 95 °C and monitored by TLC. After 96 h, the reaction was allowed to reach room temperature, and the solvent was removed in vacuo. Water (25 mL) was then added and the mixture was extracted with CH₂Cl₂ (3 x 25 mL). The combined organic layers were then washed with brine (75 mL), dried over Mg₂SO₄ and concentrated to dryness.

The crude residue was added to a 40 mL microwave vial, followed by dioxane (10 mL) and conc. HCl (2 mL). The reaction mixture was heated for 4 h at 80 °C and cooled to room temperature. Saturated Na₂CO₃ solution was then added carefully until pH 7 was reached and the mixture was concentrated in vacuo. Water (25 mL) was then added and the mixture was extracted with CH₂Cl₂ (3 x 25 mL). The combined organic layers were then washed with brine (75 mL), dried over Mg₂SO₄ and concentrated to dryness. The crude residue was purified via flash column chromatography on silica (eluting with a gradient of 3% to 5% EtOAc/hexanes) to give the title product as a white solid (331 mg, 0.67 mmol, 84% yield). Data are in accordance with literature values.¹⁴

¹H NMR (600 MHz, CDCl₃) δ 7.91 (d, J = 8.1 Hz, 2H), 7.79 (s, 2H), 7.43-7.40 (m, 2H), 7.37-7.34 (m, 2H), 7.30-7.25 (m, 4H), 7.21-7.20 (m, 4H), 5.02 (s, 2H), 2.22 (s, 6H), 2.14 (s, 6H). ¹H NMR (151 MHz, CDCl₃) δ 150.0,
(R)-3,3'-bis(2,6-dimethylphenyl)-1,1'-binaphthyl phosphate (20)

A 40 mL microwave vial was charged with (R)-3,3'-bis(2,6-dimethylphenyl)-1,1'-binaphthol (275 mg, 0.57 mmol, 1 equiv.) and set under Argon. Subsequently pyridine (1.5 ml) was added, followed by POCl₃ (135 μl, 1.47 mmol, 2.6 equiv.). The resulting mixture was heated at 90 °C for 14 h. After this time the reaction was allowed to reach RT, followed by addition of water (1.5 ml). The resulting brownish slurry was heated to 100 °C and hydrolyzed for 3 h. After the reaction reached RT, 25 ml CH₂Cl₂ were added. The resulting organic phase was thoroughly washed with 1 M HCl (3 x 25 ml), dried over MgSO₄ and purified via flash column chromatography eluting with 5% MeOH/CH₂Cl₂. The fractions were combined, concentrated to 1/3 original volume and washed with 1 M HCl (20 mL). The resulting organic layer was collected and concentrated to dryness in vacuo to give the product as a white solid (252 mg, 0.45 mmol, 79% yield).

1H NMR (400 MHz, Acetone) δ 8.09 (d, J = 8.2 Hz, 2H), 7.92 (s, 2H), 7.56-7.52 (m, 2H), 7.36-7.31 (m, 4H), 7.17-7.13 (m, 2H), 7.09-7.07 (m, 4H), 6.46 (br. s, 1H), 2.19 (s, 6H), 2.03 (s, 6H). 13C NMR (101 MHz, Acetone) δ 146.6 (d, 8.9 Hz), 138.0, 137.5, 133.8, 132.9, 132.5, 132.2, 129.3, 128.6, 128.4, 127.5, 127.4, 126.6, 123.2, 21.4, 20.5. 31P NMR (162 MHz, CDCl₃) δ 2.62 ppm. HRMS m/z: [M+H]+ calculated for [C₃₆H₂₉O₄PNa]+ 579.1696, found: 579.1692. [α]D²⁵ = -89.4 (c 1.0, CHCl₃).

S7
Preparation of starting materials

1,3-dioxoisooindolin-2-yl acetylleucinate (21)

A round bottom flask was charged with acetyl-L-leucine (4.16 g, 24 mmol, 1.2 equiv.), N,N'-dicyclohexylcarbodiimide (4.54 g, 22 mmol, 1.1 equiv.) and DMAP (122 mg, 1.0 mmol, 0.05 equiv.). CH$_2$Cl$_2$ (0.1 M) was added at room temperature (RT) and the mixture was stirred for 30 mins. N-hydroxyphthalimide (3.26 g, 20 mmol 1.0 equiv.) was then added portion-wise over 30 mins. The resulting mixture was stirred for a further 1 h, then quickly filtered and the solid residue was rinsed with a small portion of cold CH$_2$Cl$_2$. The filtrate was concentrated in vacuo and purified on deactivated silica eluting with a gradient of 40-60 petroleum ether to 30% EtOAc/40-60 petroleum ether to give the title compound as a white solid (3.1 g, 9.6 mmol, 48%).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.89-7.86 (m, 2H), 7.81-7.78 (m, 2H), 5.96 (d, $J = 8.4$ Hz, 1H), 5.10-5.04 (m, 1H), 2.06 (s, 3H), 1.92-1.69 (m, 3H), 1.02-1.00 (m, 6H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 169.9, 169.8, 161.6, 135.0, 129.0, 124.2, 49.1, 41.8, 24.9, 23.1, 22.9, 22.0. HRMS m/z: [M+H]$^+$ calculated for [C$_{16}$H$_{19}$N$_2$O$_5$]$^+$ 319.1294, found: 319.1281.

4-(tert-butyl) 1-(1,3-dioxoisooindolin-2-yl) acetylaspartate

A round bottom flask was charged with (S)-2-acetamido-4-(tert-butoxy)-4-oxobutanoic acid$^{15}$ (961 mg, 4.16 mmol, 1.04 equiv.), and N,N'-dicyclohexylcarbodiimide (842 mg, 4.08 mmol, 1.02 equiv.). CH$_2$Cl$_2$ (0.1 M) was added at room temperature (RT) and the mixture was stirred for 5 minutes. N-
hydroxyphthalimide (653 mg, 4 mmol, 1.0 equiv.) was added portion-wise over 30 mins and stirring was continued for a further 30 mins. The resulting mixture was quickly filtered and the solid residue was rinsed with a small portion of cold CH$_2$Cl$_2$. The filtrate was concentrated in vacuo and purified on deactivated silica eluting with CH$_2$Cl$_2$ to give the title compound as a white solid (598 mg, 1.59 mmol, 40%).

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.90-7.86 (m, 2H), 7.81-7.76 (m, 2H), 6.70 (d, $J = 8.8$ Hz, 1H), 5.37-5.32 (m, 1H), 3.10 (dd, $J = 17.6, 4.5$ Hz, 1H), 2.87 (dd, $J = 17.5, 4.5$ Hz, 1H), 2.07 (s, 3H), 1.50 (s, 9H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 169.8, 169.7, 167.9, 161.4, 135.0, 129.0, 124.2, 82.8, 47.1, 37.5, 28.2, 23.2. HRMS m/z: [M+H]$^+$ calculated for [C$_{18}$H$_{20}$N$_2$O$_7$Na]$^+$ 399.1163, found: 399.1155.

2-methyl-5-phenylpyrimidine (22)

Adapted from a literature procedure.$^{16}$ A mixture of 2-methyl-5-bromopyrimidine (346 mg, 2 mmol, 1 equiv.), arylboronic acid (366 mg, 3 mmol, 1.5 equiv.), Pd(OAc)$_2$ (2.3 mg, 0.1 mmol, 0.05 equiv.) K$_3$PO$_4$ (2.3 g, 1 mmol, 2 equiv.) and ethylene glycol (16 mL) was stirred at 80 °C for 14 h. The mixture was added to brine (50 mL) and extracted four times with diethyl ether (3 × 50 mL). The combined organic layers were washed with 10 % NaOH solution and dried over Mg$_2$SO$_4$, then filtered. The solvent was concentrated in vacuo, giving the title compound as a yellow solid (320 mg, 94%, 1.88 mmol). Data are in accordance with literature values.$^{17}$

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.85 (s, 2H), 7.56 (d, $J = 7.6$ Hz 2H), 7.56 (t, $J = 7.6$ Hz 2H), 7.44 (t, $J = 7.4$ Hz 1H), 2.79 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 167.0, 151.1, 134.6, 131.2, 129.5, 128.8, 126.9, 25.8.
Experimental data for MLR matrix products

*N-(2-methyl-1-(quinolin-2-yl)propyl)acetamide (A)*

![Chemical Structure](image)

$^{1}H$ NMR (400 MHz, CDCl$_3$) $\delta$ 8.10 (d, $J = 8.5$ Hz, 1H), 8.05 (d, $J = 8.5$ Hz, 1H), 7.81 (d, $J = 8.1$ Hz, 1H), 7.71 (t, $J = 7.7$ Hz, 1H), 7.53 (t, $J = 7.5$ Hz, 1H), 7.31 (d, $J = 8.5$ Hz, 1H), 7.09 (d, $J = 7.6$ Hz, 1H), 5.11 (dd, $J = 8.6, 6.3$ Hz, 1H), 2.24 (oct, $J = 6.7$ Hz, 1H), 2.10 (s, 3H), 0.94 (d, $J = 6.8$ Hz, 1H), 0.88 (d, $J = 6.8$ Hz, 1H). $^{13}C$ NMR (101 MHz, CDCl$_3$) 169.8, 159.9, 147.6, 136.3, 129.7, 129.1, 127.5, 126.4, 121.5, 59.1, 34.5, 23.8, 19.4, 18.5. HRMS m/z: [M+H]$^+$ calculated for [C$_{15}$H$_{19}$N$_2$O]$^+$ 243.1492, found: 243.1493. HPLC Analysis: Chiralpak AD-H (Hexane/iPrOH = 95/05, 1.0 mL min$^{-1}$, 30 °C) $t_R = 9.7$, 14.0 minutes;

*N-(2-methyl-1-(quinolin-4-yl)propyl)acetamide (A1)*

![Chemical Structure](image)

$^{1}H$ NMR (400 MHz, CDCl$_3$) $\delta$ 8.78 (d, $J = 4.6$ Hz, 1H), 8.19 (d, $J = 8.3$ Hz), 8.09 (d, $J = 8.3$ Hz), 7.71-7.67 (m, 1H), 7.58-7.54 (m, 1H), 7.25 (d, $J = 4.6$ Hz, 1H), 6.49 (d, $J = 8.6$ Hz, 1H), 5.65-5.60 (m, 1H), 2.22 (oct, $J = 6.9$ Hz, 1H), 1.97 (s, 3H), 0.97 (d, $J = 6.7$, 1H), 0.90 (d, $J = 6.7$, 1H). $^{13}C$ NMR (101 MHz, CDCl$_3$) $\delta$ 169.9, 149.9, 148.6, 148.1, 130.3, 129.5, 126.9, 126.8, 123.6, 118.0, 53.9, 32.7, 23.3, 20.3, 18.3. HRMS m/z: [M+H]$^+$ calculated for [C$_{15}$H$_{19}$N$_2$O]$^+$ 243.1492, found: 243.1493. HPLC Analysis: Chiralpak AD-H (Hexane/iPrOH = 95/05, 1.0 mL min$^{-1}$, 30 °C) $t_R = 21.1$, 27.8 minutes;

*N-(3-phenyl-1-(quinolin-2-yl)propyl)acetamide (B)*
**1H NMR** (400 MHz, CDCl₃) δ 8.13 (d, J = 8.5 Hz, 1H), 8.08 (d, J = 8.5 Hz, 1H), 7.82 (dd, J = 8.2, 1.2 Hz, 1H), 7.76-7.71 (m, 1H), 7.57-7.53 (m, 1H), 7.33 (d, J = 8.4 Hz, 1H), 7.25-7.21 (m, 3H), 7.16-7.12 (m, 3H), 5.38-5.33 (m, 1H), 2.69-2.61 (m, 1H), 2.59-2.51 (m, 1H), 2.41-2.32 (m, 1H), 2.25-2.13 (m, 1H), 2.09 (s, 3H).

**13C NMR** (101 MHz, CDCl₃) δ 169.8, 160.0, 147.5, 141.7, 137.0, 129.9, 129.1, 128.5, 127.8, 127.5, 126.6, 126.0, 120.5, 54.1, 38.0, 31.7, 23.7. **HRMS m/z:** [M+H]+ calculated for [C₂₀H₂₁N₂O]+ 305.1648, found: 305.1651.

**HPLC Analysis:** CHIRAL ART SC (CO₂/MeOH = 80/20, 2.5 mL min⁻¹, 40 °C) tᵣ = 4.1, 4.5 minutes;

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**N-(3-phenyl-1-(quinolin-4-yl)propyl)acetamide (B1)**

**1H NMR** (600 MHz, CDCl₃) δ 8.80 (d, J = 4.6 Hz, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.71-7.68 (m, 1H), 7.53-7.50 (m, 1H), 7.31-7.28 (m, 3H), 7.23-7.20 (m, 1H), 7.18-7.17 (m, 2H), 6.20 (d, J = 6.3 Hz, 1H), 5.83 (td, J = 8.6, 5.1 Hz, 1H), 2.80-2.76 (m, 1H), 2.74-2.69 (m, 1H), 2.28-2.22 (m, 1H), 2.21-2.15 (m, 1H), 1.98 (s, 3H). **13C NMR** (151 MHz, CDCl₃) δ 169.6, 150.1, 148.6, 148.0, 140.9, 130.3, 129.6, 128.7, 128.5, 127.1, 126.4, 126.3, 123.3, 117.3, 48.3, 37.3, 32.9, 23.3. **HRMS m/z:** [M+H]+ calculated for [C₂₀H₂₁N₂O]+ 305.1648, found: 305.1651. **HPLC Analysis:** CHIRAL ART SB (CO₂/MeOH = 80/20, 2.5 mL min⁻¹, 40 °C) tᵣ = 5.0, 8.3 minutes;

**tert-butyl (S)-3-acetamido-3-(4-methylquinolin-2-yl)propanoate (C)**
**1H NMR** (400 MHz, CDCl₃) δ 8.11 (d, J = 8.5 Hz, 1H), 8.04 (d, J = 8.5 Hz, 1H), 7.80 (dd, J = 8.1, 1.3 Hz, 1H), 7.73-7.69 (m, 1H), 7.54-7.50 (m, 1H), 7.35 (d, J = 8.4 Hz, 1H), 6.93 (d, J = 8.0 Hz, 1H), 5.38-5.33 (td, J = 8.0, 6.5 Hz, 1H), 2.06 (s, 3H), 1.80-1.69 (m, 2H), 1.67-1.56 (m, 1H), 0.98 (d, J = 6.5 Hz, 3H), 0.94 (d, J = 6.5 Hz, 3H).

**13C NMR** (101 MHz, CDCl₃) δ 169.6, 161.3, 147.7, 136.8, 129.7, 129.0, 127.8, 127.5, 126.4, 120.7, 52.9, 46.4, 25.1, 23.7, 23.1, 22.8. **HRMS m/z:** [M+H]⁺ calculated for [C₁₆H₂₁N₂O]⁺ 257.1648, found: 257.1648.

**HPLC Analysis:** CHIRAL ART SC (CO₂/MeOH = 80/20, 2.5 mL min⁻¹, 40 °C) tᵣ = 2.3 (minor), 2.5 (major) minutes;

**N-(3-methyl-1-(quinolin-4-yl)butyl)acetamide (C1)**

**1H NMR** (600 MHz, CDCl₃) δ 8.79 (d, J = 4.5, 1H), 8.17 (d, J = 8.5 Hz, 1H), 8.10 (d, J = 8.5 Hz, 1H), 7.71-7.69 (m, 1H), 7.59-7.56 (m, 1H), 7.29 (d, J = 4.5 Hz, 1H), 6.27 (d, J = 8.3 Hz, 1H), 5.90-5.86 (m, 1H), 1.99 (s, 3H), 1.76-1.70 (m, 3H), 1.07 (d, J = 6.3 Hz, 3H), 0.93 (d, J = 6.3 Hz, 3H). **13C NMR** (151 MHz, CDCl₃) δ 169.5, 150.1, 148.9, 148.6, 130.3, 129.5, 127.1, 126.3, 123.3, 117.3, 46.8, 45.0, 25.5, 23.3, 23.2, 22.1. **HRMS m/z:** [M+H]⁺ calculated for [C₁₆H₂₁N₂O]⁺ 257.1648, found: 257.1651. **HPLC Analysis:** CHIRAL ART SB (CO₂/MeOH = 90/10, 2.5 mL min⁻¹, 40 °C) tᵣ = 2.5, 3.4 minutes;

**N-(1-(5-cyanopyridin-2-yl)-2-methylpropyl)acetamide (D)**
**1H NMR** (400 MHz, CDCl₃) δ 8.82 (dd, J = 2.1, 0.7 Hz, 1H), 7.90 (dd, J = 8.0, 2.1 Hz, 1H) 7.34, (dd, J = 0.7, 8.1 Hz, 1H), 6.51, (d, J = 8.4 Hz, 1H), 4.95, (dd, J = 8.8, 7.0 Hz, 1H), 2.11 (oct, J = 6.8 Hz, 1H), 2.0 (s, 3H), 0.93 (d, J = 6.8 Hz, 3H), 0.80 (d, J = 6.8 Hz, 3H).

**13C NMR** (101 MHz, CDCl₃) δ 169.8, 164.1, 139.5, 123.2, 116.7, 108.6, 59.2, 33.8, 23.5, 19.3, 18.6. **HRMS m/z:** [M+H]⁺ calculated for [C₁₃H₁₆N₃O⁺] 218.1288, found: 218.1288. **HPLC Analysis:** Chiralpak IE (CO₂/MeOH = 95/05, 2.5 mL min⁻¹, 40 °C) tᵣ = 12.4, 13.3 minutes.

**methyl 6-(1-acetamido-2-methylpropyl)-2-methylnicotinate (E)**

![Structure of methyl 6-(1-acetamido-2-methylpropyl)-2-methylnicotinate](image)

**1H NMR** (600 MHz, CDCl₃) δ 8.13 (d, J = 7.9 Hz, 1H), 7.09 (d, J = 7.9 Hz, 1H), 6.80 (br d, J = 8.6 Hz, 1H), 4.88 (dd, J = 8.6, 6.9 Hz, 1H), 3.91 (s, 3H), 2.82 (s, 3H), 2.09 (oct, J = 6.8 Hz, 1H), 2.06 (s, 3H), 0.92 (d, J = 6.9 Hz, 3H), 0.78 (d, J = 6.9 Hz, 3H). **13C NMR** (101 MHz, CDCl₃) δ 169.6, 166.8, 161.6, 159.6, 138.7, 123.7, 120.2, 58.7, 52.3, 33.9, 25.0, 23.6, 19.1, 18.6. **HPLC Analysis:** Chiralpak IE (CO₂/MeOH = 90/10, 2.5 mL min⁻¹, 40 °C) tᵣ = 5.1, 5.6 minutes.

**methyl 6-(1-acetamido-2-methylpropyl)-2-methylnicotinate (E)**

![Structure of methyl 6-(1-acetamido-2-methylpropyl)-2-methylnicotinate](image)

**1H NMR** (400 MHz, CDCl₃) δ 8.77 (dd, J = 2.3, 0.7 Hz, 1H), 7.82 (dd, J = 8.0, 2.4 Hz, 1H), 7.59-7.61 (m, 2H), 7.50-7.43 (m, 2H), 7.43-7.39 (m, 1H), 7.27 (dd, J = 8.0, 0.6 Hz), 6.74 (d, J = 8.7 Hz, 1H), 4.93 (dd, J = 8.9, 7.0 Hz), 2.15 (oct, J = 6.9 Hz, 1H), 2.05 (s, 3H), 0.98 (d, J = 6.9 Hz, 3H), 0.84 (d, J = 6.9 Hz, 3H). **13C NMR** (101 MHz, CDCl₃) δ 169.7, 158.2, 147.7, 137.7, 135.5, 134.8, 129.3, 128.2, 127.2, 123.2, 58.9, 34.1, 23.7, 19.3, 18.9. **HPLC Analysis:** Chiralpak IE (CO₂/MeOH = 93/07, 2.5 mL min⁻¹, 40 °C) tᵣ = 17.8, 21.8 minutes.
$N$-(1-(5-cyano-6-methylpyridin-2-yl)-2-methylpropyl)acetamide (G)

\begin{center}
\includegraphics{structure.png}
\end{center}

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.81 (d, $J = 8.0$ Hz, 1H), 7.12 (d, $J = 8.0$ Hz, 1H), 6.57 (d, $J = 8.3$ Hz, 1H), 4.88 (dd, $J = 8.7, 7.2$ Hz, 1H), 2.74 (s, 3H), 2.11-2.05 (m, 1H), 2.03 (s, 3H), 0.91 (d, $J = 6.8$ Hz, 3H), 0.78 (d, $J = 6.8$ Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 169.8, 163.2, 161.4, 140.2, 120.3, 117.0, 107.6, 59.2, 33.7, 23.8, 23.6, 19.3, 18.6. **HPLC Analysis:** Chiralpak IE (CO$_2$/MeOH = 95/05, 2.5 mL min$^{-1}$, 40 °C) $t_R = 11.9, 12.6$ minutes.
General procedure A was followed with 4-methylquinoline (35.8 mg, 0.25 mmol) and 1,3-dioxoisindolin-2-yl acetylleucinate (87.5 mg, 0.275 mmol). Purification on silica gel eluting with 50% EtOAc in Pet. Ether (40-60) yielded the title compound as a pale orange solid (57.5 mg, 0.213 mmol, 85%, 73% ee).

\[ \text{HRMS m/z: [M+H]}^+ \text{ calculated for } [\text{C}_{17}\text{H}_{23}\text{N}_2\text{O}]^+ 271.1805, \text{ found: 271.1805.} \]

HPLC Analysis: Chiralpak IC (Hexane/iPrOH = 90/10, 1.0 mL min⁻¹, 30 °C) \( t_R = 15.7 \) (minor), 24.1 (major) minutes. \( \alpha_D^{25.0} = -60.4 \) (c 1.0, CHCl₃).

General procedure A was followed with methyl 5-methylnicotinate (37.8 mg, 0.20 mmol, 1.0 equiv.), 1,3-dioxoisindolin-2-yl acetylvalinate (114.1 mg, 0.22 mmol, 1.5 equiv.), \( \text{Ir[}d\text{F(CF}_{3})\text{ppy)]}_2(\text{dtbpy})\text{PF}_6 \) (2.7 mg, 0.0025 mmol, 0.01 equiv.) and (R)-TCYP (12.4 mg, 0.0125 mmol, 0.05 equiv.). Purification on silica gel
eluting with 60% EtOAc in hexane yielded the title compound as a white solid (52.2 mg, 0.198 mmol, 79% yield, 81% ee).

\(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \(\delta\) 8.93 \((d, J = 2.0 \text{ Hz}, 1\text{H})\), 8.03, \((\text{dd}, J = 2.0, 0.7 \text{ Hz}, 1\text{H})\), 6.73-6.66, \((m, 1\text{H})\), 5.18, \((\text{dd}, J = 9.0, 7.3 \text{ Hz}, 1\text{H})\), 3.91, \((s, 3\text{H})\), 2.44, \((s, 3\text{H})\), 2.10-1.98 \((m, 4\text{H})\), 0.91 \((d, J = 6.8 \text{ Hz}, 3\text{H})\), 0.81 \((d, J = 6.8 \text{ Hz}, 3\text{H})\). \(^{13}\text{C NMR}\) (101 MHz, CDCl\(_3\)) \(\delta\) 169.8, 165.9, 163.3, 147.7, 139.0, 130.9, 124.4, 54.8, 52.4, 33.8, 23.5, 19.6, 18.6, 18.2. HRMS m/z: [M+H]\(^+\) calculated for [C\(_{14}\)H\(_{21}\)N\(_2\)O\(_3\)]\(^+\) was 265.1552, found: 265.1542. HPLC Analysis: Chiralpak IE (CO\(_2/\)MeOH = 90/10, 2.5 mL min\(^{-1}\), 40 °C) \(t_R = 5.2\) (minor), 5.9 (major) minutes. \([\alpha]_D^{25.0} = -97.0\) (c 1.0, CHCl\(_3\)).

\[
\text{methyl (S)-6-(1-acetamido-2-methylpropyl)-4-methylnicotinate (L)}
\]

General procedure A was followed with methyl 4-methylnicotinate (37.8 mg, 0.25 mmol, 1.0 equiv.), 1,3-dioxoisoidolin-2-yl acetylphenylvalininate (114.1 mg, 0.375 mmol, 1.5 equiv.), Ir[dF(CF\(_3\))ppy]\(_2\)(dtbpy)PF\(_6\) (2.7 mg, 0.0025 mmol, 0.01 equiv.) and (R)-TCYP (12.4 mg, 0.0125 mmol, 0.05 equiv.). Purification on silica gel eluting with 80% EtOAc in hexane yielded the title as a white solid (54.2 mg, 0.205 mmol, 82% yield, 85% ee).

\(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \(\delta\) 8.98 \((s, 1\text{H})\), 7.06 \((s, 1\text{H})\), 6.70-6.64 \((m, 1\text{H})\), 4.87-4.82 \((m, 1\text{H})\), 3.91 \((s, 3\text{H})\), 2.59 \((s, 3\text{H})\), 2.16-2.05 \((m, 1\text{H})\), 2.01 \((s, 3\text{H})\), 0.93 \((d, J = 6.8 \text{ Hz}, 3\text{H})\), 0.78 \((d, J = 6.8 \text{ Hz}, 3\text{H})\). \(^{13}\text{C NMR}\) (101 MHz, CDCl\(_3\)) \(\delta\) 169.7, 166.5, 162.5, 151.4, 150.0, 125.8, 124.5, 58.9, 52.2, 33.8, 23.6, 21.5, 19.3, 18.7. HRMS m/z: [M+H]\(^+\) calculated for [C\(_{14}\)H\(_{21}\)N\(_2\)O\(_3\)]\(^+\) was 265.1547, found: 265.1541. HPLC Analysis: Chiralpak IC (Hexane/PrOH = 70/30, 1.0 mL min\(^{-1}\), 30 °C) \(t_R = 8.5\) (minor), 10.5 (major) minutes. \([\alpha]_D^{25.0} = -65.0\) (c 1.0, CHCl\(_3\)).

\[(S)-N-(2-methyl-1-(5-phenylpyridin-2-yl)propyl)acetamide (M)\]
General procedure A was followed with methyl 3-phenylpyridine (38.8 mg, 0.25 mmol, 1.0 equiv.), 1,3-dioxoisindolin-2-yl acetylvalinate (114.1 mg, 0.375 mmol, 1.5 equiv.), Ir[dF(CF₃)ppy]₂(dtbpy)PF₆ (2.7 mg, 0.0025 mmol, 0.01 equiv.) and (R)-TCYP (12.4 mg, 0.0125 mmol, 0.05 equiv.). Purification on silica gel eluting with 50% EtOAc in hexane yielded the title as a white solid (32.9 mg, 0.113 mmol, 49% yield, 67% ee).

**¹H NMR** (400 MHz, CDCl₃) δ 8.77 (dd, 2.3, 0.7 Hz, 1H), 7.82 (dd, J = 8.0, 2.4 Hz, 1H), 7.59-7.61 (m, 2H), 7.50-7.43 (m, 2H), 7.43-7.39 (m, 1H), 7.27 (dd, J = 8.0, 0.6 Hz), 6.74 (d, J = 8.7 Hz, 1H), 4.93 (dd, J = 8.9, 7.0 Hz), 2.15 (oct, J = 6.9 Hz, 1H), 2.05 (s, 3H), 0.98 (d, J = 6.9 Hz, 3H), 0.84 (d, J = 6.9 Hz, 3H).

**¹³C NMR** (101 MHz, CDCl₃) δ 169.7, 158.2, 147.7, 137.5, 135.4, 129.3, 128.2, 127.2, 123.2, 58.9, 34.1, 23.7, 19.3, 18.9.

**HPLC Analysis:** Chiralpak IC (Hexane/iPrOH = 70/30, 1.0 mL min⁻¹, 30 °C) tᵣ = 7.3 (minor), 10.5 (major) minutes. [α]₀²⁵.₀ = -92.8 (c 1.0, CHCl₃).

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**N-(1-(5-cyanopyridin-2-yl)-2-methylpropyl)acetamide (N)**

General procedure A was followed with nicotinonitrile (26.0 mg, 0.25 mmol, 1.0 equiv.), 1,3-dioxoisindolin-2-yl acetylvalinate (114.1 mg, 0.375 mmol, 1.5 equiv.), Ir[dF(CF₃)ppy]₂(dtbpy)PF₆ (2.7 mg, 0.0025 mmol, 0.01 equiv.) and (R)-TCYP (12.4 mg, 0.0125 mmol, 0.05 equiv.). Purification on silica gel eluting with 60% EtOAc/hexane yielded the title compound as a white solid (37.5 mg, 0.173 mmol, 69% yield, 61% ee).

**¹H NMR** (400 MHz, CDCl₃) δ 8.82 (dd, J = 2.1, 0.7 Hz, 1H), 7.90, (dd, J = 8.0, 2.1 Hz, 1H) 7.34, (dd, J = 0.7, 8.1 Hz, 1H), 6.51, (d, J = 8.4 Hz, 1H), 4.95, (dd, J = 8.8, 7.0 Hz, 1H), 2.11 (oct, J = 6.8 Hz, 1H), 2.0 (s, 3H), 0.93
(d, J = 6.8 Hz, 3H), 0.80 (d, J = 6.8 Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 169.8, 164.1, .1, 139.5, 123.2, 116.7, 108.6, 59.2, 33.8, 23.5, 19.3, 18.6. HRMS m/z: [M+H]$^+$ calculated for [C$_{12}$H$_{16}$N$_3$O]$^+$ 218.1288, found: 218.1288. HPLC Analysis: Chiralpak IE (CO$_2$/MeOH = 95/05, 2.5 mL min$^{-1}$, 40 °C) $t_R$ = 12.4, 13.3 minutes. [α]$^0_{D25} = -69.7$ (c 1.0, CHCl$_3$).

$$\text{(S)-N-(1-(8-methylquinolin-2-yl)-2-phenylethyl)acetamide (Q)}$$

General procedure A was followed with 8-methylquinoline (18.8 mg, 0.25 mmol, 1.0 equiv.), 1,3-dioxoisindolin-2-yl acetylphenylalaninate (96.9 mg, 0.275 mmol, 1.1 equiv.), Ir[dF(CF$_3$ppy)$_2$(dtbpy)]PF$_6$ (2.7 mg, 0.0025 mmol, 0.01 equiv.) and (R)-TRIP (9.4 mg, 0.0125 mmol, 0.05 equiv.). The crude product was purified via flash column chromatography (eluting with 50% EtOAc/hexanes) to give the title product as a white amorphous solid (63.9 mg, 0.21 mmol, 84% yield, 76% ee).

$^1$H NMR (600 MHz, CDCl$_3$) δ 7.96 (d, J = 8.3 Hz, 1H), 7.63 (d, J = 8.2 Hz, 1H), (d, J = 7.0 Hz, 1H), 7.43-7.40 (m, 1H), 7.24 (d, J = 7.0 Hz, 1H), 7.14-7.13 (m, 3H), 6.95 (d, J = 8.3 Hz, 1H), 6.93-6.91 (m, 2H), 5.46 (td, J = 7.8, 4.8 Hz, 1H), 3.36 (dd, J = 13.3, 4.7, 1H), 3.17 (dd, J = 13.3, 8.2, 1H), 2.74 (s, 3H), 2.10 (s, 3H). $^{13}$C NMR (151 MHz, CDCl$_3$) δ 169.4, 157.7, 146.2, 137.2, 136 .7, 136.5, 129.8, 128.1, 127.3, 126.4, 126.2, 125.7, 120.4, 55.6, 42.4, 23.7, 17.9. HRMS m/z: [M+H]$^+$ calculated for [C$_{20}$H$_{21}$N$_2$O]$^+$ 305.1648, found: 305.1644. HPLC Analysis: Chiralpak IC (Hexane/PrOH = 85/15, 1.0 mL min$^{-1}$, 30 °C) $t_R$ = 14.4(minor), 16.2 (major) minutes. [α]$^0_{D25} = +47.7$ (c 1.0, CHCl$_3$).

methyl (S)-2-(1-acetamido-2-methylpropyl)isonicotinate (2a)
General procedure B was followed with methyl methylisonicotinate (41.4 mg, 0.30 mmol, 1.5 equiv.), 1,3-dioxoisooindolin-2-yl acetylphenylvalinate (60.9 mg, 0.20 mmol, 1.0 equiv.), Ir[dF(CF3)ppy]2(dtbpyp)PF6 (2.2 mg, 0.002 mmol, 0.01 equiv.) and (R)-TCYP (9.9 mg, 0.010 mmol, 0.05 equiv.). The crude product was purified via flash column chromatography (eluting with 30% acetone/hexanes) to give the title product as a colourless oil (21.0 mg, 0.084 mmol, 42% yield, 39% ee).

$^1$H NMR (400 MHz, CDCl3) δ 8.68 (dd, $J = 4.7$, 1.0 Hz, 1H), 7.74 – 7.72 (m, 2H), 6.68 (d, $J = 8.2$ Hz, 1H), 4.96 (dd, $J = 8.7$, 7.0 H), 3.94 (s, 3H), 2.12 (oct, $J = 6.8$ Hz, 1H), 2.03 (s, 3H, H4), 0.93 (d, $J = 6.8$ Hz, 3H, H6), 0.79 (d, $J = 6.8$ Hz, 3H, H7); $^{13}$C NMR (101 MHz, CDCl3) δ 169.7, 165.6, 160.9, 150.0, 137.8, 122.3, 121.6, 59.1, 52.9, 34.0, 23.6, 19.3, 18.6. HRMS m/z: [M+H]$^+$ calculated for [C13H19N2O3]$^+$ 266.1505, found: 266.1495.

**HPLC Analysis**: Chiralpak IE (CO2/MeOH = 80/20, 2.5 mL min$^{-1}$, 40 °C) $t_R = 2.9$ (minor), 3.1 (major) minutes. $[\alpha]_D^{25.0} = -14.4$ (c 1.0, CHCl3).
Unsuccessful diazines

Attempted products **19-23** were unsuccessful under standard conditions. Low conversion to product was the result for **19** (predicted within error), whereas the heteroarene substrates for **20-23** gave no conversion to product.
Experimental data for diazine and benzothiazole substrates

\[(S)-N-(2-\text{phenyl}-1-(\text{pyrimidin-4-yl})\text{ethyl})\text{acetamide (1)}\]

\[
\begin{array}{c}
\text{N} \\
\text{Br} \\
\text{H} \\
\text{N} \\
\text{C} \quad \text{O}
\end{array}
\]

General procedure B was followed with pyrimidine (24.0 mg, 0.3 mmol, 1.5 equiv.), 1,3-dioxoisoiindolin-2-yl acetylphenylalaninate (70.5 mg, 0.20 mmol, 1.2 equiv.) and (R)-TCYP (9.9 mg, 0.01 mmol, 0.05 equiv.). The crude product was purified via flash column chromatography (eluting with a gradient of EtOAc to 1.5% MeOH/EtOAc) to give the title product as a white solid (21.2 mg, 0.088 mmol, 44% yield, 88% ee).

\[^1\text{H NMR} (400 MHz, CDCl}_3] \delta 9.14 (d, J = 1.0 Hz, 1H), 8.52 (d, J = 5.2 Hz, 1H), 7.22-7.18 (m, 3H), 6.96-6.94, (m, 2H), 6.87 (dd, J = 5.1, 1.1 Hz, 1H), 6.72 (d, J = 7.0 Hz, 1H), 5.76 (td, J = 7.9, 6.0 Hz 1H), 3.22 (dd, J = 13.3, 5.9 Hz, 1H), 3.02 (dd, J = 13.4, 8.2 Hz, 1H), 2.01 (s, 3H). \[^{13}\text{C NMR} (100 MHz, CDCl}_3] \delta 169.6, 167.4, 158.7, 156.9, 136.4, 129.4, 128.6, 127.0, 120.1, 55.0, 41.8, 23.4. \text{HRMS m/z: [M+H]^+ calculated for [C}_{14}H_{16}N_{3}O]^+ 242.1288, found: 242.1285. HPLC Analysis: Chiralpak IE (CO}_2/\text{MeOH} = 90/10, 2.5 mL min^{-1}, 40 °C) t_R = 9.3 (minor), 9.9 (major) minutes. [\alpha]_D^{25.0} = +4.5 (c 1.0, CHCl}_3).\]

General procedure B was followed with pyrimidine (24.0 mg, 0.3 mmol, 1.5 equiv.), 1,3-dioxoisoiindolin-2-yl acetylphenylalaninate (70.5 mg, 0.20 mmol, 1.2 equiv.) and (R)-TRIP (7.5 mg, 0.01 mmol, 0.05 equiv.). The crude product was purified via flash column chromatography (eluting with a gradient of EtOAc to 1.5% MeOH/EtOAc) to give the title product as a white solid (29.0 mg, 0.120 mmol, 60% yield, 78% ee).

\[(S)-N-(1-(5-\text{bromopyrimidin-4-yl})-2-\text{phenylethyl})\text{acetamide (2)}\]

\[
\begin{array}{c}
\text{N} \\
\text{Br} \\
\text{H} \\
\text{N} \\
\text{C} \quad \text{O}
\end{array}
\]
General procedure B was followed with 5-bromopyrimidine (47.4 mg, 0.30 mmol, 1.5 equiv.), 1,3-dioxoisooindolin-2-yl acetylphenylalaninate (70.5 mg, 0.20 mmol, 1.2 equiv.) and (R)-TCYP (9.9 mg, 0.01 mmol, 0.05 equiv.). The crude product was purified via flash column chromatography (eluting with a gradient of 50% to 80% EtOAc in 40-60 petroleum ether) to give the title product as a white amorphous solid (39.9 mg, 0.124 mmol, 62% yield, 83% ee).

\[ ^1H \text{NMR} \ (400 \text{ MHz, CDCl}_3) \delta 8.96 \text{ (s, 1H)}, 8.74 \text{ (s, 1H)}, 7.21-7.17 \text{ (m, 3H)}, 6.96-6.91 \text{ (m, 2H)}, 6.63 \text{ (d, } J = 7.9 \text{ Hz, 1H)}, 5.78-5.73 \text{ (m, 1H)}, 3.18 \text{ (dd, } J = 13.7, 6.3 \text{ Hz, 1H}), 3.07 \text{ (dd, } J = 13.6, 6.4 \text{ Hz, 1H}), 1.99 \text{ (s, 3H)}. \]

\[ ^13C \text{NMR} \ (101 \text{ MHz, CDCl}_3) \delta 169.4, 165.9, 159.2, 156.5, 135.7, 129.6, 128.4, 120.3, 117.0, 52.8, 40.1, 23.4. \]

HRMS m/z: [M+H]+ calculated for [C14H15BrN3O]+ 320.0399, found: 320.0390. HPLC Analysis: Chiralpak IE (CO2/MeOH = 80/20, 2.5 mL min⁻¹, 40 °C) t_R = 4.0 (minor), 4.5 (major) minutes. [\[
\alpha\]]_{D}^{25.0} = +9.5 (c 1.0, CHCl3).

(S)-\text{N}-(1-(6-methylpyrimidin-4-yl)-2-phenylethyl)acetamide (3)

General procedure A was followed with 4-methylpyrimidine (18.8 mg, 0.20 mmol, 1.0 equiv.), 1,3-dioxoisooindolin-2-yl acetylphenylalaninate (84.6 mg, 0.24 mmol, 1.2 equiv.) and (R)-TCYP (9.9 mg, 0.01 mmol, 0.05 equiv.). The crude product was purified via flash column chromatography (eluting with 40% acetone in CH₂Cl₂) to give the title product as a white amorphous solid (27.9 mg, 0.109 mmol, 55% yield, 85% ee).

\[ ^1H \text{NMR} \ (400 \text{ MHz, CDCl}_3) \delta 8.99 \text{ (d, } J = 1.1 \text{ Hz, 1H}), 7.22-7.15 \text{ (m, 3H)}, 6.96-6.94 \text{ (m, 2H)}, 6.72 \text{ (s, 1H)}, 6.68 \text{ (d, } J = 7.6 \text{ Hz, 1H)}, 5.19 \text{ (dt, } J = 7.9, 6.1 \text{ Hz, 1H}), 3.20 \text{ (dd, } J = 13.4, 6.1 \text{ Hz, 1H}), 3.01 \text{ (dd, } J = 13.4, 8.0 \text{ Hz, 1H}), 2.40 \text{ (s, 3H)}, 1.99 \text{ (s, 3H)}. \]

\[ ^13C \text{NMR} \ (101 \text{ MHz, CDCl}_3) \delta 169.6, 167.2, 166.9, 158.3, 136.6, 129.4, 128.5, 126.9, 119.5, 54.9, 41.7, 24.1, 23.4. \]

HRMS m/z: [M+H]+ calculated for [C15H18N3O]+ 256.1450, found: 256.1445. HPLC Analysis: Chiralpak IE (CO2/MeOH = 90/10, 2.5 mL min⁻¹, 40 °C) t_R = 9.5 (minor), 10.1 (major). [\[
\alpha\]]_{D}^{25.0} = -11.1 (c 1.0, CHCl3).
(S)-N-(1-(2-methylpyrimidin-4-yl)-2-phenylethyl)acetamide (4)

\[
\text{General procedure B was followed 2-methylpyrimidine (28.2 mg, 0.30 mmol, 1.5 equiv.) and 1,3-dioxoisooindolin-2-yl acetylphenylalaninate (70.5 mg, 0.20 mmol, 1.0 equiv.). The crude product was purified via flash column chromatography (eluting with a gradient of EtOAc to 4% MeOH/EtOAc) to give the title product as a white solid (23.0 mg, 0.090 mmol, 45% yield, 94% ee).}
\]

\[\text{\textbf{1H NMR} (400 MHz, CDCl}_3\text{)} \delta 8.41 (d, J = 5.2 Hz, 1H), 7.22-7.17 (m, 3H), 6.97-6.94, (m, 2H), 6.71 (d, J = 7.5 Hz, 1H), 6.63 (d, J = 5.3 Hz, 1H), 5.21 (td, J = 8.0, 5.8 Hz, 1H), 3.22 (dd, J = 13.4 , 5.8 Hz, 1H), 2.99 (dd, J = 13.4 , 8.0 Hz, 1H), 2.71 (s, 3H), 2.03 (s, 3H).}
\]

\[\text{\textbf{13C NMR} (101 MHz, CDCl}_3\text{)} \delta 169.6, 168.2, 167.2, 156.9, 136.6, 129.5, 128.5, 126.9, 116.8, 55.0, 41.9, 26.2, 23.5.}
\]

\[\text{HRMS m/z: \[M+H\]^+ calculated for [C}_{15}H_{18}N_{3}O^+ 256.1450, found: 256.1444.}
\]

\[\text{HPLC Analysis: CHIRAL ART SC (CO}_2\text{/MeOH = 90/10, 2.5 mL min}^{-1}, 40 °C) t_\text{R} = 6.4 \text{ (major), 6.9 (minor) minutes. \[\alpha\]}_{D}^{25.0} = +19.7 (c 1.0, CHCl}_3\text{).}
\]

\[\text{N,N'}-((1S,1'S)-(2-methylpyrimidine-4,6-diyl)bis(2-phenylethane-1,1-diyl))diacetamide (5)
\]

\[\text{General procedure A was followed with 2-methylpyrimidine (18.8 mg, 0.20 mmol, 1.0 equiv.), but with 10 mol% TRIP (15.1 mg, 0.02 mmol, 0.01 equiv.) and 3 equiv. 1,3-dioxoisooindolin-2-yl acetylphenylalaninate (211.4 mg, 0.60 mmol, 3.0 equiv.), The crude product was purified via flash column chromatography}
\]

S23
(eluting with a gradient of EtOAc to 4% MeOH/EtOAc) to give the title product as a white solid in a mixture of diastereomers (69.6 mg, 0.172 mmol, 86% yield, >99% ee, 20:1 d.r).

^1^H NMR (400 MHz, CDCl₃) δ 7.20-7.17 (m, 6H), 6.93-6.90, (m, 2H), 6.49 (d, J = 7.7 Hz, 2H), 6.19 (s, 1H), 5.11-5.06 (m, 2H), 3.12 (dd, J = 13.5 , 6.1 Hz, 2H), 2.93 (dd, J = 13.5 , 7.5 Hz, 2H), 2.69 (s, 3H), 1.99 (s, 3H).

^1^3^C NMR (101 MHz, CDCl₃) δ 169.5, 167.8, 167.3, 136.6, 129.6, 128.5, 126.9, 114.3, 54.8, 41.5, 26.1, 23.5.

HRMS m/z: [M+H]^+ calculated for [C₆H₁₅N₄O₂]^+ 426.2212, found: 426.2215. HPLC Analysis: Chiralpak IG (CO₂/MeOH = 80/20, 2.5 mL min⁻¹, 40 °C) t_R = 3.2 (major enantiomer), 3.7 (minor diastereomer), 4.7 (minor enantiomer) minutes. [α]^D₂⁵ = -33.7 (c 1.0, CHCl₃).

(S)-N-(1-(2,6-dimethylpyrimidin-4-yl)-2-phenylethyl)acetamide (6)

General procedure A was followed with 2,4-dimethylpyrimidine¹⁸ (21.6 mg, 0.20 mmol, 1.0 equiv.) and 1,3-dioxoisoidolin-2-yl acetylphenylalaninate (84.6 mg, 0.24 mmol, 1.2 equiv.). The crude product was purified via flash column chromatography (eluting with a gradient of EtOAc to 4% MeOH/EtOAc) to give the title product as a white solid (19.4 mg, 0.07 mmol, 36% yield, 91% ee).

^1^H NMR (400 MHz, CDCl₃) δ 7.23-7.15 (m, 3H), 6.98-6.94, (m, 2H), 6.69 (d, J = 7.7 Hz, 1H), 6.50 (s, 1H), 5.23 (td, J = 8.0, 6.0 Hz, 1H), 3.19 (dd, J = 13.4 , 6.0 Hz, 1H), 2.98 (dd, J = 13.4 , 8.0 Hz, 1H), 2.67 (s, 3H), 2.35 (s, 3H), 2.01 (s, 3H). ^1^3^C NMR (101 MHz, CDCl₃) δ 169.6, 167.7, 167.1, 166.8, 136.8, 129.5, 128.4, 126.8, 116.2, 54.9, 41.8, 26.1, 24.1, 23.5. HRMS m/z: [M+H]^+ calculated for [C₁₆H₂₀N₃O]^+ 270.1606, found: 270.1599. HPLC Analysis: CHIRAL ART SC (CO₂/MeOH = 90/10, 2.5 mL min⁻¹, 40 °C) t_R = 6.1 (minor), 5.3 (major) minutes. [α]^D₂⁵ = +2.3 (c 1.0, CHCl₃).

(S)-N-(1-(6-chloro-2-methylpyrimidin-4-yl)-2-phenylethyl)acetamide (7)
General procedure A was followed with 2-methyl-4-chloropyrimidine (0.20 mmol) and 1,3-dioxoisindolin-2-y1 acetylphenylalaninate (84.6 mg, 0.24 mmol, 1.2 equiv.). The crude product was purified via flash column chromatography (eluting with a gradient of 20% to 50% EtOAc in hexanes) to give the title product as a white amorphous solid (63%, 36.5 mg, 0.126 mmol, 97% ee).

H NMR (400 MHz, CDCl3) δ 7.30-7.25 (m, 3H), 7.03-7.01, (m, 2H), 6.77 (s, 1H), 6.52 (d, J = 7.7 Hz, 1H), 5.25-5.20 (m, 1H), 3.22 (dd, J = 13.5, 6.4 Hz, 1H), 3.04 (dd, J = 13.5, 7.7 Hz, 1H), 2.73 (s, 3H), 2.05 (s, 3H).

13C NMR (101 MHz, CDCl3) δ 169.6, 169.4, 169.2, 161.1, 163.6, 129.4, 128.7, 127.2, 116.8, 54.9, 41.5, 25.9, 23.4. HRMS m/z: [M+H]+ calculated for [C15H17ClN3O]+ 290.1060, found: 290.1052. HPLC Analysis: Chiralpak IG (CO2/MeOH = 90/10, 2.5 mL min⁻¹, 40 °C) tR = 4.1 (major), 4.7 (minor) minutes. [α]D25.0 = -9.0 (c 1.0, CHCl3).

(S)-N-(1-(2-methyl-6-phenylpyrimidin-4-y1)-2-phenylethyl)acetamide (8)

General procedure A was followed with 2-methyl-4-phenylpyrimidine (34.0 mg, 0.2 mmol, 1.0 equiv.) and 1,3-dioxoisindolin-2-y1 acetylphenylalaninate (84.6 mg, 0.24 mmol, 1.2 equiv.). The crude product was purified via flash column chromatography (eluting with 50% EtOAc in hexanes) to give the title product as a white amorphous solid (60.3 mg, 0.186 mmol, 93% yield, 97% ee).

H NMR (400 MHz, CDCl3) δ 7.83-7.83 (m, 2H), 7.48-7.41 (m, 3H), 7.25-7.18, (m, 3H), 7.03-7.01 (m, 2H), 6.92 (s, 1H), 6.83 (d, J = 7.6 Hz, 1H), 5.26 (td, J = 8.1, 5.7 Hz, 1H), 3.31 (dd, J = 13.3, 5.7 Hz, 1H), 2.98 (dd, J
= 13.3, 8.5 Hz, 1H), 2.78 (s, 3H, 2.06 (s, 3H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 169.6, 168.3, 167.4, 164.2, 137.0, 136.9, 130.9, 129.7, 129.0, 128.6, 127.4, 126.9, 112.7, 55.4, 42.2, 26.4, 23.6 HRMS m/z: [M+H]\(^+\) calculated for [C\(_{21}\)H\(_{22}\)N\(_3\)O]\(^+\) 332.1763, found: 332.1751. HPLC Analysis: Chiralpak IG (CO\(_2\)/MeOH = 90/10, 2.5 mL min\(^{-1}\), 40 °C) \(t_R\) = 8.7 (minor), 9.4 (major) minutes. \([\alpha]_D^{25.0} = -21.0\) (c 1.0, CHCl\(_3\)).

\((S)-N-(1-(2-methyl-5-phenylpyrimidin-4-yl)-2-phenylethyl)acetamide (9)\)

General procedure B was followed 2-methyl-5-phenylpyrimidine (51.1 mg, 0.3 mmol, 1.5 equiv.). The crude product was purified via flash column chromatography (eluting with 1% MeOH/EtOAc) to give the title product as a colourless oil (36.0 mg, 0.108 mmol, 54% yield, 99% ee).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.37 (s, 1H), 7.37-7.34 (m, 3H), 7.12-7.06, (m, 3H), 7.00-6.98 (m, 2H), 6.65 (d, \(J = 6.9\) Hz, 2H), 6.60 (d, \(J = 8.3\) Hz, 1H), 5.55 (q, \(J = 7.4\) Hz, 1H), 2.91-2.89 (m, 2H), 2.76 (s, 3H, 2.01 (s, 3H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 169.3, 166.9, 164.8, 157.5, 136.4, 134.5, 131.2, 129.4, 129.3, 128.8, 128.3, 128.3, 126.6, 51.3, 41.9, 25.9, 23.6. HRMS m/z: [M+H]\(^+\) calculated for [C\(_{21}\)H\(_{22}\)N\(_2\)O]\(^+\) 332.1763, found: 332.1753. HPLC Analysis: Chiralpak IG (CO\(_2\)/MeOH = 90/10, 2.5 mL min\(^{-1}\), 40 °C) \(t_R\) = 4.8 (major), 5.9 (minor) minutes. \([\alpha]_D^{25.0} = +6.9\) (c 1.0, CHCl\(_3\)).

\((S)-N-(1-(5-bromo-2-methylpyrimidin-4-yl)-2-phenylethyl)acetamide (10)\)

General procedure B was followed with 2-bromo-5-methylpyrimidine (51.9 mg, 0.3 mmol, 1.5 equiv.) and 1,3-dioxoisoinolin-2-yl acetylphenylalinate (70.5 mg, 0.20 mmol, 1.0 equiv.). The crude product was purified via flash column chromatography (eluting with 50% EtOAc in hexanes) to give the title product as
a white crystalline solid (43.4 mg, 0.130 mmol, 65% yield, 97% ee). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 8.61\) (s, 1H), 7.20-7.18 (m, 3H), 6.95-6.93 (m, 2H), 6.59 (d, \(J = 8\) Hz, 1H), 5.74-5.69 (m, 1H), 3.17 (dd, \(J = 13.7\), 6.2 Hz, 1H), 3.04 (dd, \(J = 13.5\), 6.2 Hz, 1H), 2.60 (s, 3H, 2.01 (s, 3H). \(^1^3\)C NMR (101 MHz, CDCl\(_3\)) \(\delta 169.3, 166.5, 165.3, 159.1, 134.0, 129.7, 128.3, 127.0, 117.0, 52.7, 40.3, 25.4, 23.5. HRMS m/z: [M+H]\(^+\) calculated for [C\(_{15}\)H\(_{17}\)BrN\(_3\)O]\(^+\) 344.0555, found: 344.0546. HPLC Analysis: CHIRAL ART SC (CO\(_2\)/MeOH = 90/10, 2.5 mL min\(^{-1}\), 40 °C) \(t_R = 5.9\) (major), 7.5 (minor) minutes. \([\alpha]\)\(^D\)\(_{25.0}\) = +17.1 (c 1.0, CHCl\(_3\)).

Compound 10 crystallized upon slow evaporation of chloroform and was analysed by X-ray diffraction. The absolute configuration was determined to be (S). The structure was deposited in the Cambridge Crystallographic Data Centre (deposition no.: CCDC 1924476). The absolute stereochemistry of all other diazine products in the scope have been assigned in analogy.

![Compound 10](image)

\((S)-N-(2-phenyl-1-(2-phenylpyrimidin-4-yl)ethyl)acetamide (11)\)

General procedure C was followed with 2-phenylpyrimidine\(^{20}\) (46.9, 0.3 mmol, 1.5 equiv.) and 1,3-dioxoisindolin-2-yl acetylphenylalaninate (84.6 mg, 0.24 mmol, 1.2 equiv.). The crude product was purified via flash column chromatography (eluting with a gradient of 30% to 70% EtOAc/hexanes) to give the title product as a white solid (20.8 mg, 0.066 mmol, 33% yield, 94% ee).
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.60 (d, $J = 5$ Hz, 1H), 8.43-8.40 (m, 2H), 7.53-7.50 (m, 3H), 7.23-7.18 (m, 3H), 7.02-7.01 (m, 2H), 6.73-6.73 (m, 2H), 5.34 (td, $J = 8.1$, 5.7 Hz), 3.31 (dd, $J = 13.4$, 5.6 Hz), 3.13 (dd, $J = 13.4$, 8.3 Hz), 2.06 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 169.6, 167.4, 164.5, 157.4, 137.5, 136.6, 131.1, 129.6, 128.7, 128.5, 128.3, 126.9, 117.7, 55.1, 41.9, 23.6. HRMS m/z: [M+H]$^+$ calculated for [C$_{20}$H$_{20}$N$_3$O]$^+$ 318.1606, found: 318.1599.

HPLC Analysis: CHIRAL ART SC (CO$_2$/MeOH = 90/10, 2.5 mL min$^{-1}$, 40 °C) $t_R$ = 11.9 (major), 12.9 (minor) minutes. $[\alpha]_D^{25.0} = +8.1$ (c 1.0, CHCl$_3$).

(5)-N-(1-(5-bromo-2-methoxypyrimidin-4-yl)-2-phenylethyl)acetamide (12)

General procedure C was followed with 2-methoxy-5-bromopyrimidine (56.7 mg, 0.3 mmol, 1.5 equiv.). The crude product was purified via flash column chromatography (eluting with a gradient of 20% to 60% EtOAc/hexanes) to give the title product as a white amorphous solid (30.8 mg, 0.088 mmol, 44% yield, >99% ee).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.48 (s, 1H), 7.23-7.20, (m, 3H), 7.00-6.98 (m, 2H), 6.44 (d, $J = 8.1$ Hz, 1H), 5.26 (dt, $J = 8.1$, 6.5 Hz, 1H), 3.93 (s, 3H), 3.17 (dd, $J = 13.7$, 6.1 Hz, 1H), 2.98 (dd, $J = 13.3$, 6.8 Hz, 1H), 1.97 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 169.4, 168.1, 164.3, 161.0, 135.9, 129.6, 128.5, 127.1, 111.4, 55.6, 52.8, 40.2, 23.4. HRMS m/z: [M+H]$^+$ calculated for [C$_{15}$H$_{17}$BrN$_3$O$_2$]$^+$ 350.0504, found: 350.0498. HPLC Analysis: CHIRAL ART SC (CO$_2$/MeOH = 90/10, 2.5 mL min$^{-1}$, 40 °C) $t_R$ = 7.8 (minor), 10.5 (major) minutes. $[\alpha]_D^{25.0} = +30.3$ (c 1.0, CHCl$_3$).

(5)-N-(1-(5-chloro-2-methoxypyrimidin-4-yl)-2-phenylethyl)acetamide (13)
General procedure C was followed with 2-methoxy-5-chloropyrimidine (43.5, 0.3 mmol, 1.5 equiv.). The crude product was purified via flash column chromatography (eluting with a gradient of 0% to 1% MeOH in CH$_2$Cl$_2$) to give the title product as a white amorphous solid (20.2 mg, 0.066 mmol, 33% yield, 99% ee).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.38 (s, 1H), 7.23-7.19, (m, 3H), 6.99-6.97 (m, 2H), 6.43 (d, $J$ = 8.2 Hz, 1H), 5.73 (td, $J$ = 8.4, 6.5 Hz, 1H), 3.94 (s, 3H), 3.16 (dd, $J$ = 13.6, 6.3 Hz, 1H), 3.04 (dd, $J$ = 13.7, 6.6 Hz, 1H), 1.98 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 169.4, 166.9, 163.7, 158.4, 135.8, 129.6, 128.5, 127.1, 122.3, 55.6, 51.0, 40.2, 23.4. HRMS m/z: [M+H]$^+$ calculated for [C$_{15}$H$_{17}$ClN$_3$O$_2$]$^+$ 306.1009, found: 306.1001. HPLC Analysis: Chiralpak IG (CO$_2$/MeOH = 90/10, 2.5 mL min$^{-1}$, 40 °C) t$_R$ = 5.1 (minor), 6.5 (major) minutes. [$\alpha$]$_D^{25.0}$ = +12.8 (c 1.0, CHCl$_3$).

(S)-N-(3-phenyl-1-(pyrimidin-4-yl)propyl)acetamide (14)

General procedure B was followed with pyrimidine (24.0 mg, 0.3 mmol, 1.5 equiv.), 1,3-dioxoisooindolin-2-yl 2-acetamido-4-phenylbutanoate (73.3 mg, 0.20 mmol, 1.2 equiv.) and (R)-TRIP (7.5 mg, 0.01 mmol, 0.05 equiv.). The crude product was purified via flash column chromatography (eluting with a gradient of 90% EtOAc/hexane to EtOAc to 2% MeOH/EtOAc) to give the title product as a colourless gum (24.6 mg, 0.096 mmol, 48% yield,* 65% ee). *with <5% regioisomer

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.16 (d, $J$ = 1.2 Hz, 1H), 8.66 (d, $J$ = 5.1 Hz, 1H), 7.27-7.22 (m, 3H), 7.19-7.11 (m, 3H), 6.63 (d, $J$ = 7.9 Hz), 5.13-5.07 (m, 1H), 2.6 (t, $J$ = 7.9 Hz, 2H), 2.23-2.01 (m, 6H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 169.9, 168.4, 158.9, 157.4, 140.9, 128.6, 128.4, 126.3, 119.7, 53.4, 37.2, 32.0, 23.4. HRMS m/z: [M+H]$^+$ calculated for [C$_{15}$H$_{18}$N$_3$O]$^+$ 256.1444, found: 256.1445. HPLC Analysis: Chiralpak IE (CO$_2$/MeOH = 90/10, 2.5 mL min$^{-1}$, 40 °C) t$_R$ = 11.5 (minor), 12.3 (major) minutes. [$\alpha$]$_D^{25.0}$ = -13.2 (c 1.0, CHCl$_3$).

(S)-N-(3-methyl-1-(pyrimidin-4-yl)butyl)acetamide (15)
General procedure B was followed with pyrimidine (24.0 mg, 0.3 mmol, 1.5 equiv.), 1,3-dioxoisindolin-2-yl acetylleucinate (63.7 mg, 0.20 mmol, 1.2 equiv.) and (R)-TRIP (7.5 mg, 0.01 mmol, 0.05 equiv.). The crude product was purified via flash column chromatography (eluting with a gradient of 80% EtOAc/hexane to EtOAc to 3% MeOH/EtOAc) to give the title product as a colourless gum (9.6 mg, 0.046 mmol, 23% yield,* 28% ee). *with <5% regioisomer

\[ ^1H \text{NMR (400 MHz, CDCl}_3 \] \delta 9.14 (d, J = 1.3 Hz, 1H), 8.65 (d, J = 5.1 Hz, 1H), 7.27-7.26 (m, 1H), 6.38 (d, J = 7.9 Hz), 5.09 (td, J = 8.3, 6.3 Hz 1H), 2.01 (s, 3H), 1.69-1.50 (m, 3 H), 0.95-0.93 (m, 6H). \[ ^13C \text{NMR (101 MHz, CDCl}_3 \] \delta 169.8, 169.4, 159.0, 157.3, 119.6, 52.1, 45.1, 25.0, 23.5, 22.9, 22.4. \[ \text{HRMS m/z: [M+H]^+ calculated for [C}_{11}\text{H}_{18}\text{N}_3\text{O}^+ 208.1444, found: 242.1443.} \]

**HPLC Analysis:** Chiralpak IE (CO\(_2\)/MeOH = 90/10, 2.5 mL min\(^{-1}\), 40 °C) t\(_R\) = 4.6 (minor), 5.0 (major) minutes. \([\alpha]_D^{25.0} = -13.8 \text{ (c 0.87, CHCl}_3 \].

\((S)-N-(2-methyl-1-(pyrimidin-4-yl)propyl)acetamide (16)\)

General procedure B was followed with pyrimidine (24.0 mg, 0.3 mmol, 1.5 equiv.), 1,3-dioxoisindolin-2-yl acetylvalinate (60.8 mg, 0.20 mmol, 1.2 equiv.) and (R)-TCYP (9.9 mg, 0.01 mmol, 0.05 equiv.). The crude product was purified via flash column chromatography (eluting with a gradient of 1% MeOH/EtOAc to 4% MeOH/EtOAc) to give the title product as a white solid (15.9 mg, 0.082 mmol, 41% yield,* 69% ee). *with <5% regioisomer

\[ ^1H \text{NMR (400 MHz, CDCl}_3 \] \delta 9.14 (d, J = 1.3 Hz, 1H), 8.65 (d, J = 5.1 Hz, 1H), 7.22 (dd, J = 5.1, 1.4 Hz, 1H), 6.61 (d, J = 7.5 Hz), 4.87 (dd, J = 8.8, 6.8 Hz 1H), 2.17-2.06 (m, 1H), 2.04 (s, 3H), 0.91 (d, J = 7.0 Hz, 3H), 0.82 (d, J = 7.0 Hz, 3H). \[ ^13C \text{NMR (101 MHz, CDCl}_3 \] \delta 169.9, 167.9, 158.7, 157.0, 120.5, 58.6, 33.5, 23.5, 19.3, 18.4 \[ \text{HRMS m/z: [M+H]^+ calculated for [C}_{10}\text{H}_{16}\text{N}_3\text{O}^+ 194.1288, found: 194.1287.} \]

**HPLC Analysis:** Chiralpak
IE (CO$_2$/MeOH = 90/10, 2.5 mL min$^{-1}$, 40 °C) $t_R$ = 4.8 (minor), 5.3 (major) minutes. $[\alpha]_D^{25.0} = -52.8$ (c 1.0, CHCl$_3$).

(S)-N-(2-phenyl-1-(3,5,6-trimethylpyrazin-2-yl)ethyl)acetamide (17)

General procedure A was followed with 2,3,5-trimethyl-pyrazine (24.4, 0.2 mmol, 1.0 equiv.) and 1,3-dioxoisoindolin-2-yl acetylphenylalaninate (84.6 mg, 0.24 mmol, 1.2 equiv.). The crude product was purified via flash column chromatography (eluting with a gradient of 50% EtOAc/hexanes to EtOAc) to give the title product as a white amorphous solid (34.8 mg, 0.122 mmol, 61% yield, 90% ee).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.16-7.13 (m, 3H), 6.90-6.86 (m, 2H), 6.71 (d, $J = 8.0$ Hz, 1H), 5.44 (td, $J = 8.4$, 5.2 Hz, 1H), 3.16 (dd, $J = 12.9$, 5.2 Hz, 1H), 2.98 (d, $J = 12.9$, 8.6 Hz), 2.48-2.46 (m, 6H), 2.08 (s, 3H), 2.00 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 169.2, 150.0, 148.9, 148.8, 147.8, 137.0, 129.6, 128.3, 126.7, 51.0, 42.4, 23.6, 21.7, 21.6, 20.1. HRMS m/z: [M+H]$^+$ calculated for [C$_{17}$H$_{22}$N$_3$O]$^+$ 284.1763, found: 284.1754. HPLC Analysis: Chiralpak IE (CO$_2$/MeOH = 90/10, 2.5 mL min$^{-1}$, 40 °C) $t_R$ = 9.6 (minor), 10.3 (major) minutes. $[\alpha]_D^{25.0} = -3.6$ (c 1.0, CHCl$_3$).

(S)-N-(1-(3,6-dimethylpyrazin-2-yl)-2-phenylethyl)acetamide (18)

General procedure B was followed with 2,5-dimethylpyrazine (32.4 mg, 0.3 mmol, 1.5 equiv.) and 1,3-dioxoisoindolin-2-yl acetylphenylalaninate (70.5 mg, 0.20 mmol, 1.0 equiv.). The crude product was purified via flash column chromatography (eluting with a gradient of EtOAc to 2% MeOH/EtOAc) to give the title product as a white amorphous solid (23.4 mg, 0.08 mmol, 91% ee, 40% yield).
\( ^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 8.21 (s, 1H), 7.17-7.15 (m, 3H), 6.87-6.85 (m, 2H), 6.70 (d, \( J = 8.0 \) Hz, 1H), 5.49 (td, \( J = 8.4, 5.3 \) Hz, 1H), 3.17 (dd, \( J = 12.9, 5.3 \) Hz, 1H), 3.01 (d, \( J = 12.9, 8.5 \) Hz), 2.50 (s, 3H), 2.16 (s, 3H), 2.00 (s, 3H). \( ^13\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 169.3, 151.8, 150.3, 148.7, 142.3, 136.7, 129.6, 128.4, 126.8, 51.2, 42.3, 23.6, 21.1, 20.4. HRMS m/z: [M+H]\(^+\) calculated for \([\text{C}_{16}\text{H}_{20}\text{N}_3\text{O}]^+\) 270.1606, found: 270.1599.

HPLC Analysis: Chiralpak IE (CO\(_2\)/MeOH = 90/10, 2.5 mL min\(^{-1}\), 40 °C) \( t_R \) = 8.2 (minor), 8.6 (major) minutes. \([\alpha]_D^{25.0} = +4.8 \) (c 1.0, CHCl\(_3\)).

\((S)-N-(2\text{-phenyl}-1\text{-}(\text{quinazolin-4-yl})\text{ethyl})\text{acetamide (19)}\)

\[ \text{HN} \]
\[ \text{N} \]
\[ \text{O} \]

General procedure A was followed with quinazoline (26.0 mg, 0.2 mmol) and 1,3-dioxoisindolin-2-yl acetylphenylalaninate (84.6 mg, 0.24 mmol, 1.2 equiv.). The crude product was purified via flash column chromatography (eluting first with 90\% EtOAc/hexane and then the product-containing fractions in 30\% acetone hexane) to give the title product as a white amorphous solid (5.9 mg, 0.020 mmol, 10\% yield, 56\% ee).

\( ^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 9.19 (s, 1H), 8.04 (d, \( J = 8.5 \) Hz, 1H), 7.98 (d, \( J = 8.5 \) Hz, 1H), 7.90-7.85 (m, 1H), 7.58-7.54 (m, 1H), 7.13-7.06 (m, 3H), 7.01 (d, \( J = 8.2 \) Hz, 1H), 6.80-7.78 (m, 2H), 6.24-6.19 (m, 1H), 3.34-3.24 (m, 2H), 2.07 (s, 3H). \( ^13\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 169.5, 168.0, 153.9, 150.3, 136.1, 134.2, 129.6, 129.2, 128.3, 128.1, 126.9, 124.2, 122.6, 50.6, 42.2, 23.6. HRMS m/z: [M+H]\(^+\) calculated for \([\text{C}_{18}\text{H}_{18}\text{N}_3\text{O}]^+\) 292.1444, found: 292.1434. HPLC Analysis: Chiralpak IE (CO\(_2\)/MeOH = 80/20, 2.5 mL min\(^{-1}\), 40 °C) \( t_R \) = 6.3 (major), 6.9 (major) minutes. \([\alpha]_D^{25.0} = -9.0 \) (c 0.54, CHCl\(_3\)).

\((S)-N-(1\text{-}(2\text{-aminopyrimidin-4-yl})\text{-2\text{-phenylethyl})acetamide (20)}\)
General procedure B was followed with 2-aminopyrimidine (28.5, 0.3 mmol, 1.5 equiv.) and 1,3-dioxoisindolin-2-yl acetylphenylalaninate (70.5 mg, 0.20 mmol, 1.0 equiv.). The crude product was purified via flash column chromatography (eluting with 6% Et₃N/EtOAc) to give the title product as a white amorphous solid (17.8 mg, 0.038 mmol, 35% yield, 81% ee).

\(^1\)H NMR (400 MHz, CDCl₃) δ 8.10 (d, \(J = 5.0 \) Hz, 1H), 7.24-7.16 (m, 3H), 7.00-6.98 (m, 2H), 6.59 (d, \(J = 7.4 \) Hz, 1H), 6.23 (d, \(J = 5.0 \) Hz, 1H), 5.13-5.08 (m, 3H), 3.15 (dd, \(J = 13.4, 5.7 \) Hz, 1H), 3.01 (dd, \(J = 13.4, 7.8 \) Hz, 1H), 2.01 (s, 3H). \(^13\)C NMR (101 MHz, CDCl₃) δ 169.5, 168.5, 162.9, 158.4, 136.8, 129.6, 128.4, 126.8, 110.2, 54.7, 41.7, 23.5. HRMS m/z: [M+H]\(^+\) calculated for [C\(_{14}\)H\(_{17}\)N\(_4\)O]\(^+\) 257.1397, found: 257.1396. HPLC Analysis: Chiralpak IE (CO\(_2\)/MeOH = 90/10, 2.5 mL min\(^{-1}\), 40 °C) \(t_r = 19.0 \) (minor), 19.9 (major) minutes. \([\alpha]_D^{25.0} = +29.1 \) (c 1.0, CHCl₃).

**tert-butyl (S)-(4-(1-acetamido-2-phenylethyl)pyrimidin-2-yl)carbamate (21)**

General procedure B was followed with tert-butyl pyrimidin-2-ylcarbamate (58.6 mg, 0.3 mmol, 1.5 equiv.) and 1,3-dioxoisindolin-2-yl acetylphenylalaninate (70.5 mg, 0.20 mmol, 1.0 equiv.). The crude product was purified via flash column chromatography (eluting with a gradient of 80% EtOAc/hexane to EtOAc) to give the title product as a white solid (38.5 mg, 0.108 mmol, 54% yield, 55% ee).

\(^1\)H NMR (400 MHz, CDCl₃) δ 8.39 (d, \(J = 5.0 \) Hz, 1H), 7.67 (br. s, 1H), 7.23-7.16 (m, 3H), 6.99-6.97 (m, 2H), 6.72, (d, \(J = 7.9 \) Hz, 1H), 6.48 (d, \(J = 5.0 \) Hz, 1H), 5.20 (td, \(J = 7.9, 5.7 \) Hz, 1H), 3.22 (dd, \(J = 13.4, 5.7 \) Hz, 1H), 2.99 (dd, \(J = 13.4, 8.2 \), 1H), 2.02 (s, 3H), 1.54 (s, 9H). \(^13\)C NMR (101 MHz, CDCl₃) δ 169.6, 168.9, 158.4, 157.7,
150.5, 136.5, 129.6, 128.5, 126.9, 114.3, 81.7, 54.8, 41.7, 28.3, 23.5. **HRMS m/z:** [M+H]+ calculated for [C_{19}H_{25}N_{4}O_{3}]^{+} 357.1921, found: 357.1929. **HPLC Analysis:** Chiralpak IE (CO_{2}/MeOH = 90/10, 2.5 mL min⁻¹, 40 °C) t_{R} = 12.0 (major), 12.8 (major) minutes. [α]_{D}^{25.0} = -7.0 (c 1.0, CHCl_{3}).

(S)-N-(1-(benzo[d]thiazol-2-yl)-2-phenylethyl)acetamide (22)

General procedure A was followed with benzothiazole (27.0 mg, 0.2 mmol) and 1,3-dioxoisindolin-2-yl acetylphenylalaninate (84.6 mg, 0.24 mmol, 1.2 equiv.). The crude product was purified via flash column chromatography (eluting with a gradient of CH_{2}Cl_{2} to 1% MeOH/CH_{2}Cl_{2}) to give the title product as a white amorphous solid (11.2 mg, 0.038 mmol, 19% yield, 27% ee).

^1H NMR (400 MHz, CDCl₃) δ 7.99 (d, J = 8.2 Hz, 1H), 7.84-7.81 (m, 1H), 7.50-7.46 (m, 1H), 7.40-7.36 (m, 1H), 7.25-7.21 (m, 3H), 7.13-7.10 (m, 2H), 6.43 (d, J = 7.8 Hz, 1H), 5.70 (dt, J = 8.0, 6.8 Hz, 1H), 3.37 (d, J = 6.6 Hz, 2H), 2.03 (s, 3H). ^13C NMR (101 MHz, CDCl₃) δ 171.4, 169.7, 152.9, 136.2, 135.0, 129.6, 128.7, 127.2, 126.3, 125.4, 123.0, 121.9, 52.9, 41.6, 23.4. **HRMS m/z:** [M+H]+ calculated for [C_{17}H_{17}N_{2}OS]^{+} 297.1056, found: 297.1051. **HPLC Analysis:** Chiralpak IE (CO_{2}/MeOH = 90/10, 2.5 mL min⁻¹, 40 °C) t_{R} = 12.0 (major), 12.8 (major) minutes. [α]_{D}^{25.0} = -19.0 (c 1.0, CHCl₃).
Computational Methods

Model catalyst structures were optimized with constraints in the gas-phase with the M06-2X density functional,\textsuperscript{21} and the triple-\(\zeta\) valence quality def2-TZVP basis set of Weigend and Ahlrichs,\textsuperscript{22} as implemented in Gaussian 09 (revision D.01).\textsuperscript{23} The torsion angle defined by the atoms 2, 1, 1’ and 2’, where 2 and 2’ are the oxygen bearing carbons, was constrained to 60° as this reproduces well the geometric effect of the BINOL backbone.\textsuperscript{24} All of the optimized geometries were verified by frequency computations as minima (zero imaginary frequencies). Parameters were acquired from these ground state structures. NBO charges were calculated using NBO6 as implemented in Gaussian09,\textsuperscript{25} at the same level. Sterimol values were calculated using a modified version of Paton’s Python script.\textsuperscript{26} Multidimensional regression analyses were performed using MATLAB\textsuperscript{®}.\textsuperscript{27} The same procedure was applied to substrates A-G and any out-of-sample prediction platform.

Conformational searches were performed with Macromodel version 11.7\textsuperscript{28} and the OPLS3 force field.\textsuperscript{29}
Cartesian coordinates of the model catalyst structures

Model CPA-1

M06-2X/def2-TZVP Geometry

C  -1.49340  2.76480  0.28560
C  -1.62840  1.45960  -0.18510
C   -0.42700  0.70930  -0.31780
C   0.82070  1.20060  0.03480
C   0.88930  2.51800  0.49800
C  -0.25350  3.28550  0.63720
H   -2.38010  3.38340  0.37090
H    1.85370  2.91570  0.79090
H  -0.18140  4.29650  1.01810
C  -2.89330  1.05140  -0.76970
H   -3.47690  1.87900  -1.16250
C  -3.62320  -0.06930  -0.56360
H  -4.65660  -0.14550  -0.88170
O   -0.62430  -0.57380  -0.75450
O   -3.12200  -1.22470  -0.11670
P  -1.51210  -1.61310   0.20610
O   -1.24970  -1.22450  1.60430
O   -1.32670  -2.95130  -0.36170
C   2.04110  0.36480  -0.04560
C   2.06330  -0.92360   0.49180
C   3.20250  0.87340  -0.62590
C   3.22510  -1.67880   0.43940
H   1.17170  -1.31580   0.96680
### Model CPA-2

M06-2X/def2-TZVP Geometry

| Element | X   | Y   | Z   |
|---------|-----|-----|-----|
| C       | -3.13530 | 2.49470 | 0.99520 |
| C       | -3.08420 | 1.35790 | 0.19710 |
| C       | -1.84560 | 0.73540 | -0.03230 |
| C       | -0.67170 | 1.24990 | 0.53830 |
| C       | -0.77160 | 2.37500 | 1.35650 |
| C       | -1.98900 | 2.99130 | 1.59700 |
| H       | -4.09040 | 2.98500 | 1.14510 |
| H       | 0.13080 | 2.76000 | 1.81690 |
| H       | -2.04090 | 3.85870 | 2.24250 |
| C       | -4.25940 | 0.89890 | -0.56260 |
| H       | -4.88870 | 1.63210 | -1.05110 |
| C       | -4.66950 | -0.36190 | -0.46490 |
| H       | -5.57170 | -0.73790 | -0.93620 |
| O       | -1.80530 | -0.34600 | -0.84020 |
| O       | -3.92910 | -1.28180 | 0.19730 |
| P       | -2.51630 | -1.81530 | -0.48770 |
| O       | -1.77220 | -2.45500 | 0.61390 |
| O       | -2.79970 | -2.43630 | -1.78690 |
|  | X     | Y     | Z     |
|---|-------|-------|-------|
| C | 0.6459 | 0.5974 | 0.3244 |
| C | 0.7839 | -0.7194 | 0.6080 |
| C | 1.7908 | 1.3473 | -0.1524 |
| C | 2.0394 | -1.3900 | 0.4908 |
| C | 3.0609 | 0.7227 | -0.2379 |
| C | 1.6699 | 2.6885 | -0.5759 |
| C | 3.1949 | -0.6821 | 0.1043 |
| C | 4.1563 | 1.4852 | -0.6885 |
| H | 0.6934 | 3.1517 | -0.5600 |
| C | 2.7541 | 3.4021 | -1.0223 |
| C | 4.0161 | 2.7978 | -1.0660 |
| H | 5.1339 | 1.0290 | -0.7538 |
| H | 2.6300 | 4.4273 | -1.3477 |
| H | 4.8767 | 3.3563 | -1.4123 |
| H | -0.0749 | -1.3018 | 0.9276 |
| C | 4.4150 | -1.3849 | 0.0483 |
| H | 5.3256 | -0.8757 | -0.2352 |
| C | 2.1176 | -2.7674 | 0.7796 |
| H | 1.1999 | -3.2815 | 1.0415 |
| C | 4.4766 | -2.7251 | 0.3462 |
| H | 5.4265 | -3.2426 | 0.2925 |
| C | 3.3172 | -3.4283 | 0.7084 |
| H | 3.3717 | -4.4874 | 0.9258 |

Model CPA-3

M06-2X/def2-TZVP Geometry
C  -1.7465  2.9302  0.5915
| Atom | X        | Y        | Z        |
|------|----------|----------|----------|
| C    | -2.05540 | 1.73490  | -0.04720 |
| C    | -1.09640 | 0.70870  | -0.08270 |
| C    | 0.16000  | 0.88450  | 0.51360  |
| C    | 0.41890  | 2.08790  | 1.16940  |
| C    | -0.52420 | 3.10170  | 1.22350  |
| H    | -2.48140 | 3.72720  | 0.59240  |
| H    | 1.38210  | 2.21640  | 1.64950  |
| H    | -0.30180 | 4.02360  | 1.74560  |
| C    | -3.28300 | 1.58360  | -0.84670 |
| H    | -3.60020 | 2.39990  | -1.48330 |
| C    | -4.10310 | 0.56030  | -0.62760 |
| H    | -5.05740 | 0.43930  | -1.13040 |
| O    | -1.39640 | -0.43470 | -0.73540 |
| O    | -3.75690 | -0.43800 | 0.21640  |
| P    | -2.57070 | -1.50980 | -0.23050 |
| O    | -2.13140 | -2.14010 | 1.02720  |
| O    | -2.98770 | -2.22910 | -1.44040 |
| C    | 1.19900  | -0.17740 | 0.47710  |
| C    | 0.91060  | -1.42740 | 0.96670  |
| C    | 2.50870  | 0.09430  | -0.03110 |
| C    | 1.89900  | -2.43140 | 1.01570  |
| C    | 3.50330  | -0.91990 | 0.04220  |
| C    | 2.86000  | 1.32440  | -0.64770 |
| C    | 3.16960  | -2.18350 | 0.58280  |
| C    | 4.80590  | -0.65320 | -0.44790 |
| H    | 2.10220  | 2.08810  | -0.75600 |
| C    | 4.12270  | 1.54720  | -1.12240 |
| C    | 5.11650  | 0.55120  | -1.01100 |
| H    | 5.55240  | -1.43620 | -0.37410 |
| H    | 4.36040  | 2.49130  | -1.59680 |
| H    | 6.11500  | 0.73950  | -1.38570 |
| H    | -0.09510 | -1.64980 | 1.30930  |
### Model CPA-4

**M06-2X/def2-TZVP Geometry**

| Element | X          | Y          | Z          |
|---------|------------|------------|------------|
| C       | -3.05290   | 1.84660    | 1.71480    |
| C       | -2.94160   | 1.18470    | 0.49260    |
| C       | -1.64440   | 0.70320    | 0.16770    |
| C       | -0.53320   | 0.87760    | 0.96920    |
| C       | -0.71220   | 1.54140    | 2.18550    |
| C       | -1.96270   | 1.99830    | 2.56500    |
| H       | -4.01520   | 2.25720    | 2.00040    |
| H       | 0.14630    | 1.68040    | 2.83270    |
| H       | -2.08870   | 2.49750    | 3.51770    |
| C       | -4.02820   | 1.30380    | -0.46330   |
| H       | -4.64030   | 2.18640    | -0.30030   |
| C       | -4.64160   | 0.36660    | -1.22270   |
| H       | -5.58740   | 0.56010    | -1.71500   |
| O       | -1.60220   | -0.04750   | -0.98190   |
| O       | -4.07790   | -0.78730   | -1.60100   |
| P       | -2.60090   | -1.39230   | -1.07020   |
| O       | -2.81750   | -1.86080   | 0.31190    |
| O       | -2.09780   | -2.19680   | -2.18670   |
| C       | 0.81220    | 0.37750    | 0.55800    |
| C       | 1.17320    | -0.95010   | 0.80460    |
| C       | 1.72380    | 1.25670    | -0.05390   |
| C       | 2.45960    | -1.36910   | 0.46480    |
| C       | 2.99250    | 0.79510    | -0.37790   |
| Element | X-coordinate | Y-coordinate | Z-coordinate |
|---------|--------------|--------------|--------------|
| C       | 3.38050      | -0.51700     | -0.11970     |
| H       | 2.74480      | -2.39830     | 0.65840      |
| H       | 3.69790      | 1.46970      | -0.84990     |
| C       | 4.76720      | -1.00270     | -0.48480     |
| H       | 4.82500      | -2.05600     | -0.19480     |
| C       | 5.01260      | -0.91580     | -1.99190     |
| H       | 4.98680      | 0.12390      | -2.32530     |
| H       | 5.99100      | -1.32800     | -2.25040     |
| H       | 4.24630      | -1.46150     | -2.54300     |
| C       | 5.85020      | -0.24200     | 0.28200      |
| H       | 5.69340      | -0.31930     | 1.35870      |
| H       | 6.84250      | -0.63340     | 0.04530      |
| H       | 5.83460      | 0.81780      | 0.01760      |
| C       | 0.21400      | -1.93350     | 1.44270      |
| H       | -0.78080     | -1.48960     | 1.46410      |
| C       | 0.08670      | -3.22210     | 0.63060      |
| H       | 1.01140      | -3.80670     | 0.65340      |
| H       | -0.71930     | -3.83000     | 1.04330      |
| H       | -0.17310     | -3.00590     | -0.40690     |
| C       | 0.63560      | -2.22750     | 2.88440      |
| H       | -0.07120     | -2.91790     | 3.34940      |
| H       | 1.62960      | -2.68360     | 2.91470      |
| H       | 0.66490      | -1.31220     | 3.47960      |
| C       | 1.29550      | 2.66130      | -0.43830     |
| H       | 0.56560      | 2.99990      | 0.29950      |
| C       | 0.59580      | 2.62530      | -1.80150     |
| H       | -0.24310     | 1.92900      | -1.80110     |
| H       | 0.22920      | 3.61840      | -2.07230     |
| H       | 1.30100      | 2.29660      | -2.56960     |
| C       | 2.43700      | 3.67530      | -0.45640     |
| H       | 3.12680      | 3.48890      | -1.28250     |
| H       | 2.03480      | 4.68100      | -0.59320     |
Model CPA-5

M06-2X/def2-TZVP Geometry

\[
\begin{array}{ccc}
C & -1.88740 & 2.78010 \\
C & -1.97590 & 1.44260 \\
C & -0.79320 & 0.68980 \\
C & 0.43980 & 1.24590 \\
C & 0.48350 & 2.57630 \\
C & -0.67040 & 3.34770 \\
C & -3.26570 & 0.82670 \\
O & -0.83730 & -0.55660 \\
O & -2.81600 & -1.23100 \\
P & -1.35720 & -1.86190 \\
O & -1.58660 & -2.93510 \\
C & 1.69720 & 0.45050 \\
C & 2.29110 & -0.06160 \\
C & 2.28170 & 0.24090 \\
C & 3.49020 & -0.75920 \\
C & 3.48040 & -0.45990 \\
C & 4.08680 & -0.95490 \\
C & 1.60870 & 0.74440 \\
C & 1.61690 & 0.07790 \\
H & -2.79680 & 3.36900 \\
H & 1.44260 & 3.00660 \\
H & -0.61830 & 4.38530 \\
\end{array}
\]
|   | X     | Y     | Z     |
|---|-------|-------|-------|
| H | -4.01330 | 1.42690 | 1.00820 |
| H | -4.55940 | -0.84110 | 0.42360 |
| H | 3.94650 | -1.16820 | -1.92790 |
| H | 3.93330 | -0.62390 | 2.31540 |
| H | 5.01710 | -1.50540 | 0.27360 |
| H | 2.23790 | 0.57500 | 3.38510 |
| H | 1.38840 | 1.81150 | 2.43900 |
| H | 0.65860 | 0.22610 | 2.65870 |
| H | 2.25180 | -0.32050 | -3.27640 |
| H | 1.38520 | 1.11940 | -2.71340 |
| H | 0.67900 | -0.48510 | -2.46190 |

Model CPA-6

M06-2X/def2-TZVP Geometry

|   | X     | Y     | Z     |
|---|-------|-------|-------|
| C | -1.94568 | 2.62598 | 0.86498 |
| C | -2.01195 | 1.47635 | 0.07782 |
| C | -0.76549 | 0.89480 | -0.28189 |
| C | 0.45883 | 1.43428 | 0.07533 |
| C | 0.45758 | 2.59240 | 0.85649 |
| C | -0.73178 | 3.16351 | 1.27555 |
| H | -2.87071 | 3.11977 | 1.14203 |
| H | 1.40914 | 3.02328 | 1.14565 |
| H | -0.71697 | 4.04943 | 1.89823 |
| C | -3.26861 | 1.17088 | -0.58391 |
| H | -3.91533 | 2.03640 | -0.69395 |
| C | -3.92493 | -0.00467 | -0.71940 |
| H | -4.95979 | -0.04291 | -1.03991 |
| O | -0.86813 | -0.29155 | -0.96052 |
O  -3.34715  -1.20996  -0.67426
P  -1.75166  -1.53520  -0.26431
O  -1.65692  -1.36889   1.19876
O  -1.40895  -2.74303  -1.02086
C   1.74326   0.84499  -0.39720
C   2.26281  -0.34559   0.12592
C   2.45447   1.53747  -1.37744
C   3.48592  -0.80244  -0.36555
C   3.66808   1.06841  -1.85405
C   4.18538  -0.11355  -1.34331
H   3.89685  -1.72427   0.02985
H   4.19946   1.61541  -2.62306
C   1.56702  -1.09716   1.23864
H   0.55779  -0.70296   1.35061
C   1.42271  -2.58875   0.94331
H   2.39118  -3.09844   0.96235
H   0.77766  -3.04207   1.69726
H   0.94705  -2.75466  -0.02414
C   2.30512  -0.86708   2.56058
H   1.78471  -1.37698   3.37371
H   3.32640  -1.25597   2.50812
H   2.35935   0.19719   2.80012
H   5.12953  -0.49986  -1.70849
H   2.03129   2.45308  -1.77388

Model CPA-7

M06-2X/def2-TZVP Geometry
C  -2.14990  2.72718  0.48536
| Atom | X    | Y    | Z    |
|------|------|------|------|
| C    | -2.17521 | 1.46480 | -0.10594 |
| C    | -0.91764 | 0.81737 | -0.25796 |
| C    | 0.27940  | 1.35568 | 0.18901  |
| C    | 0.23753  | 2.62673 | 0.76924  |
| C    | -0.96241 | 3.29712 | 0.93035  |
| H    | -3.08075 | 3.27353 | 0.59125  |
| H    | 1.16048  | 3.06130 | 1.13464  |
| H    | -0.97643 | 4.27164 | 1.40238  |
| C    | -3.38582 | 1.02800 | -0.77920 |
| H    | -4.01468 | 1.84853 | -1.11289 |
| C    | -4.04120 | -0.15392 | -0.71183 |
| H    | -5.05464 | -0.26764 | -1.07894 |
| O    | -1.01042 | -0.43274 | -0.81276 |
| O    | -3.47391 | -1.31423 | -0.36397 |
| P    | -1.85806 | -1.60560 | 0.01992  |
| O    | -1.69802 | -1.30918 | 1.45568  |
| O    | -1.53629 | -2.87981 | -0.63064 |
| C    | 1.55155  | 0.60318 | 0.08731  |
| C    | 1.61927  | -0.72230 | 0.50383  |
| C    | 2.70306  | 1.22116 | -0.40160 |
| C    | 2.81155  | -1.43409 | 0.41981  |
| H    | 0.73377  | -1.19609 | 0.91313  |
| C    | 3.90478  | 0.53157 | -0.49039 |
| H    | 2.64827  | 2.25133 | -0.73807 |
| C    | 3.94315  | -0.79807 | -0.07782 |
| H    | 4.87573  | -1.35013 | -0.15205 |
| C    | 2.85130  | -2.86780 | 0.87421  |
| H    | 3.75196  | -3.37094 | 0.52081  |
| H    | 2.83427  | -2.92833 | 1.96472  |
| H    | 1.97721  | -3.40615 | 0.50628  |
| C    | 5.13215  | 1.18877 | -1.06457 |
| H    | 6.03139  | 0.88401 | -0.52684 |
Model CPA-8

M06-2X/def2-TZVP Geometry

C  -4.92436  0.37553  0.24207
C  -4.58856 -0.76171 -0.38760
C  -3.30370 -1.40636 -0.66066
C  -2.07572 -0.73991 -0.54748
O  -4.19317  1.31408  0.84518
O  -2.07075  0.57917 -0.24255
C  -0.86165 -1.39420 -0.79414
C  -0.90429 -2.72029 -1.22912
C  -2.10845 -3.38528 -1.38645
C  -3.29403 -2.73218 -1.09379
P  -2.58933  1.11994  1.23141
O  -2.04805  2.47479  1.39309
O  -2.47837  0.00913  2.18962
C  0.44863 -0.73064 -0.57224
C  1.51091 -1.47695 -0.04544
C  2.75112 -0.90640  0.18913
C  2.91976  0.45231 -0.09853
C  1.88718  1.22618 -0.60741
C  0.65869  0.61184 -0.85326
C  3.92341 -1.69376  0.77675
C  2.01662  2.72780 -0.85645
C  1.05074  3.46535  0.08317
C  1.65682  3.04675 -2.31401
C  3.43481  3.23733  -0.59752
C  5.10895 -1.65107  -0.19722
C  3.57027 -3.15908   1.03179
C  4.34383 -1.06506   2.11246
H  -5.98076  0.62437   0.28601
H  -5.44698 -1.31742  -0.74832
H   0.02526 -3.22416  -1.46355
H  -2.12242 -4.41007  -1.73586
H  -4.24119 -3.24846  -1.20225
H   1.32749 -2.51078   0.21096
H   3.87979  0.90983   0.10067
H  -0.16198  1.19663  -1.23842
H   1.10392  4.54252  -0.09937
H   0.01523  3.14204  -0.03646
H   1.31454  3.27802   1.12573
H   2.31689  2.51322  -3.00217
H   0.62863  2.76705  -2.54210
H   1.76058  4.11949  -2.49599
H   4.16529  2.74503  -1.24476
H   3.47632  4.31033  -0.79671
H   3.73143  3.08097   0.44148
H   4.83332 -2.09585  -1.15551
H   5.43464 -0.62693  -0.38337
H   5.95630 -2.20783   0.21249
H   4.44198 -3.67760   1.43742
H   2.75590 -3.25508   1.75174
H   3.27488 -3.66500   0.11048
H   4.66426 -0.03077   1.98259
H   3.50956 -1.07123   2.81583
H   5.17382 -1.62574   2.55129
**Model CPA-9**

M06-2X/def2-TZVP Geometry

| Atom | X   | Y   | Z   |
|------|-----|-----|-----|
| C    | 4.88340 | -0.47900 | 1.55160 |
| C    | 4.86970 | 0.14180 | 0.37320 |
| C    | 3.82110 | -0.16710 | -0.61290 |
| C    | 2.48910 | 0.05840 | -0.24730 |
| O    | 3.87020 | -1.27690 | 1.94540 |
| O    | 2.22970 | 0.43040 | 1.02990 |
| C    | 1.44320 | -0.08940 | -1.15920 |
| C    | 1.76190 | -0.42980 | -2.47030 |
| C    | 3.07930 | -0.64180 | -2.85860 |
| C    | 4.10310 | -0.49760 | -1.93520 |
| C    | 2.34170 | -0.68910 | 2.25490 |
| O    | 1.43790 | -1.81420 | 1.95460 |
| O    | 2.35530 | 0.09140 | 3.49820 |
| C    | 0.02550 | 0.14310 | -0.75240 |
| C    | -0.44930 | 1.44940 | -0.58310 |
| C    | -1.79780 | 1.64500 | -0.29320 |
| C    | -2.67910 | 0.58460 | -0.15210 |
| C    | -2.17550 | -0.70560 | -0.27480 |
| C    | -0.83610 | -0.94990 | -0.55630 |
| C    | -0.32890 | -2.37360 | -0.62510 |
| C    | 0.46600 | 2.65130 | -0.65600 |
| C    | -4.13120 | 0.83000 | 0.18270 |
| C    | 0.03800 | 3.66760 | -1.72200 |
| C    | 1.01320 | 4.84160 | -1.78190 |
| C    | 1.15870 | 5.51380 | -0.41790 |
| C    | 1.56720 | 4.50410 | 0.65300 |
|   |      |      |      |      |
|---|------|------|------|------|
| C | 0.59020 | 3.33420 | 0.71350 |
| C | -5.09030 | 0.18760 | -0.82610 |
| C | -6.54810 | 0.48050 | -0.47900 |
| C | -6.88050 | 0.02190 | 0.93930 |
| C | -5.29400 | 0.65220 | 1.95420 |
| C | -4.47280 | 0.36120 | 1.60310 |
| C | -0.84920 | -3.25720 | 0.51470 |
| C | -0.18870 | -4.63120 | 0.44930 |
| C | -0.45010 | -5.30660 | -0.89560 |
| C | -0.00640 | -4.42050 | -2.05830 |
| C | -0.64030 | -3.03360 | -1.97490 |
| H | 5.68310 | -0.35510 | 2.27590 |
| H | 5.72970 | 0.72460 | 0.06790 |
| H | 0.96090 | -0.52090 | -3.19400 |
| H | 3.30480 | -0.90650 | -3.88420 |
| H | 5.13550 | -0.64040 | -2.23330 |
| H | -2.17060 | 2.65610 | -0.16150 |
| H | -2.83970 | -1.54920 | -0.12520 |
| H | 0.75620 | -2.34090 | -0.50040 |
| H | 1.46640 | 2.30810 | -0.93060 |
| H | -4.29800 | 1.91410 | 0.14750 |
| H | -0.02840 | 3.17330 | -2.69490 |
| H | -0.96460 | 4.04310 | -1.48800 |
| H | 0.68570 | 5.56760 | -2.53120 |
| H | 1.99290 | 4.47240 | -2.10450 |
| H | 0.19740 | 5.96130 | -0.13830 |
| H | 1.88370 | 6.33010 | -0.47440 |
| H | 1.63400 | 4.98970 | 1.62930 |
| H | 2.56650 | 4.11690 | 0.42610 |
| H | -0.39620 | 3.70000 | 1.02260 |
| H | 0.91420 | 2.59960 | 1.45240 |
| H | -4.85280 | 0.54150 | -1.83200 |
|   | X   | Y   | Z   |
|---|-----|-----|-----|
| H | -4.93140 | -0.89590 | -0.82810 |
| H | -7.21340 | -0.00050 | -1.20040 |
| H | -6.72560 | 1.55940  | -0.55600 |
| H | -6.78650 | -1.06850 | 0.99270  |
| H | -7.91770 | 0.26360  | 1.18520  |
| H | -6.15450 | 0.29230  | 2.96080  |
| H | -6.08580 | 1.73710  | 1.96360  |
| H | -4.28600 | -0.71600 | 1.67240  |
| H | -3.79770 | 0.83910  | 2.31590  |
| H | -0.62060 | -2.77220 | 1.46290  |
| H | -1.93580 | -3.38410 | 0.43110  |
| H | -0.54980 | -5.26300 | 1.26480  |
| H | 0.88670  | -4.49860 | 0.60340  |
| H | -1.52480 | -5.50480 | -0.99200 |
| H | 0.05550  | -6.27500 | -0.94580 |
| H | -0.24910 | -4.89510 | -3.01340 |
| H | 1.08240  | -4.30560 | -2.02550 |
| H | -1.72920 | -3.11320 | -2.08780 |
| H | -0.28270 | -2.40610 | -2.79410 |

![Model CPA-10](image)

**Model CPA-10**

M06-2X/def2-TZVP Geometry

|   | X   | Y   | Z   |
|---|-----|-----|-----|
| C | 3.18160 | -2.81580 | 0.91200 |
| C | 3.18650 | -1.68760 | 0.09450 |
| C | 1.92340 | -1.07400 | -0.14290 |
| C | 0.74920 | -1.51420 | 0.44600 |
| C | 0.80610 | -2.65250 | 1.25500 |
| C | 2.01080 | -3.28840 | 1.49500 |
|   |  x    |   y    |   z    |
|---|-------|-------|-------|
| H |  4.11670 | -3.33510 |  1.08970 |
| H |  -0.10230 |  -3.00350 |  1.73000 |
| H |   2.04220 |  -4.15730 |  2.13990 |
| C |   4.37460 |  -1.36770 |  -0.67470 |
| H |   5.00280 |  -2.22710 |  -0.88950 |
| C |   5.00970 |  -0.18230 |  -0.82240 |
| H |   6.01170 |  -0.11490 |  -1.22970 |
| O |   1.97770 |   0.03530 |  -0.93750 |
| O |   4.43380 |   1.00890 |  -0.63510 |
| P |   2.81160 |   1.37610 |  -0.37870 |
| O |   2.59890 |   1.40730 |   1.08100 |
| O |   2.50580 |   2.45870 |  -1.31530 |
| C |  -0.52270 |  -0.78280 |   0.25630 |
| C |  -0.58540 |   0.60230 |   0.46200 |
| C |  -1.68070 |  -1.46550 |  -0.08500 |
| C |  -1.79180 |   1.25920 |   0.31630 |
| H |   0.31060 |   1.13940 |   0.75850 |
| C |  -2.88750 |  -0.78630 |  -0.22720 |
| H |  -1.64070 |  -2.53490 |  -0.25670 |
| C |  -2.95470 |   0.57770 |  -0.03200 |
| H |  -3.89010 |   1.10890 |  -0.14480 |
| C |  -1.89880 |   2.74020 |   0.54940 |
| C |  -4.10910 |  -1.57340 |  -0.59250 |
| F |  -0.74340 |   3.30450 |   0.86270 |
| F |  -2.38550 |   3.37370 |  -0.53140 |
| F |  -2.76280 |   3.01020 |   1.55120 |
| F |  -3.94650 |  -2.25660 |  -1.73620 |
| F |  -5.19300 |  -0.80420 |  -0.74950 |
| F |  -4.41560 |  -2.48690 |   0.34540 |
Model CPA-11

M06-2X/def2-TZVP Geometry

C      -4.08750    -1.08820    0.18490
C       -3.98770     0.16120    0.62780
C       -2.94760    1.05680    0.09380
C       -1.59990    0.69390    0.24310
O       -3.13460   -1.61380   -0.62190
O       -1.31090   -0.51670     0.76740
C       -0.57640    1.59190   -0.09970
C       -0.93630    2.84970   -0.58310
C      -2.26370    3.21730   -0.73670
C      -3.26260    2.32630   -0.37870
C       0.85850    1.25250   -0.05210
C       1.75080    2.21490     0.59640
C       3.08670    1.95820     0.71830
C       3.62170    0.71460     0.30600
C       2.73510   -0.25320   -0.22990
C       1.35740     0.03930   -0.35130
C       4.99780     0.39950     0.41460
C       5.46840   -0.81880     0.01040
C       4.58360   -1.78580   -0.52060
C       3.25030   -1.50970   -0.63720
P      -1.66020   -1.97920     0.04200
O       -1.83940   -2.93430     1.14260
O       -0.74900   -2.16530   -1.10260
H       -4.88180   -1.76790     0.47700
H       -4.78090     0.58080     1.23360
H     -0.14970     3.53850   -0.86820
Model CPA-12

M06-2X/def2-TZVP Geometry

C  4.57497  -0.56323  1.63246
C  4.55864  -0.64854  0.30396
C  3.57634   0.12178 -0.47733
C  2.21683  -0.11727 -0.24190
O  3.60960   0.09079  2.31453
O  1.88106  -0.94222  0.77605
C  1.22723   0.49666 -1.01424
C  1.62352   1.33979 -2.04899
C  2.96615   1.56430 -2.31350
C  3.93626   0.94399 -1.53905
P  2.03991  -0.45955  2.35668
O  1.96280  -1.69374  3.14872
O  1.21870   0.74584  2.57132
C  -0.21066   0.25344 -0.72463
C  -0.72825  -1.05078 -0.74717
C  -2.06504  -1.27199 -0.43874
|  |  |  |  |
|---|---|---|---|
| C | -2.92749 | -0.22245 | -0.14052 |
| C | -2.41421 | 1.06918 | -0.15086 |
| C | -1.07199 | 1.31893 | -0.41979 |
| C | -0.59412 | 2.72527 | -0.32702 |
| C | 0.10059 | -2.22365 | -1.13169 |
| C | -4.34818 | -0.47902 | 0.18637 |
| C | -5.35465 | 0.38868 | -0.23972 |
| C | -6.68462 | 0.14463 | 0.06829 |
| C | -7.03661 | -0.97559 | 0.80924 |
| C | -6.04490 | -1.84578 | 1.24118 |
| C | -4.71561 | -1.59917 | 0.93431 |
| C | 0.27273 | -3.27865 | -0.23914 |
| C | 1.01887 | -4.38992 | -0.59960 |
| C | 1.60161 | -4.46155 | -1.85773 |
| C | 1.44329 | -3.40975 | -2.74951 |
| C | 0.70012 | -2.29538 | -2.38617 |
| C | -1.19204 | 3.71385 | -1.10559 |
| C | -0.77179 | 5.03443 | -1.01895 |
| C | 0.24821 | 5.37750 | -0.14317 |
| C | 0.83659 | 4.39622 | 0.64580 |
| C | 0.42479 | 3.07421 | 0.55983 |
| H | 5.33333 | -1.03954 | 2.24669 |
| H | 5.37905 | -1.13411 | -0.20925 |
| H | 0.86135 | 1.83130 | -2.64238 |
| H | 3.25452 | 2.22037 | -3.12477 |
| H | 4.98806 | 1.10335 | -1.74782 |
| H | -2.44397 | -2.28655 | -0.47881 |
| H | -3.04920 | 1.90326 | 0.12421 |
| H | -5.08832 | 1.25344 | -0.83512 |
| H | -7.44958 | 0.82855 | -0.27822 |
| H | -8.07461 | -1.16727 | 1.05011 |
| H | -6.30613 | -2.71617 | 1.83022 |
H  -3.94437  -2.26581  1.29954
H  -0.13213  -3.19304  0.76183
H   1.16584  -5.18888  0.11576
H   2.19066  -5.32669  -2.13635
H   1.90342  -3.45325  -3.72899
H   0.58632  -1.46751  -3.07568
H  -1.98335   3.43828  -1.79407
H  -1.23862   5.79178  -1.63705
H   0.58068   6.40604  -0.07211
H   1.62460   4.65801  1.34087
H   0.86692   2.31135  1.19752

Model CPA-13

M06-2X/def2-TZVP Geometry
C   1.64998  -1.99916  2.14500
C   1.86754  -1.49289  0.86481
C   0.78340  -0.77727  0.28706
C  -0.43738  -0.59913  0.90923
C  -0.58971  -1.12117  2.19641
C   0.45046  -1.79079  2.81738
H   2.43723  -2.57486  2.61936
H  -1.53878  -0.98469  2.70231
H   0.32084  -2.17885  3.82004
C   3.01290  -1.97377  0.11161
H   3.36777  -2.94372  0.44789
C   3.92843  -1.29661  -0.61933
H   4.85804  -1.75613  -0.93502
O   1.07788  -0.19293  -0.91977
| Element | X       | Y       | Z       |
|---------|---------|---------|---------|
| O       | 3.71695 | -0.10143| -1.18314|
| P       | 2.36792 | 0.87853 | -0.96554|
| O       | 2.49173 | 1.46218 | 0.38378 |
| O       | 2.23303 | 1.62190 | -2.22098|
| C       | -1.56701| 0.10541 | 0.23213 |
| C       | -1.64712| 1.50257 | 0.26546 |
| C       | -2.56039| -0.65431| -0.41196|
| C       | -2.75068| 2.12368 | -0.31848|
| C       | -3.64508| 0.00209 | -0.98244|
| C       | -3.74527| 1.38451 | -0.93034|
| H       | -2.82233| 3.20468 | -0.29491|
| H       | -4.41982| -0.56695| -1.48053|
| C       | -0.58073| 2.34870 | 0.92972 |
| H       | 0.27129 | 1.71520 | 1.17317 |
| C       | -0.05018| 3.43648 | -0.00355|
| H       | -0.81098| 4.19600 | -0.20832|
| H       | 0.80947 | 3.92112 | 0.46094 |
| H       | 0.29295 | 3.01085 | -0.94779|
| C       | -1.11373| 2.94971 | 2.23264 |
| H       | -0.33363| 3.53467 | 2.72404 |
| H       | -1.96536| 3.60861 | 2.03886 |
| H       | -1.44167| 2.16725 | 2.92058 |
| C       | -2.40363| -2.15663| -0.56305|
| H       | -1.86399| -2.52472| 0.31135 |
| C       | -1.54672| -2.45737| -1.79797|
| H       | -2.06208| -2.11275| -2.69851|
| H       | -0.58446| -1.94663| -1.74921|
| H       | -1.37033| -3.53173| -1.89155|
| C       | -3.72796| -2.91253| -0.63838|
| H       | -4.25569| -2.70902| -1.57279|
| H       | -3.54231| -3.98774| -0.60085|
| H       | -4.38849| -2.64803| 0.18947 |
Model CPA-14

M06-2X/def2-TZVP Geometry

| Element | X    | Y    | Z    |
|---------|------|------|------|
| C       | 4.61096 | 1.29998 | 0.19667 |
| C       | 3.82100 | 2.29105 | 0.60331 |
| C       | 2.45705 | 2.41704 | 0.06235 |
| C       | 1.56020 | 1.35516 | 0.25672 |
| O       | 4.14728 | 0.30431 | -0.59103 |
| O       | 2.04607 | 0.22755 | 0.82965 |
| C       | 0.22141 | 1.43677 | -0.13568 |
| C       | -0.20408 | 2.63433 | -0.72136 |
| C       | 0.66135 | 3.70222 | -0.90985 |
| C       | 1.98219 | 3.59555 | -0.49907 |
| P       | 3.03565 | -0.79425 | -0.02894 |
| O       | 2.29358 | -1.25553 | -1.21731 |
| O       | 3.65962 | -1.67539 | 0.96672 |
| Si      | -1.00417 | 0.01652 | 0.00626 |
| C       | -2.68733 | 0.85910 | 0.25103 |
| C       | -2.83437 | 1.83623 | 1.24292 |
| C       | -4.05119 | 2.46288 | 1.47002 |
| C       | -5.15774 | 2.12928 | 0.69808 |
| C       | -5.03362 | 1.17209 | -0.29743 |
| C       | -3.81086 | 0.54633 | -0.51568 |
| C       | -1.06563 | -0.98319 | -1.57786 |
| C       | -0.75247 | -1.17170 | 1.43719 |
| C       | 0.19676 | -2.19082 | 1.30533 |
| C       | 0.43782 | -3.07726 | 2.34344 |
| C       | -0.28410 | -2.97734 | 3.52570 |
| Element | X      | Y      | Z     |
|---------|--------|--------|-------|
| C       | -1.24644 | -1.98738 | 3.66613 |
| C       | -1.47493 | -1.09076 | 2.62899 |
| C       | -1.90697 | -2.09712 | -1.65768 |
| C       | -1.99162 | -2.85203 | -2.81847 |
| C       | -1.21954 | -2.50750 | -3.92118 |
| C       | -0.36400 | -1.41783 | -3.85203 |
| C       | -0.28698 | -0.66284 | -2.68908 |
| H       | 5.65084  | 1.20835  | 0.49515  |
| H       | 4.23900  | 3.10163  | 1.18681  |
| H       | -1.23740 | 2.73293  | -1.03618 |
| H       | 0.30395  | 4.61717  | -1.36560 |
| H       | 2.66409  | 4.42987  | -0.62129 |
| H       | -1.97350 | 2.12094  | 1.84030  |
| H       | -4.13710 | 3.21590  | 2.24416  |
| H       | -6.10913 | 2.61839  | 0.86898  |
| H       | -5.88901 | 0.91227  | -0.90956 |
| H       | -3.72916 | -0.19040 | -1.30659 |
| H       | 0.76782  | -2.27941 | 0.38630  |
| H       | 1.20758  | -3.82947 | 2.22897  |
| H       | -0.09415 | -3.66840 | 4.33845  |
| H       | -1.81601 | -1.90869 | 4.58464  |
| H       | -2.23163 | -0.32415 | 2.75407  |
| H       | -2.49426 | -2.38787 | -0.79123 |
| H       | -2.64477 | -3.71546 | -2.85847 |
| H       | -1.27072 | -3.10138 | -4.82606 |
| H       | 0.26401  | -1.16632 | -4.69745 |
| H       | 0.41963  | 0.15559  | -2.62821 |
Product Cartesian coordinates

![Chemical Structure](image)

**A**

M06-2X/def2-TZVP Geometry

| Atom | X     | Y     | Z     |
|------|-------|-------|-------|
| N    | -0.79973 | 0.65657 | 0.66868 |
| C    | -2.08991 | 0.32282 | 0.40584 |
| C    | -2.43463 | -0.65837 | -0.55493 |
| C    | -1.37611 | -1.29077 | -1.24323 |
| C    | -0.08675 | -0.94139 | -0.96778 |
| C    | 0.15702  | 0.05627  | 0.00997  |
| C    | 1.56980  | 0.51303  | 0.35468  |
| C    | 1.79626  | 1.96525  | -0.11013 |
| N    | 2.60216  | -0.35789 | -0.16203 |
| C    | 2.93638  | -1.59604 | 0.30802  |
| C    | 2.32376  | -2.00312 | 1.62732  |
| O    | 3.69747  | -2.31465 | -0.30545 |
| C    | -3.12145 | 0.97864  | 1.11955  |
| C    | -4.42948 | 0.66633  | 0.88077  |
| C    | -4.77369 | -0.31394 | -0.07785 |
| C    | -3.79798 | -0.96205 | -0.77999 |
| H    | 0.74282  | -1.41539 | -1.47449 |
| H    | 1.63146  | 0.51889  | 1.44551  |
| C    | 3.11187  | 2.51432  | 0.42885  |
| H    | 0.97095  | 2.52788  | 0.33158  |
| H    | 0.78248  | 1.71071  | -2.02586 |
| H    | 3.00341  | -0.14621 | -1.06403 |
| H    | 2.65367  | -1.33285 | 2.42273  |
| H    | 1.23398  | -1.96059 | 1.58662  |
| H    | 2.64451  | -3.01588 | 1.84971  |
|   | H   |      |      |
|---|-----|------|------|
|   | -2.83410 | 1.72501 | 1.84853 |
|   | -5.21493 | 1.17208 | 1.42765 |
|   | -5.81585 | -0.54707 | -0.25273 |
|   | -4.05070 | -1.71558 | -1.51678 |
|   | -1.60067 | -2.05007 | -1.98385 |
|   | 2.54690  | 1.61847 | -2.13358 |
|   | 1.76631  | 3.16933 | -1.90068 |
|   | 3.16163  | 2.42552 | 1.51542  |
|   | 3.96541  | 1.97872 | 0.00898  |
|   | 3.21816  | 3.56859 | 0.1699   |
| Element | X      | Y      | Z    |
|---------|--------|--------|------|
| C       | -1.77348 | 1.70861 | 0.37767 |
| C       | -3.12308 | 1.64456 | 0.18796 |
| C       | -3.73856 | 0.39561 | -0.04230 |
| C       | -2.90166 | -0.74654 | -0.06572 |
| N       | -1.56021 | -0.66444 | 0.12487 |
| C       | -1.02126 | 0.50806 | 0.33951 |
| C       | 0.48617  | 0.50187 | 0.55298 |
| C       | 0.84069  | 0.25769 | 1.83353 |
| C       | 2.35365  | -0.7594 | 2.06020 |
| N       | 1.07936  | 1.81968 | 0.58184 |
| C       | 1.48602  | 2.56492 | -0.48730 |
| C       | 1.31419  | 1.93515 | 1.84847 |
| O       | 1.96786  | 3.66846 | -0.33330 |
| C       | 5.12967  | 0.24289 | -0.25094 |
| C       | 5.66205  | -0.99487 | -0.47156 |
| C       | -4.82660 | -2.13564 | -0.49415 |
| C       | -3.48028 | -2.01763 | -0.29758 |
| H       | -1.27338 | 2.65206 | 0.54637 |
| H       | 0.91801  | 0.05407 | -0.28233 |
| H       | 0.38880  | -1.24687 | 1.75293 |
| H       | 0.37417  | 0.23972 | 2.69036 |
| H       | 1.20187  | 2.27636 | 1.47467 |
| H       | 0.29290  | 1.58097 | -1.99778 |
| H       | 1.56249  | 2.68028 | -2.59787 |
| H       | 1.98467  | 1.07839 | -1.94922 |
| H       | 5.76057  | 1.12380 | -0.23291 |
| H       | 6.72629  | -1.10956 | -0.63084 |
| H       | 5.26421  | -3.11013 | -0.66971 |
| H       | 2.82190  | -2.87616 | -0.31243 |
| H       | 3.73160  | 2.54161 | 0.20776 |
H   2.52276  -1.01687   2.92844
H   2.77427   0.60181   2.30105
C   4.29863  -1.97080  -1.43160
C   4.44480  -0.63051  -1.10499
C   3.83265  -0.11890   0.03253
C   3.06940  -0.93836   0.85978
C   2.93222  -2.28317   0.52258
C   3.54127  -2.79790  -0.61185
H   4.77456  -2.37108  -2.31731
H   5.03794   0.02056  -1.73500
H   3.94536   0.93106   0.28097
H   2.33918  -2.93247   1.15757
H   3.42578  -3.84599  -0.85696

\[
\text{C}
\]

M06-2X/def2-TZVP Geometry
C   -0.10033  -0.73526  -1.44689
C   -1.41757  -0.86974  -1.76394
C   -2.40312  -0.49159  -0.82255
C   -1.95587   0.01093   0.42274
N   -0.63355   0.14002   0.72116
C    0.24949  -0.21164  -0.17506
C    1.70980  -0.00023   0.18173
C    2.24766   1.27541  -0.47699
C    1.48581   2.56084  -0.15722
N    2.55434  -1.10452  -0.23263
C    2.58086  -2.36610   0.29250
C    1.68002  -2.61674   1.47758
O    3.30316  -3.22158  -0.17345
C   -3.79065  -0.60030  -1.06893
C   -4.69296  -0.22330  -0.11436
C   -4.24620   0.27670   1.12887
| Element | X    | Y    | Z    |
|---------|------|------|------|
| C       | -2.91023 | 0.39126 | 1.39406 |
| H       | 0.68080  | -1.03187 | -2.13440 |
| H       | 1.75438  | 0.11006  | 1.26679  |
| H       | 2.24781  | 1.12046  | -1.56267 |
| H       | 3.29297  | 1.39213  | -0.16991 |
| H       | 3.17903  | -0.96762 | -1.01381 |
| H       | 1.93934  | -1.95307 | 2.30402  |
| H       | 0.63565  | -2.42862 | 1.22521  |
| H       | 1.80646  | -3.65001 | 1.78485  |
| H       | -4.12415 | -0.98646 | -2.02494 |
| H       | -5.75462 | -0.30690 | -0.30630 |
| H       | -4.97262 | 0.57119  | 1.87547  |
| H       | -2.54429 | 0.77098  | 2.33907  |
| H       | -1.72578 | -1.26570 | -2.72492 |
| H       | 0.45424  | 2.44506  | -0.50483 |
| C       | 1.45485  | 2.84975  | 1.34066  |
| H       | 0.99061  | 3.81860  | 1.53177  |
| H       | 0.88690  | 2.09450  | 1.88348  |
| H       | 2.47138  | 2.88238  | 1.74398  |
| C       | 2.11832  | 3.72366  | -0.91653 |
| H       | 1.56941  | 4.64943  | -0.73960 |
| H       | 3.14923  | 3.87917  | -0.58728 |
| H       | 2.13313  | 3.53858  | -1.99212 |

![Structure](image)

**D**

M06-2X/def2-TZVP Geometry

| Element | X    | Y    | Z    |
|---------|------|------|------|
| C       | -0.76836 | -0.60823 | -0.80160 |
| C       | -2.13784 | -0.74836 | -0.92545 |
| C       | -2.95955 | -0.08669 | -0.01936 |
| C       | -2.36303 | 0.68850  | 0.97564  |
| N       | -1.05312 | 0.82401  | 1.08950  |
| C       | -0.26359 | 0.19263  | 0.21893  |
C  1.22469  0.42630  0.41923
C  1.58479  1.89476  0.11045
C  1.34745  2.26152 -1.35252
N  2.05291 -0.48002 -0.34054
C  2.29766 -1.79715 -0.06357
C  1.81652 -2.30645  1.27433
O  2.88400 -2.50181 -0.85629
C  -4.38676 -0.19288 -0.09184
C  3.01702  2.20309  0.53077
N  -5.52984 -0.27484 -0.14838
H  -0.09663 -1.11430 -1.48152
H  -2.57080 -1.35973 -1.70628
H  -2.97979  1.21021  1.69912
H  1.41701  0.27273  1.48414
H  0.90300  2.48665  0.72509
H  2.04017  1.74460 -2.02196
H  0.32946  2.03314 -1.67238
H  1.51062  3.32960 -1.49792
H  2.37228 -0.19210 -1.25390
H  2.03321 -3.36863  1.32764
H  2.33147 -1.78916  2.08553
H  0.74511 -2.14186  1.40075
H  3.73352  1.62327 -0.05384
H  3.23689  3.26012  0.37653
H  3.17877  1.97354  1.58514

E

M06-2X/def2-TZVP Geometry
C  -0.06028  0.83642 -0.58639
C  1.31923  0.91743 -0.62687
C  2.09053 -0.03051  0.03420
C  1.43402 -1.05490  0.74254
| Atom | X       | Y       | Z       |
|------|---------|---------|---------|
| N    | 0.10417 | -1.11816| 0.76828 |
| C    | -0.62810| -0.21206| 0.12375 |
| C    | -2.13034| -0.42501| 0.22165 |
| C    | -2.54011| -1.73079| -0.48943|
| C    | -2.29358| -1.67991| -1.99539|
| N    | -2.90267| 0.69305 | -0.26986|
| C    | -3.10657| 1.88769 | 0.36111 |
| C    | -2.67313| 1.97081 | 1.80565 |
| O    | -3.62532| 2.81959 | -0.21675|
| C    | -3.98879| -2.0866 | -0.17973|
| C    | 3.57556 | 0.04815 | -0.01501|
| O    | 4.00196 | 1.11631 | -0.70627|
| O    | 4.33383 | -0.73676| 0.48988 |
| C    | 5.41807 | 1.25086 | -0.79928|
| C    | 2.14903 | -2.12735| 1.50903 |
| H    | -0.67879| 1.56760 | -1.08827|
| H    | 1.80845 | 1.71461 | -1.16893|
| H    | -2.35107| -0.56375| 1.28313 |
| H    | -1.88783| -2.49610| -0.06375|
| H    | -2.97281| -0.98569| 2.49745 |
| H    | -1.26903| -1.38705| 2.23084 |
| H    | -2.47038| -2.66231| -2.43419|
| H    | -3.17097| 0.70033 | -1.24332|
| H    | -3.23947| 1.26379 | 2.41400 |
| H    | -1.61376| 1.73278 | 1.91542 |
| H    | -2.86086| 2.98105 | 2.15542 |
| H    | -4.67383| -1.33567| -0.57374|
| H    | -4.24787| -3.04684| -0.63210|
| H    | -4.15589| -2.16578| 0.89595 |
| H    | 5.85065 | 0.37564 | -1.28194|
| H    | 5.59321 | 2.14314 | -1.39269|
| H    | 5.85408 | 1.35810 | 0.19296 |
| H    | 2.82153 | -1.69975| 2.25149 |
| H    | 1.40492 | -2.75516| 1.99195 |
|     |     |     |     |
|-----|-----|-----|-----|
| H   | 2.77237 | -2.72935 | 0.84813 |

\[
\text{Ph} \quad \text{iPr} \quad \text{NHAc}
\]

**F**

**M06-2X/def2-TZVP Geometry**

|     |     |     |     |
|-----|-----|-----|-----|
| C   | -0.43384 | 0.59054 | -0.74023 |
| C   | 0.94491 | 0.67976 | -0.83292 |
| C   | 1.74544 | -0.04998 | 0.03951 |
| C   | 1.08453 | -0.84234 | 0.97953 |
| N   | -0.23356 | -0.94024 | 1.07346 |
| C   | -0.98758 | -0.24005 | 0.22693 |
| C   | -2.48674 | -0.43149 | 0.39264 |
| C   | -2.89861 | -1.86349 | -0.00192 |
| C   | -2.64180 | -2.16249 | -1.47711 |
| N   | -3.27264 | 0.54741 | -0.32556 |
| C   | -3.44652 | 1.85900 | 0.01465 |
| C   | -2.97238 | 2.26624 | 1.38972 |
| O   | -3.96940 | 2.64126 | -0.75141 |
| C   | 3.22149 | 0.01423 | -0.00588 |
| C   | -4.35075 | -2.13895 | 0.37045 |
| C   | 3.87159 | 1.22500 | -0.24449 |
| C   | 5.25569 | 1.28966 | -0.28234 |
| C   | 6.01323 | 0.14407 | -0.08178 |
| C   | 5.37695 | -1.06621 | 0.15589 |
| C   | 3.99244 | -1.13089 | 0.19305 |
| H   | -1.07202 | 1.15318 | -1.40860 |
| H   | 1.40113 | 1.30253 | -1.59325 |
| H   | 1.65972 | -1.40802 | 1.70627 |
| H   | -2.69425 | -0.32900 | 1.46072 |
| H   | -2.25251 | -2.51210 | 0.59382 |
| H   | -2.85028 | -3.21220 | -1.68624 |
| H   | -3.29243 | -1.57653 | -2.13210 |
| H   | -1.60648 | -1.96315 | -1.75825 |
H  -3.5644  0.33297  -1.26802
H  -3.14398  3.33194  1.50364
H  -3.52337  1.72382  2.15964
H  -1.91181  2.04534  1.52122
H  -4.60471  -3.17977  0.16486
H  -4.53065  -1.94883  1.42985
H  -5.03122  -1.50814  -0.20459
H  3.28766  2.12791  -0.37626
H  5.74405  2.23911  -0.46030
H  7.09382  0.19421  -0.11061
H  5.95972  -1.96600  0.30556
H  3.50228  -2.08322  0.35440

\[\text{G}\]

M06-2X/def2-TZVP Geometry

C  -0.43831  -0.89317  -0.85145
C  -1.78560  -1.15175  -1.02790
C  -2.71023  -0.42407  -0.29152
C  -2.25691  0.55107  0.61286
N  -0.96102  0.78590  0.76619
C  -0.06940  0.09165  0.05609
C  1.38059  0.46664  0.31694
C  1.66322  1.91157  -0.14459
C  1.53473  2.07950  -1.65654
N  2.32439  -0.45619  -0.26894
C  2.65726  -1.69728  0.19917
C  2.15032  -2.05799  1.57547
O  3.33732  -2.45155  -0.46283
C  -4.11545  -0.65945  -0.44059
C  3.02749  2.37886  0.34762
N  -5.24428  -0.83653  -0.55034
C  -3.22218  1.35279  1.43038
Quinoline and pyridine prediction set

H

M06-2X/def2-TZVP Geometry

N  0.43475  0.38691 -0.91946
C  1.77704  0.33306 -0.68912
C  2.33019 -0.26935  0.46620
C  1.43360 -0.83615  1.42064
C  0.09630 -0.75859  1.15767
C -0.36306 -0.13404 -0.02911
C -1.85248 -0.01935 -0.29280
C -2.47092  1.09096  0.56408
C -1.84460  2.47541  0.40113
C -1.90518  2.96408 -1.04331
|   |    x     |    y     |    z     |
|---|---------|---------|---------|
| C | -2.54525|  3.46009| 1.33275 |
| N | -2.56381| -1.25127|-0.00325 |
| C | -2.41245| -2.46183|-0.61836 |
| C | -1.35796| -2.55119|-1.69551 |
| O | -3.08612| -3.41630|-0.29064 |
| C |  2.63927|  0.90191|-1.65370 |
| C |  3.99438|  0.87408|-1.47520 |
| C |  4.54850|  0.27418|-0.32627 |
| C |  3.73534| -0.28538| 0.62140 |
| C |  1.95120| -1.49703| 2.66274 |
| H | -0.62762| -1.18697| 1.84050 |
| H | -1.96522|  0.24120|-1.34749 |
| H | -2.40266|  0.78670| 1.61509 |
| H | -3.53685|  1.15011| 0.31536 |
| H | -0.79233|  2.41255| 0.69715 |
| H | -1.28757|  2.35125|-1.69971 |
| H | -2.93569|  2.94267|-1.41028 |
| H | -1.54858|  3.99297|-1.11319 |
| H | -2.08777|  4.44828| 1.26970 |
| H | -3.59875|  3.56223| 1.05864 |
| H | -2.49893|  3.13042| 2.37233 |
| H | -3.28161| -1.23682| 0.70641 |
| H | -1.33296| -1.66828|-2.33345 |
| H | -0.37435| -2.64490|-1.23020 |
| H | -1.55710| -3.44149|-2.28467 |
| H |  2.18614|  1.35403|-2.52617 |
| H |  4.64912|  1.31235|-2.21738 |
| H |  5.62264|  0.25744|-0.19566 |
| H |  4.16872| -0.74416| 1.50057 |
| H |  2.59659| -2.34141| 2.41289 |
| H |  2.54352| -0.79971| 3.25833 |
| H |  1.13011| -1.86273| 3.27589 |
M06-2X/def2-TZVP Geometry

| Atom | X     | Y     | Z     |
|------|-------|-------|-------|
| C    | 0.32464 | -0.84447 | 1.10578 |
| C    | 1.70533 | -0.72948 | 1.13180 |
| C    | 2.36508 | -0.00625 | 0.14823 |
| C    | 1.60676 | 0.59240  | -0.84882 |
| N    | 0.28561 | 0.49134  | -0.89047 |
| C    | -0.34370 | -0.20334 | 0.05426 |
| C    | -1.85277 | -0.25211 | -0.11615 |
| C    | -2.23041 | -1.12839 | -1.33010 |
| C    | -3.74063 | -1.16317 | -1.52912 |
| N    | -2.33685 | 1.10529  | -0.26134 |
| C    | -3.35901 | 1.72374  | 0.39045 |
| C    | -4.08821 | 0.92936  | 1.45257 |
| O    | -3.66472 | 2.87009  | 0.13322 |
| C    | -1.68291 | -2.54457 | -1.18184 |
| C    | 3.84743  | 0.09578  | 0.20554  |
| O    | 4.34923  | 0.82806  | -0.79396 |
| O    | 4.52392  | -0.42142 | 1.05328 |
| C    | 5.76975  | 0.96256  | -0.79504 |
| C    | -0.40353 | -1.62433 | 2.16501 |
| H    | 2.28952  | -1.19796 | 1.91553 |
| H    | 2.08252  | 1.16755  | -1.63347 |
| H    | -2.30708 | -0.68688 | 0.77426 |
| H    | -1.76396 | -0.65660 | -2.20098 |
| H    | -4.16173 | -0.16187 | -1.62022 |
| H    | -3.99245 | -1.71793 | -2.43386 |
| H    | -4.22634 | -1.66854 | -0.68925 |
| H    | -1.84695 | 1.67846  | -0.93585 |
| H    | -3.41148 | 0.65534  | 2.26392 |
| H    | -4.88193 | 1.55729  | 1.84498 |
| H    | -4.51463 | 0.01343  | 1.04286 |
H  -2.12742  -3.03667  -0.31189
H  -1.93532  -3.14272  -2.05799
H  -0.59794  -2.55972  -1.06770
H  6.00875   1.58378  -1.65259
H  6.10448   1.43352   0.12809
H  6.24012  -0.01559  -0.88502
H  -1.09789  -0.98979   2.71922
H  -0.97901  -2.44331   1.73064
H  0.30300  -2.04846   2.87628

M06-2X/def2-TZVP Geometry
C  0.89904  -1.89661   1.29064
C  2.13243  -1.61317   0.70175
C  2.26100  -1.68203  -0.68182
C  1.16744  -2.05377  -1.45905
C  -0.04473  -2.33818  -0.86027
C  -0.18631  -2.25556   0.51775
Cl -1.41637  -2.75507  -1.83780
O  3.11306  -1.26849   1.57789
C  4.46843  -1.11736   1.17697
C  4.62929   0.01247   0.15157
C  5.18751  -0.65732   2.44392
C  5.07251  -2.41837   0.67137
O  3.86782   1.06210   0.45858
O  5.39905  -0.01826  -0.76977
C  4.00232   2.22296  -0.36768
C  3.24150   2.06717  -1.66488
O  1.87366   1.75524  -1.41381
C  1.07288   2.76994  -1.05486
| Element | X  | Y  | Z     |
|---------|----|----|-------|
| C       | -0.28696 | 2.29353 | -0.70178 |
| O       | 1.42384 | 3.91924 | -1.02560 |
| C       | -0.55576 | 0.94135 | -0.53748 |
| N       | -1.75666 | 0.47836 | -0.21727 |
| C       | -2.75294 | 1.34592 | -0.04566 |
| C       | -2.57268 | 2.72239 | -0.18713 |
| C       | -1.32006 | 3.20341 | -0.51401 |
| C       | -4.09105 | 0.76800 | 0.34615 |
| C       | -4.29286 | 0.73774 | 1.88347 |
| C       | -4.22292 | -0.55465 | -0.22587 |
| C       | -4.40690 | 2.14042 | 2.46729 |
| C       | -3.21100 | -0.06804 | 2.59210 |
| C       | -5.44168 | -1.10227 | -0.44876 |
| O       | -6.47546 | -0.52943 | -0.15709 |
| C       | -5.44087 | -2.46761 | -1.09510 |
| H       | 0.81407 | -1.82240 | 2.36655 |
| H       | 3.19293 | -1.45541 | -1.18000 |
| H       | 1.26237 | -2.10520 | -2.53521 |
| H       | -1.14537 | -2.45429 | 0.97564 |
| H       | 6.24022 | -0.46973 | 2.23248 |
| H       | 4.72530 | 0.25057 | 2.82712 |
| H       | 5.10895 | -1.44154 | 3.19616 |
| H       | 6.12997 | -2.26989 | 0.46115 |
| H       | 4.96298 | -3.17323 | 1.44964 |
| H       | 4.59729 | -2.78084 | -0.23643 |
| H       | 5.05582 | 2.40533 | -0.58171 |
| H       | 3.59218 | 3.04065 | 0.22034 |
| H       | 3.62874 | 1.23062 | -2.24205 |
| H       | 3.31802 | 2.98858 | -2.24296 |
| H       | 0.23461 | 0.21370 | -0.66488 |
| H       | -3.41091 | 3.39243 | -0.05008 |
| H       | -1.12701 | 4.26187 | -0.63642 |
| H       | -4.88788 | 1.39038 | -0.06944 |
| H       | -5.25398 | 0.23404 | 2.01344 |
| Atom | X       | Y       | Z       |
|------|---------|---------|---------|
| H    | -3.37521| -1.03071| -0.49915|
| H    | -3.45665| 2.67585 | 2.40524 |
| H    | -5.16892| 2.72715 | 1.94970 |
| H    | -4.68518| 2.08826 | 3.52070 |
| H    | -2.24280| 0.43570 | 2.53981 |
| H    | -3.46627| -0.19584| 3.64504 |
| H    | -3.10063| -1.05791| 2.14710 |
| H    | -4.44360| -2.89292| -1.19340|
| H    | -6.06774| -3.12985| -0.50048|
| H    | -5.89480| -2.37831| -2.08192|

**Chemical Structure**

MeOC

K

M06-2X/def2-TZVP Geometry

| Atom | X       | Y       | Z       |
|------|---------|---------|---------|
| C    | -0.02395| -0.69349| 0.78426 |
| C    | 1.34109 | -0.86036| 0.92967 |
| C    | 2.19761 | -0.13239| 0.11606 |
| C    | 1.64038 | 0.73753 | -0.81681|
| N    | 0.33279 | 0.90243 | -0.95979|
| C    | -0.48781| 0.20381 | -0.17392|
| C    | -1.96715| 0.47018 | -0.40212|
| C    | -2.32443| 1.91891 | -0.01185|
| C    | -2.11821| 2.19325 | 1.47591 |
| N    | -2.83167| -0.47323| 0.26870 |
| C    | -3.08216| -1.76362| -0.10623|
| C    | -2.57437| -2.18112| -1.46609|
| O    | -3.69513| -2.51750| 0.61930 |
| C    | -3.74383| 2.26596 | -0.44490|
| C    | 3.66495 | -0.31648| 0.26900 |
| O    | 4.36878 | 0.45345 | -0.56784|
| O    | 4.16773 | -1.07196| 1.05625 |
| C    | 5.78608 | 0.31836 | -0.47086|
| H    | -0.72079| -1.25138| 1.39493 |
|   | 1.75813 | -1.54510 | 1.65732 |
|---|---------|----------|---------|
| H | 2.27999 | 1.31771 | -1.47101 |
| H | -2.12942 | 0.38801 | -1.47985 |
| H | -1.62306 | 2.54036 | -0.57268 |
| H | -2.82005 | 1.63025 | 2.09707 |
| H | -1.10511 | 1.94891 | 1.79941 |
| H | -2.29103 | 3.24903 | 1.68652 |
| H | -3.15578 | -0.25255 | 1.19906 |
| H | -3.07073 | -1.60597 | -2.24953 |
| H | -1.50014 | -2.01228 | -1.55732 |
| H | -2.79353 | -3.23588 | -1.59813 |
| H | -4.47942 | 1.66726 | 0.09526 |
| H | -3.95500 | 3.31698 | -0.24363 |
| H | -3.88610 | 2.09000 | -1.51243 |
| H | 6.20023 | 1.00804 | -1.19974 |
| H | 6.12090 | 0.57199 | 0.53379 |
| H | 6.08274 | -0.70505 | -0.69581 |

L

M06-2X/def2-TZVP Geometry

|   | 0.10398 | 0.71613 | 0.55010 |
|---|---------|----------|---------|
| C | -1.26835 | 0.91485 | 0.67068 |
| C | -2.09534 | 0.01049 | -0.00846 |
| C | -1.49999 | -1.01110 | -0.74983 |
| N | -0.19295 | -1.18849 | -0.85355 |
| C | 0.60152 | -0.33391 | -0.20701 |
| C | 2.08920 | -0.60524 | -0.36240 |
| C | 2.46671 | -1.95158 | 0.28847 |
| C | 2.27982 | -1.94162 | 1.80366 |
| N | 2.92654 | 0.46173 | 0.13663 |
| C | 3.15470 | 1.66870 | -0.46254 |
| C | 2.68453 | 1.81339 | -1.89042 |
|   | X   | Y   | Z   |
|---|-----|-----|-----|
| O | 3.72110 | 2.56346 | 0.12910 |
| C | 3.88535 | -2.36070 | -0.08950 |
| C | -3.57760 | 0.12184 | 0.04118 |
| O | -4.18503 | -0.83811 | -0.67073 |
| O | -4.18926 | 0.96508 | 0.64267 |
| C | -5.60986 | -0.83811 | -0.67073 |
| C | -1.77618 | 2.05828 | 1.49758 |
| H | 0.78616 | 1.39338 | 1.04808 |
| H | -2.12583 | -1.71337 | -1.28595 |
| H | 2.26723 | -0.71586 | -1.43523 |
| H | 1.76604 | -2.67344 | -0.13608 |
| H | 3.00881 | -1.29577 | 2.30040 |
| H | 1.27943 | -1.61176 | 2.08870 |
| H | 2.42851 | -2.94518 | 2.20317 |
| H | 3.21655 | 0.43129 | 1.10342 |
| H | 1.61286 | 1.62486 | -1.97380 |
| H | 2.90617 | 2.82487 | -2.21599 |
| H | 3.20051 | 1.10102 | -2.53608 |
| H | 4.61725 | -1.65162 | 0.30159 |
| H | 4.11840 | -3.34429 | 0.32047 |
| H | 4.00786 | -2.40787 | -1.17291 |
| H | -5.93597 | -1.62379 | -1.27919 |
| H | -5.98878 | -0.88746 | 0.35032 |
| H | -5.95805 | 0.15459 | -1.08307 |
| H | -2.41559 | 1.70179 | 2.30435 |
| H | -0.93920 | 2.61410 | 1.91625 |
| H | -2.39293 | 2.72710 | 0.89850 |

M

M06-2X/def2-TZVP Geometry

|   | X   | Y   | Z   |
|---|-----|-----|-----|
| C | -0.43384 | 0.59054 | -0.74023 |
| C | 0.94491 | 0.67976 | -0.83292 |
|   |   |   |   |
|---|---|---|---|
| C | 1.74544 | -0.04998 | 0.03951 |
| C | 1.08453 | -0.84234 | 0.97953 |
| N | -0.23356 | -0.94024 | 1.07346 |
| C | -0.98758 | -0.24005 | 0.22693 |
| C | -2.48674 | -0.43149 | 0.39264 |
| C | -2.89861 | -1.86349 | -0.00192 |
| C | -2.64180 | -2.16249 | -1.47711 |
| N | -3.27264 | 0.54741 | -0.32556 |
| C | -3.44652 | 1.85900 | 0.01465 |
| C | -2.97238 | 2.26624 | 1.38972 |
| O | -3.96940 | 2.64126 | -0.75141 |
| C | 3.22149 | 0.01423 | -0.00588 |
| C | -4.35075 | -2.13895 | 0.37045 |
| C | 3.87159 | 1.22500 | -0.24449 |
| C | 5.25569 | 1.28966 | -0.28234 |
| C | 6.01323 | 0.14407 | -0.08178 |
| C | 5.37695 | -1.06621 | 0.15589 |
| C | 3.99244 | -1.13089 | 0.19305 |
| H | -1.07202 | 1.15318 | -1.40860 |
| H | 1.40113 | 1.30253 | -1.59325 |
| H | 1.65972 | -1.40802 | 1.70627 |
| H | -2.69425 | -0.32900 | 1.46072 |
| H | -2.25251 | -2.51210 | 0.59382 |
| H | -2.85028 | -3.21220 | -1.68624 |
| H | -3.29243 | -1.57653 | -2.13210 |
| H | -1.60648 | -1.96315 | -1.75825 |
| H | -3.56444 | 0.33297 | -1.26802 |
| H | -3.14398 | 3.33194 | 1.50364 |
| H | -3.52337 | 1.72382 | 2.15964 |
| H | -1.91181 | 2.04534 | 1.52122 |
| H | -4.60471 | -3.17977 | 0.16486 |
| H | -4.53065 | -1.94883 | 1.42985 |
| H | -5.03122 | -1.50814 | -0.20459 |
| H | 3.28766 | 2.12791 | -0.37626 |
H  5.74405  2.23911  -0.46030
H  7.09382  0.19421  -0.11061
H  5.95972 -1.96600  0.30556
H  3.50228 -2.08322  0.35440

\[
\begin{array}{l}
\text{N} \\
\text{M06-2X/def2-TZVP Geometry} \\
\text{C}   -0.76836  -0.60823  -0.80160 \\
\text{C}   -2.13784  -0.74836  -0.92545 \\
\text{C}   -2.95955  -0.08669  -0.01936 \\
\text{C}   -2.36303   0.68850   0.97564 \\
\text{N}   -1.05312   0.82401   1.08950 \\
\text{C}   -0.26359   0.19263   0.21893 \\
\text{C}    1.22469   0.42630   0.41923 \\
\text{C}    1.58479   1.89476   0.11045 \\
\text{C}    1.34745   2.26152  -1.35252 \\
\text{N}    2.05291  -0.48002  -0.34054 \\
\text{C}    2.29766  -1.79715  -0.06357 \\
\text{C}    1.81652  -2.30645   1.27433 \\
\text{O}    2.88400  -2.50181  -0.85629 \\
\text{C}   -4.38676  -0.19288  -0.09184 \\
\text{C}    3.01702   2.20309   0.53077 \\
\text{N}   -5.52984  -0.27484  -0.14838 \\
\text{H}   -0.09663  -1.11430  -1.48152 \\
\text{H}   -2.57080  -1.35973  -1.70628 \\
\text{H}   -2.97979   1.21021   1.69912 \\
\text{H}    1.41701   0.27273   1.48414 \\
\text{H}    0.90300   2.48665   0.72509 \\
\text{H}    2.04017   1.74460  -2.02196 \\
\text{H}    0.32946   2.03314  -1.67238 \\
\text{H}    1.51062   3.32960  -1.49792 \\
\text{H}    2.37228  -0.19210  -1.25390 
\end{array}
\]
H  2.03321  -3.36863  1.32764
H  2.33147  -1.78916  2.08553
H  0.74511  -2.14186  1.40075
H  3.73352   1.62327 -0.05384
H  3.23689   3.26012  0.37653
H  3.17877   1.97354  1.58514

O

M06-2X/def2-TZVP Geometry
C  0.34831   0.86891  0.63270
C  -0.89932  1.41492  0.51311
C  -1.96383  0.55680  0.11196
C  -1.66071 -0.80434 -0.13746
N  -0.40549 -1.31230 -0.00789
C   0.55084 -0.50640  0.36370
C   1.91954 -1.14744  0.54164
C   2.00180 -1.79783  1.91877
N   3.02172 -0.22014  0.39168
C   3.42591  0.38802 -0.76303
C   2.75717 -0.08106 -2.03308
O   4.28641  1.24283 -0.75408
C  -1.14525  2.86829  0.78729
C  -3.29707  1.00058 -0.05081
C  -4.27867  0.13177 -0.44123
C  -3.97310 -1.22293 -0.69009
C  -2.69405 -1.68034 -0.54283
H   1.19178  1.48369  0.92112
H   1.99444 -1.92993 -0.21620
H   1.90232 -1.04067  2.70041
H   1.19384 -2.51759  2.03425
H   2.95773 -2.30758  2.04096
H  3.48322  0.11882  1.22313
H  1.67481  0.04708  -1.98000
H  3.15741  0.49781  -2.85946
H  2.95579  -1.14122  -2.19861
H  -1.88285  2.99551  1.58195
H  -0.22531  3.36585  1.08719
H  -1.53422  3.70262  -0.10078
H  -3.53784  2.03879  0.13785
H  -5.29529  0.48276  -0.56121
H  -4.75927  -1.89935  -0.99989
H  -2.43094  -2.71344  -0.72837

\[
\text{P}
\]

M06-2X/def2-TZVP Geometry

C  -0.34111  0.50162  0.91401
C  -1.52398  0.08557  1.46009
C  -2.61511  -0.15645  0.57783
C  -2.40686  0.05088  -0.80815
N  -1.21466  0.46306  -1.31497
C  -0.22794  0.67408  -0.48552
C   1.08572  1.09228  -1.13358
C   1.71700  -0.09888  -1.88364
C   2.17943  -1.20024  -0.96642
C   3.51092  -1.27679  -0.56445
C   3.93607  -2.26335  0.31576
C   3.03075  -3.19371  0.80371
C   1.70196  -3.13434  0.40311
C   1.28037  -2.14680  -0.47409
N   2.04411  1.65574  -0.21034
C   1.94644  2.87554  0.40053
C   0.90948  3.82380  -0.15372
| Element | X   | Y   | Z    |
|---------|-----|-----|------|
| O       | 2.67181 | 3.17394 | 1.32553 |
| C       | -1.67101 | -0.11413 | 2.93866 |
| C       | -3.88680 | -0.58770 | 1.01940 |
| C       | -4.90175 | -0.80005 | 0.12595 |
| C       | -4.69106 | -0.59104 | -1.25375 |
| C       | -3.47259 | -0.17554 | -1.71062 |
| H       | 0.51464  | 0.69687  | 1.54776 |
| H       | 0.83273  | 1.84041  | -1.88706 |
| H       | 2.56045  | 0.27966  | -2.46336 |
| H       | 0.96468  | -0.47207 | -2.57861 |
| H       | 4.22528  | -0.55947 | -0.95441 |
| H       | 4.97543  | -2.30634 | 0.61516 |
| H       | 3.35945  | -3.96616 | 1.48677 |
| H       | 0.99190  | -3.86328 | 0.77272 |
| H       | 0.24285  | -2.10855 | -0.78796 |
| H       | 2.68990  | 1.02144  | 0.24157 |
| H       | -0.08895 | 3.38558  | -0.10054 |
| H       | 0.94082  | 4.73784  | 0.43091 |
| H       | 1.11811  | 4.05072  | -1.20038 |
| H       | -0.73848 | 0.10950  | 3.45232 |
| H       | -2.45142 | 0.53369  | 3.34276 |
| H       | -1.95246 | -1.14428 | 3.16598 |
| H       | -0.45890 | -0.74852 | 2.07603 |
| H       | -5.87137 | -1.13006 | 0.47526 |
| H       | -5.50162 | -0.76210 | -1.95039 |
| H       | -3.28207 | -0.00630 | -2.76229 |

![Diagram](image-url)

**Q**

M06-2X/def2-TZVP Geometry

| Element | X   | Y   | Z    |
|---------|-----|-----|------|
| C       | -0.51201 | 0.65724  | 0.51114 |
| C       | -1.85301 | 0.27245  | 0.73988 |
| C       | -2.64946 | -0.05911 | -0.37958 |

S80
|   | x      | y      | z      |
|---|--------|--------|--------|
| C | -2.0309| 0.0253 | -1.6528|
| N | -0.7895| 0.3803 | -1.8461|
| C | -0.0274| 0.6943 | -0.7657|
| C | 1.4029 | 1.0708 | -1.1068|
| C | 2.1486 | -0.1227| -1.7405|
| C | 2.3797 | -1.2544| -0.7751|
| C | 1.3815 | -2.1966| -0.5283|
| C | 1.5811 | -3.2162| 0.3900 |
| C | 2.7831 | -3.3101| 1.0797 |
| C | 3.7856 | -2.3823| 0.8404 |
| C | 3.5834 | -1.3644| -0.0827|
| N | 2.1517 | 1.5805 | 0.0184 |
| C | 2.0235 | 2.8219 | 0.5764 |
| C | 1.2597 | 3.8491 | -0.2261|
| O | 2.5193 | 3.0792 | 1.6533 |
| C | -2.4167| 0.2093 | 2.0361 |
| C | -3.7191| -0.1687| 2.1873 |
| C | -4.5172| -0.4983| 1.0652 |
| C | -4.0076| -0.4522| -0.2075|
| C | -4.8611| -0.8060| -1.3924|
| H | 0.1193 | 0.9190 | 1.3514 |
| H | -2.6042| -0.2152| -2.5428|
| H | 1.3482 | 1.8458 | -1.8746|
| H | 3.1034 | 0.2443 | -2.1198|
| H | 1.5507 | -0.4599| -2.5870|
| H | 0.4430 | -2.1292| -1.0674|
| H | 0.7972 | -3.9417| 0.5664 |
| H | 2.9382 | -4.1058| 1.7966 |
| H | 4.7283 | -2.4515| 1.3678 |
| H | 4.3738 | -0.6467| -0.2747|
| H | 2.5985 | 0.9036 | 0.6239 |
| H | 1.2320 | 4.7706 | 0.3467 |
| H | 1.7492 | 4.0290 | -1.1844|
| H | 0.2429 | 3.5076 | -0.4278|
H  -1.80404  0.46514  2.89147
H  -4.15770  -0.21959  3.17588
H  -5.54270  -0.79418  1.21781
H  -4.94295  0.03193  -2.08738
H  -4.44116  -1.64848  -1.94577
H  -5.86456  -1.07881  -1.07122

R

M06-2X/def2-TZVP Geometry
C  -1.35572  0.87930  0.49961
C  -2.28522  0.00769  -0.12004
C  -3.73182  0.24396  -0.00741
N  -0.03255  0.67597  0.39601
C   0.42099  -0.35679  -0.29538
C  -0.41859  -1.26840  -0.93634
C  -1.77817  -1.06908  -0.84018
C   1.91962  -0.56573  -0.33708
C   2.33018  -1.72836   0.60034
C   3.81652   -2.03036   0.45228
N   2.60532   0.66772  -0.02344
C   3.69011   1.08801  -0.72416
C   4.19881   2.46746  -0.37174
O   4.23599   0.40610  -1.56896
O  -4.24565  1.15902   0.59861
H  -0.00404  -2.09292  -1.49903
H   2.20945  -0.84232  -1.35371
H   1.76136  -2.60307   0.26860
C   1.97173  -1.43914   2.05353
H   2.09193  1.32290   0.54536
H   5.22419   2.37411  -0.01616
H   4.21702   3.06829  -1.27982
H   3.59867   2.96818   0.38598
O  -4.46219  -0.67167  -0.65614
S

M06-2X/def2-TZVP Geometry

\begin{table}[h]
\centering
\begin{tabular}{cccc}
C   & 0.04910 & -0.69833 & -0.77542 \\
C   & -1.31506 & -0.86457 & -0.91771 \\
C   & -2.17880 & -0.13273 & -0.11005 \\
C   & -1.61112 & 0.74064 & 0.81305 \\
N   & -0.30287 & 0.90856 & 0.95735 \\
C   & 0.51665 & 0.20535 & 0.17674 \\
C   & 1.99660 & 0.47172 & 0.40146 \\
C   & 2.35417 & 1.91926 & 0.00698 \\
C   & 2.14197 & 2.19098 & -1.48043 \\
N   & 2.85944 & -0.47371 & -0.26857 \\
C   & 3.11235 & -1.76256 & 0.11013 \\
C   & 2.60654 & -2.17669 & 1.47177 \\
O   & 3.72564 & -2.51770 & -0.61368 \\
C   & 3.77574 & 2.26546 & 0.43350 \\
C   & -3.65770 & -0.31557 & -0.26209
\end{tabular}
\end{table}
O  
C    
C    
H    
H    
H    
H    
H    
H    
H    
H    
H    
H    
H    

C    
C    
C    
H    
H    
H    
H    
H    
H    
H    
H    

M06-2X/def2-TZVP Geometry
C   4.22788  2.82639  0.21726
C   3.09004  2.01349  0.01536
C   1.81414  2.62111  0.01405
C   1.69621  4.01218  0.22646
|   |   |   |   |
|---|---|---|---|
| C | 2.81669 | 4.77247 | 0.42072 |
| C | 4.09286 | 4.17267 | 0.41473 |
| N | 3.26604 | 0.67517 | -0.16811 |
| C | 2.20645 | -0.06323 | -0.36173 |
| C | 0.88601 | 0.43808 | -0.40426 |
| C | 0.69247 | 1.77507 | -0.20278 |
| O | -0.50953 | 2.39928 | -0.22260 |
| C | 2.41734 | -1.55460 | -0.47407 |
| C | 2.39429 | -2.20517 | 0.92886 |
| C | 1.08274 | -2.05288 | 1.64771 |
| C | -0.02487 | -2.80557 | 1.25982 |
| C | -1.23624 | -2.68106 | 1.92579 |
| C | -1.35705 | -1.80346 | 2.99629 |
| C | -0.26459 | -1.03831 | 3.38225 |
| C | 0.94255 | -1.15867 | 2.70572 |
| N | 3.67510 | -1.82170 | -1.12969 |
| C | 3.92890 | -3.02599 | -1.69314 |
| C | 5.29234 | -3.18893 | -2.32237 |
| O | 3.10806 | -3.92539 | -1.69594 |
| H | 5.19702 | 2.34528 | 0.21181 |
| H | 0.71207 | 4.45997 | 0.22715 |
| H | 2.72629 | 5.83892 | 0.57981 |
| H | 4.97112 | 4.78624 | 0.56971 |
| H | 0.06630 | -0.24088 | -0.58654 |
| H | 1.62044 | -1.99945 | -1.07385 |
| H | 3.20154 | -1.75592 | 1.51114 |
| H | 2.62051 | -3.26274 | 0.78201 |
| H | 0.07520 | -3.50997 | 0.44075 |
| H | -2.08318 | -3.28235 | 1.61919 |
| H | -0.35006 | -0.34963 | 4.21338 |
| H | 1.79454 | -0.56022 | 3.00865 |
| H | 4.37024 | -1.09263 | -1.08883 |
| H | 5.15727 | -3.50804 | -3.35461 |
| H | 5.88835 | -2.27855 | -2.29669 |
M06-2X/def2-TZVP Geometry

C  -1.40744  1.14110  0.29395
C  -2.80831  1.15629  0.14071
C  -3.48092  0.09244  -0.15210
C  -2.68953  1.24971  -0.26878
N  -1.32029  1.23105  -0.11487
C  -0.71701  0.12642  0.15513
C   0.79948  0.18747  0.24330
C   1.37819  0.24197  0.113850
C   2.87135  0.37980  -1.08117
C   3.69759  0.72974  -1.23924
C   5.06970  0.61929  -1.06376
C   5.63498  0.60545  -0.73577
C   4.82231  1.72230  -0.59426
C   3.45046  1.60665  -0.76654
N   1.22749  0.15089  0.60109

\[ \text{U} \]

\[
\begin{align*}
\text{NHAc} & \quad \text{Ph}
\end{align*}
\]
| Element | X       | Y       | Z       |
|---------|---------|---------|---------|
| C       | 2.26823 | -1.87536| 1.41278 |
| C       | 2.99387 | -0.78163| 2.16473 |
| O       | 2.57424 | -3.04408| 1.53537 |
| C       | -4.87096| -0.21304| -0.32735|
| C       | -5.44348| -1.43090| -0.60470|
| C       | -4.64807| -2.57975| -0.71786|
| C       | -3.28939| -2.48801| -0.55209|
| C       | -0.72836| 2.34249 | 0.57212 |
| C       | -1.41403| 3.52466 | 0.69862 |
| C       | -2.80662| 3.54001 | 0.55097 |
| C       | -3.48849| 2.37991 | 0.27830 |
| H       | 1.15251 | 0.50792 | 1.00412 |
| H       | 0.92094 | 1.18596 | -1.43815|
| H       | 1.07675 | -0.51954| -1.85652|
| H       | 3.25888 | -1.69198| -1.47566|
| H       | 5.69693 | -1.49428| -1.17539|
| H       | 6.70484 | 0.69066 | -0.59611|
| H       | 5.25733 | 2.68298 | -0.34966|
| H       | 2.81714 | 2.48050 | -0.65326|
| H       | 0.70524 | -2.27403| 0.20121 |
| H       | 3.44808 | -0.05860| 1.48601 |
| H       | 2.30602 | -0.24927| 2.82464 |
| H       | 3.76839 | -1.25483| 2.76046 |
| H       | -5.50606| 0.65801 | -0.24603|
| H       | -6.51535| -1.50285| 0.73564 |
| H       | -5.10727| -3.53558| -0.93356|
| H       | -2.64456| -3.35352| -0.62882|
| H       | 0.34726 | 2.34319 | 0.68625 |
| H       | -0.88161| 4.4164  | 0.91342 |
| H       | -3.34808| 4.47164 | 0.65270 |
| H       | -4.56293| 2.41485 | 0.16886 |
M06-2X/def2-TZVP Geometry

C  0.51101  -0.46533  1.37106
C  1.79984  -0.89824  1.51439
C  2.82734  -0.42435  0.67037
C  2.46916   0.51528  -0.32182
N  1.18891   0.94250  -0.46316
C  0.26172   0.48466   0.33345
C  -1.13597  1.01119   0.04329
C  -1.71473   0.29465  -1.20049
C  -1.93893  -1.16992  -0.95171
C  -3.14943  -1.61477  -0.42523
C  -3.33597  -2.95015  -0.09740
C  -2.30696  -3.86171  -0.29152
C  -1.09962  -3.43222  -0.82663
C  -0.91936  -2.09644  -1.15682
N  -1.06681   2.44067  -0.15949
C  -2.04663   3.35407   0.07935
C  -3.28612   2.85579   0.79275
O  -1.92010   4.51824  -0.23853
C  4.17562  -0.83816   0.77574
C  5.11969  -0.33258  -0.07303
C  4.75898   0.60705  -1.06499
C  3.46358   1.02346  -1.18933
C  -0.58379  -0.97481   2.26412
H  2.04630  -1.61813   2.28821
H  -1.78489   0.80675   0.89422
H  -1.01409   0.45403  -2.02259
H  -2.65464   0.78433  -1.46279
H  -3.95294  -0.90275  -0.26881
H  -4.28393  -3.28015   0.30812
H  -2.44866  -4.90374  -0.03585
| X | M06-2X/def2-TZVP Geometry |
|---|--------------------------|
| H | -0.29696  -4.14025  -0.98876 |
| H | 0.02705   -1.76092  -1.56721 |
| H | -0.25154   2.78027   -0.65257 |
| H | -3.74096   2.00854   0.27743 |
| H | -3.03767   2.53745   1.80691 |
| H | -3.99476   3.67670   0.83979 |
| H | 4.44482   -1.55767   1.54010 |
| H | 6.15084   -0.65010   0.01093 |
| H | 5.51875    0.99783  -1.72936 |
| H | 3.16205    1.74238  -1.93999 |
| H | -1.34929  -1.50464   1.69252 |
| H | -0.17616  -1.66350   3.00246 |
| H | -1.07361  -0.15945   2.80059 |

\[
\text{\text{\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{image.png}
\caption{X}
\end{figure}}}
\]

| C | 0.03530  0.51704  -1.05563 |
| C | 1.24711  0.17679  -1.57956 |
| C | 2.36721  0.05690  -0.72711 |
| C | 2.16178  0.30471   0.65234 |
| N | 0.94666  0.64146   1.15526 |
| C | -0.07026  0.73989   0.33944 |
| C | -1.40392  1.07140   0.99447 |
| C | -1.93938  -0.15167   1.76738 |
| C | -2.27211  -1.31967   0.87662 |
| C | -3.57042  -1.52273   0.41486 |
| C | -3.86635  -2.57746  -0.43962 |
| C | -2.86426  -3.44865  -0.83904 |
| C | -1.56741  -3.26253  -0.37773 |
| C | -1.27513  -2.20684   0.47204 |
| N | -2.40646   1.54662   0.06900 |
| C | -2.42319   2.77077  -0.54133 |

s89
Cl
\begin{align*}
\text{N} & \quad \text{HAc} \\
\text{Ph} & \\
\end{align*}

\textbf{Y}

\textbf{M06-2X/def2-TZVP Geometry}

\begin{align*}
\text{C} & \quad -0.26135 \quad 0.52033 \quad -1.02164 \\
\text{C} & \quad 0.97855 \quad 0.21690 \quad -1.50043 \\
\text{C} & \quad 2.07421 \quad 0.15921 \quad -0.61031 \\
\text{C} & \quad 1.81723 \quad 0.42735 \quad 0.75557 \\
\text{N} & \quad 0.57549 \quad 0.72646 \quad 1.21419 \\
\end{align*}
| Element | X         | Y         | Z         |
|---------|-----------|-----------|-----------|
| C       | -0.41809  | 0.76756   | 0.36478   |
| C       | -1.78290  | 1.06105   | 0.97154   |
| C       | -2.29990  | -0.16955  | 1.74538   |
| C       | -2.57838  | -1.35585  | 0.86042   |
| C       | -3.86036  | -1.59941  | 0.37334   |
| C       | -4.10889  | -2.66941  | -0.47685  |
| C       | -3.07490  | -3.51637  | -0.84626  |
| C       | -1.79412  | -3.29055  | -0.35870  |
| C       | -1.54910  | -2.21943  | 0.48677   |
| N       | -2.77071  | 1.48908   | 0.00845   |
| C       | -2.80766  | 2.70204   | -0.62326  |
| C       | -1.88633  | 3.76998   | -0.08242  |
| O       | -3.55743  | 2.90001   | -1.55495  |
| C       | 3.38901   | -0.14869  | -1.02920  |
| C       | 4.39454   | -0.18326  | -0.10882  |
| C       | 4.15401   | 0.08243   | 1.25735   |
| C       | 2.89095   | 0.38187   | 1.67703   |
| Cl      | 6.01181   | -0.55781  | -0.60237  |
| H       | -1.11953  | 0.56874   | -1.67786  |
| H       | 1.13643   | 0.01595   | -2.55359  |
| H       | -1.63051  | 1.85275   | 1.70688   |
| H       | -3.20828  | 0.12577   | 2.27298   |
| H       | -1.54131  | -0.42038  | 2.48720   |
| H       | -4.67663  | -0.95116  | 0.67427   |
| H       | -5.11194  | -2.84261  | -0.84487  |
| H       | -3.26680  | -4.35311  | -1.50524  |
| H       | -0.98402  | -3.95344  | -0.63447  |
| H       | -0.54832  | -2.05003  | 0.86928   |
| H       | -3.34409  | 0.77973   | -0.42892  |
| H       | -0.84511  | 3.44374   | -0.11444  |
| H       | -2.01040  | 4.66186   | -0.68850  |
| H       | -2.13136  | 3.99730   | 0.95629   |
| H       | 3.59060   | -0.35360  | -2.07280  |
| H       | 4.98110   | 0.04371   | 1.95288   |
| Atom | X      | Y      | Z      |
|------|--------|--------|--------|
| H    | 2.6762 | 0.5912 | 2.7166 |

**Z**

M06-2X/def2-TZVP Geometry

| Atom | X      | Y      | Z      |
|------|--------|--------|--------|
| C    | -0.20045 | 0.52741 | -0.98083 |
| C    | 1.06102  | 0.22041  | -1.40480 |
| C    | 2.11885  | 0.16287  | -0.47293 |
| C    | 1.79979  | 0.43487  | 0.87761  |
| N    | 0.54280  | 0.73582  | 1.28331  |
| C    | -0.41691 | 0.77770  | 0.39371  |
| C    | -1.80408 | 1.07666  | 0.94472  |
| C    | -2.34886 | -0.14052 | 1.72028  |
| C    | -2.60897 | -1.33669 | 0.84327  |
| C    | -1.57226 | -2.20116 | 0.49227  |
| C    | -1.80297 | -3.27958 | -0.34794 |
| C    | -3.07575 | -3.51248 | -0.85295 |
| C    | -4.11681 | -2.66467 | -0.50620 |
| C    | -3.88277 | -1.58721 | 0.33852  |
| N    | -2.75745 | 1.48514  | -0.06197 |
| C    | -2.76814 | 2.68279  | -0.72114 |
| C    | -1.86777 | 3.76226  | -0.16796 |
| O    | -3.48030 | 2.86146  | -1.68645 |
| C    | 3.45259  | -0.14549 | -0.84206 |
| C    | 4.43002  | -0.17711 | 0.11656  |
| C    | 4.11285  | 0.09440  | 1.47465  |
| C    | 2.83919  | 0.39142  | 1.84351  |
| O    | 5.73433  | -0.45337 | -0.11157 |
| C    | 6.12131  | -0.71539 | -1.44190 |
| H    | -1.02735 | 0.57813  | -1.67616 |
| H    | 1.26054  | 0.01821  | -2.45094 |
| H    | -1.68255 | 1.88195  | 1.67123  |
| H    | -3.27078 | 0.16446  | 2.21828  |
|   |  X   |  Y   |  Z   |
|---|------|------|------|
| H | -1.61174 | -0.38391 | 2.48581 |
| H | -0.57737 | -2.02596 | 0.88711 |
| H | -0.98726 | -3.94255 | -0.60663 |
| H | -3.25582 | -4.35471 | -1.50835 |
| H | -5.11381 | -2.84236 | -0.88840 |
| H | -4.70392 | -0.93644 | 0.61985 |
| H | -3.31065 | 0.76526 | -0.50817 |
| H | -0.82773 | 3.43169 | -0.14541 |
| H | -1.96171 | 4.63847 | -0.80168 |
| H | -2.15785 | 4.01644 | 0.85277 |
| H | 3.66691 | -0.34756 | -1.88240 |
| H | 4.91920 | 0.05606 | 2.19534 |
| H | 2.58248 | 0.60310 | 2.87322 |
| H | 7.19175 | -0.89970 | -1.41816 |
| H | 5.60701 | -1.59725 | -1.83390 |
| H | 5.91154 | 0.14228 | -2.08694 |

**ZA**

M06-2X/def2-TZVP Geometry

|   |  X   |  Y   |  Z   |
|---|------|------|------|
| C | 1.67727 | 1.70234 | 0.06271 |
| C | 3.03791 | 1.78284 | 0.06281 |
| C | 3.80992 | 0.60079 | 0.03591 |
| C | 3.10946 | -0.62840 | 0.01428 |
| N | 1.75219 | -0.68946 | 0.01150 |
| C | 1.06479 | 0.42174 | 0.03213 |
| C | -0.45525 | 0.28777 | 0.07638 |
| C | -0.95429 | -0.92288 | -0.73803 |
| C | -2.41289 | -1.17139 | -0.47656 |
| C | -3.39974 | -0.49243 | -1.18620 |
| C | -4.73942 | -0.63452 | -0.85222 |
| C | -5.11202 | -1.46763 | 0.19348 |
| C | -4.13818 | -2.16451 | 0.89722 |
| Atom | X  | Y  | Z  |
|------|----|----|----|
| C    | -2.8008 | -2.01432 | 0.56323 |
| N    | -1.09832 | 1.51454 | -0.34389 |
| C    | -2.22150 | 2.10355 | 0.17587 |
| C    | -2.68612 | 1.64800 | 1.53766 |
| O    | -2.79413 | 2.97730 | -0.44117 |
| C    | 5.22429 | 0.59551 | 0.03377 |
| C    | 5.90883 | -0.58623 | 0.01361 |
| C    | 5.20949 | -1.81415 | -0.00601 |
| C    | 3.84359 | -1.83804 | -0.00627 |
| H    | 1.06253 | 2.59023 | 0.08928 |
| H    | 3.53816 | 2.74438 | 0.08667 |
| H    | -0.72203 | 0.11653 | 1.12252 |
| H    | -0.35544 | -1.78900 | -0.46409 |
| H    | -0.77423 | -0.71988 | -1.79731 |
| H    | -3.11723 | 0.16990 | -1.99622 |
| H    | -5.49184 | -0.08795 | -1.40582 |
| H    | -6.15616 | -1.57709 | 0.45617 |
| H    | -4.42140 | -2.82219 | 1.70911 |
| H    | -2.03984 | -2.55079 | 1.12063 |
| H    | -0.90680 | 1.82248 | -1.28906 |
| H    | -3.45432 | 2.33967 | 1.86991 |
| H    | -3.10987 | 0.64334 | 1.47362 |
| H    | -1.86817 | 1.63216 | 2.25861 |
| H    | 5.75150 | 1.54210 | 0.04956 |
| H    | 6.99087 | -0.58811 | 0.01294 |
| H    | 5.76660 | -2.74204 | -0.02108 |
| H    | 3.28730 | -2.76598 | -0.02190 |

ZB

M06-2X/def2-TZVP Geometry

| Atom | X  | Y  | Z  |
|------|----|----|----|
| C    | 0.35237 | 0.47282 | -0.87892 |
| C    | 0.23170 | 1.83231 | -0.93251 |
|   | x    | y    | z    |
|---|------|------|------|
| C | 1.2752 | 2.6115 | -0.3521 |
| C | 2.3603 | 1.9309 | 0.2522 |
| N | 2.4355 | 0.5723 | 0.2967 |
| C | 1.4761 | -0.1190 | -0.2520 |
| C | 1.5637 | -1.6295 | -0.1301 |
| N | 2.9450 | -2.0407 | -0.1135 |
| C | 3.4592 | -3.2224 | -0.5476 |
| C | 2.4924 | -4.1880 | -1.2013 |
| O | 4.6398 | -3.4806 | -0.4385 |
| C | -0.9596 | 2.4830 | -1.5674 |
| C | 1.2744 | 4.0254 | -0.3530 |
| C | 2.3018 | 4.7247 | 0.2184 |
| C | 3.3795 | 4.0429 | 0.8208 |
| C | 3.4087 | 2.6766 | 0.8375 |
| C | -0.6462 | -1.7649 | 1.0858 |
| C | -1.1614 | -0.6315 | 1.7078 |
| C | -2.4822 | -0.2543 | 1.5243 |
| C | -3.2930 | -1.0218 | 0.7087 |
| C | -2.8190 | -2.1678 | 0.0986 |
| C | -1.4959 | -2.5339 | 0.2948 |
| O | -4.6246 | -0.6626 | 0.5231 |
| C | -4.8772 | 0.3228 | -0.3770 |
| C | -6.3476 | 0.6050 | -0.4489 |
| O | -4.0234 | 0.8705 | -1.0089 |
| H | -0.4228 | -0.1615 | -1.2938 |
| H | 1.0616 | -2.0696 | -0.9945 |
| H | 1.2946 | -1.6028 | 2.0031 |
| H | 0.9699 | -3.1666 | 1.2584 |
| H | 3.6003 | -1.3811 | 0.2856 |
| H | 2.1318 | -3.7783 | -2.1466 |
| H | 3.0251 | -5.1139 | -1.3943 |
| H | 1.6257 | -4.3888 | -0.5704 |
| H | -0.6577 | 3.1049 | -2.4130 |
|  | X   | Y   | Z   |
|---|-----|-----|-----|
| H | -1.67391 | 1.73867 | -1.91117 |
| H | -1.47221 | 3.13021 | -0.85284 |
| H | 0.45139  | 4.55395 | -0.81606 |
| H | 2.29106  | 5.80679 | 0.20974  |
| H | 4.18611  | 4.60762 | 1.27048  |
| H | 4.22365  | 2.12821 | 1.29173  |
| H | -0.51100 | -0.01871 | 2.32129 |
| H | -2.88301 | 0.63557 | 1.99161  |
| H | -3.48181 | -2.75599 | -0.52231 |
| H | -1.11267 | -3.42660 | -0.18807 |
| H | -6.88444 | -0.30895 | -0.70007 |
| H | -6.70056 | 0.93653  | 0.52729  |
| H | -6.53032 | 1.37079  | -1.19588 |

ZC

M06-2X/def2-TZVP Geometry

|  | X   | Y   | Z   |
|---|-----|-----|-----|
| C | -4.45062 | -2.18600 | 0.87245  |
| C | -3.30929 | -1.64067 | 0.24287  |
| C | -2.37976 | -2.50787 | -0.38003 |
| C | -2.62146 | -3.90066 | -0.35182 |
| C | -3.73372 | -4.40412 | 0.26560  |
| C | -4.65783 | -3.53724 | 0.88374  |
| N | -3.14537 | -0.28847 | 0.26489  |
| C | -2.09444 | 0.21913  | -0.31896 |
| C | -1.11897 | -0.56935 | -0.97832 |
| C | -1.24145 | -1.92813 | -1.01355 |
| C | -0.21495 | -2.78488 | -1.69102 |
| C | -1.90165 | 1.71606  | -0.22640 |
| C | -0.98225 | 2.08060  | 0.96586  |
| C | 0.41006  | 1.54614  | 0.79695  |
| C | 1.28832  | 2.15164  | -0.09878 |
| C | 2.54878  | 1.62220  | -0.33570 |
| Atom | X     | Y     | Z     |
|------|-------|-------|-------|
| N    | -1.29048 | -0.91077 | 0.05750 |
| C    | -2.62542 | -1.09637 | -0.11606 |

**ZD**

M06-2X/def2-TZVP Geometry

N    -1.29048  -0.91077  0.05750
C    -2.62542  -1.09637  -0.11606
| C  | -3.56121 | -0.03624 | -0.03322 |
| C  | -3.06557 | 1.27019  | 0.23837  |
| C  | -1.71614 | 1.41921  | 0.40454  |
| C  | 0.64227  | 0.42295  | 0.51689  |
| C  | 1.04948  | -0.22794 | 1.84090  |
| C  | 2.56531  | -0.20274 | 2.08032  |
| N  | 1.13025  | 1.78316  | 0.46857  |
| C  | 1.46579  | 2.49679  | -0.64542 |
| C  | 1.32410  | 1.78123  | -1.96691 |
| O  | 1.86672  | 3.63945  | -0.55957 |
| C  | -3.08589 | -2.40515 | -0.39396 |
| C  | -4.41763 | -2.64713 | -0.57805 |
| C  | -5.35251 | -1.59333 | -0.49417 |
| C  | -4.93399 | -0.31899 | -0.22906 |
| C  | -3.99591 | 2.44256  | 0.33029  |
| C  | 3.33938  | -0.75903 | 0.91389  |
| C  | 4.01951  | 0.08394  | 0.03923  |
| C  | 4.68492  | -0.42839 | -1.06743 |
| C  | 4.67709  | -1.79361 | -1.31452 |
| C  | 4.00384  | -2.64381 | -0.44685 |
| C  | 3.34070  | -2.12820 | 0.65643  |
| H  | -1.29334 | 2.39625  | 0.59905  |
| H  | 1.11899  | -0.14689 | -0.28330 |
| H  | 0.68515  | -1.25574 | 1.81647  |
| H  | 0.53526  | 0.27639  | 2.66589  |
| H  | 2.78162  | -0.78153 | 2.98103  |
| H  | 2.89764  | 0.81856  | 2.27428  |
| H  | 1.23095  | 2.29473  | 1.33359  |
| H  | 1.50280  | 2.50072  | -2.75989 |
| H  | 2.05783  | 0.97433  | -2.03379 |
| H  | 0.33183  | 1.34079  | -2.07710 |
| H  | -2.34670 | -3.19308 | -0.45529 |
| H  | -4.76249 | -3.65093 | -0.79055 |
H  -6.40478  -1.79824  -0.64221
H  -5.65644   0.48460  -0.16750
H  -3.44711   3.35352   0.56000
H  -4.52824   2.59003  -0.61151
H  -4.74651   2.28583   1.10727
H   4.02322   1.15275   0.22512
H   5.21116   0.24185  -1.73558
H   5.19489  -2.19448  -2.17623
H   3.99652  -3.71064  -0.63023
H   2.81442  -2.79623   1.32968

H      -0.62753  -1.00499  -0.62945
C     -1.93944  -0.68389  -0.47814
C     -2.36667   0.46734   0.22782
C     -1.36880   1.31332   0.78922
C     -0.05906   0.95851   0.61548
C      0.27039  -0.21815  -0.09989
C      1.71561  -0.66457  -0.28496
C      1.99117  -1.94520   0.52761
C      1.84516  -1.72941   2.03197
N      2.68585   0.36039   0.03067
C      2.97391   1.46923  -0.71206
C      2.37821   1.52316  -2.09906
O      3.68323   2.35080  -0.27354
C     -2.90630  -1.54143  -1.05388
C     -4.23860  -1.26629  -0.92942
C     -4.66757  -0.12138  -0.22475
C     -3.75370   0.72461   0.33971
C     -1.74641   2.55151   1.54608
C      3.35646  -2.52870   0.18331

ZE

M06-2X/def2-TZVP Geometry

N    -0.62753 -1.00499  -0.62945
C    -1.93944 -0.68389  -0.47814
C    -2.36667   0.46734   0.22782
C    -1.36880   1.31332   0.78922
C    -0.05906   0.95851   0.61548
C     0.27039  -0.21815  -0.09989
C     1.71561  -0.66457  -0.28496
C     1.99117  -1.94520   0.52761
C     1.84516  -1.72941   2.03197
N     2.68585   0.36039   0.03067
C     2.97391   1.46923  -0.71206
C     2.37821   1.52316  -2.09906
O     3.68323   2.35080  -0.27354
C    -2.90630  -1.54143  -1.05388
C    -4.23860  -1.26629  -0.92942
C    -4.66757  -0.12138  -0.22475
C    -3.75370   0.72461   0.33971
C    -1.74641   2.55151   1.54608
C     3.35646  -2.52870   0.18331
Diazine prediction set

\[
\begin{align*}
\text{N} & & \text{N} \\
\text{NHAc} & & \text{Ph}
\end{align*}
\]

1

M06-2X/def2-TZVP Geometry

\begin{align*}
\text{C} & & 0.70204 & 3.36925 & 0.40674 \\
\text{N} & & -0.37051 & 3.80044 & -0.23929 \\
\text{N} & & 1.15854 & 2.12126 & 0.44351 \\
\text{C} & & 0.47451 & 1.20596 & -0.23912 \\
\text{C} & & -0.66560 & 1.54987 & -0.95602 \\
\text{C} & & -1.04783 & 2.87771 & -0.92020 \\
\text{C} & & 0.95145 & -0.22180 & -0.15593 \\
\text{C} & & 0.16993 & -0.99460 & 0.93561
\end{align*}
\[
\begin{align*}
\text{C} & -1.28021 -1.16628 0.58442 \\
\text{N} & 2.36948 -0.25240 0.10776 \\
\text{C} & 3.09893 -1.36202 -0.16129 \\
\text{C} & -1.64554 -2.05466 -0.42586 \\
\text{C} & -2.97103 -2.17814 -0.81429 \\
\text{C} & -3.95288 -1.41524 -0.19359 \\
\text{C} & -3.60059 -0.53481 0.81887 \\
\text{C} & -2.27162 -0.41152 1.20239 \\
\text{O} & 2.59915 -2.35927 -0.64866 \\
\text{C} & 4.56713 -1.29070 0.18311 \\
\text{H} & -1.22776 0.80884 -1.50834 \\
\text{H} & 0.77291 -0.72128 -1.11081 \\
\text{H} & 0.28384 -0.46151 1.88205 \\
\text{H} & 0.65558 -1.96745 1.02630 \\
\text{H} & 2.77700 0.56517 0.53377 \\
\text{H} & -0.87721 -2.65205 -0.90605 \\
\text{H} & -3.24021 -2.87318 -1.59944 \\
\text{H} & -4.98790 -1.51250 -0.49459 \\
\text{H} & -4.36093 0.05779 1.31147 \\
\text{H} & -1.99822 0.28349 1.98848 \\
\text{H} & 4.87938 -0.30733 0.52969 \\
\text{H} & 5.14105 -1.56729 -0.69964 \\
\text{H} & 4.77320 -2.02918 0.95742 \\
\text{H} & -1.92690 3.21860 -1.45683 \\
\text{H} & 1.26826 4.10872 0.96308 \\
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \\
\text{NHAc} & \text{Br}
\end{align*}
\]

\begin{align*}
\text{N} & -1.29701 1.91505 -1.12781 \\
\text{C} & -0.68219 1.11822 -0.25257 \\
\text{C} & 0.46301 1.57093 0.39662 \\
\text{C} & 0.92163 2.84297 0.08170
\end{align*}

\textbf{2} \\
M06-2X/def2-TZVP Geometry
| Atom | X      | Y      | Z      |
|------|--------|--------|--------|
| N    | 0.30595| 3.62064| -0.79702|
| C    | -0.78524| 3.11454| -1.35591|
| C    | -1.27852| -0.25803| -0.09031|
| Br   | 1.40230| 0.56168| 1.67598|
| C    | -0.76905| -1.19299| -1.21456|
| C    | 0.69526| -1.19299| -1.21456|
| C    | 1.11713| -2.51668| -0.23328|
| C    | 2.46777| -2.76241| -0.04040|
| C    | 3.41647| -1.98905| -0.69716|
| C    | 3.00663| -0.97920| -1.55604|
| C    | 1.65299| -0.74009| -1.75079|
| N    | -2.71997| -0.15262| -0.12983|
| C    | -3.49839| -1.15017| 0.36108|
| C    | -4.98885| -0.95617| 0.21629|
| O    | -3.02511| -2.13119| 0.90145|
| H    | 1.81253| 3.23526| 0.55991|
| H    | -1.30867| 3.74177| -2.06894|
| H    | -0.99799| -0.68775| 0.87145|
| H    | -0.99080| -0.71756| -2.17291|
| H    | -1.35646| -2.10880| -1.13781|
| H    | 0.37319| -3.10931| 0.28852|
| H    | 2.78178| -3.55708| 0.62426|
| H    | 4.47127| -2.17797| -0.54502|
| H    | 3.74137| -0.37906| -2.07744|
| H    | 1.33402| 0.04928| -2.42363|
| H    | -3.11276| 0.59879| -0.67422|
| H    | -5.25305| -0.07555| -0.36646|
| H    | -5.40888| -1.84547| -0.25028|
| H    | -5.42002| -0.86930| 1.21319|

3

M06-2X/def2-TZVP Geometry

N 0.76058 2.17190 0.63869
|   |   |   |   |
|---|---|---|---|
| C | 0.31156 | 1.14709 | -0.08222 |
| C | -0.92535 | 1.19443 | -0.71024 |
| C | -1.68711 | 2.34204 | -0.54865 |
| N | -1.23323 | 3.37008 | 0.17701 |
| C | -0.03782 | 3.23172 | 0.72382 |
| C | 1.16897 | -0.09230 | -0.13520 |
| C | 0.69793 | -1.12209 | 0.92287 |
| C | -3.04310 | 2.49249 | -1.16310 |
| C | -0.66619 | -1.66904 | 0.61436 |
| C | -0.82690 | -2.56908 | -0.43790 |
| C | -2.08724 | -3.02758 | -0.79121 |
| C | -3.20755 | -2.59391 | -0.09277 |
| C | -3.05727 | -1.70569 | 0.96254 |
| C | -1.79371 | -1.24689 | 1.31109 |
| N | 2.55278 | 0.25902 | 0.06952 |
| C | 3.54512 | -0.58095 | -0.30932 |
| O | 3.31644 | -1.64957 | -0.84630 |
| C | 4.95319 | -0.11714 | -0.02305 |
| H | -1.28529 | 0.35648 | -1.29314 |
| H | 0.33160 | 4.06985 | 1.30595 |
| H | 1.07650 | -0.55883 | -1.11851 |
| H | 0.71568 | -0.63916 | 1.90241 |
| H | 1.43774 | -1.92412 | 0.91866 |
| H | -3.32189 | 1.61286 | -1.73981 |
| H | -3.78208 | 2.65534 | -0.37771 |
| H | -3.05836 | 3.37115 | -1.80855 |
| H | 0.04993 | -2.90783 | -0.98050 |
| H | -2.19614 | -3.72877 | -1.60875 |
| H | -4.19126 | -2.95296 | -0.36615 |
| H | -3.92473 | -1.36942 | 1.51637 |
| H | -1.68061 | -0.54337 | 2.12841 |
| H | 2.73964 | 1.13596 | 0.53036 |
| H | 4.99835 | 0.88926 | 0.38902 |
| H | 5.40748 | -0.81592 | 0.67878 |
|  | X   | Y   | Z   |
|-----------------|-----|-----|-----|
| H               | 5.52388 | -0.15950 | -0.94917 |
| N               | -2.03844 | -0.93186 | 0.20607 |
| C               | -0.87936 | -0.60400 | -0.35383 |
| C               | -0.11381 | -1.54600 | -1.03095 |
| C               | -0.62380 | -2.82881 | -1.08072 |
| N               | -1.78356 | -3.16615 | -0.52174 |
| C               | -2.45055 | -2.19772 | 0.09862 |
| C               | -0.40346 | 0.81593 | -0.17493 |
| C               | 0.60328 | 0.90671 | 0.99991 |
| C               | 1.94458 | 0.33248 | 0.64289 |
| C               | 2.76314 | 1.02995 | -0.24478 |
| C               | 3.98543 | 0.50887 | -0.63844 |
| C               | 4.40841 | -0.72097 | -0.14787 |
| C               | 3.60342 | -1.42052 | 0.73918 |
| C               | 2.37777 | -0.89599 | 1.13036 |
| N               | -1.53133 | 1.68938 | 0.03847 |
| C               | -1.41612 | 3.02279 | -0.16678 |
| C               | -2.65655 | 3.84493 | 0.08728 |
| O               | -0.37243 | 3.53010 | -0.53674 |
| C               | -3.77556 | -2.53749 | 0.70771 |
| H               | 0.83143 | -1.28551 | -1.48700 |
| H               | -0.08656 | -3.62228 | -1.58958 |
| H               | 0.11251 | 1.14453 | -1.07987 |
| H               | 0.17342 | 0.40593 | 1.87012 |
| H               | 0.70751 | 1.96791 | 1.22972 |
| H               | 2.42870 | 1.99148 | -0.62143 |
| H               | 4.61225 | 1.06419 | -1.32449 |
| H               | 5.36379 | -1.12817 | -0.45276 |
| H               | 3.92952 | -2.37663 | 1.12858 |
| H               | 1.74745 | -1.44868 | 1.81812 |
H  -2.38867   1.26656    0.35806
H  -3.51663   3.24501    0.37903
H  -2.43582   4.56879    0.87083
H  -2.89079   4.40048   -0.81958
H  -3.88047  -3.61481    0.80261
H  -4.57633  -2.16279   -0.81958
H  -3.87940  -2.05722    1.67926

M06-2X/def2-TZVP Geometry

N  -1.10165  -1.76649    0.37657
C  -0.44547  -0.79939   -0.25370
C   0.76594  -1.03974   -0.88814
C   1.27050  -2.32779   -0.82519
N   0.60665  -3.29933   -0.18910
C  -0.54943  -2.98390    0.37890
C  -1.03714   0.58736   -0.20095
C  -0.39685   1.40950    0.94559
C   1.05752   1.69231    0.69973
C   1.42543   2.61803   -0.27516
C   2.76177   2.83773   -0.57461
C   3.75189   2.13545    0.10204
C   3.39639   1.21932    1.08142
C   2.05703   0.99999    1.37559
N  -2.46782   0.50495   -0.03547
C  -3.26471   1.55454   -0.34560
C  -4.74477   1.35200   -0.12444
O  -2.81686   2.59975   -0.78154
C  -1.30862  -4.06900    1.07922
H   1.29848  -0.24672   -1.39640
C   2.57436  -2.70468   -1.45573
H  -0.83189   1.10739   -1.13941
H  -0.53817   0.86179   1.87989
H  -0.95995   2.34221   1.00232
H  0.64972    3.16602  -0.80025
H  3.03237   3.56072  -1.33373
H  4.79518   2.30836  -0.12855
H  4.16277    0.67397   1.61753
H  1.78205   0.27552   2.13416
H  -2.83487  -0.35391   0.34410
H  -5.09564   2.10936   0.57531
H  -5.25739  1.51360  -1.07163
H  -4.98996   0.36268   0.25758
H  -0.73381  -4.99056   1.07815
H  -2.26291  -4.23436   0.57694
H  -1.52914  -3.76780   2.10343
H  3.24138  -3.11389  -0.69633
H  2.41143  -3.48666  -2.19820
H  3.05198  -1.84987  -1.93036

M06-2X/def2-TZVP Geometry
N  -0.40840  -2.03351   0.47095
C  -0.21129  -0.87271  -0.15786
C   1.01358  -0.54618  -0.71449
C   2.01025  -1.49655  -0.55719
N   1.83605  -2.64280   0.05747
C   0.61604  -2.87619   0.54974
C  -1.35971   0.10315  -0.18132
C  -1.21750   1.12987   0.97083
C  -0.06416   2.06639   0.74939
C   1.13089   1.93456   1.44847
C   2.21047   2.76319   1.17013
C   2.10527   3.73424   0.18491
\begin{align*}
\text{C} & \quad 0.91330 \quad 3.87907 \quad -0.51432 \\
\text{C} & \quad -0.16271 \quad 3.05120 \quad -0.23239 \\
\text{N} & \quad -2.61215 \quad -0.60705 \quad -0.09611 \\
\text{C} & \quad -3.76754 \quad -0.01590 \quad -0.48690 \\
\text{C} & \quad -5.02136 \quad -0.84143 \quad -0.32783 \\
\text{O} & \quad -3.79259 \quad 1.11612 \quad -0.93321 \\
\text{Cl} & \quad 3.58464 \quad -1.17724 \quad -1.19721 \\
\text{C} & \quad 0.40690 \quad -4.19184 \quad 1.23073 \\
\text{H} & \quad -1.34764 \quad 0.65717 \quad -1.12230 \\
\text{H} & \quad -1.11120 \quad 0.58505 \quad 1.91143 \\
\text{H} & \quad -2.15533 \quad 1.68648 \quad 0.99742 \\
\text{H} & \quad 1.22038 \quad 1.16953 \quad 2.21179 \\
\text{H} & \quad 3.13527 \quad 2.64695 \quad 1.72056 \\
\text{H} & \quad 2.94639 \quad 4.37860 \quad -0.03549 \\
\text{H} & \quad 0.82107 \quad 4.64045 \quad -1.27837 \\
\text{H} & \quad -1.09590 \quad 3.16201 \quad -0.77533 \\
\text{H} & \quad -2.59209 \quad -1.53492 \quad 0.29666 \\
\text{H} & \quad -4.82015 \quad -1.87656 \quad -0.05777 \\
\text{H} & \quad -5.64000 \quad -0.38207 \quad 0.44297 \\
\text{H} & \quad -5.57657 \quad -0.80691 \quad -1.26321 \\
\text{H} & \quad 1.16461 \quad -4.33356 \quad 2.00080 \\
\text{H} & \quad 0.52695 \quad -4.99883 \quad 0.50668 \\
\text{H} & \quad -0.58568 \quad -4.24080 \quad 1.66920 \\
\text{H} & \quad 1.18867 \quad 0.38987 \quad -1.22430 \\
\end{align*}

\begin{align*}
\text{N} & \quad -1.01475 \quad -2.09757 \quad 0.53099 \\
\text{C} & \quad 0.87371 \quad -0.90625 \quad -0.04900 \\
\text{C} & \quad 0.36978 \quad -0.41196 \quad -0.40125 \\
\text{C} & \quad 1.47835 \quad -1.19238 \quad -0.08764 \\
\text{N} & \quad 1.32882 \quad -2.39283 \quad 0.47635 \\
\end{align*}
- C  0.09542  -2.80167  0.75179
- C  -2.11851  -0.07880  -0.24732
- C  -2.25474  0.96681  0.88866
- C  -1.21710  2.04874  0.79056
- C  -0.12810  2.10408  1.65451
- C   0.85201  3.07708  1.49990
- C   0.75626  4.00337  0.47102
- C  -0.32877  3.95784  -0.39641
- N  -3.27853  -0.93349  -0.30597
- C  -4.43774  -0.49032  -0.84734
- O  -4.54798   0.63155  -1.30839
- C  -0.04750  -4.16186  1.36396
H   -2.04828   0.46435  -1.19254
H   -2.19507   0.44767   1.84762
H   -3.25225   1.39670   0.78879
H   -0.04146   1.37265   2.45008
H    1.69334   3.10645   2.18075
H    1.51910   4.76154   0.34840
H   -0.41502   4.68299  -1.19555
H   -2.15950   2.95567  -0.90641
H   -3.18633  -1.85877   0.08354
H   -6.36963  -1.07180  -0.18884
H   -5.99709  -1.52599  -1.84730
H   -5.30561  -2.46041  -0.49944
H    0.55229  -4.22239   2.27195
H    0.33249  -4.91592   0.67361
H   -1.08881  -4.36993   1.59375
H    0.46322   0.54161  -0.90082
C    5.46717   0.09978  -0.88267
C    5.18030  -1.25359  -0.75823
C    3.88582  -1.66926  -0.49370
C    2.85969  -0.73473  -0.36440
C  3.15421  0.62273  -0.48513  
C  4.45276  1.03639  -0.74010  
H  6.47993  0.42360  -1.08571  
H  5.96879  -1.98702  -0.86724  
H  3.65022  -2.71911  -0.38395  
H  2.37558  1.36427  -0.35066  
H  4.67269  2.09294  -0.82241

\[
\begin{array}{c}
N \quad 2.17677 \quad 1.44809 \quad 0.15211 \\
C \quad 1.14062 \quad 0.70427 \quad -0.23688 \\
C \quad 0.03445 \quad 1.27492 \quad -0.86618 \\
C \quad 0.09215 \quad 2.65985 \quad -1.01455 \\
N \quad 1.11216 \quad 3.40377 \quad -0.61894 \\
C \quad 2.13564 \quad 2.75999 \quad -0.05720 \\
C \quad 1.22539 \quad -0.75520 \quad 0.14658 \\
C \quad 0.76909 \quad -0.94368 \quad 1.61017 \\
C \quad -0.69292 \quad -0.65487 \quad 1.80833 \\
C \quad -1.64833 \quad -1.57978 \quad 1.38963 \\
C \quad -2.99983 \quad -1.32767 \quad 1.56324 \\
C \quad -3.41729 \quad -0.14215 \quad 2.15609 \\
C \quad -2.47572 \quad 0.79114 \quad 2.56313 \\
C \quad -1.12138 \quad 0.53577 \quad 2.38591 \\
N \quad 2.58313 \quad -1.21893 \quad -0.03175 \\
C \quad 2.85242 \quad -2.53827 \quad -0.18498 \\
C \quad 4.31371 \quad -2.90745 \quad -0.28355 \\
O \quad 1.97234 \quad -3.37694 \quad -0.24354 \\
C \quad 3.32161 \quad 3.57806 \quad 0.35000 \\
H \quad 0.58441 \quad -1.36615 \quad -0.48381 \\
H \quad 1.38258 \quad -0.29954 \quad 2.24399 \\
H \quad 0.98250 \quad -1.98340 \quad 1.86528 \\
H \quad -1.32016 \quad -2.50641 \quad 0.92984 \\
\end{array}
\]
|   |   |   |   |
|---|---|---|---|
| H | -3.72965 | -2.05546 | 1.23181 |
| H | -4.47280 | 0.05268  | 2.29798 |
| H | -2.79350 | 1.71759  | 3.02524 |
| H | -0.38601 | 1.26353  | 2.71195 |
| H | 3.31794  | -0.54257 | 0.10399 |
| H | 4.97329  | -2.04201 | -0.31335|
| H | 4.57011  | -3.52779 | 0.57484 |
| H | 4.45664  | -3.50762 | -1.18054|
| H | 2.99237  | 4.50187  | 0.82258 |
| H | 3.89617  | 3.85210  | -0.53713|
| H | 3.96136  | 3.01337  | 1.02298 |
| H | -0.73497 | 3.17898  | -1.49078|
| C | -3.41640 | -0.81040 | -2.27553|
| C | -3.54848 | 0.26304  | -1.40790|
| C | -2.42270 | 0.93074  | -0.94938|
| C | -1.15086 | 0.53139  | -1.35054|
| C | -1.02738 | -0.53913 | -2.23649|
| C | -2.15194 | -1.20832 | -2.69142|
| H | -4.29426 | -1.33577 | -2.62895|
| H | -4.52907 | 0.57375  | -1.07061|
| H | -2.52508 | 1.74496  | -0.24238|
| H | -0.04505 | -0.84233 | -2.57854|
| H | -2.04107 | -2.03828 | -3.37702|

```
\[ \text{N} = \text{Br} \quad \text{Ph} \quad \overset{\text{N}}{\text{NHAc}} \]
```

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M06-2X/def2-TZVP Geometry

|   |   |   |   |
|---|---|---|---|
| N | -0.11357 | -0.81876 | 1.41672 |
| C | -0.73307 | 0.03734  | 0.61459 |
| C | -2.04151 | -0.22409 | 0.21271 |
| C | -2.63017 | -1.38972 | 0.66782 |
| N | -1.98805 | -2.24959 | 1.44788 |
| Element | X       | Y       | Z       |
|---------|---------|---------|---------|
| C       | -0.74548| -1.92918| 1.79743 |
| C       | 0.06284 | 1.21485 | 0.11305 |
| Br      | -3.02428| 0.93652 | -0.90226|
| C       | 0.57289 | 0.93112 | -1.32890|
| C       | 1.46568 | -0.27516| -1.39041|
| C       | 0.93628 | -1.54471| -1.61234|
| C       | 1.74992 | -2.66819| -1.60169|
| C       | 3.11247 | -2.53694| -1.36896|
| C       | 3.65404 | -1.27681| -1.15693|
| C       | 2.83520 | -0.15576| -1.16895|
| N       | 1.14792 | 1.47758 | 1.02501 |
| C       | 1.83814 | 2.64276 | 0.97832 |
| C       | 3.01526 | 2.74565 | 1.91928 |
| O       | 1.53573 | 3.54664 | 0.22261 |
| H       | -3.64984| -1.63450| 0.39002 |
| C       | 0.01708 | -2.87765| 2.66691 |
| H       | -0.57000| 2.10277 | 0.06631 |
| H       | 1.10449 | 1.82936 | -1.64396|
| H       | -0.29025| 0.80358 | -1.98412|
| H       | -0.12828| -1.65182| -1.79531|
| H       | 1.32049 | -3.64623| -1.77889|
| H       | 3.75000 | -3.41161| -1.36371|
| H       | 4.71757 | -1.16520| -0.98774|
| H       | 3.26230 | 0.82939 | -1.01589|
| H       | 1.46523 | 0.70151 | 1.58551 |
| H       | 3.92945 | 2.75349 | 1.32517 |
| H       | 2.95417 | 3.69619 | 2.44564 |
| H       | 3.06162 | 1.92843 | 2.63671 |
| H       | -0.59735| -3.73679| 2.91943 |
| H       | 0.33687 | -2.37088| 3.57786 |
| H       | 0.91596 | -3.20483| 2.14239 |
M06-2X/def2-TZVP Geometry

N  0.96072  0.18965  0.28701
C  -0.28123  0.02326  0.72483
C  -0.64463 -1.10132  1.45426
C   0.35760 -2.02242  1.69801
N  1.60113 -1.86338  1.26296
C   1.85951 -0.75745  0.56669
C  -1.28976  1.07643  0.34093
C  -1.99500  0.68851  0.98106
C  -2.84520 -0.54051  0.83224
C  -4.06219 -0.46386 -0.15664
C  -4.83199 -1.59956  0.04539
C  -4.39525 -2.83091  0.42773
C  -3.18760 -3.91689 -1.10574
C  -2.41899 -1.77793 -1.30403
N  -0.63692  2.35838  0.22044
C  -1.35097  3.50914  0.26476
C  -0.56215  4.78563  0.09607
O  -2.55703  3.51410  0.42784
H  -1.65705 -1.24728  1.80452
H   0.15626 -2.92542  2.26504
H  -2.05291  1.15538  1.11805
H  -1.22923  0.54499  1.74645
H  -2.60994  1.54437  1.26238
H  -4.40430  0.49948  0.20751
H  -5.77717 -1.52374  0.56786
H  -4.99641 -3.71744  0.27223
H  -2.84212 -3.87178 -1.48104
H  -1.47174 -1.84935  1.82720
H   0.35736  2.35470  0.05697
H  -0.88664  5.27042 -0.82429
H  -0.80367   5.45009   0.92378
H   0.51354   4.62341   0.05889
C   5.83976  -0.21263  -0.88314
C   5.53834  -1.28899  -0.05913
C   4.24704  -1.46687   0.41120
C   3.24314  -0.56512   0.06363
C   3.55123   0.51292  -0.76421
C   4.84256   0.68678  -1.23521
H   6.84835  -0.07645  -1.25181
H   6.31252  -1.99302   0.21741
H   3.99957  -2.30315   1.05003
H   2.76790   1.20505  -1.04003
H   5.07214   1.52518  -1.88012

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M06-2X/def2-TZVP Geometry
N   2.06867   0.01903  -0.43875
C   0.89135   0.06725   0.17053
C   0.42511  -1.03933   0.88258
C   1.23480  -2.16146   0.90084
N   2.40852  -2.20826   0.28409
C   2.77200  -1.10351  -0.35146
C   0.11871   1.34955  -0.01959
Br  -1.20815  -1.07230   1.81505
C  -0.63878   1.31716  -1.36953
C  -1.75445   0.31189  -1.37939
C  -1.55547  -0.98414  -1.84500
C  -2.57075  -1.92774  -1.76825
C  -3.80162  -1.58085  -1.22965
C  -4.01412  -0.28589  -0.77475
C  -2.99556   0.65153  -0.84735
N  1.04033   2.46266   0.01959
C   0.59201   3.72166   0.25400
| Element | X         | Y         | Z        |
|---------|-----------|-----------|----------|
| C       | 1.63513   | 4.81254   | 0.20866  |
| O       | -0.57528  | 3.95638   | 0.50248  |
| H       | 0.92323   | -3.05203  | 1.43540  |
| O       | 3.94578   | -1.06764  | -0.97671 |
| H       | -0.60784  | 1.48271   | 0.78168  |
| H       | 0.08883   | 1.11107   | -2.15795 |
| H       | -1.03525  | 2.32230   | -1.51706 |
| H       | -0.59367  | -1.25607  | -2.26748 |
| H       | -2.40182  | -2.93328  | -2.13218 |
| H       | -4.59462  | -2.31506  | -1.16912 |
| H       | -4.97454  | -0.00742  | -0.35995 |
| H       | -3.15270  | 1.65965   | -0.47873 |
| H       | 1.98199   | 2.29073   | -0.29637 |
| H       | 1.71699   | 5.24943   | 1.20345  |
| H       | 2.61362   | 4.45781   | -0.10981 |
| H       | 1.28849   | 5.59141   | -0.46837 |
| C       | 4.75390   | -2.23733  | -0.91785 |
| H       | 4.24158   | -3.08329  | -1.37503 |
| H       | 5.65461   | -1.99274  | -1.47299 |
| H       | 4.99627   | -2.48679  | 0.11461  |

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M06-2X/def2-TZVP Geometry

| Element | X         | Y         | Z        |
|---------|-----------|-----------|----------|
| N       | 0.98761   | 0.04641   | 0.98551  |
| C       | 0.69119   | -0.91027  | 0.12326  |
| C       | 1.69626   | -1.47388  | -0.66922 |
| C       | 2.97546   | -0.97991  | -0.51901 |
| N       | 3.26568   | -0.00683  | 0.33767  |
| C       | 2.25217   | 0.45491   | 1.05377  |
| C       | -0.75551  | -1.31172  | -0.00558 |
| C       | -1.37002  | -0.70541  | -1.29821 |
| C       | -1.38180  | 0.79636   | -1.28503 |
| C       | -2.45376  | 1.48925   | -0.72812 |
\[
\begin{array}{cccc}
C & -2.44990 & 2.87565 & -0.66885 \\
C & -1.37066 & 3.59050 & -1.16891 \\
C & -0.29942 & 2.91171 & -1.73316 \\
C & -0.30787 & 1.52571 & -1.78970 \\
N & -1.46957 & -0.90173 & 1.17673 \\
C & -2.70444 & -1.38491 & 1.45290 \\
O & -3.24120 & -2.22826 & 0.75916 \\
C & -3.37803 & -0.80613 & 2.67435 \\
Cl & 1.38824 & -2.75290 & -1.78401 \\
O & 2.46637 & 1.41964 & 1.94220 \\
H & -0.82752 & -2.39785 & -0.09551 \\
H & -2.38364 & -1.10102 & -1.36355 \\
H & -0.80934 & -1.07669 & -2.15709 \\
H & -3.30394 & 0.93143 & -0.35043 \\
H & -3.29313 & 3.39861 & -0.23574 \\
H & -1.36757 & 4.67190 & -1.12612 \\
H & 0.54171 & 3.46262 & -2.13451 \\
H & 0.52868 & 0.99858 & -2.23756 \\
H & -1.06889 & -0.14498 & 1.71005 \\
H & -4.25125 & -0.24017 & 2.34954 \\
H & -3.72888 & -1.62821 & 3.29560 \\
H & -2.72569 & -0.15766 & 3.25620 \\
H & 3.79149 & -1.38534 & -1.10764 \\
C & 3.79688 & 1.90582 & 2.07293 \\
H & 3.74632 & 2.67972 & 2.83315 \\
H & 4.46980 & 1.10719 & 2.38386 \\
H & 4.15102 & 2.31912 & 1.12914 \\
\end{array}
\]

![Structure Image]

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M06-2X/def2-TZVP Geometry

N  -2.73779  -1.03939  0.15067

S115
| Element | X      | Y      | Z      |
|---------|--------|--------|--------|
| C       | -1.4478| -0.8859| -0.1388|
| C       | -0.6858| -1.9499| -0.6072|
| C       | -1.3308| -3.1647| -0.7480|
| N       | -2.6201| -3.3291| -0.4573|
| C       | -3.2563| -2.2509| -0.0247|
| C       | -0.8358| 0.4693 | 0.1043 |
| C       | -0.2130| 0.5473 | 1.5144 |
| C       | 0.9736 | -0.3838| 1.7458 |
| N       | -1.8419| 1.4952 | -0.0621|
| C       | -1.4895| 2.7826 | -0.2819|
| C       | -2.6239| 3.7681 | -0.4270|
| O       | -0.3240| 3.1292 | -0.3661|
| C       | 2.1231 | -0.2311| 0.7738 |
| C       | 2.4131 | 0.9847 | 0.1576 |
| C       | 3.4914 | 1.0975 | -0.7100|
| C       | 4.2976 | 0.0056 | -0.9775|
| C       | 4.0156 | -1.2166| -0.3728|
| C       | 2.9368 | -1.3275| 0.4924 |
| H       | 0.3614 | -1.8236| -0.8522|
| H       | -0.8009| -4.0395| -1.1103|
| H       | -4.3092| -2.3658| 0.2103 |
| H       | -0.0539| 0.6436 | 0.6370 |
| H       | -0.9984| 0.3273 | 2.2390 |
| H       | 0.0842 | 1.5861 | 1.6625 |
| H       | 0.6411 | -1.4251| 1.7345 |
| H       | 1.3459 | -0.2041| 2.7588 |
| H       | -2.8044| 1.2204 | 0.0555 |
| H       | -3.6062| 3.3113 | -0.3215|
| H       | -2.5009| 4.5471 | 0.3241 |
| H       | -2.5445| 4.2373 | -1.4068|
| H       | 1.7826 | 1.8502 | 0.3278 |
| H       | 3.6940 | 2.0497 | -1.1837|
H  5.13515  0.09070  -1.65703
H  4.63383  -2.08160  -0.57763
H  2.71978  -2.28191  0.96074

M06-2X/def2-TZVP Geometry
N  2.01251  0.57603  -0.84425
C  1.43661  -0.06510  0.16947
C  2.19391  -0.80118  1.07245
C  3.56034  -0.82887  0.86865
N  4.14523  -0.19099  -0.14389
C  3.33433  0.47938  -0.94813
C  -0.07028  -0.01638  0.25926
C  -0.64725  -1.25168  -0.45227
C  -2.16476  -1.39617  -0.34635
N  -0.55337  1.21818  -0.31909
C  -1.53870  1.95246  0.25462
C  -1.85858  3.26347  -0.42464
O  -2.14011  1.58542  1.24616
H  1.73096  -1.32098  1.90063
H  4.21466  -1.37710  1.53836
H  3.79481  1.00511  -1.77790
H  -0.37169  -0.02073  1.30809
H  -0.17372  -2.14935  -0.03845
H  -0.34824  -1.19103  -1.50423
|   | X       | Y       | Z       |
|---|---------|---------|---------|
| C | -2.60573| -1.69078| 1.08394 |
| H | -0.01297| 1.59498 | -1.08234|
| H | -1.22124| 3.47295 | -1.28172|
| H | -2.89973| 3.23908 | -0.74412|
| H | -1.75682| 4.06093 | 0.30995 |
| C | -2.63859| -2.49630| -1.29201|
| H | -2.61822| -0.45015| -0.65880|
| H | -3.68533| -1.84291| 1.12658 |
| H | -2.12669| -2.60480| 1.44824 |
| H | -2.36648| -0.86717| 1.75564 |
| H | -3.72252| -2.61088| -1.24543|
| H | -2.36369| -2.28155| -2.32624|
| H | -2.19066| -3.45534| -1.01691|

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M06-2X/def2-TZVP Geometry

|   | X       | Y       | Z       |
|---|---------|---------|---------|
| N | 1.42217 | -0.90940| 0.69656 |
| C | 1.09357 | -0.07491| -0.28572|
| C | 2.06569 | 0.44124 | -1.13612|
| C | 3.37047 | 0.04754 | -0.91195|
| N | 3.70764 | -0.78383| 0.07326 |
| C | 2.70921 | -1.21879| 0.82538 |
| C | -0.35323| 0.33956 | -0.41711|
| C | -0.54447| 1.78880 | 0.09654 |
| At. | X       | Y       | Z       |
|-----|---------|---------|---------|
| C   | -0.16445| 1.92648 | 1.56611 |
| C   | -1.97744| 2.24895 | -0.14320|
| N   | -1.20231| -0.61129| 0.26266 |
| C   | -2.36475| -1.05525| -0.28606|
| C   | -3.08255| -2.12954| 0.49722 |
| O   | -2.81920| -0.60222| -1.31764|
| H   | 1.80713 | 1.11231 | -1.94413|
| H   | 4.17851 | 0.40425 | -1.54189|
| H   | 2.96428 | -1.89770| 1.63229 |
| H   | -0.63535| 0.32227 | -1.47300|
| H   | 0.12740 | 2.41499 | -0.50032|
| H   | -0.78369| 1.26991 | 2.18133 |
| H   | 0.88154 | 1.67686 | 1.74926 |
| H   | -0.33091| 2.95044 | 1.90259 |
| H   | -2.67114| 1.65854 | 0.45860 |
| H   | -2.08935| 3.29585 | 0.14278 |
| H   | -2.26898| 2.13196 | -1.18673|
| H   | -0.78054| -1.11986| 1.02453 |
| H   | -3.94173| -1.67555| 0.99194 |
| H   | -3.45571| -2.87493| -0.20159|
| H   | -2.45276| -2.60431| 1.24762 |
| Atom | X      | Y      | Z      |
|------|--------|--------|--------|
| N    | 1.60392| 0.98588| -0.47542|
| C    | 0.67355| 0.43474| 0.30114|
| C    | 0.98432| -0.63860| 1.14092|
| N    | 2.22603| -1.12812| 1.15172|
| C    | 3.14758| -0.59003| 0.36679|
| C    | 2.83549| 0.49844| -0.46029|
| C    | -0.71429| 1.01492| 0.15163|
| C    | -1.43905| 0.39048| -1.06352|
| C    | -1.74565| -1.06125| -0.83611|
| C    | -2.86385| -1.42109| -0.08623|
| C    | -3.11473| -2.75095| 0.21709|
| C    | -2.24698| -3.74153| -0.22542|
| C    | -1.13460| -3.39442| -0.98059|
| C    | -0.88890| -2.06208| -1.28438|
| N    | -0.61970| 2.45098| 0.00199|
| C    | -1.68711| 3.24820| 0.24471|
| C    | -1.48389| 4.72293| -0.01220|
| O    | -2.74785| 2.80732| 0.64842|
| C    | 3.86689| 1.13981| -1.33841|
| H    | -1.31577| 0.81820| 1.03862|
| H    | -0.80469| 0.52728| -1.94251|
| H    | -2.36168| 0.95459| -1.20739|
| H    | -3.53319| -0.64406| 0.26797|
| H    | -3.98671| -3.01595| 0.80146|
| H    | -2.43958| -4.77958| 0.01309|
| H    | -0.45627| -4.16148| -1.33189|
| H    | -0.01426| -1.79076| -1.86577|
| H    | 0.22466| 2.81173| -0.41300|
| H    | -0.45909| 4.97432| -0.28007|
| H    | -2.15308| 5.02735| -0.81645|
H  -1.77199  5.27068  0.88340
H   4.27468  0.42210 -2.05363
H   4.70621  1.51580 -0.74920
H   3.41812  1.96588 -1.88460
C  -0.00453 -1.30686  2.05059
C   4.53002 -1.16821  0.40291
H   0.54049 -1.81435  2.84343
H  -0.58875 -2.05190  1.50378
H  -0.70454 -0.59858  2.49184
H   5.25439 -0.42851  0.75193
H   4.54660 -2.02332  1.07353
H   4.84994 -1.48607 -0.59155

\[
\begin{array}{c}
\text{N} \\
\text{C} \\
\text{N} \\
\text{C} \\
\text{N} \\
\text{C} \\
\text{N} \\
\text{C} \\
\text{O}
\end{array}
\]

M06-2X/def2-TZVP Geometry

N   1.16232 -0.10758  1.02545
C   1.06305 -0.91605  0.01722
C   2.19698 -1.30098 -0.75339
N   3.38928 -0.81553 -0.43195
C   3.46869  0.02416  0.59448
C   2.36009  0.37904  1.35027
C  -0.32597 -1.34251 -0.42627
C  -0.86089 -0.43282 -1.56827
C  -1.00376  1.00107 -1.14475
C   0.06361  1.89016 -1.24884
C  -0.05485  3.19920  0.80629
C  -1.24837  3.63973 -0.24969
C  -2.32113  2.76559 -0.14573
C  -2.19746  1.45692 -0.59156
N  -1.19688 -1.31414  0.72386
C  -2.40536 -1.92338  0.70578
C  -3.26038 -1.72665  1.93536
O  -2.78523 -2.58565 -0.24262
C  2.44095  1.30059  2.52692  
H  -0.31078 -2.36452 -0.80928  
H  -1.82472 -0.84505 -1.86849  
H  -0.18513 -0.50642 -2.42198  
H   1.00041  1.54809 -1.67755  
H   0.78348  3.87808 -0.89893  
H  -1.34421  4.66173  0.09358  
H  -3.25838  3.10545  0.27656  
H  -3.03993  0.77733 -0.52262  
H  -0.93524 -0.68874  1.47056  
H  -4.13329 -1.13674  1.65488  
H  -3.61290 -2.70031  2.27057  
H  -2.73477 -1.22577  2.74634  
H   3.44616  1.70012  2.64996  
H   2.16045  0.77145  3.43879  
H   1.74090  2.12642  2.39665  
C   2.12752 -2.27792 -1.89030  
H   1.45789 -1.93801 -2.68118  
H   1.75780 -3.24672 -1.54811  
H   3.12422 -2.40733 -2.30420  
H   4.45054  0.41990  0.83090

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M06-2X/def2-TZVP Geometry

C  -0.43996  -1.12918  -0.15998  
N  -0.81835  -2.06606  -0.99387  
C   0.06887  -3.04418  -1.29373  
N   1.28512  -3.15661  -0.85008  
C   1.70300  -2.20166   0.02392

S122
| Atom | X      | Y      | Z      |
|------|--------|--------|--------|
| C    | 0.85627| -1.14235| 0.42757|
| C    | 3.01870| -2.27685| 0.53480|
| C    | 3.46226| -1.33162| 1.41440|
| C    | 2.61626| -0.27862| 1.82841|
| C    | 1.34042| -0.18418| 1.35063|
| C    | -1.43713| -0.01717| 0.07790|
| C    | -1.26864| 1.09821| -0.98674|
| N    | -2.77401| -0.56124| 0.02733|
| C    | -3.81649| 0.10951| 0.57355|
| C    | -5.17311| -0.53363| 0.41150|
| O    | -3.66922| 1.16623| 1.15986|
| C    | 0.01667| 1.85813| -0.83328|
| C    | 0.11225| 2.86855| 0.12152|
| C    | 1.31627| 3.52096| 0.34283|
| C    | 2.44217| 3.17224| -0.39292|
| C    | 2.35334| 2.17775| -1.35690|
| C    | 1.14676| 1.52745| -1.57496|
| H    | -0.28564| -3.80293| -1.98347|
| H    | 3.64178| -3.09771| 0.20621|
| H    | 4.47041| -1.38759| 1.80492|
| H    | 2.98522| 0.46054| 2.52712|
| H    | 0.70948| 0.63477| 1.66555|
| H    | -1.30157| 0.42819| 1.06349|
| H    | -2.11927| 1.76902| -0.85824|
| H    | -1.33848| 0.63262| -1.97228|
| H    | -2.90505| -1.39928| -0.51727|
| H    | -5.63258| -0.61972| 1.39464|
|   |   |   |   |
|---|---|---|---|
| H | -5.12722 | -1.51501 | -0.05723 |
| H | -5.79734 | 0.12590 | -0.19063 |
| H | -0.76834 | 3.13463 | 0.69759 |
| H | 1.37680 | 4.30493 | 1.08716 |
| H | 3.38256 | 3.67989 | -0.22121 |
| H | 3.22524 | 1.90544 | -1.93792 |
| H | 1.08120 | 0.74355 | -2.32204 |

M06-2X/def2-TZVP Geometry

|   |   |   |   |
|---|---|---|---|
| N | -2.04235 | -0.93408 | 0.24863 |
| C | -0.90424 | -0.60901 | -0.35334 |
| C | -0.16501 | -1.53829 | -1.07378 |
| C | -0.67992 | -2.82330 | -1.11848 |
| N | -1.81244 | -3.17443 | -0.52674 |
| C | -2.45218 | -2.20183 | 0.12866 |
| C | -0.41699 | 0.80671 | -0.17001 |
| C | 0.58940 | 0.88600 | 1.00560 |
| C | 1.93440 | 0.32415 | 0.64249 |
| C | 2.36876 | -0.91366 | 1.10428 |
| C | 3.60045 | -1.42292 | 0.71251 |
| C | 4.41041 | -0.69872 | -0.15000 |
| C | 3.98550 | 0.53972 | -0.61630 |
| C | 2.75699 | 1.04559 | -0.22189 |
| N | -1.53782 | 1.68981 | 0.04632 |
| C | -1.41528 | 3.02169 | -0.16215 |
| C | -2.66040 | 3.84650 | 0.06032 |
| O | -0.36670 | 3.52439 | -0.52454 |
| H | 0.76125 | -1.27256 | -1.56166 |
| H | -0.15939 | -3.60999 | -1.65502 |
|   | X      | Y      | Z       |
|---|--------|--------|---------|
| H | 0.10121| 1.13313| -1.07407|
| H | 0.16175| 0.37139| 1.86881 |
| H | 0.68910| 1.94431| 1.25019 |
| H | 1.73404| -1.48573| 1.77177 |
| H | 3.92729| -2.38669| 1.08187 |
| H | 5.37066| -1.09406| -0.45522|
| H | 4.61551| 1.11375| -1.28382|
| H | 2.42054| 2.01338| -0.58023|
| H | -2.40089| 1.27275| 0.35687 |
| H | -2.40011| 4.70648| 0.67428 |
| H | -3.00133| 4.21861| 0.90579 |
| H | -3.46613| 3.28671| 0.53208 |
| H | -3.87293| -3.49920| 0.77172 |
| N | -3.63875| -2.52488| 0.70555 |
| H | -4.03884| -1.87813| 1.36076 |

M06-2X/def2-TZVP Geometry

|   | X      | Y      | Z       |
|---|--------|--------|---------|
| N | -0.37867| -2.68459| -1.03801|
| C | 0.92339| -2.64701| -1.29756|
| C | 1.70062| -1.51469| -1.11831|
| C | 1.04527| -0.39792| -0.61426|
| N | -0.25154| -0.42761| -0.33304|
| C | -0.90244| -1.55154| -0.57558|
| C | 1.75222| 0.90030| -0.31225|
| C | 2.57407| 0.78999| 0.99683 |
| C | 3.82102| -0.02981| 0.82368 |
| C | 3.95431| -1.29894| 1.37675 |
| C | 5.10092| -2.05167| 1.15542 |
| C | 6.12745| -1.54224| 0.37382 |
| C | 6.00631| -0.27249| -0.17877|
| C | 4.86253| 0.47684| 0.04693 |
N   0.78024  1.96321  -0.22646
C   1.16274  3.25390  -0.35465
C   0.06121  4.28139  -0.25367
O   2.32630  3.56924  -0.53755
H   2.75589  -1.50265  -1.35028
H   2.44797   1.13362  -1.12205
H   1.93377   0.37965   1.78053
H   2.84036   1.81177   1.27039
H   3.15051  -1.70290   1.98195
H   5.19194  -3.03712   1.59461
H   7.02116  -2.12742   0.19946
H   6.80724   0.13490  -0.78251
H   4.76506   1.47119  -0.37738
H  -0.18633   1.69710  -0.09151
H  -0.92447   3.83663  -0.12856
H   0.27735   4.93362   0.59178
H   0.07703   4.89198  -1.15529
H   1.35962  -3.56548  -1.67540
N  -2.26492  -1.60128  -0.33041
H  -2.69391  -2.50108  -0.48032
C  -3.10954  -0.54879  -0.03082
O  -2.79574   0.60311   0.08664
O  -4.34623  -1.04985   0.09853
C  -5.47173  -0.17092   0.39633
C  -6.64739  -1.13408   0.44451
C  -5.65768   0.84243  -0.72394
C  -5.27205   0.49610   1.74998
H  -7.56209  -0.58782   0.67496
H  -6.77031  -1.63288  -0.51718
H  -6.48858  -1.89081   1.21313
H  -6.58703   1.38870  -0.55668
H  -4.83401   1.55093  -0.75771
H  -5.73103   0.33037  -1.68459
H  -6.18350   1.03133   2.01973
Benzothiazole substrate

\[
\text{NHAc} \quad \text{Ph} \quad \text{S} \quad \text{N}
\]

\[
\begin{array}{lll}
\text{H} & -5.07941 & -0.25788 \\
\text{H} & -4.44499 & 1.20119
\end{array}
\]

\[
\text{M06-2X/def2-TZVP Geometry}
\]

\[
\begin{array}{lll}
\text{C} & 2.98950 & 0.14760 \\
\text{C} & 2.24708 & -0.29781 \\
\text{C} & 2.87073 & -0.46784 \\
\text{C} & 4.22595 & -0.20401 \\
\text{C} & 4.94645 & 0.23653 \\
\text{C} & 4.33309 & 0.41125 \\
\text{S} & 1.70182 & -1.02773 \\
\text{C} & 0.48876 & -0.98042 \\
\text{N} & 0.89636 & -0.60059 \\
\text{C} & -0.94413 & -1.31138 \\
\text{C} & -1.57868 & -0.23293 \\
\text{C} & -1.69467 & 1.10244 \\
\text{N} & -1.64735 & -1.45714 \\
\text{C} & -2.91202 & -1.93996 \\
\text{C} & -3.55866 & -1.90483 \\
\text{O} & -3.49096 & -2.34830 \\
\text{C} & -2.85570 & 1.43413 \\
\text{C} & -2.95909 & 2.64329 \\
\text{C} & -1.89883 & 3.53897 \\
\text{C} & -0.73842 & 3.22043
\end{array}
\]
\[
\begin{array}{ccc}
\text{C} & -0.63907 & 2.01040 \quad -0.92967 \\
\text{H} & 2.50096 & 0.27853 \quad 2.81549 \\
\text{H} & 4.70152 & -0.33876 \quad -1.61556 \\
\text{H} & 6.00155 & 0.44933 \quad 0.33017 \\
\text{H} & 4.92322 & 0.75684 \quad 2.52530 \\
\text{H} & -0.99070 & -2.26178 \quad -1.21971 \\
\text{H} & -2.56265 & -0.60554 \quad -1.88036 \\
\text{H} & -0.97431 & -0.15751 \quad -2.50490 \\
\text{H} & -1.20542 & -1.06344 \quad 1.38740 \\
\text{H} & -4.04778 & -0.93709 \quad 2.11277 \\
\text{H} & -4.31394 & -2.68432 \quad 2.03676 \\
\text{H} & -2.83323 & -2.03129 \quad 2.78827 \\
\text{H} & -3.68778 & 0.73751 \quad -0.22808 \\
\text{H} & -3.87021 & 2.88942 \quad 0.97750 \\
\text{H} & -1.97882 & 4.48414 \quad 0.95520 \\
\text{H} & 0.09048 & 3.91630 \quad -0.27753 \\
\text{H} & 0.26881 & 1.76666 \quad -1.47139 \\
\end{array}
\]

Unsuccessful diazines

\[
\begin{array}{ccc}
\text{N} & -1.24588 & 1.06620 \quad 0.23536 \\
\text{C} & -0.27501 & 0.42355 \quad -0.34681 \\
\text{C} & -0.51417 & -0.78521 \quad -1.07241 \\
\text{N} & -1.69735 & -1.30710 \quad -1.18946 \\
\text{C} & 1.12817 & 0.96072 \quad -0.20793 \\
\text{C} & 1.88009 & 0.24731 \quad 0.94193 \\
\end{array}
\]
|  | X   | Y   | Z   |
|---|-----|-----|-----|
| C | 2.08959 | -1.21298 | 0.66011 |
| C | 1.29000 | -2.18612 | 1.25068 |
| C | 1.44163 | -3.52604 | 0.91991 |
| C | 2.39801 | -3.90807 | -0.00928 |
| C | 3.20667 | -2.94507 | -0.60032 |
| C | 3.05339 | -1.60799 | -0.26596 |
| N | 1.08261 | 2.38504 | 0.01541 |
| C | 2.17055 | 3.16103 | -0.20738 |
| C | 2.00644 | 4.63215 | 0.09129 |
| O | 3.21870 | 2.70049 | -0.62064 |
| H | 1.68148 | 0.77726 | -1.13286 |
| H | 1.30826 | 0.39037 | 1.86155 |
| H | 2.83901 | 0.75695 | 1.04677 |
| H | 0.53398 | -1.88661 | 1.96922 |
| H | 0.80897 | -4.27092 | 1.38524 |
| H | 2.51654 | -4.95163 | -0.27021 |
| H | 3.96038 | -3.23790 | -1.32026 |
| H | 3.68537 | -0.85429 | -0.72437 |
| H | 0.22090 | 2.76594 | 0.37344 |
| H | 2.30375 | 5.19754 | -0.79024 |
| H | 0.99000 | 4.90152 | 0.37284 |
| H | 2.68712 | 4.89615 | 0.90007 |
| H | 0.31625 | -1.29443 | -1.55305 |
| C | -2.72434 | -0.65401 | -0.57860 |
| C | -2.49879 | 0.54311 | 0.13574 |
| C | -3.58480 | 1.20129 | 0.75175 |
| C | -4.84288 | 0.67513 | 0.65426 |
| C | -5.06934 | -0.52247 | -0.06029 |
| C | -4.03289 | -1.17614 | -0.66630 |
| H | -3.38593 | 2.11647 | 1.29404 |
| H | -5.67663 | 1.17708 | 1.12783 |
| H | -6.07329 | -0.92099 | -0.12589 |
| H | -4.17533 | -2.09456 | -1.22055 |
|  | X  | Y  | Z  |
|---|---|---|---|
| N | 1.15722 | 2.11344 | 0.42791 |
| C | 0.45662 | 1.20503 | -0.23367 |
| C | -0.70661 | 1.52829 | -0.93876 |
| C | -1.10302 | 2.84051 | -0.92154 |
| C | -0.31316 | 3.73653 | -0.20301 |
| N | 0.78054 | 3.37901 | 0.44684 |
| C | 0.95063 | -0.21835 | -0.14918 |
| C | 0.17857 | -1.00894 | 0.93490 |
| C | -1.27232 | -1.17818 | 0.58559 |
| C | -2.26243 | -0.42576 | 1.20892 |
| C | -3.59125 | -0.54065 | 0.82165 |
| C | -3.94505 | -1.41024 | -0.19970 |
| C | -2.96480 | -2.17160 | -0.82509 |
| C | -1.63959 | -2.05652 | -0.43300 |
| N | 2.36903 | -0.23640 | 0.11502 |
| C | 3.10774 | -1.33700 | -0.16276 |
| C | 4.57591 | -1.25358 | 0.17864 |
| O | 2.61607 | -2.33681 | -0.65443 |
| H | 0.78080 | -0.71596 | -1.10729 |
| H | 0.29437 | -0.48692 | 1.88711 |
| H | 0.66627 | -1.98201 | 1.01115 |
| H | -1.98752 | 0.26078 | 2.00191 |
| H | -4.35065 | 0.04912 | 1.31920 |
| H | -4.97992 | -1.50126 | -0.50323 |
| H | -3.23514 | -2.85884 | -1.61668 |
| H | -0.87237 | -2.65192 | -0.91736 |
| H | 2.76990 | 0.58714 | 0.53658 |
| H | 5.15037 | -1.52842 | -0.70427 |
| H | 4.88058 | -0.26681 | 0.52210 |
| H | 4.78893 | -1.98808 | 0.95492 |
| Atom | X        | Y        | Z       |
|------|----------|----------|---------|
| H    | -1.98876 | 3.17748  | -1.44320|
| H    | -1.25965 | 0.76123  | -1.46658|
| H    | -0.56088 | 4.78930  | -0.14516|

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M06-2X/def2-TZVP Geometry

| Atom | X        | Y        | Z       |
|------|----------|----------|---------|
| N    | -0.99440 | -0.69312 | -0.79325|
| C    | -0.69282 | -1.00394 | 0.45331 |
| C    | -1.66759 | -1.05512 | 1.45867 |
| C    | -2.95591 | -0.75771 | 1.11388 |
| C    | -3.17547 | -0.42687 | -0.22690|
| N    | -2.23899 | -0.40311 | -1.14053|
| C    | 0.75870  | -1.25503 | 0.77818 |
| C    | 1.33857  | -0.08842 | 1.62216 |
| C    | 1.36926  | 1.20890  | 0.86630 |
| C    | 0.28181  | 2.07857  | 0.87940 |
| C    | 0.29865  | 3.25006  | 0.13624 |
| C    | 1.40878  | 3.56828  | -0.63346|
| C    | 2.50174  | 2.71285  | -0.65015|
| C    | 2.48026  | 1.54252  | 0.09498 |
| N    | 1.50026  | -1.46974 | -0.43833|
| C    | 2.76218  | -1.96042 | -0.41173|
| C    | 3.46378  | -2.03268 | -1.74647|
| O    | 3.30198  | -2.30098 | 0.62496 |
| H    | 0.83549  | -2.15915 | 1.38912 |
| H    | 2.34443  | -0.38849 | 1.91531 |
| H    | 0.74137  | 0.01084  | 2.53152 |
| H    | -0.58771 | 1.83626  | 1.48163 |
| H    | -0.55523 | 3.91484  | 0.15824 |
| H    | 1.42372  | 4.48137  | -1.21419|
| H    | 3.37450  | 2.96060  | -1.24091|
| H    | 3.33931  | 0.88008  | 0.09362 |
| H    | 1.08272  | -1.13417 | -1.29332|
M06-2X/def2-TZVP Geometry

N  -0.78736  1.39799  0.36128
C   0.03955  0.57289 -0.26848
C  -0.41407 -0.55449 -0.95878
C  -1.76489 -0.78506 -0.96191
C  -2.56543  0.12690 -0.27365
N  -2.08561  1.18181  0.36158
C   1.50963  0.88584 -0.15432
C   2.16170  0.04355  0.97069
C   2.17343 -1.42217  0.64359
C   3.05450 -1.90285 -0.32449
C   3.03076 -3.23658 -0.70316
C   2.12554 -4.11159 -0.11488
C   1.25174 -3.64564  0.85699
C   1.27666 -2.30823  1.23162
N   1.70152  2.29617  0.07989
C   2.89479  2.88101 -0.18553
C   2.99053  4.35743  0.11319
O   3.83335  2.25215 -0.63936
H   2.00853  0.62930 -1.09212
H   1.62237  0.23697  1.90033
H   3.18122  0.41650  1.07755
H   3.76310 -1.21778 -0.77880
H   3.72237 -3.59663 -1.45414
|   | X   | Y   | Z   |
|---|-----|-----|-----|
| H | 2.10712 | -5.15325 | -0.40843 |
| H | 0.54819 | -4.32332 | 1.32365 |
| H | 0.58620 | -1.94421 | 1.98446 |
| H | 0.92936 | 2.80875 | 0.47649 |
| H | 3.76978 | 4.50677 | 0.85964 |
| H | 3.29903 | 4.87222 | -0.79542 |
| H | 2.05599 | 4.78241 | 0.47461 |
| H | -2.22274 | -1.62488 | -1.46607 |
| H | 0.28619 | -1.20965 | -1.46171 |
| C | -4.05015 | -0.10056 | -0.25549 |
| O | -4.55897 | -1.03743 | -0.81234 |
| O | -4.71558 | 0.81913 | 0.42496 |
| C | -6.13027 | 0.63575 | 0.46822 |
| H | -6.37212 | -0.31930 | 0.93261 |
| H | -6.51496 | 1.46057 | 1.05943 |
| H | -6.54392 | 0.65588 | -0.53911 |
Parameters Collected

The parameters calculated and considered for the systems are reported in Tables S1-S26. Torsion, NBO, Sterimol, vibrations and intensities were calculated and collected from simple model phosphoric acid structures.\textsuperscript{30-32} $L_{\text{whole}}$, $B_{1\text{whole}}$ and $B_{5\text{whole}}$ are the length, minimum width and maximum width of the whole aryl group at the 3-position. Similarly, $L_x$, $B_{1x}$ and $B_{5x}$ where $X$ represents the position of a substituent on the aryl ring are the length, minimum width and maximum width of the substituents at the 2-6 positions. Analogously defined parameter sets were collected from the product structures. The product structures are deconstructed into two portions the heterocycle and redox active ester. $N_{\text{het}}$ represents the heterocycle parameters and $\text{RAE}$ describes the redox active ester parameters. As before, $L_{\text{whole}}$, $B_{1\text{whole}}$ and $B_{5\text{whole}}$ are the length, minimum width and maximum width of the whole heterocycle. Similarly, $L_x$, $B_{1x}$ and $B_{5x}$ where $X$ represents the position of a substituent on the aryl ring are the length, minimum width and maximum width of the substituents at the 2-6 positions, where applicable. 0 digits are used to represent examples where there is no substituent. Similarly, $L_{\text{RAE}}$, $B_{1\text{RAE}}$ and $B_{5\text{RAE}}$ represent the size of the RAE as the Sterimol sub-parameters. NBOs are also calculated at these positions in addition to vibrations and intensities of N-H and C=O of the RAE. In dealing with benzothiazole we used 0 digits as descriptors for the missing components. Atom numbering for parameter collection is shown in Figure S1. Since the model is constructed of Sterimol and NBO terms from the same reference atom in both heterocycle and redox active ester components we have simplified the labels to RAE and $N_{\text{het}}$. Where model RAE terms = RAE\textsubscript{C1} terms and $N_{\text{het}}$ terms = $N_{\text{hetC6}}$ terms.

![Figure S1. Atom labelling for parameter acquisition from model catalyst and product structures.](image)

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Table S1. Torsion parameters.

| catalyst         | $\alpha$ | $\alpha^*B1_3$ |
|------------------|----------|----------------|
| TRIP             | 84.4     | 92.0           |
| 2-ipr            | 74.7     | 81.4           |
| 2,6-Me           | 77.0     | 83.9           |
| 9-phenanthryl    | 53.7     | 125.1          |
| 1-naphth         | 56.2     | 114.0          |
| Ph               | 48.3     | 52.6           |
| 3,5-Me           | 47.7     | 81.1           |
| 3,5-tbu          | 37.5     | 106.5          |
| 2,6-ipr          | 84.2     | 91.8           |
| TCYP             | 75.8     | 82.6           |
| 2,4,6-Ph         | 58.1     | 63.3           |
| 3,5-CF$_3$       | 49.7     | 103.4          |
| 2-naphthyl       | 45.0     | 99.5           |

Table S2. Sterimol values using Bondi radii collected from the C1-C3 positions of the aromatic ring.

| catalyst         | L$_{whole}$ | B1$_{whole}$ | BS$_{whole}$ | L$_2$ | B1$_2$ | B5$_2$ | L$_3$ | B1$_3$ | B5$_3$ |
|------------------|-------------|--------------|--------------|-------|--------|--------|-------|--------|--------|
| TRIP             | 8.99        | 3.25         | 5.71         | 4.71  | 1.97   | 3.27   | 2.57  | 1.09   | 1.09   |
| 2-ipr            | 6.85        | 2.06         | 5.61         | 2.57  | 1.09   | 1.09   |       |        |        |
| 2,6-Me           | 6.84        | 1.79         | 4.46         | 3.60  | 1.70   | 2.13   | 2.57  | 1.09   | 1.09   |
| 9-phenanthryl    | 8.91        | 1.73         | 5.71         | 4.70  | 2.40   | 8.70   | 4.70  | 2.33   | 7.03   |
| 1-naphth         | 6.94        | 1.72         | 5.70         | 4.70  | 2.40   | 8.66   | 4.70  | 2.03   | 7.00   |
| Ph               | 6.85        | 1.70         | 3.26         | 2.57  | 1.09   | 1.09   |       |        |        |
| 3,5-Me           | 6.85        | 1.89         | 4.45         | 2.57  | 1.09   | 1.09   |       |        |        |
| 3,5-tbu          | 7.99        | 3.14         | 5.82         | 2.57  | 1.09   | 1.09   |       |        |        |
| 2,6-ipr          | 6.84        | 2.97         | 5.71         | 4.71  | 1.97   | 3.27   | 2.57  | 1.09   | 1.09   |
| TCYP             | 11.07       | 3.36         | 7.52         | 6.78  | 2.03   | 3.55   | 2.57  | 1.09   | 1.09   |
| 2,4,6-Ph         | 11.16       | 2.96         | 7.11         | 6.85  | 1.7    | 3.26   | 2.57  | 1.09   | 1.09   |
| 3,5-CF$_3$       | 7.48        | 2.40         | 5.02         | 2.57  | 1.09   | 1.09   | 3.89  | 2.08   | 2.72   |
| 2-naphthyl       | 8.99        | 1.70         | 4.38         | 2.57  | 1.09   | 1.09   | 4.69  | 2.21   | 8.72   |

Table S3. Sterimol values using Bondi radii collected from the C4-C6 positions of the aromatic ring.
Table S4. NBO charges collected from the phosphorus and aromatic ring.

| catalyst       | L_4 B_14 B_54 L_5 B_15 B_55 L_6 B_16 B_56 |
|----------------|--------------------------------------------|
| TRIP           | 4.66 2.00 3.26 2.57 1.09 1.09 4.66 1.99 3.26 |
| 2-ipr          | 2.57 1.09 1.09 2.57 1.09 1.09 4.67 1.98 3.26 |
| 2,6-Me Ph      | 2.57 1.09 1.09 2.57 1.09 1.09 3.60 1.70 2.13 |
| 9-phenanthryl  | 4.69 2.81 6.48 4.68 2.32 8.74 2.57 1.09 1.09 |
| 1-naphth       | 2.57 1.09 1.09 2.57 1.09 1.09 2.57 1.09 1.09 |
| Ph             | 2.57 1.09 1.09 2.57 1.09 1.09 2.57 1.09 1.09 |
| 3.5-Me Ph      | 2.57 1.09 1.09 3.61 1.70 2.11 2.57 1.09 1.09 |
| 3.5-tbu        | 2.57 1.09 1.09 4.69 2.84 3.29 2.57 1.09 1.09 |
| 2,6-ipr TCYP   | 2.57 1.09 1.09 2.57 1.09 1.09 4.66 1.99 3.26 |
| 2,4,6-PhPh     | 6.86 1.7 3.24 2.57 1.09 1.09 6.85 1.7 3.25 |
| 3,5-CF_3       | 2.57 1.09 1.09 3.90 2.07 2.73 2.57 1.09 1.09 |
| 2-naphthyl     | 4.69 2.33 6.44 2.57 1.09 1.09 2.57 1.09 1.09 |

Table S5. Frequency derived parameter sets.

| catalyst       | P C_1 C_2 C_3 C_4 C_5 C_6 |
|----------------|-----------------------------|
| TRIP           | 2.557 -0.040 0.023 -0.246 -0.012 -0.223 0.050 |
| 2-ipr          | 2.558 -0.029 -0.195 -0.233 -0.219 -0.215 0.040 |
| 2,6-Me Ph      | 2.573 -0.031 0.027 -0.222 -0.212 -0.228 0.009 |
| 9-phenanthryl  | 2.570 -0.023 -0.034 -0.037 -0.040 -0.052 -0.151 |
| 1-naphth       | 2.567 -0.11 -0.049 -0.067 -0.202 -0.195 -0.183 |
| Ph             | 2.552 -0.030 -0.209 -0.227 -0.228 -0.211 -0.173 |
| 3.5-Me Ph      | 2.553 -0.015 -0.217 -0.034 -0.227 -0.012 -0.183 |
| 3.5-tbu        | 2.559 -0.019 -0.215 -0.011 -0.238 0.005 -0.186 |
| 2,6-ipr TCYP   | 2.557 -0.032 0.013 -0.241 -0.208 -0.223 0.041 |
| 2,4,6-PhPh     | 2.576 0.007 -0.014 -0.183 -0.059 -0.182 -0.009 |
| 3,5-CF_3       | 2.552 -0.012 -0.166 -0.162 -0.171 -0.148 -0.134 |
| 2-naphthyl     | 2.569 -0.047 -0.152 -0.061 -0.069 -0.202 -0.195 |
| catalyst          | $\nu_{P=O_{sy}}$ | $\nu_{P=O_{sy}}$ | $\nu_{P=O_{as}}$ | $\nu_{P=O_{as}}$ |
|-------------------|------------------|------------------|------------------|------------------|
| TRIP              | 1151.38          | 157.4071         | 1386.72          | 174.1557         |
| 2-ipr             | 1150.63          | 156.8394         | 1385.16          | 223.7019         |
| 2,6-Me            | 1157.69          | 239.5191         | 1382.03          | 292.4540         |
| 9-phenanthryl     | 1151.95          | 242.6293         | 1377.95          | 286.4177         |
| it                  | 1150.74          | 225.1452         | 1379.67          | 294.1352         |
| Ph                | 1153.11          | 172.9857         | 1387.07          | 290.8121         |
| 3,5-Me            | 1154.24          | 169.4313         | 1385.75          | 283.6669         |
| 3,5-tbu           | 1155.14          | 257.8944         | 1390.44          | 233.1034         |
| 2,6-ipr           | 1152.2           | 164.3429         | 1388.31          | 202.6837         |
| TCYP              | 1154.50          | 214.3551         | 1382.80          | 143.0937         |
| 2,4,6-Ph          | 1153.41          | 147.3600         | 1375.58          | 292.3162         |
| 3,5-CF$_3$        | 1155.53          | 90.6110          | 1392.53          | 289.9098         |
| 2-naphthyl        | 1152.34          | 188.2477         | 1379.60          | 304.1894         |

Table S6. SiPh3 parameter sets.

| catalyst | $\alpha$ | $L_\text{whole}$ | $B_{1\text{whole}}$ | $B_{5\text{whole}}$ |
|----------|----------|-------------------|---------------------|---------------------|
| TIPSY    | 31.8     | 7.04              | 4.33                | 6.71                |
**Quinoline and pyridine products (matrix data set)**

Table S7. Frequency derived RAE parameter sets.

| Substrate | C=O | /C=O | N-H | /N-H |
|-----------|-----|------|-----|------|
| A         | 1795.72 | 539.8055 | 3607.65 | 31.5280 |
| B         | 1799.98 | 523.9409 | 3605.25 | 26.5167 |
| C         | 1800.63 | 580.7849 | 3603.99 | 31.0689 |
| D         | 1801.30 | 508.2388 | 3616.04 | 31.9067 |
| E         | 1802.13 | 542.0914 | 3613.04 | 31.5258 |
| F         | 1798.52 | 521.8265 | 3611.78 | 30.2665 |
| G         | 1804.56 | 514.2547 | 3609.19 | 32.6790 |

Table S8. NBO charges collected from the RAE.

| Substrate | H1  | C1   | C2   |
|-----------|-----|------|------|
| A         | 0.222 | -0.075 | -0.210 |
| B         | 0.236 | -0.088 | -0.380 |
| C         | 0.220 | -0.082 | -0.379 |
| D         | 0.225 | -0.077 | -0.209 |
| E         | 0.223 | -0.075 | -0.211 |
| F         | 0.221 | -0.071 | -0.211 |
| G         | 0.224 | -0.076 | -0.210 |

Table S9. NBO charges collected from the N-acetyl group.

| Substrate | N   | H   | C=O  | O   | C   |
|-----------|-----|-----|------|-----|-----|
| A         | -0.637 | 0.402 | 0.678 | -0.612 | -0.713 |
| B         | -0.637 | 0.402 | 0.679 | -0.617 | -0.716 |
| C         | -0.630 | 0.402 | 0.680 | -0.611 | -0.713 |
| D         | -0.641 | 0.404 | 0.678 | -0.605 | -0.712 |
| E         | -0.638 | 0.403 | 0.678 | -0.611 | -0.712 |
| F         | -0.638 | 0.402 | 0.679 | -0.613 | -0.712 |
| G         | -0.639 | 0.404 | 0.678 | -0.607 | -0.712 |

Table S10. NBO charges collected from the heterocycle.
Table S11. Sterimol parameters collected from the RAE.

| Substrate | N  | C2  | C3  | C4  | C5  | C6  |
|-----------|----|-----|-----|-----|-----|-----|
| A         | -0.435 | 0.231 | -0.275 | -0.128 | -0.107 | 0.154 |
| B         | -0.424 | 0.224 | -0.272 | -0.127 | -0.109 | 0.150 |
| C         | -0.437 | 0.236 | -0.271 | -0.128 | -0.107 | 0.148 |
| D         | -0.436 | 0.231 | -0.265 | -0.110 | -0.221 | 0.100 |
| E         | -0.464 | 0.237 | -0.287 | -0.110 | -0.223 | 0.283 |
| F         | -0.439 | 0.200 | -0.262 | -0.149 | -0.093 | 0.063 |
| G         | -0.453 | 0.239 | -0.278 | -0.102 | -0.227 | 0.283 |

Table S12. Sterimol parameters collected from the heterocycle.

| Substrate | L_{RAE} | B_{1RAE} | B_{5RAE} |
|-----------|---------|----------|----------|
| A         | 4.70    | 2.01     | 3.26     |
| B         | 4.70    | 1.70     | 7.00     |
| C         | 5.81    | 1.70     | 4.47     |
| D         | 4.70    | 2.00     | 3.27     |
| E         | 4.70    | 2.00     | 3.27     |
| F         | 4.70    | 2.01     | 3.26     |
| G         | 4.70    | 2.00     | 3.27     |

Table S13. Sterimol parameters collected from positions C5 and C6 of the heterocycle.

| Substrate | C5L | C5_{B1} | C5_{B5} | C6L | C6_{B1} | C6_{B5} |
|-----------|-----|---------|---------|-----|---------|---------|
| A         | 4.68 | 3.04    | 4.88    | 4.68 | 2.81    | 6.80    |
| B         | 4.68 | 2.48    | 6.40    | 4.68 | 2.39    | 9.15    |
| C         | 4.68 | 3.07    | 5.95    | 4.68 | 3.00    | 6.79    |
| D         | 4.53 | 1.70    | 1.70    | 2.57 | 1.09    | 1.09    |
| E         | 5.52 | 1.75    | 3.47    | 3.60 | 1.70    | 2.12    |
| F         | 6.85 | 1.70    | 3.24    | 2.57 | 1.09    | 1.09    |
| G         | 4.53 | 1.70    | 1.70    | 3.60 | 1.70    | 2.11    |

Quinoline and pyridine products (prediction set)

Table S14. Frequency derived RAE parameter sets.
### Table S15. NBO charges collected from the RAE.

| Substrate | \(\nu_{C=O}\) | /C=O | \(\nu_{N-H}\) | /N-H |
|-----------|---------------|------|---------------|------|
| H         | 1803.56       | 580.5677 | 3597.5        | 33.1939 |
| I         | 1793.63       | 615.9151 | 3576.21       | 48.2849 |
| J         | 1772.85       | 346.0198 | 3596.38       | 30.6040 |
| K         | 1798.89       | 489.6877 | 3613.06       | 31.0685 |
| L         | 1805.85       | 457.9893 | 3609.82       | 30.8797 |
| M         | 1798.52       | 521.8265 | 3611.78       | 30.2665 |
| N         | 1801.3        | 508.2388 | 3616.04       | 31.9067 |
| O         | 1795.22       | 524.509  | 3605.73       | 32.4019 |
| P         | 1801.61       | 489.8771 | 3573.23       | 67.0537 |
| Q         | 1795.39       | 463.6672 | 3568.72       | 65.0553 |
| R         | 1782.77       | 384.8331 | 3626.19       | 91.3371 |
| S         | 1799.17       | 498.8316 | 3612.64       | 31.1581 |
| T         | 1766.13       | 253.0333 | 3619.93       | 90.1344 |
| U         | 1784.42       | 524.5282 | 3580.88       | 70.4414 |
| V         | 1791.37       | 671.1602 | 3581.76       | 64.8322 |
| X         | 1802.69       | 507.4867 | 3574.1        | 65.9853 |
| Y         | 1801.76       | 514.9501 | 3571.92       | 67.252  |
| Z         | 1795.72       | 509.8885 | 3574.38       | 67.4786 |
| ZA        | 1797.25       | 460.0256 | 3568.91       | 21.3635 |
| ZB        | 1794.32       | 703.2778 | 3600.41       | 88.3988 |
| ZC        | 1770.85       | 269.2926 | 3625.12       | 108.2182|
| ZD        | 1796.37       | 513.6983 | 3600.11       | 25.5659 |
| ZE        | 1796.12       | 530.9263 | 3611.11       | 30.3672 |

### Table S16. NBO charges collected from the N-acetyl group.

| Substrate | H1 | C1 | C2 |
|-----------|----|----|----|
| H         | 0.216 | -0.081 | -0.380 |
| I         | 0.213 | -0.075 | -0.220 |
| J         | 0.230 | -0.079 | -0.211 |
| K         | 0.223 | -0.076 | -0.210 |
| L         | 0.223 | -0.075 | -0.211 |
| M         | 0.221 | -0.071 | -0.211 |
| N         | 0.225 | -0.077 | -0.209 |
| O         | 0.218 | -0.081 | -0.593 |
| P         | 0.226 | -0.069 | -0.409 |
| Q         | 0.223 | -0.061 | -0.411 |
| R         | 0.240 | -0.090 | -0.199 |
| S         | 0.223 | -0.076 | -0.210 |
| T         | 0.226 | -0.067 | -0.416 |
| U         | 0.215 | -0.067 | -0.415 |
| V         | 0.213 | -0.064 | -0.416 |
| X         | 0.226 | -0.069 | -0.408 |
| Y         | 0.227 | -0.070 | -0.408 |
| Z         | 0.225 | -0.067 | -0.409 |
| ZA        | 0.224 | -0.064 | -0.421 |
| ZB        | 0.208 | -0.058 | -0.413 |
| ZC        | 0.225 | -0.066 | -0.415 |
| ZD        | 0.236 | -0.087 | -0.379 |
| ZE        | 0.222 | -0.074 | -0.210 |
### Table S17. NBO charges collected from the heterocycle.

| Substrate | N     | H    | C=O  | O    | C    |
|-----------|-------|------|------|------|------|
| H         | -0.63 | 0.402| 0.68 | -0.614| -0.713|
| I         | -0.626| 0.42 | 0.674| -0.614| -0.711|
| J         | -0.63 | 0.43 | 0.673| -0.641| -0.694|
| K         | -0.639| 0.403| 0.678| -0.609| -0.712|
| L         | -0.638| 0.403| 0.678| -0.611| -0.712|
| M         | -0.638| 0.402| 0.679| -0.613| -0.712|
| N         | -0.641| 0.404| 0.678| -0.605| -0.712|
| O         | -0.63 | 0.402| 0.675| -0.611| -0.713|
| P         | -0.64 | 0.411| 0.679| -0.61 | -0.713|
| Q         | -0.64 | 0.412| 0.679| -0.611| -0.713|
| R         | -0.629| 0.421| 0.675| -0.636| -0.692|
| S         | -0.639| 0.403| 0.678| -0.609| -0.712|
| T         | -0.616| 0.424| 0.671| -0.642| -0.691|
| U         | -0.634| 0.426| 0.684| -0.619| -0.717|
| V         | -0.626| 0.424| 0.673| -0.612| -0.709|
| X         | -0.64 | 0.411| 0.678| -0.607| -0.712|
| Y         | -0.64 | 0.411| 0.677| -0.607| -0.712|
| Z         | -0.639| 0.411| 0.678| -0.61 | -0.713|
| ZA        | -0.636| 0.398| 0.687| -0.616| -0.718|
| ZB        | -0.629| 0.431| 0.674| -0.613| -0.709|
| ZC        | -0.618| 0.426| 0.671| -0.644| -0.69|
| ZD        | -0.638| 0.401| 0.68 | -0.618| -0.716|
| ZE        | -0.636| 0.401| 0.678| -0.614| -0.712|

### Table S18. Sterimol parameters collected from the RAE.

| Substrate | N    | C2   | C3   | C4   | C5   | C6   |
|-----------|------|------|------|------|------|------|
| H         | -0.443| 0.248| -0.277| 0.064| -0.106| 0.151|
| I         | -0.452| 0.247| -0.067| -0.115| -0.209| 0.083|
| J         | -0.471| 0.244| -0.255| -0.115| -0.224| 0.095|
| K         | -0.449| 0.228| -0.273| -0.112| -0.218| 0.091|
| L         | -0.457| 0.233| -0.278| 0.091| -0.228| 0.099|
| M         | -0.439| 0.200| -0.262| -0.149| -0.093| 0.063|
| N         | -0.436| 0.231| -0.265| -0.110| -0.221| 0.100|
| O         | -0.436| 0.235| -0.279| 0.066| -0.107| 0.154|
| P         | -0.444| 0.235| -0.273| 0.065| -0.108| 0.153|
| Q         | -0.447| 0.173| -0.229| -0.023| -0.119| 0.093|
| R         | -0.530| 0.284| -0.327| -0.087| -0.288| 0.437|
| S         | -0.450| 0.228| -0.270| -0.110| -0.212| 0.078|
| T         | -0.472| 0.258| -0.350| 0.377| -0.140| 0.161|
| U         | -0.431| 0.286| -0.108| -0.005| -0.071| 0.132|
| V         | -0.445| 0.250| -0.054| -0.135| -0.095| 0.145|
| X         | -0.432| 0.224| -0.258| -0.136| -0.086| 0.135|
| Y         | -0.434| 0.229| -0.260| -0.131| -0.094| 0.144|
| Z         | -0.431| 0.211| -0.260| -0.141| -0.081| 0.131|
| ZA        | -0.424| 0.222| -0.264| -0.128| -0.106| 0.149|
| ZB        | -0.452| 0.240| -0.255| 0.067| -0.104| 0.153|
| ZC        | -0.458| 0.243| -0.251| 0.063| -0.104| 0.153|
| ZD        | -0.429| 0.231| -0.275| 0.065| -0.108| 0.153|
| ZE        | -0.441| 0.238| -0.279| 0.066| -0.108| 0.157|
Table S19. Sterimol parameters collected from the heterocycle.

| Substrate | $L_{\text{RAE}}$ | $B_{1\text{RAE}}$ | $B_{5\text{RAE}}$ |
|-----------|------------------|-------------------|------------------|
| H         | 5.81             | 1.70              | 4.47             |
| I         | 4.68             | 2.00              | 3.27             |
| J         | 4.70             | 2.00              | 3.26             |
| K         | 4.70             | 2.01              | 3.26             |
| L         | 4.70             | 2.00              | 3.27             |
| M         | 4.70             | 2.01              | 3.26             |
| N         | 4.70             | 2.00              | 3.27             |
| O         | 3.63             | 1.70              | 2.12             |
| P         | 5.26             | 1.70              | 6.08             |
| Q         | 5.26             | 1.70              | 6.09             |
| R         | 4.70             | 2.00              | 3.26             |
| S         | 4.70             | 2.01              | 3.26             |
| T         | 5.42             | 1.70              | 5.99             |
| U         | 4.99             | 1.70              | 6.21             |
| V         | 5.06             | 1.70              | 6.18             |
| X         | 5.27             | 1.70              | 6.08             |
| Y         | 5.27             | 1.70              | 6.08             |
| Z         | 5.27             | 1.70              | 6.08             |
| ZA        | 4.92             | 1.70              | 6.23             |
| ZB        | 5.24             | 1.70              | 9.53             |
| ZC        | 6.05             | 1.70              | 7.99             |
| ZD        | 4.70             | 1.70              | 6.99             |
| ZE        | 4.70             | 2.01              | 3.26             |

Table S20. Sterimol parameters collected from positions C4, C5 and C6 of the heterocycle.

| Substrate | $L_{\text{whole}}$ | $B_{1\text{whole}}$ | $B_{5\text{whole}}$ | $C_{3L}$ | $C_{3B1}$ | $C_{3B5}$ |
|-----------|---------------------|----------------------|----------------------|----------|----------|----------|
| H         | 8.83                | 1.76                 | 4.61                 | 2.57     | 1.09     | 1.09     |
| I         | 9.63                | 1.93                 | 4.40                 | 3.60     | 1.70     | 2.11     |
| J         | 10.47               | 2.05                 | 8.83                 | 2.57     | 1.09     | 1.09     |
| K         | 9.66                | 1.81                 | 3.89                 | 2.57     | 1.09     | 1.09     |
| L         | 9.57                | 1.93                 | 4.33                 | 2.57     | 1.09     | 1.09     |
| M         | 11.07               | 2.07                 | 3.80                 | 2.57     | 1.09     | 1.09     |
| N         | 8.75                | 1.70                 | 3.39                 | 2.57     | 1.09     | 1.09     |
| O         | 8.79                | 1.74                 | 4.71                 | 2.57     | 1.09     | 1.09     |
| P         | 8.78                | 1.75                 | 4.75                 | 2.57     | 1.09     | 1.09     |
| Q         | 9.02                | 1.77                 | 4.26                 | 2.57     | 1.09     | 1.09     |
| R         | 9.82                | 1.74                 | 4.34                 | 2.57     | 1.09     | 1.09     |
| S         | 9.98                | 1.80                 | 3.72                 | 2.57     | 1.09     | 1.09     |
| T         | 8.83                | 1.93                 | 9.81                 | 2.57     | 1.09     | 1.09     |
| U         | 8.79                | 1.70                 | 5.71                 | 5.89     | 2.32     | 8.76     |
| V         | 8.75                | 1.79                 | 4.83                 | 3.60     | 1.70     | 2.11     |
| X         | 9.39                | 1.70                 | 4.74                 | 2.57     | 1.09     | 1.09     |
| Y         | 10.08               | 1.70                 | 4.74                 | 2.57     | 1.09     | 1.09     |
| Z         | 10.93               | 1.79                 | 4.74                 | 2.57     | 1.09     | 1.09     |
| ZA        | 8.83                | 1.69                 | 4.66                 | 2.57     | 1.09     | 1.09     |
| ZB        | 8.82                | 1.70                 | 4.61                 | 2.57     | 1.09     | 1.09     |
| ZC        | 8.83                | 1.70                 | 4.58                 | 2.57     | 1.09     | 1.09     |
| ZD        | 8.79                | 1.80                 | 4.73                 | 2.57     | 1.09     | 1.09     |
| ZE        | 8.79                | 1.77                 | 4.75                 | 2.57     | 1.09     | 1.09     |
| Substrates | C4, | C4B1 | C4B5 | C5, | C5B1 | C5B5 | C6, | C6B1 | C6B5 |
|------------|-----|------|------|-----|------|------|-----|------|------|
| H          | 3.60| 1.70 | 2.11 | 4.68| 3.81 | 5.93 | 4.68| 3.34 | 6.77 |
| I          | 2.57| 1.09 | 1.09 | 5.52| 1.75 | 3.45 | 2.57| 1.09 | 1.09 |
| J          | 2.57| 1.09 | 1.09 | 6.41| 1.70 | 8.55 | 2.57| 1.09 | 1.09 |
| K          | 2.57| 1.09 | 1.09 | 5.53| 1.75 | 3.45 | 2.57| 1.09 | 1.09 |
| L          | 3.60| 1.70 | 2.11 | 5.52| 1.75 | 3.46 | 2.57| 1.09 | 1.09 |
| M          | 2.57| 1.09 | 1.09 | 6.85| 1.70 | 3.24 | 2.57| 1.09 | 1.09 |
| N          | 2.57| 1.09 | 1.09 | 4.53| 1.70 | 1.70 | 2.57| 1.09 | 1.09 |
| O          | 3.60| 1.70 | 2.11 | 4.68| 3.08 | 4.93 | 4.68| 2.60 | 5.53 |
| P          | 3.60| 1.70 | 2.11 | 4.68| 3.41 | 7.05 | 4.68| 3.29 | 6.38 |
| Q          | 4.66| 3.14 | 7.98 | 4.75| 3.03 | 7.15 | 2.57| 1.09 | 1.09 |
| R          | 2.57| 1.09 | 1.09 | 5.52| 1.75 | 3.44 | 3.34| 0.97 | 1.98 |
| S          | 2.57| 1.09 | 1.09 | 5.83| 1.78 | 3.24 | 2.57| 1.09 | 1.09 |
| T          | 6.94| 1.37 | 6.86 | 4.67| 3.44 | 9.67 | 4.68| 3.21 | 7.76 |
| U          | 4.68| 2.44 | 9.18 | 4.68| 3.11 | 5.68 | 4.67| 2.30 | 8.91 |
| V          | 2.57| 1.09 | 1.09 | 4.68| 3.00 | 6.94 | 4.67| 2.34 | 7.21 |
| X          | 2.57| 1.09 | 1.09 | 5.28| 3.40 | 7.08 | 4.68| 3.16 | 6.33 |
| Y          | 2.57| 1.09 | 1.09 | 5.97| 3.41 | 7.08 | 4.68| 3.38 | 6.29 |
| Z          | 2.57| 1.09 | 1.09 | 6.74| 3.39 | 7.08 | 4.68| 3.70 | 6.59 |
| ZA         | 2.57| 1.09 | 1.09 | 4.68| 2.83 | 4.92 | 4.68| 2.19 | 9.51 |
| ZB         | 3.60| 1.70 | 2.11 | 4.68| 2.96 | 9.33 | 4.68| 2.41 | 7.25 |
| ZC         | 3.60| 1.70 | 2.11 | 4.68| 2.69 | 8.73 | 4.68| 2.52 | 7.82 |
| ZD         | 3.60| 1.70 | 2.11 | 4.68| 2.97 | 6.43 | 4.68| 2.61 | 9.17 |
| ZE         | 3.60| 1.70 | 2.11 | 4.68| 3.37 | 4.85 | 4.68| 3.12 | 6.80 |

*Diazines and benzothiazole products (prediction set)*
Table S21. Frequency derived RAE parameter sets.

| Substrate | $v_{C=O}$ | $v/C=O$ | $v_{N-H}$ | $v/N-H$ |
|-----------|-----------|---------|-----------|---------|
| 1         | 1774.19   | 246.3746| 3633.71   | 91.0799 |
| 2         | 1777.80   | 240.2254| 3633.92   | 70.5741 |
| 3         | 1772.05   | 247.1994| 3629.49   | 97.0194 |
| 4         | 1769.26   | 237.7564| 3632.54   | 102.8598|
| 6         | 1777.62   | 251.3836| 3638.50   | 100.5507|
| 7         | 1772.90   | 241.6976| 3630.89   | 96.5037 |
| 8         | 1774.34   | 246.8153| 3639.66   | 106.3147|
| 9         | 1772.16   | 219.1408| 3644.40   | 72.7547 |
| 10        | 1778.05   | 275.3768| 3625.25   | 84.0351 |
| 11        | 1774.07   | 262.4074| 3637.68   | 112.3657|
| 12        | 1781.53   | 229.6649| 3627.39   | 76.0898 |
| 13        | 1774.94   | 262.5803| 3613.32   | 89.2896 |
| 14        | 1765.06   | 257.4635| 3627.21   | 89.1466 |
| 15        | 1779.40   | 269.1199| 3621.95   | 80.5401 |
| 16        | 1791.26   | 269.8189| 3623.07   | 82.3922 |
| 17        | 1778.05   | 277.3329| 3639.75   | 78.3216 |
| 18        | 1776.35   | 296.2283| 3618.55   | 85.5048 |
| 19        | 1772.28   | 232.8980| 3623.63   | 82.6221 |
| 20        | 1769.05   | 219.5100| 3636.80   | 98.4450 |
| 21        | 1763.46   | 264.5634| 3561.44   | 188.4916|
| 22        | 1777.57   | 288.7331| 3618.04   | 88.2971 |

Table S22. NBO charges collected from the RAE.

| Substrate | H1  | C1  | C2  |
|-----------|-----|-----|-----|
| 1         | 0.231 | -0.074 | -0.412 |
| 2         | 0.245 | -0.081 | -0.412 |
| 3         | 0.230 | -0.073 | -0.413 |
| 4         | 0.231 | -0.074 | -0.412 |
| 6         | 0.229 | -0.072 | -0.412 |
| 7         | 0.233 | -0.073 | -0.413 |
| 8         | 0.230 | -0.072 | -0.414 |
| 9         | 0.246 | -0.085 | -0.412 |
| 10        | 0.247 | -0.083 | -0.417 |
| 11        | 0.230 | -0.073 | -0.413 |
| 12        | 0.246 | -0.082 | -0.412 |
| 13        | 0.246 | -0.083 | -0.417 |
| 14        | 0.239 | -0.094 | -0.389 |
| 15        | 0.239 | -0.096 | -0.376 |
| 16        | 0.242 | -0.095 | -0.198 |
| 17        | 0.233 | -0.065 | -0.415 |
| 18        | 0.234 | -0.072 | -0.416 |
| 19        | 0.231 | -0.081 | -0.413 |
| 20        | 0.231 | -0.074 | -0.412 |
| 21        | 0.232 | -0.075 | -0.413 |
| 22        | 0.236 | -0.088 | -0.418 |

Table S23. NBO charges collected from the N-acetyl group.
Table S24. NBO charges collected from the heterocycle.

| Substrate | N   | H   | C=O | O   | C   |
|-----------|-----|-----|-----|-----|-----|
| 1         | -0.620 | 0.425 | 0.671 | -0.640 | -0.690 |
| 2         | -0.618 | 0.419 | 0.670 | -0.634 | -0.690 |
| 3         | -0.619 | 0.425 | 0.671 | -0.641 | -0.690 |
| 4         | -0.620 | 0.426 | 0.672 | -0.643 | -0.691 |
| 6         | -0.619 | 0.425 | 0.670 | -0.642 | -0.690 |
| 7         | -0.621 | 0.424 | 0.672 | -0.638 | -0.691 |
| 8         | -0.619 | 0.426 | 0.672 | -0.642 | -0.691 |
| 9         | -0.619 | 0.421 | 0.670 | -0.639 | -0.691 |
| 10        | -0.624 | 0.429 | 0.673 | -0.635 | -0.694 |
| 11        | -0.620 | 0.422 | 0.671 | -0.639 | -0.690 |
| 12        | -0.620 | 0.421 | 0.672 | -0.635 | -0.691 |
| 13        | -0.623 | 0.430 | 0.674 | -0.637 | -0.694 |
| 14        | -0.617 | 0.423 | 0.674 | -0.649 | -0.690 |
| 15        | -0.622 | 0.420 | 0.675 | -0.642 | -0.692 |
| 16        | -0.631 | 0.422 | 0.677 | -0.633 | -0.694 |
| 17        | -0.616 | 0.418 | 0.668 | -0.641 | -0.690 |
| 18        | -0.621 | 0.427 | 0.672 | -0.641 | -0.693 |
| 19        | -0.617 | 0.423 | 0.671 | -0.641 | -0.690 |
| 20        | -0.620 | 0.423 | 0.672 | -0.643 | -0.691 |
| 21        | -0.626 | 0.443 | 0.673 | -0.649 | -0.691 |
| 22        | -0.623 | 0.428 | 0.676 | -0.636 | -0.695 |

Table S25. Sterimol parameters collected from the RAE.

| Substrate | N   | C2  | C3  | C4  | C5  | C6  |
|-----------|-----|-----|-----|-----|-----|-----|
| 1         | -0.497 | 0.251 | -0.286 | 0.074 | -0.443 | 0.262 |
| 2         | -0.478 | 0.231 | -0.181 | 0.063 | -0.427 | 0.254 |
| 3         | -0.504 | 0.256 | -0.289 | 0.251 | -0.458 | 0.269 |
| 4         | -0.504 | 0.260 | -0.302 | 0.084 | -0.457 | 0.421 |
| 6         | -0.516 | 0.266 | -0.302 | 0.258 | -0.471 | 0.430 |
| 7         | -0.505 | 0.266 | -0.309 | 0.218 | -0.464 | 0.434 |
| 8         | -0.509 | 0.258 | -0.287 | 0.244 | -0.466 | 0.429 |
| 9         | -0.502 | 0.277 | -0.128 | 0.104 | -0.451 | 0.418 |
| 10        | -0.481 | 0.249 | -0.201 | 0.067 | -0.441 | 0.426 |
| 11        | -0.499 | 0.264 | -0.294 | 0.087 | -0.451 | 0.407 |
| 12        | -0.497 | 0.259 | -0.220 | 0.085 | -0.503 | 0.469 |
| 13        | -0.486 | 0.270 | -0.180 | 0.086 | -0.506 | 0.674 |
| 14        | -0.491 | 0.255 | -0.300 | 0.076 | -0.444 | 0.261 |
| 15        | -0.492 | 0.262 | -0.299 | 0.077 | -0.445 | 0.264 |
| 16        | -0.493 | 0.263 | -0.301 | 0.077 | -0.444 | 0.263 |
| 17        | -0.436 | 0.166 | 0.190 | -0.400 | 0.180 | 0.175 |
| 18        | -0.426 | 0.193 | 0.168 | -0.381 | -0.011 | 0.103 |
| 19        | -0.506 | 0.313 | -0.141 | 0.164 | -0.426 | 0.255 |
| 20        | -0.545 | 0.275 | -0.351 | 0.103 | -0.499 | 0.553 |
| 21        | -0.499 | 0.277 | -0.325 | 0.093 | -0.481 | 0.559 |
| 22        | -0.446 | 0.113 | 0.000 | 0.385 | -0.233 | 0.093 |
| Substrate | L_{RAE} | B1_{RAE} | B5_{RAE} |
|-----------|---------|----------|----------|
| 1         | 5.24    | 1.70     | 6.14     |
| 2         | 5.13    | 1.70     | 6.14     |
| 3         | 5.21    | 1.70     | 6.15     |
| 4         | 5.26    | 1.70     | 6.13     |
| 6         | 5.22    | 1.70     | 6.15     |
| 7         | 5.19    | 1.70     | 6.16     |
| 8         | 5.25    | 1.70     | 6.15     |
| 9         | 5.30    | 1.70     | 6.05     |
| 10        | 5.16    | 1.70     | 6.14     |
| 11        | 5.20    | 1.70     | 6.13     |
| 12        | 5.13    | 1.70     | 6.14     |
| 13        | 5.22    | 1.70     | 6.10     |
| 14        | 4.76    | 1.70     | 7.28     |
| 15        | 5.77    | 1.70     | 4.45     |
| 16        | 4.70    | 2.00     | 3.26     |
| 17        | 5.04    | 1.70     | 6.19     |
| 18        | 5.20    | 1.70     | 6.11     |
| 19        | 5.14    | 1.70     | 6.14     |
| 20        | 5.26    | 1.70     | 6.12     |
| 21        | 5.33    | 1.70     | 6.12     |
| 22        | 5.20    | 1.70     | 6.11     |

Table S26. Sterimol parameters collected from the heterocycle.

| Substrate | L_{whole} | B1_{whole} | B5_{whole} | C3\_L  | C3\_B1 | C3\_B5 |
|-----------|-----------|------------|------------|--------|--------|--------|
| 1         | 6.18      | 1.70       | 3.24       | 2.57   | 1.09   | 1.09   |
| 2         | 6.19      | 1.70       | 4.74       | 4.13   | 1.85   | 1.85   |
| 3         | 6.68      | 1.70       | 4.32       | 2.57   | 1.09   | 1.09   |
| 4         | 6.64      | 1.78       | 4.40       | 2.57   | 1.09   | 1.09   |
| 6         | 6.69      | 1.85       | 4.35       | 2.57   | 1.09   | 1.09   |
| 7         | 6.73      | 1.74       | 4.42       | 2.57   | 1.09   | 1.09   |
| 8         | 9.13      | 1.86       | 6.78       | 2.57   | 1.09   | 1.09   |
| 9         | 6.30      | 2.39       | 7.28       | 6.84   | 1.70   | 3.28   |
| 10        | 6.64      | 1.82       | 4.74       | 4.14   | 1.85   | 1.85   |
| 11        | 8.69      | 1.70       | 7.09       | 2.57   | 1.09   | 1.09   |
| 12        | 7.41      | 1.85       | 4.80       | 4.13   | 1.85   | 1.85   |
| 13        | 7.51      | 1.78       | 4.64       | 3.87   | 1.75   | 1.75   |
| 14        | 6.18      | 1.70       | 3.24       | 2.57   | 1.09   | 1.09   |
| 15        | 6.19      | 1.70       | 3.24       | 2.57   | 1.09   | 1.09   |
| 16        | 6.19      | 1.70       | 3.24       | 2.57   | 1.09   | 1.09   |
| 17        | 7.78      | 1.78       | 4.51       | 3.60   | 1.70   | 2.12   |
| 18        | 6.72      | 1.93       | 4.40       | 3.60   | 1.70   | 2.12   |
| 19        | 7.08      | 1.70       | 5.68       | 5.78   | 2.26   | 7.64   |
| 20        | 6.53      | 1.70       | 4.31       | 2.57   | 1.09   | 1.09   |
| 21        | 7.70      | 1.88       | 8.85       | 2.57   | 1.09   | 1.09   |
| 22        | 8.71      | 1.69       | 3.85       | 0.00   | 0.00   | 0.00   |

Table S27. Sterimol parameters collected from positions C4, C5 and C6 of the heterocycle.
Unsuccessful diazines

Table S28. Frequency derived RAE parameter sets.

| Substrate | C₄₁ | C₄₂ | C₄₃ | C₅₁ | C₅₂ | C₅₃ | C₆₁ | C₆₂ | C₆₃ |
|-----------|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| 1         | 2.57| 1.09| 1.09| 0.00| 0.00| 0.00| 2.57| 1.09| 1.09|
| 2         | 2.57| 1.09| 1.09| 0.00| 0.00| 0.00| 2.57| 1.09| 1.09|
| 3         | 3.60| 1.70| 2.12| 0.00| 0.00| 0.00| 2.57| 1.09| 1.09|
| 4         | 3.60| 1.70| 2.12| 0.00| 0.00| 0.00| 3.60| 1.70| 2.12|
| 5         | 3.88| 1.75| 1.75| 0.00| 0.00| 0.00| 3.60| 1.70| 2.12|
| 6         | 6.84| 1.70| 3.26| 0.00| 0.00| 0.00| 3.60| 1.70| 2.12|
| 7         | 2.57| 1.09| 1.09| 0.00| 0.00| 0.00| 3.60| 1.70| 2.12|
| 8         | 2.57| 1.09| 1.09| 0.00| 0.00| 0.00| 4.54| 1.40| 3.13|
| 9         | 2.57| 1.09| 1.09| 0.00| 0.00| 0.00| 4.54| 1.40| 3.13|
| 10        | 2.57| 1.09| 1.09| 0.00| 0.00| 0.00| 4.54| 1.40| 3.13|
| 11        | 2.57| 1.09| 1.09| 0.00| 0.00| 0.00| 6.84| 1.70| 3.24|
| 12        | 2.57| 1.09| 1.09| 0.00| 0.00| 0.00| 4.54| 1.40| 3.13|
| 13        | 2.57| 1.09| 1.09| 0.00| 0.00| 0.00| 4.54| 1.40| 3.13|
| 14        | 2.57| 1.09| 1.09| 0.00| 0.00| 0.00| 4.54| 1.40| 3.13|
| 15        | 2.57| 1.09| 1.09| 0.00| 0.00| 0.00| 2.57| 1.09| 1.09|
| 16        | 2.57| 1.09| 1.09| 0.00| 0.00| 0.00| 2.57| 1.09| 1.09|
| 17        | 0.00| 0.00| 0.00| 0.00| 0.00| 0.00| 2.57| 1.09| 1.09|
| 18        | 0.00| 0.00| 0.00| 2.57| 1.09| 1.09| 3.60| 1.70| 2.12|
| 19        | 4.67| 2.16| 7.69| 0.00| 0.00| 0.00| 2.57| 1.09| 1.09|
| 20        | 2.57| 1.09| 1.09| 0.00| 0.00| 0.00| 3.32| 0.98| 1.98|
| 21        | 2.57| 1.09| 1.09| 0.00| 0.00| 0.00| 3.60| 2.12| 3.13|
| 22        | 0.00| 0.00| 0.00| 4.61| 2.07| 6.95| 4.63| 1.87| 7.67|

Table S29. NBO charges collected from the RAE.

| Substrate | υC=O | ωC=O | υN-H | ωN-H |
|-----------|------|------|-------|-------|
| 23        | 1779.64 | 283.6243 | 3644.49 | 95.9423 |
| 24        | 1772.25 | 259.4249 | 3628.27 | 98.8282 |
| 25        | 1773.58 | 284.8008 | 3615.26 | 98.6490 |
| 26        | 1769.24 | 256.8461 | 3620.12 | 101.2779 |

Table S30. NBO charges collected from the N-acetyl group.

| Substrate | N   | H   | C=O | O   | C   |
|-----------|-----|-----|-----|-----|-----|
| 23        | -0.619 | 0.423 | 0.670 | -0.639 | -0.690 |
| 24        | -0.620 | 0.428 | 0.671 | -0.643 | -0.690 |
| 25        | -0.626 | 0.433 | 0.675 | -0.639 | -0.694 |
| 26        | -0.621 | 0.428 | 0.671 | -0.641 | -0.690 |

Table S31. NBO charges collected from the heterocycle.
Table S32. Sterimol parameters collected from the RAE.

| Substrate | L_{RAE} | B1_{RAE} | B5_{RAE} |
|-----------|---------|----------|----------|
| 23        | 5.16    | 1.70     | 6.15     |
| 24        | 5.21    | 1.70     | 6.15     |
| 25        | 5.20    | 1.70     | 6.11     |
| 26        | 5.19    | 1.70     | 6.16     |

Table S33. Sterimol parameters collected from the heterocycle.

| Substrate | L_{whole} | B1_{whole} | B5_{whole} | C3_L | C3_{B1} | C3_{B5} |
|-----------|-----------|------------|------------|------|---------|---------|
| 23        | 8.85      | 1.70       | 4.35       | 2.57 | 1.09    | 1.09    |
| 24        | 6.71      | 1.70       | 3.24       | 2.57 | 1.09    | 1.09    |
| 25        | 8.00      | 1.70       | 3.24       | 2.57 | 1.09    | 1.09    |
| 26        | 9.56      | 1.70       | 3.96       | 2.57 | 1.09    | 1.09    |

Table S34. Sterimol parameters collected from positions C4, C5 and C6 of the heterocycle.

| Substrate | C4_L | C4_{B1} | C4_{BS} | C5_L | C5_{B1} | C5_{BS} | C6_L | C6_{B1} | C6_{BS} |
|-----------|------|---------|---------|------|---------|---------|------|---------|---------|
| 23        | 0    | 0       | 0       | 4.67 | 2.19    | 7.02    | 4.66 | 2.23    | 7.71    |
| 24        | 2.57 | 1.09    | 1.09    | 2.57 | 1.09    | 1.09    | 0    | 0       | 0       |
| 25        | 2.57 | 1.09    | 1.09    | 3.88 | 1.75    | 1.75    | 0    | 0       | 0       |
| 26        | 2.57 | 1.09    | 1.09    | 5.56 | 1.76    | 3.40    | 0    | 0       | 0       |
Model development

Measured $\Delta \Delta G^\ddagger$ values were calculated using the formula $\Delta \Delta G^\ddagger = -RT \ln(\varepsilon r)$ where $R$ is the gas constant, $T$ is temperature (298.15 K), and $\varepsilon r$ is the enantiomeric ratio. Linear regression models were developed using an in-house script implemented in MATLAB$^\text{®}$ (version R2018b), to obtain the predicted $\Delta \Delta G^\ddagger$. A good linear correlation ($R^2$ close to 1.0 and intercept close to 0.0) between the predicted $\Delta \Delta G^\ddagger$ and the measured $\Delta \Delta G^\ddagger$ indicates that the obtained model adequately approximates the system under study. As the model search process can produce a large pool of model candidates, we truncated the models on the recorded statistics as well as the number of included parameters and presence of cross-terms, because this allows for a mechanistically informative interrogation. The model development is an iterative process in which the “best” model is assessed in various manners at each stage of the development process as described in Figure S2.

Models were validated using external and cross-validation techniques. Cross-validation generally refers to the statistical method of excluding part of the dataset as validations, predicting their values using the remaining set of data, evaluating the predictions, and repeating the process to reduce variability. Such analysis is generally employed to test the stability of a model and identify if overfitting occurs. Leave-one-out cross-validation is where only one data point would be removed each time and predicted by the remaining set. All validation predictions would then be combined and fitted to the measured values, the $R^2$ value of the resulting fit is called $Q^2$.

Another method to test model robustness is $k$-fold cross-validation. In this validation method, the dataset is divided randomly into $k$ subsets with same/similar sizes, each set would then be predicted out by the other $k-1$ subsets, and the goodness of fit would be tested based on these predictions. However, it is important to note that the $k$-fold statistics is dependent on the partitioning of the dataset, and that there’s a necessity of executing the process multiple times for average results.

The training reactions were split into 70:30 TS:VS sets for external validation. The split was partitioned based on the response values using the MATLAB “equidistant” function. This process can be described as pseudorandom as it is generated using a deterministic algorithm. Since we are searching for general models that would be effective in predicting out-of-sample, the lead models from this process is then subjected to additional rounds of external validation. For this purpose, we performed additional tests with two out-of-sample prediction platforms (catalysts not included, some catalyst and substrate components not included, see page S155). The top model (model 1 on page S151) with the lead statistical scores ($R^2$, LOO, k-fold, out-of-sample) from this process was taken forward for virtual
screening with the diazine set (out-of-sample prediction set 3, see page S156) and we found that the predictions were remarkably accurate.

Figure S2. Flow-chart describing the model development process.

The discarded models at step 6, which were only slightly less statistically significant, were also found to predict the diazine data set quite accurately with different parameters. This suggests one or more parameters can account for the observations. However, using a correlation matrix we can determine that the parameters are measuring the same general properties meaning mechanistic interpretation of a singular model does not affect the overall analysis. The top 10 models as described by their statistical scores and the correlation matrix are shown on pages S157 and S158. Ultimately, this suggests that alternative models can capture the same mechanistic features and have similar prediction capabilities. The use of a single model however, is much more straightforward for analysis and as a prediction platform. Furthermore, this demonstrates that the workflow described in Figure S2 is effective in producing models with sufficient generality.
Catalyst/Substrate Matrix

Data points for the matrix were measured at least twice and the reported value is the averaged result between the experiments.

| Substrate | TRIP | 2-iPr | 2,6-Me | 9-phen | 1-naphth | Ph | 3,5-Me | 3,5-tBu |
|-----------|------|-------|--------|--------|----------|----|--------|---------|
| A         | 97   | 71    | 87     | 70     | 49       | 56 | 76     | 70      |
| B         | 86   | 53    | 48     | 27     | 29       | 26 | 32     | 45      |
| C         | 76   | 32    | 32     | 24     | 26       | 6  | 15     | 28      |
| D         | 53   | 17    | 27     | 17     | 9        | -4 | 10     | 11      |
| E         | 95   | 72    | 81     | 52     | 45       | 39 | 55     | 47      |
| F         | 74   | n/a   | 36     | 11     | 17       | 13 | 40     | 58      |
| G         | 95   | 80    | 85     | 72     | 59       | 56 | 72     | 54      |

n/a = result not obtained due to poor conversion
## Training set

| measured $\Delta \Delta G^\ddagger$ | predicted $\Delta \Delta G^\ddagger$ | LOO  |
|----------------------------------|----------------------------------|------|
| 1.05                             | 1.27                             | 1.34 |
| 1.58                             | 1.20                             | 1.10 |
| 1.03                             | 1.13                             | 1.15 |
| 0.63                             | 1.05                             | 1.14 |
| 0.75                             | 0.80                             | 0.81 |
| 1.18                             | 0.83                             | 0.75 |
| 1.53                             | 1.39                             | 1.35 |
| 0.70                             | 0.69                             | 0.68 |
| 0.62                             | 0.61                             | 0.61 |
| 0.33                             | 0.55                             | 0.59 |
| 0.35                             | 0.47                             | 0.49 |
| 0.32                             | 0.21                             | 0.20 |
| 0.39                             | 0.25                             | 0.22 |
| 0.57                             | 0.59                             | 0.59 |
| 1.18                             | 1.21                             | 1.23 |
| 0.39                             | 0.43                             | 0.44 |
| 0.29                             | 0.37                             | 0.39 |
| 0.07                             | 0.03                             | 0.02 |
| 0.18                             | 0.07                             | 0.03 |
| 0.70                             | 1.01                             | 1.09 |
| 0.20                             | 0.30                             | 0.32 |
| 0.33                             | 0.23                             | 0.21 |
| 0.11                             | 0.09                             | 0.08 |
| -0.05                            | -0.17                            | -0.19|
| 0.13                             | 0.21                             | 0.22 |
| 2.17                             | 1.98                             | 1.93 |
| 1.07                             | 1.27                             | 1.31 |
| 0.57                             | 1.06                             | 1.14 |
| 0.73                             | 0.84                             | 0.85 |
| 1.13                             | 1.06                             | 1.04 |
| 0.45                             | 0.28                             | 0.24 |
| 0.13                             | 0.21                             | 0.23 |
| 0.20                             | 0.14                             | 0.12 |
| 2.17                             | 1.95                             | 1.89 |
| 1.30                             | 1.24                             | 1.23 |
| 1.49                             | 1.17                             | 1.09 |
| 0.80                             | 1.03                             | 1.06 |
| 1.07                             | 0.80                             | 0.75 |
Validation set

| measured ΔΔG‡ | predicted ΔΔG‡ |
|---------------|---------------|
| 2.48          | 1.98          |
| 1.03          | 1.17          |
| 0.39          | 0.51          |
| 0.32          | 0.29          |
| 0.34          | 0.41          |
| 0.20          | 0.16          |
| 0.12          | -0.13         |
| 1.33          | 1.20          |
| 0.68          | 1.13          |
| 0.49          | 0.80          |
| 0.60          | 1.18          |
| 0.15          | -0.12         |
| 0.50          | -0.08         |
| 0.78          | 0.26          |
| 1.07          | 1.10          |
| 0.75          | 0.77          |
| 0.72          | 1.15          |
Out-of-sample predictions

We evaluated the ability to transfer the mechanistic principles leading to enantioselective catalysis captured by the statistical model to genuinely different structural motifs not contained in the training dataset. The workflow for ee prediction is straightforward and is initiated by locating the ground state of the targeted reaction variable by DFT computation, collecting the requisite parameters and submitting them to the equation as pictorially described below.

1. Conformational sampling

2. DFT calculation

3. Parameter collection

4. Submit parameters to equation

5. Predict result

![Chemical structure and predicted ee](image)

17
61% yield
90% ee
(predicted 93% ee)
Treating the test reactions as virtual predictions and using all the training data, the ability to predict was determined by both enantioselectivity values and the average absolute $\Delta\Delta G^\ddagger$ error ($\Delta\Delta G^\ddagger$ error = absolute(model measured – experimentally measured)/ no. of examples).

Out-of-Sample prediction set 1: Variation in catalyst

| catalyst Ar | measured $\Delta\Delta G^\ddagger$ | predicted $\Delta\Delta G^\ddagger$ | experiment $\Delta\Delta G^\ddagger$ |
|-------------|-----------------------------------|-----------------------------------|-----------------------------------|
| 2,6-ipr     | 2.07                              | 1.84                              | 2.30                              |
| TCYP        | 2.60                              | 2.28                              | 2.17                              |
| 2,4,6-Ph    | 1.28                              | 1.18                              | 1.45                              |
| 3,5-CF$_3$  | 0.97                              | 0.93                              | 0.60                              |
| 2-naphthyl  | 0.88                              | 0.86                              | 0.60                              |

Out-of-Sample prediction set 2: Variation in substrate(s) and/or catalyst

| Product | catalyst Ar | measured $\Delta\Delta G^\ddagger$ | predicted $\Delta\Delta G^\ddagger$ | experiment $\Delta\Delta G^\ddagger$ |
|---------|-------------|-----------------------------------|-----------------------------------|-----------------------------------|
| E       | TCYP        | 2.40                              | 2.12                              | 1.88                              |
| G       | TCYP        | 2.36                              | 2.08                              | 1.88                              |
| H       | TRIP        | 1.54                              | 1.40                              | 1.10                              |
| I       | TCYP        | 1.51                              | 1.38                              | 1.33                              |
| J       | TCYP        | 1.36                              | 1.25                              | 1.96                              |
| K       | TCYP        | 1.48                              | 1.35                              | 1.74                              |
| L       | TCYP        | 1.55                              | 1.41                              | 1.49                              |
| M       | TCYP        | 1.61                              | 1.46                              | 0.96                              |
| N       | TCYP        | 1.46                              | 1.34                              | 0.84                              |
| O       | TRIP        | 2.72                              | 2.38                              | 2.06                              |
| P       | TRIP        | 2.43                              | 2.14                              | 2.30                              |
| Q       | TRIP        | 1.46                              | 1.34                              | 1.18                              |
| R       | TCYP        | 1.83                              | 1.65                              | 1.45                              |
| S       | TCYP        | 1.44                              | 1.32                              | 1.96                              |
| T       | TRIP        | 2.39                              | 2.10                              | 2.48                              |
| U       | TRIP        | 2.14                              | 1.90                              | 1.88                              |
| V       | TRIP        | 2.28                              | 2.01                              | 2.48                              |
| X       | TRIP        | 2.30                              | 2.04                              | 2.17                              |
| Y       | TRIP        | 2.40                              | 2.12                              | 2.06                              |
| Z       | TRIP        | 2.66                              | 2.33                              | 2.06                              |
| ZA      | TRIP        | 2.31                              | 2.04                              | 2.30                              |
| ZB      | TRIP        | 2.47                              | 2.17                              | 2.48                              |
| ZC      | TRIP        | 1.60                              | 1.45                              | 1.74                              |
| ZD      | TRIP        | 1.70                              | 1.54                              | 1.74                              |
| ZE      | TRIP        | 2.54                              | 2.23                              | 2.48                              |
Out-of-Sample prediction Set 3: Diazines

| Product | catalyst Ar | measured ΔΔG‡ | predicted ΔΔG‡ | experiment ΔΔG‡ |
|---------|-------------|---------------|----------------|-----------------|
| 1       | TCYP        | 1.69          | 1.52           | 1.63            |
| 2       | TCYP        | 1.44          | 1.32           | 1.41            |
| 3       | TCYP        | 1.77          | 1.59           | 1.49            |
| 4       | TRIP        | 2.19          | 1.94           | 2.06            |
| 5       | TRIP        | 2.33          | 2.05           | 1.81            |
| 6       | TRIP        | 2.32          | 2.05           | 2.48            |
| 7       | TRIP        | 2.30          | 2.03           | 2.48            |
| 8       | TRIP        | 1.67          | 1.51           | 3.13            |
| 9       | TRIP        | 1.88          | 1.69           | 2.48            |
| 10      | TRIP        | 2.23          | 1.97           | 2.06            |
| 11      | TRIP        | 2.51          | 2.21           | 3.13            |
| 12      | TRIP        | 2.42          | 2.13           | 3.13            |
| 13      | TRIP        | 1.42          | 1.30           | 1.24            |
| 14      | TRIP        | 2.01          | 1.79           | 1.74            |
| 15      | TRIP        | 1.57          | 1.43           | 1.81            |

Other RAE predictions

| Product | measured ΔΔG‡ | predicted ΔΔG‡ | experiment ΔΔG‡ |
|---------|---------------|----------------|----------------|
| 14      | 0.89          | 0.86           | 0.92           |
| 15      | 0.09          | 0.20           | 0.34           |
| 16      | 1.17          | 1.09           | 1.00           |

Other predictions: Substrates revealed as limitations

| Product | measured ΔΔG‡ | predicted ΔΔG‡ | experiment ΔΔG‡ |
|---------|---------------|----------------|----------------|
| 19      | 1.16          | 1.09           | 0.75           |
| 20      | 2.20          | 1.95           | 1.33           |
| 21      | 2.48          | 2.18           | 0.73           |
| 22      | 0.74          | 0.74           | 0.33           |
| 23      | 1.84          | 1.65           | N/A            |
| 24      | -0.05         | 0.08           | N/A            |
| 25      | -0.17         | -0.02          | N/A            |
| 26      | -0.05         | 0.08           | N/A            |
Alternative Models and Correlation Maps

Catalyst terms highlighted in blue and product terms in red.

| model | Model terms                                                                 |
|-------|-----------------------------------------------------------------------------|
| 1     | 0.72 - 0.28iPOas + 0.19NBO_{C2} + 0.19NBO_{RAEC1} + 0.19NBO_{HetC6} - 0.23L_{RAE} + 0.31B_{1HetC6} |
| 2     | 0.72 + 0.27\alpha + 0.05L_{whole} + 0.19B_{1whole} + 0.29NBO_{RAEC1} - 0.21L_{RAE} + 0.40L_{HetC6} |
| 3     | 0.72 + 0.25\alpha + 0.20B_{1whole} + 0.06L_{4} + 0.22NBO_{RAEC1} + 0.11NBO_{HetC6} + 0.27B_{5wholeHet} |
| 4     | 0.72 + 0.29\alpha + 0.21B_{1whole} + 0.04L_{5} + 0.22NBO_{RAEC1} + 0.10NBO_{HetC6} + 0.27B_{5wholeHet} |
| 5     | 0.72 + 0.28\alpha + 0.21B_{1whole} + 0.02B_{15} + 0.22NBO_{RAEC1} + 0.10NBO_{HetC6} + 0.27B_{5wholeHet} |
| 6     | 0.72 + 0.26\alpha + 0.21B_{1whole} - 0.02NBO_{C1} + 0.22NBO_{RAEC1} + 0.10NBO_{HetC6} + 0.27B_{5wholeHet} |
| 7     | 0.72 + 0.30\alpha + 0.21B_{1whole} + 0.04NBO_{C3} + 0.22NBO_{RAEC1} + 0.10NBO_{HetC6} + 0.27B_{5wholeHet} |
| 8     | 0.72 + 0.34\alpha + 0.19B_{1whole} + 0.09NBO_{C5} + 0.22NBO_{RAEC1} + 0.10NBO_{HetC6} + 0.27B_{5wholeHet} |
| 9     | 0.72 + 0.45\alpha + 0.20NBO_{C5} + 0.21NBO_{RAEC1} + 0.10NBO_{HetC6} + 0.30B_{5wholeHet} - 0.30L_{HetC6} |
| 10    | 0.72 + 0.26\alpha + 0.22B_{1whole} + 0.01L_{3} + 0.22NBO_{RAEC1} + 0.10NBO_{HetC6} + 0.27B_{5wholeHet} |

| model | R2 | LOO | k-fold | predicted R2 (out-of-sample platform 1 and 2) | predicted R2 (out-of-sample platform 3) |
|-------|----|-----|--------|-----------------------------------------------|----------------------------------------|
| 1     | 0.83 | 0.78 | 0.76 | 0.92 | 0.84 |
| 2     | 0.80 | 0.74 | 0.72 | 0.88 | 0.52 |
| 3     | 0.81 | 0.74 | 0.72 | 0.66 | 0.83 |
| 4     | 0.80 | 0.74 | 0.72 | 0.67 | 0.83 |
| 5     | 0.80 | 0.74 | 0.72 | 0.67 | 0.83 |
| 6     | 0.80 | 0.74 | 0.72 | 0.67 | 0.83 |
| 7     | 0.80 | 0.74 | 0.72 | 0.67 | 0.83 |
| 8     | 0.81 | 0.75 | 0.73 | 0.67 | 0.83 |
| 9     | 0.80 | 0.73 | 0.71 | 0.63 | 0.82 |
| 10    | 0.80 | 0.74 | 0.72 | 0.67 | 0.83 |
The catalyst correlation map determines that each model (1-10) emphasises the importance of large substituents at the 2 and 6 positions for high levels of enantioselectivity through a variety of descriptors. $B_{\text{whole}}$, $L_{\text{whole}}$ and $iPO_{\text{as}}$ are highly correlated suggesting they capture comparable structural effects. Similar relationships between parameters can be observed with the torsion angle, $\alpha$, and $NBO_{C2}$. The substrate parameters are more conserved in models 1-10 than that of the catalyst, however, variance is detected in the description of the proximal N-heterocycle steric profile. The correlation map show that this molecular feature can be described through $B_{\text{wholeNHet}}$, $L_{\text{HetC6}}$ and $B_{1\text{HetC6}}$. Thus, by combining the interpretation of models 1-10 the incorporated parameters suggest that large catalyst and N-heterocycle substituents, in addition to the collective structure effects described by the $NBO_{\text{RAEC1}}$ term are important in determining the enantioselectivity.
A correlation of the C2:C4 isomeric ratio (rr) with the enantioselectivity of the product reveals a linear relationship, in which, as the ee increases the rr generally increases, see below.

\[
y = 1.26x - 0.75 \\
R^2 = 0.95
\]

| measured regioselectivity $\Delta \Delta G^\ddagger$ | measured enantioselectivity $\Delta \Delta G^\ddagger$ |
|-----------------------------------------------|---------------------------------|
| 1.77                                          | 1.53                            |
| 1.15                                          | 0.70                            |
| 1.15                                          | 0.62                            |
| 0.95                                          | 0.33                            |
| 0.95                                          | 0.35                            |
| 0.82                                          | 0.32                            |
| 0.82                                          | 0.39                            |
| 0.95                                          | 0.57                            |
Result with non-aromatic derived chiral phosphoric acid catalysts

In our analyses we collect a diverse array of molecular descriptor values from DFT optimized geometries to describe the structural features of the substrate and catalyst. Unfortunately, the lack of structural commonality for particular molecular subsets creates a challenge in identifying readily comprehensible and extensive parameter sets for each of these components. For example, when comparing catalysts with aromatic substituents at the 3 and 3’ positions, it is apparent that they have overlapping and distinctive features that are probably required for determining selectivity patterns. By contrast, the inclusion non-aromatic derived catalysts reduce the commonality in substructure and consequently results in a decrease in important feature space. Despite this, model 2 on page S157 contains features that are common to both aromatic and non-aromatic derived catalysts and therefore may be able to gauge the effect of the latter catalyst class. To test this, the reaction yielding product A catalysed by TIPSY (3,3’ = SiPh3) was performed, providing A in 75% ee. This result was used to validate model 2 as shown below. The comparison of predicted (86% ee) and experiment (75% ee) corresponds to a $\Delta G^\ddagger$ error of 0.38 kcal/mol. This suggests that the secondary model which contain features common to both catalyst classes could potentially predict the effects of these catalysts.
Spectra of starting materials and catalyst

$^1$H NMR (400 MHz, Acetone) (R)-3,3'-bis(2,6-dimethylphenyl)-1,1'-binaphthyl phosphate (20)

$^{13}$C NMR (101 MHz, Acetone) (R)-3,3'-bis(2,6-dimethylphenyl)-1,1'-binaphthyl phosphate (20)
$^{31}$P NMR (162 MHz, CDCl$_3$) (R)-3,3'-bis(2,6-dimethylphenyl)-1,1'-binaphthyl phosphate (20)
$^1$H NMR (400 MHz, CDCl$_3$) 1,3-dioxoisooindolin-2-yl acetylleucinate (21)

$^{13}$C NMR (101 MHz, CDCl$_3$) 1,3-dioxoisooindolin-2-yl acetylleucinate (21)
Spectra of products

$^1$H NMR (400 MHz, CDCl$_3$) $N$-(2-methyl-1-(quinolin-2-yl)propyl)acetamide (A)
$^{13}$C NMR (101 MHz, CDCl$_3$) $N$-(2-methyl-1-(quinolin-2-yl)propyl)acetamide (A)
$^1$H NMR (400 MHz, CDCl$_3$) $N$-(2-methyl-1-(quinolin-4-yl)propyl)acetamide (A1)
$^{13}$C NMR (101 MHz, CDCl$_3$) $N$-(2-methyl-1-(quinolin-4-yl)propyl)acetamide (A1)
$^{13}$C NMR (101 MHz, CDCl₃) $N$-{(3-phenyl-1-(quinolin-2-yl)propyl)acetamide (B)
$^1$H NMR (600 MHz, CDCl$_3$) $N$-(3-phenyl-1-(quinolin-4-yl)propyl)acetamide (B1)
$^{13}$C NMR (151 MHz, CDCl$_3$) $N$-(3-phenyl-1-(quinolin-4-yl)propyl)acetamide (B1)
$^1$H NMR (400 MHz, CDCl$_3$) $N$-(3-methyl-1-(quinolin-2-yl)butyl)acetamide (C)
$^{13}$C NMR (101 MHz, CDCl$_3$) $N$-(3-methyl-1-(quinolin-2-yl)butyl)acetamide (C)
$^1$H NMR (600 MHz, CDCl$_3$) \textit{N}-\text{(2-methyl-1-quinolin-4-yl)propyl}acetamide (C1)
$^{13}$C NMR (151 MHz, CDCl$_3$) N-(2-methyl-1-(quinolin-4-yl)propyl)acetamide (C1)
$^1$H NMR (400 MHz, CDCl$_3$) N-(1-(5-cyanopyridin-2-yl)-2-methylpropyl)acetamide (D)/(N)
$^{13}$C NMR (101 MHz, CDCl$_3$) $N$-(1-(5-cyanopyridin-2-yl)-2-methylpropyl)acetamide (D)/(N)
$^1$H NMR (400 MHz, CDCl$_3$) (S)-N-(2-methyl-1-(5-phenylpyridin-2-yl)propyl)acetamide (F)/(M)
$^{13}$C NMR (101 MHz, CDCl$_3$) (S)-N-(2-methyl-1-(5-phenylpyridin-2-yl)propyl)acetamide (F)/(M)
$^1$H NMR (400 MHz, CDCl$_3$) (S)-N-(3-methyl-1-(4-methylquinolin-2-yl)butyl)acetamide (H)
$^{13}$C NMR (101 MHz, CDCl$_3$) (S)-$N$-(3-methyl-1-(4-methylquinolin-2-yl)butyl)acetamide (H)
$^1$H NMR (400 MHz, CDCl$_3$) methyl (S)-6-(1-acetamido-2-methylpropyl)-5-methylnicotinate (I)
$^{13}$C NMR (101 MHz, CDCl₃) methyl (S)-6-(1-acetamido-2-methylpropyl)-5-methylnicotinate (I)
$^1$H NMR (400 MHz, CDCl$_3$) methyl (S)-6-(1-acetamido-2-methylpropyl)-4-methylnicotinate (L)
$^{13}$C NMR (101 MHz, CDCl$_3$) methyl (S)-6-(1-acetamido-2-methylpropyl)-4-methylnicotinate (L)
$^1$H NMR (600 MHz, CDCl$_3$) (S)-N-\{(1-(8-methylquinolin-2-yl)-2-phenylethyl)acetamide (Q)
$^{13}$C NMR (151 MHz, CDCl$_3$) (S)-N-(1-(8-methylquinolin-2-yl)-2-phenylethyl)acetamide (Q)
$^1$H NMR (400 MHz, CDCl$_3$) methyl (5)-2-(1-acetamido-2-methylpropyl)isonicotinate (2a)
$^{13}$C NMR (101 MHz, CDCl₃) methyl (S)-2-(1-acetamido-2-methylpropyl)isonicotinate (2a)
$^1$H NMR (400 MHz, CDCl$_3$) (S)-N-(2-phenyl-1-(pyrimidin-4-yl)ethyl)acetamide (1)
$^{13}$C NMR (101 MHz, CDCl$_3$) (S)-N-(2-phenyl-1-(pyrimidin-4-yl)ethyl)acetamide (1)
$^1$H NMR (400 MHz, CDCl$_3$) (S)-$N$-(1-(5-bromopyrimidin-4-yl)-2-phenylethyl)acetamide (2)
$^{13}$C NMR (101 MHz, CDCl$_3$) (S)-$N$-(1-(5-bromopyrimidin-4-yl)-2-phenylethyl)acetamide (2)
$^1$H NMR (400 MHz, CDCl$_3$) (S)-N-(1-(6-methylpyrimidin-4-yl)-2-phenylethyl)acetamide (3)
$^{13}$C NMR (101 MHz, CDCl$_3$) (S)-$N$-{(1-(6-methylpyrimidin-4-yl)-2-phenylethyl)acetamide (3)
$^{13}$C NMR (400 MHz, CDCl$_3$) (S)-N-(1-(2-methylpyrimidin-4-yl)-2-phenylethyl)acetamide (4)
$^{13}$C NMR (101 MHz, CDCl$_3$) (5)-N-(1-(2-methylpyrimidin-4-yl)-2-phenylethyl)acetamide (4)
$^1$H NMR (400 MHz, CDCl$_3$) $N,N'-(1S,1'S)-(2$-methylpyrimidine-4,6-diyl)bis(2-phenylethane-1,1-diyl)diacetamide (5)
$^{13}$C NMR (101 MHz, CDCl$_3$) $N,N'$-((1S,1'S)-(2-methylpyrimidine-4,6-diyl)bis(2-phenylethane-1,1-diyl))diacetamide (5)
$^{1}$H NMR (400 MHz, CDCl$_3$) (S)-N-(1-(2,6-dimethylpyrimidin-4-yl)-2-phenylethyl)acetamide (6)
$^{13}$C NMR (101 MHz, CDCl$_3$) $\text{S}^{-}$-N-(1-(2,6-dimethylpyrimidin-4-yl)-2-phenylethyl)acetamide (6)
$^1$H NMR (400 MHz, CDCl$_3$) (S)-N-(1-(6-chloro-2-methylpyrimidin-4-yl)-2-phenylethyl)acetamide (7)
$^{13}$C NMR (101 MHz, CDCl$_3$) (S)-N-(1-(6-chloro-2-methylpyrimidin-4-yl)-2-phenylethyl)acetamide (7)
$^1$H NMR (400 MHz, CDCl$_3$) (S)-N-(1-(2-methyl-6-phenylpyrimidin-4-yl)-2-phenylethyl)acetamide (8)
$^{13}$C NMR (101 MHz, CDCl$_3$) (5)-$N$-(1-(2-methyl-6-phenylpyrimidin-4-yl)-2-phenylethyl)acetamide (8)
$^1$H NMR (400 MHz, CDCl$_3$) (S)-N-(1-(2-methyl-5-phenylpyrimidin-4-yl)-2-phenylethyl)acetamide (9)
$^{13}$C NMR (101 MHz, CDCl$_3$) (S)-N-(1-(2-methyl-5-phenylpyrimidin-4-yl)-2-phenylethyl)acetamide (9)
$^1$H NMR (400 MHz, CDCl$_3$) (S)-N-(1-(5-bromo-2-methylpyrimidin-4-yl)-2-phenylethyl)acetamide (10)
$^{13}$C NMR (101 MHz, CDCl$_3$) (S)-N-(1-(5-bromo-2-methylpyrimidin-4-yl)-2-phenylethyl)acetamide (10)
$^1$H NMR (101 MHz, CDCl₃) (5)-N-(2-phenyl-1-(2-phenylpyrimidin-4-yl)ethyl)acetamide (11)
$^1$H NMR (400 MHz, CDCl$_3$) (S)-N-(1-(5-bromo-2-methoxypyrimidin-4-yl)-2-phenylethyl)acetamide (12)
$^{13}$C NMR (101 MHz, CDCl$_3$) (S)-N-(1-(5-bromo-2-methoxypyrimidin-4-yl)-2-phenylethyl)acetamide (12)
$^1$H NMR (400 MHz, CDCl$_3$) (S)-N-(1-(5-chloro-2-methoxypyrimidin-4-yl)-2-phenylethyl)acetamide (13)
$^{13}$C NMR (101 MHz, CDCl$_3$) (S)-N-(1-(5-chloro-2-methoxypyrimidin-4-yl)-2-phenylethyl)acetamide (13)
$^1$H NMR (400 MHz, CDCl$_3$) (5)-N-(3-phenyl-1-(pyrimidin-4-yl)propyl)acetamide (14)
$^1$H NMR (400 MHz, CDCl$_3$) (5)-N-(3-phenyl-1-(pyrimidin-4-yl) propyl)acetamide (14)
$^1$H NMR (400 MHz, CDCl$_3$) (S)-N-(3-methyl-1-(pyrimidin-4-yl)butyl)acetamide (15)
$^1$H NMR (400 MHz, CDCl₃) (S)-N-(3-methyl-1-(pyrimidin-4-yl)butyl)acetamide (15)
$^1$H NMR (400 MHz, CDCl$_3$) (S)-$N$-(2-methyl-1-(pyrimidin-4-yl)propyl)acetamide (16)
\(^1\)H NMR (400 MHz, CDCl\(_3\)) (S)-N-(2-methyl-1-(pyrimidin-4-yl)propyl)acetamide (16)
$^1$H NMR (400 MHz, CDCl$_3$) (S)-N-(2-phenyl-1-(3,5,6-trimethylpyrazin-2-yl)ethyl)acetamide (17)
$^{13}$C NMR (101 MHz, CDCl$_3$) (S)-N-(2-phenyl-1-(3,5,6-trimethylpyrazin-2-yl)ethyl)acetamide (17)
$^1$H NMR (400 MHz, CDCl$_3$) (S)-N-(1-(3,6-dimethylpyrazin-2-yl)-2-phenylethyl)acetamide (18)
$^{13}$C NMR (101 MHz, CDCl$_3$) (S)-N-(1-(3,6-dimethylpyrazin-2-yl)-2-phenylethyl)acetamide (18)
(S)-N-(2-phenyl-1-(quinazolin-4-yl)ethyl)acetamide (19)
(S)-N-(2-phenyl-1-(quinazolin-4-yl)ethyl)acetamide (19)
$^1$H NMR (400 MHz, CDCl$_3$) (S)-N-(1-(2-aminopyrimidin-4-yl)-2-phenylethyl)acetamide (20)
$^{13}$C NMR (101 MHz, CDCl$_3$) (S)-N-(1-(2-aminopyrimidin-4-yl)-2-phenylethyl)acetamide (20)
$^1$H NMR (400 MHz, CDCl$_3$) tert-butyl (S)-(4-(1-acetamido-2-phenylethyl)pyrimidin-2-yl)carbamate (21)
$^{13}$C NMR (101 MHz, CDCl$_3$) tert-butyl (S)-(4-(1-acetamido-2-phenylethyl)pyrimidin-2-yl)carbamate (21)
$^1$H NMR (400 MHz, CDCl$_3$) (S)-N-1-(benzo[d]thiazol-2-yl)-2-phenylethyl)acetamide (22)
\(^{13}\text{C NMR (101 MHz, CDCl\text{3}) (S)}\)-\(N\)-(1-(benzo[d]thiazol-2-yl)-2-phenylethyl)acetamide (22)
HPLC Traces

\[ N-(2\text{-methyl-1-quinolin-2-yl})\text{propyl}acacetamide (A) \]

Chiralpak AD-H (Hexane/iPrOH = 95/05, 1.0 mL min\(^{-1}\), 30 °C, 239 nm)

\[ t_R = 10.5 \text{ minutes, 15.1 minutes.} \]

\[ N-(2\text{-methyl-1-quinolin-4-yl})\text{propyl}acacetamide (A1) \]

Chiralpak AD-H (Hexane/iPrOH = 95/05, 1.0 mL min\(^{-1}\), 30 °C, 286 nm)

\[ t_R = 24.8 \text{ minutes, 32.0 minutes.} \]
**$N$-(3-phenyl-1-(quinolin-2-yl)propyl)acetamide (B)**

CHIRAL ART SC (CO$_2$/MeOH = 80/20, 2.5 mL min$^{-1}$, 40 °C, 315 nm)

$t_R = 2.8$ minutes, 3.0 minutes

**$N$-(3-phenyl-1-(quinolin-4-yl)propyl)acetamide (B1)**

CHIRAL ART SB (CO$_2$/MeOH = 80/20, 2.5 mL min$^{-1}$, 40 °C, 281 nm)

$t_R = 5.0$ minutes (minor), 8.3 minutes (major)
**tert-butyl (S)-3-acetamido-3-(4-methylquinolin-2-yl)propanoate (C)**

CHIRAL ART SC (CO$_2$/MeOH = 80/20, 2.5 mL min$^{-1}$, 40 °C, 315 nm)

$t_R = 2.3$ minutes, 2.5 minutes

**N-(3-methyl-1-(quinolin-4-yl)butyl)acetamide (C1)**

CHIRAL ART SB (CO$_2$/MeOH = 80/20, 2.5 mL min$^{-1}$, 40 °C, 315 nm)

$t_R = 3.0$ minutes, 10.4 minutes
$N$-(1-(5-cyanopyridin-2-yl)-2-methylpropyl)acetamide (D)

Chiralpak IE ($\text{CO}_2/\text{MeOH} = 95/05$, 2.5 mL min$^{-1}$, 40 °C, 268 nm)

t$\text{R}$ = 12.4 minutes, 13.2 minutes

methyl 6-(1-acetamido-2-methylpropyl)-2-methyl nicotinate (E)

Chiralpak IE ($\text{CO}_2/\text{MeOH} = 90/10$, 2.5 mL min$^{-1}$, 40 °C, 269 nm)

t$\text{R}$ = 5.1 minutes, 5.6 minutes
(S)-N-(2-methyl-1-(5-phenylpyridin-2-yl)propyl)acetamide (F)

Chiralpak IE (CO$_2$/MeOH = 93/07, 2.5 mL min$^{-1}$, 40 °C, 244 nm)

t$_R$ = 17.8 minutes, 21.8 minutes

N-(1-(5-cyano-6-methylpyridin-2-yl)-2-methylpropyl)acetamide (G)

Chiralpak IE (CO$_2$/MeOH = 93/07, 2.5 mL min$^{-1}$, 40 °C, 272 nm)

t$_R$ = 17.8 minutes, 21.8 minutes
(5)-N-(3-methyl-1-(4-methylquinolin-2-yl)butyl)acetamide (H)

HPLC Conditions: Chiralpak IC (Hexane/iPrOH = 90/10, 1.0 mL min⁻¹, 30 °C, 235 nm) indicated 73% ee.

tR = 15.7 minutes (minor), 24.1 minutes (major)
methyl (S)-6-(1-acetamido-2-methylpropyl)-5-methylnicotinate (I)

Chiralpak IE (CO₂/MeOH = 90/10, 2.5 mL min⁻¹, 40 °C, 272 nm)

81% ee

$\tau_R = 5.2$ minutes (minor), 5.9 minutes (major)
methyl (S)-6-(1-acetamido-2-methylpropyl)-4-methylnicotinate (L)

Chiralpak IC (Hexane/iPrOH = 70/30, 1.0 mL min⁻¹, 30 °C, 239 nm)  
85% ee  
$t_R$ = 8.5 minutes (minor), 10.5 minutes (major)
(S)-N-(2-methyl-1-(5-phenylpyridin-2-yl)propyl)acetamide (M)

Chiralpak IC (Hexane/iPrOH = 70/30, 1.0 mL min⁻¹, 30 °C, 239 nm)

67% ee

tₚ = 7.3 minutes (minor), 10.5 minutes (major)
N-(1-(5-cyanopyridin-2-yl)-2-methylpropyl)acetamide (N)

Chiralpak IC (Hexane/iPrOH = 85/15, 1.0 mL min⁻¹, 30 °C, 260 nm)

61% ee.

t_R = 15.0 minutes (minor), 18.7 minutes (major)
(S)-N-(1-(8-methylquinolin-2-yl)-2-phenylethyl)acetamide (Q)

Chiralpak IC (Hexane/iPrOH = 85/15, 1.0 mL min⁻¹, 30 °C, 222 nm)

76% ee.

$t_R = 14.4$ minutes (minor), 16.2 minutes (major)
methyl (S)-2-(1-acetamido-2-methylpropyl)isonicotinate

Chiralpak IE (CO₂/MeOH = 80/20, 2.5 mL min⁻¹, 40 °C, 279 nm)

39% ee

$t_R = 2.8$ minutes (minor), $3.0$ minutes (major)
(5)-N-(2-phenyl-1-(pyrimidin-4-yl)ethyl)acetamide (1)

Chiralpak IE (CO₂/MeOH = 90/10, 2.5 mL min⁻¹, 40 °C, 245 nm)

88% ee

$t_\alpha = 9.3$ minutes, 9.9 minutes
78% ee (with $\text{(R)}$-TRIP)
(S)-N-(1-(5-bromopyrimidin-4-yl)-2-phenylethyl)acetamide (2)

Chiralpak IE (CO$_2$/MeOH = 80/20, 2.5 mL min$^{-1}$, 40 °C, 262 nm)

83% ee

$t_e = 4.0$ minutes, 4.5 minutes
(5)-N-(1-(6-methylpyrimidin-4-yl)-2-phenylethyl)acetamide (3)

Chiralpak IE (CO₂/MeOH = 90/10, 2.5 mL min⁻¹, 40 °C, 245 nm)

85% ee

tₐ₉ = 9.5 minutes, 10.1 minutes
(5)-N-(1-(2-methylpyrimidin-4-yl)-2-phenylethyl)acetamide (4)

CHIRAL ART SC (CO$_2$/MeOH = 90/10, 2.5 mL min$^{-1}$, 40 °C, 250 nm)

94% ee

t$_R$ = 6.4 minutes (minor), 6.9 minutes (major)
$N,N'-(\text{15,1}'\text{S})-(2\text{-methylpyrimidine-4,6-diyl})\text{bis(2-phenylethane-1,1-diyl)}\text{diacetamide (5)}$  

Chiralpak IG (CO$_2$/MeOH = 80/20, 2.5 mL min$^{-1}$, 40 °C, 252 nm)  

$\geq$99% ee  

$\tau_R = 3.2$ minutes (major enantiomer), 3.7 minutes (minor diastereomer), 4.7 minutes (minor enantiomer)
(S)-N-(1-(2,6-dimethylpyrimidin-4-yl)-2-phenylethyl)acetamide (6)

CHIRAL ART SC (CO₂/MeOH = 90/10, 2.5 mL min⁻¹, 40 °C, 252 nm)

91% ee

$t_R = 5.3$ minutes (minor), $6.1$ minutes (major)
(S)-N-(1-(6-chloro-2-methylpyrimidin-4-yl)-2-phenylethyl)acetamide (7)

Chiralpak IG (CO₂/MeOH = 90/10, 2.5 mL min⁻¹, 40 °C, 253 nm)

97% ee

tᵣ = 4.1 minutes (major), 4.7 minutes (minor)
(S)-N-(1-(2-methyl-6-phenylpyrimidin-4-yl)-2-phenylethyl)acetamide (8)

CHIRAL ART SC (CO\textsubscript{2}/MeOH = 90/10, 2.5 mL min\textsuperscript{-1}, 40 °C, 275 nm)

97% ee

t\textsubscript{R} = 7.9 minutes (minor), 8.7 minutes (major)
(S)-N-(1-(2-methyl-5-phenylpyrimidin-4-yl)-2-phenylethyl)acetamide (9)

Chiralpak IG (CO₂/MeOH = 90/10, 2.5 mL min⁻¹, 40 °C, 275 nm)

99% ee

\( t_R = 5.0 \text{ minutes (major)}, 6.1 \text{ minutes (minor)} \)
(S)-N-(1-(5-bromo-2-methylpyrimidin-4-yl)-2-phenylethyl)acetamide (10)

CHIRAL ART SC (CO₂/MeOH = 90/10, 2.5 mL min⁻¹, 40 °C, 266 nm)

97% ee

tᵣ = 5.9 minutes (minor), 7.5 minutes (major)
(S)-N-(2-phenyl-1-(2-phenylpyrimidin-4-yl)ethyl)acetamide (11)

CHIRAL ART SC (CO₂/MeOH = 90/10, 2.5 mL min⁻¹, 40 °C, 266 nm)

94% ee

$t_R = 12.0$ minutes (major), 13.1 minutes (minor)
(5)-N-(1-(5-bromo-2-methoxypyrimidin-4-yl)-2-phenylethyl)acetamide (12)

CHIRAL ART SC (CO₂/MeOH = 90/10, 2.5 mL min⁻¹, 40 °C, 266 nm)

>99% ee

$t_R = 7.8$ minutes (minor), 10.5 minutes (major)
(S)-N-(1-(5-chloro-2-methoxypyrimidin-4-yl)-2-phenylethyl)acetamide (13)

CHIRAL ART SC ($\text{CO}_2$/MeOH = 90/10, 2.5 mL min$^{-1}$, 40 °C, 266 nm)

99% ee

$t_R = 5.5$ minutes (minor), 6.1 minutes (major)
(S)-N-(3-phenyl-1-(pyrimidin-4-yl)propyl)acetamide (14)

Chiralpak IE (CO\textsubscript{2}/MeOH = 90/10, 2.5 mL min\textsuperscript{-1}, 40 °C, 244 nm)

65% ee

$t_R$ = 11.5 minutes (minor), 12.3 minutes (major)
(S)-N-(3-methyl-1-(pyrimidin-4-yl)butyl)acetamide (15)

Chiralpak IE (CO₂/MeOH = 90/10, 2.5 mL min⁻¹, 40 °C, 244 nm)

28% ee

\[ t_R = 4.6 \text{ minutes (minor), 5.0 minutes (major)} \]
(S)-N-(2-methyl-1-(pyrimidin-4-yl)propyl)acetamide (16)

Chiralpak IE (CO₂/MeOH = 90/10, 2.5 mL min⁻¹, 40 °C, 244 nm)

69% ee

$t_R$ = 4.8 minutes (minor), 5.3 minutes (major)
(S)-N-(2-phenyl-1-(3,5,6-trimethylpyrazin-2-yl)ethyl)acetamide (17)

Chiralpak IE (CO₂/MeOH = 90/10, 2.5 mL min⁻¹, 40 °C, 279 nm)

90% ee

\( t_R = 9.6 \text{ minutes (minor), 10.3 minutes (major)} \)
(S)-N-(1-(3,6-dimethylpyrazin-2-yl)-2-phenylethyl)acetamide (18)

Chiralpak IE (CO₂/MeOH = 90/10, 2.5 mL min⁻¹, 40 °C, 279 nm)

91% ee

$t_R$ = 8.2 minutes (minor), 8.6 minutes (major)
(S)-N-(2-phenyl-1-(quinazolin-4-yl)ethyl)acetamide (19)

Chiralpak IE (CO₂/MeOH = 80/20, 2.5 mL min⁻¹, 40 °C, 219 nm)

56% ee
t_R = 6.3 minutes (major), 6.9 minutes (minor)
(S)-N-(1-(2-aminopyrimidin-4-yl)-2-phenylethyl)acetamide (20)

Chiralpak IE (CO₂/MeOH = 90/10, 2.5 mL min⁻¹, 40 °C, 230 nm)

81% ee

$t_R = 19.0$ minutes (minor), 19.9 minutes (major)
tert-butyl (S)-(4-(1-acetamido-2-phenylethyl)pyrimidin-2-yl)carbamate (21)

Chiralpak IE (CO₂/MeOH = 90/10, 2.5 mL min⁻¹, 40 °C, 230 nm)

54% ee

$t_R = 7.8$ minutes (major), 8.5 minutes (minor)
(S)-N-(1-({benzo[d]thiazol-2-yl}-2-phenylethyl)acetamide (22)

![Chemical structure of (S)-N-(1-({benzo[d]thiazol-2-yl}-2-phenylethyl)acetamide (22)](image)

Chiralpak IG (CO2/MeOH = 80/20, 2.5 mL min⁻¹, 40 °C, 252 nm)

27% ee

$t_R$ = 8.8 minutes (major), 10.6 minutes (minor)
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