

Supplementary Information

Dialkyl ether synthesis through heteroatom homolytic substitution

Johannes J. Großkopf^{1,†}, Johnny Z. Wang^{1,†}, Jacqueline W. Gu¹, Cheng Bi², Sarah N. Dishman³,
Xiaoshen Ma³, Yu-hong Lam⁴ and David W. C. MacMillan^{1*}

¹Merck Center for Catalysis at Princeton University, Princeton, New Jersey 08544, United States

²Department of Process Research & Development, Merck & Co., Inc., 33 Ave. Louis Pasteur, Boston, Massachusetts, 02215, United States

³Department of Discovery Chemistry, Merck & Co., Inc., 33 Ave. Louis Pasteur, Boston, Massachusetts, 02215, United States

⁴Department of Modeling & Informatics, Merck & Co., Inc., 126 E Lincoln Ave, Rahway, NJ 07065, United States

[†] These authors contributed equally to this work.

*Corresponding author: dmacmill@princeton.edu

Table of Contents

1. General Information	3
2. Reaction Optimization and Control Experiments	8
3. General Procedures	17
4. Reaction Limitations	20
5. UV-vis Data	22
5.1 Ti-Alkoxide (6) Formation	22
5.2 LMCT Investigations	24
6. Stern-Volmer Quenching	28
7. Cyclic Voltammetry Measurement.....	30
8. Mechanistic Studies on the Heteroatom Homolytic Substitution	33
8.1 Alcohol Competition Experiment.....	33
8.2 Influence on Diastereomeric Ratio.....	34
8.3 PhotoNMR Studies	40
8.4 Light Independent Product Formation via Thermal Reduction	42
8.5 Light Independent Product Formation via Thermal Decomposition	45
8.6 Comparison Versus Carbocation Reactivity	47
9. Computational Analysis of the Ether Formation via Radical Substitution	48
9.1 Energetic Analysis	49
9.2 Bond Dissociation Energies	52
9.3 Spin Density Analysis	53
9.4 Selectivity for Oxygen versus Chloride Transfer.....	54
9.5 Cartesian Coordinates of Optimized Structures	56
10. Chemical Space Analysis and HTE Setup	64
11. Experimental Details and Characterization Data of Redox Active Esters	69
12. Experimental Details and Characterization Data for Dialkyl Ethers	86
13. NMR Spectra for Redox Active Ester	187
14. NMR Spectra for Dialkyl Ethers.....	218
15. References.....	310

1. General Information

Commercial reagents were used without prior purification unless otherwise indicated. All solvents were purchased in their anhydrous form or dried over activated 4Å molecular sieves. Ir(dF(CF₃)ppy)₂(dtbbpy)PF₆ (CAS: 870987-63-6), Ir(F(Me)ppy)₂(dtbbpy)PF₆ (CAS: 808142-88-3) and Ir(ppy)₂(dtbbpy)PF₆ (CAS: 676525-77-2) were prepared according to literature procedure (1) but are also available from Sigma Aldrich. 4CzIPN (CAS: 1416881-52-1), Cp₂TiCl₂ (CAS: 1271-19-8, 97%), Zn₃(PO₄)₂ (CAS: 7779-90-0, 99.998% trace metals basis), zinc carbonate basic ([ZnCO₃]₂·[Zn(OH)₂]₃, CAS: 5263-02-5, purum p.a., ≥58% Zn basis (KT)), dry dichloromethane and dry dichloroethane were purchased from Sigma Aldrich and used as received. 4DPAIPN (CAS: 1846598-27-3, 95%) was purchased from Ambeed and used as received.

Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator using a temperature-controlled water bath. Chromatographic purification of products was performed on an automated Teledyne ISCO CombiFlash[®] NextGen 300+ system using RediSep Rf Silver[®] Silica Gel Disposable Flash Columns (20–40 microns) or Biotage[®] Sfär Silica Gel Disposable Flash Columns (60 µm). Reverse-phase chromatography was performed on a Biotage IsoleraOne[™] with a Biotage[®] Sfär C18D, 30 g or 60 g cartridge. High Performance Liquid Chromatography was performed on a Teledyne ISCO ACCQPrep[®] HP150 system using Waters XBridge BEH C18 OBD Prep Column (30 mm X 150 mm, 130 Å, 5 µm) with 0.1% ammonium hydroxide buffered water and acetonitrile solutions or RediSep Prep C18 Column (30 mm x 250 mm, 100 Å, 5 µm) with 0.1% formic acid buffered water and acetonitrile solutions. Thin-layer chromatography (TLC) was performed on Silicycle 0.25 mm or Supelco 0.20 mm silica gel F-254 plates. Visualization of the developed chromatogram was performed by PMA, KMnO₄, *p*-anisaldehyde, iodine, or vanillin stains. ¹H and ¹³C NMR spectra were recorded on Bruker Avance

III NMR 500 MHz, NanoBay Avance III HD NMR 400 MHz or Ultrashield NMR 300 MHz instruments, and are internally referenced to the residual proteo-solvent signals (7.26 ppm and 77.16 ppm, respectively, for CDCl₃ and 5.32 ppm and 53.8 ppm, respectively, for CD₂Cl₂). ¹⁹F NMR spectra were recorded on Bruker NanoBay Avance III HD NMR 400 MHz or Bruker Avance III NMR 500 MHz instruments. Data for ¹H is reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, h = hexet, hept = heptet, m = multiplet, b = broad), coupling constant (Hz), and integration. Peaks assigned to minor diastereomers and minor rotamers are specifically marked if an assignment was possible. Data for ¹³C NMR and ¹⁹F NMR are reported in terms of chemical shift, and multiplicity and coupling constant were reported where necessary. Quantitative ¹³C NMR were taken with a relaxation delay of 28 s.

Ultra-Performance liquid chromatography (UPLC) analysis was performed on an Agilent 1200 or Agilent 1290 Infinity II LC system. Infrared (IR) spectroscopy was performed on a Thermo Nicolet 6700 FTIR spectrometer with diamond Smart Orbit ATR accessory, and spectra are reported in wavenumbers (cm⁻¹). High resolution mass spectra (HRMS) were obtained from the Princeton University Mass Spectral Facility on Agilent 6220 ESI-TOF LC/MS or Agilent 7200 GC-QTOF systems.

Photoreaction setup

Lumidox setup

Optimization and most metallaphotoredox mediated ether couplings were performed using a cyan 505 nm Lumidox[®] II 24-Well, 18 mm Spacing LED Array setup, fixed onto a thermal transfer deck allowing for a temperature-controlled reaction. Therefore, the transfer deck as well as the

sample chamber were connected to an external cooling system allowing for a constant temperature of 20 °C during irradiation. A 24-position temperature-controlled reactor (TCR) with temperature transfer cover was used as the sample chamber and set on top of the LED array. A stir rate of 800 rpm on a conventional stir plate was used as default settings as well as 8x3 mm PTFE stir bars with pivot rings to ensure optimal reproducibility and mixing during the irradiation. The optimal LED intensity was determined to be level 2 (4.1 W) for 0.05 mmol scale and level 5 (8.4 W) for 0.25 mmol scale examples.



Figure S1.1. Lumidox[®] II 24-Well setup, side view.



Figure S1.2. Lumidox[®] II 24-Well setup, front view, including Lumidox[®] II Controller.



Figure S1.3. External cooling setup for temperature-controlled irradiation.

Integrated Photoreactor

A selection of metallaphotoredox ether couplings were conducted using a PennOC/PennPhD Integrated Photoreactor (IPR) (2). For these experiments, 505 nm cyan light LED modules were utilized using a M2 photoreactor. The cyan LED module is currently a prototype. A stir rate of 800 rpm, and 2000 rpm fan speed were used as default settings to ensure optimal reproducibility. The optimal LED intensity was determined to be 100% for these examples. In order to allow for a general reaction setup, the irradiation time was set kept constant between lumidox and IPR setup which did not result in diminished yields. When performing reactions according to previously standardized IPR guidelines, each reaction vessel is typically maintained near room temperature for the duration of irradiation.

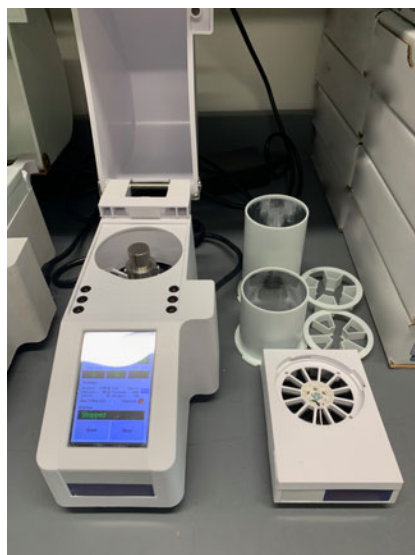


Figure S1.4. Standard Integrated Photoreactor assembly.

2. Reaction Optimization and Control Experiments

Tertiary carboxylic acids

blue light irradiation (450 nm, integrated photoreactor)

Initial reaction screening established the requirement for an inorganic, non-coordinating base and identified 1,2-dichloroethane (DCE) as the optimal solvent. The organic photocatalyst 4CzIPN was identified as suitable for this transformation, providing redox potentials compatible with efficient redox-active ester reduction and catalyst turnover.

During these initial screens, rapid consumption of the unsubstituted parent NHPI redox-active ester was observed without corresponding product formation. This behavior is attributed to its lower reduction potential, which results in accelerated radical generation and a high concentration of alkyl radicals in solution. We hypothesize that this leads to a rate mismatch between radical formation and the subsequent heteroatom S_H2 reaction with the titanium alkoxide. To probe this effect, the influence of NHPI substitution was examined, revealing that a methoxy-substituted redox-active ester consistently provided improved product formation relative to more readily reduced analogues.

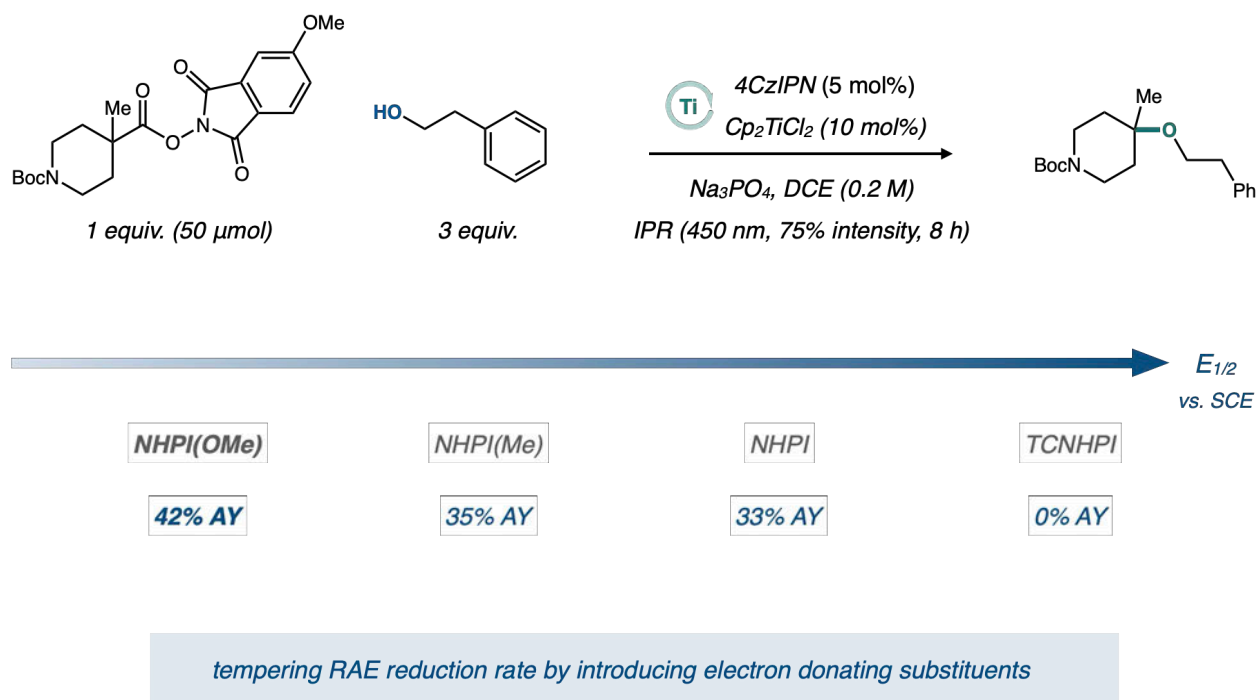


Figure S2.1. Initial reaction conditions and influence of NHPI substitution on reaction outcome.

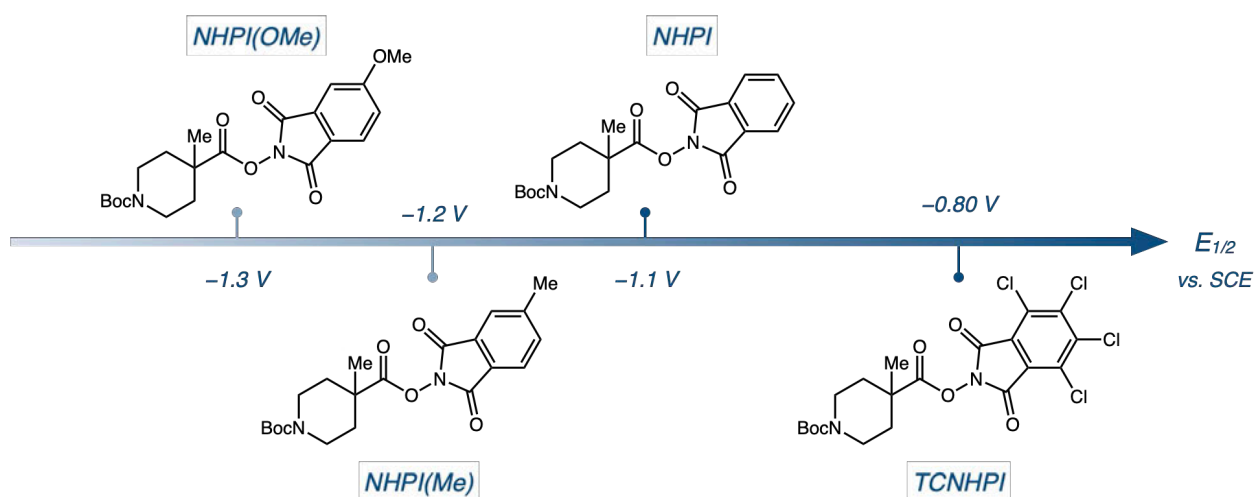


Figure S2.2. Redox potential of tested RAE in acetonitrile. Values are approximated based on literature reports (3).

While product formation was observed in PhCF_3 and EtOAc , the highest yields were obtained using DCE or DCM as the solvent. Other solvents examined either coordinated to the titanium center, thereby inhibiting Ti-alkoxide formation, or participated in competitive hydrogen-atom transfer with the intermediate alkyl radical. Evaluation of mixed-solvent systems and co-solvents in combination with DCE did not result in any further improvement in yield.

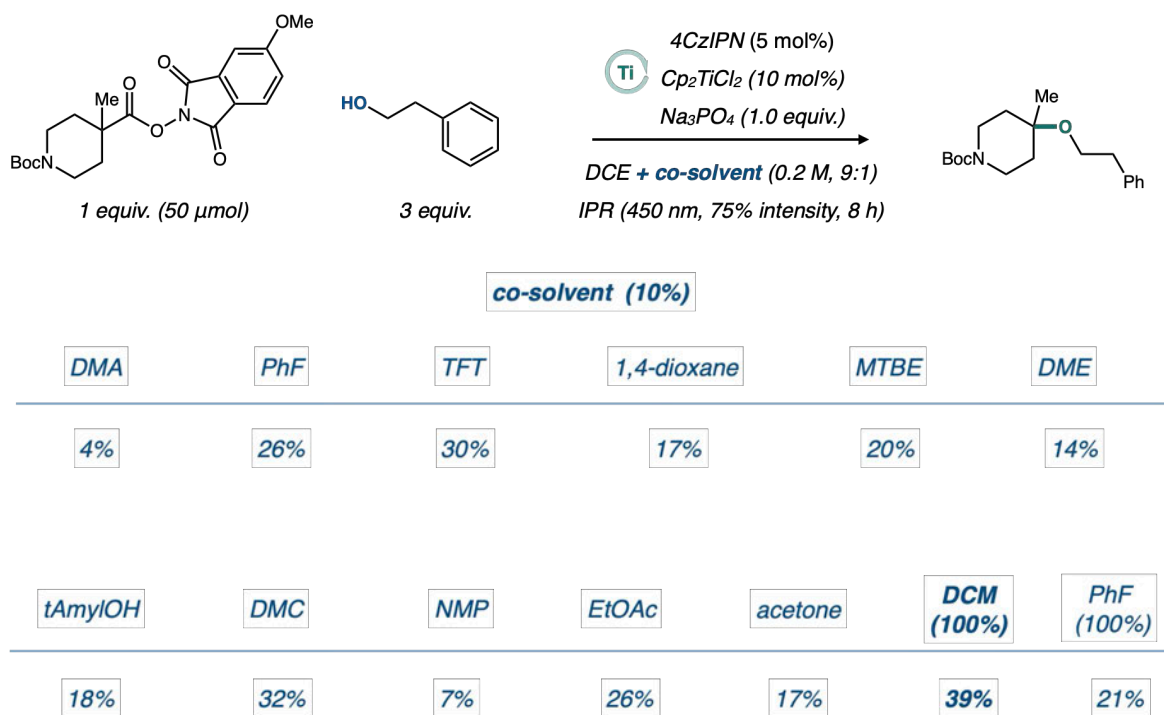


Figure S2.3. Comparison of different solvents and co-solvents

Cp_2TiCl_2 was identified as the optimal titanium catalyst for this transformation, as alternative titanocene analogues failed to deliver comparable product yields. The diminished performance of Cp^* -substituted complexes is attributed to the increased electron density at the titanium center, which facilitates rapid reduction to Ti(III) , potentially leading to an unproductive accumulation of Ti(III) species. In addition, the increased steric and electronic donation of Cp^* ligands are proposed to slow Ti –alkoxide formation, further suppressing productive reactivity.

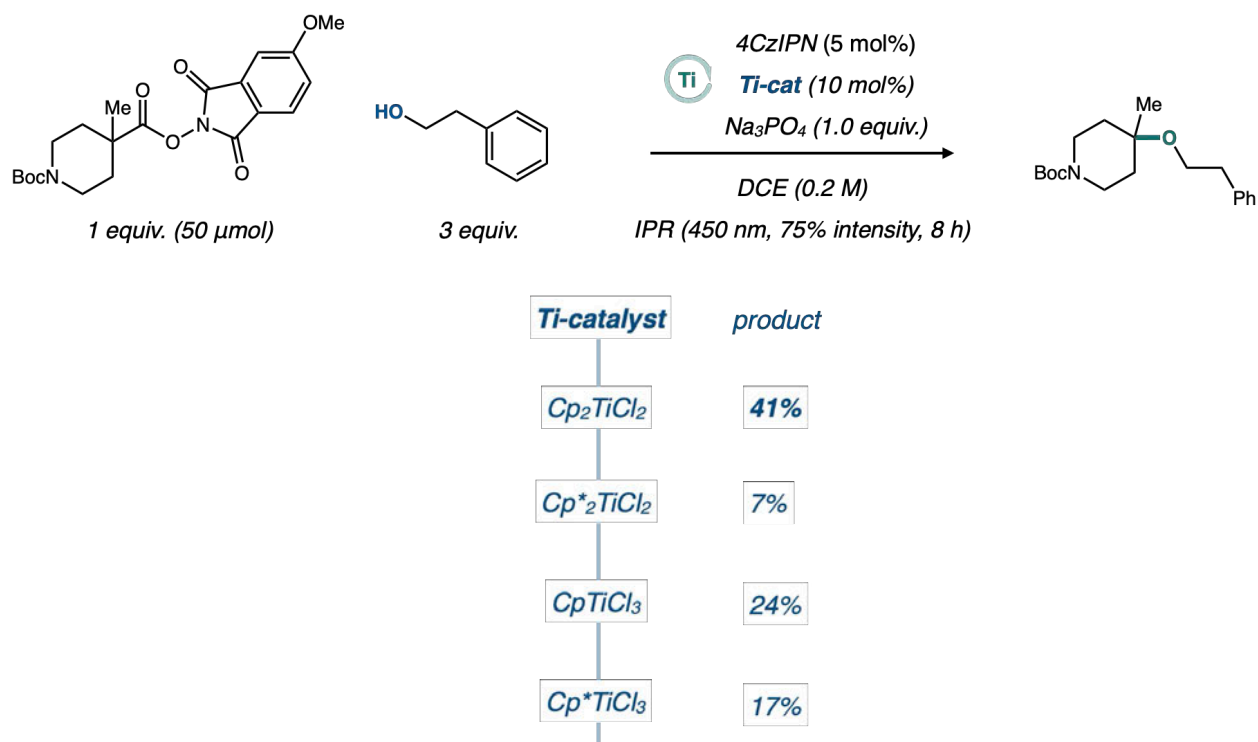
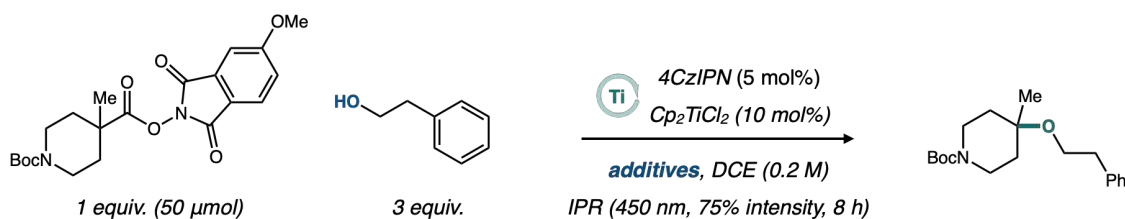


Figure S2.4. Influence of titanocene catalyst on reaction outcome.

Despite moderating the reduction rate of the redox-active ester (RAE) through introduction of a methoxy substituent, substantial consumption of the RAE was still observed without corresponding product formation. We therefore hypothesized that the titanium catalyst, in either its Ti(IV) or Ti(III) oxidation state, may engage the RAE through chelating coordination, enabled by the residual Lewis acidity and pronounced oxophilicity of the titanium center. Such coordination could promote deleterious off-cycle reduction of the RAE, either directly mediated by titanium or facilitated by the reduced photocatalyst through electronic activation of the ester upon metal coordination. On this basis, we reasoned that introduction of a weaker, redox-inactive Lewis acid could competitively disrupt titanium–RAE association while preserving productive reactivity. Accordingly, a range of inorganic bases in combination with mild Lewis acids was evaluated, which identified zinc-containing salts as superior bases relative to Na_3PO_4 . The beneficial effect of zinc salts is attributed to several contributing factors:

- 1) Zinc ions may competitively block coordination of the RAE to the titanium catalyst, thereby enforcing more controlled, photocatalyst-mediated reduction.
- 2) Zinc bases may facilitate formation of the active titanium alkoxide, potentially via initial generation of a zinc alkoxide intermediate followed by rapid alkoxide transfer to titanium.
- 3) Cyclic voltammetry (see below) shows that addition of ZnCl_2 gives rise to a second cathodic wave at more negative potential than the parent RAE (≈ -1.55 vs -1.30 V vs SCE), while the original RAE reduction persists. We assign this new wave to a Zn-coordinated form of the RAE; a ZnCl_2 -only control confirms that although Zn^{2+} contributes a reductive background in this region, the new feature appears as a discrete peak superimposed on it. Coordination thus shifts the RAE reduction to a more negative (more demanding) potential. We propose that ZnCl_2 acts as a redox modulator: because reduction of the coordinated form is more demanding, the Zn–RAE equilibrium gates efficient reduction to the unbound RAE, offering a handle to regulate the concentration of alkyl radicals generated in solution.



base + additives	product	base	product
1 equiv. $\text{Zn}_3(\text{PO}_4)_2$, 5 mg 3 Å Ms	40%	1 equiv. MgCl_2	11%
1 equiv. $\text{Zn}_3(\text{PO}_4)_2$, 5 mg 4 Å Ms	42%	1 equiv. $\text{Mg}(\text{OTf})_2$	21%
1 equiv. Na_3PO_4 , MgCl_2	12%	1 equiv. $\text{Zn}(\text{OTf})_2$	13%
1 equiv. Na_3PO_4 , $\text{Mg}(\text{OTf})_2$	31%	1 equiv. $\text{Sc}(\text{OTf})_3$	0%
1 equiv. Na_3PO_4 , $\text{Zn}(\text{OTf})_2$	20%	1 equiv. Li_3PO_4	20%
1 equiv. Na_3PO_4 , $\text{Sc}(\text{OTf})_3$	0%		
1 equiv. Na_3PO_4 , Li_3PO_4	28%		

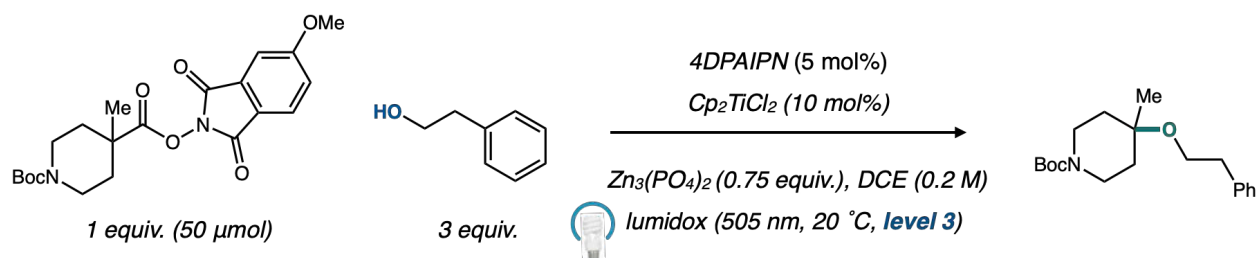
base	product
1 equiv. $\text{Zn}_3(\text{PO}_4)_2$	43%
1 equiv. $\text{ZnCO}_3 \cdot \text{H}_2\text{O}$	55%
1 equiv. $[\text{ZnCO}_3]_2 \cdot [\text{Zn}(\text{OH})_2]_3$	54%
1 equiv. ZnO	38%
1 equiv. MgCO_3	29%
1 equiv. BaCO_3	19%
1 equiv. CaCO_3	16%

Figure S2.5. Influence of Lewis acid additives and bases.

Cyan light irradiation (505 nm, Lumidox photoreactor)

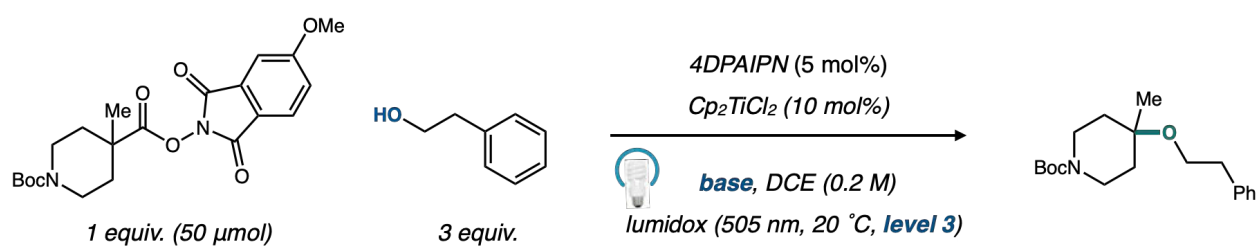
Guided by UV–vis absorption and ligand-to-metal charge transfer (LMCT) studies (see Section 5), the irradiation wavelength was switched to cyan light (505 nm). Under these conditions, all reaction parameters were re-evaluated, and the same trends observed under the initial screening conditions were preserved. Specifically, methoxy-substituted redox-active esters in combination with zinc salts and Cp_2TiCl_2 as the titanium catalyst in DCE consistently delivered the highest product yields.

Owing to the low absorbance of 4CzIPN at 505 nm, the photocatalyst was replaced with 4DPAIPN, which exhibits a less oxidizing yet more reducing redox profile relative to its carbazole analogue (4). Systematic variation of photocatalyst-to-titanium ratios, zinc salt identity and loading, and irradiation intensity revealed that optimal yields could be achieved using either $\text{Zn}_3(\text{PO}_4)_2$ (0.75 equiv) or $[\text{ZnCO}_3]_2 \cdot [\text{Zn}(\text{OH})_2]_3$ (0.5 equiv) in DCE under cyan-light irradiation at level 2 of the Lumidox setup (4.1 W).



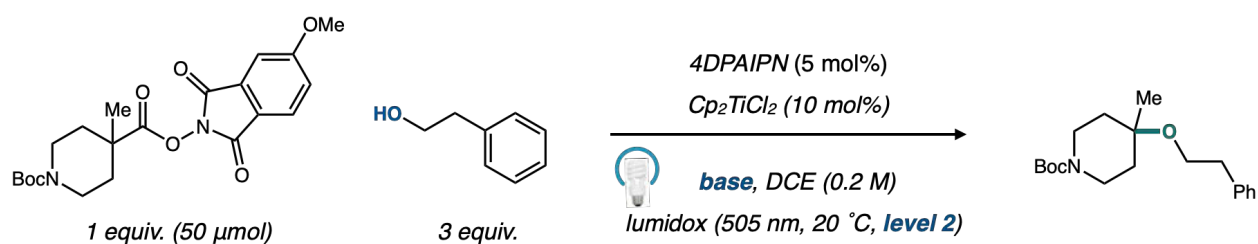
Ti-loading	product	PC loading	product
5% PC, 7.5% Ti	56%	2% PC, 10% Ti	47%
5% PC, 10% Ti	64%	3% PC, 10% Ti	52%
5% PC, 12.5% Ti	61%	4% PC, 10% Ti	60%

Figure S2.6. Optimization of the titanium to photocatalyst ratio.



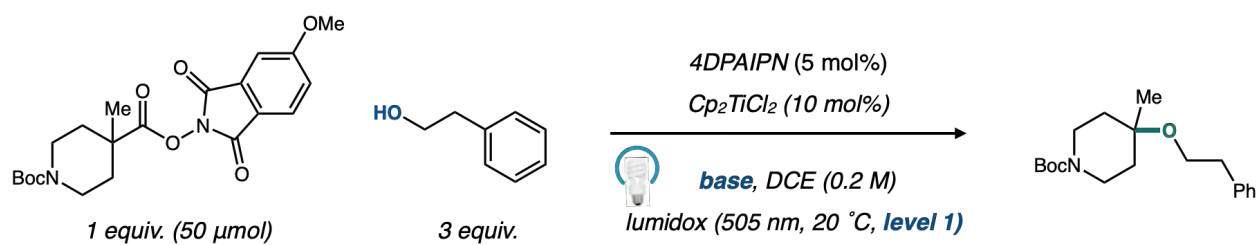
$\text{Zn}_3(\text{PO}_4)_2$	product	$[\text{ZnCO}_3]_2 \cdot [\text{Zn}(\text{OH})_2]_3$	product
1.25 equiv.	64%	1.25 equiv.	74%
1 equiv.	68%	1 equiv.	74%
0.75 equiv.	65%	0.75 equiv.	75%
0.5 equiv.	74%	0.5 equiv.	74%
0.25 equiv.	55%	0.25 equiv.	62%

Figure S2.7. Evaluation of the zinc base and base loading at level 3 in the lumidox setup.



$\text{Zn}_3(\text{PO}_4)_2$	product	$[\text{ZnCO}_3]_2 \cdot [\text{Zn}(\text{OH})_2]_3$	product
1.25 equiv.	74%	1.25 equiv.	61%
1 equiv.	78%	1 equiv.	70%
0.75 equiv.	83%	0.75 equiv.	69%
0.5 equiv.	76%	0.5 equiv.	76%
0.25 equiv.	74%	0.25 equiv.	73%

Figure S2.8. Evaluation of the zinc base and base loading at level 2 in the lumidox setup.



$\text{Zn}_3(\text{PO}_4)_2$	product	$[\text{ZnCO}_3]_2 \cdot [\text{Zn}(\text{OH})_2]_3$	product
1 equiv.	66%	1 equiv.	64%
0.75 equiv.	70%	0.75 equiv.	72%
0.5 equiv.	71%	0.5 equiv.	60%
0.25 equiv.	59%	0.25 equiv.	56%

Figure S2.9. Evaluation of the zinc base and base loading at level 1 in the lumidox setup.

Control experiments

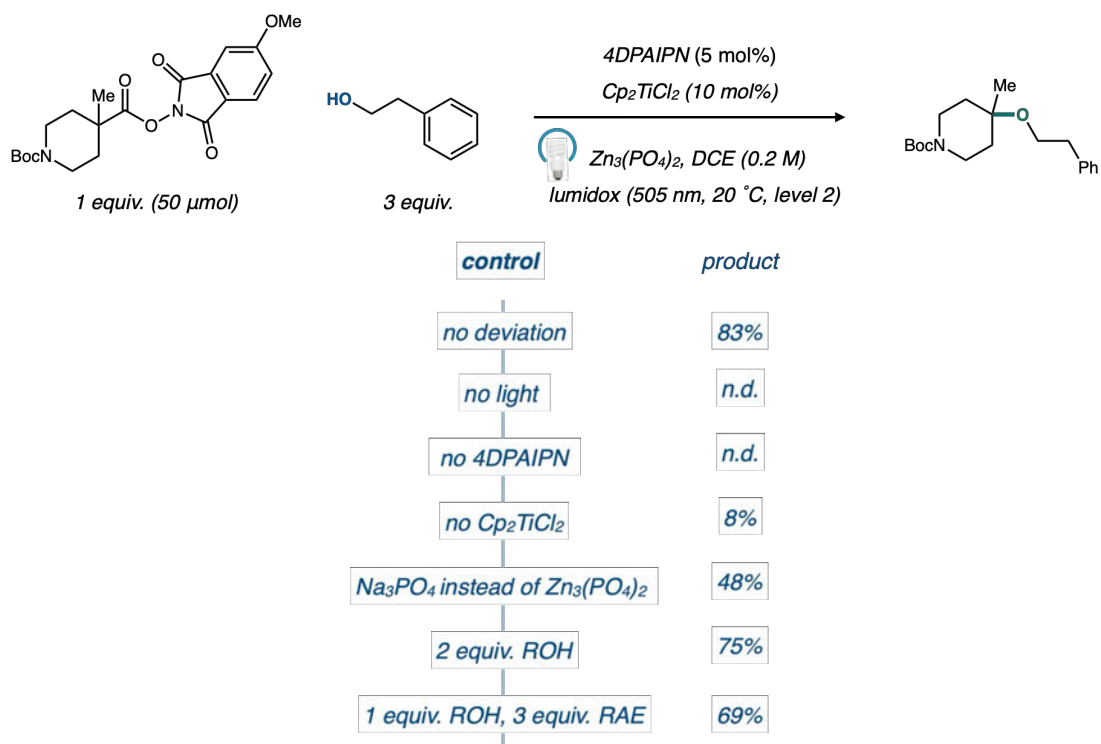
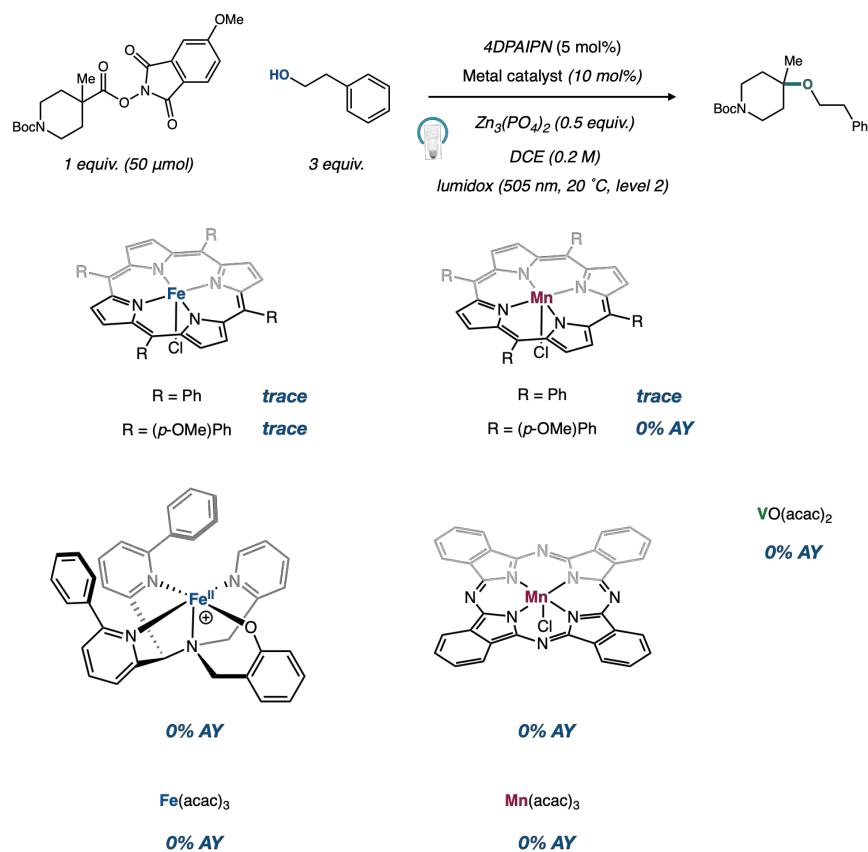


Figure S2.10. Control experiments for the titanium-mediated formation of dialkyl ethers.



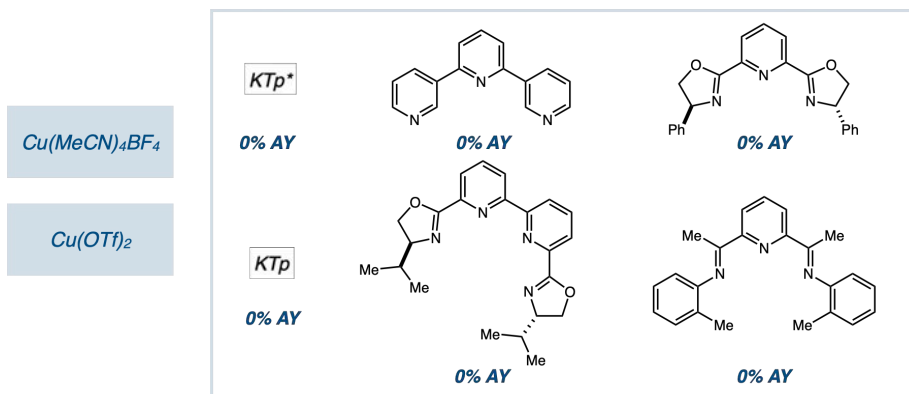


Figure S2.12. Evaluating other metal systems typically used for radical rebound or $\text{S}_{\text{H}}2$.

3. General Procedures

General Procedure A: Synthesis of redox-active esters

According to a literature precedence (5), a round-bottom flask or 40 mL vial was charged with carboxylic acid (1.0 equiv), 2-hydroxy-5-methoxyisoindoline-1,3-dione (1.1 equiv.) and DMAP (0.1 equiv.). Dichloromethane was added (0.15 M) and the mixture was stirred vigorously. *N,N'*-diisopropylcarbodiimide (1.1 equiv.) was then added dropwise and the reaction mixture was allowed to stir until the acid was consumed (usually 2 –12 h). The mixture was filtered through a pad of Celite and rinsed with CH₂Cl₂ (3 x 10 mL). The solvent was removed under reduced pressure, and purification of the resulting residue by column chromatography afforded the desired NHPI(OMe) redox-active ester as colorless to beige solids. In some cases prolonged drying under reduced pressure was necessary to enable crystallization.

General Procedure B: Synthesis of dialkyl ethers

An oven-dried 8 mL vial with 8x3 mm PTFE stir bar with pivot ring (Lumidox setup) or an oven-dried 40 mL vial with a cross-shaped PTFE stir bar (IPR setup) was charged with the corresponding redox-active ester (1.00 or 3.00 equiv.), the corresponding alcohol (if solid; 1.00 or 3.00 equiv.), Zn₃(PO₄)₂ (0.75 equiv.) or [ZnCO₃]₂·[Zn(OH)₂]₃ (0.5 equiv.), 4DPAIPN (5 mol%) and Cp₂TiCl₂ (10 mol%). The vial was capped and dichloroethane (DCE, 0.2 M) was added to the reaction. The corresponding alcohol (if liquid; 1.00 or 3.00 equiv.) was added. To ensure that all soluble compounds are fully dissolved, the vial is sonicated for 5 min and subsequently the suspension is sparged with nitrogen for 1 minute, followed by sparging of the headspace with nitrogen for 5–10 min (for 40 mL vials 10 min of sparging ensure for full exchange of atmosphere). Afterwards, the vial is sealed using molten parafilm and the suspension is sonicated again shortly before being placed in the Lumidox or IPR setup. For the Lumidox setup, the output is set to level 5 (8.4 W) for 0.25 mmol scale and level 2 (4.1 W) for 0.05 mmol scale reactions using 24-reaction 505 nm LED arrays, the temperature of the external cooler is set to 20 °C and the stir rate to 800 rpm. For the IPR setup, a light intensity of 100%, a stir rate of 800 rpm and a fan speed of 2000 rpm is chosen. In both cases, an irradiation time of 20 h for 0.25 mmol scale reactions is chosen (for 0.05 mmol: 14 h).

After the irradiation, the vials were opened to air and mesitylene (0.05 mmol) was added as an internal standard and aliquot (50 μ L) was taken for analysis by NMR or UPLC. The solvent was subsequently removed under reduced pressure and directly subjected to purification.



employed chemicals



dried vials and stir bars

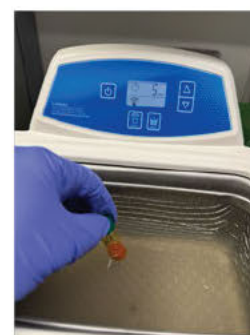
Figure S3.1. Chemicals and vials/stir bars used for ether coupling.



vial charged with solids



addition of solvent



sonication for 5 min



sparging with N₂



parafilm-sealed vial



additional short sonication

Figure S3.2. Setup of the Ti-mediated ether coupling.



*placement of vial
in Lumidox*



*level 5 (8.4 W)
intensity*



20 h irradiation time

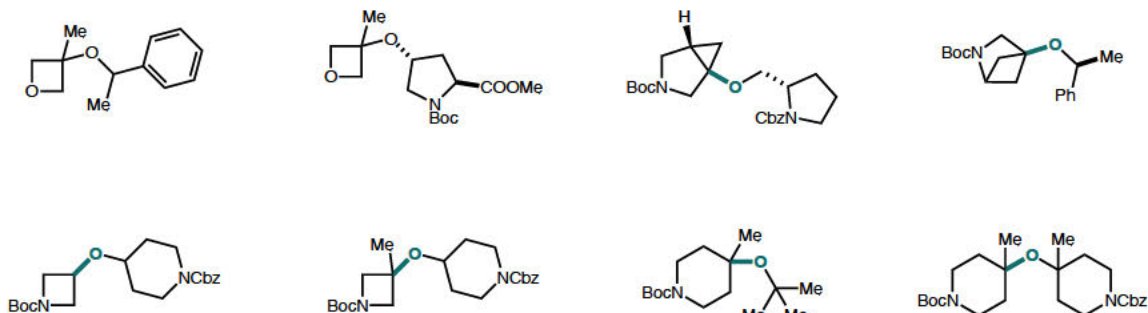


20 °C thermostat

Figure S3.3. Irradiation setup and settings of the Lumidox irradiation platform.

4. Reaction Limitations

— failed (<10% yield) —



— unsatisfactory (<30% yield) —

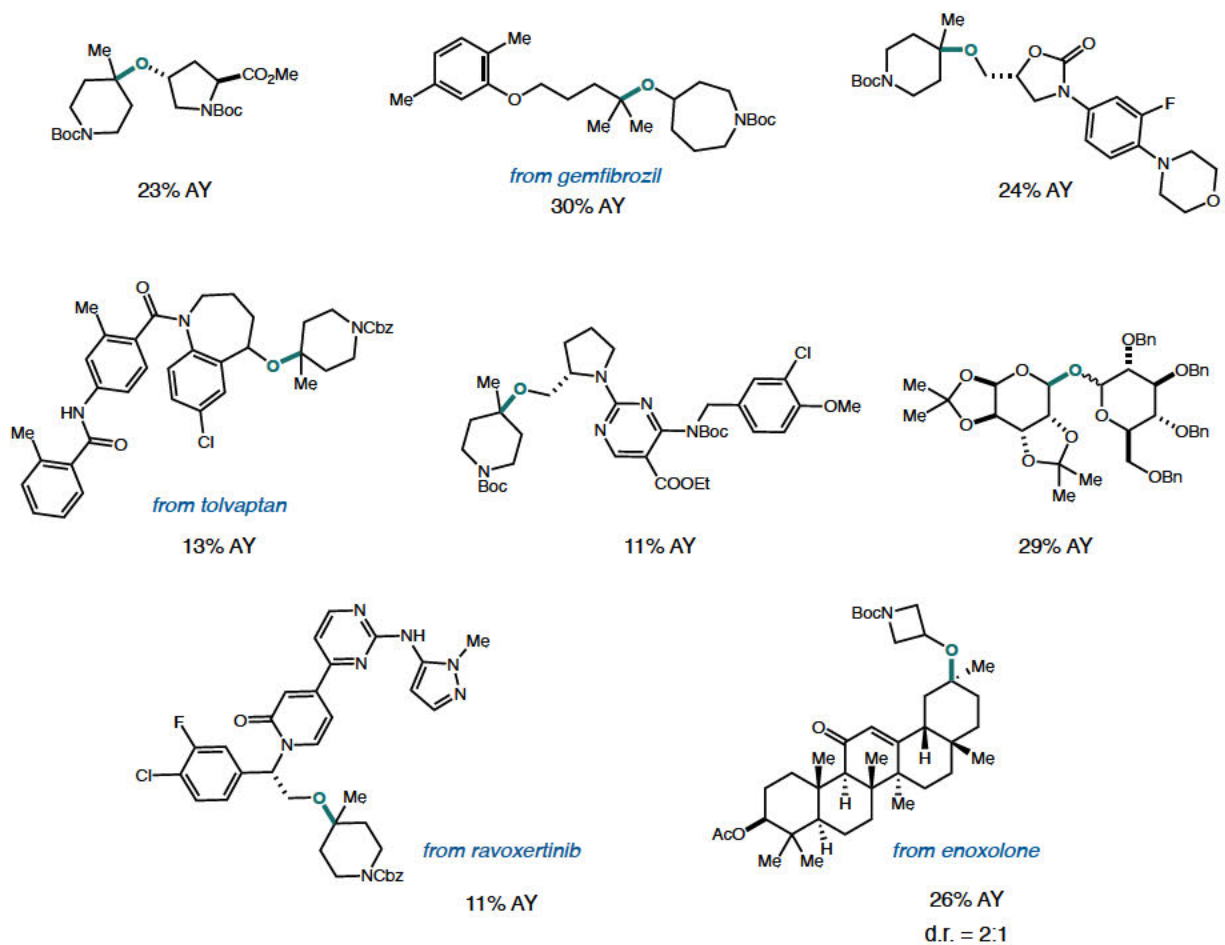


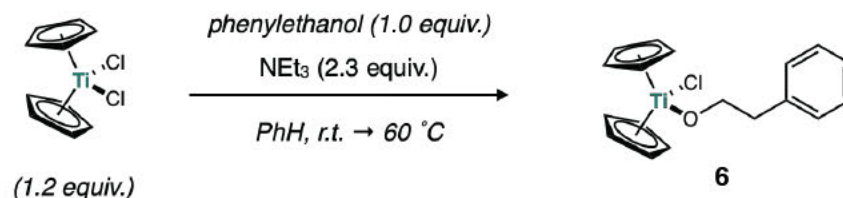
Figure S4.1. Representative examples of scope limitations of the presented ether formation, including failed examples as well as substrates in unsatisfactory yield. Yields given are ¹H-NMR assay yields, performed on 0.05 mmol scale.

Primary alkyl radicals, generated from the corresponding primary redox-active esters, were found to be incompatible with the het-S_H2 platform. Under the standard conditions, none of the desired dialkyl ether product was observed. Instead, the primary radical underwent predominant hydrogen-atom transfer to give the defunctionalized alkane as the major fate of the radical intermediate. This outcome is consistent with the proposed het-S_H2 mechanism: efficient C–O bond formation requires a sufficiently nucleophilic, persistent radical to engage the titanium alkoxide, whereas the comparatively unstabilized primary radical is intercepted by competing HAT before productive substitution can occur. An analogous limitation is well documented in C–C S_H2 chemistry, where primary radicals likewise do not serve as the attacking partner (6).

A set of limitations was identified during substrate evaluation. Epoxides and oxetanes were incompatible, as these strained heterocycles are readily opened by the intermediate Ti(III) species, consistent with prior reports of titanocene-mediated reductive ring opening (7, 8). In addition, alkyl radicals with low nucleophilicity do not participate productively in the coupling step, including highly strained radicals and azetidine-derived radicals. Tertiary alcohols exhibiting substantial steric bulk are likewise unreactive, as congestion around the oxygen atom hinders the required trajectory of the incoming alkyl radical; notably, bicyclo[1.1.1]pentyl (BCP) alcohols remain compatible, presumably due to their compact geometry despite formal tertiary substitution. Practical constraints were also observed for alcohol substrates with poor solubility in DCM or DCE, which generally resulted in diminished yields. Finally, substrates containing tertiary amines or other highly electron-rich functionalities may undergo competitive oxidation by the excited-state photocatalyst, becoming preferred quenching partners for photocatalyst turnover when the steady-state concentration of Ti(III) is low.

5. UV-vis Data

5.1 Ti-Alkoxide (6) Formation



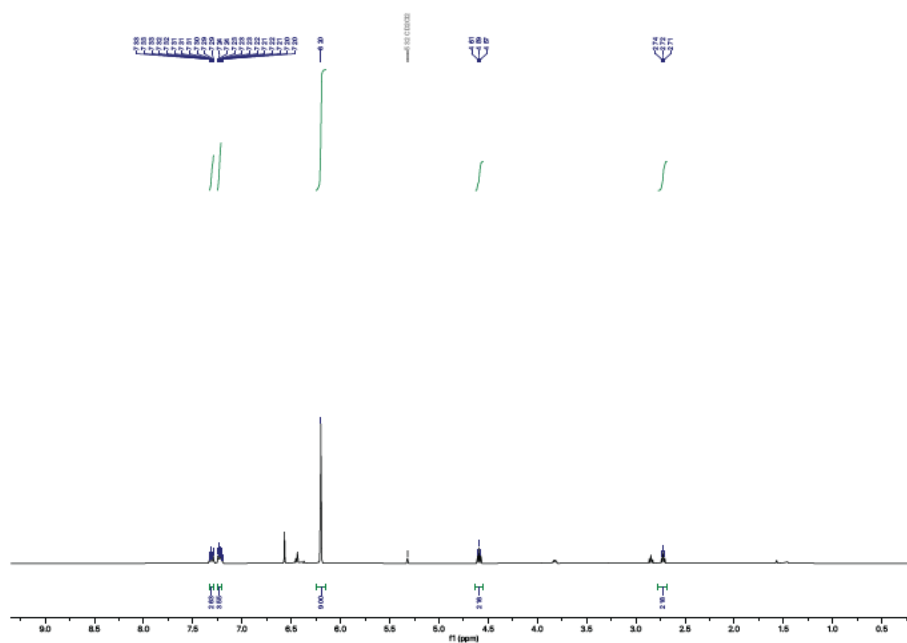
To an oven-dried 4 mL vial equipped with a magnetic stir bar were added Cp_2TiCl_2 (124 mg, 0.5 mmol, 1.2 equiv) and benzene (10 mL). Et_3N (124 μL , 0.895 mmol, 2.15 equiv) was added, and the resulting mixture was heated at 60 °C for 1 h. This solution was then treated with 2-phenylethanol (50.9 mg, 0.417 mmol, 1.0 equiv) in benzene (1 mL). The reaction mixture was heated at 60 °C for an additional 1 h, after which heating was discontinued, and the mixture was stirred at room temperature for 16 h. The mixture was subsequently filtered through a syringe filter and the solvent was removed under reduced pressure. The residue was washed with cold hexane (3x 1mL) and the residue was extracted with cold diethyl ether (3x 1mL). The ether phase was concentrated in vacuo to afford the desired compound as an orange-red solid. UV–Vis absorption spectra were acquired in DCE using a 1 mm cuvette under air.

^1H NMR (400 MHz, CD_2Cl_2) δ 7.35 – 7.27 (m, 2H), 7.27 – 7.18 (m, 3H), 6.57 (s, 2H), 6.20 (s, 7H), 4.59 (t, $J = 6.5$ Hz, 2H), 2.72 (t, $J = 6.5$ Hz, 2H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ 140.27, 129.50, 128.83, 126.68, 120.63, 116.78, 83.55, 39.84.

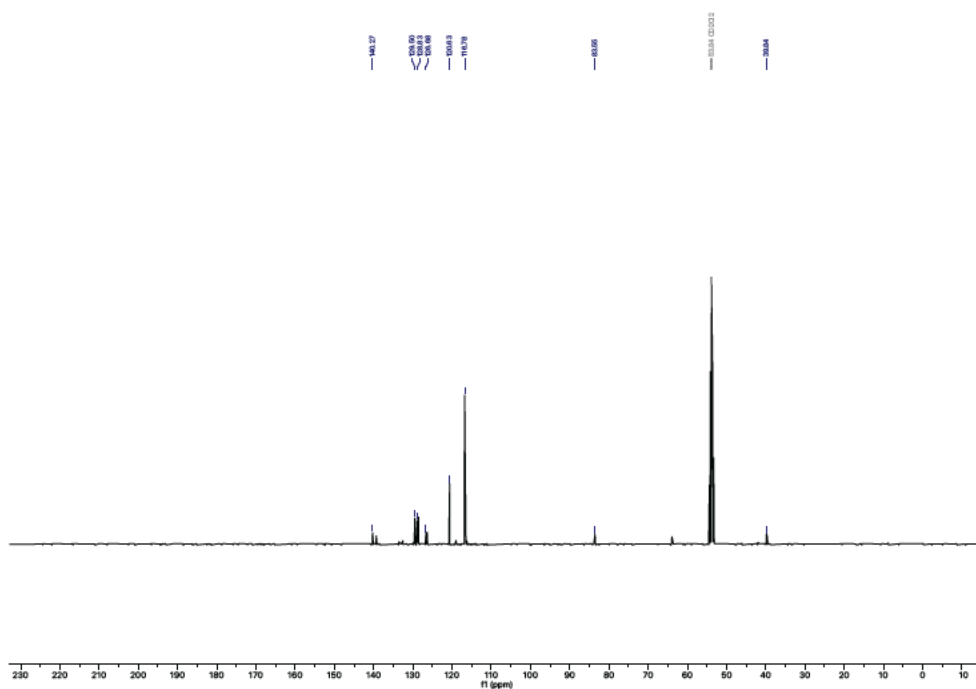
HRMS (ESI-TOF) m/z calcd. for $\text{C}_{18}\text{H}_{19}\text{OTi} [\text{M}-\text{Cl}]^+$ 299.09153; found: 299.09148.

¹H NMR (500 MHz, CD₂Cl₂) of Ti-alkoxide 6



The additional peaks stem from residual 2-phenylethanol (peaks at 2.85 and 3.82 ppm), formed due to slow hydrolysis of the Ti-alkoxide in the NMR solvent.

^{13}C NMR (101 MHz, CD_2Cl_2) of Ti-alkoxide 6



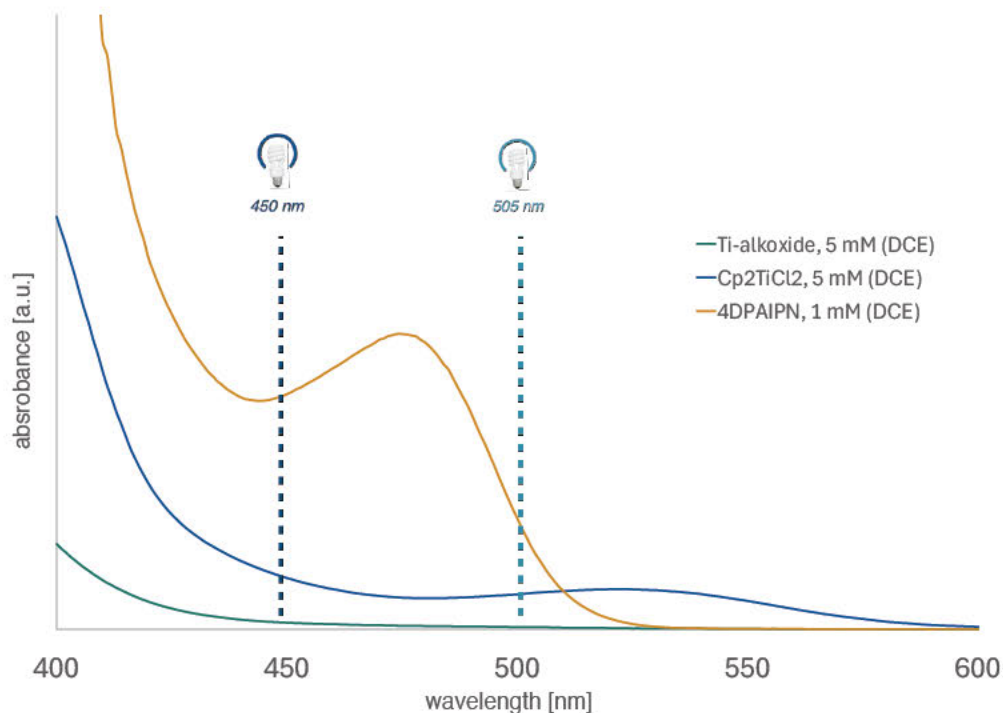
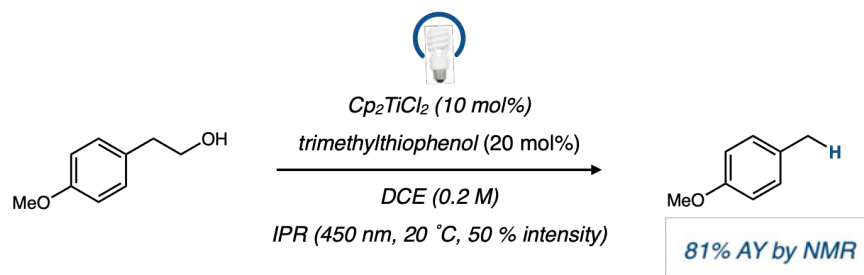


Figure S5.1. UV-vis spectra of 4DPAIPN, $\text{Cp}_2\text{Ti(IV)Cl}_2$ and Ti-alkoxide **6** in DCE.

5.2 LMCT Investigations

According to literature (9), in an oven dried 8 mL vial equipped with a stir bar, 2-(4-methoxyphenyl)ethanol (38.1 mg, 0.25 mmol, 1.00 equiv.) and Cp_2TiCl_2 (6.22 mg, 25 μmol , 10 mol%) are added followed by DCE (1.25 mL, 0.2 M). The reaction is degassed by bubbling N_2 through the solution for 5 min before 2,4,6-trimethylthiophenol (7.61 mg, 50 μmol , 20 mol%) is added via microsyringe. The vials are sealed with melted parafilm and placed in the M2 integrated photoreactor either using a 450 nm or 505 nm plate with 50% light intensity, as stir rate of 800 rpm and lowest fan speed. After 8 h of irradiation, the vials are opened to air and mesitylene (50 μmol) is added as an internal standard. Subsequently, 50 μL of the reaction solution is taken as an aliquot for $^1\text{H-NMR}$ analysis.

blue light (450 nm):



cyan light (505 nm):

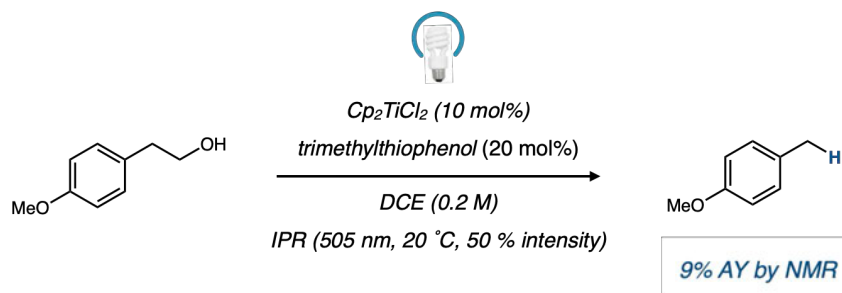


Figure S5.2. Preparative experiments for probing occurring LMCT events under different light irradiation.

Upon irradiation with blue light, the defunctionalized product was observed in 81% assay yield by NMR analysis. This outcome is attributed to ligand-to-metal charge transfer (LMCT) pathways that generate alkoxy radical intermediates, which rapidly undergo β -scission to release formaldehyde and the corresponding benzylic radical.

In contrast, irradiation with cyan light resulted in only trace formation of the scission product, concomitant with a substantially higher yield of the desired ether. This observation is consistent with suppression of LMCT-driven pathways under these conditions and supports the conclusion that both LMCT side reactivity and elevated concentrations of Ti(III) are deleterious to productive catalysis. Moreover, owing to the significantly higher extinction coefficient of 4DPAIPN at 505 nm relative to the titanium alkoxide, excitation of the titanium species is expected to be strongly disfavored, thereby effectively suppressing LMCT-mediated side reactivity.

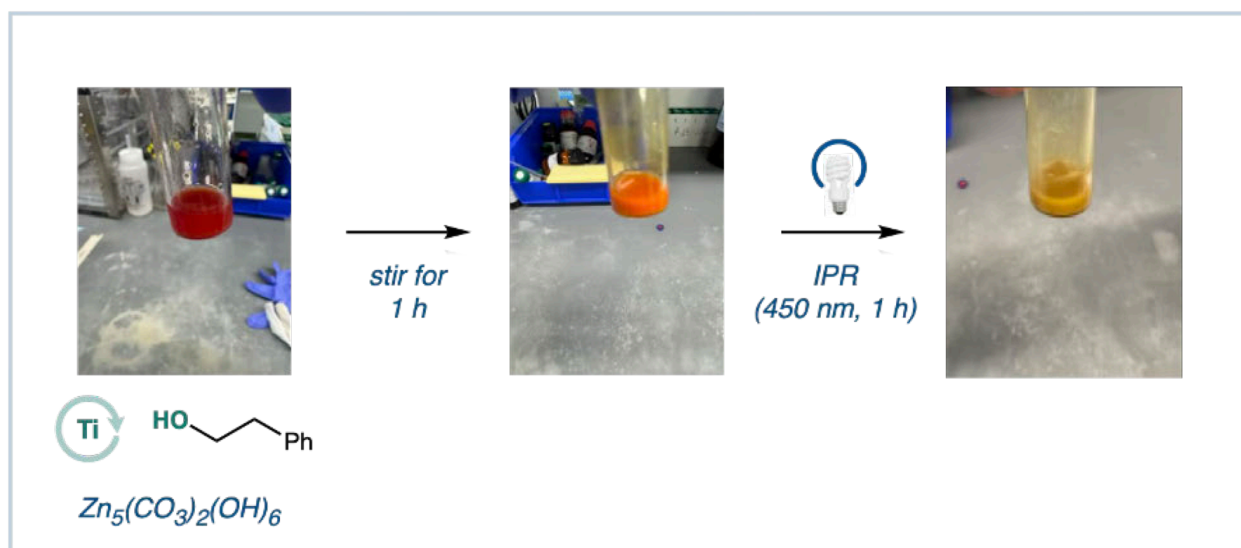


Figure S5.3. Phenotypic analysis of a mixture of Cp_2TiCl_2 , 2-phenylethanol and Zn-base in DCE before and after irradiation with blue (450 nm) light.

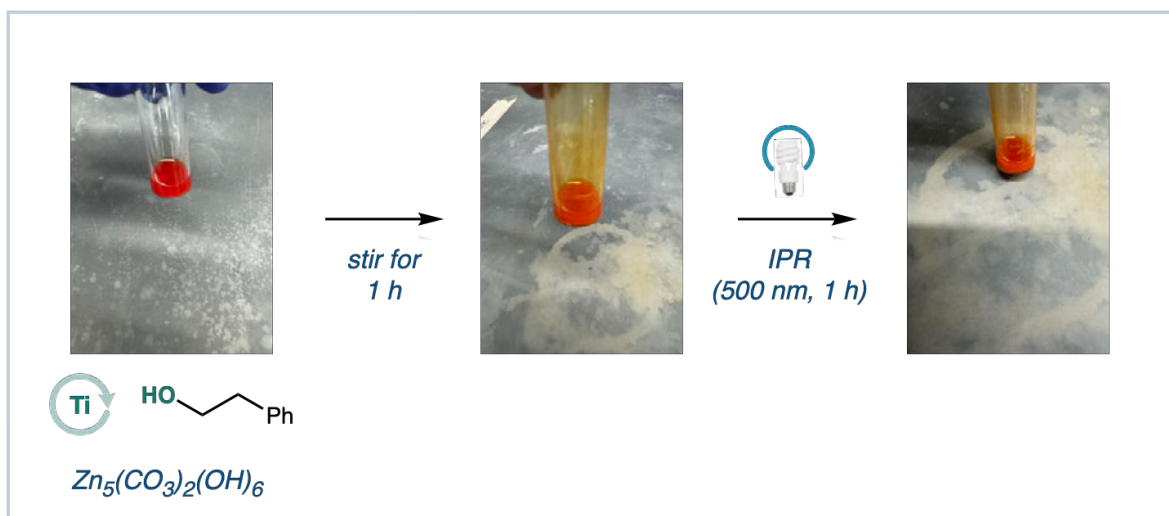


Figure S5.4. Phenotypic analysis of a mixture of Cp_2TiCl_2 , 2-phenylethanol and Zn-base in DCE before and after irradiation with cyan (505 nm) light.

Cp_2TiCl_2 (12.4 mg, 0.050 mmol, 1.0 equiv), 2-phenylethanol (6 μL , 0.050 mmol, 1.0 equiv), and zinc carbonate (13.8 mg, ca. 0.025 mmol, 0.5 equiv) were combined and dissolved in 1,2-dichloroethane (0.50 mL), affording an initially bright red solution characteristic of Cp_2TiCl_2 (Figure S1). After stirring at room temperature for 1 h, the solution gradually turned bright orange, consistent with the formation of a titanium alkoxide species. The resulting solution was irradiated with blue light (450 nm, IPR, 100% intensity) or cyan light (505 nm, IPR, 100% intensity) for 1 h. Upon completion of irradiation, the reaction mixture adopted a dull yellow color in the case of

blue light irradiation, consistent with decomposition of the titanium alkoxide species, presumably via a ligand-to-metal charge transfer (LMCT) pathway, but basically unchanged in the case of cyan light.

6. Stern-Volmer Quenching

Steady-state emission quenching studies were performed using an Agilent Cary Eclipse Fluorescence Spectrophotometer. In each experiment, the photocatalyst and varying amount of quencher were dispensed in the glovebox and combined in DCE in screw-top 10.0 mm optical glass cuvettes. DCE was degassed separately outside the glovebox by vigorously sparging with nitrogen for 30 minutes.

For emission quenching of the 4DPAIPN photocatalyst, a 10 μM stock solution was prepared with the desired quencher concentration, the solution was irradiated at $\lambda_{\text{ex}} = 450 \text{ nm}$, and the emission intensity was observed at $\lambda_{\text{em}} = 532 \text{ nm}$ (slit: 5 mm; emission measured from 500 – 650 nm). Sample absorbance at the wavelength of photoexcitation and emission measurement was never above 0.1 OD to avoid inner filter effects (IFE) and ensure single photon emission behavior (10). Linear least squares regression analysis was performed, and the data were modeled according to the Stern–Volmer equation:

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

where I_0 is the emission intensity without quencher present, I is the emission intensity with a quenching concentration $[Q]$, τ_0 is the excited state lifetime of 4DPAIPN in DCE and k_q is the rate constant for excited state quenching. While the excited state lifetime τ_0 is not reported in the literature for the solvent mixture and photocatalyst used in this experiment, calculation of the Stern-Volmer quenching constant $K_{\text{sq}} = k_q \tau_0$ permits the determination of relative rates of quenching by different species.

The Ti(III) quencher solution was freshly prepared in the glovebox by adding 3 equiv. of Zn to a solution of $\text{Cp}_2\text{Ti(IV)Cl}_2$ in DCE at room temperature, followed by stirring for 30 min and subsequent filtration through a syringe filter. The resulting emerald green solution was immediately used in the measurement.

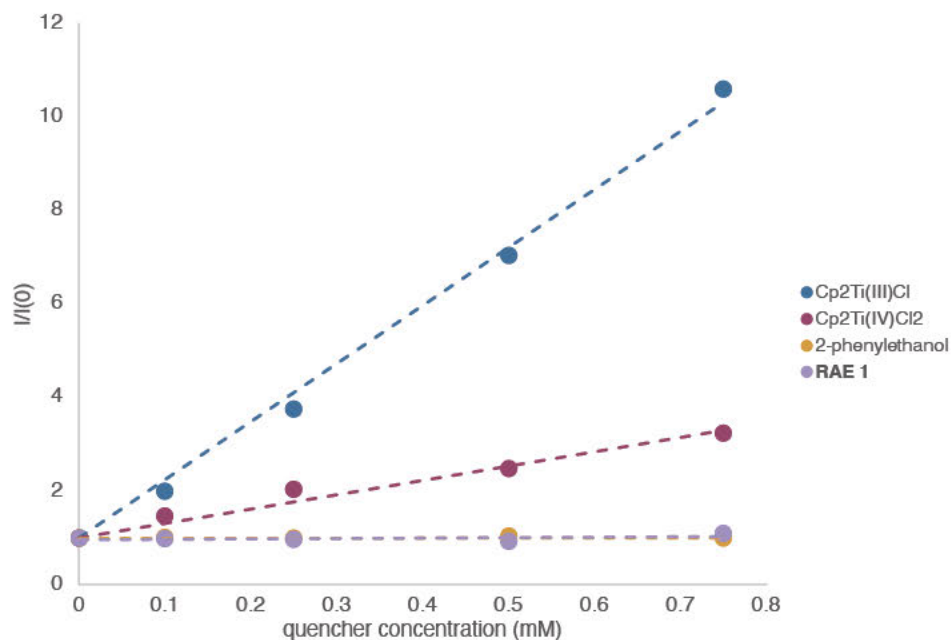


Figure S6.1. Emission quenching of 4DPAIPN by Cp₂Ti(III)Cl, Cp₂Ti(IV)Cl₂, 2-phenylethanol and RAE1 in DCE.

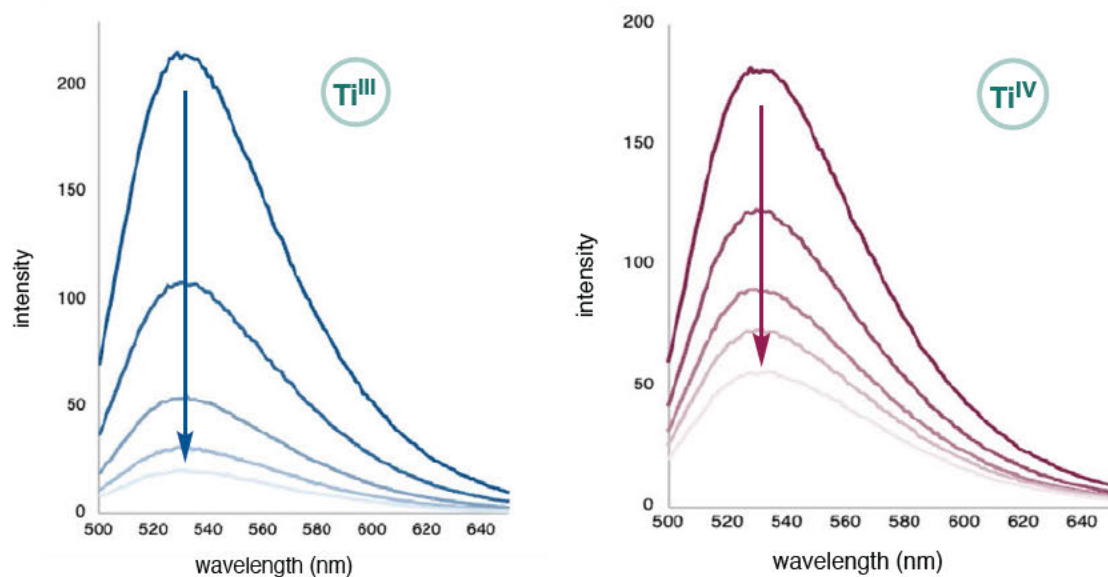


Figure S6.2. Comparison of emission quenching of 4DPAIPN by Cp₂Ti(III)Cl and Cp₂Ti(IV)Cl₂ in DCE.

7. Cyclic Voltammetry Measurement

Cyclic voltammetry (CV) was performed using a CHI (model 600E) electrochemical analyzer/workstation. A three-electrode setup was used, consisting of a glassy carbon working electrode, Pt wire counter electrode, and a saturated calomel (SCE) reference electrode. Data was acquired in DCE, with a scan rate of 100 mV/s, in the presence of tetrabutylammonium hexafluorophosphate electrolyte (1 M), and reported in reference to SCE. The samples were sparged with N₂ for at least 15 minutes prior to data collection.

ZnCl₂ was employed as a soluble proxy for the sparingly soluble zinc bases used in the preparative photoreaction. This choice is justified by the preparative chemistry: the photoreaction proceeds in 69% yield when ZnCl₂ is used as the Lewis acid in combination with Na₃PO₄. ZnCl₂ therefore reproduces the relevant Lewis-acid activation while remaining soluble in the electrolyte, allowing its effect on the redox behavior of the analytes to be probed directly by CV.

Redox-active ester (RAE) titrated with ZnCl₂

CVs of **14** (RAE-OMe) (1 mM) were recorded with 0, 0.25, 0.5, 1, and 2 equiv of ZnCl₂. A ZnCl₂-only solution (no RAE) was recorded as a control under identical conditions.

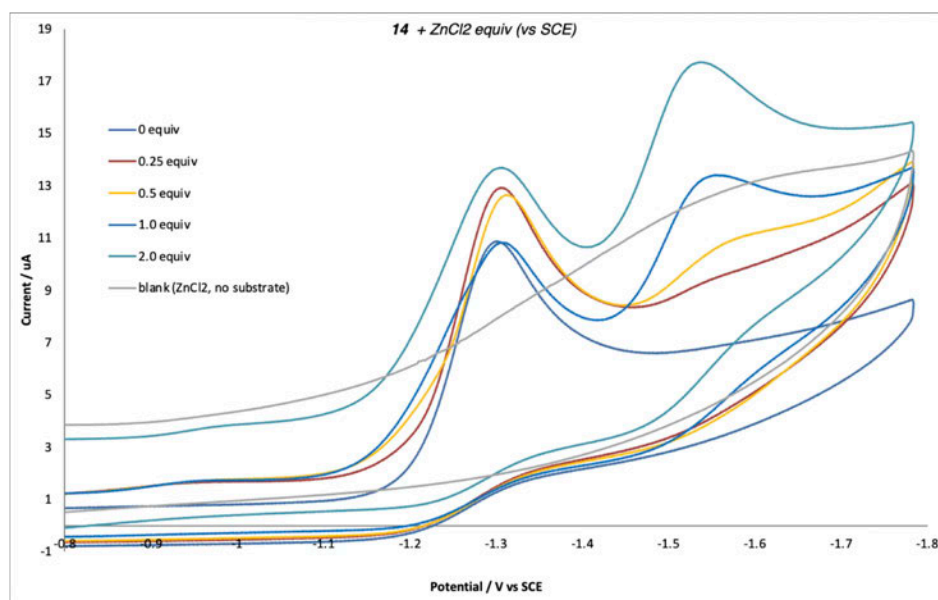


Figure S7.1. Forward (cathodic) CV branches of the RAE (1 mM) with 0–2 equiv ZnCl₂ in 1 M TBAPF₆/DCE and a ZnCl₂-only control (grey). The free-RAE reduction stays fixed at -1.31 V; a new Zn-bound-RAE wave grows in at ≈ -1.54 V. Potentials vs SCE.

The RAE shows a cathodic reduction at -1.31 V vs SCE. This peak remains at essentially the same potential (-1.30 to -1.31 V) across the whole $0 \rightarrow 2$ equiv range — the free-RAE reduction is not shifted by ZnCl_2 .

On addition of ZnCl_2 , a second, more negative cathodic wave grows in at ≈ -1.54 V vs SCE. This feature is resolved as a distinct peak at ≥ 1 equiv of ZnCl_2 . Its current increases with added ZnCl_2 .

The ZnCl_2 -only control (grey) shows a featureless rising reductive background in this window (no discrete peak). The new wave in the RAE + ZnCl_2 traces appears as a discrete peak superimposed on that background, which is the basis for assigning it to a genuine new redox-active species rather than to free ZnCl_2 reduction.

The persistence of the free-RAE peak at -1.31 V vs SCE together with the emergence of a separate peak at -1.54 V vs SCE is consistent with a distinct second species in slow-exchange equilibrium, assigned to a Zn-coordinated form of the RAE. Coordination shifts the reduction to a more negative (thermodynamically more demanding) potential ($\Delta \approx 0.24$ V). We propose that ZnCl_2 thereby acts as a redox modulator: because reduction of the coordinated form is more demanding, respectively on the thermodynamic edge when compared to the redox potential of the reduced photocatalyst [$E^{\text{Red}}(4\text{DPAIPN}/4\text{DPAIPN}^{\bullet-}) = -1.52$ V vs SCE], the Zn-RAE equilibrium gates efficient reduction toward the unbound RAE, offering a handle on the rate of alkyl-radical generation. We note that the free-RAE peak current does not visibly deplete over this range; the CV evidences a new, more-demanding reduction pathway rather than quantitative sequestration of the free ester.

Ti-alkoxide 6 titrated with ZnCl_2

CVs of *Ti-alkoxide 6* (1 mM) were recorded with 0, 0.25, 0.5, 1, and 2 equiv of ZnCl_2 . Cp_2TiCl_2 was recorded separately as a reference for the Ti(IV)/Ti(III) couple.

Cp_2TiCl_2 shows a well-defined Ti(IV)/Ti(III) couple with $E_{1/2} = -0.76$ V vs SCE ($E_{\text{pc}} = -0.80$ V, $E_{\text{pa}} = -0.73$ V, $\Delta E_{\text{p}} = 67$ mV).

Ti-alkoxide 6 shows a non-reversible reduction at -0.75 V vs SCE, as the alkoxide is not reformed upon reoxidation but rather extruded as the alkoxide. As ZnCl_2 is added, the wave sharpens into a defined reduction peak and moves to more positive (anodic) potential, approaching the Cp_2TiCl_2 reference position ($E_{\text{pc}} \approx -0.75$ to -0.77 V at 1–2 equiv). The peak current grows monotonically ($\approx 2 \rightarrow 7$ μA over $0 \rightarrow 2$ equiv).

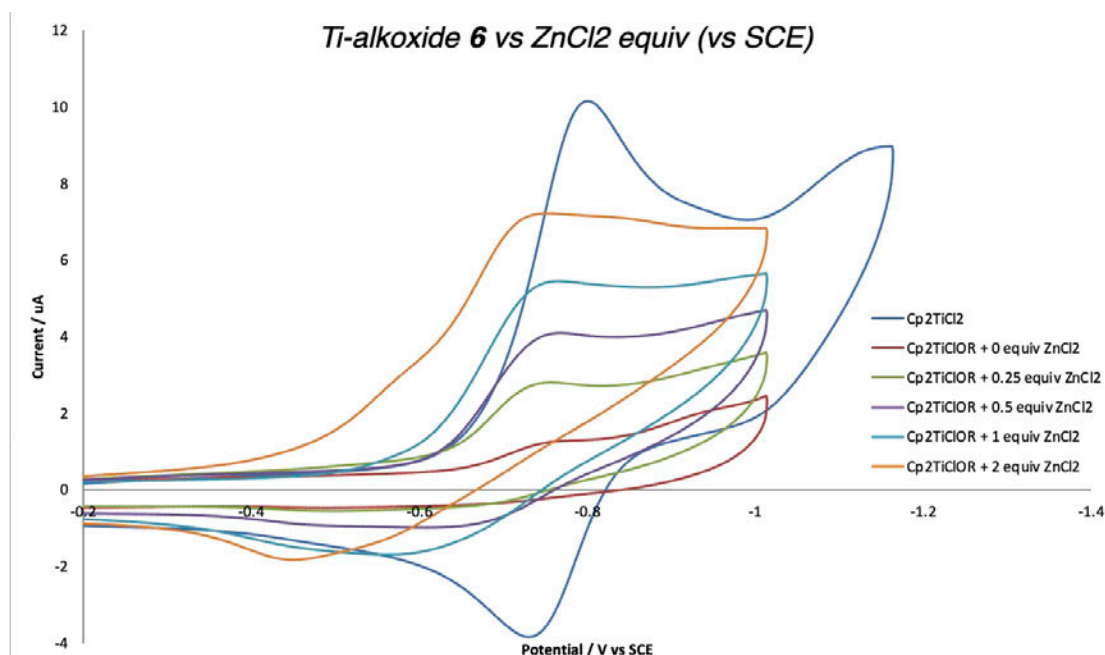


Figure S7.2. Forward (cathodic) CV branches of Ti-alkoxide **6** (1 mM) with 0–2 equiv ZnCl_2 , and a Cp_2TiCl_2 reference (blue). Potentials vs SCE.

In contrast to the RAE, ZnCl_2 shifts the Ti-alkoxide reduction anodic, making the species marginally easier to reduce. Moreover, the redox event becomes more reversible, consistent with either accelerated regeneration of the Ti(IV) alkoxide upon reoxidation or stabilization of the reduced Ti(III) alkoxide species by zinc coordination.

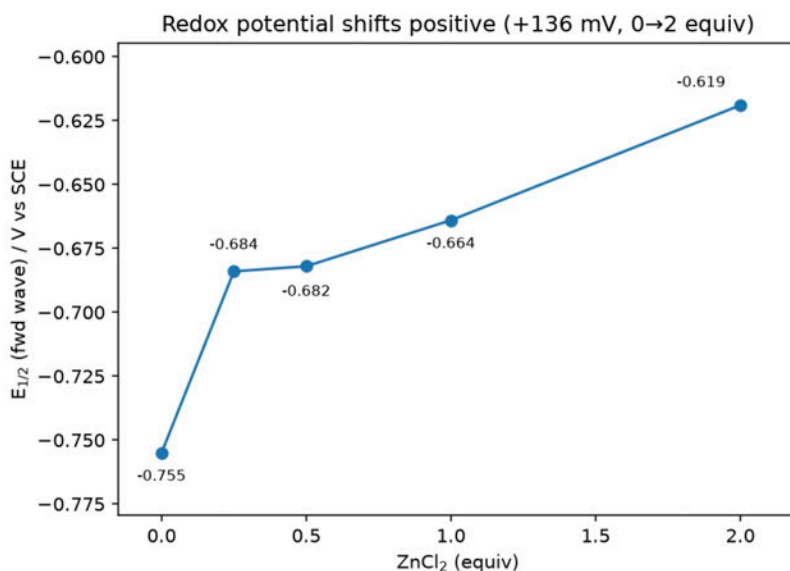


Figure S7.3. Anodic shift of the redox potential of Ti-alkoxide **6** upon ZnCl_2 addition.

8. Mechanistic Studies on the Heteroatom Homolytic Substitution

8.1 Alcohol Competition Experiment

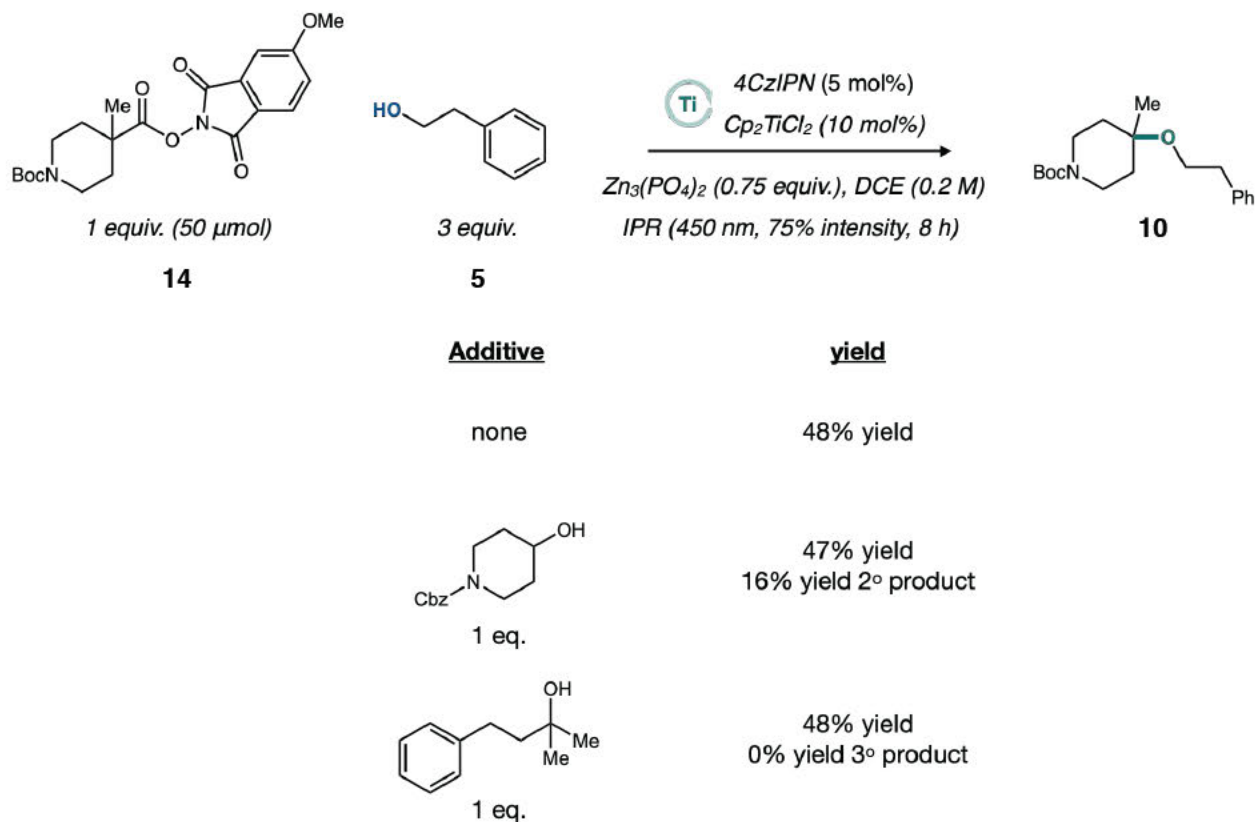


Figure S8.1. Intermolecular competition experiment under blue light irradiation (450 nm).

To probe the relative reactivity of primary, secondary, and tertiary alcohols, a series of intermolecular competition experiments was conducted. Under unoptimized conditions (blue light irradiation, zinc phosphate as base), a model reaction was performed in the presence of 1.0 equiv of either a secondary or a tertiary alcohol as a competing nucleophile.

In the case of the secondary alcohol, a substantial amount of the ether derived from secondary alcohol coupling was observed, indicating only minimal intrinsic selectivity for the primary over the secondary alcohol under these conditions. Notably, under optimized conditions, preferential coupling of the primary alcohol is achieved in a modest 1.8:1 ratio (see substrate **75** in the main text).

In contrast, when 1.0 equiv of a tertiary alcohol was added, exclusive formation of the primary alcohol-derived ether was observed. No detectable coupling of the tertiary alcohol occurred, demonstrating complete selectivity for primary over tertiary alcohols. This trend is consistent with the product ratios observed for substrate **76** in the optimized reaction scope.

8.2 Influence on Diastereomeric Ratio

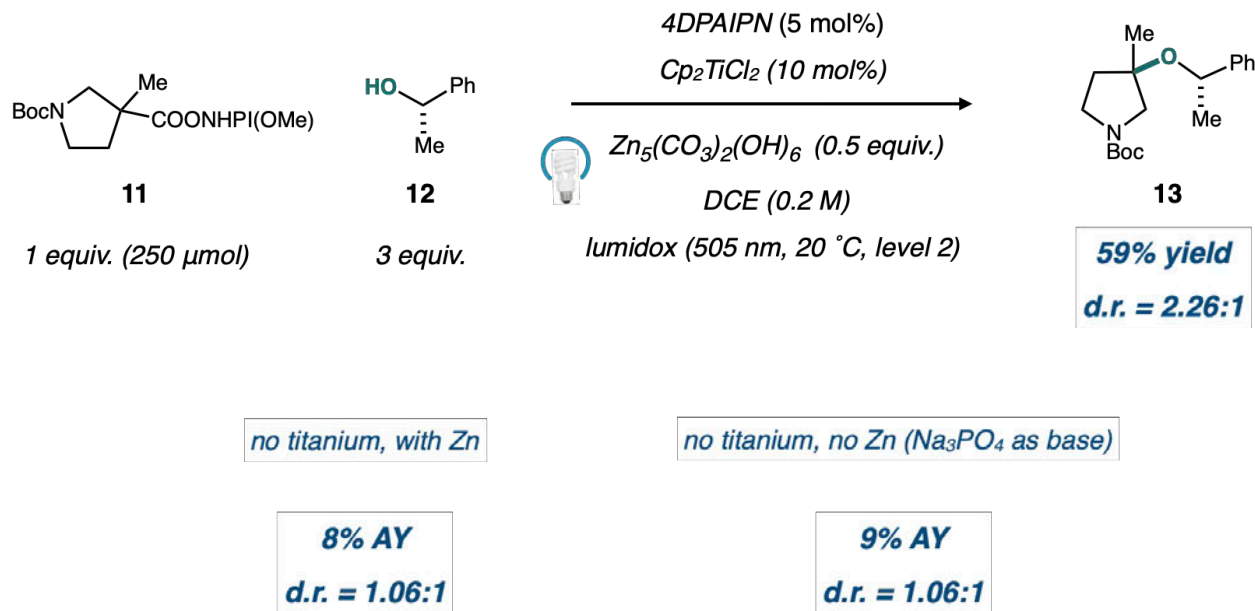


Figure S8.2. Influence of the titanium catalyst on the observed diastereomeric ratio.

Prepared according to the general procedure B with redox-active ester **11** (101 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μ mol, 5 mol%), Cp_2TiCl_2 (6.22 mg, 25.0 μ mol, 10 mol%), $[\text{ZnCO}_3]_2 \cdot [\text{Zn}(\text{OH})_2]_3$ (68.6 mg, 125 μ mol, 0.5 equiv.), (S)-1-phenylethanol (**12**, 91.6 μ L, 750 μ mol, 3.00 equiv.), in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the lumidox setup, the solvent was removed under reduced pressure. An aliquot was taken for analysis by UPLC to determine the crude diastereomeric ratio. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 15% to 100% EtOAc in hexanes. The fractions containing product were concentrated and further purified by preparative HPLC (RediSep C18 column, 25% to 80% MeCN in H_2O with 0.1% NH_4OH) to provide the product as a colorless oil (45.3 mg, 148 μ mol, 59% yield, d.r. = 2.2:1).

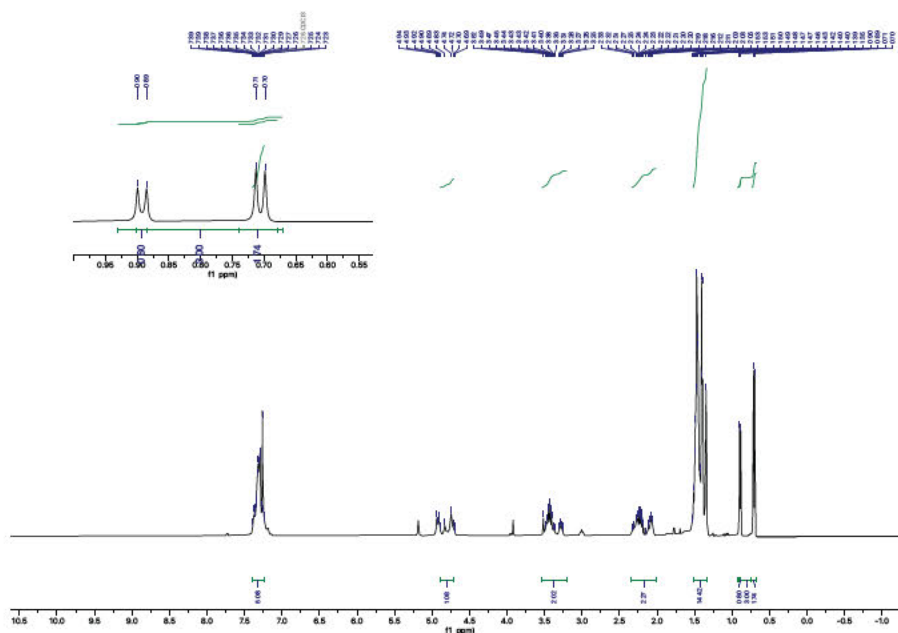
^1H NMR (500 MHz, CDCl_3) δ 7.41 – 7.23 (m, 5H + 5H*), 4.98 – 4.66 (m, 1H + 1H*), 3.52 – 3.22 (m, 2H + 2H*), 2.36 – 2.02 (m, 2H + 2H*), 1.56 – 1.32 (m, 14H + 14H*), 0.89 (d, $J = 7.2$ Hz, 3H*), 0.71 (d, $J = 7.2$ Hz, 3H). (*minor diastereoisomer; integrals normed; d.r. based on crude reaction mixture)

^{13}C NMR (125 MHz, CDCl_3) δ 145.97, 128.64, 127.61, 125.52, 124.29, 118.41, 79.81, 79.64, 70.56, 45.89, 45.40, 34.32, 33.32, 28.62, 28.49, 25.33, 16.73, 13.83, 13.78. (mixture of diastereoisomers)

HRMS (ESI-TOF) m/z calcd. for $[\text{M}+\text{Na}]^+$ 328.18886; found: 328.18865.

IR (film) ν_{max} 2971, 1734, 1697, 1453, 1388, 1366, 1254, 1170, 1128, 1067, 873, 760, 700 cm^{-1}

^1H NMR (500 MHz, CDCl_3) of 13:



^{13}C NMR (125 MHz, CDCl_3) of **13**:

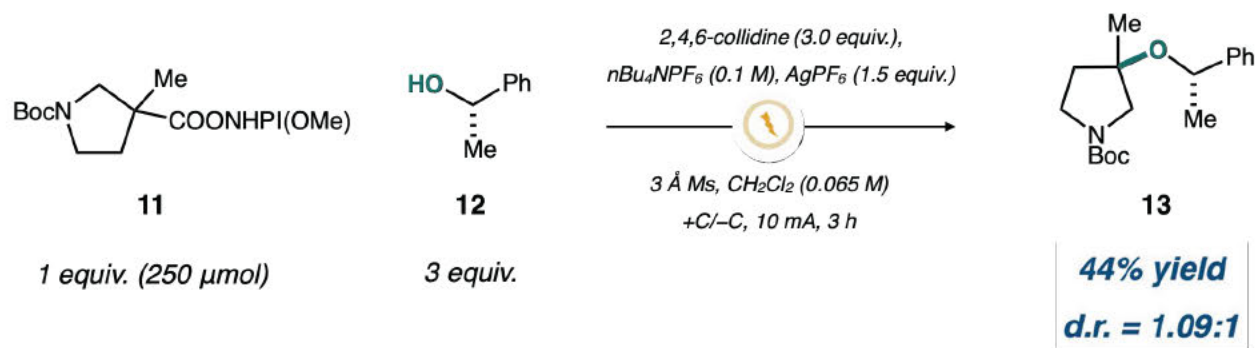
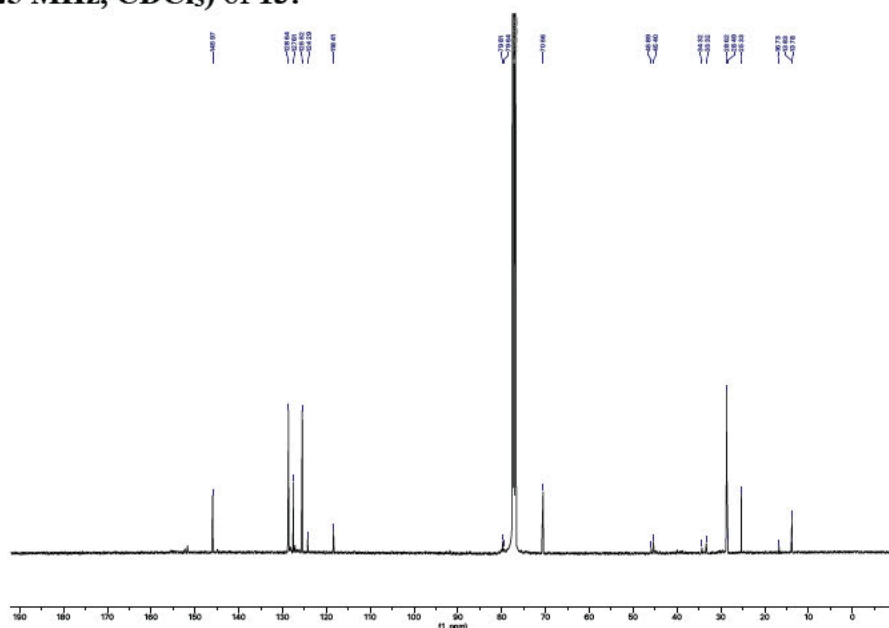


Figure S8.3. Control experiment for the diastereomeric ratio in the carbocation regime.

According to a literature procedure (11), with no precautions to exclude air or moisture, the ElectraSyn vial (5 mL) with a stir bar was charged with 1-*tert*-butoxycarbonyl-3-methylpyrrolidine-3-carboxylic acid (45.85 mg, 0.2 mmol), (*S*)-1-phenylethanol (73.30 mg, 600.00 μ mol), 2,4,6-collidine (72.6 mg, 0.6 mmol, 3 equiv.), *n* Bu₄NPF₆ (116 mg, 0.3 mmol, 1.5 equiv.), 3 Å molecular sieves (150 mg), AgPF₆ (76 mg, 0.3 mmol, 1.5 equiv.), and CH₂Cl₂ (3.0 mL). The ElectraSyn vial cap equipped with anode (graphite) and cathode (graphite) were inserted into the mixture. After pre-stirring for 15 minutes, the reaction mixture was electrolyzed at a constant current of 10 mA for 3 hours. The ElectraSyn vial cap was removed, and electrodes were rinsed with Et₂O (2 mL), which was combined with the crude mixture. Mesitylene was added as a standard and an aliquot was taken for analysis by UPLC and ¹H-NMR to determine the crude diastereomeric ratio.

UPLC traces of crude diastereocontrol experiment:

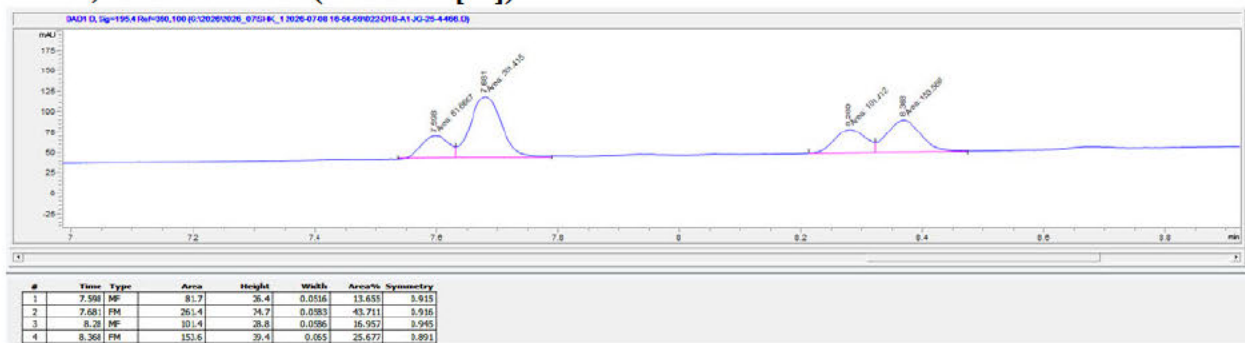
UPLC analysis: Waters Acquity UPLC BEH C18 1.7 μ m column (3.0 x 50 mm), 20–75% MeCN/H₂O containing 0.40 mM 1:1 ammonium formate/formic acid buffer, 10 min, 1.0 mL/min, visualization at 195 nm.

major diastereomer (*t_R* = 7.68 + 8.37 min); minor diastereomer (*t_R* = 7.59 + 8.28 min)

The compound elutes as two peaks despite being a single, diastereomerically pure species. To establish that this arises from slow conformational (rotameric) interconversion rather than the presence of two distinct compounds, one peak was collected and immediately re-injected. The re-injected fraction slowly regenerated the original two-peak pattern, confirming that the two signals correspond to slowly interconverting conformers of the same compound rather than to separable diastereomers, which would have remained pure.

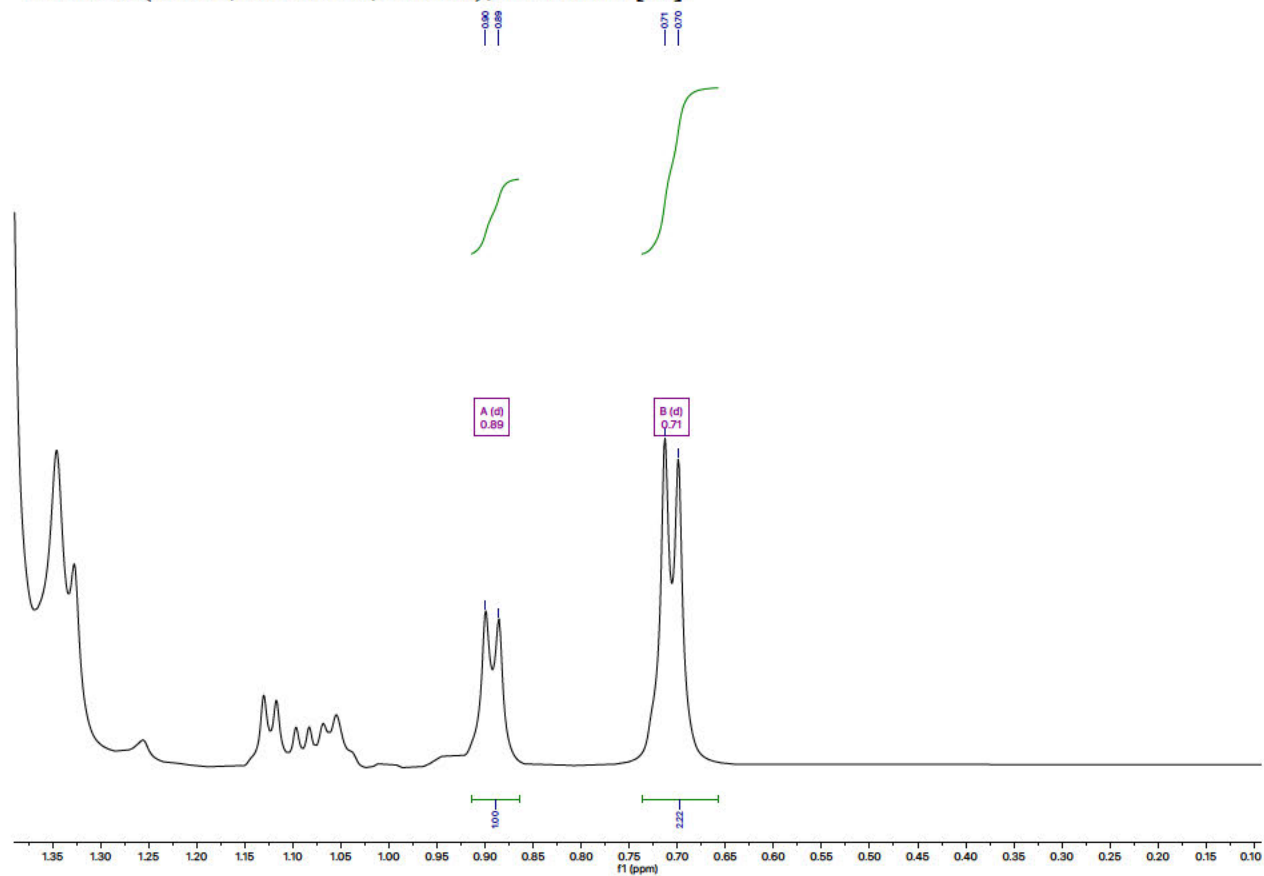
The identity of peaks in the crude UPLC is verified by (1) comparing to the authentic sample; (2) tandem mass spectrometry analysis; (3) spiking the crude with the authentic samples to see concomitant increase in peak intensity.

UPLC, crude reaction (10 mol% [Ti]): d.r. = 2.26:1

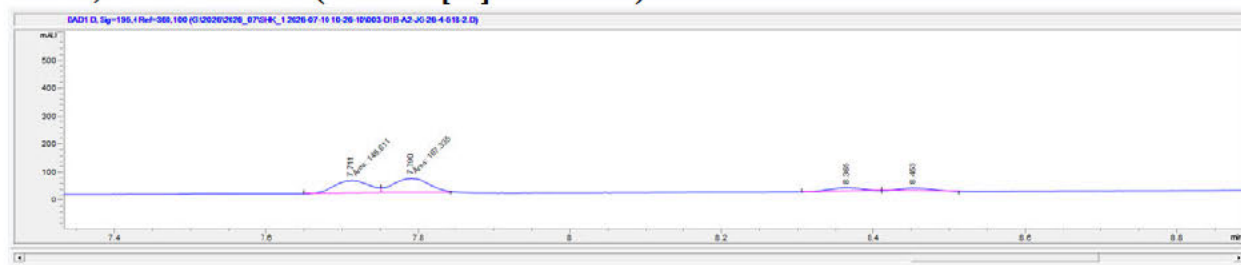


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	7.598	MF	81.7	26.4	0.0516	13.655	0.915
2	7.681	FM	261.4	74.7	0.0583	43.711	0.916
3	8.28	MF	101.4	28.8	0.0586	16.957	0.945
4	8.368	FM	153.6	39.4	0.065	25.677	0.891

¹H NMR (crude, 500 MHz, CDCl₃), 10 mol% [Ti]:



UPLC, crude reaction (0 mol% [Ti] + Zn-base): d.r. = 1.06:1



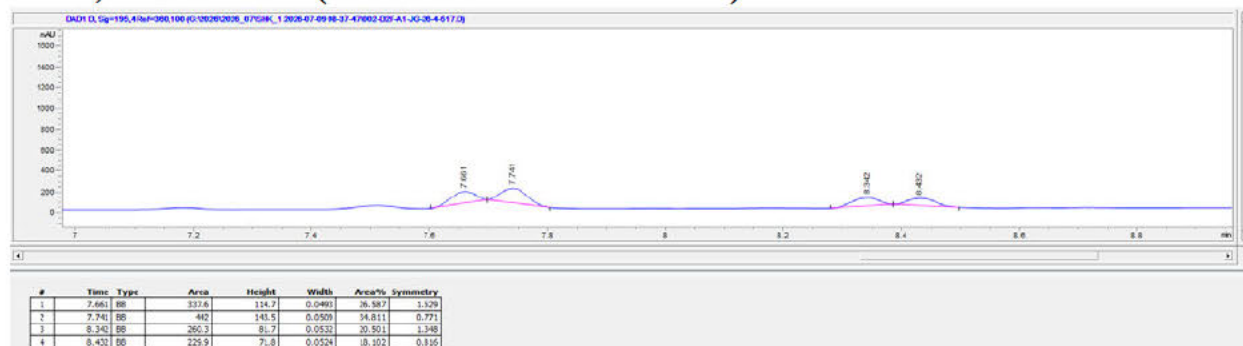
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	7.711	MF	148.6	44.8	0.0553	39.006	0.933
2	7.79	FM	167.3	49.5	0.0563	43.92	1.007
3	8.365	BB	35.8	11.6	0.0499	9.407	1.183
4	8.453	BB	29.2	9.4	0.0524	7.667	0.698

UPLC, crude reaction (0 mol% [Ti] without Zn-base): d.r. = 1.06:1



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	8.169	MF	136.5	41.8	0.0544	38.527	1.039
2	8.244	FM	153.0	47.4	0.0538	43.192	0.879
3	8.805	BB	35.8	12.1	0.0435	10.106	1.07
4	8.899	BB	29.0	9.7	0.0472	8.175	0.922

UPLC, crude reaction (electrochemical etherification): d.r. = 1.09:1



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	7.661	BB	337.6	114.7	0.0493	26.587	1.529
2	7.741	BB	442.0	143.5	0.0509	34.811	0.771
3	8.342	BB	260.3	81.7	0.0532	20.501	1.348
4	8.432	BB	229.9	71.8	0.0524	18.102	0.816

8.3 PhotoNMR Studies

Experimental Setup: To an oven-dried 4-mL vial with a stir bar was added redox-active ester **14** (41.8 mg, 0.10 mmol, 1.00 equiv.), 4DPAIPN (3.98 mg, 5.00 μ mol, 5 mol%), Cp_2TiCl_2 (2.49 mg, 10.0 μ mol, 10 mol%), $[\text{ZnCO}_3]_2 \cdot [\text{Zn}(\text{OH})_2]_3$ (27.5 mg, 50 μ mol, 0.5 equiv.). The reaction vial was then taken into a nitrogen-filled glovebox, and degassed CD_2Cl_2 (0.5 mL, 0.2 M) was added followed by 2-phenylethanol (37.0 μ L, 0.3 mmol, 3.0 eq.). The reaction mixture was stirred for 10 min to ensure all soluble components are fully dissolved, and subsequently the suspension was transferred into a PhotoNMR Sampling Device (New Era, 5 mm for Bruker probes, NE-379-5-Br). The tube was then removed from the glovebox, an LED cable (Prizmatix Mic-LED-445CA with controller Prizmatix LED Current Controller, 1000mA, BLCC-04) was inserted into the capillary attachment in the middle of the tube to ensure complete irradiation of the entire sample mixture. Following this, the tube with the LED cable was lowered into the NMR instrument (500 MHz probe) to prepare for collection. The solution was then irradiated at 505 nm while ^1H NMR spectra were collected at 30 min to 2 hr time intervals.



Figure S8.4. PhotoNMR setup.

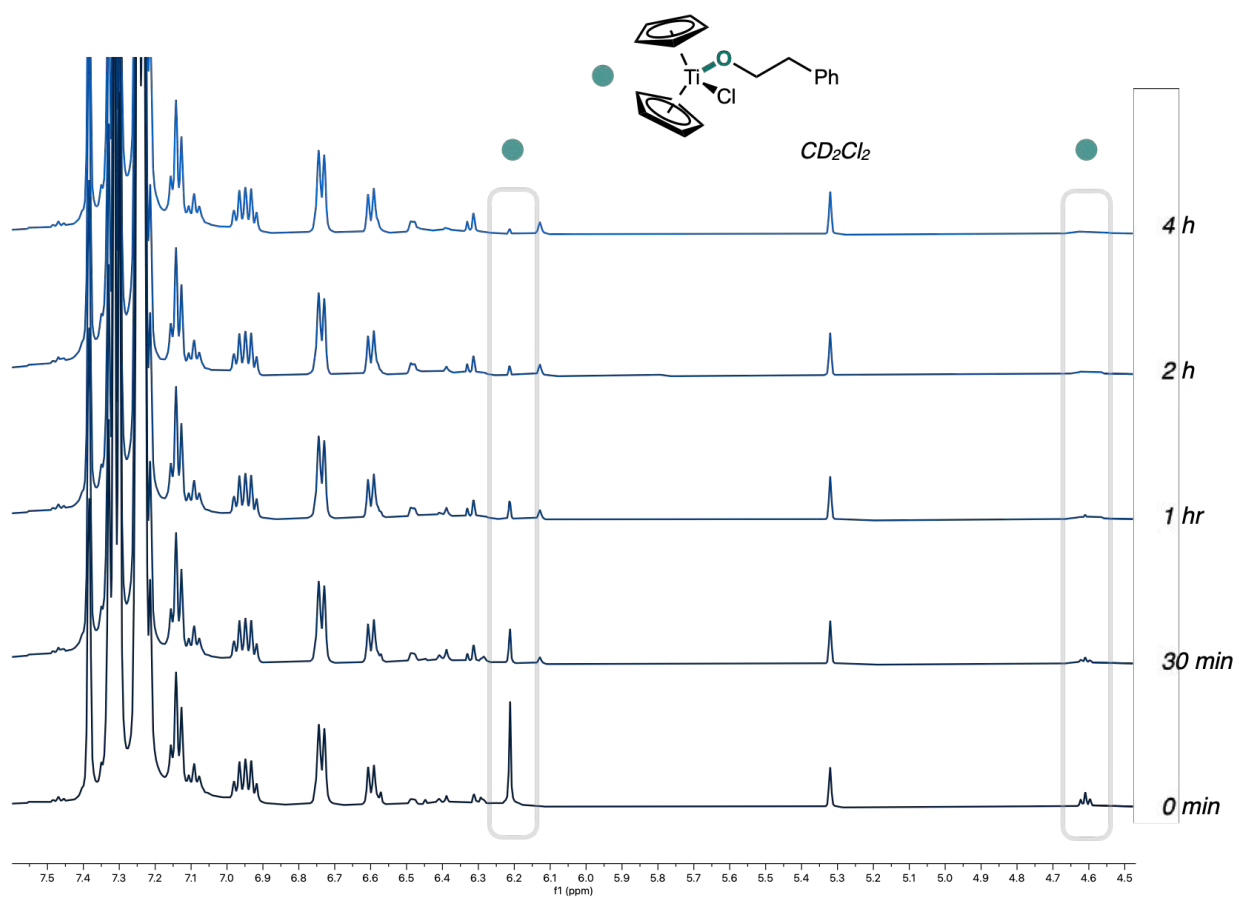


Figure S8.5. Recorded NMR spectra during irradiation. The highlighted signal corresponds to $Cp_2TiCl(OCH_2CH_2Ph)$.

PhotoNMR analysis revealed that the titanium alkoxide species is present both prior to and during the initial stages of irradiation. However, due to the heterogeneous nature of the reaction mixture, the zinc base gradually precipitated to the bottom of the NMR tube over the course of irradiation, resulting in inefficient mixing and a reduced effective base concentration in solution. This accounts for the observed decrease in the titanium alkoxide signal intensity during irradiation. Consistent with control experiments under standard conditions, the reaction does not proceed productively in the absence of sufficient base. Notably, once the titanium alkoxide signal is no longer detectable, substrate conversion ceases, indicating that sustained formation of the titanium alkoxide species is required for productive catalysis.

8.4 Light Independent Product Formation via Thermal Reduction

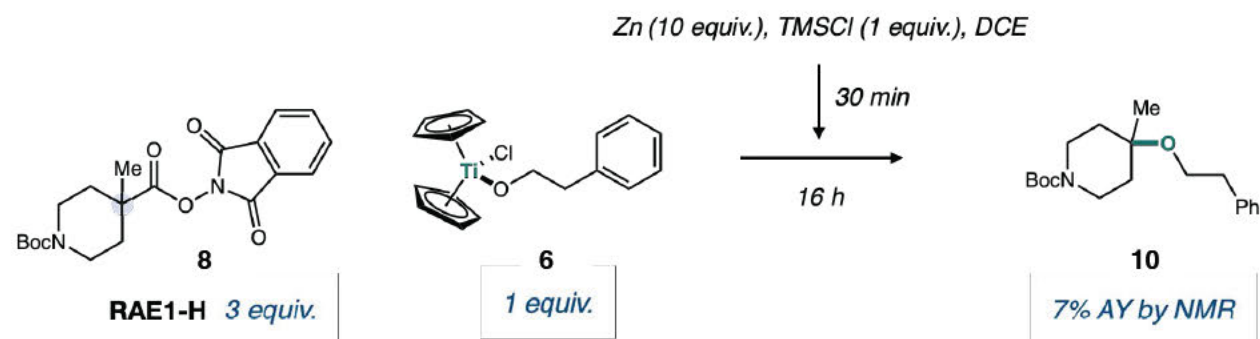
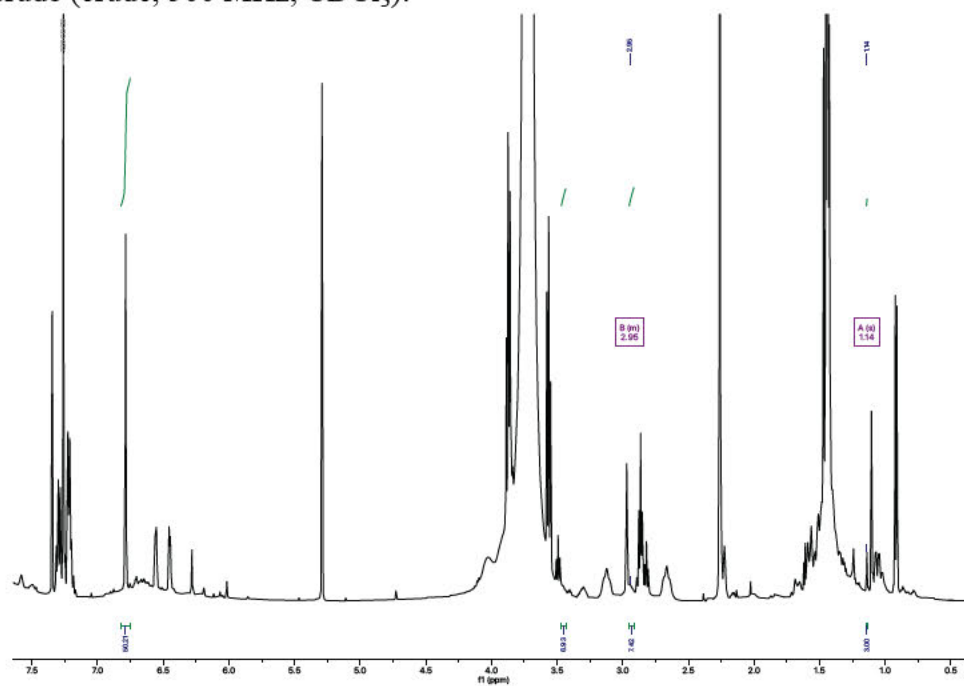


Figure S8.6. Reaction scheme for the thermal generation of a tertiary radical to probe for heteroatom homolytic substitution (preformed Ti-alkoxide).

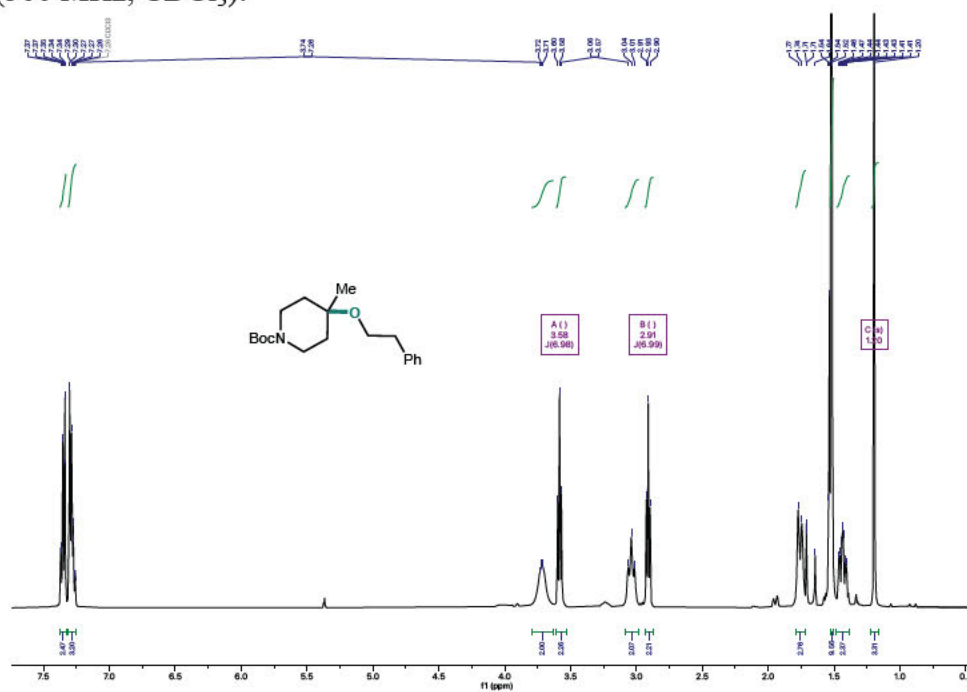
Ti-alkoxide **6** (8.37 mg, 25.0 μmol , 1.00 equiv.), **8** (29.13 mg, 75.0 μmol , 3.0 equiv.), and $\text{Zn}_3(\text{PO}_4)_2$ (19.3 mg, 50.0 μmol , 2.0 equiv.) were added to an oven-dried 4 mL vial, the atmosphere was exchanged with N_2 and 100 μL DCE was added. In parallel, to a second oven-dried 4 mL vial zinc dust (89.4 mg, 250 μmol , 10.0 equiv.) was added, followed by 100 μL DCE. To this suspension, TMSCl (3.17 μL , 25.0 μmol , 1.00 equiv.) was added and the suspension was stirred for 30 min at room temperature. Subsequently, the titanium alkoxide suspension was added in one portion to the activated zinc suspension, resulting in a yellowish suspension. Stirring was continued for 16 h after which 25.0 μmol mesitylene were added as an internal standard and 50 μL of the suspension were taken as an aliquot for ^1H -NMR analysis. According to the NMR analysis of the crude product mixture, an assay yield of 6% for **10** was determined. The signals in the crude

spectrum correspond to the product signals obtained from material made by the corresponding photoreaction.

^1H NMR crude (crude, 500 MHz, CDCl_3):



^1H NMR (500 MHz, CDCl_3):



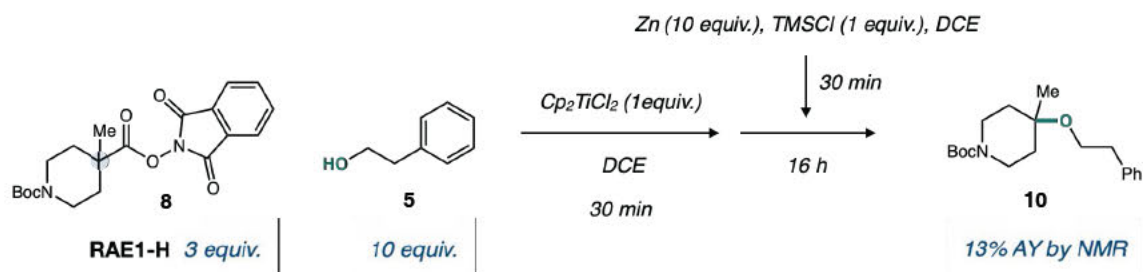
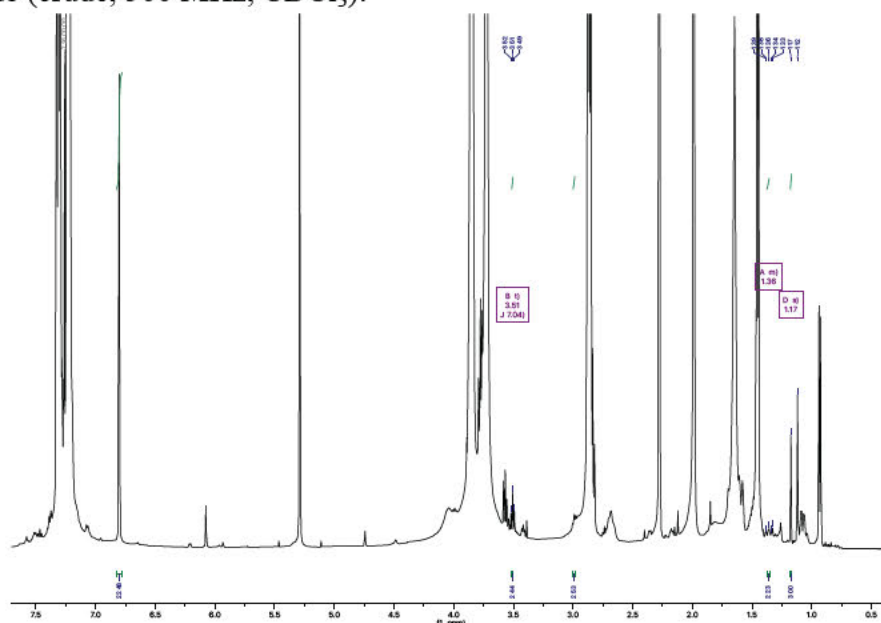


Figure S8.7. Reaction scheme for the thermal generation of a tertiary radical to probe for heteroatom homolytic substitution (in situ Ti-alkoxide formation).

Cp_2TiCl_2 (6.22 mg, 25.0 μmol , 1.00 equiv.), **8** (29.13 mg, 75.0 μmol , 3.0 equiv.), 2-phenylethanol (**5**, 30.5 mg, 250 μmol , 10.0 equiv.) and $\text{Zn}_3(\text{PO}_4)_2$ (19.3 mg, 50.0 μmol , 2.0 equiv.) were added to an oven-dried 4 mL vial, the atmosphere was exchanged with N_2 and 100 μL DCE was added. The resulting suspension was stirred for 30 min, resulting in an orange suspension. In parallel, to a second oven-dried 4 mL vial zinc dust (89.4 mg, 250 μmol , 10.0 equiv.) was added, followed by 100 μL DCE. To this suspension, TMSCl (3.17 μL , 25.0 μmol , 1.00 equiv.) is added and the suspension is stirred for 30 min at room temperature. Subsequently, the titanium alkoxide suspension was added in one portion to the activated zinc suspension, resulting in a brownish suspension which turned blueish green upon further stirring. Stirring was continued for 16 h after which 25.0 μmol mesitylene were added as an internal standard and 50 μL of the suspension were taken as an aliquot for ^1H -NMR analysis. According to the NMR analysis of the crude product mixture, an assay yield of 13% for **10** was determined. The signals in the crude spectrum correspond to the product signals obtained from material made by the corresponding photoreaction.

^1H NMR crude (crude, 500 MHz, CDCl_3):



8.5 Light Independent Product Formation via Thermal Decomposition

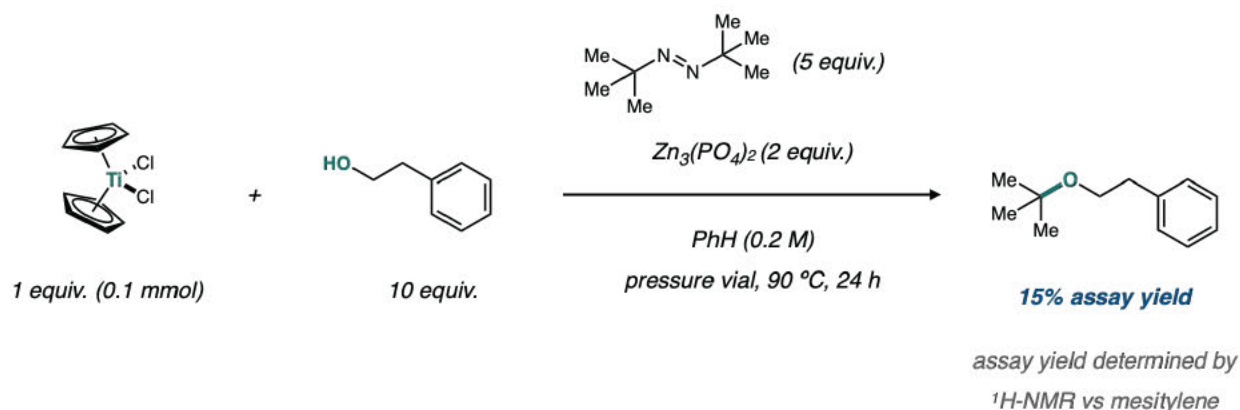
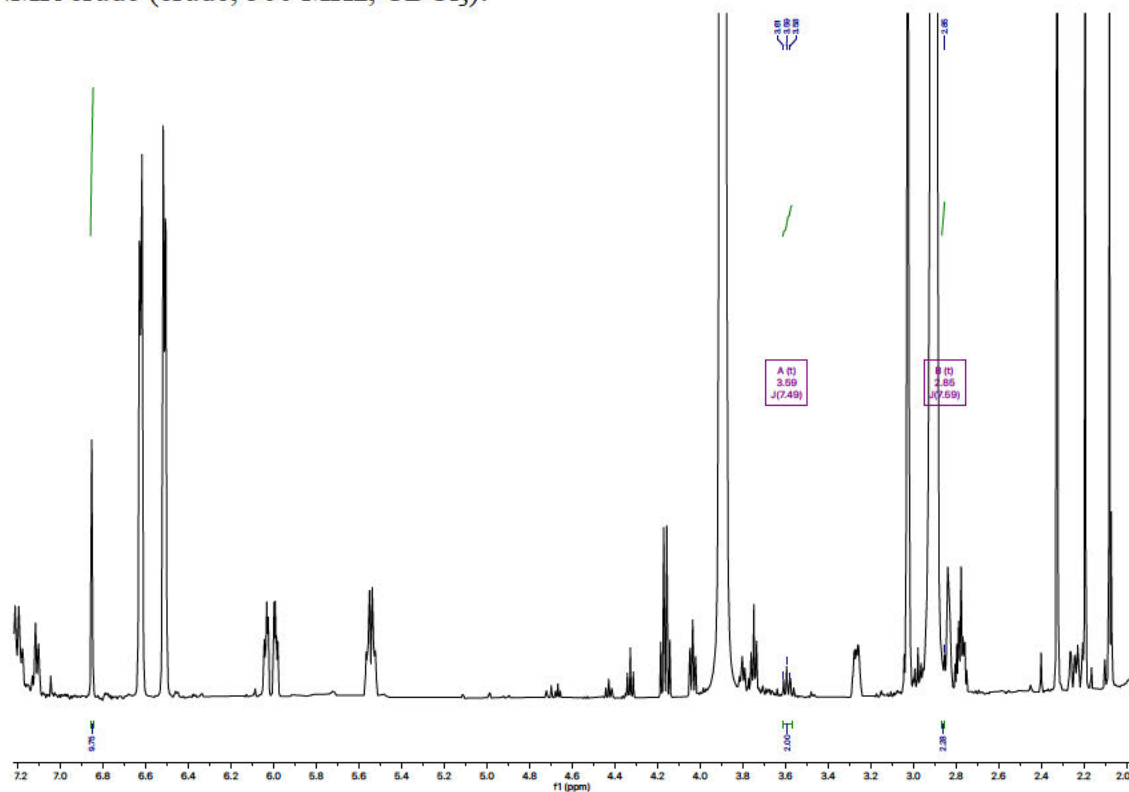


Figure S8.8. Reaction scheme for the thermal generation of a tertiary radical using di-tert-butyl diazene to probe for heteroatom homolytic substitution.

In adoption of a literature procedure⁽¹²⁾, Cp_2TiCl_2 (24.9 mg, 100 μmol , 1.00 equiv.), 2-phenylethanol (122 mg, 1.00 mmol, 10.0 equiv.) and $\text{Zn}_3(\text{PO}_4)_2$ (77.2 mg, 200 μmol , 2.0 equiv.) were added to an oven-dried 20 mL pressure vial, and 0.5 mL benzene was added. The resulting suspension was sonicated for 15 min, resulting in an orange suspension. Subsequently, di-tert-butyl diazene (71.1 mg, 500 μmol , 5.0 equiv.) was added to the titanium alkoxide suspension and

the sealed vial was heated to 90 °C for 24 h, resulting in a brownish suspension. After cooling to room temperature, 50 μmol mesitylene were added as an internal standard and 50 μL of the suspension were taken as an aliquot for ^1H -NMR and GCMS analysis. According to the NMR analysis of the crude product mixture, an assay yield of 15% was determined. The signals in the crude spectrum correspond to the literature reported data (13).

^1H NMR crude (crude, 500 MHz, CDCl_3):



8.6 Comparison Versus Carbocation Reactivity

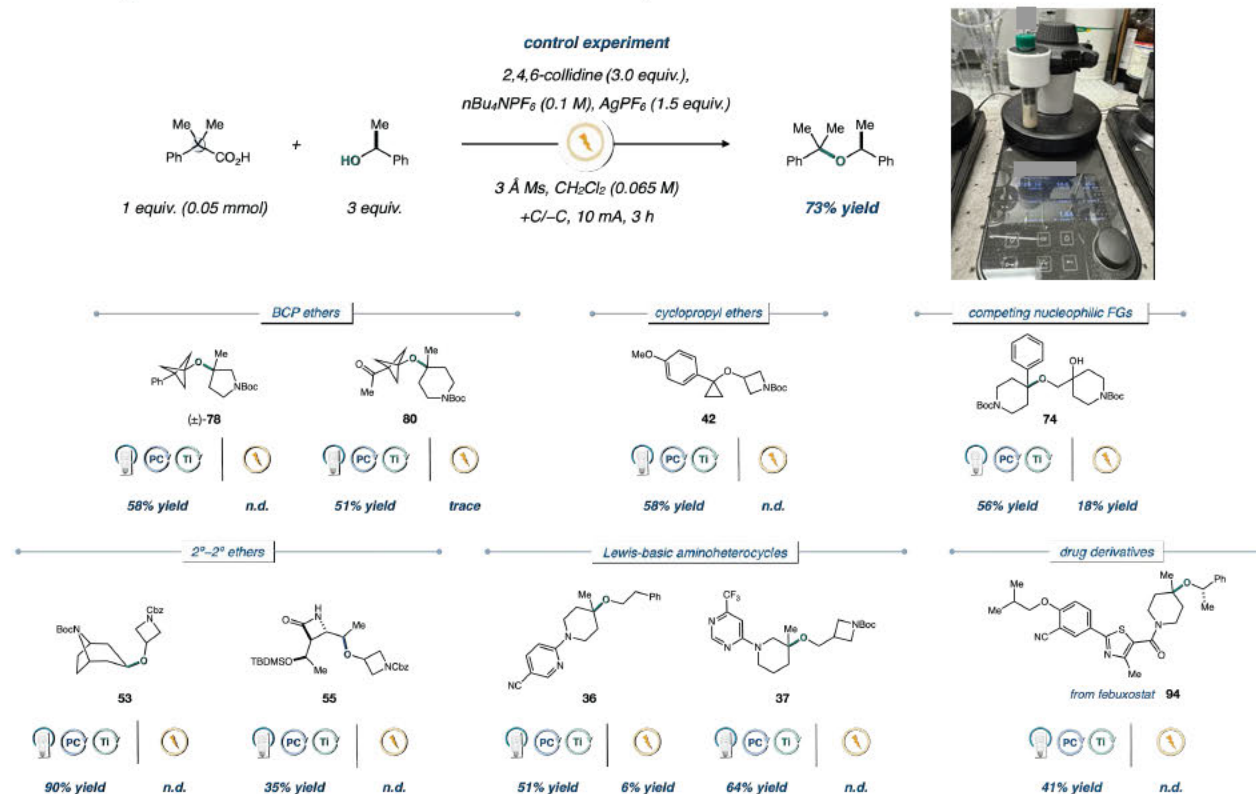


Figure 8.9 Comparison of Radical Heteroatom S_H2 and Carbocation S_N1 Reactivity

To probe the involvement of a carbocation intermediate under our reaction conditions we sought to compare our reaction to a previously published carbocation-based etherification reaction¹¹. If C–O bond formation proceeds through carbocation under our reaction conditions, we would expect comparable scopes between our reaction and previously reported carbocation-based approaches. We observed that for many challenging substrate classes including, strained intermediates, protic containing and Lewis basic substrates, as well as secondary derived examples, gave no or poor yields for the carbocation-based reaction. On the other hand, under our reported reaction conditions moderate to good yields were obtained for these challenging substrates. The orthogonality in scope demonstrates that our reported reaction is capable of forming ethers not compatible with reactive carbocation intermediates suggesting that it is unlikely product formation proceeds through a carbocation, further supporting the importance of a radical based Het-S_H2 mechanism for C–O bond formation.

9. Computational Analysis of the Ether Formation via Radical Substitution

All electronic-structure calculations were performed with Gaussian 16 (Revision A.03) (14). The reaction studied is the homolytic bimolecular substitution ($\text{het-S}_{\text{H}}2$) of a *tert*-butyl radical at the alkoxide oxygen of the titanocene(IV) complex $\text{Cp}_2\text{Ti}(\text{Cl})(\text{OEt})$, which proceeds to *tert*-butyl ethyl ether ($\text{EtO}t\text{Bu}$) and the titanocene(III) complex Cp_2TiCl . The system comprises 43 atoms and was treated throughout as an open-shell doublet (net charge 0, spin multiplicity 2). Exhaustive conformational searches were performed for all structures, and the lowest-energy conformers were re-optimized at the DFT level. All 3-D structures were generated using CYLview.

Geometry optimizations and frequencies. Stationary points — the reactant complex (RC), the transition state (TS), and the product complex (PC) — were optimized with the B3LYP hybrid density functional (15) together with Grimme's D3 empirical dispersion correction (empiricaldispersion=gd3) (16) and the def2-SVP basis set (17). All optimizations used an unrestricted formalism (UB3LYP) with a broken-symmetry initial guess (guess=mix) to allow the doublet to localize the spin correctly and were carried out without symmetry constraints (nosymm). Solvation in dichloromethane ($\epsilon = 8.93$) was described with the polarizable continuum model in its conductor-like formulation, CPCM (scrf=(CPCM,solvent=dichloromethane)) (18). Analytical harmonic frequencies were computed at the same level for every stationary point to (i) confirm its nature and (ii) supply the zero-point, thermal, and entropic corrections. Thermochemical corrections are reported at 298.15 K and 1 atm.

The transition state was located with an eigenvector-following TS optimization (opt=(ts,calcfc,noeigentest))(19, 20), computing exact force constants at the first step. The quadratically convergent SCF procedure (scf=xqc) was used to ensure convergence of the open-shell wavefunction (21).

The exact route section used for the transition-state optimization was:

```
#UB3LYP/def2SVP empiricaldispersion=gd3 guess=mix nosymm opt=(ts,calcfc,noeigentest)
freq scf=xqc scrf=(CPCM,solvent=dichloromethane)
```

Transition-state verification. The TS was confirmed to be a first-order saddle point by three independent criteria: (i) the Hessian has exactly one negative eigenvalue, corresponding to a single imaginary frequency of -498.1 cm^{-1} ; (ii) animation of the associated normal mode shows the forming-bond motion — the alkoxide oxygen (O23) and the *tert*-butyl carbon (C31) move antiphase along the $\text{C}\cdots\text{O}$ axis (largest displacement components on O23 and C31), while the titanium center is essentially stationary; and (iii) an intrinsic reaction coordinate (IRC) calculation (22, 23) launched from the TS connects it, without any intervening intermediate, to the reactant and product complexes.

Energy refinement. Single-point energies were evaluated on the def2-SVP-optimized geometries at two higher levels to test the robustness of the computed energetics: (a) the range-separated hybrid ω B97X-D with the def2-SVP basis (24), and (b) B3LYP-D3 with the larger triple- ζ def2-TZVPP basis (17). Both refinements retained the CPCM(DCM) solvation model and the broken-symmetry guess. For these single points, Gibbs energies are obtained by adding the def2-SVP thermal correction (from the corresponding opt+freq calculation) to the refined electronic energy — i.e. the electronic energy is improved while vibrational/thermal contributions are taken from the def2-SVP surface.

Spin and charge analysis. Mulliken atomic spin densities and Natural Population Analysis (NPA) charges (25) were used to characterize the electron transfer along the reaction coordinate. Spin density tracks the migration of the unpaired electron from the *tert*-butyl carbon to titanium (Ti(IV)→Ti(III)) as the substitution proceeds.

9.1 Energetic Analysis

All values in kcal•mol⁻¹, relative to the reactant complex (RC), in CPCM(dichloromethane). Geometries and thermal corrections from UB3LYP-D3/def2-SVP; single-point (SP) rows refine the electronic energy at the indicated level on the same geometry.

Table S9.1. Activation barrier (RC → TS).

Level	$\Delta E^\ddagger$	$\Delta H^\ddagger$	$\Delta G^\ddagger$ (298 K)	$\langle S^2 \rangle$ RC / TS
UB3LYP-D3/def2-SVP (opt+freq)	11.3	11.0	14.2	0.750 / 0.750
ω B97X-D/def2-SVP (SP)	14.9	—	17.8 ^a	0.750 / 0.750
B3LYP-D3/def2-TZVPP (SP)	13.2	—	16.2 ^a	0.750 / 0.750

^aGibbs energy for single-point levels = refined electronic ΔE + def2-SVP thermal correction ($\Delta G - \Delta E = +2.9$ for the barrier, +3.5 for the reaction).

Table S9.2. Overall reaction free energy (RC → PC).

Level	ΔE	ΔH	ΔG (298 K)
UB3LYP-D3/def2-SVP (opt+freq)	-15.5	-13.7	-12.1
ω B97X-D/def2-SVP (SP)	-22.2	—	-18.8 ^a
B3LYP-D3/def2-TZVPP (SP)	-14.1	—	-10.6 ^a

^aGibbs energy for single-point levels = refined electronic ΔE + def2-SVP thermal correction ($\Delta G - \Delta E = +2.9$ for the barrier, $+3.5$ for the reaction).

The barrier is robust to both basis-set enlargement (def2-SVP→def2-TZVPP) and functional choice (B3LYP→ ω B97X-D), spanning $\Delta G^\ddagger = 14$ – 18 kcal mol^{−1}. The reaction is exergonic at every level ($\Delta G = -11$ to -19 kcal mol^{−1}). Of the three levels, B3LYP-D3/def2-TZVPP employs the most complete (triple- ζ) basis and provides the reference energetics: $\Delta G^\ddagger = 16.2$ kcal mol^{−1}, $\Delta G = -10.6$ kcal mol^{−1}.

Table S9.3. Absolute energies (Hartree). E = electronic (SCF) energy; H, G = sum of electronic and thermal enthalpy / Gibbs free energy at 298.15 K (def2-SVP opt+freq).

Species	E (B3LYP-D3/def2-SVP)	H	G	E (ω B97X-D/def2-SVP)	E (B3LYP-D3/def2-TZVPP)
RC	-2008.464577	-2008.081359	-2008.159194	-2008.172158	-2009.509856
TS	-2008.446518	-2008.063838	-2008.136486	-2008.148428	-2009.488758
PC	-2008.489348	-2008.103221	-2008.178422	-2008.207600	-2009.532337

Figure S9.1. Free-energy profile at all three levels of theory and transition state including Ti-O-C angle and bond lengths.

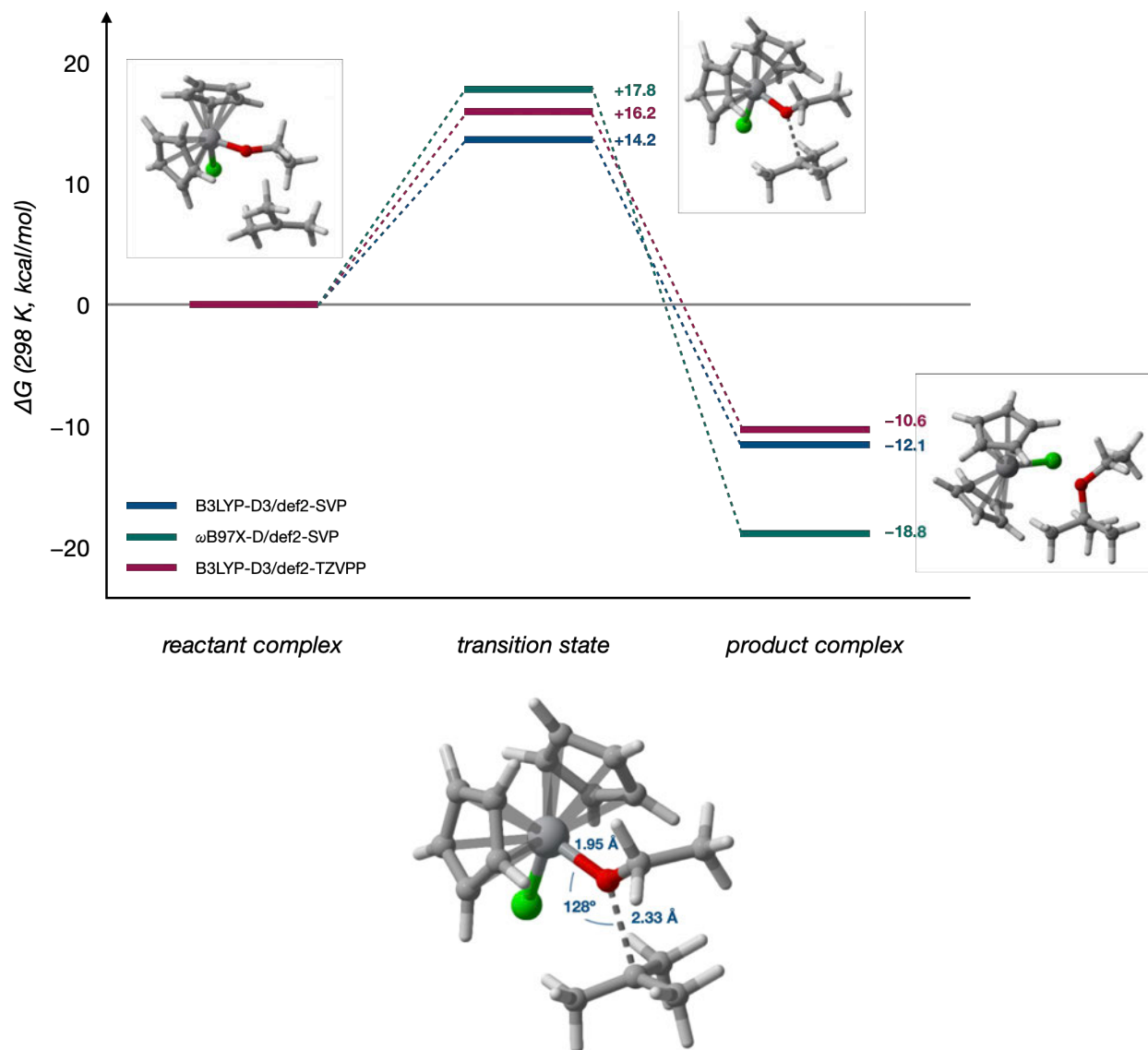


Table S9.4. Atomic Distances of the Respective Complexes and the Transitions State.

	Ti-O (Å)	C-O (Å)
Reactant complex (RC)	1.815	3.772
Transition state (TS)	1.946	2.33
Product complex (PC)	4.09	1.442

9.2 Bond Dissociation Energies

The exergonicity of the substitution can be traced to a single balance of bond strengths: the reaction breaks the Ti–O bond of the titanocene(IV) alkoxide and forms the C–O bond of the ether product. Both processes share the ethoxyl radical ($\bullet\text{OEt}$) as a common fragment, so the overall reaction energy is exactly the difference of the two bond dissociation energies:

$$\Delta_{\text{rxn}} = \text{BDE}(\text{Ti} - \text{O}) - \text{BDE}(\text{C} - \text{O})$$

where the two homolytic dissociations are

- **BDE(Ti–O):** $\text{Cp}_2\text{TiCl}(\text{OEt}) \rightarrow \text{Cp}_2\text{TiCl}\bullet + \bullet\text{OEt}$ (breaking, in the reactant)
- **BDE(C–O):** $t\text{-BuOEt} \rightarrow t\text{-Bu}\bullet + \bullet\text{OEt}$ (forming, in the product)

Each fragment — the closed-shell Ti(IV) alkoxide $\text{Cp}_2\text{Ti}(\text{Cl})(\text{OEt})$, the Ti(III) species $\text{Cp}_2\text{TiCl}\bullet$, the ethoxyl radical $\bullet\text{OEt}$, the *tert*-butyl radical $\bullet\text{C}(\text{CH}_3)_3$, and the ether *t*-BuOEt — was optimized independently (UB3LYP-D3/def2-SVP, CPCM(DCM), broken-symmetry doublet for the open-shell species) and characterized by frequencies. Single-point refinements at $\omega\text{B97X-D/def2-SVP}$ and B3LYP-D3/def2-TZVPP were carried out on those geometries, exactly as for the stationary points. The optimized Cartesian coordinates of all five fragments are listed. Bond dissociation energies are reported three ways: D_e (electronic only), the 298 K bond dissociation enthalpy ($D_{\text{H},298}$, the experimentally comparable quantity), and the 298 K free energy of dissociation (ΔG_{298}).

Table S9.4. Bond dissociation energies and the reaction driving force (kcal mol^{−1}). Positive BDE = energy required to break the bond homolytically. $\Delta_{\text{rxn}} = \text{BDE}(\text{Ti} - \text{O}) - \text{BDE}(\text{C} - \text{O})$, is the net thermodynamic driving force.

Level	Quantity	BDE/BDFE (Ti–O)	BDE/BDFE (C–O)	Δ_{rxn}
B3LYP-D3/def2-SVP	D_e (electronic)	70.7	84.6	−13.9
	$D_{\text{H},298}$ (enthalpy)	66.8	80.0	−13.2
	ΔG_{298} (BDFE)	54.6	63.7	−9.1
$\omega\text{B97X-D/def2-SVP}$	D_e (electronic)	65.7	87.4	−21.7
	$D_{\text{H},298}$ (enthalpy)	61.8	82.8	−21.0
	ΔG_{298} (BDFE)	49.6	66.5	−16.9
B3LYP-D3/def2-TZVPP	D_e (electronic)	64.9	80.3	−15.4

Level	Quantity	BDE/BDFE (Ti–O)	BDE/BDFE (C–O)	Δ_{rxn}
	$D_{\text{H},298}$ (enthalpy)	61.0	75.7	–14.8
	ΔG_{298} (BDFE)	48.8	59.5	– 10.7

At every level the forming C–O bond is stronger than the breaking Ti–O bond, so the substitution is thermodynamically downhill regardless of functional or basis set. The titanium–alkoxide bond (BDE $\approx$ 61–67 kcal mol^{–1} at 298 K) is comparatively weak; the electron-rich, sterically encumbered Ti(IV) center releases the alkoxide readily upon reduction to Ti(III), whereas the *tert*-butyl–oxygen bond of the ether ($\approx$ 76–83 kcal mol^{–1}) is a strong, fully covalent C–O σ -bond. The $\approx$ 13–21 kcal mol^{–1} bond-strength difference is the thermodynamic origin of the driving force that renders the het-S_H2 substitution exergonic.

This bond-additivity analysis is an independent check on the supermolecule energetics of the previous section: the free-energy driving force obtained by differencing the two BDEs at the reference level (Δ_{rxn} = –10.7 kcal mol^{–1}, B3LYP-D3/def2-TZVPP) agrees to within a few tenths of a kcal mol^{–1} with the direct RC→PC reaction free energy computed from the intact complexes (ΔG = –10.6 kcal mol^{–1}, Table S9.2). The two routes to the reaction energy, one through the associated complexes, one through free fragments, are mutually consistent.

9.3 Spin Density Analysis

Mulliken atomic spin densities show the unpaired electron migrating from carbon to titanium as the reaction proceeds. In the reactant complex the spin is localized entirely on the *tert*-butyl carbon (C31 = +0.97; Ti = 0.00 — a closed-shell Ti(IV) alkoxide). At the transition state the spin is shared between carbon and titanium (C31 = +0.52, Ti = +0.63), capturing the Ti(IV)→Ti(III) electron transfer in progress. The bridging oxygen carries a small **negative** spin density (O23 = –0.11): sitting between two α -spin-bearing centers, its doubly occupied orbitals spin-polarize, leaving a slight β excess — a marker that O is the atom linking the two radical centers rather than bearing an unpaired electron itself. NPA charges at the TS (Ti = +0.69, O23 = –0.59, C31 = +0.22) are consistent with this picture.

Table S9.5. Mulliken atomic spin densities.

	<i>Ti</i>	<i>O23</i>	<i>C31</i>
Reactant complex	0.00	0.00	+0.97
Transition state	+0.63	−0.11	+0.52

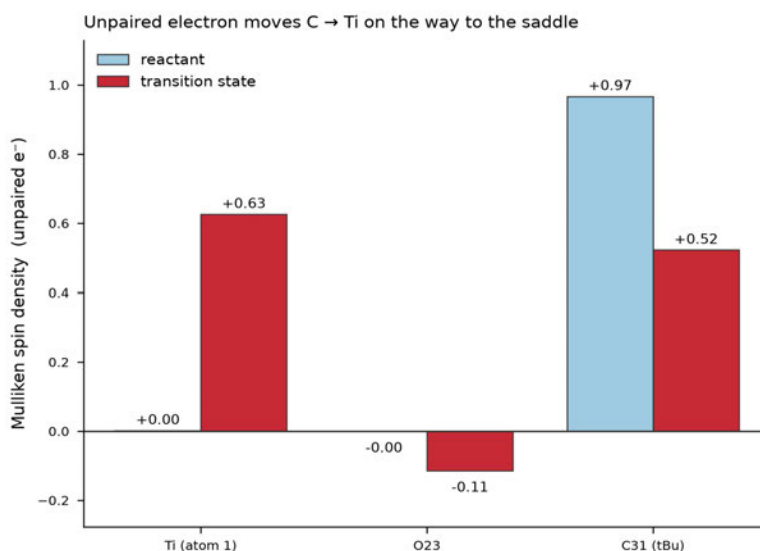


Figure S9.2. Spin-density redistribution from reactant to transition state.

9.4 Selectivity for Oxygen versus Chloride Transfer

To confirm that the tert-butyl radical abstracts the ethoxide oxygen rather than the chloride ligand of $\text{Cp}_2\text{Ti}(\text{Cl})(\text{OEt})$, we compared the thermodynamics of the two competing transfers from titanium alkoxide, using the same protocol as for the main reaction [B3LYP-D3(BJ)/def2-TZVPP//B3LYP-D3(BJ)/def2-SVP with CPCM(CH_2Cl_2); 298.15 K, 1 atm]:

O-transfer (observed): $\text{tBu}\cdot + \text{Cp}_2\text{Ti}(\text{Cl})(\text{OEt}) \rightarrow \text{tBuOEt} + \text{Cp}_2\text{TiCl}\cdot$

Cl-transfer (hypothetical): $\text{tBu}\cdot + \text{Cp}_2\text{Ti}(\text{Cl})(\text{OEt}) \rightarrow \text{tBuCl} + \text{Cp}_2\text{Ti}(\text{OEt})\cdot$

In the chloride pathway titanium retains the ethoxide ligand, since only the Ti–Cl bond is broken; the resulting $\text{Cp}_2\text{Ti}(\text{OEt})\cdot$ was optimized as a ground-state doublet and verified as a true minimum (no imaginary frequencies). It is a hypothetical fragment computed solely to quantify the preference and is not proposed as an observed species. Reaction free energies were obtained as $\text{net-}\Delta G = \text{BDFE}(\text{Ti-X}) - \text{BDFE}(\text{C-X})$, in which the free chlorine atom cancels exactly. Oxygen transfer is favored by $7.4 \text{ kcal mol}^{-1}$ at the def2-TZVPP level ($\text{net } \Delta G = -10.7 \text{ vs } -3.3 \text{ kcal mol}^{-1}$ for chloride), and the same ordering holds at the two other levels ($6.8 \text{ kcal mol}^{-1}$ at def2-SVP; 8.7

kcal mol⁻¹ at ω B97X-D/def2-SVP; Table S9.6). The origin of the selectivity is that titanium binds chloride more strongly than the alkoxide [BDFE(Ti–Cl) = 65.0 vs BDFE(Ti–O) = 48.8 kcal mol⁻¹], so cleaving Ti–Cl is thermodynamically less favored, whereas the two carbon-centered product bonds are comparable [BDFE(C–Cl) = 68.3 vs BDFE(C–O) = 59.5 kcal mol⁻¹]. Transfer of the oxygen-bound ethoxide to carbon is therefore strongly preferred, consistent with exclusive ether formation and the absence of chlorinated products.

Table S9.6. Ti–Cl vs C–Cl bond energies (B3LYP-D3(BJ)/def2-TZVPP basis set; in kcal mol⁻¹).

Quantity	Ti–Cl	C–Cl	net Δ (Cl-transfer)	net Δ (O-transfer)
De (electronic)	76.8	82.1	-5.3	-15.4
BDE (D _H 298)	75.4	79.5	-4.1	-14.8
BDFE (Δ G ₂₉₈)	65.0	68.3	-3.3	-10.7

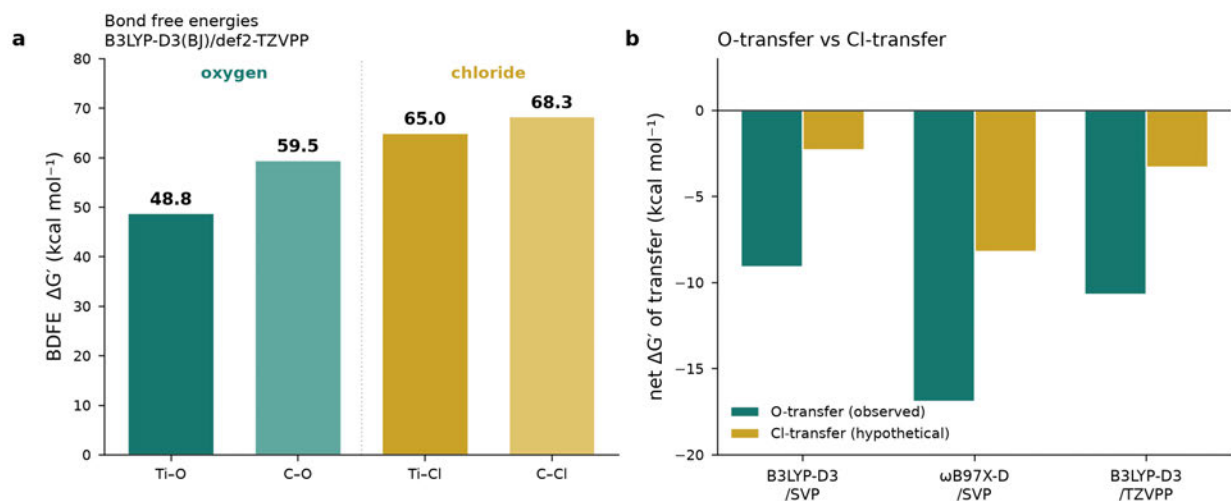
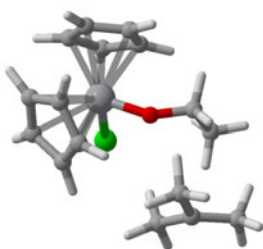


Figure S9.3. a. Comparison of BDFE values between Ti–O/C–O and Ti–Cl/C–Cl (B3LYP-D3(BJ)/def2-TZVPP level of theory); b. Free energy comparison between O- vs Cl-transfer across different level of theories.

9.5 Cartesian Coordinates of Optimized Structures

Coordinates in Ångström, from UB3LYP-D3/def2-SVP CPCM(dichloromethane) optimizations. Atom numbering matches the text (atom 1 = Ti; O23 = alkoxide oxygen; C31 = tert-butyl carbon). Key distances are given for each structure.

Reactant Complex (RC)

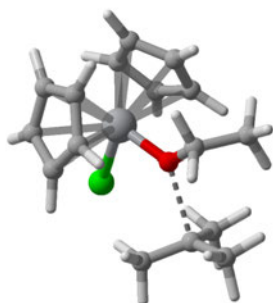


Doublet, $\langle S^2 \rangle = 0.750$, no imaginary frequencies. $E = -2008.464577$ Ha. Ti–O23 = 1.815 Å, C31...O23 = 3.772 Å.

Ti	0.24558500	0.01709500	-0.12416000
Cl	0.43551500	1.36805700	-2.09802100
C	2.03592400	-0.42592900	1.42212800
C	2.58115900	0.41637300	0.41819000
C	1.93196400	1.67079600	0.50188900
C	0.97089400	1.60526900	1.53554500
C	1.04287000	0.30471200	2.11394100
H	2.30053000	-1.46611200	1.60454000
H	3.34344700	0.14378200	-0.30752700
H	2.10243200	2.51874600	-0.15490200
H	0.30447900	2.41019000	1.83794200
H	0.44526700	-0.06323100	2.94454900
C	-2.01915900	0.92994300	-0.12250200
C	-2.02425300	-0.18880500	-1.01507600
C	-1.78970200	-1.34989600	-0.26099800
C	-1.57493900	-0.96441700	1.08732800
C	-1.78040400	0.44622500	1.17485600
H	-2.14804100	1.97184100	-0.40808000
H	-2.14034700	-0.13637700	-2.09390200
H	-1.66430600	-2.35108900	-0.66050100
H	-1.34737200	-1.63313800	1.91588400
H	-1.72463900	1.04371800	2.08116500
O	0.84475000	-1.49782400	-0.92514500
C	1.98883200	-2.17961900	-1.35966500
H	1.72585200	-3.24409100	-1.50400500
H	2.77299800	-2.15196300	-0.57890900
C	2.53286300	-1.59706000	-2.65887300
H	2.75661600	-0.52719900	-2.53715300
H	1.79391100	-1.69087000	-3.46768900
H	3.44908200	-2.12967100	-2.96023100
C	-0.59991800	-3.92113800	-3.42852800
C	-1.07888200	-2.51834400	-3.63745100
H	-0.53663600	-1.80266100	-2.98683500
H	-2.14887200	-2.41241000	-3.38292800
H	-0.93799500	-2.18393500	-4.67869500
C	-0.97411600	-4.62035500	-2.15906400
H	-2.03093300	-4.44649600	-1.89050200
H	-0.37095800	-4.25662500	-1.29850600
H	-0.80989300	-5.70923700	-2.22064300
C	0.56095400	-4.43844500	-4.21863200
H	0.59006800	-4.01291400	-5.23558100

H	0.53995000	-5.53933500	-4.30369300
H	1.53530000	-4.18655900	-3.74554600

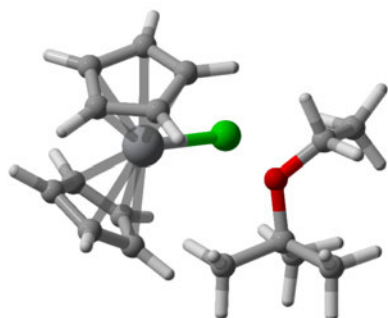
Transition State (TS)



Doublet, $\langle S^2 \rangle = 0.750$, one imaginary frequency (-498.1 cm^{-1}). $E = -2008.446518 \text{ Ha}$. $\text{Ti}-\text{O}23 = 1.946 \text{ \AA}$, $\text{C}31 \cdots \text{O}23 = 2.330 \text{ \AA}$.

Ti	0.01889000	-0.16952800	-0.49638200
Cl	-0.82101800	0.88567000	-2.55334600
C	2.24174900	-0.21474500	0.44611600
C	2.42809700	0.07147600	-0.93398000
C	1.85177800	1.32887800	-1.19929700
C	1.29689100	1.83246200	0.00806400
C	1.57014900	0.88718900	1.02913400
H	2.56888200	-1.10562600	0.97691400
H	2.86711100	-0.59247500	-1.67424400
H	1.78373500	1.80334200	-2.17375100
H	0.76019300	2.77253800	0.12498700
H	1.31286100	0.98097800	2.08088800
C	-2.13844700	0.66353400	0.27483300
C	-2.35794200	-0.65699300	-0.21496100
C	-1.67427500	-1.55596400	0.62965700
C	-0.98228800	-0.80349600	1.60817600
C	-1.30596200	0.57328100	1.40424200
H	-2.51492400	1.57934600	-0.17456500
H	-2.93192400	-0.91881600	-1.09911800
H	-1.62302500	-2.63400000	0.49886600
H	-0.34149900	-1.20180700	2.39357000
H	-0.96134000	1.41130200	2.00464100
O	0.41091800	-1.94763900	-1.18206900
C	0.91581200	-3.04500100	-0.45571100
H	0.26404800	-3.92208400	-0.62283100
H	0.85405200	-2.83986300	0.62905100
C	2.35935200	-3.40880200	-0.80092700
H	2.63137700	-4.36028700	-0.31518400
H	3.07057400	-2.64382400	-0.46208100
H	2.49538600	-3.52720400	-1.88397300
C	-0.14022800	-2.84341300	-3.26107800
C	-1.57795400	-2.46811300	-3.17918200
H	-2.08251600	-2.99669700	-2.35584800
H	-2.08113500	-2.77870800	-4.11869100
H	-1.70931400	-1.38695400	-3.06172600
C	0.14884100	-4.30746300	-3.23638700
H	-0.16609700	-4.72815800	-4.21453900
H	-0.43269400	-4.84079600	-2.46937900
H	1.21467600	-4.54186600	-3.11894200
C	0.80134000	-1.95677100	-3.99852400
H	0.66800200	-0.90850500	-3.70221600
H	0.58835700	-2.02782900	-5.08612900
H	1.84939000	-2.25556600	-3.85006700

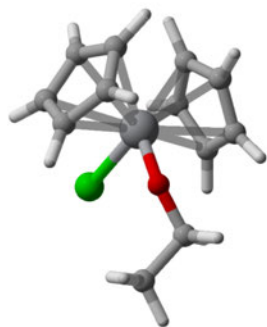
Product Complex (PC)



Doublet, $\langle S^2 \rangle = 0.750$, no imaginary frequencies. $E = -2008.489348$ Ha. $\text{Ti} \cdots \text{O23} = 4.090$ Å, $\text{C31}-\text{O23} = 1.442$ Å.

Ti	-0.12679500	0.24924300	0.05216300
Cl	0.29853300	1.43814300	-1.95311800
C	1.22242400	-1.68804000	0.21306500
C	2.03179000	-0.65923200	-0.34032900
C	2.19484200	0.35840600	0.63575900
C	1.48122100	-0.03124200	1.79579300
C	0.89109300	-1.30141300	1.53722200
H	0.90410300	-2.58227200	-0.31778700
H	2.41568000	-0.63418500	-1.35676500
H	2.73036300	1.29675500	0.49760600
H	1.38980200	0.54321300	2.71666100
H	0.27195000	-1.86836700	2.22975300
C	-2.20038400	1.42991500	-0.06525900
C	-2.49389000	0.06452300	-0.31312700
C	-2.18314700	-0.67101000	0.85820900
C	-1.70458500	0.24606400	1.83345700
C	-1.70286900	1.54546300	1.26148200
H	-2.28980700	2.23847600	-0.78665900
H	-2.85271000	-0.35111700	-1.25343700
H	-2.28261300	-1.74770100	0.98652200
H	-1.37923200	-0.00560400	2.84077500
H	-1.38354500	2.46368500	1.75294200
O	0.56752600	-2.69139400	-2.70459000
C	1.70357100	-2.62684000	-3.54866500
H	1.75452600	-3.50209100	-4.22283400
H	2.55652600	-2.72052300	-2.85587700
C	1.85593600	-1.33426000	-4.34892100
H	1.66714800	-0.45994300	-3.70668800
H	1.16297800	-1.28616100	-5.20147800
H	2.88081900	-1.26618300	-4.74930700
C	-0.76416300	-2.89795500	-3.21671200
C	-1.35179700	-1.59167400	-3.77945000
H	-1.16621900	-0.76184600	-3.08252100
H	-2.43806400	-1.69705300	-3.92942200
H	-0.90768000	-1.32594200	-4.74852400
C	-1.55132900	-3.31760100	-1.97032900
H	-2.61592400	-3.46934800	-2.20377100
H	-1.46553700	-2.53586200	-1.20234100
H	-1.14118800	-4.25173600	-1.55678500
C	-0.80486900	-4.01152800	-4.26976000
H	-0.28712100	-3.72133600	-5.19686100
H	-1.84971900	-4.23680200	-4.53257600
H	-0.33957600	-4.93121700	-3.88132300

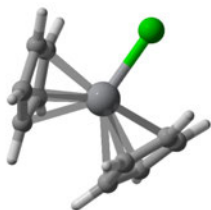
Titanocene(IV) ethoxide, $Cp_2Ti(Cl)(OEt)$



Singlet (closed shell), no imaginary frequencies. E = -1850.762650 Ha.

Ti	0.26266600	0.04191300	0.10634400
Cl	0.66140200	1.63934100	-1.64156600
C	2.32577200	-0.93211500	0.93538500
C	2.65702700	0.30615000	0.35389500
C	2.03865500	1.33621000	1.12771800
C	1.33045600	0.72666100	2.17838000
C	1.46344600	-0.68653400	2.03553500
H	2.61293300	-1.91411100	0.56614000
H	3.24098700	0.46175700	-0.55001800
H	2.08149700	2.40161100	0.91379400
H	0.75082400	1.23848500	2.94269100
H	1.02548700	-1.44361200	2.68306600
C	-1.91579800	1.14075100	-0.10306500
C	-2.08810500	-0.20521200	-0.50815600
C	-1.84294500	-1.03426500	0.61312500
C	-1.51552400	-0.20001300	1.71148700
C	-1.55602200	1.15022800	1.26609900
H	-1.99467100	2.01313400	-0.74550500
H	-2.29428300	-0.54432100	-1.52077000
H	-1.84527800	-2.12256100	0.61707300
H	-1.28732100	-0.53403500	2.72084700
H	-1.34430500	2.03405600	1.86426500
O	0.40043000	-1.37900700	-1.02065400
C	1.32985400	-1.89919600	-1.93401600
H	1.48865900	-2.97166300	-1.70809400
H	2.31181500	-1.39863900	-1.83644000
C	0.80758500	-1.72163700	-3.35453900
H	0.65314800	-0.65030900	-3.55346300
H	-0.15407900	-2.24361600	-3.48082600
H	1.52556800	-2.12308500	-4.08797700

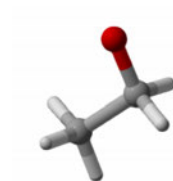
Titanocene(III) chloride, $Cp_2TiCl\bullet$



Doublet, $\langle S^2 \rangle = 0.756$; one residual small imaginary mode (-14.6 cm^{-1} , a hindered Cp/Cl libration) — effectively a minimum. E = -1696.391811 Ha.

Ti	0.00000000	0.23474200	0.18168200
Cl	0.00000000	1.00649500	-2.04548000
C	1.80783200	-1.18032800	0.79865300
C	2.29258000	-0.32231000	-0.22226600
C	2.26736300	1.00973900	0.26670500
C	1.76483500	0.98577300	1.59226600
C	1.49350500	-0.37068000	1.92475700
H	1.70270000	-2.26262800	0.73622100
H	2.57340400	-0.62105700	-1.23057800
H	2.52425700	1.89935700	-0.30573900
H	1.61765900	1.84759900	2.24176900
H	1.12797500	-0.72917300	2.88321800
C	-2.26736300	1.00973900	0.26670500
C	-2.29258000	-0.32231000	-0.22226600
C	-1.80783200	-1.18032800	0.79865300
C	-1.49350500	-0.37068000	1.92475700
C	-1.76483500	0.98577300	1.59226600
H	-2.52425700	1.89935700	-0.30573900
H	-2.57340400	-0.62105700	-1.23057800
H	-1.70270000	-2.26262800	0.73622100
H	-1.12797500	-0.72917300	2.88321800
H	-1.61765900	1.84759900	2.24176900

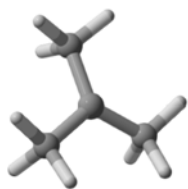
Ethoxyl radical, •OEt (•OCH₂CH₃)



Doublet, $\langle S^2 \rangle = 0.753$, no imaginary frequencies. E = -154.258119 Ha.

O	-1.27900300	1.16137700	-0.18864800
C	-0.77777900	-0.08611100	0.03111100
C	0.77248200	0.03832900	-0.02209200
H	-1.05036200	-0.48329900	1.03265300
H	-1.08500800	-0.81145000	-0.75289100
H	1.20462100	-0.95810100	0.15196400
H	1.09019800	0.40812800	-1.00727200
H	1.12484900	0.73112800	0.75517400

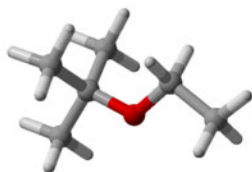
tert-butyl radical, $\bullet\text{C}(\text{CH}_3)_3$



Doublet, $\langle S^2 \rangle = 0.754$, no imaginary frequencies. E = -157.690736 Ha.

C	-0.00330600	0.04172800	0.20097500
C	0.13175200	-1.44273900	0.33201900
C	1.21506800	0.84682500	-0.12528700
C	-1.34825500	0.61407500	-0.11931000
H	1.05741800	-1.72828000	0.86028900
H	0.17416700	-1.93909600	-0.66377800
H	-0.72466000	-1.88995200	0.86495600
H	1.07641500	1.91720600	0.10388800
H	1.46566600	0.78887200	-1.20862600
H	2.10541600	0.48745000	0.41840000
H	-1.58916900	0.51168500	-1.20155700
H	-2.15682800	0.10026500	0.42811700
H	-1.40368300	1.69196000	0.10991100

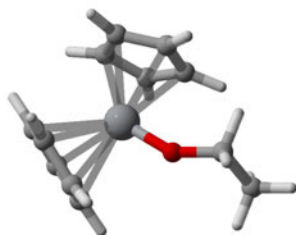
tert-butyl ethyl ether, EtOtBu



Singlet (closed shell); E = -312.083646 Ha.

C	2.77384800	-0.06424900	0.88686500
C	1.50830500	0.51884300	0.28120900
O	0.50689900	-0.47858700	0.33246800
C	-0.80317900	-0.18539300	-0.18260100
C	-1.58035500	-1.48386800	0.05072000
C	-0.74574900	0.13391900	-1.68439400
C	-1.45546500	0.96808700	0.59499000
H	3.58952800	0.67548200	0.87145400
H	3.09620900	-0.95328000	0.32200500
H	2.59605300	-0.36812000	1.93061300
H	1.70426200	0.84023500	-0.76029300
H	1.20542000	1.42340500	0.84372500
H	-1.09569300	-2.31528600	-0.48403300
H	-2.61799400	-1.39260400	-0.30421100
H	-1.59389900	-1.72760400	1.12426800
H	-0.23774900	1.09013100	-1.88188700
H	-1.76312000	0.20783100	-2.09834100
H	-0.20757300	-0.66334400	-2.22068500
H	-0.94959500	1.92749200	0.40775800
H	-2.50792700	1.08456200	0.29397700
H	-1.42222700	0.76234800	1.67639200

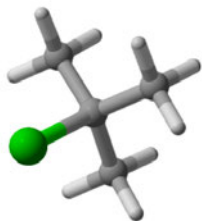
Titanocene(III) ethoxide, $Cp_2Ti(OEt)$



Doublet, $\langle S^2 \rangle = 0.754$; E(def2-SVP) = -1390.632333 Ha; E(def2-TZVPP) = -1391.341771 Ha;
E(ω B97X-D) = -1390.419730 Ha; H_{corr} = 0.253037 Ha; G_{corr} = 0.195188 Ha

Ti	0.11655000	-0.37129000	0.34187800
C	2.30365000	-1.14786500	0.99687900
C	2.49398500	0.01662900	0.21113100
C	1.90859600	1.11538400	0.89442900
C	1.37508200	0.62543000	2.11664500
C	1.60091000	-0.77680900	2.17367800
H	2.60207100	-2.15914500	0.72253500
H	2.96625300	0.05496400	-0.76915500
H	1.88841600	2.14951200	0.55279800
H	0.87301500	1.22388700	2.87308700
H	1.29733800	-1.44395700	2.97957600
C	-2.01732000	0.52288700	-0.37079200
C	-2.22721300	-0.83276700	-0.02051600
C	-1.96829900	-0.98006600	1.36958000
C	-1.63616100	0.30364700	1.88261200
C	-1.64256700	1.22768000	0.80643600
H	-2.09060200	0.94278500	-1.37338300
H	-2.46415500	-1.63781700	-0.71364500
H	-2.04267200	-1.90205200	1.94526100
H	-1.39365200	0.52843500	2.91879900
H	-1.40259200	2.28847700	0.87056200
O	0.31426100	-1.27312000	-1.24766200
C	1.17674200	-1.83227500	-2.18645100
H	0.77504300	-2.81115700	-2.51931600
H	2.17165700	-2.04028800	-1.73955100
C	1.34348300	-0.91434500	-3.39340200
H	1.77659400	0.05006600	-3.08143000
H	0.36507200	-0.71248700	-3.85832300
H	2.00499100	-1.36731700	-4.14994000

***tert*-butyl chloride, (CH₃)₃CCl**



Singlet (closed shell); E(def2-SVP) = -617.827888 Ha; E(def2-TZVPP) = -618.168621 Ha; E(ω B97X-D) = -617.758227 Ha; H_{corr} = 0.129189 Ha; G_{corr} = 0.092317 Ha

C	-0.00751000	0.09457300	0.45547100
C	0.12967600	-1.41907900	0.32163000
C	1.19436200	0.83134800	-0.12803600
C	-1.32516500	0.60256800	-0.12206700
H	1.06008400	-1.77417000	0.78863600
H	0.15206100	-1.68870000	-0.74741200
H	-0.71973000	-1.93578500	0.79210500
H	1.10351500	1.91705600	0.02296900
H	1.25030500	0.63426100	-1.21159000
H	2.13094200	0.48870300	0.33588800
H	-1.35016000	0.39751000	-1.20529100
H	-2.18257600	0.09753500	0.34657200
H	-1.43030100	1.68706700	0.02840300
Cl	-0.03780500	0.47468700	2.28588400

10. Chemical Space Analysis and HTE Setup

Chemical Space Analysis

Data availability: All structures (as SMILES strings), features and code used to generate the UMAP chemical spaces and determination of the Vendi scores can be found on this GitHub repository: https://github.com/JohannesGrosskopf/Ether_SH2_ChemicalSpaceAnalysis

The diversity of the 84 compounds used in the reaction scope was assessed initially by comparison of the starting amines with the Enamine alcohol library chemical space. The Enamine alcohol library of 55,928 total compounds was obtained from the Enamine website in the form of 2D structures (SD files): <https://enamine.net/building-blocks/functional-classes>, version dated 10/07/2026.

The alcohol substrates were featurized using circular Morgan fingerprints as implemented in RDKit. Morgan fingerprints were generated for all compounds in the Enamine alcohol library using the `rdFingerprintGenerator.GetMorganGenerator` function with a radius of 2 and a fingerprint length of 2048 bits. These fingerprints were used both for chemical space embedding and for similarity-based diversity analysis. Owing to the size of the Enamine alcohol library, the Uniform Manifold Approximation and Projection (UMAP) dimensionality reduction algorithm (`umap-learn`, version 0.5.9.post2) was employed to construct low-dimensional representations of chemical space while preserving its global structure. UMAP models were fit exclusively to the Enamine library and subsequently used to project all experimentally tested and newly proposed substrates into the same latent space using the following hyperparameters: `n_components = 2`, `random_state = 42`, `n_neighbors = 25`, and `min_dist = 0.15`.

In parallel with the UMAP-based chemical space analysis, the diversity of the substrate scope was quantified using the Vendi score. Pairwise molecular similarities were computed using the Tanimoto coefficient derived from the 2048-bit Morgan fingerprints, and the resulting similarity matrix was used to calculate the Vendi score as an effective-rank-based measure of chemical diversity. Prior to visualization, robust axis limits were determined using percentile-based clipping of the embedded Enamine dataset to mitigate the influence of outlier structures while preserving the overall organization of chemical space.

Vendi Score (scope; 2048-bit Morgan, Tanimoto): 32

Vendi Score (scope + HTE; 2048-bit Morgan, Tanimoto): 38

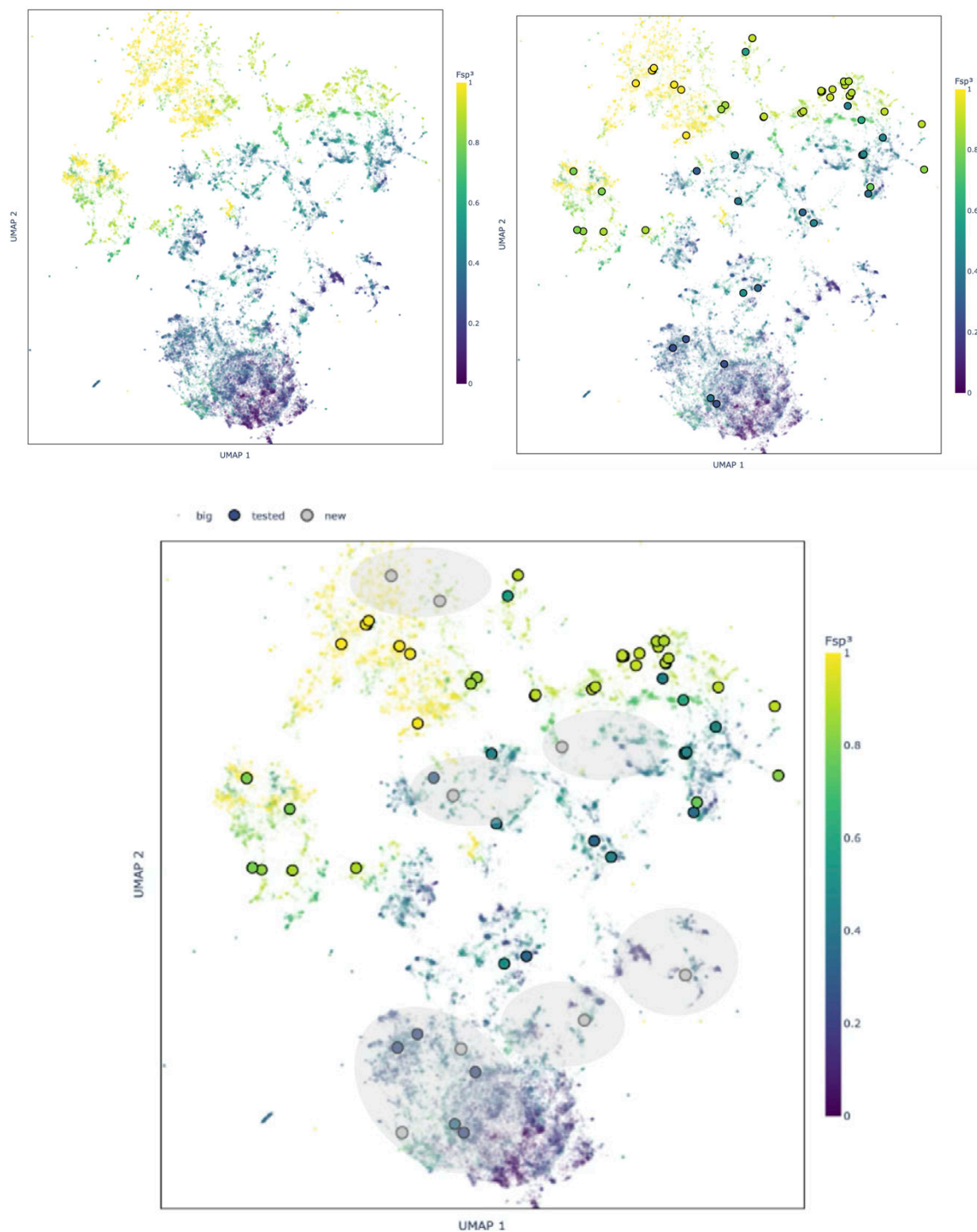


Figure S10.1. top left: Mapped chemical space of the Enamine alcohol library (55,928 compounds); top right: projection of tested alcohols of the reaction scope (56 compounds, excluding complex examples and drugs) onto chemical space; bottom: identification of underrepresented areas and selection of representative examples.

HTE Matrix Screen

For the HTE screening, reactions were set up on a 10 μmol scale. The same equivalencies as given in general procedure B were used, comprising the respective redox-active ester (1.00 equiv.), 4DPAIPN (5 mol%), Cp_2TiCl_2 (10 mol%), $\text{Zn}_3(\text{PO}_4)_2$ (0.75 equiv. for primary alcohols) or $[\text{ZnCO}_3]_2 \cdot [\text{Zn}(\text{OH})_2]_3$ (0.5 equiv. for secondary alcohols), and the corresponding alcohols (3.00 equiv.) in DCE (0.1 M). To expedite reaction setup as well as maintain accuracy on the chosen reaction scale, stock solutions were used to ensure for exact reagent measurements.

Each HPLC reaction vial (8×30 mm) was charged with the appropriate Zn salt and transferred into a glove bag that was continuously purged with nitrogen to ensure oxygen-free conditions. Within the glove bag, 50 μmol of a pre-degassed stock solution containing 4DPAIPN, Cp_2TiCl_2 , and the corresponding redox-active ester in DCE was added to each vial, followed by 50 μmol of a DCE stock solution of the respective alcohol. The vials were placed in a high-throughput experimentation (HTE) temperature-controlled reactor (TCR) compatible with a 48-well Lumidox setup. A PFA film was placed over the vials, followed by a blue fluorosilicone gasket to seal the array. The corresponding lid was positioned on top of the gasket and tightly secured. To ensure mixing, the array was placed on an orbital shaker for 1 min prior to irradiation. Irradiation was conducted without stirring using a 48-reaction 505 nm LED array at output level 2 (4.1 W), with the external cooling unit set to 20 $^\circ\text{C}$. After 14 h of irradiation, the lid was removed and 50 μmol of mesitylene was added to each vial as an internal standard. Reaction outcomes were analyzed by UPLC or ^1H -NMR spectroscopy. Due to variations in UPLC response factors across the reaction matrix, product formation was quantified by monitoring the conversion of the alcohol, for which response factors had been independently determined. For ^1H NMR analysis, product formation was assessed directly from the product peaks.

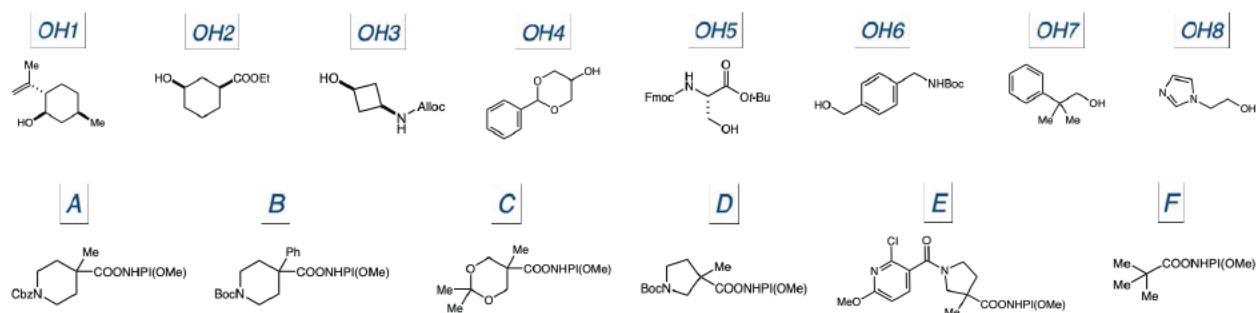


Figure S10.2. List of tested alcohols, picked from underrepresented areas of chemical space and redox active esters.

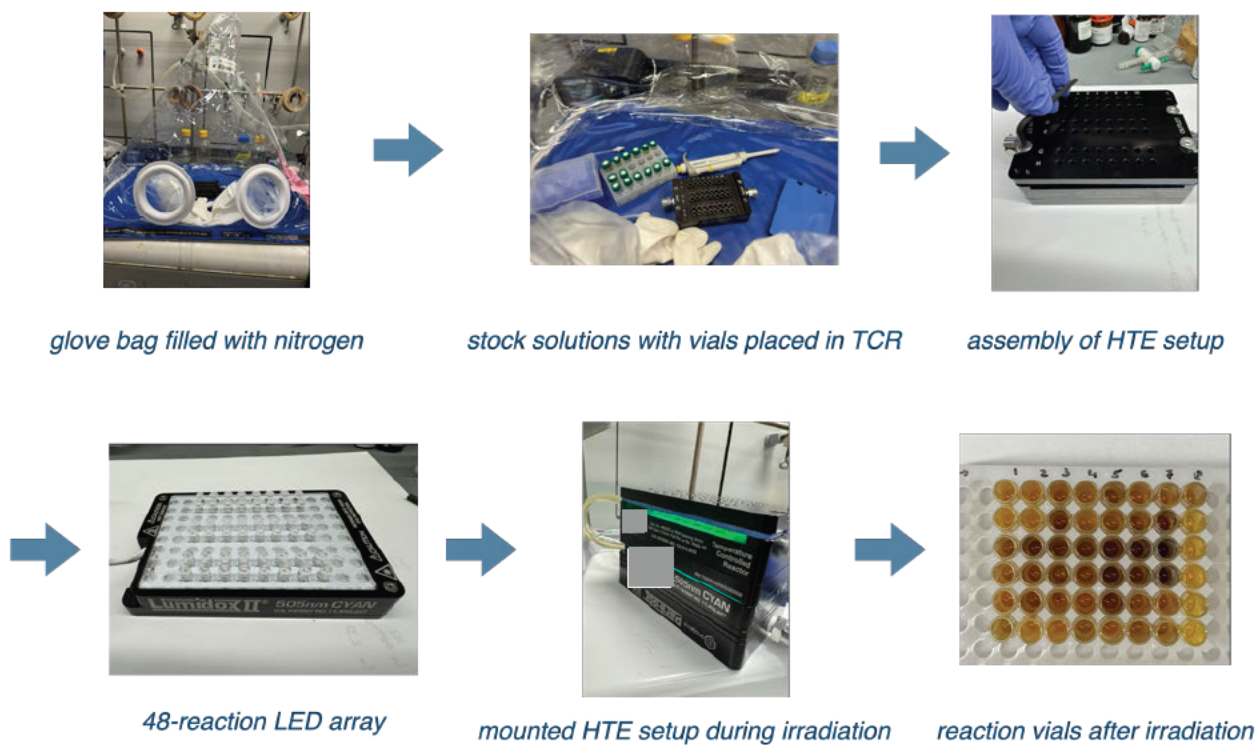


Figure S10.3. Irradiation setup for HTE screening.

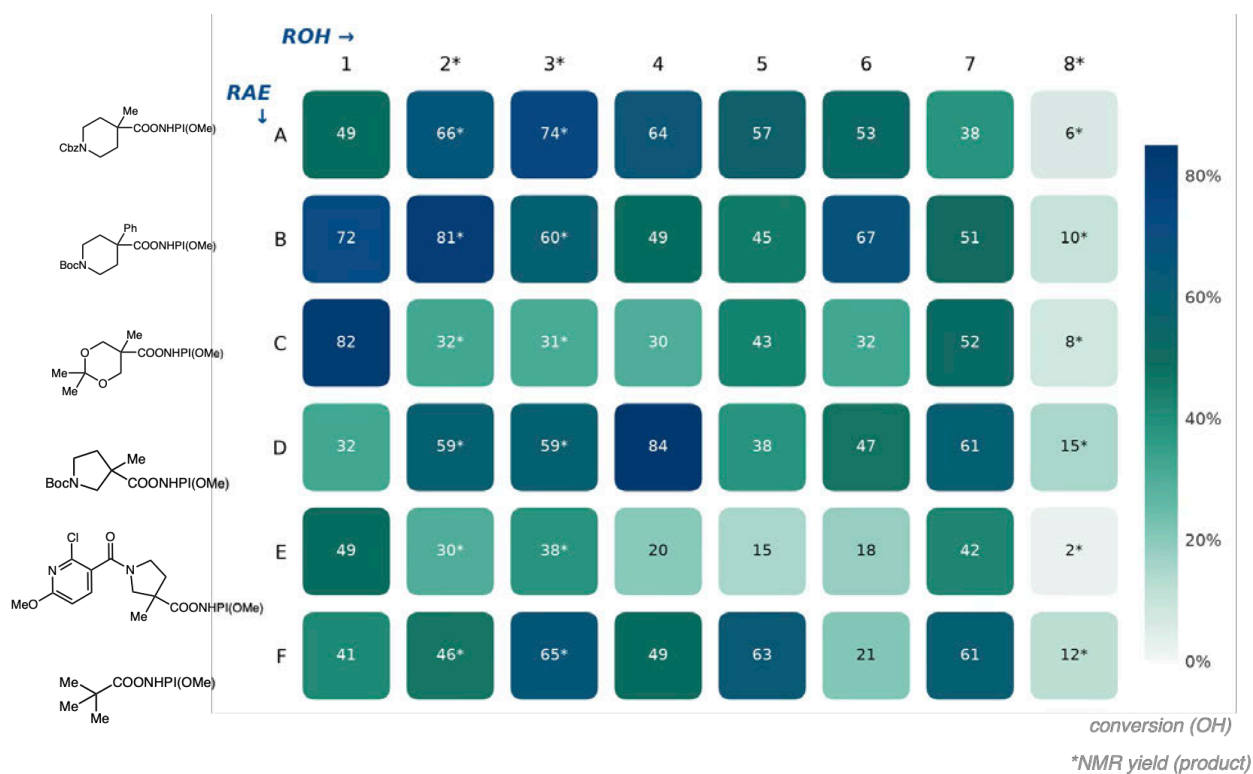


Figure S10.4. Matrix screen between six redox active esters and eight alcohols with the respective, color-coded yields based on UPLC or ^1H -NMR analysis.

Table S10.1. Results of the matrix screen between six redox active esters and eight alcohols with the respective based on UPLC or ^1H -NMR analysis (conversion of alcohol; *product yield; values in %).

	OH1	OH2*	OH3*	OH4	OH5	OH6	OH7	OH8*
RAE1	49	66	74	64	57	53	38	6
RAE2	72	81	60	49	45	67	51	10
RAE3	82	32	31	30	43	32	52	8
RAE4	32	59	59	84	38	47	61	15
RAE5	49	30	38	20	15	18	42	2
RAE6	41	46	65	49	63	21	61	12

RAE1

RAE2

RAE3

RAE4

RAE5

RAE6

RAE7

RAE8

RAE9

RAE10

RAE11

RAE12

RAE13

RAE14

RAE15

RAE16

RAE17

RAE18

RAE19

RAE20

RAE21

RAE22

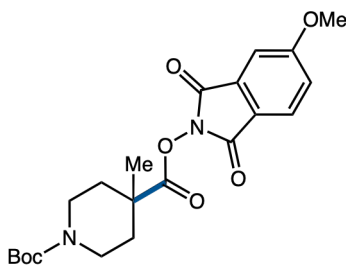
RAE23

RAE24

RAE25

RAE26

RAE27

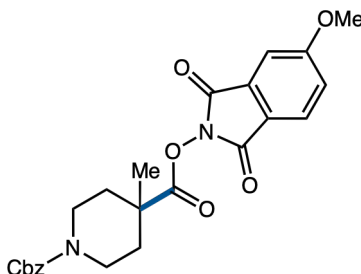


RAE-1 (14)

Prepared according to the general procedure A.

^1H NMR (500 MHz, CDCl_3) δ 7.79 (d, J = 8.4 Hz, 1H), 7.36 (d, J = 2.3 Hz, 1H), 7.22 (dd, J = 8.4, 2.3 Hz, 1H), 3.94 – 3.92 (m, 5H), 3.13 (t, J = 12.1 Hz, 2H), 2.25 (dq, J = 13.7, 2.3 Hz, 2H), 1.56 – 1.49 (m, 3H), 1.48 (s, 3H), 1.46 (s, 9H).

^{13}C NMR (125 MHz, CDCl_3) δ 172.97, 165.33, 162.33, 162.18, 154.84, 131.68, 126.06, 120.84, 120.47, 109.12, 79.74, 56.34, 41.91, 34.96, 28.59, 26.33.

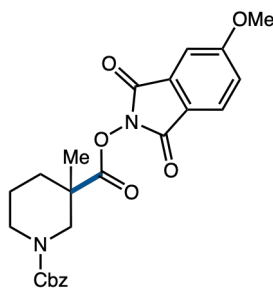


RAE-2

Prepared according to the general procedure A.

^1H NMR (500 MHz, CDCl_3) δ 7.79 (d, J = 8.4 Hz, 1H), 7.37 – 7.35 (m, 5H), 7.32 (ddd, J = 8.7, 5.3, 3.5 Hz, 1H), 7.22 (dd, J = 8.4, 2.3 Hz, 1H), 5.14 (s, 2H), 4.03 (m, 2H), 3.95 (s, 3H), 3.21 (m, 2H), 2.29 – 2.26 (m, 2H), 1.54 (m, 2H), 1.48 (s, 3H).

^{13}C NMR (125 MHz, CDCl_3) δ 172.86, 165.35, 162.31, 162.15, 155.35, 136.92, 131.67, 128.65, 128.15, 128.04, 126.09, 120.82, 120.50, 109.14, 67.30, 56.35, 41.88, 41.47, 35.05, 34.82, 26.41.

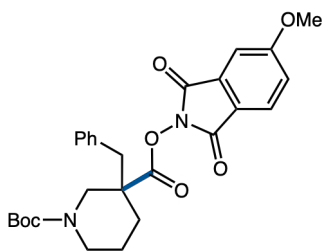


RAE-3

Prepared according to the general procedure A.

¹H NMR (500 MHz, CDCl₃) δ 7.78 (d, J = 8.4 Hz, 1H), 7.36 – 7.18 (m, 7H), 5.16 – 5.13 (m, 3H), 4.26 – 4.15 (m, 1H), 3.94 (s, 3H), 3.73 (dd, J = 13.1, 5.6 Hz, 1H), 3.29 – 3.26 (m, 2H), 2.31 – 2.28 (m, 1H), 1.72 – 1.65 (m, 3H), 1.42 (s, 3H).

¹³C NMR (125 MHz, CDCl₃) δ 172.06, 165.26, 155.36, 131.71, 128.56, 128.10, 128.01, 126.00, 120.89, 120.42, 109.04, 67.40, 56.33, 50.91, 43.95, 42.60, 34.03, 22.27, 21.87.

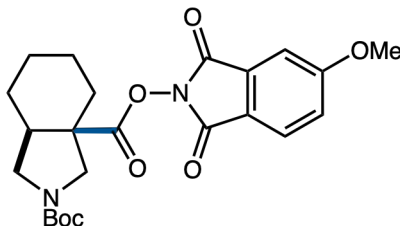


RAE-4

Prepared according to the general procedure A.

¹H NMR (500 MHz, CDCl₃) δ 7.79 (d, J = 8.4 Hz, 1H), 7.38 – 7.29 (m, 7H), 7.21 (dd, J = 8.4, 2.4 Hz, 1H), 4.42 – 3.61 (s, 6H), 3.34 – 2.93 (m, 3H), 2.21 (m, 1H), 1.75 – 1.58 (m, 4H), 1.43 (s, 9H), 1.14 (d, J = 6.4 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃) δ 170.98, 165.23, 154.83, 131.71, 130.54, 128.51, 127.25, 125.97, 120.90, 120.40, 109.01, 79.96, 56.31, 47.69, 42.41, 28.49, 23.65.

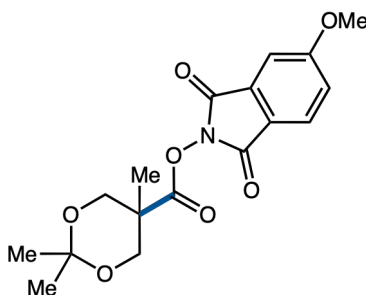


RAE-5

Prepared according to the general procedure A.

¹H NMR (500 MHz, CDCl₃) δ 7.80 (dd, *J* = 8.4, 3.2 Hz, 1H), 7.36 (d, *J* = 2.4 Hz, 1H), 7.22 (dt, *J* = 9.1, 2.9 Hz, 1H), 4.17 (d, *J* = 12.2 Hz, 1H), 3.95 – 3.94(m, 4H), 3.91 – 3.75 (m, 3H), 3.74 – 3.55 (m, 3H), 3.46 – 3.35 (m, 1H), 2.98 – 2.92 (m, 1H), 2.06 – 1.99 (m, 1H), 1.60 – 1.54 (m, 21H), 1.48 (s, 9H).

¹³C NMR (125 MHz, CDCl₃) δ 170.07, 170.02, 165.40, 165.36, 162.01, 161.95, 161.83, 154.68, 131.58, 126.18, 126.15, 120.71, 120.61, 120.59, 109.20, 109.15, 80.22, 80.04, 67.60, 65.22, 56.36, 50.10, 49.81, 49.40, 49.22, 48.84, 37.48, 36.59, 28.62, 24.82.

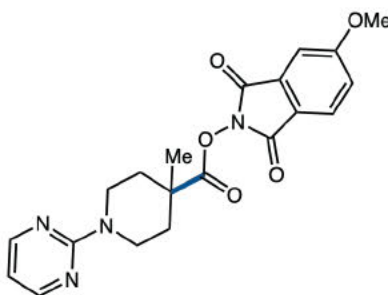


RAE-6

Prepared according to the general procedure A.

¹H NMR (500 MHz, CDCl₃) δ 7.80 (d, *J* = 8.4 Hz, 1H), 7.36 (d, *J* = 2.3 Hz, 1H), 7.22 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.34 (d, *J* = 11.8 Hz, 2H), 3.94 (s, 3H), 3.79 (d, *J* = 11.9 Hz, 2H), 1.49 (s, 3H), 1.47 (s, 6H).

^{13}C NMR (125 MHz, CDCl_3) δ 170.92, 165.31, 162.09, 161.92, 131.66, 126.07, 120.83, 120.52, 109.08, 98.74, 65.80, 56.33, 42.04, 24.19, 23.25, 18.55.

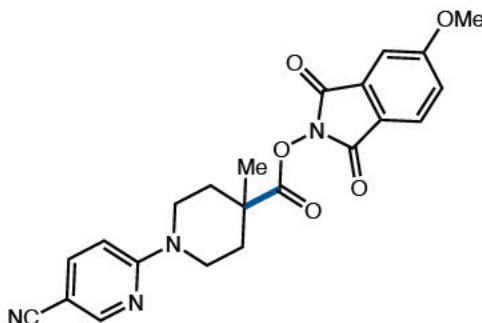


RAE-7

Prepared according to the general procedure A.

^1H NMR (500 MHz, CDCl_3) δ 8.30 (d, J = 4.7 Hz, 2H), 7.79 (d, J = 8.3 Hz, 1H), 7.36 (d, J = 2.3 Hz, 1H), 7.22 (dd, J = 8.4, 2.3 Hz, 1H), 6.47 (t, J = 4.8 Hz, 1H), 4.56 – 4.38 (m, 2H), 3.94 (s, 3H), 3.42 (ddd, J = 14.0, 11.1, 2.8 Hz, 2H), 2.35 (dq, J = 13.9, 2.4 Hz, 2H), 1.60 (ddd, J = 13.8, 11.1, 4.1 Hz, 2H), 1.51 (s, 3H).

^{13}C NMR (125 MHz, CDCl_3) δ 173.23, 165.30, 162.35, 162.19, 161.69, 157.89, 131.72, 126.04, 120.88, 120.46, 109.76, 109.09, 56.33, 42.25, 41.29, 34.81, 26.25.



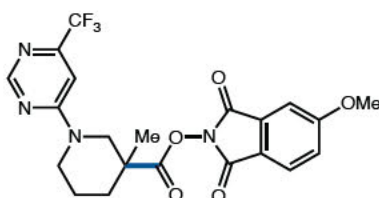
RAE-8

Prepared according to the general procedure A.

^1H NMR (500 MHz, CDCl_3) δ 8.40 (d, J = 2.3 Hz, 1H), 7.80 (d, J = 8.3 Hz, 1H), 7.60 (dd, J = 9.0, 2.3 Hz, 1H), 7.36 (d, J = 2.3 Hz, 1H), 7.23 (dd, J = 8.4, 2.4 Hz, 1H), 6.62 (d, J = 9.0 Hz,

1H), 4.26 (d, $J = 14.2$ Hz, 2H), 3.95 (s, 3H), 3.36 (ddd, $J = 14.1, 11.4, 2.7$ Hz, 2H), 2.39 (dt, $J = 13.8, 2.5$ Hz, 2H), 1.61 (ddd, $J = 13.8, 11.5, 4.2$ Hz, 2H), 1.51 (s, 3H).

^{13}C NMR (125 MHz, CDCl_3) δ 172.86, 165.39, 162.32, 162.17, 159.28, 152.92, 139.99, 131.63, 126.12, 120.76, 120.51, 118.87, 109.20, 105.85, 96.23, 56.36, 42.28, 42.09, 34.68, 26.34.



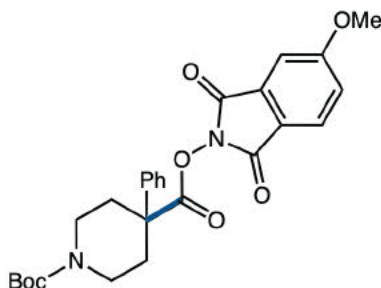
RAE-9

Prepared according to the general procedure A.

^1H NMR (500 MHz, CDCl_3) δ 8.66 (d, $J = 1.1$ Hz, 1H), 7.75 (d, $J = 8.4$ Hz, 1H), 7.32 (d, $J = 2.3$ Hz, 1H), 7.20 (dd, $J = 8.4, 2.4$ Hz, 1H), 6.92 (d, $J = 1.1$ Hz, 1H), 3.93 (s, 3H), 3.25 – 3.19 (m, 2H), 2.51 (dt, $J = 13.8, 4.7$ Hz, 1H), 1.90 – 1.84 (m, 2H), 1.75 – 1.70 (m, 1H), 1.58 (m, 1H), 1.51 (s, 3H).

^{13}C NMR (125 MHz, CDCl_3) δ 171.81, 165.34, 162.08, 158.92, 154.62, 154.35, 131.56, 126.09, 122.28, 120.71, 120.55, 120.10, 109.11, 99.51, 56.33, 51.46, 44.08, 43.34, 34.38, 23.22, 22.45.

^{19}F NMR (282 MHz, CDCl_3) δ -70.55.



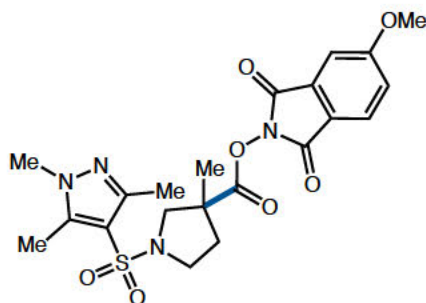
RAE-10

Prepared according to the general procedure A.

¹H NMR (500 MHz, CDCl₃) δ 7.77 (d, J = 8.3 Hz, 1H), 7.50 – 7.48 (m, 2H), 7.43 (dd, J = 8.6, 6.9 Hz, 2H), 7.36 – 7.35 (m, 1H), 7.33 (d, J = 2.3 Hz, 1H), 7.21 (dd, J = 8.3, 2.4 Hz, 1H), 4.30 – 4.07 (m, 2H), 3.93 (s, 3H), 3.24 (m, 2H), 2.64 – 2.62f (m, 2H), 2.01 (ddd, J = 18.1, 11.2, 4.5 Hz, 2H), 1.48 (s, 9H).

¹³C NMR (125 MHz, CDCl₃) δ 171.14, 165.33, 162.19, 162.04, 154.81, 140.77, 131.62, 129.12, 128.15, 126.07, 126.01, 120.78, 120.47, 109.13, 79.85, 56.32, 49.92, 34.49, 28.60.

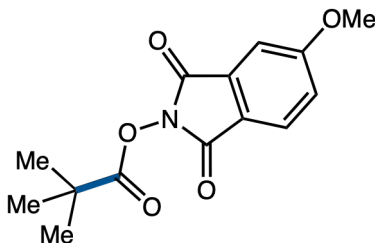
RAE-11



Prepared according to the general procedure A.

¹H NMR (500 MHz, CDCl₃) δ 7.77 (d, J = 8.3 Hz, 1H), 7.34 (d, J = 2.3 Hz, 1H), 7.22 (dd, J = 8.4, 2.3 Hz, 1H), 3.94 (s, 3H), 3.83 (dq, J = 13.0, 6.5 Hz, 1H), 3.74 (d, J = 10.2 Hz, 1H), 3.70 (s, 3H), 3.57 (ddd, J = 9.5, 7.9, 4.6 Hz, 1H), 3.38 – 3.27 (m, 2H), 2.56 (ddd, J = 12.7, 7.7, 4.7 Hz, 1H), 2.49 (s, 3H), 2.40 (s, 3H), 2.08 – 1.98 (m, 1H), 1.14 (d, J = 6.4 Hz, 5H).

¹³C NMR (125 MHz, CDCl₃) δ 171.73, 165.40, 161.91, 161.75, 148.31, 142.61, 131.50, 126.10, 120.60, 120.50, 113.13, 109.24, 56.36, 55.73, 48.04, 46.48, 42.37, 36.49, 36.36, 23.62, 22.94, 13.59, 11.14.

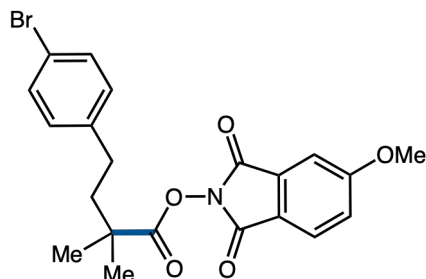


RAE-12

Prepared according to the general procedure A.

^1H NMR (500 MHz, CDCl_3) δ 7.79 (d, J = 8.3 Hz, 1H), 7.35 (d, J = 2.3 Hz, 1H), 7.21 (dd, J = 8.3, 2.3 Hz, 1H), 3.94 (s, 3H), 1.43 (s, 9H).

^{13}C NMR (125 MHz, CDCl_3) δ 174.67, 165.24, 162.39, 162.25, 131.75, 125.95, 120.94, 120.38, 109.00, 56.31, 38.54, 27.19.

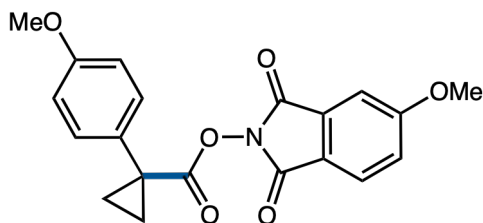


RAE-13

Prepared according to the general procedure A.

^1H NMR (500 MHz, CDCl_3) δ 7.80 (d, J = 8.3 Hz, 1H), 7.41 (d, J = 8.3 Hz, 2H), 7.37 (d, J = 2.4 Hz, 1H), 7.22 (dd, J = 8.3, 2.4 Hz, 1H), 7.16 (d, J = 8.3 Hz, 2H), 3.95 (s, 3H), 2.73 – 2.70 (m, 2H), 2.01 – 1.96 (m, 2H), 1.45 (s, 6H).

^{13}C NMR (125 MHz, CDCl_3) δ 173.77, 165.30, 162.42, 162.26, 141.06, 131.72, 131.63, 130.40, 126.02, 120.89, 120.45, 119.82, 109.08, 56.33, 43.14, 42.43, 31.01, 25.27.

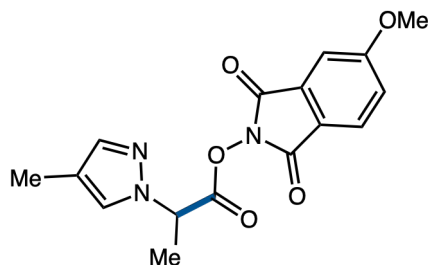


RAE-14

Prepared according to the general procedure A.

¹H NMR (500 MHz, CDCl₃) δ 7.76 (d, J = 8.4 Hz, 1H), 7.45 – 7.42 (m, 2H), 7.32 (d, J = 2.3 Hz, 1H), 7.18 (dd, J = 8.4, 2.3 Hz, 1H), 6.90 – 6.87 (m, 2H), 3.92 (s, 3H), 3.80 (s, 3H), 1.87 (q, J = 4.1 Hz, 2H), 1.43 (q, J = 4.3 Hz, 2H).

¹³C NMR (125 MHz, CDCl₃) δ 171.59, 165.20, 162.17, 162.03, 159.33, 131.88, 131.66, 129.30, 125.94, 120.84, 120.37, 113.97, 108.98, 56.30, 55.42, 26.68, 18.98.

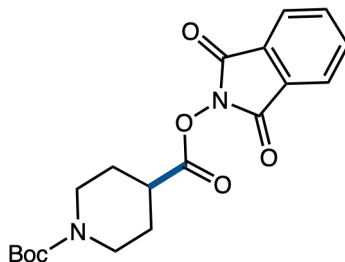


RAE-15

Prepared according to the general procedure A.

¹H NMR (500 MHz, CDCl₃) δ 7.78 (d, J = 8.4 Hz, 1H), 7.40 (s, 1H), 7.39 (s, 1H), 7.35 (d, J = 2.4 Hz, 1H), 7.21 (dd, J = 8.3, 2.4 Hz, 1H), 5.46 (q, J = 7.3 Hz, 1H), 3.93 (s, 3H), 2.10 (s, 3H), 1.97 (d, J = 7.4 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃) δ 167.64, 165.40, 161.70, 161.52, 140.84, 140.22, 131.49, 128.13, 127.23, 126.18, 125.44, 120.64, 120.61, 119.54, 117.53, 109.18, 108.91, 58.98, 57.54, 56.35, 19.11, 18.08, 9.09.

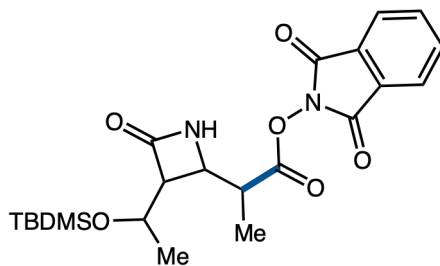


RAE-16

Prepared according to the general procedure A.

^1H NMR (500 MHz, CDCl_3) δ 7.89 (dd, $J = 5.5, 3.1$ Hz, 2H), 7.79 (dd, $J = 5.5, 3.1$ Hz, 2H), 4.04 (s, 2H), 3.01 (t, $J = 12.0$ Hz, 2H), 2.91 (tt, $J = 10.3, 4.0$ Hz, 1H), 2.07 (dd, $J = 13.4, 3.9$ Hz, 2H), 1.86 (dtd, $J = 14.4, 10.6, 4.1$ Hz, 2H), 1.47 (s, 9H).

^{13}C NMR (125 MHz, CDCl_3) δ 170.80, 162.06, 154.72, 134.95, 129.08, 124.15, 79.98, 38.71, 28.57, 27.90.

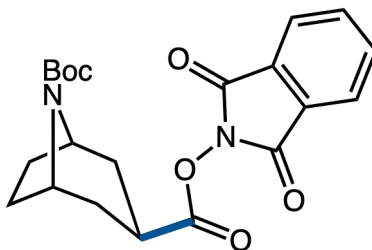


RAE-17

Prepared according to the general procedure A.

^1H NMR (500 MHz, CDCl_3) δ 7.90 (dd, $J = 5.5, 3.1$ Hz, 2H), 7.81 (dd, $J = 5.5, 3.1$ Hz, 2H), 5.98 (s, 1H), 4.26 – 4.20 (m, 1H), 4.14 (dd, $J = 4.8, 2.3$ Hz, 1H), 3.14 (qd, $J = 7.1, 4.8$ Hz, 1H), 3.09 (dd, $J = 4.7, 2.3$ Hz, 1H), 1.44 (d, $J = 7.1$ Hz, 3H), 1.24 (d, $J = 6.3$ Hz, 3H), 0.89 (s, 9H), 0.09 (d, $J = 2.1$ Hz, 6H).

^{13}C NMR (125 MHz, CDCl_3) δ 170.65, 167.81, 161.92, 135.06, 128.99, 124.26, 65.46, 61.76, 51.46, 40.04, 25.90, 22.70, 18.09, 11.92, -4.10, -4.85.

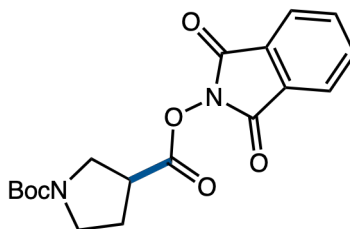


RAE-18

Prepared according to the general procedure A.

¹H NMR (500 MHz, CDCl₃) δ 7.88 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.79 (dd, *J* = 5.5, 3.1 Hz, 2H), 4.38 – 4.29 (m, 2H), 3.24 (tt, *J* = 11.9, 5.5 Hz, 1H), 2.08 – 2 (m, 4H), 1.94 (ddd, *J* = 13.5, 5.5, 2.5 Hz, 2H), 1.734 – 1.70 (m, 1H), 1.48 (s, 9H).

¹³C NMR (125 MHz, CDCl₃) δ 171.17, 162.06, 153.26, 134.93, 129.07, 124.14, 79.82, 53.10, 52.40, 32.95, 28.64.

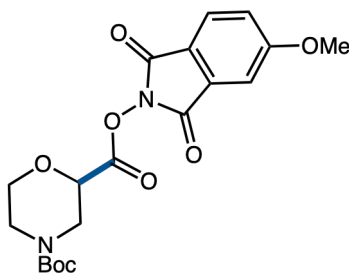


RAE-19

Prepared according to the general procedure A.

¹H NMR (500 MHz, CDCl₃) δ 7.90 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.80 (dd, *J* = 5.5, 3.1 Hz, 2H), 3.78 – 3.40 (m, 5H), 2.35 – 2.33 (m, 2H), 1.47 (s, 9H).

¹³C NMR (125 MHz, CDCl₃) δ 169.78, 161.91, 154.25, 135.01, 129.02, 124.21, 47.98, 47.66, 45.26, 45.05, 40.76, 39.93, 28.62.

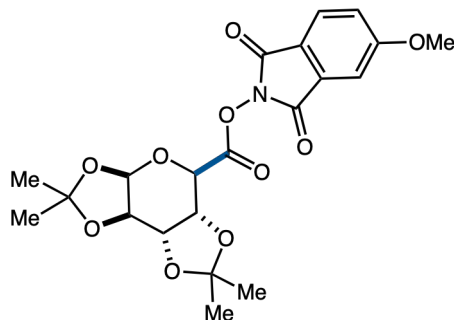


RAE-20

Prepared according to the general procedure A.

¹H NMR (500 MHz, CDCl₃) δ 7.77 (d, J = 7.6 Hz, 1H), 7.70 (s, 1H), 7.58 (d, J = 7.7 Hz, 1H), 4.52 (dd, J = 8.8, 3.4 Hz, 1H), 4.27 – 4.03 (m, 2H), 3.77 – 3.65 (m, 2H), 3.48 (m, 1H), 3.26 (ddd, J = 13.2, 9.5, 3.4 Hz, 1H), 2.53 (s, 3H), 1.49 (s, 9H).

¹³C NMR (125 MHz, CDCl₃) δ 165.84, 161.80, 161.68, 154.40, 146.60, 135.53, 134.98, 129.25, 126.27, 124.80, 124.34, 124.23, 123.69, 81.02, 72.53, 66.26, 28.45, 22.33.

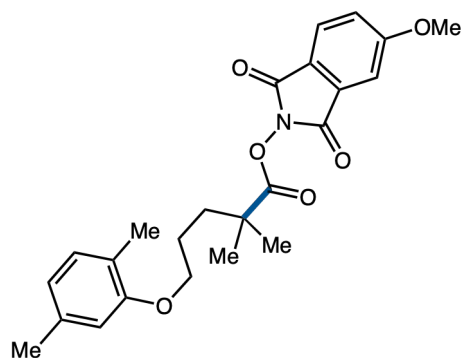


RAE-21

Prepared according to the general procedure A.

¹H NMR (500 MHz, CDCl₃) δ 7.80 (d, J = 8.4 Hz, 1H), 7.37 (d, J = 2.3 Hz, 1H), 7.22 (dd, J = 8.3, 2.3 Hz, 1H), 5.70 (d, J = 4.9 Hz, 1H), 4.82 (d, J = 2.3 Hz, 1H), 4.73 (qd, J = 7.5, 2.5 Hz, 2H), 4.45 (dd, J = 5.0, 2.7 Hz, 1H), 3.94 (s, 3H), 1.60 (s, 3H), 1.54 (s, 3H), 1.41 (s, 3H), 1.37 (s, 3H).

¹³C NMR (125 MHz, CDCl₃) δ 165.30, 165.00, 161.65, 161.46, 131.58, 126.12, 120.76, 120.58, 111.06, 109.62, 109.06, 96.64, 72.09, 70.98, 70.34, 68.48, 56.32, 26.22, 26.07, 25.13, 24.92.

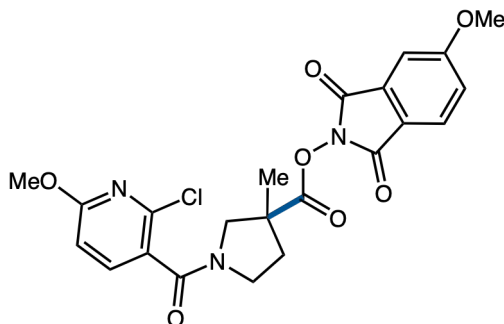


RAE-22

Prepared according to the general procedure A.

^1H NMR (500 MHz, CDCl_3) δ 7.79 (d, J = 8.3 Hz, 1H), 7.36 (d, J = 2.3 Hz, 1H), 7.21 (dd, J = 8.4, 2.3 Hz, 1H), 7.00 (d, J = 7.3 Hz, 1H), 6.66 (d, J = 7.8 Hz, 2H), 4.00 (t, J = 3.5 Hz, 2H), 3.94 (s, 3H), 2.31 (s, 3H), 2.19 (s, 3H), 1.98 – 1.92 (m, 4H), 1.44 (s, 6H).

^{13}C NMR (125 MHz, CDCl_3) δ 174.05, 165.25, 162.39, 162.24, 157.12, 136.62, 131.74, 130.40, 125.97, 123.76, 120.93, 120.82, 120.38, 112.15, 109.03, 67.90, 56.32, 42.08, 37.55, 25.28, 25.13, 21.54, 15.93.

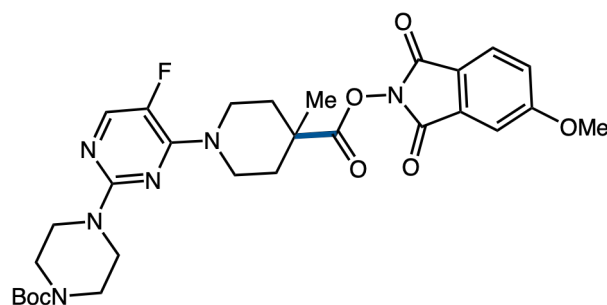


RAE-23

Prepared according to the general procedure A.

^1H NMR (500 MHz, CDCl_3) δ (summary of rotamers) 7.81 – 7.73 (m, 1H), 7.64 – 7.54 (m, 1H), 7.37 – 7.32 (m, 1H), 7.24 – 7.14 (m, 1H), 6.74 – 6.70 (m, 1H), 4.14 – 3.50 (m, 10H), 2.73 – 2.41 (m, 1H), 2.14 – 1.85 (m, 1H), 1.68 – 1.35 (m, 3H).

¹³C NMR (125 MHz, CDCl₃) δ (summary of rotamers) 171.73, 171.46, 165.92, 165.87, 165.43, 165.41, 165.01, 164.02, 163.96, 162.06, 162.01, 161.88, 161.83, 157.45, 144.42, 144.27, 139.59, 139.40, 139.30, 139.27, 131.60, 131.54, 126.20, 126.18, 125.53, 125.21, 125.10, 120.72, 120.65, 120.63, 120.61, 119.67, 110.17, 110.04, 110.03, 109.99, 109.22, 109.20, 108.98, 60.56, 56.49, 56.39, 56.37, 56.25, 54.94, 54.56, 54.48, 48.76, 48.18, 47.21, 46.79, 46.51, 44.79, 44.66, 42.74, 36.55, 36.08, 35.04, 34.78, 23.48, 22.38, 22.20, 21.82, 21.61, 21.21, 14.35.



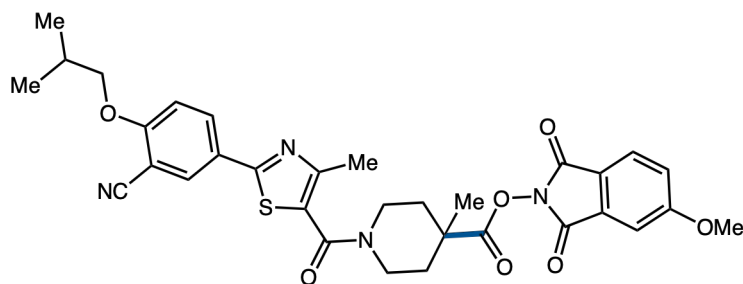
RAE-24

Prepared according to the general procedure A.

¹H NMR (500 MHz, CDCl₃) δ 7.80 (m, 2H), 7.37 (d, *J* = 2.3 Hz, 1H), 7.23 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.29 (d, *J* = 13.9 Hz, 2H), 3.95 (s, 3H), 3.67 (m, 4H), 3.48 (m, 4H), 3.34 (t, *J* = 12.7 Hz, 2H), 2.37 (d, *J* = 13.8 Hz, 2H), 1.68 – 1.62 (m, 2H), 1.51 (s, 3H), 1.48 (s, 9H).

¹³C NMR (125 MHz, CDCl₃) δ 173.04, 165.37, 162.36, 162.20, 155.03, 151.63, 131.67, 126.10, 120.81, 120.51, 109.17, 80.00, 56.36, 44.45, 43.58, 43.52, 42.20, 35.01, 28.59, 26.41.

¹⁹F NMR (282 MHz, CDCl₃) δ -159.93.

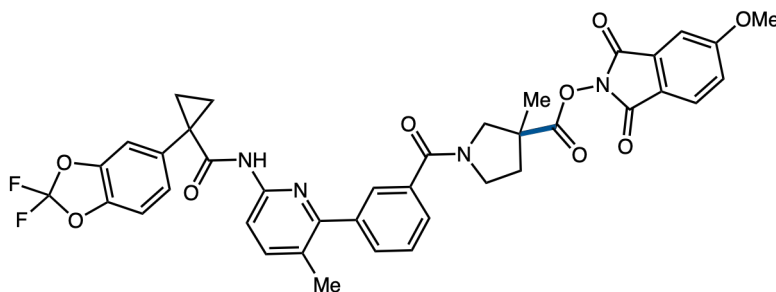


RAE-25

Prepared according to the general procedure A.

¹H NMR (500 MHz, CDCl₃) δ 8.13 (d, *J* = 2.3 Hz, 1H), 8.04 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.81 (d, *J* = 8.4 Hz, 1H), 7.37 (d, *J* = 2.3 Hz, 1H), 7.24 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.00 (d, *J* = 8.9 Hz, 1H), 3.95 (s, 3H), 3.89 (d, *J* = 6.5 Hz, 2H), 3.35 (m, 2H), 2.49 (s, 3H), 2.38 (d, *J* = 13.6 Hz, 2H), 2.20 (dp, *J* = 13.3, 6.7 Hz, 1H), 1.66 – 1.59 (m 3H), 1.53 (s, 3H), 1.15 (d, *J* = 6.5 Hz, 1H), 1.09 (d, *J* = 6.7 Hz, 6H).

¹³C NMR (125 MHz, CDCl₃) δ 172.63, 165.43, 165.13, 162.41, 162.32, 162.16, 153.07, 132.49, 131.98, 131.62, 126.24, 126.17, 124.67, 120.73, 120.57, 115.64, 112.76, 109.24, 103.09, 75.80, 56.38, 42.20, 28.32, 26.49, 23.59, 19.22, 16.69.



RAE-26

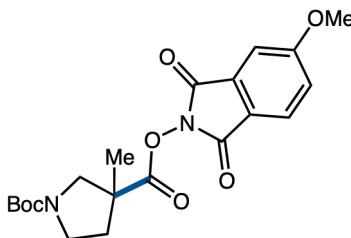
Prepared according to the general procedure A.

¹H NMR (500 MHz, CDCl₃) δ 8.08 – 8.06 (m, 1H), 7.79 (t, *J* = 7.2 Hz, 1H), 7.68 (s, 1H), 7.61 – 7.54 (m, 3H), 7.51 – 7.45 (m, 2H), 7.36 (d, *J* = 6.2 Hz, 1H), 7.23 (d, *J* = 8.5 Hz, 2H), 7.18 (d, *J* = 2.7 Hz, 1H), 7.08 (t, *J* = 8.0 Hz, 1H), 4.35 – 4.09 (m, 1H), 3.95 (s, 3H), 3.84 (dq, *J* = 13.4, 6.8

Hz, 3H), 3.72 – 3.40 (m, 2H), 2.70 – 2.58 (m, 1H), 2.27 (s, 3H), 2.14 – 1.96 (m, 1H), 1.74 (m, 2H), 1.66 (s, 1.5H), 1.51 (s, 1.5H).

¹³C NMR (125 MHz, CDCl₃) δ (summary of peaks) 172.06, 171.87, 171.49, 169.73, 169.62, 165.40, 162.09, 162.00, 161.82, 157.00, 155.53, 149.00, 144.28, 143.76, 141.09, 140.15, 136.54, 136.34, 135.05, 133.85, 131.81, 131.58, 130.83, 129.78, 128.55, 128.37, 128.22, 127.94, 127.15, 127.02, 126.73, 126.15, 120.71, 120.59, 112.95, 112.51, 110.34, 109.19, 57.75, 56.36, 55.14, 48.40, 48.30, 47.10, 44.98, 42.40, 37.21, 34.92, 31.32, 23.63, 22.29, 21.58, 19.40, 17.29.

¹⁹F NMR (282 MHz, CDCl₃) δ -49.58.



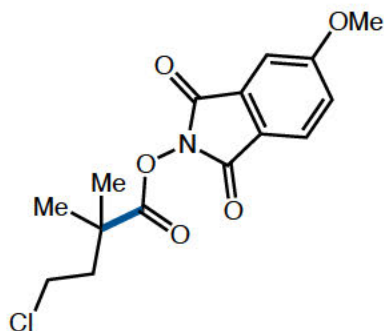
RAE-27

Prepared according to the general procedure A.

¹H NMR (500 MHz, CDCl₃) δ 7.80 (d, *J* = 8.3 Hz, 1H), 7.36 (d, *J* = 2.4 Hz, 1H), 7.22 (dd, *J* = 8.4, 2.3 Hz, 1H), 4.02 – 3.93 (s, 4H), 3.63 – 3.49 (m, 2H), 3.40 – 3.34 (m, 1H), 2.58 – 2.50 (m, 1H), 2.01 – 1.95 (m, 1H), 1.57 (s, 3H), 1.47 (s, 9H).

¹³C NMR (125 MHz, CDCl₃) δ 172.03, 165.35, 162.13, 161.96, 154.42, 131.63, 126.10, 120.54, 109.13, 79.92, 79.76, 56.35, 54.93, 54.46, 47.89, 47.18, 44.88, 44.51, 36.41, 35.43, 28.63, 22.35.

RAE-28



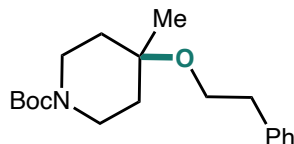
Prepared according to the general procedure A.

¹H NMR (500 MHz, CDCl₃) δ 7.79 (d, *J* = 8.4 Hz, 1H), 7.35 (d, *J* = 2.3 Hz, 1H), 7.21 (dd, *J* = 8.4, 2.4 Hz, 1H), 3.94 (s, 3H), 3.71 – 3.64 (m, 2H), 2.27 – 2.20 (m, 2H), 1.44 (s, 6H).

¹³C NMR (125 MHz, CDCl₃) δ 173.18, 165.32, 162.24, 162.09, 131.62, 126.05, 120.77, 120.46, 109.12, 56.32, 43.40, 41.77, 40.08, 25.31.

12. Experimental Details and Characterization Data for Dialkyl Ethers

***Tert*-butyl 4-methyl-4-phenethoxypiperidine-1-carboxylate (10)**



Prepared according to the general procedure B with redox-active ester **RAE1** (105 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μ mol, 5 mol%), Cp_2TiCl_2 (6.22 mg, 25.0 μ mol, 10 mol%), $\text{Zn}_3(\text{PO}_4)_2$ (72.4 mg, 187 μ mol, 0.75 equiv.), 2-phenylethanol (89.3 μ L, 750 μ mol, 3.00 equiv.), in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the lumidox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 5% to 60% EtOAc in hexanes. The resulting product fractions were concentrated to provide the product as a yellowish oil (64.5 mg, 202 μ mol, 81% yield).

¹H NMR (500 MHz, CDCl₃) δ 7.40 – 7.33 (m, 2H), 7.33 – 7.20 (m, 2H), 3.78 – 3.65 (m, 2H), 3.58 (td, *J* = 7.1, 1.3 Hz, 2H), 3.04 (t, *J* = 12.3 Hz, 2H), 2.91 (t, *J* = 7.0 Hz, 2H), 1.76 (d, *J* = 13.9 Hz, 2H), 1.52 (s, 9H), 1.47 – 1.39 (m, 2H), 1.20 (s, 3H).

¹³C NMR (125 MHz, CDCl₃) δ 155.09, 139.60, 129.17, 128.39, 126.31, 79.30, 71.56, 62.22, 40.13, 37.30, 35.69, 28.61, 28.57, 24.71.

HRMS (ESI-TOF) m/z calcd. for $C_{15}H_{22}NO_3$ $[M-Boc+2H]^+$ 220.17014; found: 220.17036.

IR (film) ν_{max} 2970, 2930, 2868, 1688, 1419, 1364, 1241, 1134, 987, 964, 698 cm^{-1}

CN1CCCCC1C2CCCCC2C3CCCCC3C4CCCCC4C5CCCCC5C6CCCCC6C7CCCCC7C8CCCCC8C9CCCCC9C10CCCCC10C11CCCCC11C12CCCCC12C13CCCCC13C14CCCCC14C15CCCCC15C16CCCCC16C17CCCCC17C18CCCCC18C19CCCCC19C20CCCCC20C21CCCCC21C22CCCCC22C23CCCCC23C24CCCCC24C25CCCCC25C26CCCCC26C27CCCCC27C28CCCCC28C29CCCCC29C30CCCCC30C31CCCCC31C32CCCCC32C33CCCCC33C34CCCCC34C35CCCCC35C36CCCCC36C37CCCCC37C38CCCCC38C39CCCCC39C40CCCCC40C41CCCCC41C42CCCCC42C43CCCCC43C44CCCCC44C45CCCCC45C46CCCCC46C47CCCCC47C48CCCCC48C49CCCCC49C50CCCCC50C51CCCCC51C52CCCCC52C53CCCCC53C54CCCCC54C55CCCCC55C56CCCCC56C57CCCCC57C58CCCCC58C59CCCCC59C60CCCCC60C61CCCCC61C62CCCCC62C63CCCCC63C64CCCCC64C65CCCCC65C66CCCCC66C67CCCCC67C68CCCCC68C69CCCCC69C70CCCCC70C71CCCCC71C72CCCCC72C73CCCCC73C74CCCCC74C75CCCCC75C76CCCCC76C77CCCCC77C78CCCCC78C79CCCCC79C80CCCCC80C81CCCCC81C82CCCCC82C83CCCCC83C84CCCCC84C85CCCCC85C86CCCCC86C87CCCCC87C88CCCCC88C89CCCCC89C90CCCCC90C91CCCCC91C92CCCCC92C93CCCCC93C94CCCCC94C95CCCCC95C96CCCCC96C97CCCCC97C98CCCCC98C99CCCCC99C100CCCCC100C101CCCCC101C102CCCCC102C103CCCCC103C104CCCCC104C105CCCCC105C106CCCCC106C107CCCCC107C108CCCCC108C109CCCCC109C110CCCCC110C111CCCCC111C112CCCCC112C113CCCCC113C114CCCCC114C115CCCCC115C116CCCCC116C117CCCCC117C118CCCCC118C119CCCCC119C120CCCCC120C121CCCCC121C122CCCCC122C123CCCCC123C124CCCCC124C125CCCCC125C126CCCCC126C127CCCCC127C128CCCCC128C129CCCCC129C130CCCCC130C131CCCCC131C132CCCCC132C133CCCCC133C134CCCCC134C135CCCCC135C136CCCCC136C137CCCCC137C138CCCCC138C139CCCCC139C140CCCCC140C141CCCCC141C142CCCCC142C143CCCCC143C144CCCCC144C145CCCCC145C146CCCCC146C147CCCCC147C148CCCCC148C149CCCCC149C150CCCCC150C151CCCCC151C152CCCCC152C153CCCCC153C154CCCCC154C155CCCCC155C156CCCCC156C157CCCCC157C158CCCCC158C159CCCCC159C160CCCCC160C161CCCCC161C162CCCCC162C163CCCCC163C164CCCCC164C165CCCCC165C166CCCCC166C167CCCCC167C168CCCCC168C169CCCCC169C170CCCCC170C171CCCCC171C172CCCCC172C173CCCCC173C174CCCCC174C175CCCCC175C176CCCCC176C177CCCCC177C178CCCCC178C179CCCCC179C180CCCCC180C181CCCCC181C182CCCCC182C183CCCCC183C184CCCCC184C185CCCCC185C186CCCCC186C187CCCCC187C188CCCCC188C189CCCCC189C190CCCCC190C191CCCCC191C192CCCCC192C193CCCCC193C194CCCCC194C195CCCCC195C196CCCCC196C197CCCCC197C198CCCCC198C199CCCCC199C200CCCCC200C201CCCCC201C202CCCCC202C203CCCCC203C204CCCCC204C205CCCCC205C206CCCCC206C207CCCCC207C208CCCCC208C209CCCCC209C210CCCCC210C211CCCCC211C212CCCCC212C213CCCCC213C214CCCCC214C215CCCCC215C216CCCCC216C217CCCCC217C218CCCCC218C219CCCCC219C220CCCCC220C221CCCCC221C222CCCCC222C223CCCCC223C224CCCCC224C225CCCCC225C226CCCCC226C227CCCCC227C228CCCCC228C229CCCCC229C230CCCCC230C231CCCCC231C232CCCCC232C233CCCCC233C234CCCCC234C235CCCCC235C236CCCCC236C237CCCCC237C238CCCCC238C239CCCCC239C240CCCCC240C241CCCCC241C242CCCCC242C243CCCCC243C244CCCCC244C245CCCCC245C246CCCCC246C247CCCCC247C248CCCCC248C249CCCCC249C250CCCCC250C251CCCCC251C252CCCCC252C253CCCCC253C254CCCCC254C255CCCCC255C256CCCCC256C257CCCCC257C258CCCCC258C259CCCCC259C260CCCCC260C261CCCCC261C262CCCCC262C263CCCCC263C264CCCCC264C265CCCCC265C266CCCCC266C267CCCCC267C268CCCCC268C269CCCCC269C270CCCCC270C271CCCCC271C272CCCCC272C273CCCCC273C274CCCCC274C275CCCCC275C276CCCCC276C277CCCCC277C278CCCCC278C279CCCCC279C280CCCCC280C281CCCCC281C282CCCCC282C283CCCCC283C284CCCCC284C285CCCCC285C286CCCCC286C287CCCCC287C288CCCCC288C289CCCCC289C290CCCCC290C291CCCCC291C292CCCCC292C293CCCCC293C294CCCCC294C295CCCCC295C296CCCCC296C297CCCCC297C298CCCCC298C299CCCCC299C300CCCCC300C301CCCCC301C302CCCCC302C303CCCCC303C304CCCCC304C305CCCCC305C306CCCCC306C307CCCCC307C308CCCCC308C309CCCCC309C310CCCCC310C311CCCCC311C312CCCCC312C313CCCCC313C314CCCCC314C315CCCCC315C316CCCCC316C317CCCCC317C318CCCCC318C319CCCCC319C320CCCCC320C321CCCCC321C322CCCCC322C323CCCCC323C324CCCCC324C325CCCCC325C326CCCCC326C327CCCCC327C328CCCCC328C329CCCCC329C330CCCCC330C331CCCCC331C332CCCCC332C333CCCCC333C334CCCCC334C335CCCCC335C336CCCCC336C337CCCCC337C338CCCCC338C339CCCCC339C340CCCCC340C341CCCCC341C342CCCCC342C343CCCCC343C344CCCCC344C345CCCCC345C346CCCCC346C347CCCCC347C348CCCCC348C349CCCCC349C350CCCCC350C351CCCCC351C352CCCCC352C353CCCCC353C354CCCCC354C355CCCCC355C356CCCCC356C357CCCCC357C358CCCCC358C359CCCCC359C360CCCCC360C361CCCCC361C362CCCCC362C363CCCCC363C364CCCCC364C365CCCCC365C366CCCCC366C367CCCCC367C368CCCCC368C369CCCCC369C370CCCCC370C371CCCCC371C372CCCCC372C373CCCCC373C374CCCCC374C375CCCCC375C376CCCCC376C377CCCCC377C378CCCCC378C379CCCCC379C380CCCCC380C381CCCCC381C382CCCCC382C383CCCCC383C384CCCCC384C385CCCCC385C386CCCCC386C387CCCCC387C388CCCCC388C389CCCCC389C390CCCCC390C391CCCCC391C392CCCCC392C393CCCCC393C394CCCCC394C395CCCCC395C396CCCCC396C397CCCCC397C398CCCCC398C399CCCCC399C400CCCCC400C401CCCCC401C402CCCCC402C403CCCCC403C404CCCCC404C405CCCCC405C406CCCCC406C407CCCCC407C408CCCCC408C409CCCCC409C410CCCCC410C411CCCCC411C412CCCCC412C413CCCCC413C414CCCCC414C415CCCCC415C416CCCCC416C417CCCCC417C418CCCCC418C419CCCCC419C420CCCCC420C421CCCCC421C422CCCCC422C423CCCCC423C424CCCCC424C425CCCCC425C426CCCCC426C427CCCCC427C428CCCCC428C429CCCCC429C430CCCCC430C431CCCCC431C432CCCCC432C433CCCCC433C434CCCCC434C435CCCCC435C436CCCCC436C437CCCCC437C438CCCCC438C439CCCCC439C440CCCCC440C441CCCCC441C442CCCCC442C443CCCCC443C444CCCCC444C445CCCCC445C446CCCCC446C447CCCCC447C448CCCCC448C449CCCCC449C450CCCCC450C451CCCCC451C452CCCCC452C453CCCCC453C454CCCCC454C455CCCCC455C456CCCCC456C457CCCCC457C458CCCCC458C459CCCCC459C460CCCCC460C461CCCCC461C462CCCCC462C463CCCCC463C464CCCCC464C465CCCCC465C466CCCCC466C467CCCCC467C468CCCCC468C469CCCCC469C470CCCCC470C471CCCCC471C472CCCCC472C473CCCCC473C474CCCCC474C475CCCCC475C476CCCCC476C477CCCCC477C478CCCCC478C479CCCCC4

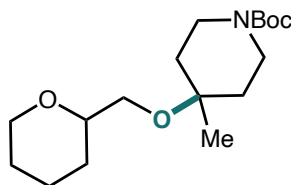
After irradiation for 20 hours at level 5 (8.4 W) in the luminox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 10% to 80% EtOAc in hexanes. The fractions containing product were concentrated and further purified by preparative HPLC (RediSep C18 column, 25% to 90% MeCN in H₂O with 0.1% NH₄OH) to provide the product as an orange oil (73.7 mg, 155 μmol, 62% yield).

¹³C NMR (126 MHz, CDCl₃) δ 155.49, 155.03, 137.10, 128.59, 128.04, 127.96, 79.29, 71.12, 67.07, 60.95, 44.16, 40.17, 36.14, 35.39, 33.46, 32.32, 28.61, 27.76, 24.73.

S87

IR (film) ν_{max} 2933, 1679, 1426, 1365, 1280, 1239, 1162, 1078, 907, 726, 696 cm^{-1}

***Tert*-butyl 4-methyl-4-((tetrahydro-2*H*-pyran-2-yl)methoxy)piperidine-1-carboxylate (16)**



Prepared according to the general procedure B with redox-active ester **RAE1** (105 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μmol , 5 mol%), Cp_2TiCl_2 (6.22 mg, 25.0 μmol , 10 mol%), $\text{Zn}_3(\text{PO}_4)_2$ (72.4 mg, 187 μmol , 0.75 equiv.), tetrahydropyran-2-ylmethanol (87.1 mg, 750 μmol , 3.00 equiv.), in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the luminox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 0% to 50% EtOAc in hexanes. The fractions containing product were concentrated and further purified by preparative HPLC (RediSep C18 column, 45% to 90% MeCN in H_2O with 0.1% NH_4OH) to provide the product as a colorless solid (52.2 mg, 167 μmol , 67% yield).

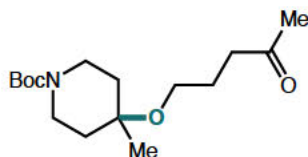
^1H NMR (500 MHz, CDCl_3) δ 3.99 (ddt, $J = 11.7, 3.9, 1.7$ Hz, 1H), 3.74 – 3.62 (m, 2H), 3.43 (dddd, $J = 10.9, 8.6, 7.4, 2.2$ Hz, 2H), 3.35 (dd, $J = 9.1, 5.6$ Hz, 1H), 3.20 (dd, $J = 9.1, 5.1$ Hz, 1H), 3.13 (q, $J = 11.9$ Hz, 2H), 1.84 (ddp, $J = 12.4, 5.2, 2.6$ Hz, 1H), 1.73 (dd, $J = 12.8, 3.5$ Hz, 2H), 1.65 (ddt, $J = 15.4, 5.0, 2.3$ Hz, 1H), 1.60 – 1.46 (m, 3H), 1.44 (s, 9H), 1.42 – 1.24 (m, 3H), 1.14 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 155.09, 79.32, 77.32, 71.59, 68.70, 64.89, 39.90, 35.68, 29.24, 28.61, 26.25, 24.60, 23.31.

HRMS (ESI-TOF) m/z calcd. for $C_{17}H_{31}NO_4Na$ $[M+Na]^+$ 336.21508; found: 336.21512.

IR (film) ν_{max} 2934, 2859, 1690, 1420, 1364, 1258, 1241, 1155, 1133, 1093, 987, 963, 730 cm^{-1}

***Tert*-butyl 4-methyl-4-(4-oxopentoxypiperidine-1-carboxylate (17)**



Prepared according to the general procedure B with redox-active ester **RAE1** (105 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μ mol, 5 mol%), Cp_2TiCl_2 (6.22 mg, 25.0 μ mol, 10 mol%), $Zn_3(PO_4)_2$ (72.4 mg, 187 μ mol, 0.75 equiv.), 5-hydroxypentan-2-one (76.1 μ L, 750 μ mol, 3.00 equiv.), in DCE (0.2 M, 1.25 mL).

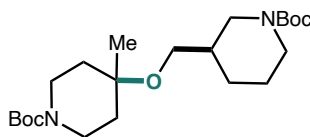
After irradiation for 20 hours at level 5 (8.4 W) in the luminox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 0% to 70% EtOAc in hexanes. The fractions containing product were concentrated and further purified by preparative HPLC (RediSep C18 column, 45% to 90% MeCN in H_2O with 0.1% NH_4OH) to provide the product as a colorless oil (47.1 mg, 157 μ mol, 63% yield).

1H NMR (500 MHz, $CDCl_3$) δ 3.70 (dt, J = 13.4, 4.2 Hz, 2H), 3.31 (t, J = 6.0 Hz, 2H), 3.13 – 3.04 (m, 2H), 2.53 (t, J = 7.2 Hz, 2H), 2.15 (s, 3H), 1.85 – 1.78 (m, 2H), 1.72 – 1.64 (m, 2H), 1.45 (s, 9H), 1.42 – 1.34 (m, 2H), 1.13 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 208.97, 155.09, 79.42, 71.43, 59.66, 40.81, 39.95, 35.75, 30.09, 28.62, 28.59, 24.77, 24.62.

The recorded analytical data correspond to literature reports.

***Tert*-butyl (S)-4-((1-(*tert*-butoxycarbonyl)piperidin-3-yl)methoxy)-4-methylpiperidine-1-carboxylate (18)**



Prepared according to the general procedure B with redox-active ester **RAE1** (105 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μmol , 5 mol%), Cp_2TiCl_2 (6.22 mg, 25.0 μmol , 10 mol%), $\text{Zn}_3(\text{PO}_4)_2$ (72.4 mg, 187 μmol , 0.75 equiv.), *tert*-butyl (3*S*)-3-(hydroxymethyl)piperidine-1-carboxylate (161 mg, 750 μmol , 3.00 equiv.) in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the lumidox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 20% to 60% EtOAc in hexanes (2x). The resulting product fractions were concentrated to provide the product as a yellowish oil (62.4 mg, 174 μmol , 61% yield).

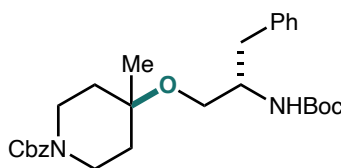
^1H NMR (500 MHz, CDCl_3) δ 4.06 – 3.99 (m, 1H), 3.89 (dt, J = 13.3, 4.1 Hz, 1H), 3.73 (dd, J = 11.8, 5.1 Hz, 2H), 3.19 – 3.12 (m, 2H), 3.12 – 3.01 (m, 2H), 2.78 (ddd, J = 13.8, 11.3, 3.1 Hz, 1H), 2.59 (t, J = 11.5 Hz, 1H), 1.77 (dt, J = 13.0, 4.4 Hz, 1H), 1.72 – 1.66 (m, 2H), 1.62 (dt, J = 13.2, 3.9 Hz, 1H), 1.44 (s, 18H), 1.37 (ddt, J = 14.8, 12.6, 3.9 Hz, 3H), 1.27 – 1.16 (m, 2H), 1.12 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 155.12, 155.07, 79.38, 79.35, 71.14, 63.16, 47.66, 44.61, 39.87, 36.95, 35.80, 35.55, 28.60, 28.59, 27.94, 24.76, 24.70.

HRMS (ESI-TOF) m/z calcd. for $\text{C}_{22}\text{H}_{40}\text{N}_2\text{O}_5\text{Na}$ $[\text{M}+\text{Na}]^+$ 435.28349; found: 435.28351.

IR (film) ν_{max} 2973, 2930, 2858, 1678, 1420, 1364, 1259, 1242, 1175, 1149, 1080, 909, 728 cm^{-1}

Benzyl (S)-4-(2-((*tert*-butoxycarbonyl)amino)-3-phenylpropoxy)-4-methylpiperidine-1-carboxylate (19)



Note: Due to lower yields (15% less) upon scaling up from 0.05 mmol to 0.25 mmol, 5 reactions on a 0.05 mmol scale were set up in parallel and pooled after completed irradiation, before being subjected to purification.

Prepared according to the general procedure B with **5 parallel reaction** of 0.05 mmol scale each, with redox-active ester **RAE2** (22.6 mg, 0.05 mmol, 1.00 equiv.), 4DPAIPN (1.99 mg, 2.5 μmol , 5 mol%), Cp_2TiCl_2 (1.24 mg, 5.0 μmol , 10 mol%), $\text{Zn}_3(\text{PO}_4)_2$ (14.5 mg, 37.5 μmol , 0.75 equiv.), *tert*-butyl *N*-[(*S*)-1-benzyl-2-hydroxy-ethyl]carbamate (37.7 mg, 150 μmol , 3.00 equiv.), in DCE (0.2 M, 0.25 mL).

After irradiation for 20 hours at level 2 (4.1 W) in the lumidox setup, the reactions were pooled, and the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 0% to 70% EtOAc in hexanes.

The fractions containing product were concentrated to provide the product as a yellowish oil (77.8 mg, 161 μ mol, 64% yield, >99% ee).

^1H NMR (500 MHz, CDCl_3) δ 7.38 – 7.35 (m, 4H), 7.34 – 7.30 (m, 1H), 7.30 – 7.26 (m, 2H), 7.23 – 7.18 (m, 3H), 5.16 – 5.11 (m, 2H), 4.78 (d, J = 8.9 Hz, 1H), 3.99 – 3.71 (m, 3H), 3.30 (dd, J = 8.8, 4.1 Hz, 1H), 3.22 (dd, J = 8.9, 3.1 Hz, 1H), 3.20 – 3.09 (m, 2H), 2.90 – 2.80 (m, 2H), 1.78 – 1.67 (m, 2H), 1.49 – 1.43 (m, 2H), 1.41 (s, 9H), 1.12 (s, 3H).

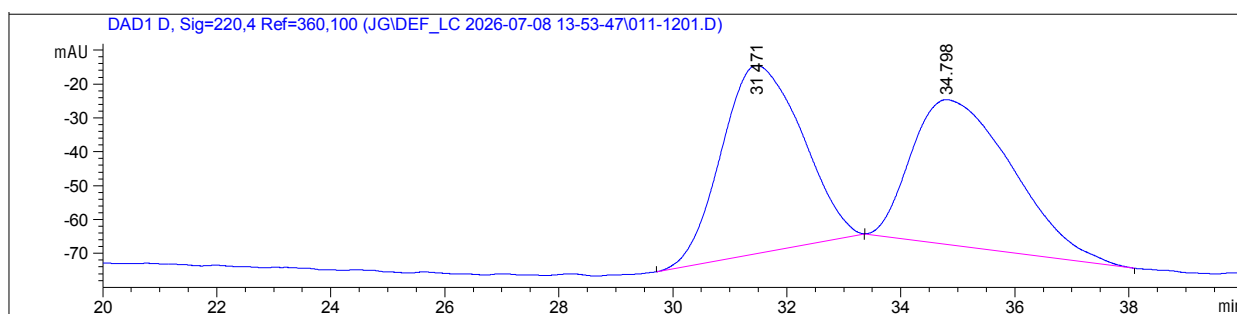
^{13}C NMR (126 MHz, CDCl_3) δ 155.47, 138.44, 137.05, 129.48, 128.61, 128.53, 128.09, 127.99, 126.50, 79.45, 71.62, 67.15, 60.86, 52.04, 40.20, 40.16, 38.02, 35.68, 28.51, 24.66.

HRMS (ESI-TOF) m/z calcd. for $\text{C}_{28}\text{H}_{39}\text{N}_2\text{O}_5$ $[\text{M}+\text{H}]^+$ 505.26784; found: 505.26789.

IR (film) ν_{max} 2970, 2931, 1695, 1496, 1430, 1363, 1281, 1237, 1162, 1085, 1021, 732 cm^{-1}

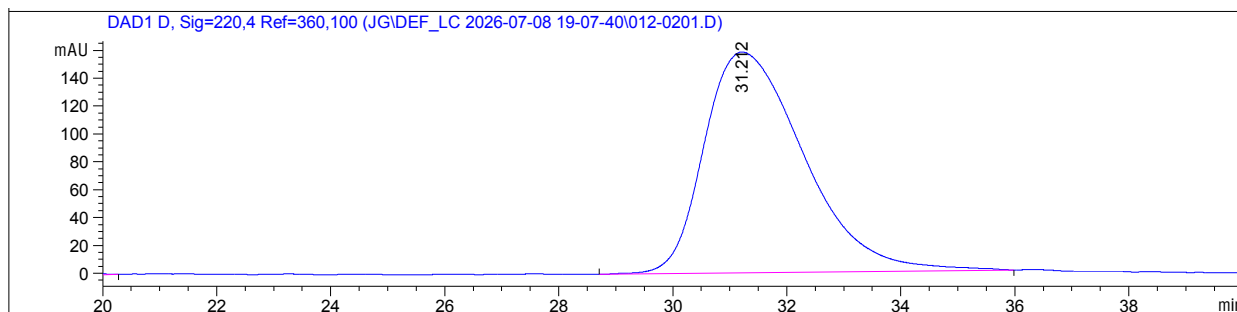
Chiral HPLC: >99% ee (AD-H 250 $\times$ 4.6 mm, n-Hex/i-PrOH = 95/5 over 60 min, 1 ml/min, λ = 220 nm); t_{R} = 31.5 min (major, **19**), 34.8 (minor, *ent*-**19**).

rac-**19**:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	31.471	BB	1.4202	5444.75586	55.51573	50.6809
2	34.798	BB	1.6795	5298.45605	42.70472	49.3191

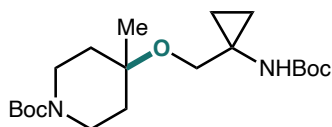
19:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	31.212	BB	1.8863	1.93029e4	158.55934	100.0000

Optical Rotation: $[\alpha]_D^{20}$: -31.3 ($c = 1.0$, CHCl_3) [$>99\%$ ee].

***Tert*-butyl 4-((1-((*tert*-butoxycarbonyl)amino)cyclopropyl)methoxy)-4-methylpiperidine-1-carboxylate (20)**



Prepared according to the general procedure B with redox-active ester **RAE1** (105 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μmol , 5 mol%), Cp_2TiCl_2 (6.22 mg, 25.0 μmol , 10 mol%), $\text{Zn}_3(\text{PO}_4)_2$ (72.4 mg, 187 μmol , 0.75 equiv.), *tert*-butyl N-[1-(hydroxymethyl)cyclopropyl]carbamate (140 mg, 750 μmol , 3.00 equiv.), in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the luminox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 10% to 80% EtOAc in hexanes. The fractions containing product were concentrated and further purified by preparative HPLC (RediSep C18 column, 40% to 100% MeCN in H₂O with 0.1% NH₄OH) to provide the product as a colorless, crystalline solid (63.8 mg, 166 μ mol, 66% yield).

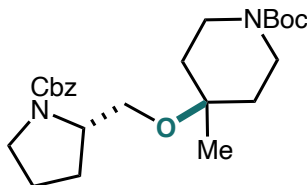
¹H NMR (500 MHz, CDCl₃) δ 5.03 (br s, 1H), 3.84 – 3.59 (m, 2H), 3.39 – 3.25 (m, 2H), 3.10 (t, *J* = 12.5 Hz, 2H), 1.70 (d, *J* = 13.5 Hz, 2H), 1.45 (s, 9H), 1.43 (s, 9H), 1.41 – 1.35 (m, 2H), 1.11 (s, 3H), 0.81 – 0.76 (m, 2H), 0.71 (t, *J* = 3.4 Hz, 2H).

¹³C NMR (500 MHz, CDCl₃) δ 155.85, 155.11, 79.51, 79.38, 71.44, 64.95, 40.22, 35.87, 33.47, 28.62, 28.52, 24.72, 11.89.

HRMS (ESI-TOF) *m/z* calcd. for C₂₀H₃₆N₂O₅Na [M+Na]⁺ 407.25219; found: 407.25225.

IR (film) ν_{max} 3333, 2975, 2946, 2877, 1710, 1682, 1508, 1422, 1365, 1287, 1243, 1157, 1141, 1070, 964 cm⁻¹

***Tert*-butyl (S)-4-((1-((benzyloxy)carbonyl)pyrrolidin-2-yl)methoxy)-4-methylpiperidine-1-carboxylate (21)**



Prepared according to the general procedure B with redox-active ester **RAE1** (105 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μ mol, 5 mol%), Cp₂TiCl₂ (6.22 mg, 25.0 μ mol, 10 mol%),

Zn₃(PO₄)₂ (72.4 mg, 187 μmol, 0.75 equiv.), benzyl (2*S*)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (176 mg, 750 μmol, 3.00 equiv.), in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the lumidox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 10% to 80% EtOAc in hexanes. The fractions containing product were concentrated and further purified by preparative HPLC (RediSep C18 column, 45% to 90% MeCN in H₂O with 0.1% NH₄OH) to provide the product as a yellowish oil (71.8 mg, 166 μmol, 67% yield).

¹H NMR (500 MHz, CDCl₃) δ 7.39 – 7.29 (m, 5H), 5.26 – 4.99 (m, 2H), 4.03 – 3.88 (m, 1H), 3.77 – 3.59 (m, 2H), 3.50 – 3.32 (m, 3H), 3.20 – 2.89 (m, 2H), 2.00 – 1.88 (m, 3H), 1.86 – 1.77 (m, 1H), 1.71 – 1.63 (m, 2H), 1.60 – 1.53 (m, 1H), 1.45 (s, 9H), 1.41 – 1.25 (m, 2H), 1.07 (d, *J* = 47.3 Hz, 3H). (mixture of rotamers)

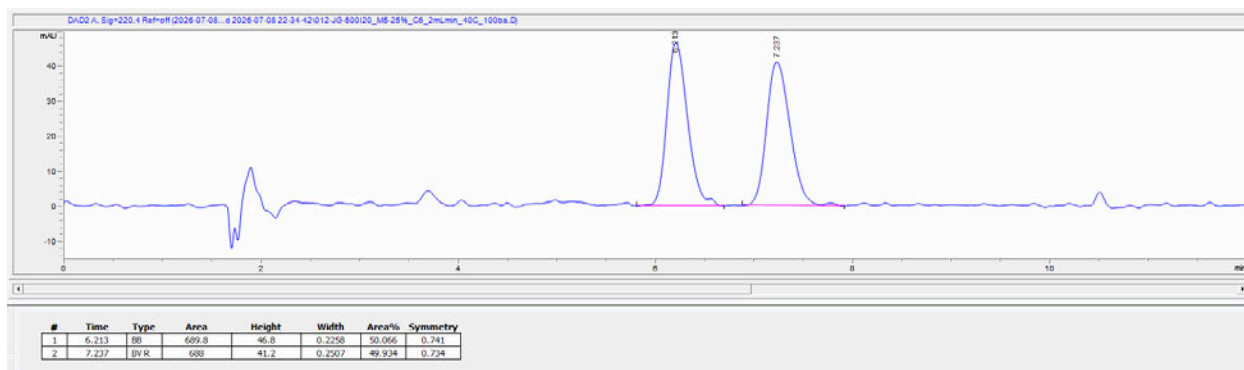
¹³C NMR (126 MHz, CDCl₃) δ 155.04, 154.98, 137.18, 136.91, 128.59, 128.24, 128.18, 128.00, 127.90, 79.36, 71.54, 66.94, 66.65, 61.96, 61.26, 57.89, 57.29, 47.21, 46.96, 39.85, 36.14, 35.74, 35.56, 35.38, 29.13, 28.61, 28.29, 24.80, 24.65, 24.11, 23.14. (mixture of rotamers)

HRMS (ESI-TOF) *m/z* calcd. for C₂₄H₃₆N₂O₅Na [M+Na]⁺ 455.25219; found: 455.25234.

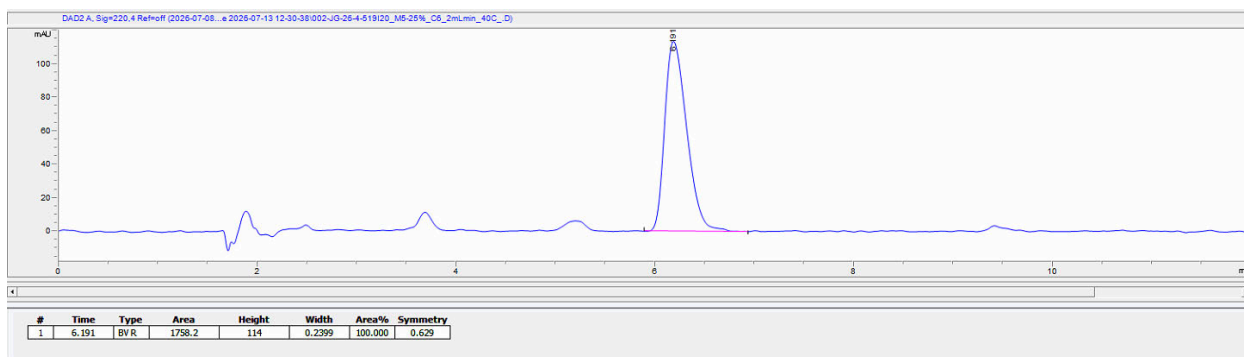
IR (film) ν_{max} 2970, 2932, 2873, 1690, 1410, 1363, 1258, 1241, 1134, 1080, 987, 912 cm⁻¹

Chiral HPLC: >99% ee [Regis Whelk-O1(*R,R*) (250 x 4.6 mm); 25 % methanol (0.1% diethylamine); 2.0 mL/min; λ = 220 nm]; t_R = 6.2 min (major, **21**), 7.2 (minor, *ent*-**21**).

rac-21:

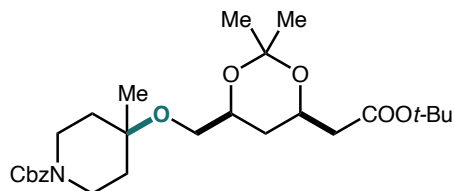


21:



Optical Rotation: $[\alpha]_D^{20}$: -40.4 ($c = 1.0$, CHCl_3) [$>99\%$ *ee*].

Benzyl 4-(((4*S*,6*R*)-6-(2-(*tert*-butoxy)-2-oxoethyl)-2,2-dimethyl-1,3-dioxan-4-yl)methoxy)-4-methylpiperidine-1-carboxylate (22)



Prepared according to the general procedure B with redox-active ester **RAE2** (113 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μmol , 5 mol%), Cp_2TiCl_2 (6.22 mg, 25.0 μmol , 10 mol%),

Zn₃(PO₄)₂ (72.4 mg, 187 μmol, 0.75 equiv.), tert-butyl 2-[(4*R*,6*S*)-6-(hydroxymethyl)-2,2-dimethyl-1,3-dioxan-4-yl]acetate (195 mg, 750 μmol, 3.00 equiv.) in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the lumidox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 15% to 100% EtOAc in hexanes. The fractions containing product were concentrated and further purified by preparative HPLC (RediSep C18 column, 40% to 100% MeCN in H₂O with 0.1% NH₄OH) to provide the product as a colorless solid (79.8 mg, 162 μmol, 65% yield).

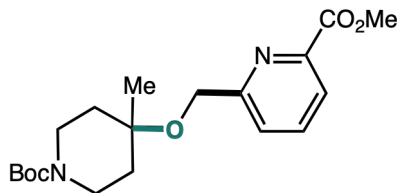
¹H NMR (500 MHz, CDCl₃) δ 7.38 – 7.33 (m, 4H), 7.33 – 7.28 (m, 1H), 5.14 – 5.10 (m, 2H), 4.31 – 4.24 (m, 0.5H), 4.21 (tt, *J* = 7.5, 5.5 Hz, 0.5H), 4.13 (qd, *J* = 6.5, 4.4 Hz, 0.5H), 4.07 (dd, *J* = 8.1, 5.9 Hz, 0.5H), 4.00 (dddd, *J* = 11.5, 7.3, 5.2, 2.5 Hz, 0.5H), 3.89 – 3.75 (m, 1H), 3.73 – 3.61 (m, 1H), 3.52 (t, *J* = 7.7 Hz, 0.5H), 3.40 (dd, *J* = 8.8, 5.0 Hz, 1H), 3.36 – 3.28 (m, 1.5H), 3.23 – 3.10 (m, 1.5H), 2.53 – 2.39 (m, 0.5H), 2.32 (dd, *J* = 15.0, 5.9 Hz, 1H), 1.83 (qdd, *J* = 14.0, 7.3, 4.6 Hz, 1H), 1.77 – 1.63 (m, 2.5H), 1.46 (s, 1.5H), 1.45 – 1.43 (m, 9H), 1.38 (s, 1.5H), 1.36 (s, 1.5H), 1.34 (s, 1.5H), 1.21 (s, 1.5H), 1.14 (s, 1.5H). (1:1 mixture of rotamers)

¹³C NMR (126 MHz, CDCl₃) δ 170.91, 170.36, 155.48, 155.40, 137.12, 137.07, 128.61, 128.08, 128.06, 127.99, 108.79, 98.87, 80.80, 80.75, 73.25, 72.86, 71.61, 70.13, 68.65, 67.13, 67.09, 66.23, 65.88, 64.92, 42.97, 42.16, 40.55, 40.48, 40.36, 40.06, 35.63, 34.41, 30.12, 28.27, 28.24, 27.15, 25.96, 25.27, 24.82, 19.88.

HRMS (ESI-TOF) *m/z* calcd. for C₂₇H₄₁NO₇Na [M+Na]⁺ 514.27807; found: 514.27801.

IR (film) ν_{max} 2976, 2937, 2875, 1725, 1697, 1429, 1367, 1281, 1236, 1151, 1086, 990, 839, 731 cm⁻¹

Methyl 6-(((1-(*tert*-butoxycarbonyl)-4-methylpiperidin-4-yl)oxy)methyl)picolinate (23)



Prepared according to the general procedure B with redox-active ester **RAE1** (313.8 mg, 0.75 mmol, 3.00 equiv.), 4DPAIPN (10.0 mg, 12.5 μ mol, 5 mol%), Cp_2TiCl_2 (6.2 mg, 25.0 μ mol, 10 mol%), $[\text{ZnCO}_3]_2 \cdot [\text{Zn}(\text{OH})_2]_3$ (68.6 mg, 125 μ mol, 0.5 equiv.), methyl 6-(hydroxymethyl)pyridine-2-carboxylate (41.8 mg, 250 μ mol, 1.00 equiv.), in DCE (0.1 M, 2.5 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the lumidox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 5% to 45% EtOAc in hexanes. The resulting product fractions were concentrated to provide the product as a yellowish oil (74 mg, 203 μ mol, 81% yield).

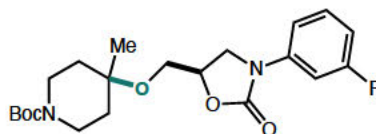
^1H NMR (500 MHz, CDCl_3) δ 8.08–8.06 (dd, $J = 7.8, 1.1$ Hz, 1H), 7.88–7.85 (t, $J = 7.8$ Hz, 1H), 7.50–7.48 (dd, $J = 7.8, 1.1$ Hz, 1H), 5.35 (s, 2H), 3.99 (s, 3H), 3.75–3.73 (d, $J = 13.3$ Hz, 2H), 3.09–3.03 (ddd, $J = 13.9, 10.5, 3.0$ Hz, 2H), 2.13 – 2.10 (m, 2H), 1.44 (m, 11H), 1.27 (s, 3H).

^{13}C NMR (125 MHz, CDCl_3) δ 176.16, 165.62, 156.66, 154.94, 147.86, 137.98, 124.72, 124.46, 79.62, 66.68, 53.11, 42.00, 34.71, 28.56, 25.90.

HRMS (ESI-TOF) m/z calcd. for $\text{C}_{19}\text{H}_{28}\text{N}_2\text{O}_5\text{Na}$ $[\text{M}+\text{Na}]^+$ 387.1891; found: 397.1870.

IR (film) ν_{max} 2943, 1723, 1686, 1423, 1281, 1166, 1110, 1038, 972, 765

***Tert*-butyl (R)-4-((3-(3-fluorophenyl)-2-oxooxazolidin-5-yl)methoxy)-4-methylpiperidine-1-carboxylate (24)**



Prepared according to the general procedure B with redox-active ester **RAE1** (313 mg, 0.75 mmol, 3.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μ mol, 5 mol%), Cp_2TiCl_2 (6.22 mg, 25.0 μ mol, 10 mol%), $\text{Zn}_3(\text{PO}_4)_2$ (48.3 mg, 125 μ mol, **0.50 equiv.**), (5*R*)-3-(3-fluorophenyl)-5-(hydroxymethyl)oxazolidin-2-one (52.8 mg, 250 μ mol, 1.00 equiv.) in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the luminox setup, the solvent was removed under reduced pressure. The crude residue was dissolved in a minimal amount of DMSO, loaded on a 30 g Biotage Sfär C18 D phase column, and purified with eluents 20% to 100% MeCN in water (0.1% NH_4OH modifier). The fractions containing product were concentrated and loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 10% to 60% EtOAc in hexanes to provide the product as a colorless oil (53.3 mg, 130 μ mol, 52% yield).

^1H NMR (500 MHz, CDCl_3) δ 7.43 (dt, J = 11.3, 2.3 Hz, 1H), 7.32 (td, J = 8.2, 6.4 Hz, 1H), 7.26 – 7.23 (m, 1H)*, 6.83 (tdd, J = 8.2, 2.5, 0.9 Hz, 1H), 4.80 – 4.71 (m, 1H), 4.06 (t, J = 8.7 Hz, 1H), 3.92 (td, J = 9.4, 5.7 Hz, 1H), 3.73 – 3.65 (m, 2H), 3.62 (dd, J = 10.0, 4.6 Hz, 1H), 3.57 (dd, J = 9.9, 3.9 Hz, 1H), 3.13 – 2.94 (m, 2H), 1.75 – 1.64 (m, 2H), 1.47 – 1.39 (m, 11H), 1.19 (s, 3H).

*Signal partially overlaps with residual solvent signal.

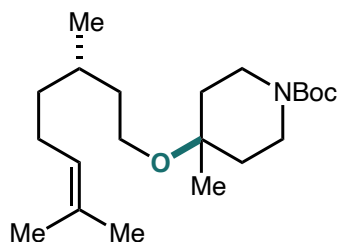
^{13}C NMR (126 MHz, CDCl_3) δ 163.23 (d, J = 245.1 Hz), 139.95 (d, J = 10.7 Hz), 130.38 (d, J = 9.5 Hz), 113.31 (d, J = 2.9 Hz), 110.81 (d, J = 21.2 Hz), 105.79 (d, J = 26.9 Hz), 79.57, 72.64, 71.54, 61.76, 47.44, 40.01, 35.59, 28.58, 24.59.

^{19}F NMR (376 MHz, CDCl_3) δ -110.98 (dt, J = 11.3, 7.4 Hz).

HRMS (ESI-TOF) m/z calcd. for $\text{C}_{21}\text{H}_{29}\text{FN}_2\text{O}_5\text{Na}$ $[\text{M}+\text{Na}]^+$ 431.19582; found: 431.19578.

IR (film) ν_{max} 2972, 2938, 2875, 1756, 1686, 1614, 1496, 1410, 1365, 1260, 1195, 1162, 1137 cm^{-1}

***Tert*-butyl (*S*)-4-((3,7-dimethyloct-6-en-1-yl)oxy)-4-methylpiperidine-1-carboxylate (**25**)**



Prepared according to the general procedure B with redox-active ester **RAE1** (105 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μ mol, 5 mol%), Cp_2TiCl_2 (6.22 mg, 25.0 μ mol, 10 mol%), $\text{Zn}_3(\text{PO}_4)_2$ (72.4 mg, 187 μ mol, 0.75 equiv.), (–)-citronellol (137 μ L, 750 μ mol, 3.00 equiv.), in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the luminox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 5% to 40% EtOAc in hexanes. The fractions containing product were concentrated and further purified by preparative HPLC (RediSep C18 column, 45% to 100% MeCN in H_2O with 0.1% NH_4OH) to provide the product as a yellow oil (56.4 mg, 160 μ mol, 64% yield).

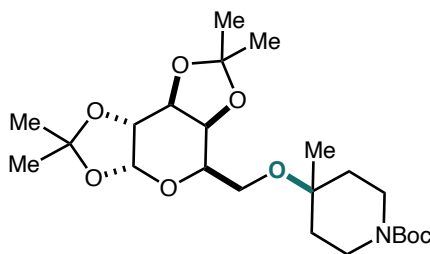
^1H NMR (500 MHz, CDCl_3) δ 5.09 (ddp, J = 7.2, 5.9, 1.5 Hz, 1H), 3.75 – 3.65 (m, 2H), 3.37 – 3.26 (m, 2H), 3.11 (t, J = 12.3 Hz, 2H), 2.05 – 1.89 (m, 2H), 1.76 – 1.68 (m, 3H), 1.68 (d, J = 1.4 Hz, 3H), 1.60 (d, J = 1.2 Hz, 3H), 1.59 – 1.52 (m, 2H), 1.45 (s, 9H), 1.42 – 1.29 (m, 4H), 1.14 (s, 3H), 0.89 (d, J = 6.4 Hz, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 155.10, 131.29, 124.98, 79.32, 71.20, 58.87, 37.68, 37.36, 29.67, 28.62, 25.86, 25.61, 24.71, 19.84, 17.78.

HRMS (ESI-TOF) m/z calcd. for $\text{C}_{17}\text{H}_{32}\text{NO}_3$ [$\text{M-Boc}+2\text{H}$] $^+$ 254.24839; found: 254.24844.

IR (film) ν_{max} 2966, 2926, 2870, 1692, 1420, 1364, 1258, 1242, 1154, 1133, 1077, 986, 736 cm^{-1}

Tert-butyl 4-methyl-4-(((3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-5H-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)methoxy)piperidine-1-carboxylate (26)



Prepared according to the general procedure B with redox-active ester **RAE1** (105 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μmol , 5 mol%), Cp_2TiCl_2 (6.22 mg, 25.0 μmol , 10 mol%), $\text{Zn}_3(\text{PO}_4)_2$ (72.4 mg, 187 μmol , 0.75 equiv.), ((3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-5H-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)methanol (195 mg, 750 μmol , 3.00 equiv.), in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the lumidox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 0% to 70% EtOAc in hexanes. The fractions containing product were concentrated and further purified by preparative HPLC (RediSep C18 column, 35% to 80% MeCN in H_2O with 0.1% NH_4OH) to provide the product as a colorless solid (57.4 mg, 125 μmol , 50% yield).

^1H NMR (500 MHz, CDCl_3) δ 5.51 (d, $J = 4.9$ Hz, 1H), 4.59 (dd, $J = 8.0, 2.3$ Hz, 1H), 4.32 – 4.26 (m, 2H), 3.90 (ddd, $J = 7.4, 5.9, 1.8$ Hz, 1H), 3.72 (d, $J = 13.0$ Hz, 2H), 3.51 (dd, $J = 8.8, 7.1$

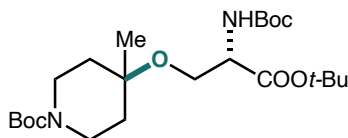
Hz, 1H), 3.45 (dd, $J = 8.8, 6.0$ Hz, 1H), 3.17 – 3.08 (m, 2H), 1.74 (ddq, $J = 21.8, 13.6, 2.8$ Hz, 2H), 1.54 (s, 3H), 1.45 (s, 9H), 1.44 (s, 3H), 1.42 – 1.34 (m, 2H), 1.33 (s, 6H), 1.16 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 155.09, 109.14, 108.63, 96.46, 79.28, 71.95, 71.08, 70.98, 70.71, 67.35, 59.97, 39.96, 36.18, 35.15, 28.63, 26.30, 26.14, 25.10, 24.84, 24.49.

HRMS (ESI-TOF) m/z calcd. for $\text{C}_{23}\text{H}_{39}\text{NO}_8\text{Na}$ $[\text{M}+\text{Na}]^+$ 480.25734; found: 480.25751.

IR (film) ν_{max} 2976, 2935, 1687, 1421, 1380, 1365, 1243, 1210, 1164, 1115, 1067, 998, 734 cm^{-1}

***Tert*-butyl (S)-4-(3-(*tert*-butoxy)-2-((*tert*-butoxycarbonyl)amino)-3-oxopropoxy)-4-methylpiperidine-1-carboxylate (27)**



Prepared according to the general procedure B with redox-active ester **RAE1** (120 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μmol , 5 mol%), Cp_2TiCl_2 (6.22 mg, 25.0 μmol , 10 mol%), $\text{Zn}_3(\text{PO}_4)_2$ (72.4 mg, 187 μmol , 0.75 equiv.), *tert*-butyl (S)-2-(*tert*-butoxycarbonylamino)-3-hydroxy-propanoate (196 mg, 750 μmol , 3.00 equiv.), in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the lumidox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 10% to 70% EtOAc in hexanes. The fractions containing product were concentrated and further purified by preparative HPLC (RediSep C18 column, 25% to 90% MeCN in H_2O with 0.1% NH_4OH) to provide the product as a colorless oil (58.1 mg, 127 μmol , 51% yield).

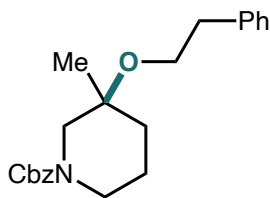
¹H NMR (500 MHz, CDCl₃) δ 5.31 (d, J = 8.8 Hz, 1H), 4.28 (dt, J = 8.8, 2.9 Hz, 1H), 3.91 – 3.60 (m, 4H), 3.54 (dd, J = 8.7, 3.0 Hz, 1H), 3.11 – 2.94 (m, 2H), 1.71 – 1.60 (m, 4H), 1.46 (s, 9H), 1.45 (s, 9H), 1.44 (s, 9H), 1.12 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 169.89, 155.63, 155.10, 82.05, 79.84, 79.45, 71.82, 61.64, 54.71, 40.08, 35.47, 28.59, 28.49, 28.19, 24.55.

HRMS (ESI-TOF) m/z calcd. for C₂₃H₄₂N₂O₇Na [M+Na]⁺ 481.28897; found: 481.28900.

IR (film) ν_{max} 2977, 2933, 1680, 1496, 1424, 1392, 1243, 1152, 1099, 907 cm⁻¹

Benzyl 3-methyl-3-phenethoxypiperidine-1-carboxylate (28)



Prepared according to the general procedure B with redox-active ester **RAE2** (113 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μmol, 5 mol%), Cp₂TiCl₂ (6.22 mg, 25.0 μmol, 10 mol%), Zn₃(PO₄)₂ (72.4 mg, 187 μmol, 0.75 equiv.), 2-phenylethanol (89.3 μL, 750 μmol, 3.00 equiv.), in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the luminox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 5% to 70% EtOAc in hexanes. The resulting product fractions were concentrated to provide the product as a yellowish oil (63.6 mg, 180 μmol, 72% yield).

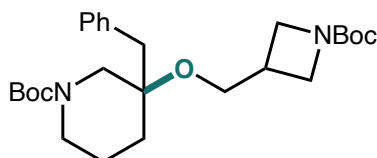
¹H NMR (500 MHz, CDCl₃) δ 7.41 – 7.28 (m, 5H), 6.73 – 6.46 (m, 1H), 5.18 – 5.12 (m, 2H), 3.99 (dd, *J* = 8.9, 8.3 Hz, 2H), 3.77 (d, *J* = 6.6 Hz, 2H), 3.68 (dd, *J* = 8.8, 5.2 Hz, 2H), 3.61 – 3.51 (m, 2H), 2.70 (ttt, *J* = 8.2, 6.6, 5.2 Hz, 1H), 1.96 (q, *J* = 4.7 Hz, 2H), 1.81 (tq, *J* = 12.4, 6.2 Hz, 3H), 1.70 – 1.63 (m, 3H), 1.43 (s, 9H). (mixture of rotamers)

¹³C NMR (126 MHz, CDCl₃) δ 156.59, 153.59, 153.23, 136.70, 128.64, 128.19, 128.16, 128.09, 120.21, 119.72, 115.83, 115.43, 79.51, 67.43, 67.32, 64.69, 51.50, 41.87, 41.77, 30.62, 28.53, 28.48, 28.44, 27.09, 26.84, 21.94, 21.87, 21.05, 21.02. (mixture of rotamers)

HRMS (ESI-TOF) *m/z* calcd. for C₂₃H₃₄N₂O₅Na [M+Na]⁺ 441.23654; found: 441.23613.

IR (film) *v*_{max} 2966, 2935, 2880, 1693, 1455, 1413, 1364, 1261, 1161, 1075, 985, 863 cm⁻¹

***Tert*-butyl 3-benzyl-3-((1-(*tert*-butoxycarbonyl)azetidin-3-yl)methoxy)piperidine-1-carboxylate (30)**



Prepared according to the general procedure B with redox-active ester **RAE4** (124 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μmol, 5 mol%), Cp₂TiCl₂ (6.22 mg, 25.0 μmol, 10 mol%), Zn₃(PO₄)₂ (72.4 mg, 187 μmol, 0.75 equiv.), *tert*-butyl 3-(hydroxymethyl)azetidine-1-carboxylate (140 mg, 750 μmol, 3.00 equiv.), in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the luminox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 10% to 70% EtOAc in hexanes. The fractions containing product were concentrated and further purified by preparative HPLC (RediSep C18 column, 45%

to 100% MeCN in H₂O with 0.1% NH₄OH) to provide the product as a yellow oil (92.1 mg, 200 μ mol, 80% yield).

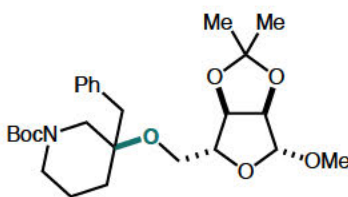
¹H NMR (500 MHz, CDCl₃) δ 7.31 – 7.24 (m, 2H), 7.22 – 7.12 (m, 3H), 3.99 (td, *J* = 8.4, 3.1 Hz, 2H), 3.95 – 3.76 (m, 1H), 3.70 (dddd, *J* = 12.1, 8.8, 6.0, 3.0 Hz, 2H), 3.52 – 3.23 (m, 2H), 2.93 – 2.47 (m, 4H), 1.90 – 1.72 (m, 1H), 1.62 (ddt, *J* = 28.1, 12.6, 3.3 Hz, 2H), 1.55 – 1.47 (m, 2H), 1.46 – 1.31 (m, 18H), 1.42 – 1.38 (m, 1H). (mixture of rotamers)

¹³C NMR (126 MHz, CDCl₃) δ 156.59, 153.03, 152.53, 140.23, 140.13, 128.84, 128.41, 126.21, 122.10, 121.70, 117.71, 117.09, 116.49, 80.57, 80.42, 79.51, 64.75, 64.74, 51.64, 42.30, 42.02, 41.97, 41.28, 30.63, 28.58, 28.54, 28.52, 24.94, 24.65, 22.00, 21.86. (mixture of rotamers)

HRMS (ESI-TOF) *m/z* calcd. for C₂₆H₄₀N₂O₅Na [M+Na]⁺ 483.28349; found: 483.28441.

IR (film) ν_{max} 2974, 2936, 2882, 1690, 1391, 1365, 1269, 1150, 1131, 966, 770, 734 cm⁻¹

***Tert*-butyl 3-benzyl-3-(((3*aR*,4*R*,6*R*,6*aR*)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methoxy)piperidine-1-carboxylate (31)**



Prepared according to the general procedure B with redox-active ester **RAE4** (124 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μ mol, 5 mol%), Cp₂TiCl₂ (6.22 mg, 25.0 μ mol, 10 mol%), Zn₃(PO₄)₂ (72.4 mg, 187 μ mol, 0.75 equiv.), [(3*aR*,4*R*,6*R*,6*aR*)-4-methoxy-2,2-dimethyl-3*a*,4,6,6*a*-tetrahydrofuro[3,4-*d*][1,3]dioxol-6-yl]methanol (153 mg, 750 μ mol, 3.00 equiv.), in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the lumidox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 10% to 70% EtOAc in hexanes. The fractions containing product were concentrated and further purified by preparative HPLC (RediSep C18 column, 35% to 90% MeCN in H₂O with 0.1% NH₄OH) to provide the product as a colorless oil as a 1:1 mixture of diastereoisomers (76.6 mg, 160 μ mol, 64% yield, d.r. = 1:1).

¹H NMR (500 MHz, CDCl₃) unassigned diastereoisomers

diastereomer 1: δ 7.32 – 7.26 (m, 2H), 7.24 – 7.14 (m, 3H), 5.35 – 4.81 (m, 2H), 4.65 – 4.39 (m, 2H), 4.28 – 3.79 (m, 1H), 3.71 – 3.45 (m, 1H), 3.46 – 3.12 (m, 6H), 3.01 – 2.49 (m, 2H), 2.21 – 1.93 (m, 1H), 1.90 – 1.65 (m, 2H), 1.51 – 1.40 (m, 14H), 1.34 – 1.29 (m, 3H).

diastereomer 2: ¹H NMR (500 MHz, CDCl₃) δ 7.32 – 7.23 (m, 2H), 7.23 – 7.14 (m, 3H), 5.34 – 4.93 (m, 2H), 4.87 – 4.52 (m, 2H), 4.46 – 4.29 (m, 1H), 4.00 – 3.57 (m, 1H), 3.52 – 3.13 (m, 6H), 2.95 – 2.66 (m, 2H), 2.58 (tt, J = 14.0, 7.6 Hz, 1H), 1.89 – 1.73 (m, 1H), 1.68 – 1.60 (m, 1H), 1.53 – 1.42 (m, 9H), 1.40 – 1.34 (m, 8H).

¹³C NMR (126 MHz, CDCl₃)

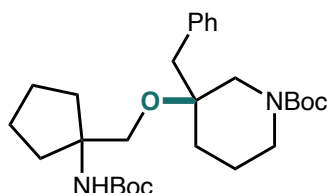
diastereomer 1: δ 153.02, 152.52, 140.25, 140.13, 128.85, 128.41, 126.21, 122.11, 121.71, 117.69, 117.07, 112.25, 110.14, 88.52, 85.98, 81.62, 80.55, 80.41, 64.16, 55.67, 42.30, 41.98, 41.29, 28.52, 26.49, 24.94, 24.84, 24.65, 22.01, 21.86.

diastereomer 2: δ 153.02, 152.52, 140.24, 140.13, 128.85, 128.41, 126.21, 122.11, 121.71, 117.68, 117.07, 112.25, 110.14, 88.52, 85.97, 81.62, 80.55, 80.40, 64.16, 55.66, 42.30, 42.01, 41.97, 41.28, 28.52, 26.49, 24.94, 24.83, 24.65, 22.00, 21.86.

HRMS (ESI-TOF) m/z calcd. for C₂₆H₃₉NO₇Na [M+Na]⁺ 500.26242; found: 500.26254.

IR (film) ν_{max} 2937, 2867, 1693, 1455, 1411, 1380, 1365, 1272, 1160, 1090, 1051, 1030, 977 cm⁻¹

***Tert*-butyl 3-benzyl-3-((1-((*tert*-butoxycarbonyl)amino)cyclopentyl)methoxy)piperidine-1-carboxylate (32)**



Prepared according to the general procedure B with redox-active ester **RAE4** (124 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μ mol, 5 mol%), Cp₂TiCl₂ (6.22 mg, 25.0 μ mol, 10 mol%), Zn₃(PO₄)₂ (72.4 mg, 187 μ mol, 0.75 equiv.), *tert*-butyl *N*-[1-(hydroxymethyl)cyclopentyl]carbamate (161 mg, 750 μ mol, 3.00 equiv.), in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the luminox setup, the solvent was removed under reduced pressure. The crude residue was dissolved in a minimal amount of DMSO, loaded on a 30 g Biotage Sfär C18 D reverse phase column, and purified with eluents 25% to 100% MeCN in water (0.1% NH₄OH modifier). The fractions containing product were concentrated and the product was obtained as a colorless oil (75.5 mg, 155 μ mol, 61% yield).

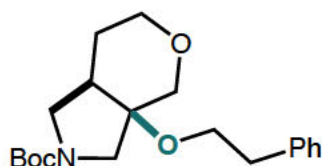
¹H NMR (500 MHz, CDCl₃) δ 7.31 – 7.23 (m, 2H), 7.21 – 7.13 (m, 3H), 5.36 – 4.97 (m, 1H), 4.73 – 4.56 (m, 1H), 4.06 – 3.70 (m, 1H), 3.55 – 3.15 (m, 1H), 3.01 – 2.78 (m, 1H), 2.72 (dddd, *J* = 21.7, 18.0, 12.3, 6.4 Hz, 1H), 2.61 – 2.47 (m, 1H), 2.23 – 2.05 (m, 1H), 1.93 – 1.70 (m, 8H), 1.64 – 1.52 (m, 4H), 1.47 – 1.33 (m, 18H). (mixture of rotamers)

¹³C NMR (126 MHz, CDCl₃) δ 155.50, 155.18, 154.88, 154.59, 140.47, 140.29, 140.26, 129.22, 129.20, 129.09, 128.83, 128.46, 128.44, 128.39, 126.16, 126.06, 126.05, 82.87, 81.97, 80.18, 79.96, 79.81, 78.90, 70.34, 70.16, 63.46, 63.41, 63.16, 43.21, 42.81, 39.67, 39.25, 39.21, 39.01, 38.14, 37.94, 36.40, 36.09, 35.82, 35.52, 28.61, 28.55, 28.51, 28.49, 28.46, 28.40, 25.50, 25.26, 25.07, 25.01, 24.62, 24.50, 24.45, 24.39, 24.09. (mixture of rotamers)

HRMS (ESI-TOF) *m/z* calcd. for C₂₈H₄₄N₂O₅Na [*M*+Na]⁺ 511.31479; found: 511.31472.

IR (film) ν_{max} 3444, 2974, 2940, 2868, 1684, 1494, 1391, 1365, 1245, 1152, 1077, 978, 907, 646 cm^{-1}

***Tert*-butyl (3aR/S,7aR)-3a-phenethoxyhexahydropyrano[3,4-c]pyrrole-2(3H)-carboxylate (33)**



Prepared according to the general procedure B with redox-active ester **RAE5** (112 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μmol , 5 mol%), Cp_2TiCl_2 (6.22 mg, 25.0 μmol , 10 mol%), $[\text{ZnCO}_3]_2 \cdot [\text{Zn}(\text{OH})_2]_3$ (68.6 mg, 125 μmol , 0.5 equiv.), 2-phenylethanol (92 μL , 750 μmol , 3.00 equiv.), in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the luminox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 10% to 60% EtOAc in hexanes. The fractions containing product were concentrated and further purified by preparative HPLC (RediSep C18 column, 30% to 80% MeCN in H_2O with 0.1% NH_4OH) to provide the product as a yellowish oil (44.7 mg, 129 μmol , 51% yield, d.r. = 2.2:1).

^1H NMR (500 MHz, CDCl_3) δ 7.32 – 7.27 (m, 2H+2H*), 7.24 – 7.17 (m, 3H+3H*), 3.84 – 3.68 (m, 2H+2H*), 3.68 – 3.58 (m, 1H+1H*), 3.58 – 3.47 (m, 3H+3H*), 3.47 – 3.41 (m, 1H+1H*), 3.41 – 3.29 (m, 2H+2H*), 3.29 – 3.09 (m, 1H+1H*), 2.90 – 2.78 (m, 2H+2H*), 2.24 – 2.12 (m, 1H+1H*), 1.83 – 1.63 (m, 2H+2H*), 1.46 (s, 9H*), 1.46 (s, 9H). (unassigned mixture of

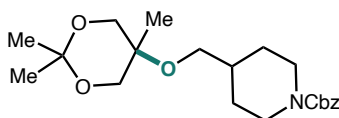
diastereoisomers; d.r. determined by crude NMR; integrals are normalized for each diastereoisomer)

^{13}C NMR (500 MHz, CDCl_3) δ 155.22, 155.13, 155.01, 139.16, 139.15, 138.89, 138.87, 129.13, 129.10, 129.08, 128.49, 128.47, 128.44, 126.52, 126.49, 126.42, 79.86, 79.61, 79.52, 79.47, 67.84, 67.77, 66.29, 66.08, 64.61, 64.10, 64.08, 63.70, 63.58, 50.28, 49.93, 49.75, 48.91, 46.66, 42.39, 40.70, 39.65, 37.22, 37.18, 37.13, 37.08, 29.11, 29.04, 28.67, 28.64, 27.98, 27.81. (unassigned mixture of diastereoisomers + rotamers)

HRMS (ESI-TOF) m/z calcd. for $\text{C}_{20}\text{H}_{29}\text{NO}_4\text{Na}$ $[\text{M}+\text{Na}]^+$ 370.19943; found: 370.19979.

IR (film) ν_{max} 2930, 2865, 1693, 1401, 1364, 1166, 1096, 986, 879, 750 cm^{-1}

Benzyl 4-(((2,2,5-trimethyl-1,3-dioxan-5-yl)oxy)methyl)piperidine-1-carboxylate (34)



Prepared according to the general procedure B with redox-active ester **RAE6** (87.3 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μmol , 5 mol%), Cp_2TiCl_2 (6.22 mg, 25.0 μmol , 10 mol%), $\text{Zn}_3(\text{PO}_4)_2$ (72.4 mg, 187 μmol , 0.75 equiv.), benzyl 4-(hydroxymethyl)piperidine-1-carboxylate (187 mg, 750 μmol , 3.00 equiv.), in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the lumidox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 0% to 60% EtOAc in hexanes. The fractions containing product were concentrated and further purified by preparative HPLC (RediSep C18 column, 35%

to 90% MeCN in H₂O with 0.1% NH₄OH) to provide the product as a colorless oil (50.9 mg, 135 μ mol, 54% yield).

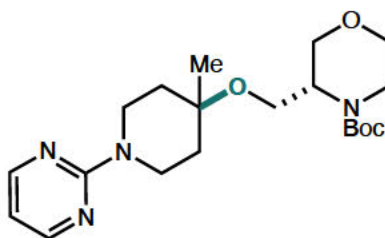
¹H NMR (500 MHz, CDCl₃) δ 7.36 (d, J = 4.3 Hz, 4H), 7.34 – 7.28 (m, 1H), 5.12 (s, 2H), 4.47 (d, J = 7.0 Hz, 1H), 4.26 – 4.12 (m, 2H), 3.88 (dd, J = 11.7, 4.8 Hz, 1H), 3.73 (dd, J = 9.6, 5.6 Hz, 1H), 3.49 (dd, J = 11.8, 9.2 Hz, 1H), 3.18 (dd, J = 9.5, 6.8 Hz, 1H), 2.86 – 2.68 (m, 2H), 1.84 – 1.67 (m, 4H), 1.46 (s, 3H), 1.42 (s, 3H), 1.25 – 1.12 (m, 2H), 0.92 (d, J = 6.8 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 155.44, 137.10, 128.62, 128.07, 127.98, 101.62, 99.53, 73.19, 67.12, 64.55, 44.03, 36.58, 34.65, 29.43, 28.60, 22.55, 12.77.

HRMS (ESI-TOF) m/z calcd. for C₂₁H₃₁NO₅Na [M+Na]⁺ 400.20999; found: 400.20993.

IR (film) ν_{max} 2931, 2856, 1696, 1429, 1363, 1271, 1245, 1219, 1133, 1063, 1010, 958 cm⁻¹

***Tert*-butyl (S)-3-(((4-methyl-1-(pyrimidin-2-yl)piperidin-4-yl)oxy)methyl)morpholine-4-carboxylate (35)**



Prepared according to the general procedure B with redox-active ester **RAE7** (99.1 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μ mol, 5 mol%), Cp₂TiCl₂ (6.22 mg, 25.0 μ mol, 10 mol%), Zn₃(PO₄)₂ (72.4 mg, 187 μ mol, 0.75 equiv.), *tert*-butyl (3*R*)-3-(hydroxymethyl)morpholine-4-carboxylate (163 mg, 750 μ mol, 3.00 equiv.), in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the luminox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 5% to 80% EtOAc in hexanes. The fractions containing product were concentrated and further purified by preparative HPLC (RediSep C18 column, 30% to 90% MeCN in H₂O with 0.1% NH₄OH) to provide the product as a colorless oil (53.7 mg, 137 μ mol, 55% yield).

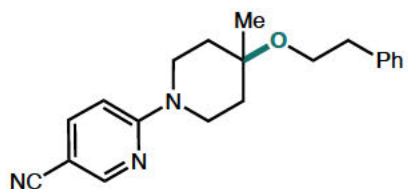
¹H NMR (500 MHz, CDCl₃) δ 8.29 (d, J = 4.8 Hz, 2H), 6.44 (t, J = 4.8 Hz, 1H), 4.34 (d, J = 13.3 Hz, 2H), 4.03 (d, J = 11.6 Hz, 1H), 4.01 – 3.91 (m, 1H), 3.84 (d, J = 11.3 Hz, 1H), 3.75 (d, J = 12.9 Hz, 1H), 3.62 (t, J = 8.7 Hz, 1H), 3.51 (dd, J = 11.6, 3.3 Hz, 1H), 3.48 – 3.39 (m, 2H), 3.35 (tq, J = 12.9, 2.9 Hz, 2H), 3.14 – 2.97 (m, 1H), 1.86 – 1.78 (m, 2H), 1.53 – 1.46 (m, 2H), 1.45 (s, 9H), 1.20 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 161.06, 157.71, 154.83, 109.17, 79.99, 72.20, 66.68, 66.27, 56.96, 51.30, 40.09, 35.61, 35.49, 28.42, 24.63.

HRMS (ESI-TOF) m/z calcd. for C₂₀H₃₂N₄O₄Na [M+Na]⁺ 415.23212; found: 415.23209.

IR (film) ν_{max} 2970, 2929, 2864, 1695, 1586, 1545, 1508, 1390, 1364, 1259, 1168, 1079 cm⁻¹

6-(4-methyl-4-phenethoxypiperidin-1-yl)nicotinonitrile (**36**)



Prepared according to the general procedure B with redox-active ester **RAE8** (105 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μ mol, 5 mol%), Cp_2TiCl_2 (6.22 mg, 25.0 μ mol, 10 mol%), $[\text{ZnCO}_3]_2 \cdot [\text{Zn}(\text{OH})_2]_3$ (**137 mg, 250 μ mol, 1.0 equiv.**), 1-phenylethanol (89.3 μ L, 750 μ mol, 3.00 equiv.), in DCE (**0.1 M, 2.5 mL**).

After irradiation for 20 hours at level 5 (8.4 W) in the lumidox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 10% to 70% EtOAc in hexanes. The fractions containing product were concentrated and further purified by preparative HPLC (RediSep C18 column, 35% to 85% MeCN in H_2O with 0.1% NH_4OH) to provide the product as a yellow oil (41.6 mg, 129 μ mol, 51% yield).

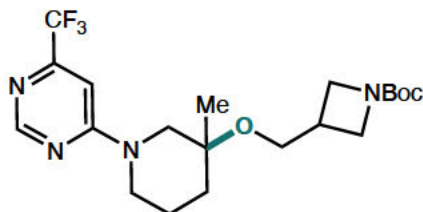
^1H NMR (500 MHz, CDCl_3) δ 8.37 (d, J = 2.4 Hz, 1H), 7.54 (dd, J = 9.1, 2.4 Hz, 1H), 7.29 – 7.21 (m, 4H), 7.21 – 7.15 (m, 1H), 6.54 (d, J = 9.1 Hz, 1H), 3.97 (dt, J = 13.3, 3.8 Hz, 2H), 3.56 (t, J = 6.9 Hz, 2H), 3.10 (td, J = 12.7, 2.8 Hz, 2H), 2.86 (t, J = 6.9 Hz, 2H), 1.81 (dq, J = 14.3, 2.7 Hz, 2H), 1.43 (ddd, J = 13.8, 12.1, 4.4 Hz, 2H), 1.16 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 159.28, 152.91, 139.68, 139.63, 129.19, 128.40, 126.36, 119.08, 105.76, 95.44, 71.55, 62.39, 40.78, 37.25, 35.40, 24.76.

HRMS (ESI-TOF) m/z calcd. for $\text{C}_{20}\text{H}_{24}\text{N}_3\text{O}$ $[\text{M}+\text{H}]^+$ 322.19194; found: 322.19184.

IR (film) ν_{max} 2922, 2865, 2213, 1598, 1541, 1502, 1423, 1254, 1213, 1135, 1074, 973, 733 cm^{-1}

***Tert*-butyl 3-(((4-methyl-1-(6-(trifluoromethyl)pyrimidin-4-yl)piperidin-4-yl)oxy)methyl)azetidine-1-carboxylate (37)**



Prepared according to the general procedure B with redox-active ester **RAE9** (116 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μmol , 5 mol%), Cp_2TiCl_2 (6.22 mg, 25.0 μmol , 10 mol%), $[\text{ZnCO}_3]_2 \cdot [\text{Zn}(\text{OH})_2]_3$ (68.6 mg, 125 μmol , 0.5 equiv.), *tert*-butyl 3-(hydroxymethyl)azetidine-1-carboxylate (140 mg, 750 μmol , 3.00 equiv.), in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the luminox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 10% to 70% EtOAc in hexanes. The fractions containing product were concentrated and further purified by preparative HPLC (RediSep C18 column, 20% to 90% MeCN in H_2O with 0.1% NH_4OH) to provide the product as a colorless solid (68.5 mg, 159 μmol , 64% yield).

^1H NMR (500 MHz, CDCl_3) δ 8.65 (s, 1H), 6.84 (d, J = 1.2 Hz, 1H), 3.96 (td, J = 8.4, 6.8 Hz, 2H), 3.64 (dt, J = 9.6, 4.9 Hz, 2H), 3.51 – 3.39 (m, 2H), 3.28 – 3.19 (m, 1H), 2.77 – 2.67 (m, 1H), 2.25 – 2.14 (m, 1H), 2.09 (tt, J = 13.1, 4.7 Hz, 1H), 1.82 – 1.69 (m, 1H), 1.59 (dt, J = 13.6, 3.7 Hz, 1H), 1.42 (s, 9H), 1.42 – 1.36 (m, 3H), 0.96 (d, J = 7.2 Hz, 3H).

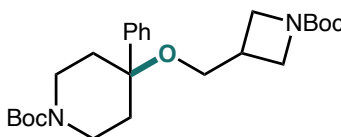
¹³C NMR (126 MHz, CDCl₃) δ 163.51, 159.04, 156.54, 155.18 (q, *J* = 34.5 Hz), 121.08 (q, *J* = 274.7 Hz), 98.76, 79.50, 69.23, 51.85, 32.58, 28.60, 28.53, 24.7i3, 19.58, 15.54.

¹⁹F NMR (471 MHz, CDCl₃) δ -70.60.

HRMS (ESI-TOF) *m/z* calcd. for C₂₀H₂₉F₃N₄O₃Na [M+Na]⁺ 453.20894; found: 453.20885.

IR (film) *v*_{max} 2967, 2883, 1694, 1601, 1491, 1444, 1391, 1364, 1301, 1138, 1061, 944 cm⁻¹

***Tert*-butyl 4-((1-(*tert*-butoxycarbonyl)azetidin-3-yl)methoxy)-4-phenylpiperidine-1-carboxylate (38)**



Prepared according to the general procedure B with redox-active ester **RAE10** (120 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μmol, 5 mol%), Cp₂TiCl₂ (6.22 mg, 25.0 μmol, 10 mol%), Zn₃(PO₄)₂ (72.4 mg, 187 μmol, 0.75 equiv.), *tert*-butyl 3-(hydroxymethyl)azetidine-1-carboxylate (140 mg, 750 μmol, 3.00 equiv.), in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the lumidox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 10% to 70% EtOAc in hexanes. The fractions containing product were concentrated and further purified by preparative HPLC (RediSep C18 column, 20% to 100% MeCN in H₂O with 0.1% NH₄OH) to provide the product as a colorless oil (75.3 mg, 169 μmol, 67% yield).

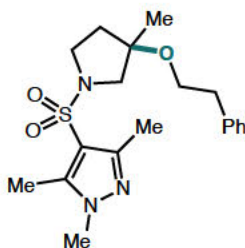
¹H NMR (500 MHz, CDCl₃) δ 7.38 – 7.35 (m, 4H), 7.31 – 7.27 (m, 1H), 4.07 – 3.98 (m, 2H), 3.94 (t, J = 8.5 Hz, 2H), 3.60 (dd, J = 8.6, 5.3 Hz, 2H), 3.22 – 3.08 (m, 4H), 2.71 – 2.61 (m, 1H), 2.11 – 2.01 (m, 2H), 1.92 – 1.77 (m, 2H), 1.47 (s, 9H), 1.42 (s, 9H).

¹³C NMR (126 MHz, CDCl₃) δ 156.52, 155.08, 144.27, 128.66, 127.72, 125.99, 79.60, 79.41, 75.21, 63.65, 51.42, 39.34, 34.13, 28.99, 28.60, 28.54.

HRMS (ESI-TOF) m/z calcd. for C₂₅H₃₈N₂O₅Na [M+Na]⁺ 469.26784; found: 469.26780.

IR (film) ν_{max} 2975, 2882, 1682, 1447, 1413, 1365, 1245, 1162, 1133, 1068, 907 cm⁻¹

1,3,5-trimethyl-4-((3-methyl-3-phenethoxypyrrolidin-1-yl)sulfonyl)-1H-pyrazole (39)



Prepared according to the general procedure B with redox-active ester **RAE11** (119 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μmol, 5 mol%), Cp₂TiCl₂ (6.22 mg, 25.0 μmol, 10 mol%), Zn₃(PO₄)₂ (72.4 mg, 187 μmol, 0.75 equiv.), 2-phenylethanol (92 μL, 750 μmol, 3.00 equiv.), in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the lumidox setup, the solvent was removed under reduced pressure. The crude residue was dissolved in a minimal amount of DMSO, loaded on a 30 g Biotage Sfär C18 D reverse phase column, and purified with eluents 15% to 80% MeCN in water (0.1% NH₄OH modifier). The fractions containing product were concentrated and the product was obtained as a colorless solid (59.8 mg, 158 μmol, 64% yield).

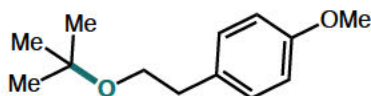
¹H NMR (500 MHz, CDCl₃) δ 7.32 – 7.26 (m, 2H), 7.24 – 7.16 (m, 3H), 4.84 (s, 1H), 3.95 – 3.83 (m, 1H), 3.76 – 3.63 (m, 4H), 3.29 (td, J = 8.8, 2.7 Hz, 1H), 3.20 (td, J = 9.2, 7.3 Hz, 1H), 2.84 (t, J = 7.2 Hz, 2H), 2.43 (s, 3H), 2.38 (s, 3H), 2.26 – 2.15 (m, 2H), 1.48 (ddd, J = 12.0, 6.0, 2.2 Hz, 1H), 0.72 (d, J = 6.9 Hz, 3H). (mixture of rotamers)

¹³C NMR (126 MHz, CDCl₃) δ 148.47, 147.85, 147.82, 147.69, 142.61, 142.22, 142.21, 142.03, 139.36, 139.11, 138.62, 129.20, 129.14, 129.11, 128.69, 128.37, 128.28, 126.57, 126.23, 126.12, 124.85, 122.00, 115.40, 114.99, 112.47, 95.48, 91.26, 68.80, 68.51, 63.78, 47.23, 46.33, 45.35, 39.88, 39.53, 39.34, 36.53, 36.46, 36.45, 36.35, 36.22, 34.23, 30.67, 30.21, 15.81, 13.72, 13.57, 13.48, 13.07, 11.18, 11.06, 10.98. (mixture of rotamers)

HRMS (ESI-TOF) m/z calcd. for C₁₉H₂₈N₃O₃S [M+H]⁺ 378.18514; found: 378.18503.

IR (film) ν_{max} 2933, 2876, 1527, 1495, 1452, 1410, 1331, 1207, 1149, 1105, 1020, 992 cm⁻¹

1-(2-(*Tert*-butoxy)ethyl)-4-methoxybenzene (40)



Prepared according to the general procedure B with redox-active ester **RAE12** (69.3 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μmol, 5 mol%), Cp₂TiCl₂ (6.22 mg, 25.0 μmol, 10 mol%), Zn₃(PO₄)₂ (72.4 mg, 187 μmol, 0.75 equiv.), 2-(4-methoxyphenyl)ethanol (114 mg, 750 μmol, 3.00 equiv.), in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the luminox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 0% to 40% EtOAc in hexanes. The fractions containing

product were concentrated to provide the product as a yellowish oil (30.1 mg, 145 μ mol, 58% yield).

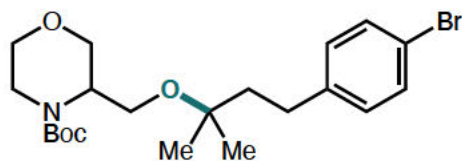
^1H NMR (500 MHz, CDCl_3) δ 7.18 – 7.11 (m, 2H), 6.87 – 6.79 (m, 2H), 3.79 (s, 3H), 3.50 (t, J = 7.6 Hz, 2H), 2.77 (t, J = 7.6 Hz, 2H), 1.17 (s, 9H).

^{13}C NMR (126 MHz, CDCl_3) δ 158.14, 131.58, 130.06, 113.82, 72.99, 63.45, 55.40, 36.70, 27.68.

HRMS (EI, 70 eV) m/z calcd. for $\text{C}_{13}\text{H}_{20}\text{O}_2$ $[\text{M}]^+$ 208.14633; found: 208.14609.

IR (film) ν_{max} 2970, 2929, 2863, 1612, 1512, 1361, 1244, 1197, 1175, 1076, 1037, 821, 563 cm^{-1}

***Tert*-butyl 3-(((4-(4-bromophenyl)-2-methylbutan-2-yl)oxy)methyl)morpholine-4-carboxylate (41)**



Prepared according to the general procedure B with redox-active ester **RAE13** (112 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μ mol, 5 mol%), Cp_2TiCl_2 (6.22 mg, 25.0 μ mol, 10 mol%), $\text{Zn}_3(\text{PO}_4)_2$ (72.4 mg, 187 μ mol, 0.75 equiv.), *tert*-butyl 3-(hydroxymethyl)morpholine-4-carboxylate (163 mg, 750 μ mol, 3.00 equiv.), in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the luminox setup, the solvent was removed under reduced pressure. The crude residue was dissolved in a minimal amount of DMSO, loaded on a 30 g Biotage Sfär C18 D reverse phase column, and purified with eluents 35% to 100%

MeCN in water (0.1% NH₄OH modifier). The fractions containing product were concentrated and the product was obtained as a yellow oil (41.2 mg, 175 μ mol, 70% yield).

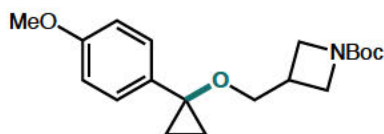
¹H NMR (500 MHz, CDCl₃) δ 7.42 – 7.34 (m, 2H), 7.10 – 7.04 (m, 2H), 4.02 (d, J = 11.6 Hz, 1H), 3.98 – 3.89 (m, 1H), 3.88 – 3.81 (m, 1H), 3.78 – 3.67 (m, 1H), 3.66 – 3.58 (m, 1H), 3.53 – 3.41 (m, 2H), 3.36 (dd, J = 8.2, 5.6 Hz, 1H), 3.06 (t, J = 9.8 Hz, 1H), 2.63 – 2.55 (m, 2H), 1.76 – 1.69 (m, 2H), 1.46 (s, 9H), 1.21 (s, 6H).

¹³C NMR (126 MHz, CDCl₃) δ 154.99, 142.05, 131.48, 130.27, 119.43, 66.79, 66.28, 57.48, 51.53, 42.60, 40.00, 29.79, 28.60, 28.56, 25.63, 25.59.

HRMS (ESI-TOF) m/z calcd. for C₂₁H₃₂BrNO₄Na [M+Na]⁺ 464.14124; found: 464.14163.

IR (film) ν_{max} 2972, 2926, 2864, 1693, 1488, 1405, 1389, 1364, 1293, 1169, 1094, 1073, 864 cm⁻¹

***Tert*-butyl 3-((1-(4-methoxyphenyl)cyclopropoxy)methyl)azetidine-1-carboxylate (42)**



Prepared according to the general procedure B with redox-active ester **RAE14** (276 mg, 0.75 mmol, 3.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μ mol, 5 mol%), Cp₂TiCl₂ (6.22 mg, 25.0 μ mol, 10 mol%), [ZnCO₃]₂·[Zn(OH)₂]₃ (68.6 mg, 125 μ mol, 0.5 equiv.), *tert*-butyl 3-(hydroxymethyl)azetidine-1-carboxylate (46.8 mg, 250 μ mol, 1.00 equiv.), in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the lumidox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 10% to 60% EtOAc in hexanes. The fractions containing

product were concentrated and further purified by preparative HPLC (RediSep C18 column, 35% to 80% MeCN in H₂O with 0.1% NH₄OH) to provide the product as a colorless oil (48.2 mg, 144 μ mol, 58% yield).

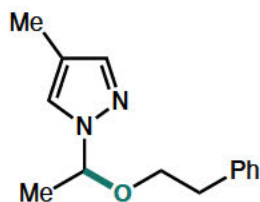
¹H NMR (500 MHz, CDCl₃) δ 7.30 – 7.27 (m, 2H), 6.90 – 6.86 (m, 2H), 3.92 (t, J = 8.4 Hz, 2H), 3.81 (s, 3H), 3.53 (dd, J = 8.7, 5.2 Hz, 2H), 3.45 (d, J = 7.0 Hz, 2H), 2.70 – 2.58 (m, 1H), 1.42 (s, 9H), 1.14 – 1.06 (m, 2H), 0.94 – 0.88 (m, 2H).

¹³C NMR (126 MHz, CDCl₃) δ 158.99, 156.52, 132.60, 128.71, 113.89, 79.41, 69.18, 62.99, 55.43, 52.55, 28.62, 28.55, 14.13.

HRMS (ESI-TOF) m/z calcd. for C₁₉H₂₇NO₄Na [M+Na]⁺ 356.18378; found: 356.18337.

IR (film) ν_{max} 2972, 2883, 1700, 1611, 1514, 1408, 1386, 1365, 1248, 1232, 1138, 1033, 831 cm⁻¹

4-Methyl-1-(1-phenethoxyethyl)-1H-pyrazole (43)



Prepared according to the general procedure B with redox-active ester **RAE15** (82.3 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μ mol, 5 mol%), Cp₂TiCl₂ (6.22 mg, 25.0 μ mol, 10 mol%), Zn₃(PO₄)₂ (72.4 mg, 187 μ mol, 0.75 equiv.), 2-phenylethanol (91.6 mg, 750 μ mol, 3.00 equiv.), in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the luminox setup, the solvent was removed under reduced pressure. The crude residue was dissolved in a minimal amount of DMSO, loaded on a 30 g Biotage Sfär C18 D reverse phase column, and purified with eluents 35% to 85%

MeCN in water (0.1% NH₄OH modifier). The fractions containing product were concentrated and the product was obtained as a yellow oil (40.7 mg, 177 μ mol, 71% yield).

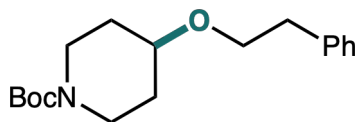
¹H NMR (500 MHz, CDCl₃) δ 7.29 – 7.23 (m, 3H), 7.21 – 7.16 (m, 2H), 7.14 – 7.11 (m, 2H), 5.43 (q, J = 6.0 Hz, 1H), 3.60 (ddd, J = 9.5, 7.7, 6.5 Hz, 1H), 3.45 (ddd, J = 9.6, 7.7, 6.7 Hz, 1H), 2.82 (dt, J = 14.0, 7.0 Hz, 1H), 2.74 (dt, J = 14.0, 7.1 Hz, 1H), 2.05 (s, 3H), 1.61 (d, J = 6.0 Hz, 3H).

¹³C NMR (500 MHz, CDCl₃) δ 139.45, 138.72, 129.05, 128.40, 126.35, 124.82, 117.07, 87.49, 69.20, 36.05, 21.96, 9.13.

HRMS (ESI-TOF) m/z calcd. for C₁₄H₁₉N₂O [M+H]⁺ 231.14974; found: 231.14966.

IR (film) ν_{max} 2921, 2871, 1496, 1453, 1379, 1339, 1155, 1111, 1060, 971, 748, 728 cm⁻¹

***Tert*-butyl 4-(2-phenylethoxy)piperidine-1-carboxylate (44)**



Isolated through a scale out consisting of pooling 5 vials at 0.05 mmol scale. Prepared according to the general procedure B with redox-active ester **RAE16** (105 mg, 0.15 mmol, 3.00 equiv.), 4DPAIPN (4 mg, 5 μ mol, 10 mol%), Cp₂TiCl₂ (2.5 mg, 10 μ mol, 20 mol%), [ZnCO₃]₂·[Zn(OH)₂]₃ (13.6 mg, 25 μ mol, 0.5 equiv.), 2-phenylethanol (6.1 mg, 50 μ mol, 1.00 equiv.), in DCE (0.2 M, .25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the luminox setup, the vials were pooled, filtered through a silica plug with MeCN. The solvent was removed under reduced pressure and filtered through a celite plug with MeCN and then purified by preparative HPLC (XBridge BEH

C18 OBD column, 50–70% MeCN/H₂O with 0.1% NH₄OH) to provide the title compound as a yellow oil (47 mg, 154 μmol, 62% yield).

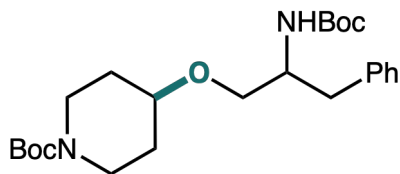
¹H NMR (500 MHz, CDCl₃) δ 7.30 – 7.27 (t, *J* = 7.6 Hz, 2H), 7.22 – 7.18 (m, 3H), 5.77 – 5.70 (m, 1H), 5.05 – 4.98 (m, 2H), 4.75 – 4.71 (m, 2H), 3.69 – 3.64 (m, 2H), 3.29 – 3.20 (m, 2H), 2.89 – 2.86 (t, *J* = 7.0 Hz, 2H), 2.30 – 2.22 (hm, 2H), 1.47 (s, 9H).

¹³C NMR (125 MHz, CDCl₃) δ (summary of rotamers) 155.96, 155.07, 139.13, 135.69, 129.04, 128.95, 128.46, 126.37, 126.30, 116.58, 80.32, 80.17, 68.75, 68.38, 45.80, 45.50, 36.28, 33.63, 32.94, 31.73, 31.06, 28.48.

HRMS (ESI-TOF) *m/z* calcd. for C₁₈H₂₇NO₃Na [M+Na]⁺ 328.1884; found: 328.1891.

IR (film) ν_{max} 2975, 2934, 1695, 1496, 1477, 1453, 1365, 1284, 1268, 1150, 1074, 1028, 912, 870, 771, 698

***Tert*-butyl 4-(2-((*tert*-butoxycarbonyl)amino)-3-phenylpropoxy)piperidine-1-carboxylate (45)**



Isolated through a scale out consisting of pooling 5 vials at 0.05 mmol scale. Prepared according to the general procedure B with redox-active ester **RAE16** (105 mg, 0.15 mmol, 3.00 equiv.), 4DPAIPN (4 mg, 5 μmol, 10 mol%), Cp₂TiCl₂ (2.5 mg, 10 μmol, 20 mol%), [ZnCO₃]₂·[Zn(OH)₂]₃ (13.6 mg, 25 μmol, 0.5 equiv.), *tert*-butyl N-(2-benzyl-3-hydroxypropyl)carbamate (13.3 mg, 50 μmol, 1.00 equiv.), in DCE (0.2 M, .25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the lumidox setup, the vials were pooled, filtered through a silica plug with MeCN. The solvent was removed under reduced pressure and filtered through a celite plug with MeCN and then purified by preparative HPLC (XBridge BEH C18 OBD column, 50–80% MeCN/H₂O with 0.1% NH₄OH) to provide the title compound as a yellow oil (76 mg, 175 μ mol, 70% yield).

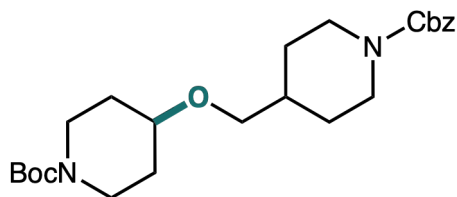
¹H NMR (500 MHz, CDCl₃) δ 7.29–7.18 (m, 5H), 5.81–5.72 (m, 1H), 5.08 – 5.01 (m, 2H), 4.87 – 4.69 (m, 3H), 3.92 (m, 1H), 3.39 – 3.29 (m, 4H), 2.89–2.71 (m, 2H), 2.33 – 2.29 (m, 2H), 1.41 (s, 18H).

¹³C NMR (125 MHz, CDCl₃) δ 155.44, 138.20, 135.52, 129.52, 128.53, 126.45, 116.82, 116.72, 80.46, 80.34, 78.29, 78.03, 68.24, 67.95, 51.65, 46.24, 45.98, 38.06, 33.77, 33.12, 28.50, 28.42.

HRMS (ESI-TOF) m/z calcd. for C₂₄H₃₈N₂O₅Na [M+Na]⁺ 457.2673; found: 457.2554.

IR (film) ν_{max} 2976, 1697, 1495, 1391, 1290, 1249, 1160, 1058, 1028, 913, 875, 775, 700

4-(((1-(*tert*-butoxycarbonyl)piperidin-4-yl)oxy)methyl)piperidine-1-carboxylate (46)



Isolated through a scale out consisting of pooling 5 vials at 0.05 mmol scale. Prepared according to the general procedure B with redox-active ester **RAE16** (56.2 mg, 0.15 mmol, 3.00 equiv.), 4DPAIPN (4 mg, 5 μ mol, 10 mol%), Cp₂TiCl₂ (2.5 mg, 10 μ mol, 20 mol%), [ZnCO₃]₂·[Zn(OH)₂]₃ (13.6 mg, 25 μ mol, 0.5 equiv.), benzyl 4-(hydroxymethyl)piperidine-1-carboxylate (12.4 mg, 50 μ mol, 1.00 equiv.), in DCE (0.2 M, .25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the lumidox setup, the vials were pooled, filtered through a silica plug with MeCN. The solvent was removed under reduced pressure and filtered through a celite plug with MeCN and then purified by preparative HPLC (XBridge BEH C18 OBD column, 50–80% MeCN/H₂O with 0.1% NH₄OH) to provide the title compound as a yellow oil (82 mg, 190 μ mol, 76% yield).

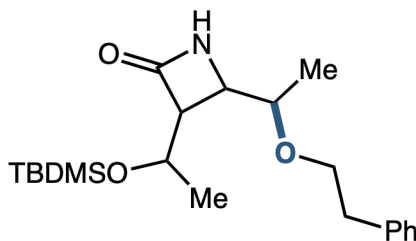
¹H NMR (500 MHz, CDCl₃) δ 7.37 – 7.28 (m, 5H), 5.80 – 5.73 (m, 1H), 5.12 (s, 2H), 5.07 – 5.00 (m, 2H), 4.72 – 4.69 (m, 2H), 4.19 – 4.12 (m, 2H), 3.33 – 3.24 (m, 4H), 2.77 (m, 2H), 2.32 – 2.27 (m, 2H), 1.72 – 1.69 (m, 3H), 1.46 (s, 9H), 1.17 – 1.15 (m, 2H).

¹³C NMR (125 MHz, CDCl₃) δ 155.39, 137.06, 135.59, 128.58, 128.04, 127.96, 116.71, 116.62, 80.23, 77.95, 77.61, 72.61, 72.29, 67.09, 45.84, 45.55, 43.99, 36.45, 33.69, 33.01, 29.13, 28.46.

HRMS (ESI-TOF) m/z calcd. for C₂₄H₃₆N₂O₅Na [M+Na]⁺ 455.2517; found: 455.2528.

IR (film) ν_{max} 2930, 1693, 1469, 1416, 1364, 1276, 1246, 1217, 1149, 1068, 1041, 912, 764, 696

3-(1-((*tert*-butyldimethylsilyl)oxy)ethyl)-4-(1-phenethoxyethyl)azetidin-2-one (47)



Isolated through a scale out consisting of pooling 5 vials at 0.05 mmol scale. Prepared according to the general procedure B with redox-active ester **RAE17** (67 mg, 0.15 mmol, 3.00 equiv.), 4DPAIPN (4 mg, 5 μ mol, 10 mol%), Cp₂TiCl₂ (2.5 mg, 10 μ mol, 20 mol%), [ZnCO₃]₂·[Zn(OH)₂]₃ (13.6 mg, 25 μ mol, 0.5 equiv.), 2-phenylethanol (6.1 mg, 50 μ mol, 1.00 equiv.), in DCM (0.14 M, .35 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the lumidox setup, the vials were pooled, filtered through a silica plug with MeCN. The solvent was removed under reduced pressure and filtered through a celite plug with MeCN and then purified by preparative HPLC (XBridge BEH C18 OBD column, 50–80% MeCN/H₂O with 0.1% NH₄OH) to provide the title compound as a yellow oil (45 mg, 119 μ mol, 48% yield, 2.2:1 d.r. unassigned).

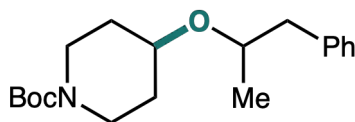
¹H NMR (500 MHz, CDCl₃) δ (summary of diastereomers) 7.31 – 7.27 (m, 2H), 7.23 – 7.20 (m, 3H), 6.56 (s, 0.30H), 6.48 (s, 0.67H), 4.65 – 4.64 (m, 0.30 H), 4.43 – 4.40 (m, 1H), 4.25 – 4.21 (m, 0.69H), 3.76 – 3.67 (m, 1H), 3.59 – 3.52 (m, 1H), 2.89 – 2.87 (m, 2H), 2.79 – 2.75 (m, 0.33H), 2.60 – 2.52 (m, 1.35H), 2.04 – 2.00 (m, 0.36H), 1.38 – 1.37 (d, J = 6.3 Hz, 2H), 1.22 – 1.21 (d, J = 6.5 Hz, 1H), 1.14 – 1.11 (dd, J = 7.0, 5.3 Hz, 3H), 0.86 (s, 6.14H), 0.82 (s, 2.69H), 0.08 (s, 2H), 0.05 – 0.04 (m, 3H), 0.00 (s, 1H).

¹³C NMR (125 MHz, CDCl₃) δ (summary of diastereomers) 178.94, 177.93, 138.88, 138.61, 129.13, 129.04, 128.59, 128.50, 126.57, 126.48, 91.06, 86.69, 69.45, 68.73, 66.62, 66.53, 53.97, 50.16, 39.26, 36.53, 36.50, 33.94, 26.00, 25.92, 22.97, 22.95, 18.10, 18.06, 15.15, 14.45, -3.66, -4.25, -4.83, -5.01.

HRMS (ESI-TOF) m/z calcd. for C₂₁H₃₅NO₃SiNa [M+Na]⁺ 400.2279; found: 400.2235.

IR (film) ν_{max} 2954, 2929, 2884, 2856, 1703, 1354, 1367, 1253, 1134, 1065, 953, 835, 776, 698

***Tert*-butyl 4-((1-phenylpropan-2-yl)oxy)piperidine-1-carboxylate (48)**



Isolated through a scale out consisting of pooling 5 vials at 0.05 mmol scale. Prepared according to the general procedure B with redox-active ester **RAE16** (56 mg, 0.15 mmol, 3.00 equiv.), 4DPAIPN (4 mg, 5 μ mol, 10 mol%), Cp_2TiCl_2 (2.5 mg, 10 μ mol, 20 mol%), $[\text{ZnCO}_3]_2 \cdot [\text{Zn}(\text{OH})_2]_3$ (13.6 mg, 25 μ mol, 0.5 equiv.), 1-phenylpropan-2-ol (6.8 mg, 50 μ mol, 1.00 equiv.), in DCE (0.2 M, .25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the luminox setup, the vials were pooled, filtered through a silica plug with MeCN. The solvent was removed under reduced pressure and filtered through a celite plug with MeCN and then purified by preparative HPLC (XBridge BEH C18 OBD column, 50–80% MeCN/ H_2O with 0.1% NH_4OH) to provide the title compound as a yellow oil (63 mg, 197 μ mol, 79% yield).

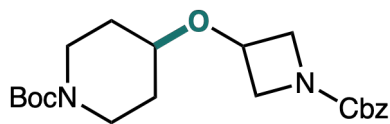
^1H NMR (500 MHz, CDCl_3) δ 7.28 – 7.24 (m, 2H), 7.21 – 7.17 (m, 3H), 5.73 – 5.65 (m, 1H), 5.02 – 4.96 (m, 2H), 4.78 – 4.58 (m, 2H), 3.82 – 3.77 (m, 1H), 3.19 – 3.00 (m, 2H), 2.88 – 2.78 (m, 1H), 2.72 – 2.61 (m, 1H), 2.22 – 2.17 (m, 2H), 1.47 (s, 9H), 1.16 (d, J = 6.2 Hz, 3H).

^{13}C NMR (125 MHz, CDCl_3) δ (summary of rotamers) 155.97, 154.96, 139.25, 138.98, 138.64, 135.73, 129.60, 129.53, 128.71, 128.29, 126.64, 126.29, 126.13, 116.46, 80.23, 80.00, 75.30, 75.08, 73.93, 72.91, 45.95, 45.09, 44.77, 43.38, 43.27, 33.33, 32.64, 28.63, 28.49, 24.65, 22.95, 20.10, 19.76.

HRMS (ESI-TOF) m/z calcd. for $\text{C}_{19}\text{H}_{29}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ 342.2040; found: 342.2027.

IR (film) ν_{max} 2936, 1695, 1469, 1420, 1365, 1282, 1257, 1233, 1148, 1075, 1025, 913, 766, 696.

***Tert*-butyl 4-((1-((benzyloxy)carbonyl)azetidin-3-yl)oxy)piperidine-1-carboxylate (49)**



Isolated through a scale out consisting of pooling 5 vials at 0.05 mmol scale. Prepared according to the general procedure B with redox-active ester **RAE16** (56 mg, 0.15 mmol, 3.00 equiv.), 4DPAIPN (4 mg, 5 μ mol, 10 mol%), Cp_2TiCl_2 (2.5 mg, 10 μ mol, 20 mol%), $[\text{ZnCO}_3]_2 \cdot [\text{Zn}(\text{OH})_2]_3$ (13.6 mg, 25 μ mol, 0.5 equiv.), benzyl 3-hydroxyazetidine-1-carboxylate (10.4 mg, 50 μ mol, 1.00 equiv.), in DCE (0.2 M, 0.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the luminox setup, the vials were pooled, filtered through a silica plug with MeCN. The solvent was removed under reduced pressure and filtered through a celite plug with MeCN and then purified by preparative HPLC (XBridge BEH C18 OBD column, 50–80% MeCN/ H_2O with 0.1% NH_4OH) to provide the title compound as a yellow oil (64 mg, 164 μ mol, 64% yield (98% pure with 2% Phthalimide by mass)).

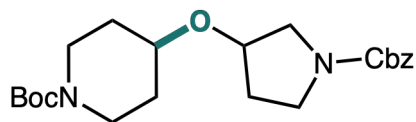
^1H NMR (500 MHz, CDCl_3) δ 7.36 – 7.28 (m, 5H), 5.78 – 5.70 (m, 1H), 5.09 – 5.01 (m, 4H), 4.72 – 4.69 (m, 2H), 4.43 – 4.34 (m, 1H), 4.17 – 4.13 (dd, J = 9.7, 6.4 Hz, 2H), 3.91 – 3.88 (dd, J = 9.6, 4.4 Hz, 2H), 3.34 – 3.27 (m, 2H), 2.33 – 2.27 (m, 2H), 1.47 (s, 9H).

^{13}C NMR (125 MHz, CDCl_3) δ (summary of rotamers) 162.03, 156.54, 155.77, 154.53, 136.79, 135.29, 134.92, 134.37, 128.58, 128.12, 128.04, 124.11, 116.98, 116.84, 80.84, 80.71, 76.69, 76.42, 66.77, 66.52, 65.41, 57.14, 46.24, 45.61, 38.67, 33.66, 32.89, 29.82, 28.54, 28.41.

HRMS (ESI-TOF) m/z calcd. for $\text{C}_{21}\text{H}_{30}\text{N}_2\text{O}_5\text{Na}$ $[\text{M}+\text{Na}]^+$ 413.2047; found: 413.2037.

IR (film) ν_{max} 2974, 1696, 1414, 1365, 1292, 1252, 1154, 1058, 992, 916, 878, 768, 697, 606.

***tert*-butyl 4-(1-benzyloxycarbonylpyrrolidin-3-yl)oxypiperidine-1-carboxylate (50)**



Isolated through a scale out consisting of pooling 5 vials at 0.05 mmol scale. Prepared according to the general procedure B with redox-active ester **RAE16** (56 mg, 0.15 mmol, 3.00 equiv.), 4DPAIPN (4 mg, 5 μ mol, 10 mol%), Cp_2TiCl_2 (2.5 mg, 10 μ mol, 20 mol%), $[\text{ZnCO}_3]_2 \cdot [\text{Zn}(\text{OH})_2]_3$ (13.6 mg, 25 μ mol, 0.5 equiv.), benzyl 3-hydroxypyrrolidine-1-carboxylate (11.1 mg, 50 μ mol, 1.00 equiv.), in DCE (0.2 M, .25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the luminox setup, the vials were pooled, filtered through a silica plug with MeCN. The solvent was removed under reduced pressure and filtered through a celite plug with MeCN and then purified by preparative HPLC (XBridge BEH C18 OBD column, 50–80% MeCN/ H_2O with 0.1% NH_4OH) to provide the title compound as a yellow oil (71 mg, 176 μ mol, 70% yield).

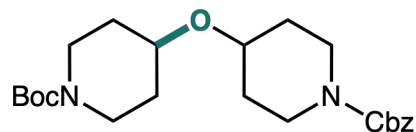
^1H NMR (500 MHz, CDCl_3) δ 7.38 – 7.27 (m, 5H), 5.79 – 5.71 (m, 1H), 5.13 (s, 2H), 5.07 – 5.00 (m, 2H), 4.83 – 4.67 (m, 2H), 4.21 – 4.16 (m, 1H), 3.54 – 3.44 (m, 4H), 3.34 – 3.27 (dq, J = 13.6, 6.7 Hz, 2H), 2.36 – 2.27 (m, 2H), 2.03 – 1.86 (m, 2H), 1.47 – 1.45 (m, 9H).

^{13}C NMR (125 MHz, CDCl_3) δ (summary of rotamers) 155.96, 155.04, 137.09, 135.50, 128.58, 128.06, 128.03, 128.00, 116.83, 116.75, 80.64, 80.48, 76.10, 75.87, 75.05, 74.55, 73.56, 66.89, 52.18, 51.63, 51.43, 46.04, 45.63, 44.40, 44.08, 33.69, 32.98, 31.67, 31.04, 30.79, 28.46.

HRMS (ESI-TOF) m/z calcd. for $\text{C}_{22}\text{H}_{32}\text{N}_2\text{O}_5\text{Na}$ $[\text{M}+\text{Na}]^+$ 427.2204; found: 427.2195.

IR (film) ν_{max} 2975, 1695, 1415, 1365, 1294, 1155, 1114, 1064, 1030, 913, 876, 769, 697

benzyl 4-[(1-tert-butoxycarbonyl-4-piperidyl)oxy]piperidine-1-carboxylate (51)



Isolated through a scale out consisting of pooling 5 vials at 0.05 mmol scale. Prepared according to the general procedure B with redox-active ester **RAE16** (56 mg, 0.15 mmol, 3.00 equiv.), 4DPAIPN (4 mg, 5 μ mol, 10 mol%), Cp_2TiCl_2 (2.5 mg, 10 μ mol, 20 mol%), $[\text{ZnCO}_3]_2 \cdot [\text{Zn}(\text{OH})_2]_3$ (13.6 mg, 25 μ mol, 0.5 equiv.), benzyl 4-hydroxypiperidine-1-carboxylate (11.8 mg, 50 μ mol, 1.00 equiv.), in DCE (0.2 M, .25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the lumidox setup, the vials were pooled, filtered through a silica plug with MeCN. The solvent was removed under reduced pressure and filtered through a celite plug with MeCN and then purified by preparative HPLC (XBridge BEH C18 OBD column, 50–80% MeCN/ H_2O with 0.1% NH_4OH) to provide the title compound as a yellow oil (85 mg, 203 μ mol, 81% yield).

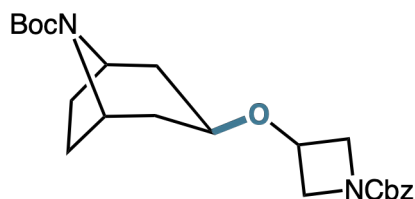
^1H NMR (500 MHz, CDCl_3) δ 7.37 – 7.28 (m, 5H), 5.80 – 5.72 (m, 1H), 5.12 (s, 2H), 5.07 – 5.00 (m, 2H), 4.79 – 4.75 (m, 2H), 3.82 – 3.77 (m, 2H), 3.63 – 3.58 (m, 1H), 3.35 – 3.27 (m, 2H), 3.21 – 3.17 (m, 2H), 2.34 – 2.28 (m, 2H), 1.85 – 1.81 (m, 2H), 1.55 – 1.52 (m, 2H), 1.46 (s, 9H).

^{13}C NMR (125 MHz, CDCl_3) δ 155.84, 155.36, 136.97, 135.55, 128.59, 128.07, 127.95, 116.71, 80.40, 80.27, 75.01, 74.84, 71.54, 70.25, 67.19, 67.14, 45.72, 45.37, 41.50, 41.45, 33.65, 32.95, 31.27, 28.42.

HRMS (ESI-TOF) m/z calcd. for $\text{C}_{23}\text{H}_{34}\text{N}_2\text{O}_5\text{Na}$ $[\text{M}+\text{Na}]^+$ 441.2360; found: 441.2318.

IR (film) ν_{max} 2975, 1693, 1472, 1418, 1365, 1273, 1224, 1155, 1069, 1026, 913, 874, 764, 733, 697

benzyl 3-(1-tert-butoxycarbonylazetidin-3-yl)oxy-8-azabicyclo[3.2.1]octane-8-carboxylate
(52)



Isolated through a scale out consisting of pooling 5 vials at 0.05 mmol scale. Prepared according to the general procedure B with redox-active ester **RAE18** (65.7 mg, 0.15 mmol, 3.00 equiv.), 4DPAIPN (4 mg, 5 μ mol, 10 mol%), Cp_2TiCl_2 (2.5 mg, 10 μ mol, 20 mol%), $[\text{ZnCO}_3]_2 \cdot [\text{Zn}(\text{OH})_2]_3$ (13.6 mg, 25 μ mol, 0.5 equiv.), benzyl 3-hydroxyazetidine-1-carboxylate (10.4 mg, 50 μ mol, 1.00 equiv.), in DCE (0.2 M, .25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the luminox setup, the vials were pooled, filtered through a silica plug with MeCN. The solvent was removed under reduced pressure and filtered through a celite plug with MeCN and then purified by preparative HPLC (XBridge BEH C18 OBD column, 50–80% MeCN/ H_2O with 0.1% NH_4OH) to provide the title compound as a yellow oil (94 mg, 226 μ mol, 90% yield, 2:1 d.r.).

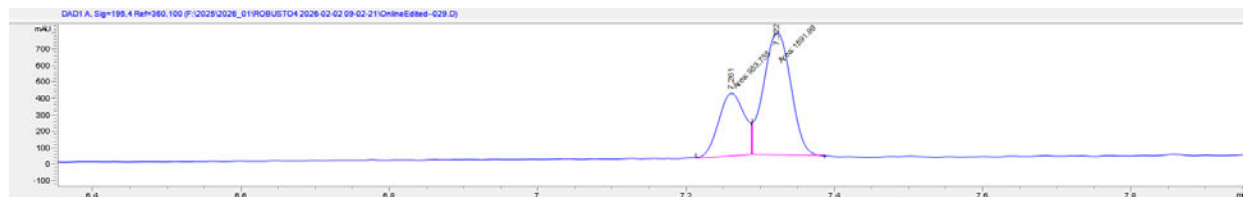
^1H NMR (500 MHz, CDCl_3) δ (Summary of diastereomers and rotamers) 7.37 – 7.29 (m, 5H), 5.79 – 5.67 (m, 1H), 5.30 – 5.29 (m, 1H), 5.09 – 5.02 (m, 4H), 4.64 – 4.40 (m, 1H), 4.25 – 4.13 (m, 2H), 3.95 – 3.73 (m, 3H), 2.74 – 2.44 (m, 1H), 2.21 – 2.00 (m, 2H), 1.90 – 1.71 (m, 2H), 1.47 (s, 9H).

^{13}C NMR (125 MHz, CDCl_3) δ (Summary of diastereomers and rotamers) 156.60, 155.18, 154.46, 153.39, 136.77, 135.13, 134.80, 129.67, 128.61, 128.58, 128.19, 128.13, 128.06, 117.53, 117.46, 117.20, 88.04, 87.94, 87.68, 80.41, 67.61, 66.85, 66.69, 66.18, 65.91, 65.24, 62.03, 59.32,

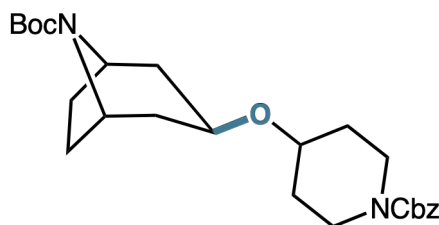
58.03, 57.50, 56.97, 45.91, 40.83, 40.19, 38.06, 36.97, 32.50, 31.80, 30.92, 30.61, 29.31, 28.63, 28.56, 27.12, 26.21, 25.87, 23.84, 22.67, 17.70.

HRMS (ESI-TOF) m/z calcd. for $C_{23}H_{32}N_2O_5Na$ $[M+Na]^+$ 439.2204; found: 439.2197.

IR (film) ν_{max} 2977, 1692, 1416, 1380, 1354, 1255, 1164, 1106, 1054, 967, 769, 698.



Benzyl 3-[(1-tert-butoxycarbonyl-4-piperidyl)oxy]-8-azabicyclo[3.2.1]octane-8-carboxylate (53)



Isolated through a scale out consisting of pooling 5 vials at 0.05 mmol scale. Prepared according to the general procedure B with redox-active ester **RAE18** (65.7 mg, 0.15 mmol, 3.00 equiv.), 4DPAIPN (4 mg, 5 μ mol, 10 mol%), Cp_2TiCl_2 (2.5 mg, 10 μ mol, 20 mol%), $[ZnCO_3]_2 \cdot [Zn(OH)_2]_3$ (13.6 mg, 25 μ mol, 0.5 equiv.), benzyl 4-hydroxypiperidine-1-carboxylate (11.6 mg, 50 μ mol, 1.00 equiv.), in DCE (0.2 M, .25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the lumidox setup, the vials were pooled, filtered through a silica plug with MeCN. The solvent was removed under reduced pressure and filtered through a celite plug with MeCN and then purified by preparative HPLC (XBridge BEH C18 OBD

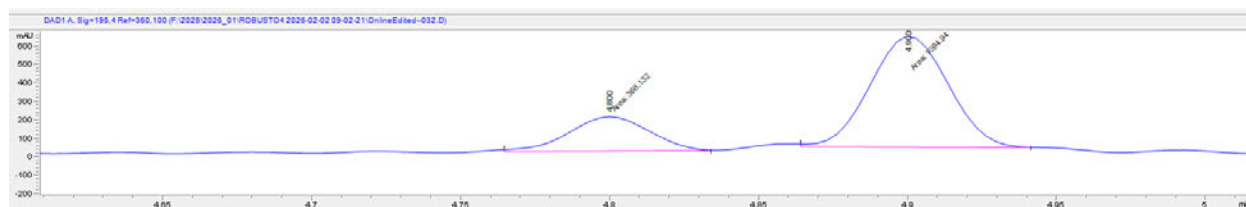
column, 50–80% MeCN/H₂O with 0.1% NH₄OH) to provide the title compound as a yellow oil (102 mg, 229 μmol, 92% yield, 3:1 d.r.).

¹H NMR (500 MHz, CDCl₃) δ (Summary of diastereomers and rotamers) 7.38 – 7.30 (m, 5H), 5.80 – 5.68 (m, 1H), 5.45 – 5.35 (m, 1H), 5.13 – 5.01 (m, 4H), 3.95 – 3.78 (m, 4H), 3.22 – 3.12 (m, 2H), 2.79 – 2.51 (m, 1H), 2.36 – 2.14 (m, 1H), 2.05 – 1.68 (m, 6H), 1.53 – 1.44 (m, 11H).

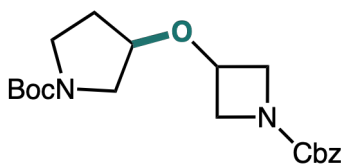
¹³C NMR (125 MHz, CDCl₃) δ (Summary of diastereomers and rotamers) 155.45, 155.40, 154.32, 153.71, 137.10, 136.96, 133.91, 129.68, 128.61, 128.13, 128.06, 128.01, 127.97, 117.81, 116.91, 106.46, 106.28, 87.03, 85.95, 85.47, 80.16, 80.05, 73.63, 70.93, 69.86, 67.58, 67.25, 67.14, 57.68, 57.50, 56.82, 56.27, 41.79, 41.66, 41.48, 41.08, 40.47, 39.02, 38.25, 37.13, 34.21, 32.73, 32.27, 31.74, 31.09, 30.64, 29.26, 28.68, 28.62, 28.57, 28.27, 26.94, 26.44, 25.76, 22.79.

HRMS (ESI-TOF) m/z calcd. for C₂₅H₃₆N₂O₅Na [M+Na]⁺ 467.2517; found: 467.2536.

IR (film) ν_{max} 2974, 1691, 1429, 1380, 1364, 1319, 1225, 1167, 1106, 1071, 1036, 912, 765, 697.



***Tert*-butyl 3-(1-benzyloxycarbonylazetidin-3-yl)oxypyrrolidine-1-carboxylate (54)**



Isolated through a scale out consisting of pooling 5 vials at 0.05 mmol scale. Prepared according to the general procedure B with redox-active ester **RAE19** (54.0 mg, 0.15 mmol, 3.00 equiv.), 4DPAIPN (4 mg, 5 μ mol, 10 mol%), Cp_2TiCl_2 (2.5 mg, 10 μ mol, 20 mol%), $[\text{ZnCO}_3]_2 \cdot [\text{Zn}(\text{OH})_2]_3$ (13.6 mg, 25 μ mol, 0.5 equiv.), benzyl 3-hydroxyazetidine-1-carboxylate (10.4 mg, 50 μ mol, 1.00 equiv.), in DCE (0.2 M, .25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the lumidox setup, the vials were pooled, filtered through a silica plug with MeCN. The solvent was removed under reduced pressure and filtered through a celite plug with MeCN and then purified by preparative HPLC (XBridge BEH C18 OBD column, 50–80% MeCN/ H_2O with 0.1% NH_4OH) to provide the title compound as a yellow oil (32 mg, 85 μ mol, 33% yield). (97% pure with 3% Phthalimide by mass)

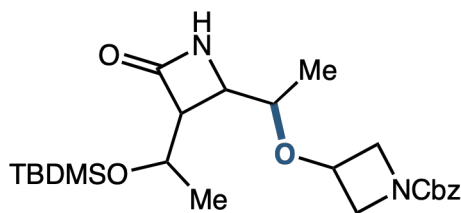
^1H NMR (500 MHz, CDCl_3) δ (Summary of rotamers) 7.36 – 7.31 (m, 5H), 5.30 – 5.09 (m, 3H), 4.61 – 4.45 (m, 1H), 4.27 – 4.11 (m, 2H), 3.92 – 3.83 (m, 2H), 3.41 – 3.25 (m, 2H), 2.25 – 1.99 (m, 1H), 1.97 – 1.74 (m, 3H), 1.48 – 1.46 (m, 9H).

^{13}C NMR (125 MHz, CDCl_3) δ (Summary of rotamers) 156.60, 155.11, 136.94, 136.76, 135.01, 134.46, 128.63, 128.58, 128.21, 128.15, 128.09, 128.02, 124.20, 123.75, 107.69, 87.00, 81.98, 81.66, 80.71, 80.23, 66.89, 66.82, 66.69, 66.51, 65.44, 62.12, 59.32, 57.86, 57.23, 46.11, 45.65, 33.36, 32.77, 29.85, 28.61, 28.52, 22.85, 21.80.

HRMS (ESI-TOF) m/z calcd. for $\text{C}_{25}\text{H}_{36}\text{N}_2\text{O}_5\text{Na}$ $[\text{M}+\text{Na}]^+$ 467.2517; found: 467.2536.

IR (film) ν_{max} 2975, 1698, 1389, 1356, 1163, 1117, 1053, 949, 770, 698, 606.

Benzyl 3-[1-[3-[1-[tert-butyl(dimethyl)silyl]oxyethyl]-4-oxo-azetidin-2-yl]ethoxy]azetidine-1-carboxylate (55)



Isolated through a scale out consisting of pooling 5 vials at 0.05 mmol scale. Prepared according to the general procedure B with redox-active ester **RAE17** (67 mg, 0.15 mmol, 3.00 equiv.), 4DPAIPN (4 mg, 5 μ mol, 10 mol%), Cp_2TiCl_2 (2.5 mg, 10 μ mol, 20 mol%), $[\text{ZnCO}_3]_2 \cdot [\text{Zn}(\text{OH})_2]_3$ (13.6 mg, 25 μ mol, 0.5 equiv.), benzyl 3-hydroxyazetidine-1-carboxylate (10.4 mg, 50 μ mol, 1.00 equiv.), in DCM (0.14 M, .35 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the luminox setup, the vials were pooled, filtered through a silica plug with MeCN. The solvent was removed under reduced pressure and filtered through a celite plug with MeCN and then purified by preparative HPLC (XBridge BEH C18 OBD column, 50–80% MeCN/ H_2O with 0.1% NH_4OH) to provide the title compound as a yellow oil (41 mg, 89 μ mol, 35% yield, 2.2:1 d.r. unassigned).

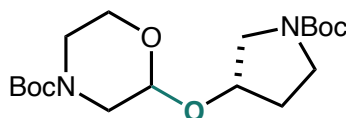
^1H NMR (500 MHz, CDCl_3) δ (summary of diastereomers) δ 7.43 (s, 0.3H), 7.37 – 7.30 (m, 5H), 7.25 (s, 0.7H), 5.09 (s, 2H), 4.65 (dd, J = 6.1, 1.3 Hz, 0.3 H), 4.45 – 4.40 (m, 1H), 4.35 – 4.30 (tt, J = 6.7, 4.4 Hz, 1H), 4.24 – 4.17 (m, 2.8H), 3.95 – 3.90 (m, 2H), 2.83 – 2.76 (m, 0.3 H), 2.62 (dd, J = 7.1, 5.9 Hz, 0.7H), 2.57 – 2.52 (m, 0.7H), 2.08 – 2.05 (m, 0.3 H), 1.38 – 1.37 (d, J = 6.3 Hz, 2.1H), 1.23 – 1.22 (d, J = 6.6 Hz, 0.9H), 1.17 – 1.14 (dd, J = 10.2, 7.1 Hz, 3H), 0.85 (s, 6.1H), 0.82 (s, 2.7H), 0.08 (s, 2.1H), 0.04 (m, 3H), -0.01 (s, 0.9H).

¹³C NMR (125 MHz, CDCl₃) δ (summary of diastereomers) 179.48, 178.31, 156.52, 136.70, 136.69, 128.63, 128.23, 128.22, 128.15, 128.14, 89.97, 85.48, 66.93, 66.92, 66.45, 66.33, 65.75, 65.36, 57.57, 56.95, 53.66, 50.16, 39.47, 33.68, 25.97, 25.90, 22.93, 22.87, 18.09, 18.04, 15.13, 14.30, -3.64, -4.23, -4.86, -5.02.

HRMS (ESI-TOF) m/z calcd. for C₂₄H₃₈N₂O₅SiNa [M+Na]⁺ 485.2443; found: 485.2417.

IR (film) ν_{max} 2954, 2884, 2856, 1705, 1421, 1355, 1253, 1167, 1109, 1062, 954, 835, 775, 697

***Tert*-butyl 2-(((*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)oxy)morpholine-4-carboxylate (56)**



Prepared according to the general procedure B with redox-active ester **RAE20** (102 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μmol, 5 mol%), Cp₂TiCl₂ (6.22 mg, 25.0 μmol, 10 mol%), Zn₃(PO₄)₂ (72.4 mg, 187 μmol, 0.75 equiv.), *tert*-butyl (3*S*)-3-hydroxypyrrolidine-1-carboxylate (140 mg, 750 μmol, 3.00 equiv.), in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the lumidox setup, the solvent was removed under reduced pressure. The crude residue was dissolved in a minimal amount of DMSO, loaded on a 30 g Biotage Sfär C18 D reverse phase column, and purified with eluents 10% to 80% MeCN in water (0.1% NH₄OH modifier). The fractions containing product were concentrated and the product was obtained as a colorless oil (63.5 mg, 170 μmol, 68% yield, d.r. = 1:1).

¹H NMR (500 MHz, CDCl₃) δ 4.66 – 4.55 (m, 1H+1H*), 4.42 – 4.32 (m, 1H+1H*), 3.95 – 3.85 (m, 1H+1H*), 3.59 – 3.47 (m, 2H+2H*), 3.47 – 3.34 (m, 6H+6H*), 3.35 – 3.19 (m, 1H+1H*),

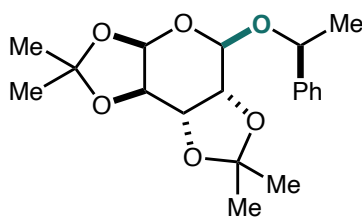
2.09 – 1.87 (m, 2H+2H*), 1.46 (s, 9H), 1.46 (s, 9H*), 1.46 *(s, 9H), 1.45 (s, 9H*). (mixture of diastereoisomers; d.r. = 1:1; *second diastereoisomer)

¹³C NMR (126 MHz, CDCl₃) δ 155.07, 154.78, 154.66, 95.25, 80.28, 79.46, 79.39, 75.56, 61.74, 52.26, 51.05, 48.35, 46.89, 44.16, 43.72, 42.79, 32.34, 30.80, 28.66, 28.51. (mixture of diastereoisomers)

HRMS (ESI-TOF) m/z calcd. for C₁₈H₃₂N₂O₆Na [M+Na]⁺ 395.21581; found: 395.21589.

IR (film) ν_{max} 2974, 2930, 2880, 1689, 1477, 1402, 1364, 1279, 1163, 1120, 1085, 1046 cm⁻¹

(3aR,5R,5aR,8aS,8bR)-2,2,7,7-tetramethyl-5-((S)-1-phenylethoxy)tetrahydro-5H-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran (57)



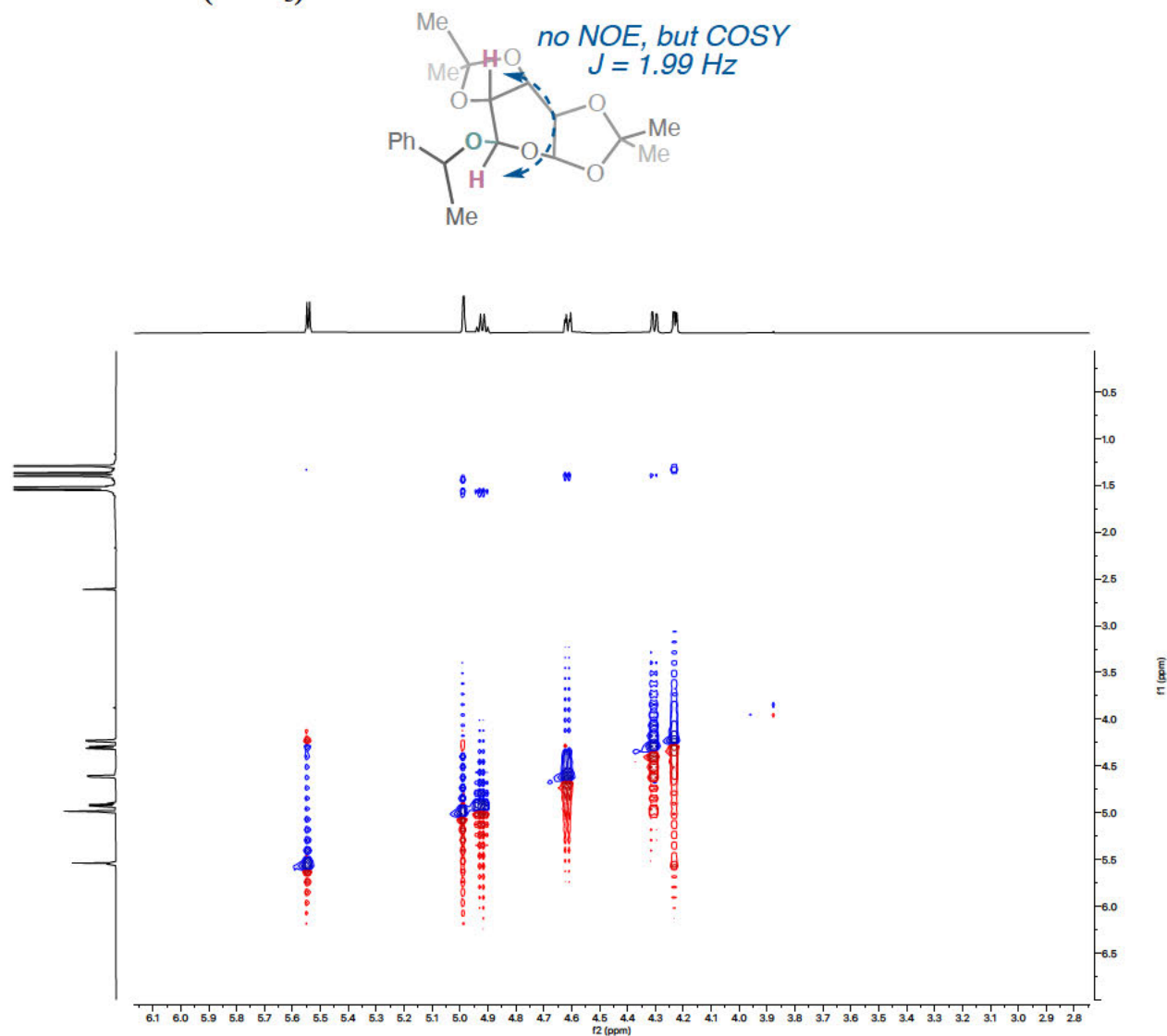
Prepared according to the general procedure B with redox-active ester **RAE21** (112 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μmol, 5 mol%), Cp₂TiCl₂ (6.22 mg, 25.0 μmol, 10 mol%), Zn₃(PO₄)₂ (72.4 mg, 187 μmol, 0.75 equiv.), (S)-1-phenylethanol (92 μL, 750 μmol, 3.00 equiv.), in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the luminox setup, the solvent was removed under reduced pressure. The crude residue was dissolved in a minimal amount of DMSO, loaded on a 30 g Biotage Sfär C18 D reverse phase column, and purified with eluents 10% to 80% MeCN in water (0.1% NH₄OH modifier). The fractions containing product were concentrated and

the product was obtained as a colorless solid (41.2 mg, 118 μmol , 47% yield, single diastereoisomer).

^1H NMR (500 MHz, CDCl_3) δ 7.44 – 7.39 (m, 2H), 7.34 – 7.29 (m, 2H), 7.26 – 7.21 (m, 1H), 5.54 (d, $J = 4.7$ Hz, 1H), 4.99 (d, $J = 1.9$ Hz, 1H), 4.92 (q, $J = 6.5$ Hz, 1H), 4.61 (dd, $J = 7.7$, 2.1 Hz, 1H), 4.30 (dd, $J = 7.8$, 1.9 Hz, 1H), 4.23 (dd, $J = 4.7$, 2.1 Hz, 1H), 1.54 (d, $J = 6.6$ Hz, 3H), 1.52 (s, 3H), 1.37 (s, 3H), 1.29 (s, 3H). (Assignment of diastereoisomer based on J-coupling and ^1H - ^1H COSY NMR)

^1H - ^1H NOESY (CDCl_3)

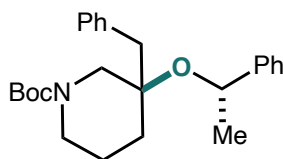


¹³C NMR (126 MHz, CDCl₃) δ 143.07, 128.33, 127.43, 126.59, 110.14, 108.84, 96.78, 91.03, 75.78, 72.79, 72.22, 71.33, 26.23, 26.10, 25.08, 24.47, 21.85.

HRMS (ESI-TOF) m/z calcd. for C₁₉H₂₆O₆Na [M+Na]⁺ 373.16271; found: 373.16290.

IR (film) ν_{max} 2934, 1697, 1585, 1545, 1498, 1453, 1431, 1364, 1258, 1221, 1065, 1040, 991, 698 cm⁻¹

***Tert*-butyl 3-benzyl-3-((*S*)-1-phenylethoxy)piperidine-1-carboxylate (**58**)**



Prepared according to the general procedure B with redox-active ester **RAE4** (124 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μmol, 5 mol%), Cp₂TiCl₂ (6.22 mg, 25.0 μmol, 10 mol%), [ZnCO₃]₂·[Zn(OH)₂]₃ (68.6 mg, 125 μmol, 0.5 equiv.), (*S*)-1-phenylethanol (130 mg, 750 μmol, 3.00 equiv.), in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the lumidox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 15% to 70% EtOAc in hexanes. The fractions containing product were concentrated and further purified by preparative HPLC (RediSep C18 column, 35% to 100% MeCN in H₂O with 0.1% NH₄OH) to provide the product as a yellowish oil (51.9 mg, 131 μmol, 52% yield, single diastereoisomer).

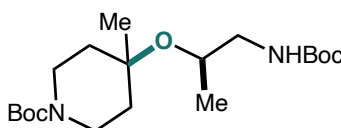
¹H NMR (500 MHz, CDCl₃) δ 7.41 – 7.32 (m, 4H), 7.30 – 7.26 (m, 3H), 7.22 – 7.17 (m, 3H), 4.91 (q, J = 6.5 Hz, 1H), 3.48 (dt, J = 17.6, 5.5 Hz, 2H), 3.29 (s, 2H), 1.91 – 1.71 (m, 6H), 1.51 (d, J = 6.5 Hz, 3H), 1.49 (s, 9H).

¹³C NMR (126 MHz, CDCl₃) δ 153.02, 152.52, 145.96, 140.24, 140.13, 128.88, 128.85, 128.64, 128.45, 128.41, 127.62, 126.21, 125.52, 122.11, 121.71, 117.69, 117.08, 80.56, 80.41, 70.57, 42.30, 42.02, 41.97, 41.28, 28.52, 25.32, 24.94, 24.65, 22.00, 21.86.

HRMS (ESI-TOF) m/z calcd. for $C_{25}H_{33}NO_3Na$ $[M+Na]^+$ 418.23581; found: 418.23552.

IR (film) ν_{max} 2974, 2932, 1690, 1413, 1390, 1365, 1348, 1278, 1255, 1148, 1071, 1027, 985, 909, 760 cm^{-1}

***Tert*-butyl (*R*)-4-((1-((*tert*-butoxycarbonyl)amino)propan-2-yl)oxy)-4-methylpiperidine-1-carboxylate (**59**)**



Prepared according to the general procedure B with redox-active ester **RAE1** (105 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μ mol, 5 mol%), Cp_2TiCl_2 (6.22 mg, 25.0 μ mol, 10 mol%), $Zn_3(PO_4)_2$ (72.4 mg, 187 μ mol, 0.75 equiv.), *tert*-butyl (*R*)-(2-hydroxypropyl)carbamate (131 mg, 750 μ mol, 3.00 equiv.) in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the lumidox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 0% to 60% EtOAc in hexanes. The fractions containing product were concentrated and further purified by preparative HPLC (RediSep C18 column, 25% to 80% MeCN in H_2O with 0.1% NH_4OH) to provide the product as a yellowish oil (56.7 mg, 152 μ mol, 61% yield).

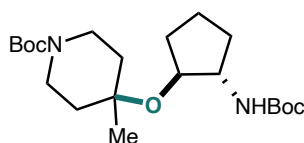
1H NMR (500 MHz, $CDCl_3$) δ 4.82 (br s, 1H), 3.88 – 3.77 (m, 1H), 3.62 – 3.52 (m, 2H), 3.32 (ddt, J = 12.8, 10.1, 3.1 Hz, 2H), 3.12 (q, J = 6.5 Hz, 1H), 3.05 (dt, J = 13.3, 6.2 Hz, 1H), 1.74 – 1.60 (m, 4H), 1.47 (s, 9H), 1.46 (s, 9H), 1.21 (s, 3H), 1.13 (d, J = 6.2 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 156.26, 154.96, 79.48, 79.37, 73.00, 65.97, 47.31, 40.35, 36.83, 36.66, 28.60, 28.56, 25.48, 20.75.

HRMS (ESI-TOF) m/z calcd. for C₁₉H₃₆N₂O₅Na [M+Na]⁺ 395.25219; found: 395.25250.

IR (film) ν_{max} 2974, 2933, 1694, 1518, 1423, 1390, 1244, 1160, 1131, 1080, 1017, 989 cm⁻¹

***Tert*-butyl 4-(((1*S*,2*S*)-2-((*tert*-butoxycarbonyl)amino)cyclopentyl)oxy)-4-methylpiperidine-1-carboxylate (60)**



Prepared according to the general procedure B with redox-active ester **RAE1** (105 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μmol, 5 mol%), Cp₂TiCl₂ (6.22 mg, 25.0 μmol, 10 mol%), Zn₃(PO₄)₂ (72.4 mg, 187 μmol, 0.75 equiv.), *tert*-butyl *N*-[(1*S*,2*S*)-2-hydroxycyclopentyl]carbamate (151 mg, 750 μmol, 3.00 equiv.), in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the luminox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 10% to 70% EtOAc in hexanes. The fractions containing product were concentrated and further purified by preparative HPLC (RediSep C18 column, 25% to 100% MeCN in H₂O with 0.1% NH₄OH) to provide the product as a yellow oil (49.5 mg, 124 μmol, 50% yield).

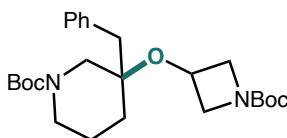
¹H NMR (500 MHz, CDCl₃) δ 4.41 (br s, 1H), 3.80 (s, 1H), 3.75 – 3.55 (m, 3H), 3.24 – 3.10 (m, 2H), 2.06 – 1.96 (m, 1H), 1.86 (ddt, *J* = 13.1, 9.0, 6.3 Hz, 1H), 1.78 – 1.67 (m, 2H), 1.67 – 1.48 (m, 4H), 1.44 (s, 9H), 1.42 (s, 9H), 1.40 – 1.35 (m, 2H), 1.17 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 155.43, 155.01, 79.26, 72.39, 58.54, 40.45, 39.58, 36.94, 36.06, 32.37, 29.49, 28.60, 28.54, 26.33, 20.80.

HRMS (ESI-TOF) m/z calcd. for $\text{C}_{21}\text{H}_{38}\text{N}_2\text{O}_5\text{Na}$ $[\text{M}+\text{Na}]^+$ 421.26784; found: 421.26797.

IR (film) ν_{max} 3349, 2970, 2875, 1672, 1525, 1423, 1390, 1364, 1243, 1157, 1088, 989 cm^{-1}

***Tert*-butyl 3-benzyl-3-((1-(*tert*-butoxycarbonyl)azetidin-3-yl)oxy)piperidine-1-carboxylate (61)**



Prepared according to the general procedure B with redox-active ester **RAE4** (124 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μmol , 5 mol%), Cp_2TiCl_2 (6.22 mg, 25.0 μmol , 10 mol%), $[\text{ZnCO}_3]_2 \cdot [\text{Zn}(\text{OH})_2]_3$ (68.6 mg, 125 μmol , 0.5 equiv.), *tert*-butyl 3-hydroxyazetidine-1-carboxylate (130 mg, 750 μmol , 3.00 equiv.), in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the luminox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 5% to 60% EtOAc in hexanes. The fractions containing product were concentrated and further purified by preparative HPLC (RediSep C18 column, 35% to 100% MeCN in H_2O with 0.1% NH_4OH) to provide the product as a yellowish oil (75.9 mg, 170 μmol , 68% yield).

^1H NMR (500 MHz, CDCl_3) δ 7.31 – 7.25 (m, 2H), 7.23 – 7.16 (m, 3H), 4.58 (t, J = 5.8 Hz, 1H), 4.14 (ddd, J = 9.6, 6.7, 1.2 Hz, 2H), 3.80 (ddd, J = 9.5, 4.4, 1.1 Hz, 2H), 3.48 (dt, J = 16.9, 5.9 Hz,

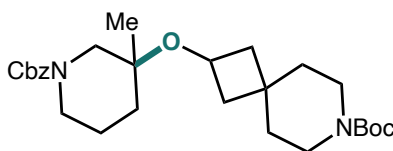
2H), 3.28 (s, 2H), 2.46 – 2.41 (s, 1H), 1.87 (q, $J = 6.2$ Hz, 2H), 1.76 (h, $J = 5.9$ Hz, 2H), 1.49 (s, 9H), 1.43 (s, 9H).

^{13}C NMR (126 MHz, CDCl_3) δ 156.51, 153.04, 152.55, 140.23, 140.12, 128.85, 128.41, 126.22, 122.08, 121.68, 117.75, 117.14, 80.59, 80.44, 79.75, 61.79, 59.15, 42.30, 42.02, 41.96, 41.29, 28.51, 24.93, 24.65, 22.00, 21.85.

HRMS (ESI-TOF) m/z calcd. for $\text{C}_{25}\text{H}_{38}\text{N}_2\text{O}_5\text{Na}$ $[\text{M}+\text{Na}]^+$ 469.26784; found: 469.26763.

IR (film) ν_{max} 2974, 2939, 2878, 1693, 1390, 1364, 1277, 1255, 1152, 1055, 982, 936 cm^{-1}

***Tert*-butyl 2-((1-((benzyloxy)carbonyl)-3-methylpiperidin-3-yl)oxy)-7-azaspiro[3.5]nonane-7-carboxylate (62)**



Prepared according to the general procedure B with redox-active ester **RAE3** (113 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μmol , 5 mol%), Cp_2TiCl_2 (6.22 mg, 25.0 μmol , 10 mol%), $[\text{ZnCO}_3]_2 \cdot [\text{Zn}(\text{OH})_2]_3$ (68.6 mg, 125 μmol , 0.5 equiv.), *tert*-butyl 2-hydroxy-7-azaspiro[3.5]nonane-7-carboxylate (181 mg, 750 μmol , 3.00 equiv.), in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the lumidox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 0% to 50% EtOAc in hexanes. The fractions containing product were concentrated and further purified by preparative HPLC (RediSep C18 column, 35%

to 80% MeCN in H₂O with 0.1% NH₄OH) to provide the product as a yellowish oil (71.1 mg, 150 μmol, 60% yield).

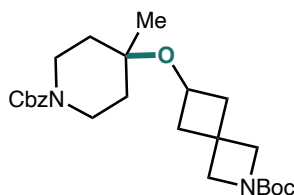
¹H NMR (500 MHz, CDCl₃) δ 7.37 – 7.33 (m, 4H), 7.33 – 7.28 (m, 1H), 5.33 – 4.93 (m, 3H), 4.02 – 3.80 (m, 2H), 3.34 – 3.13 (m, 5H), 3.07 – 2.89 (m, 1H), 2.01 – 1.90 (m, 4H), 1.71 – 1.61 (m, 2H), 1.44 (s, 9H), 1.42 – 1.22 (m, 6H), 0.94 (d, J = 6.9 Hz, 3H). (mixture of rotamers)

¹³C NMR (126 MHz, CDCl₃) δ 156.11, 155.87, 155.05, 136.82, 136.70, 128.62, 128.31, 128.17, 128.15, 127.94, 84.09, 79.38, 79.35, 67.12, 66.39, 40.81, 39.79, 39.48, 39.24, 38.96, 36.41, 32.33, 30.96, 28.58, 24.51, 19.57, 19.38, 15.71. (mixture of rotamers)

HRMS (ESI-TOF) m/z calcd. for C₂₇H₄₀N₂O₅Na [M+Na]⁺ 495.28349; found: 495.28383.

IR (film) ν_{max} 2963, 2926, 1689, 1419, 1364, 1341, 1267, 1240, 1171, 1057, 957, 909, 729cm⁻¹

***Tert*-butyl 6-((1-((benzyloxy)carbonyl)-4-methylpiperidin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate (63)**



Prepared according to the general procedure B with redox-active ester **RAE2** (113 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μmol, 5 mol%), Cp₂TiCl₂ (6.22 mg, 25.0 μmol, 10 mol%), [ZnCO₃]₂·[Zn(OH)₂]₃ (68.6 mg, 125 μmol, 0.5 equiv.), *tert*-butyl 6-hydroxy-2-azaspiro[3.3]heptane-2-carboxylate (160 mg, 750 μmol, 3.00 equiv.), in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the luminox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 0% to 50% EtOAc in hexanes. The fractions containing product were concentrated and further purified by preparative HPLC (RediSep C18 column, 35% to 100% MeCN in H₂O with 0.1% NH₄OH) to provide the product as a colorless solid (63.2 mg, 142 μ mol, 57% yield).

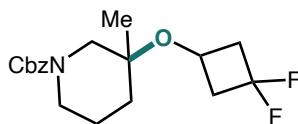
¹H NMR (500 MHz, CDCl₃) δ 7.39 – 7.28 (m, 4H), 5.13 – 5.09 (m, 2H), 3.93 (p, J = 7.5 Hz, 1H), 3.89 (s, 2H), 3.83 (s, 2H), 3.81 – 3.66 (m, 2H), 3.27 – 3.12 (m, 2H), 2.43 (ddd, J = 12.5, 5.7, 2.2 Hz, 2H), 2.12 (td, J = 8.0, 3.1 Hz, 2H), 1.72 – 1.63 (m, 2H), 1.46 – 1.35 (m, 11H), 1.12 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 156.29, 155.44, 137.06, 128.61, 128.08, 127.99, 79.47, 72.56, 67.12, 60.85, 43.99, 40.19, 35.95, 30.29, 28.53, 25.77.

HRMS (ESI-TOF) m/z calcd. for C₂₅H₃₆N₂O₅Na [M+Na]⁺ 467.25219; found: 467.25239.

IR (film) ν_{max} 2968, 2930, 2871, 1692, 1400, 1364, 1238, 1166, 1088, 1060, 917, 728 cm⁻¹

Benzyl 3-(3,3-difluorocyclobutoxy)-3-methylpiperidine-1-carboxylate (**64**)



Prepared according to the general procedure B with redox-active ester **RAE4** (113 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μ mol, 5 mol%), Cp₂TiCl₂ (6.22 mg, 25.0 μ mol, 10 mol%),

$[\text{ZnCO}_3]_2 \cdot [\text{Zn}(\text{OH})_2]_3$ (68.6 mg, 125 μmol , 0.5 equiv.), 3,3-difluorocyclobutanol (81.1 mg, 750 μmol , 3.00 equiv.), in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the lumidox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 0% to 45% EtOAc in hexanes. The fractions containing product were concentrated to provide the product as a yellowish oil (65.7 mg, 194 μmol , 77% yield).

^1H NMR (500 MHz, CDCl_3) δ 7.43 – 7.31 (m, 5H), 5.34 – 5.03 (m, 3H), 4.20 – 3.49 (m, 2H), 3.07 – 2.82 (m, 1H), 2.81 – 2.61 (m, 1H), 2.61 – 2.35 (m, 2H), 1.97 (m, 1H), 1.89 – 1.61 (m, 2H), 1.61 – 1.30 (m, 2H), 1.05 – 0.87 (m, 3H). (mixture of rotamers)

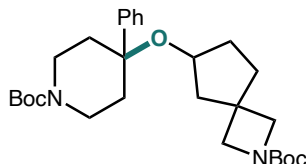
^{13}C NMR (126 MHz, CDCl_3) δ 156.33, 155.64, 155.45, 154.95, 153.59, 153.23, 137.18, 137.03, 136.71, 136.67, 136.37, 128.81, 128.72, 128.67, 128.64, 128.61, 128.58, 128.54, 128.31, 128.26, 128.20, 128.17, 128.10, 128.02, 127.97, 127.92, 121.40 – 113.94 (m), 84.69, 83.45, 83.42, 67.57, 67.44, 67.32, 67.12, 67.03, 60.95 – 59.94 (m), 57.25 (dd, $J = 19.1, 6.3$ Hz), 51.46, 45.56 (dd, $J = 23.1, 21.0$ Hz), 44.51, 43.47, 43.38, 43.30, 43.20, 43.12, 43.06, 43.01, 41.88, 41.77, 38.87, 38.55, 35.57, 35.40, 33.05, 32.15, 27.09, 26.84, 26.51, 25.49, 25.22, 24.37, 21.95, 21.87, 21.05, 21.02, 20.67, 19.41, 19.21, 19.04, 17.82, 17.77, 15.71. (mixture of rotamers)

^{19}F NMR (376 MHz, CDCl_3) δ -82.76 – -84.89 (m, 1F), -96.95 – -99.37 (m, 1F).

HRMS (ESI-TOF) m/z calcd. for $\text{C}_{18}\text{H}_{23}\text{F}_2\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ 362.15437; found: 362.15401.

IR (film) ν_{max} 2939, 1695, 1420, 1342, 1295, 1263, 1240, 1168, 1056, 956, 893 cm^{-1}

***Tert*-butyl 6-((1-(*tert*-butoxycarbonyl)-4-phenylpiperidin-4-yl)oxy)-2-azaspiro[3.4]octane-2-carboxylate (65)**



Prepared according to the general procedure B with redox-active ester **RAE10** (120 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μ mol, 5 mol%), Cp_2TiCl_2 (6.22 mg, 25.0 μ mol, 10 mol%), $[\text{ZnCO}_3]_2 \cdot [\text{Zn}(\text{OH})_2]_3$ (68.6 mg, 125 μ mol, 0.5 equiv.), *tert*-butyl 6-hydroxy-2-azaspiro[3.4]octane-2-carboxylate (170 mg, 750 μ mol, 3.00 equiv.), in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the luminox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 10% to 60% EtOAc in hexanes. The fractions containing product were concentrated and further purified by preparative HPLC (RediSep C18 column, 40% to 100% MeCN in H_2O with 0.1% NH_4OH) to provide the product as a colorless solid (71.0 mg, 143 μ mol, 57% yield).

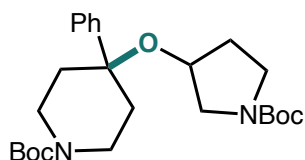
^1H NMR (500 MHz, CDCl_3) δ 7.40 – 7.32 (m, 4H), 7.30 – 7.24 (m, 1H), 4.00 – 3.79 (m, 2H), 3.85 (d, J = 8.4 Hz, 1H), 3.74 (d, J = 8.4 Hz, 1H), 3.62 – 3.52 (m, 3H), 3.32 – 3.12 (m, 2H), 2.07 – 1.98 (m, 2H), 1.93 – 1.78 (m, 3H), 1.78 – 1.67 (m, 2H), 1.65 – 1.51 (m, 3H), 1.45 (s, 9H), 1.41 (s, 9H).

^{13}C NMR (126 MHz, CDCl_3) δ 156.47, 155.01, 145.02, 128.38, 127.66, 126.41, 79.53, 79.34, 76.16, 74.02, 61.07, 46.08, 40.51, 39.22, 35.99, 34.96, 33.41, 28.60, 28.53.

HRMS (ESI-TOF) m/z calcd. for $\text{C}_{28}\text{H}_{42}\text{N}_2\text{O}_5\text{Na}$ $[\text{M}+\text{Na}]^+$ 509.29914; found: 509.30001.

IR (film) ν_{max} 2977, 1680, 1477, 1413, 1366, 1247, 1163, 1040, 905, 726 cm^{-1}

***Tert*-butyl 4-((1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)oxy)-4-phenylpiperidine-1-carboxylate (66)**



Prepared according to the general procedure B with redox-active ester **RAE10** (120 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μmol , 5 mol%), Cp_2TiCl_2 (6.22 mg, 25.0 μmol , 10 mol%), $[\text{ZnCO}_3]_2 \cdot [\text{Zn}(\text{OH})_2]_3$ (68.6 mg, 125 μmol , 0.5 equiv.), *tert*-butyl 3-hydroxypyrrolidine-1-carboxylate (140 mg, 750 μmol , 3.00 equiv.), in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the luminox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 10% to 80% EtOAc in hexanes. The fractions containing product were concentrated and further purified by preparative HPLC (RediSep C18 column, 40% to 100% MeCN in H_2O with 0.1% NH_4OH) to provide the product as a colorless oil (68.2 mg, 153 μmol , 61% yield).

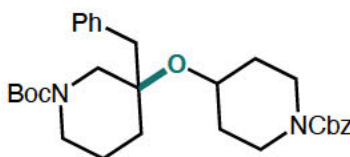
^1H NMR (500 MHz, CDCl_3) δ 7.42 – 7.33 (m, 4H), 7.32 – 7.27 (m, 1H), 4.04 – 3.80 (m, 2H), 3.73 (tt, J = 13.0, 6.5 Hz, 1H), 3.39 (ddt, J = 34.5, 12.5, 5.9 Hz, 1H), 3.32 – 3.13 (m, 3H), 3.14 – 3.01 (m, 2H), 2.12 – 1.99 (m, 2H), 1.95 – 1.67 (m, 4H), 1.45 (s, 9H), 1.41 (s, 9H).

^{13}C NMR (500 MHz, CDCl_3) δ 154.97, 154.58, 154.49, 144.46, 128.56, 127.92, 126.27, 79.58, 79.27, 76.46, 76.26, 71.91, 71.25, 51.78, 51.45, 43.82, 43.47, 40.38, 39.61, 36.08, 35.39, 33.06, 32.41, 28.59, 28.57. (1:1 mixture of rotamers)

HRMS (ESI-TOF) m/z calcd. for $\text{C}_{25}\text{H}_{38}\text{N}_2\text{O}_5\text{Na}$ $[\text{M}+\text{Na}]^+$ 469.26784; found: 469.26798.

IR (film) ν_{max} 2975, 1679, 1473, 14191, 1364, 1257, 1123, 1054, 911.

***Tert*-butyl 3-benzyl-3-((1-((benzyloxy)carbonyl)piperidin-4-yl)oxy)piperidine-1-carboxylate (67)**



Prepared according to the general procedure B with redox-active ester **RAE4** (124 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μmol , 5 mol%), Cp_2TiCl_2 (6.22 mg, 25.0 μmol , 10 mol%), $[\text{ZnCO}_3]_2 \cdot [\text{Zn}(\text{OH})_2]_3$ (68.6 mg, 125 μmol , 0.5 equiv.), benzyl 4-hydroxypiperidine-1-carboxylate (176 mg, 750 μmol , 3.00 equiv.), in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the luminox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 0% to 50% EtOAc in hexanes. The fractions containing product were concentrated and further purified by preparative HPLC (RediSep C18 column, 35% to 100% MeCN in H_2O with 0.1% NH_4OH) to provide the product as a yellowish oil (83.9 mg, 165 μmol , 66% yield).

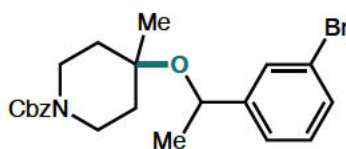
¹H NMR (500 MHz, CDCl₃) δ 7.38 – 7.27 (m, 7H), 7.23 – 7.14 (m, 3H), 5.12 (d, *J* = 10.5 Hz, 2H), 4.03 – 3.83 (m, 2H), 3.83 – 3.66 (m, 1H), 3.58 – 3.40 (m, 2H), 3.29 (s, 1H), 3.24 – 3.09 (m, 2H), 2.75 – 2.49 (m, 1H), 2.17 – 1.92 (m, 1H), 1.92 – 1.64 (m, 6H), 1.56 – 1.40 (m, 11H). (mixture of rotamers)

¹³C NMR (126 MHz, CDCl₃) δ 155.38, 155.25, 152.99, 152.49, 140.34, 140.20, 140.09, 137.01, 136.92, 129.19, 129.05, 128.85, 128.81, 128.60, 128.58, 128.49, 128.45, 128.38, 128.34, 128.09, 127.98, 127.96, 126.22, 126.18, 122.07, 121.67, 117.68, 117.07, 80.80, 80.53, 80.39, 80.19, 80.00, 79.93, 67.45, 67.21, 42.27, 41.98, 41.93, 41.57, 41.46, 41.26, 39.87, 38.08, 36.43, 34.15, 32.15, 29.86, 28.52, 28.49, 24.90, 24.62, 23.02, 21.97, 21.82, 19.98, 19.85. (mixture of rotamers)

HRMS (ESI-TOF) *m/z* calcd. for C₃₀H₄₀N₂O₅Na [M+Na]⁺ 531.28349; found: 531.28360.

IR (film) *v*_{max} 2945, 1683, 1430, 1392, 1365, 1271, 1224, 1149, 1069, 1027, 908 cm⁻¹

Benzyl 4-(1-(3-bromophenyl)ethoxy)-4-methylpiperidine-1-carboxylate (68)



Prepared according to the general procedure B with redox-active ester **RAE2** (113 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μmol, 5 mol%), Cp₂TiCl₂ (6.22 mg, 25.0 μmol, 10 mol%), [ZnCO₃]₂·[Zn(OH)₂]₃ (68.6 mg, 125 μmol, 0.5 equiv.), *tert*-butyl 4 1-(3-bromophenyl)ethanol (151 mg, 750 μmol, 3.00 equiv.) in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the luminox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 10% to 70% EtOAc in hexanes. The fractions containing

product were concentrated and further purified by preparative HPLC (RediSep C18 column, 45% to 100% MeCN in H₂O with 0.1% NH₄OH) to provide the product as a yellowish oil (57.9 mg, 134 μ mol, 54% yield).

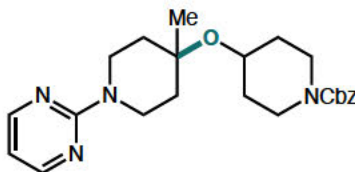
¹H NMR (500 MHz, CDCl₃) δ 7.47 (t, J = 1.8 Hz, 1H), 7.37 – 7.32 (m, 4H), 7.33 – 7.28 (m, 1H), 7.27 – 7.23 (m, 1H), 7.17 (t, J = 7.8 Hz, 1H), 5.11 (s, 2H), 4.57 (q, J = 6.4 Hz, 1H), 3.92 – 3.55 (m, 2H), 3.36 – 2.97 (m, 2H), 1.87 – 1.62 (m, 2H), 1.50 – 1.37 (m, 2H), 1.36 (d, J = 6.4 Hz, 3H), 1.07 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 155.37, 149.47, 137.06, 130.10, 130.07, 128.87, 128.59, 128.06, 127.98, 124.37, 122.52, 73.39, 69.29, 67.10, 40.39, 40.26, 36.87, 36.51, 35.98, 26.74, 26.00.

HRMS (ESI-TOF) m/z calcd. for C₂₂H₂₆BrNO₃Na [M+Na]⁺ 454.09938; found: 454.09907.

IR (film) ν_{max} 2970, 2927, 1691, 1471, 1427, 1359, 1255, 1236, 1156, 1136, 1074, 1028, 976, 907, 728 cm⁻¹

Benzyl 4-((4-methyl-1-(pyrimidin-2-yl)piperidin-4-yl)oxy)piperidine-1-carboxylate (69)



Prepared according to the general procedure B with redox-active ester **RAE7** (99.1 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μ mol, 5 mol%), Cp₂TiCl₂ (6.22 mg, 25.0 μ mol, 10 mol%), [ZnCO₃]₂·[Zn(OH)₂]₃ (68.6 mg, 125 μ mol, 0.5 equiv.), benzyl 4-hydroxypiperidine-1-carboxylate (176 mg, 750 μ mol, 3.00 equiv.) in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the luminox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 15% to 100% EtOAc in hexanes. The fractions containing

product were concentrated and further purified by preparative HPLC (RediSep C18 column, 25% to 80% MeCN in H₂O with 0.1% NH₄OH) to provide the product as a colorless oil (54.7 mg, 133 μ mol, 53% yield).

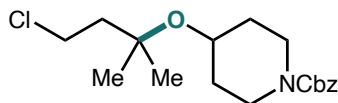
¹H NMR (500 MHz, CDCl₃) δ 8.29 (d, J = 4.7 Hz, 2H), 7.37 – 7.34 (m, 4H), 7.33 – 7.28 (m, 1H), 6.44 (t, J = 4.7 Hz, 1H), 5.12 (s, 2H), 4.20 (dt, J = 13.4, 4.3 Hz, 2H), 3.86 – 3.79 (m, 2H), 3.72 (tt, J = 7.8, 3.7 Hz, 1H), 3.48 (ddd, J = 13.5, 10.8, 3.1 Hz, 2H), 3.25 (ddd, J = 12.9, 8.8, 3.5 Hz, 2H), 1.82 – 1.68 (m, 4H), 1.59 – 1.47 (m, 4H), 1.22 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 161.74, 157.89, 155.46, 137.08, 128.62, 128.08, 127.96, 109.47, 73.21, 67.15, 66.17, 41.73, 40.41, 36.52, 34.09, 25.92.

HRMS (ESI-TOF) m/z calcd. for C₂₃H₃₁N₄O₃ [M+H]⁺ 411.23962; found: 411.23916.

IR (film) ν_{max} 2942, 2867, 1693, 1584, 1545, 1498, 1430, 1361, 1259, 1221, 1133, 1071, 1039, 965, 908, 728 cm⁻¹

Benzyl 4-((4-chloro-2-methylbutan-2-yl)oxy)piperidine-1-carboxylate (70)



Prepared according to the general procedure B with redox-active ester **RAE28** (81.4 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μ mol, 5 mol%), Cp₂TiCl₂ (6.22 mg, 25.0 μ mol, 10 mol%), Zn₃(PO₄)₂ (72.4 mg, 187 μ mol, 0.75 equiv.), benzyl 4-hydroxypiperidine-1-carboxylate (176 mg, 750 μ mol, 3.00 equiv.), in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the luminox setup, the solvent was removed under reduced pressure. The crude residue was dissolved in a minimal amount of DMSO, loaded on a 30 g Biotage Sfär C18 D reverse phase column, and purified with eluents 30% to 95%

MeCN in water (0.1% NH₄OH modifier). The fractions containing product were concentrated and the product was obtained as a yellow oil (50.8 mg, 149 μmol, 60% yield).

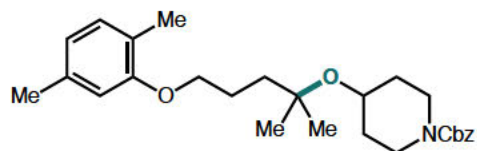
¹H NMR (500 MHz, CDCl₃) δ 7.38 – 7.33 (m, 4H), 7.33 – 7.29 (m, 1H), 5.12 (s, 2H), 3.79 (dt, J = 12.5, 4.8 Hz, 3H), 3.68 – 3.57 (m, 2H), 3.23 (ddd, J = 13.0, 8.8, 3.6 Hz, 2H), 2.00 – 1.93 (m, 2H), 1.73 – 1.63 (m, 2H), 1.52 – 1.40 (m, 2H), 1.19 (s, 6H).

¹³C NMR (500 MHz, CDCl₃) δ 155.43, 137.06, 128.62, 128.08, 127.96, 74.92, 67.15, 66.37, 45.42, 41.68, 40.62, 33.91, 26.19.

HRMS (ESI-TOF) m/z calcd. for C₁₈H₂₇ClNO₃ [M+H]⁺ 340.16796; found: 340.16787.

IR (film) ν_{max} 2947, 1695, 1427, 1397, 1364, 1271, 1224, 1174, 1131, 1073, 1034, 915 cm⁻¹

Benzyl 4-((5-(2,5-dimethylphenoxy)-2-methylpentan-2-yl)oxy)piperidine-1-carboxylate (71)



Prepared according to the general procedure B with redox-active ester **RAE22** (106 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μmol, 5 mol%), Cp₂TiCl₂ (6.22 mg, 25.0 μmol, 10 mol%), Zn₃(PO₄)₂ (72.4 mg, 187 μmol, 0.75 equiv.), benzyl 4-hydroxypiperidine-1-carboxylate (176 mg, 750 μmol, 3.00 equiv.), in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the luminox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 10% to 70% EtOAc in hexanes. The fractions containing

product were concentrated and further purified by preparative HPLC (RediSep C18 column, 20% to 100% MeCN in H₂O with 0.1% NH₄OH) to provide the product as a beige oil (57.2 mg, 130 μ mol, 52% yield).

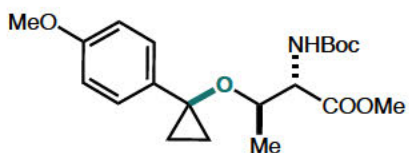
¹H NMR (500 MHz, CDCl₃) δ 7.37 – 7.34 (m, 4H), 7.33 – 7.28 (m, 1H), 7.00 (d, J = 7.4 Hz, 1H), 6.66 (d, J = 7.5 Hz, 1H), 6.62 (d, J = 1.7 Hz, 1H), 5.12 (s, 2H), 3.94 (t, J = 6.3 Hz, 2H), 3.88 – 3.79 (m, 2H), 3.65 (tt, J = 8.0, 3.7 Hz, 1H), 3.18 (ddd, J = 13.1, 9.2, 3.4 Hz, 2H), 2.30 (s, 3H), 2.17 (s, 3H), 1.90 – 1.81 (m, 2H), 1.75 – 1.67 (m, 2H), 1.67 – 1.60 (m, 2H), 1.53 – 1.44 (m, 2H), 1.19 (s, 6H).

¹³C NMR (126 MHz, CDCl₃) δ 157.14, 155.46, 137.12, 136.63, 130.44, 128.61, 128.05, 127.93, 123.65, 120.80, 112.11, 75.40, 68.32, 67.10, 66.36, 41.92, 38.21, 34.10, 26.36, 24.47, 21.55, 15.97.

HRMS (ESI-TOF) m/z calcd. for C₂₇H₃₇NO₄Na [M+Na]⁺ 462.26203; found: 462.26222.

IR (film) ν_{max} 2950, 1694, 1508, 1429, 1363, 1268, 1224, 1156, 1129, 1073, 1037, 908 cm⁻¹

Methyl *N*-(*tert*-butoxycarbonyl)-*O*-(1-(4-methoxyphenyl)cyclopropyl)-*L*-threoninate (72)



Prepared according to the general procedure B with redox-active ester **RAE14** (276 mg, 0.75 mmol, **3.00 equiv.**), 4DPAIPN (9.96 mg, 12.5 μ mol, 5 mol%), Cp₂TiCl₂ (6.22 mg, 25.0 μ mol, 10 mol%), [ZnCO₃]₂·[Zn(OH)₂]₃ (68.6 mg, 125 μ mol, 0.5 equiv.), *N*-(*tert*-butoxycarbonyl)-*L*-threonine methyl ester (58.3 mg, 250 μ mol, **1.00 equiv.**), in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the lumidox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal

phase column and purified with eluents 10% to 70% EtOAc in hexanes. The fractions containing product were concentrated and further purified by preparative HPLC (RediSep C18 column, 35% to 70% MeCN in H₂O with 0.1% NH₄OH) to provide the product as a colorless oil (46.3 mg, 122 μmol, 49% yield).

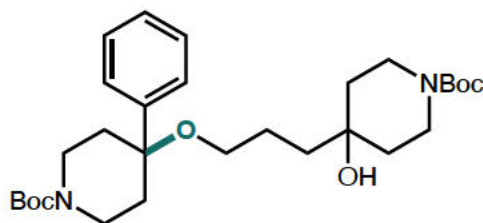
¹H NMR (500 MHz, CDCl₃) δ 7.32 – 7.27 (m, 2H), 6.92 – 6.79 (m, 2H), 5.17 (d, *J* = 9.8 Hz, 1H), 4.15 – 4.05 (m, 2H), 3.80 (s, 3H), 3.64 (s, 3H), 1.45 (s, 9H), 1.06 – 1.00 (m, 4H), 0.98 – 0.92 (m, 1H), 0.90 (ddd, *J* = 10.7, 6.4, 4.3 Hz, 1H), 0.76 (ddd, *J* = 9.5, 6.6, 4.4 Hz, 1H).

¹³C NMR (126 MHz, CDCl₃) δ 171.63, 159.23, 156.35, 132.71, 130.03, 113.68, 79.96, 72.81, 62.13, 58.95, 55.41, 52.24, 28.46, 17.94, 14.23, 12.20.

HRMS (ESI-TOF) *m/z* calcd. for C₂₀H₂₉NO₆Na [M+Na]⁺ 394.22296; found: 394.22189.

IR (film) ν_{max} 3443, 2977, 2837, 1752, 1713, 1611, 1513, 1366, 1247, 1225, 1161, 1089, 1071, 1031, 832 cm⁻¹

***Tert*-butyl 4-(3-(1-(*tert*-butoxycarbonyl)-4-hydroxypiperidin-4-yl)propoxy)-4-phenylpiperidine-1-carboxylate (73)**

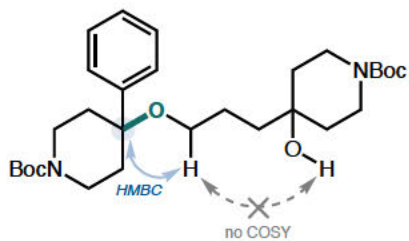


Prepared according to the general procedure B with redox-active ester **RAE10** (360 mg, 0.75 mmol, 3.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μ mol, 5 mol%), Cp_2TiCl_2 (6.22 mg, 25.0 μ mol, 10 mol%), $\text{Zn}_3(\text{PO}_4)_2$ (72.4 mg, 187 μ mol, 0.75 equiv.), *tert*-butyl 4-hydroxy-4-(3-hydroxypropyl)piperidine-1-carboxylate (64.8 mg, 0.25 mmol, 1.00 equiv.), in DCE (0.2 M, 1.25 mL).

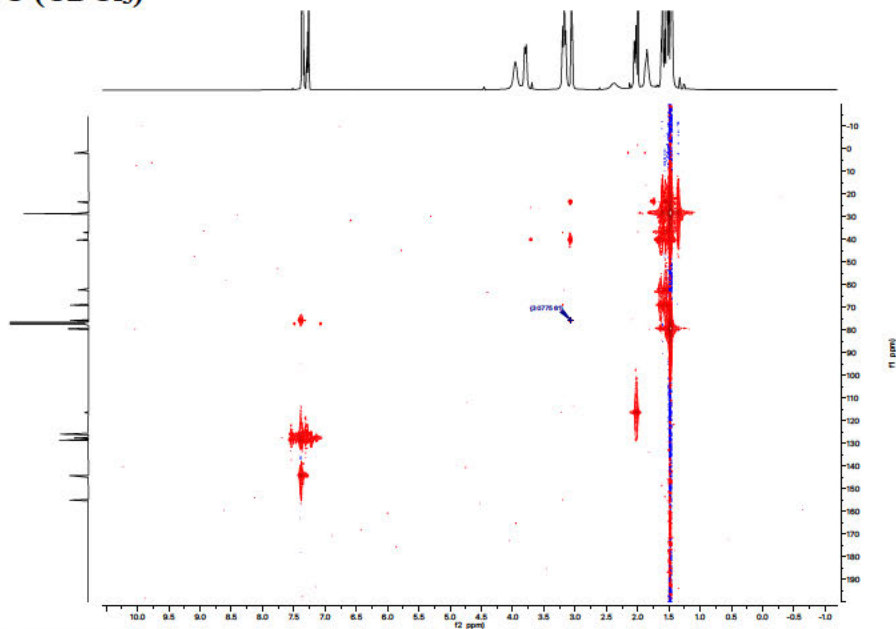
After irradiation for 20 hours at level 5 (8.4 W) in the lumidox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 20% to 90% EtOAc in hexanes. The fractions containing product were concentrated and further purified by preparative HPLC (RediSep C18 column, 45% to 100% MeCN in H_2O with 0.1% NH_4OH) to provide the product as a colorless solid (101.9 mg, 196 μ mol, 79% yield).

^1H NMR (500 MHz, CDCl_3) δ 7.40 – 7.32 (m, 4H), 7.30 – 7.26 (m, 1H), 4.03 – 3.88 (m, 2H), 3.83 – 3.76 (m, 2H), 3.22 – 3.13 (m, 4H), 3.05 (t, J = 5.9 Hz, 2H), 2.38 (br s, 1H), 2.08 – 2.00 (m, 2H), 1.90 – 1.80 (m, 2H), 1.64 – 1.57 (m, 2H), 1.57 – 1.47 (m, 6H), 1.46 (s, 9H), 1.45 (s, 9H).

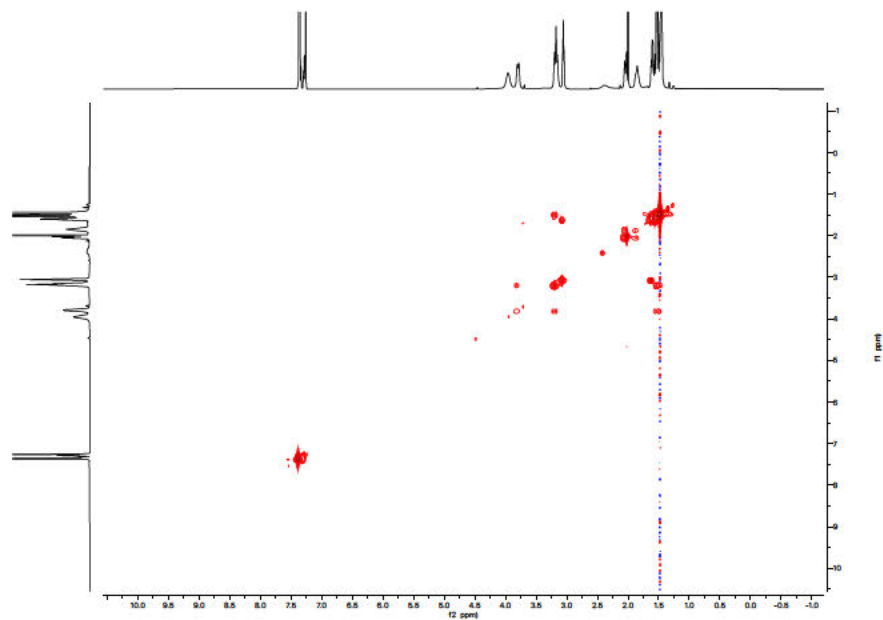
^{13}C NMR (126 MHz, CDCl_3) δ 155.05, 155.00, 144.24, 128.60, 127.64, 126.00, 116.47, 79.61, 79.41, 75.83, 69.08, 62.39, 40.36, 40.23, 37.06, 35.59, 34.06, 28.60, 23.53.



^1H - ^{13}C HMBC (CDCl_3)



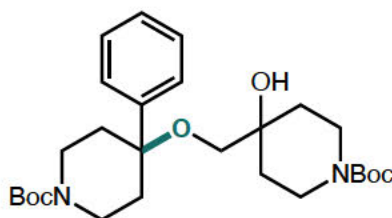
^1H - ^1H COSY (CDCl_3)



HRMS (ESI-TOF) m/z calcd. for $\text{C}_{29}\text{H}_{46}\text{N}_2\text{O}_6\text{Na}$ $[\text{M}+\text{Na}]^+$ 541.32536; found: 541.32542.

IR (film) ν_{max} 3444, 2929, 1689, 1666, 1421, 1364, 1279, 1243, 1155, 1076, 1038, 1023, 760, 699 cm^{-1}

***Tert*-butyl 4-((1-(*tert*-butoxycarbonyl)-4-hydroxypiperidin-4-yl)methoxy)-4-phenylpiperidine-1-carboxylate (74)**



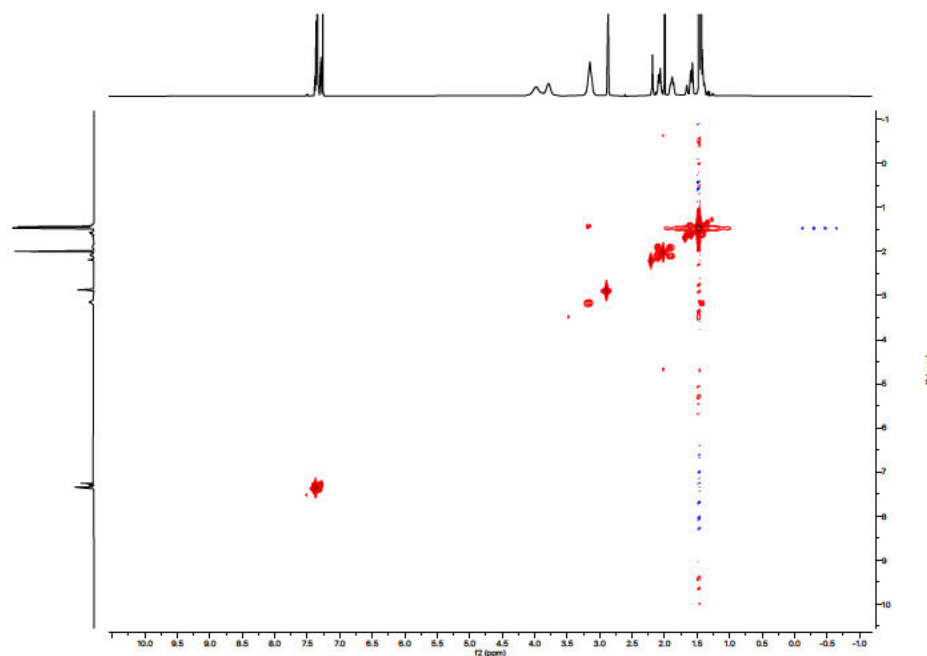
Prepared according to the general procedure B with redox-active ester **RAE10** (360 mg, 0.75 mmol, 3.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μmol , 5 mol%), Cp_2TiCl_2 (6.22 mg, 25.0 μmol , 10 mol%), $\text{Zn}_3(\text{PO}_4)_2$ (72.4 mg, 187 μmol , 0.75 equiv.), *tert*-butyl 4-hydroxy-4-(hydroxymethyl)piperidine-1-carboxylate (57.8 mg, 0.25 mmol, 1.00 equiv.), in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the luminox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 20% to 90% EtOAc in hexanes. The fractions containing product were concentrated and further purified by preparative HPLC (RediSep C18 column, 45% to 100% MeCN in H_2O with 0.1% NH_4OH) to provide the product as a colorless solid (68.3 mg, 139 μmol , 56% yield).

^1H NMR (500 MHz, CDCl_3) δ 7.39 – 7.32 (m, 4H), 7.31 – 7.26 (m, 1H), 4.11 – 3.87 (m, 2H), 3.87 – 3.69 (m, 2H), 3.23 – 3.05 (m, 4H), 2.87 (s, 2H), 2.19 (s, 1H), 2.08 (d, J = 13.8 Hz, 2H), 1.88 (t, J = 12.2 Hz, 2H), 1.62 – 1.55 (m, 2H), 1.46 (s, 9H), 1.44 (s, 9H), 1.43 – 1.37 (m, 2H).

^1H - ^{13}C HMBC (CDCl_3)

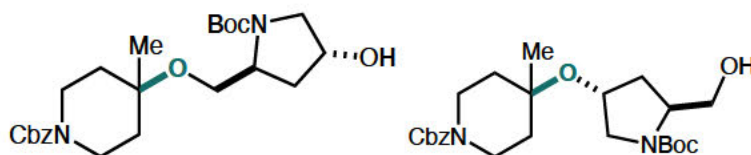
^1H - ^1H COSY (CDCl_3)



HRMS (ESI-TOF) m/z calcd. for $\text{C}_{27}\text{H}_{42}\text{N}_2\text{O}_6\text{Na}$ $[\text{M}+\text{Na}]^+$ 513.29406; found: 513.29401.

IR (film) ν_{max} 3438, 2975, 2871, 1681, 1422, 1364, 1277, 1244, 1157, 1067, 1023, 766, 734, 700 cm^{-1} .

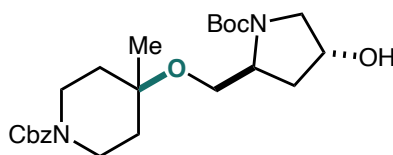
Benzyl 4-(((2S,4R)-1-(tert-butoxycarbonyl)-4-hydroxypyrrolidin-2-yl)methoxy)-4-methylpiperidine-1-carboxylate + benzyl 4-(((3R,5S)-1-(tert-butoxycarbonyl)-5-(hydroxymethyl)pyrrolidin-3-yl)oxy)-4-methylpiperidine-1-carboxylate (75)



Prepared according to the general procedure B with redox-active ester **RAE2** (339 mg, 0.75 mmol, **3.00 equiv.**), 4DPAIPN (9.96 mg, 12.5 μmol , 5 mol%), Cp_2TiCl_2 (6.22 mg, 25.0 μmol , 10 mol%), $[\text{ZnCO}_3]_2 \cdot [\text{Zn}(\text{OH})_2]_3$ (68.6 mg, 125 μmol , 0.5 equiv.), *tert*-butyl (2*S*,4*R*)-4-hydroxy-2-

(hydroxymethyl)pyrrolidine-1-carboxylate (54.3 mg, 250 μmol , **1.00 equiv.**) in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the lumidox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 10% to 90% EtOAc in hexanes. The fractions containing product were concentrated and further purified by preparative HPLC (RediSep C18 column, 25% to 85% MeCN in H_2O with 0.1% NH_4OH) to provide the product as a colorless oil (63.9 mg, 142 μmol , 57% yield, r.r. = 1.8:1; regioisomeric ratio taken from crude NMR).

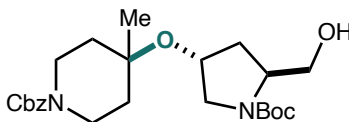


^1H NMR (500 MHz, CDCl_3) δ 7.37 – 7.31 (m, 4H), 7.31 – 7.25 (m, 1H), 5.09 (d, J = 2.5 Hz, 2H), 4.46 – 4.44 (m, 1H), 4.15 – 3.95 (m, 1H), 3.90 – 3.74 (m, 2H), 3.73 – 3.61 (m, 1H), 3.59 – 3.45 (m, 1H), 3.45 – 3.24 (m, 2H), 3.06 (d, J = 15.8 Hz, 2H), 2.75 – 2.70 (brs, 1H), 2.21 – 2.07 (m, 1H), 2.07 – 1.90 (m, 1H), 1.73 – 1.63 (m, 2H), 1.45 (s, 2H), 1.43 (s, 9H), 1.10 (s, 3H). (mixture of rotamers)

^{13}C NMR (126 MHz, CDCl_3) δ 175.25, 157.19, 155.43, 154.68, 136.96, 136.84, 136.11, 136.06, 128.67, 128.66, 128.64, 128.54, 128.38, 128.20, 128.06, 128.01, 127.92, 127.88, 116.47, 80.62, 79.69, 79.48zz, 71.24, 70.11, 69.47, 69.26, 67.17, 67.07, 62.19, 61.04, 58.97, 56.18, 55.90, 55.37, 55.02, 41.44, 40.90, 40.12, 40.00, 38.15, 37.60, 37.27, 36.35, 35.59, 34.86, 28.57, 28.51, 25.13, 24.80, 23.35, 22.79, 1.93. (mixture of rotamers)

HRMS (ESI-TOF) m/z calcd. for $\text{C}_{24}\text{H}_{36}\text{N}_2\text{O}_6\text{Na}$ $[\text{M}+\text{Na}]^+$ 471.24711; found: 471.24726.

IR (film) ν_{max} 3429, 2972, 2932, 2874, 1679, 1405, 1238, 1161, 910, 729 cm^{-1} .



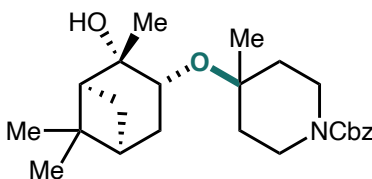
¹H NMR (500 MHz, CDCl₃) δ 7.39 – 7.33 (m, 4H), 7.33 – 7.28 (m, 1H), 5.12 (s, 2H), 3.79 (d, *J* = 13.1 Hz, 2H), 3.75 – 3.65 (m, 2H), 3.60 – 3.50 (m, 2H), 3.50 – 3.40 (m, 2H), 3.32 (dd, *J* = 11.3, 4.6 Hz, 1H), 3.18 (t, *J* = 12.3 Hz, 2H), 2.97 – 2.63 (brs, 1H), 2.09 – 1.94 (m, 2H), 1.8 – 1.71 (m, 1H), 1.47 (s, 2H), 1.46 (s, 9H), 1.17 (s, 3H). (mixture of rotamers).

¹³C NMR (126 MHz, CDCl₃) δ 155.43, 137.01, 128.62, 128.10, 127.99, 80.78, 80.63, 72.69, 69.58, 68.60, 67.17, 58.77, 55.95, 54.44, 40.21, 40.19, 37.72, 37.03, 28.58, 28.57, 28.53, 25.96. (mixture of rotamers)

HRMS (ESI-TOF) *m/z* calcd. for C₂₄H₃₆N₂O₆Na [M+Na]⁺ 471.24711; found: 471.24731.

IR (film) ν_{max} 3438, 2973, 2933, 2877, 1689, 1401, 1242, 1161, 697 cm⁻¹.

Benzyl 4-(((1*S*,2*S*,3*R*,5*S*)-2-hydroxy-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)oxy)-4-methylpiperidine-1-carboxylate (76)



Prepared according to the general procedure B with redox-active ester **RAE2** (113 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μmol, 5 mol%), Cp₂TiCl₂ (6.22 mg, 25.0 μmol, 10 mol%), Zn₃(PO₄)₂ (72.4 mg, 187 μmol, 0.75 equiv.), (+)-pinanediol (128 mg, 750 μmol, 3.00 equiv.), in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the lumidox setup, the solvent was removed under reduced pressure. The crude residue was dissolved in a minimal amount of DMSO, loaded on a 30 g Biotage Sfär C18 D reverse phase column, and purified with eluents 30% to 100% MeCN in water (0.1% NH₄OH modifier). The fractions containing product were concentrated and the product was obtained as a yellow oil (40.9 mg, 102 µmol, 41% yield).

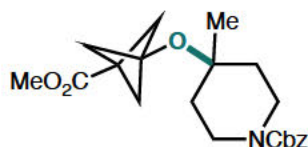
¹H NMR (500 MHz, CDCl₃) δ 7.39 – 7.32 (m, 4H), 7.34 – 7.27 (m, 1H), 5.13 (d, J = 2.3 Hz, 2H), 3.93 + 3.80 (td, J = 8.7, 6.8 Hz; dd, J = 9.3, 4.7 Hz; 1H), 3.72 – 3.56 (m, 3H), 3.55 – 3.39 (m, 2H), 2.39 + 2.31 (dddd, J = 13.4, 9.0, 4.3, 2.3 Hz; ddt, J = 12.8, 9.5, 2.9 Hz; 1H), 2.24 + 1.98 (t, J = 5.9 Hz; t, J = 5.8 Hz; 1H), 2.15 (dtd, J = 10.2, 5.8, 2.2 Hz, 1H), 1.92 – 1.84 (m, 2H), 1.80 – 1.69 (m, 2H), 1.61 – 1.50 (m, 3H), 1.44 + 1.23 (s; s; 3H), 1.33 + 1.26 (s; s; 3H), 1.27 + 1.25 (s; s; 3H), 0.98 + 0.92 (s, 3H). (1.3:1 mixture of rotamers)

¹³C NMR (500 MHz, CDCl₃) δ 155.39, 155.35, 136.97, 136.95, 128.62, 128.61, 128.12, 128.10, 128.04, 128.01, 127.99, 80.77, 74.51, 73.76, 73.44, 71.52, 68.94, 67.23, 67.20, 55.36, 54.08, 40.72, 40.66, 40.59, 40.58, 40.44, 40.43, 39.52, 39.14, 38.81, 38.22, 36.81, 36.45, 30.39, 29.43, 29.25, 28.22, 27.85, 27.49, 27.04, 26.24, 24.57, 24.26. (mixture of rotamers)

HRMS (ESI-TOF) m/z calcd. for C₂₄H₃₅NO₄Na [M+Na]⁺ 424.24638; found: 424.24640.

IR (film) ν_{max} 3493, 2972, 2917, 1697, 1427, 1359, 1280, 1234, 1154, 119, 1085, 1045, 1014, 991 cm⁻¹

Benzyl 4-((3-(methoxycarbonyl)bicyclo[1.1.1]pentan-1-yl)oxy)-4-methylpiperidine-1-carboxylate (77)



Prepared according to the general procedure B with redox-active ester **RAE2** (113 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μmol , 5 mol%), Cp_2TiCl_2 (6.22 mg, 25.0 μmol , 10 mol%), $[\text{ZnCO}_3]_2 \cdot [\text{Zn}(\text{OH})_2]_3$ (68.6 mg, 125 μmol , 0.5 equiv.), methyl 3-hydroxybicyclo[1.1.1]pentane-1-carboxylate (107 mg, 750 μmol , 3.00 equiv.), in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the lumidox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 0% to 80% EtOAc in hexanes. The fractions containing product were concentrated to provide the product as a yellowish solid (40.9 mg, 110 μmol , 44% yield).

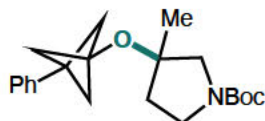
^1H NMR (500 MHz, CDCl_3) δ 7.37 – 7.34 (m, 4H), 7.34 – 7.28 (m, 1H), 5.12 (s, 2H), 3.90 – 3.74 (m, 2H), 3.68 (s, 3H), 3.29 – 3.15 (m, 2H), 2.28 (s, 6H), 1.84 – 1.72 (m, 2H), 1.50 – 1.36 (m, 2H), 1.27 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 170.33, 155.45, 137.02, 128.62, 128.10, 128.01, 74.67, 67.16, 63.59, 56.93, 52.00, 40.15, 37.13, 33.02, 26.59.

HRMS (ESI-TOF) m/z calcd. for $\text{C}_{21}\text{H}_{28}\text{NO}_5$ $[\text{M}+\text{H}]^+$ 374.19675; found: 374.19684.

IR (film) ν_{max} 2953, 1728, 1688, 1436, 1345, 1236, 1207, 1068, 905, 724, 697, 647 cm^{-1}

***Tert*-butyl (R)-3-methyl-3-((3-phenylbicyclo[1.1.1]pentan-1-yl)oxy)pyrrolidine-1-carboxylate (78)**



Prepared according to the general procedure B with redox-active ester **RAE27** (101 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μ mol, 5 mol%), Cp_2TiCl_2 (6.22 mg, 25.0 μ mol, 10 mol%), $[\text{ZnCO}_3]_2 \cdot [\text{Zn}(\text{OH})_2]_3$ (68.6 mg, 125 μ mol, 0.5 equiv.), 3-phenylbicyclo[1.1.1]pentan-1-ol (120 mg, 750 μ mol, 3.00 equiv.) in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the luminox setup, the solvent was removed under reduced pressure. The crude residue was dissolved in a minimal amount of DMSO, loaded on a 30 g Biotage Sfär C18 D reverse phase column, and purified with eluents 30% to 100% MeCN in water (0.1% NH_4OH modifier). The fractions containing product were concentrated and the product was obtained as a yellowish oil (49.7 mg, 145 μ mol, 58% yield).

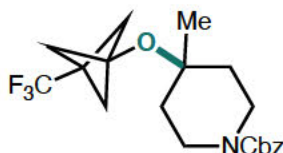
^1H NMR (500 MHz, CDCl_3) δ 7.34 – 7.27 (m, 2H), 7.25 – 7.18 (m, 3H), 3.45 (qd, J = 17.8, 9.9 Hz, 2H), 2.31 – 2.16 (m, 8H), 1.59 – 1.40 (m, 11H), 0.94 (dd, J = 7.3, 3.4 Hz, 3H).

^{13}C NMR (500 MHz, CDCl_3) δ 154.66, 154.50, 139.13, 138.75, 128.33, 128.27, 128.24, 126.69, 126.62, 126.58, 126.50, 90.99, 90.79, 80.27, 79.78, 64.56, 64.35, 56.01, 54.71, 54.65, 44.30, 43.92, 39.44, 38.89, 35.53, 35.30, 29.21, 28.68, 28.60, 28.14, 16.62.

HRMS (ESI-TOF) m/z calcd. for $\text{C}_{21}\text{H}_{29}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ 366.20451; found: 366.20456.

IR (film) ν_{max} 2970, 2908, 2873, 1699, 1387, 1365, 1344, 1251, 1225, 1164, 1151, 1097, 1006, 901 cm^{-1}

Benzyl 4-methyl-4-((3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)oxy)piperidine-1-carboxylate (79)



Prepared according to the general procedure B with redox-active ester **RAE2** (113 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μmol , 5 mol%), Cp_2TiCl_2 (6.22 mg, 25.0 μmol , 10 mol%), $[\text{ZnCO}_3]_2 \cdot [\text{Zn}(\text{OH})_2]_3$ (68.6 mg, 125 μmol , 0.5 equiv.), 3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-ol (**57.0 mg, 375 μmol , 1.50 equiv.**), in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the luminox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 15% to 85% EtOAc in hexanes. The fractions containing product were concentrated and further purified by preparative HPLC (RediSep C18 column, 45% to 85% MeCN in H_2O with 0.1% NH_4OH) to provide the product as a yellowish oil (43.5 mg, 113 μmol , 45% yield).

^1H NMR (500 MHz, CDCl_3) δ 7.38 – 7.34 (m, 4H), 7.34 – 7.29 (m, 1H), 5.12 (s, 2H), 3.95 – 3.70 (m, 2H), 3.28 – 3.13 (m, 2H), 2.21 (s, 6H), 1.85 – 1.70 (m, 2H), 1.51 – 1.38 (m, 2H), 1.28 (s, 3H).

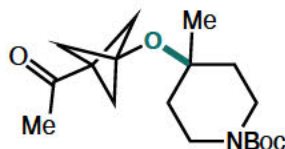
^{13}C NMR (126 MHz, CDCl_3) δ 155.42, 136.99, 128.62, 128.11, 128.00, 124.06 (q, $J = 273.5$ Hz), 75.00, 67.18, 63.47 (q, $J = 2.4$ Hz), 54.06 (q, $J = 1.6$ Hz), 40.10, 37.06, 36.66, 32.74 (q, $J = 39.4$ Hz), 26.47.

^{19}F NMR (126 MHz, CDCl_3) δ -70.14.

HRMS (ESI-TOF) m/z calcd. for $\text{C}_{20}\text{H}_{25}\text{F}_3\text{NO}_3$ $[\text{M}+\text{H}]^+$ 384.17865; found: 384.17881.

IR (film) ν_{max} 2922, 1695, 1430, 1397, 1267, 1234, 1194, 1173, 1129, 1088, 1032, 996 cm^{-1}

***Tert*-butyl 4-((3-acetylbicyclo[1.1.1]pentan-1-yl)oxy)-4-methylpiperidine-1-carboxylate (80)**



Attention: We observed that the product is highly sensitive to elevated temperatures as well as highly basic conditions. Therefore, instead of removing solvent by evaporation under reduced pressure, we applied pressurized air.

Prepared according to the general procedure B with redox-active ester **RAE1** (105 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μ mol, 5 mol%), Cp_2TiCl_2 (6.22 mg, 25.0 μ mol, 10 mol%), $[\text{ZnCO}_3]_2 \cdot [\text{Zn}(\text{OH})_2]_3$ (68.6 mg, 125 μ mol, 0.5 equiv 1-(3-hydroxy-1-bicyclo[1.1.1]pentanyl)ethanone (**47.3 mg, 375 μ mol, 1.50 equiv.**), in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the lumidox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 15% to 85% EtOAc in hexanes. The fractions containing product were concentrated and further purified by preparative HPLC (RediSep C18 column, 35% to 80% MeCN in H_2O with 0.1% NH_4OH). The fractions containing product were collected and MeCN was removed using pressurized air. Subsequently, the aqueous phase was extracted with Et_2O , dried and the solvent was again removed using pressurized air, followed by drying under reduced pressure at room temperature, which provided the product as a yellowish oil (41.1 mg, 127 μ mol, 51% yield).

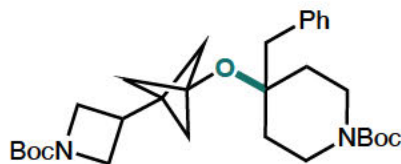
^1H NMR (500 MHz, CDCl_3) δ 3.76 – 3.58 (m, 2H), 3.15 (t, J = 12.0 Hz, 2H), 2.25 (s, 6H), 2.14 (s, 3H), 1.80 – 1.73 (m, 2H), 1.45 (s, 9H), 1.43 – 1.37 (m, 2H), 1.28 (s, 3H).

^{13}C NMR (500 MHz, CDCl_3) δ 205.36, 155.03, 79.54, 74.83, 63.56, 56.57, 39.80, 39.71, 37.07, 28.60, 27.12, 26.55.

HRMS (ESI-TOF) m/z calcd. for $\text{C}_{14}\text{H}_{22}\text{NO}_4$ $[\text{M}-\text{Boc}+2\text{H}]^+$ 224.16505; found: 224.16521.

IR (film) ν_{max} 2973, 2918, 2875, 1692, 1421, 1363, 1237, 1161, 1042, 964, 863 cm^{-1} .

Tert-butyl 4-benzyl-4-((3-(1-(*tert*-butoxycarbonyl)azetidin-3-yl)bicyclo[1.1.1]pentan-1-yl)oxy)piperidine-1-carboxylate (**81**)



Prepared according to the general procedure B with redox-active ester **RAE4** (124 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μmol , 5 mol%), Cp_2TiCl_2 (6.22 mg, 25.0 μmol , 10 mol%), $[\text{ZnCO}_3]_2 \cdot [\text{Zn}(\text{OH})_2]_3$ (68.6 mg, 125 μmol , 0.5 equiv.), *tert*-butyl 3-(3-hydroxy-1-bicyclo[1.1.1]pentanyl)azetidine-1-carboxylate (179 mg, 750 μmol , 3.00 equiv.) in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the luminox setup, the solvent was removed under reduced pressure. The crude residue was dissolved in a minimal amount of DMSO, loaded on a 30 g Biotage Sfär C18 D reverse phase column, and purified with eluents 45% to 100% MeCN in water (0.1% NH_4OH modifier). The fractions containing product were concentrated and the product was obtained as a yellow solid (69.9 mg, 136 μmol , 54% yield).

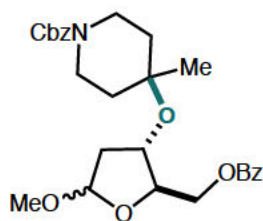
¹H NMR (500 MHz, CDCl₃) δ 7.28 (q, J = 6.3 Hz, 2H), 7.18 (d, J = 7.6 Hz, 3H), 4.04 – 3.76 (m, 3H), 3.53 – 3.47 (m, 2H), 3.12 – 2.93 (m, 1H), 2.75 – 2.62 (m, 2H), 2.54 (ddd, J = 28.6, 13.6, 7.5 Hz, 1H), 2.09 (p, J = 7.4 Hz, 1H), 2.01 – 1.85 (m, 2H), 1.83 – 1.64 (m, 9H), 1.54 – 1.45 (m, 9H), 1.42 (s, 9H). (mixture of rotamers)

¹³C NMR (500 MHz, CDCl₃) δ 156.52, 154.51, 154.39, 140.48, 140.29, 129.27, 129.12, 128.47, 126.25, 126.09, 81.80, 81.10, 80.30, 79.91, 79.44, 79.35, 65.37, 65.31, 52.56, 51.96, 51.48, 50.45, 40.27, 39.74, 39.17, 38.01, 36.05, 33.62, 33.48, 28.67, 28.62, 28.52, 27.92, 27.76, 22.75, 22.42, 20.07, 19.83. (mixture of rotamers)

HRMS (ESI-TOF) m/z calcd. for C₃₀H₄₄N₂O₅Na [M+Na]⁺ 535.31479; found: 535.31451.

IR (film) ν_{max} 2972, 2876, 1692, 1413, 1391, 1364, 1251, 1238, 1128, 1087, 981, 919 cm⁻¹

Benzyl 4-(((2*R*,3*S*)-2-((benzyloxy)methyl)-5-methoxytetrahydrofuran-3-yl)oxy)-4-methylpiperidine-1-carboxylate (82)



Prepared according to the general procedure B with redox-active ester **RAE2** (113 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μmol, 5 mol%), Cp₂TiCl₂ (6.22 mg, 25.0 μmol, 10 mol%), [ZnCO₃]₂·[Zn(OH)₂]₃ (68.6 mg, 125 μmol, 0.5 equiv.), (2*R*,3*S*,5*S*/*R*)-3-hydroxy-5-methoxy-tetrahydrofuran-2-yl]methyl benzoate (1.5:1 mixture of epimers at C-5, 189 mg, 750 μmol, 3.00 equiv.), in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the lumidox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal

phase column and purified with eluents 10% to 70% EtOAc in hexanes. The fractions containing product were concentrated to provide the product as a colorless oil (72.8 mg, 151 μ mol, 60% yield, 1.5:1 mixture of epimers at C-5 from starting material).

^1H NMR (500 MHz, CDCl_3) major epimer: δ 8.05 – 8.02 (m, 2H), 7.60 – 7.52 (m, 1H), 7.48 – 7.42 (m, 2H), 7.38 – 7.28 (m, 5H), 5.11 (s, 2H), 5.04 (dd, J = 5.8, 2.4 Hz, 1H), 4.56 (dd, J = 12.1, 2.8 Hz, 1H), 4.42 – 4.36 (m, 1H), 4.20 (tt, J = 4.9, 3.1 Hz, 1H), 4.07 (ddd, J = 8.6, 6.5, 4.8 Hz, 1H), 3.78 – 3.64 (m, 2H), 3.40 (s, 3H), 3.29 – 3.19 (m, 1H), 2.42 (ddd, J = 14.1, 8.6, 5.9 Hz, 1H), 1.90 (ddd, J = 13.7, 4.8, 2.4 Hz, 1H), 1.75 – 1.63 (m, 2H), 1.52 – 1.37 (m, 2H), 1.17 (s, 3H).

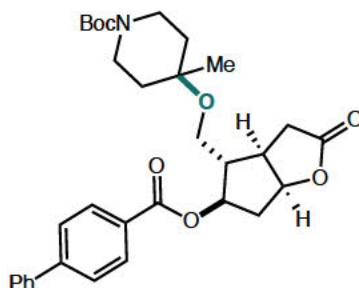
minor epimer: δ 8.10 – 8.06 (m, 2H), 7.60 – 7.52 (m, 1H), 7.48 – 7.41 (m, 2H), 7.38 – 7.28 (m, 5H), 5.11 (s, 2H), 5.06 (d, J = 4.6 Hz, 1H), 4.53 (dd, J = 11.8, 4.2 Hz, 1H), 4.39 – 4.30 (m, 2H), 4.24 – 4.17 (m, 1H), 3.80 – 3.63 (m, 2H), 3.29 (s, 3H), 3.29 – 3.19 (m, 2H), 2.23 (dd, J = 13.0, 6.9 Hz, 1H), 2.07 (ddd, J = 12.8, 7.5, 5.2 Hz, 1H), 1.74 – 1.64 (m, 2H), 1.52 – 1.37 (m, 2H), 1.18 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 166.55, 166.50, 155.36, 137.01, 136.99, 133.29, 133.25, 130.09, 130.01, 129.89, 129.81, 129.78, 128.61, 128.57, 128.55, 128.50, 128.10, 128.09, 128.02, 128.00, 127.94, 105.29, 104.81, 82.70, 80.08, 73.11, 73.07, 71.36, 70.95, 67.18, 67.16, 65.18, 63.85, 55.34, 54.96, 42.02, 41.86, 40.32, 40.24, 40.22, 40.18, 36.51, 36.07, 25.92, 25.89. (unassigned mixture of epimers)

HRMS (ESI-TOF) m/z calcd. for $\text{C}_{27}\text{H}_{33}\text{NO}_7\text{Na}$ $[\text{M}+\text{Na}]^+$ 506.21547; found: 506.21557.

IR (film) ν_{max} 2949, 1691, 1640, 1597, 1431, 1399, 1349, 1305, 1227, 1064, 1020, 908, 726 cm^{-1}

***Tert*-butyl 4-(((3*aR*,4*S*,5*R*,6*aS*)-5-(((1,1'-biphenyl)-4-carbonyl)oxy)-2-oxohexahydro-2*H*-cyclopenta[*b*]furan-4-yl)methoxy)-4-methylpiperidine-1-carboxylate (83)**



Prepared according to the general procedure B with redox-active ester **RAE1** (314 mg, 0.75 mmol, **3.00 equiv.**), 4DPAIPN (9.96 mg, 12.5 μ mol, 5 mol%), Cp_2TiCl_2 (6.22 mg, 25.0 μ mol, 10 mol%), $[\text{ZnCO}_3]_2 \cdot [\text{Zn}(\text{OH})_2]_3$ (68.6 mg, 125 μ mol, 0.5 equiv.), [(4*S*,5*R*)-4-(hydroxymethyl)-2-oxo-3,3*a*,4,5,6,6*a*-hexahydrocyclopenta[*b*]furan-5-yl] 4-phenylbenzoate (88.1 mg, 250 μ mol, **1.00 equiv.**), in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours in the **integrated photoreactor** using the 505 nm plate, 100% light intensity, full fan speed and a stir rate of 800 rpm, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 10% to 80% EtOAc in hexanes. The fractions containing product were concentrated and further purified by preparative HPLC (RediSep C18 column, 35% to 90% MeCN in H_2O with 0.1% NH_4OH) to provide the product as a colorless solid (69.7 mg, 127 μ mol, 51% yield).

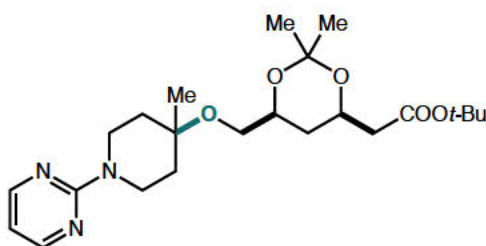
^1H NMR (500 MHz, CDCl_3) δ 8.06 (d, J = 8.3 Hz, 2H), 7.67 (d, J = 8.1 Hz, 2H), 7.62 (d, J = 7.4 Hz, 2H), 7.46 (t, J = 7.5 Hz, 2H), 7.39 (t, J = 7.3 Hz, 1H), 5.39 (dt, J = 6.1, 3.0 Hz, 1H), 5.11 (t, J = 5.9 Hz, 1H), 3.79 – 3.67 (m, 2H), 3.48 (dd, J = 8.9, 5.0 Hz, 1H), 3.42 (dd, J = 8.9, 4.5 Hz, 1H), 3.11 – 3.00 (m, 2H), 2.98 – 2.87 (m, 2H), 2.64 – 2.55 (m, 1H), 2.50 (dt, J = 15.7, 6.0 Hz, 1H), 2.42 – 2.33 (m, 2H), 1.70 (d, J = 13.1 Hz, 2H), 1.47 – 1.41 (m, 11H), 1.17 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 176.93, 166.11, 155.00, 146.11, 140.09, 130.31, 129.07, 128.57, 128.31, 127.43, 127.33, 85.52, 79.65, 79.13, 72.01, 61.46, 53.67, 41.38, 39.97, 39.28, 36.47, 35.74, 28.59, 24.58.

HRMS (ESI-TOF) m/z calcd. for C₃₂H₃₉NO₇Na [M+Na]⁺ 572.26242; found: 572.26210.

IR (film) ν_{max} 2971, 2933, 2870, 1770, 1710, 1683, 1608, 1421, 1364, 1275, 1242, 1154, 1094 cm⁻¹

***Tert*-butyl 2-((4*R*,6*S*)-2,2-dimethyl-6-(((4-methyl-1-(pyrimidin-2-yl)piperidin-4-yl)oxy)methyl)-1,3-dioxan-4-yl)acetate (**84**)**



Prepared according to the general procedure B with redox-active ester **RAE7** (99.1 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μmol, 5 mol%), Cp₂TiCl₂ (6.22 mg, 25.0 μmol, 10 mol%), Zn₃(PO₄)₂ (72.4 mg, 187 μmol, 0.75 equiv.), *tert*-butyl 2-[(4*R*,6*S*)-6-(hydroxymethyl)-2,2-dimethyl-1,3-dioxan-4-yl]acetate (195 mg, 750 μmol, 3.00 equiv.), in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the luminox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 10% to 70% EtOAc in hexanes to provide the product as a yellowish oil (69.0 mg, 158 μmol, 63% yield).

¹H NMR (500 MHz, CDCl₃) δ 8.28 (d, *J* = 4.7 Hz, 2H), 6.42 (t, *J* = 4.7 Hz, 1H), 4.34 – 4.23 (m, 3H), 4.04 (dddd, *J* = 11.6, 7.2, 4.9, 2.5 Hz, 1H), 3.47 (dd, *J* = 8.7, 4.9 Hz, 1H), 3.40 – 3.28 (m, 2H),

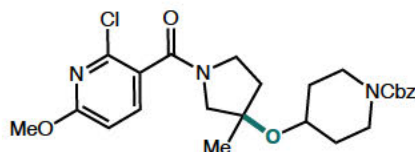
3.23 (dd, J = 8.8, 6.8 Hz, 1H), 2.42 (dd, J = 14.9, 7.3 Hz, 1H), 2.32 (dd, J = 14.9, 5.9 Hz, 1H), 1.79 (ddt, J = 17.9, 12.8, 2.3 Hz, 3H), 1.51 – 1.43 (m, 6H), 1.43 (s, 9H), 1.36 (s, 3H), 1.17 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 170.38, 161.78, 157.86, 109.35, 98.87, 80.71, 72.17, 68.72, 66.27, 64.96, 56.24, 42.99, 40.00, 35.77, 35.44, 34.57, 30.12, 28.22, 24.77, 19.89.

HRMS (ESI-TOF) m/z calcd. for $\text{C}_{23}\text{H}_{38}\text{N}_3\text{O}_5$ $[\text{M}+\text{H}]^+$ 436.28115; found: 436.28111.

IR (film) ν_{max} 2972, 2936, 1724, 1586, 1507, 1455, 1365, 1307, 1258, 1151, 1085, 729 cm^{-1}

Benzyl 4-((1-(2-chloro-6-methoxynicotinoyl)-3-methylpyrrolidin-3-yl)oxy)piperidine-1-carboxylate (85)



Prepared according to the general procedure B with redox-active ester **RAE23** (118 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μmol , 5 mol%), Cp_2TiCl_2 (6.22 mg, 25.0 μmol , 10 mol%), $[\text{ZnCO}_3]_2 \cdot [\text{Zn}(\text{OH})_2]_3$ (68.6 mg, 125 μmol , 0.5 equiv.), benzyl 4-hydroxypiperidine-1-carboxylate (176 mg, 750 μmol , 3.00 equiv.), in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the luminox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 10% to 80% EtOAc in hexanes. The fractions containing product were concentrated and further purified by preparative HPLC (RediSep C18 column, 30% to 80% MeCN in H_2O with 0.1% NH_4OH) to provide the product as a colorless solid (67.9 mg, 139 μmol , 56% yield).

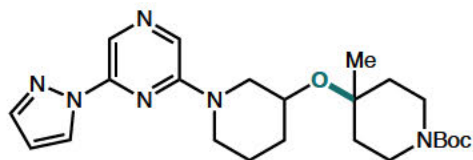
¹H NMR (500 MHz, CDCl₃) δ 7.60 – 7.48 (m, 1H), 7.40 – 7.28 (m, 5H), 6.76 – 6.68 (m, 1H), 5.16 – 5.04 (m, 2H), 4.12 – 3.92 (m, 4H), 3.89 – 3.78 (m, 1H), 3.79 – 3.40 (m, 2H), 3.30 – 3.16 (m, 2H), 3.10 – 2.84 (m, 1H), 2.32 – 2.20 (m, 2H), 2.03 – 1.77 (m, 1H), 1.69 – 1.48 (m, 4H), 1.37 – 1.03 (m, 2H), 1.03 – 0.95 (m, 3H). (mixture of rotamers)

¹³C NMR (126 MHz, CDCl₃) δ 167.82, 166.84, 163.91, 163.87, 155.44, 155.27, 144.12, 138.93, 137.07, 136.85, 128.65, 128.62, 128.19, 128.07, 128.03, 128.01, 127.96, 125.44, 109.99, 109.43, 67.29, 67.15, 54.53, 54.50, 46.05, 43.92, 41.81, 41.60, 41.48, 41.42, 39.27, 39.02, 32.31, 31.32, 30.11, 27.82, 16.87, 16.68. (mixture of rotamers)

HRMS (ESI-TOF) m/z calcd. for C₂₅H₃₀ClN₃O₅Na [M+Na]⁺ 510.17717; found: 510.17753.

IR (film) ν_{max} 2973, 2930, 2858, 1678, 1420, 1364, 1259, 1242, 1175, 1149, 1080, 909, 728 cm⁻¹

Tert-butyl 4-((1-(6-(1*H*-pyrazol-1-yl)pyrazin-2-yl)piperidin-3-yl)oxy)-4-methylpiperidine-1-carboxylate (86)



Prepared according to the general procedure B with redox-active ester **RAE1** (314 mg, 0.75 mmol, **3.00 equiv.**), 4DPAIPN (9.96 mg, 12.5 μmol, 5 mol%), Cp₂TiCl₂ (6.22 mg, 25.0 μmol, 10 mol%), [ZnCO₃]₂·[Zn(OH)₂]₃ (68.6 mg, 125 μmol, 0.5 equiv.), 1-(6-pyrazol-1-ylpyrazin-2-yl)piperidin-3-ol (61.3 mg, 250 μmol, **1.00 equiv.**), in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours in the **integrated photoreactor** using the 505 nm plate, 100% light intensity, full fan speed and a stir rate of 800 rpm, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified

with eluents 15% to 100% EtOAc in hexanes. The fractions containing product were concentrated and further purified by preparative HPLC (RediSep C18 column, 35% to 80% MeCN in H₂O with 0.1% NH₄OH) to provide the product as a colorless oil (64.9 mg, 147 μ mol, 59% yield).

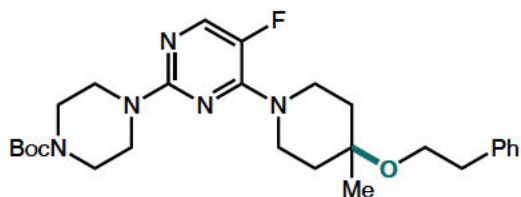
¹H NMR (500 MHz, CDCl₃) δ 9.05 (s, 1H), 8.43 (dd, J = 2.6, 0.7 Hz, 1H), 7.77 (dd, J = 1.6, 0.7 Hz, 1H), 6.48 (dd, J = 2.6, 1.7 Hz, 1H), 3.96 (tt, J = 7.7, 3.7 Hz, 1H), 3.71 – 3.63 (m, 2H), 3.18 (dd, J = 11.5, 3.5 Hz, 1H), 3.01 (ddt, J = 13.0, 9.8, 3.0 Hz, 2H), 2.93 – 2.81 (m, 3H), 2.67 – 2.55 (m, 2H), 2.02 – 1.95 (m, 1H), 1.90 (dtt, J = 13.2, 6.7, 3.9 Hz, 1H), 1.68 (dtd, J = 12.9, 9.0, 4.0 Hz, 4H), 1.62 – 1.51 (m, 1H), 1.44 (s, 9H), 1.41 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 156.43, 155.17, 153.36, 143.97, 142.86, 130.16, 127.33, 108.28, 79.35, 67.06, 58.89, 53.40, 41.16, 40.14, 36.75, 32.58, 28.62, 27.33, 22.40.

HRMS (ESI-TOF) m/z calcd. for C₂₃H₃₅N₆O₃ [M+H]⁺ 443.27706; found: 443.27718.

IR (film) $\nu_{\max}$ 2936, 2864, 1667, 1539, 1448, 1426, 1391, 1365, 1165, 1150, 1109, 1057, 962, 906 cm⁻¹

***Tert*-butyl 4-(5-fluoro-4-(4-methyl-4-phenethoxypiperidin-1-yl)pyrimidin-2-yl)piperazine-1-carboxylate (87)**



Prepared according to the general procedure B with redox-active ester **RAE24** (150 mg, 0.725 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μ mol, 5 mol%), Cp₂TiCl₂ (6.22 mg, 25.0 μ mol, 10 mol%), [ZnCO₃]₂·[Zn(OH)₂]₃ (68.6 mg, 125 μ mol, 0.5 equiv.), 2-phenylethanol (91.6 mg, 750 μ mol, 3.00 equiv.) in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the lumidox setup, the solvent was removed under reduced pressure. The crude residue was dissolved in a minimal amount of DMSO, loaded on a 30 g Biotage Sfär C18 D reverse phase column, and purified with eluents 15% to 80% MeCN in water (0.1% NH₄OH modifier). The fractions containing product were concentrated and the product was obtained as a colorless oil (63.9 mg, 128 µmol, 51% yield).

¹H NMR (500 MHz, CDCl₃) δ 7.79 (m, 1H), 7.28 (t, *J* = 7.4 Hz, 2H), 7.24 (d, *J* = 7.1 Hz, 1H), 7.22 – 7.17 (m, 2H), 4.01 (dd, *J* = 13.4, 3.8 Hz, 2H), 3.71 – 3.58 (m, 4H), 3.55 (t, *J* = 6.9 Hz, 2H), 3.49 – 3.42 (m, 4H), 3.15 (td, *J* = 12.7, 2.6 Hz, 2H), 2.87 (q, *J* = 7.1 Hz, 2H), 1.80 – 1.75 (m, 2H), 1.51 – 1.44 (m, 11H), 1.14 (s, 3H).

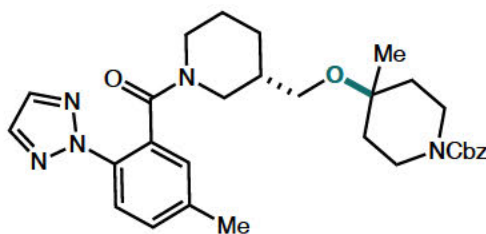
¹³C NMR (126 MHz, CDCl₃) δ 157.81, 157.66, 155.04, 155.01, 151.59 (d, *J* = 5.1 Hz), 151.01 (d, *J* = 5.6 Hz), 143.88 (d, *J* = 26.9 Hz), 143.12, 142.85 (d, *J* = 26.4 Hz), 142.61, 141.71 (d, *J* = 247.2 Hz), 140.66, 139.63, 138.91, 129.19, 129.00, 128.50, 128.41, 126.43, 126.35, 111.88, 80.02, 79.95, 71.70, 68.77, 62.31, 44.43, 44.39, 43.17, 42.00, 41.93, 37.31, 36.58, 36.42, 35.83, 28.58, 24.82, 22.75. (mixture of rotamers)

¹⁹F NMR (471 MHz, CDCl₃) δ -159.75 (s), -161.82 (s). (mixture of rotamers)

HRMS (ESI-TOF) *m/z* calcd. for C₂₇H₃₉FN₅O₃ [M+H]⁺ 500.30369; found: 500.30374.

IR (film) ν_{max} 2971, 2929, 2862, 1693, 1595, 1565, 1477, 1441, 1417, 1364, 1234, 1165, 1130, 1076 cm⁻¹

Benzyl (S)-4-methyl-4-((1-(5-methyl-2-(2H-1,2,3-triazol-2-yl)benzoyl)piperidin-3-yl)methoxy)piperidine-1-carboxylate (88)



Prepared according to the general procedure B with redox-active ester **RAE2** (113 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μmol , 5 mol%), Cp_2TiCl_2 (6.22 mg, 25.0 μmol , 10 mol%), $[\text{ZnCO}_3]_2 \cdot [\text{Zn}(\text{OH})_2]_3$ (68.6 mg, 125 μmol , 0.5 equiv.), 1-phenylethanol (89.3 μL , 750 μmol , 3.00 equiv.), in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the lumidox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 15% to 100% EtOAc in hexanes. The fractions containing product were concentrated to provide the product as a yellow oil (62.5 mg, 118 μmol , 47% yield).

^1H NMR (500 MHz, CDCl_3) δ 7.86 – 7.72 (m, 3H), 7.39 – 7.28 (m, 6H), 7.24 – 7.13 (m, 1H), 5.13 (s, 2H), 4.77 – 4.44 (m, 1H), 3.92 – 3.63 (m, 2H), 3.57 – 3.28 (m, 1H), 3.27 – 3.17 (m, 1H), 3.16 – 2.93 (m, 1H), 2.91 – 2.78 (m, 1H), 2.71 – 2.61 (m, 1H), 2.58 – 2.44 (m, 1H), 2.41 – 2.35 (m, 3H), 1.86 – 1.61 (m, 4H), 1.59 – 1.47 (m, 2H), 1.45 – 1.33 (m, 2H), 1.32 – 1.21 (m, 2H), 1.17 – 0.92 (m, 3H). (mixture of rotamers)

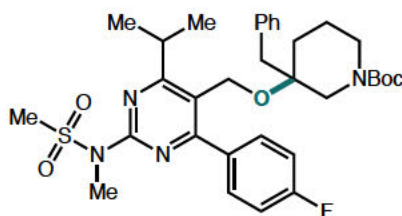
^{13}C NMR (126 MHz, CDCl_3) δ 168.55, 168.49, 168.03, 167.87, 155.51, 155.40, 138.66, 138.61, 138.50, 137.12, 137.10, 135.75, 135.69, 135.58, 134.10, 134.06, 133.96, 130.47, 130.41, 130.39, 129.80, 129.55, 129.40, 129.29, 128.70, 128.64, 128.62, 128.59, 128.12, 128.11, 128.04, 128.03, 128.01, 127.97, 122.48, 122.23, 122.00, 121.95, 71.15, 70.92, 70.90, 67.08, 63.39, 63.14, 62.75, 50.76, 47.89, 47.27, 45.31, 45.16, 42.52, 42.30, 40.14, 39.79, 39.72, 37.78, 36.99, 36.37, 35.99,

35.30, 28.07, 27.89, 27.76, 25.16, 24.76, 24.71, 24.13, 23.85, 22.78, 21.18, 21.13, 21.11, 21.04.
(mixture of rotamers)

HRMS (ESI-TOF) m/z calcd. for $C_{30}H_{37}N_5O_4Na$ $[M+Na]^+$ 554.27432; found: 554.27440.

IR (film) ν_{max} 2926, 2856, 1693, 1631, 1505, 1438, 1279, 1237, 1156, 1075, 961, 908, 824, 727 cm^{-1}

***Tert*-butyl 3-benzyl-3-((4-(4-fluorophenyl)-6-isopropyl-2-(*N*-methylethanesulfonamido)pyrimidin-5-yl)methoxy)piperidine-1-carboxylate (89)**



Prepared according to the general procedure B with redox-active ester **RAE4** (370 mg, 0.75 mmol, 3.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μ mol, 5 mol%), Cp_2TiCl_2 (6.22 mg, 25.0 μ mol, 10 mol%), $[ZnCO_3]_2 \cdot [Zn(OH)_2]_3$ (68.6 mg, 125 μ mol, 0.5 equiv.), *N*-[4-(4-fluorophenyl)-5-(hydroxymethyl)-6-isopropyl-pyrimidin-2-yl]-*N*-methyl-methanesulfonamide (88.3 mg, 250 μ mol, 1.00 equiv.), in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the luminox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfar normal phase column and purified with eluents 10% to 60% EtOAc in hexanes. The fractions containing product were concentrated and further purified by preparative HPLC (RediSep C18 column, 35% to 100% MeCN in H_2O with 0.1% NH_4OH) to provide the product as a colorless solid (112.3 mg, 179 μ mol, 72% yield).

¹H NMR (500 MHz, CDCl₃) δ 7.74 – 7.53 (m, 2H), 7.39 – 7.26 (m, 3H), 7.25 – 7.18 (m, 2H), 7.17 – 7.03 (m, 1H), 6.97 – 6.80 (m, 1H), 4.45 – 4.30 (m, 1H), 4.22 – 4.02 (m, 1H), 4.02 – 3.81 (m, 1H), 3.59 – 3.54 (m, 3H), 3.54 – 3.47 (m, 3H), 3.47 – 3.19 (m, 1H), 3.07 – 2.84 (m, 1H), 2.84 – 2.69 (m, 1H), 2.66 – 2.52 (m, 1H), 2.25 – 2.00 (m, 1H), 1.95 – 1.66 (m, 2H), 1.62 – 1.55 (m, 1H), 1.45 (d, J = 27.6 Hz, 6H), 1.39 – 1.33 (m, 2H), 1.33 – 1.23 (m, 9H). (mixture of rotamers)

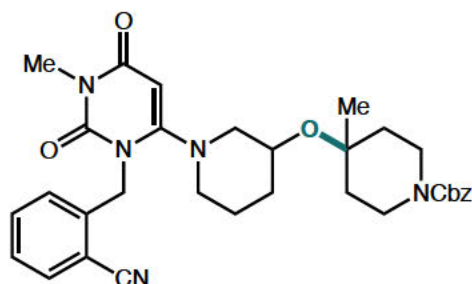
¹³C NMR (126 MHz, CDCl₃) δ 178.15, 178.02, 177.83, 177.64, 166.79, 166.68, 166.59, 164.73, 162.74, 158.18, 158.15, 158.06, 155.75, 155.22, 155.09, 154.21, 140.50, 140.45, 140.06, 139.85, 134.29, 134.26, 134.12, 134.01, 133.98, 131.44, 131.38, 131.31, 131.21, 131.14, 129.25, 129.13, 128.95, 128.65, 128.53, 126.54, 126.38, 126.28, 126.23, 119.02, 118.91, 118.90, 118.81, 115.62, 115.52, 115.45, 115.35, 115.28, 84.24, 83.88, 83.64, 83.47, 80.57, 80.43, 80.28, 80.26, 63.28, 63.07, 62.51, 62.37, 42.72, 42.64, 42.55, 42.55, 40.64, 40.43, 39.79, 39.61, 39.20, 38.80, 38.59, 38.41, 36.94, 33.22, 33.19, 31.81, 31.74, 31.64, 28.42, 28.40, 28.37, 28.34, 25.40, 25.18, 24.50, 24.42, 23.96, 23.48, 22.81, 22.64, 22.53, 22.32, 22.23, 22.03, 21.97, 20.07, 19.96. (mixture of rotamers)

¹⁹F NMR (471 MHz, CDCl₃) δ -111.17 – -111.56 (m, 1F).

HRMS (ESI-TOF) m/z calcd. for C₃₃H₄₄FN₄O₅S [M+H]⁺ 627.30164; found: 627.30172.

IR (film) ν_{max} 2937, 1685, 1606, 1551, 1511, 1375, 1230, 1151, 1029, 964, 907, 727 cm⁻¹

Benzyl 4-((1-(3-(2-cyanobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperidin-3-yl)oxy)-4-methylpiperidine-1-carboxylate (90)



Prepared according to the general procedure B with redox-active ester **RAE2** (339 mg, 0.75 mmol, 3.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μmol , 5 mol%), Cp_2TiCl_2 (6.22 mg, 25.0 μmol , 10 mol%), $[\text{ZnCO}_3]_2 \cdot [\text{Zn}(\text{OH})_2]_3$ (68.6 mg, 125 μmol , 0.5 equiv.), 2-[[6-(3-hydroxy-1-piperidyl)-3-methyl-2,4-dioxo-pyrimidin-1-yl]methyl]benzonitrile (85.1 mg, 250 μmol , 1.00 equiv.), in **DCE** (**0.1 M**, **2.5 mL**).

After irradiation for **30 hours** at level 5 (8.4 W) in the luminox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 10% to 100% EtOAc in hexanes. The fractions containing product were concentrated to provide the product as a colorless solid (77.4 mg, 135 μmol , 54% yield).

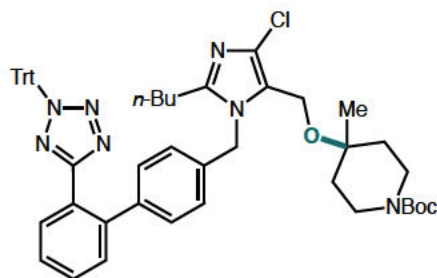
^1H NMR (500 MHz, CDCl_3) δ 7.65 (dd, J = 7.6, 1.4 Hz, 1H), 7.53 (t, J = 7.7 Hz, 1H), 7.40 – 7.29 (m, 6H), 7.14 (d, J = 7.9 Hz, 1H), 5.34 (d, J = 16.4 Hz, 2H), 5.22 (d, J = 16.0 Hz, 1H), 5.13 – 5.09 (m, 2H), 3.75 – 3.53 (m, 3H), 3.31 (s, 3H), 3.23 – 3.08 (m, 2H), 3.02 – 2.95 (m, 1H), 2.87 (d, J = 11.7 Hz, 1H), 2.67 – 2.41 (m, 2H), 1.89 – 1.74 (m, 2H), 1.65 – 1.52 (m, 3H), 1.48 – 1.33 (m, 3H), 1.08 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 163.21, 159.75, 155.30, 152.77, 140.94, 136.99, 133.36, 133.28, 128.63, 128.61, 128.14, 128.08, 128.05, 126.78, 117.24, 110.89, 91.04, 73.17, 67.19, 58.02, 51.72, 46.37, 40.37, 40.28, 36.87, 35.91, 28.11, 25.45.

HRMS (ESI-TOF) m/z calcd. for $\text{C}_{32}\text{H}_{38}\text{N}_5\text{O}_5$ $[\text{M}+\text{H}]^+$ 572.28729; found: 572.28726.

IR (film) ν_{max} 2945, 1873, 2223, 1695, 1651, 1433, 1360, 1237, 1157, 1074, 909, 789 cm^{-1} .

Tert-butyl 4-((2-butyl-4-chloro-1-((2'-(2-trityl-2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-1H-imidazol-5-yl)methoxy)-4-methylpiperidine-1-carboxylate (91)



Note: Due to lower yields (15% less) upon scaling up from 0.05 mmol to 0.25 mmol, 5 reactions on a 0.05 mmol scale were set up in parallel and pooled after completed irradiation, before being subjected to purification.

Prepared according to the general procedure B with **5 parallel reaction** of 0.05 mmol scale each, with redox-active ester **RAE1** (62.8 mg, 0.15 mmol, 3.00 equiv.), 4DPAIPN (1.99 mg, 2.5 μ mol, 5 mol%), Cp_2TiCl_2 (1.24 mg, 5.0 μ mol, 10 mol%), $[\text{ZnCO}_3]_2 \cdot [\text{Zn}(\text{OH})_2]_3$ (13.7 mg, 25.0 μ mol, 0.5 equiv.), [2-butyl-5-chloro-3-[[4-[2-(2-trityltetrazol-5-yl)phenyl]phenyl]methyl]imidazol-4-yl]methanol (33.3 mg, 0.05 mmol, 1.00 equiv.), in **DCM** (0.2 M, 0.25 mL).

After irradiation for 20 hours at level 2 (4.1 W) in the luminox setup, the reactions were pooled, and the solvent was removed under reduced pressure. The crude residue was dissolved in a minimal amount of DMSO, loaded on a 30 g Biotage Sfär C18 D reverse phase column, and purified with eluents 30% to 100% MeCN in water (0.1% NH_4OH modifier). The fractions containing product were concentrated and the residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 0% to 80% EtOAc in hexanes. The fractions containing product were concentrated to provide the product as a colorless solid (97.8mg, 113 μ mol, 45% yield).

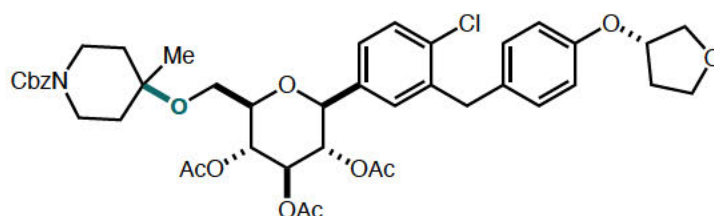
¹H NMR (500 MHz, CDCl₃) δ 7.96 – 7.88 (m, 1H), 7.53 – 7.42 (m, 2H), 7.34 (tt, *J* = 6.8, 1.1 Hz, 4H), 7.29 – 7.22 (m, 6H), 7.11 (dd, *J* = 8.3, 2.4 Hz, 2H), 6.97 – 6.89 (m, 6H), 6.75 (d, *J* = 7.9 Hz, 2H), 5.16 – 4.98 (m, 2H), 4.71 (d, *J* = 80.3 Hz, 1H), 4.33 – 4.07 (m, 3H), 3.64 (s, 1H), 2.55 – 2.36 (m, 2H), 2.23 – 1.99 (m, 2H), 1.77 – 1.57 (m, 5H), 1.52 – 1.47 (m, 9H), 1.48 – 1.41 (m, 2H), 1.32 – 1.22 (m, 3H), 0.86 (t, *J* = 7.3 Hz, 3H). (mixture of rotamers)

¹³C NMR (126 MHz, CDCl₃) δ 164.04, 154.95, 148.70, 148.50, 141.48, 141.45, 141.43, 141.40, 141.33, 141.11, 140.99, 138.37, 134.81, 134.70, 130.87, 130.47, 130.41, 130.35, 130.33, 130.14, 130.12, 130.09, 130.02, 129.94, 128.45, 127.89, 127.84, 127.79, 127.69, 127.63, 126.89, 126.42, 126.37, 126.12, 125.34, 124.79, 83.01, 60.54, 53.34, 47.27, 31.37, 31.07, 29.89, 29.86, 29.83, 28.59, 28.41, 26.90, 26.88, 22.54, 14.34, 13.90. (mixture of rotamers)

HRMS (ESI-TOF) *m/z* calcd. for C₅₂H₅₇ClN₇O₃ [M+H]⁺ 862.42114; found: 862.42121.

IR (film) ν_{max} 2958, 2932, 2872, 1690, 1446, 1366, 1251, 1152, 1028, 907, 757, 729, 698 cm⁻¹

(2*R*,3*R*,4*R*,5*S*,6*S*)-2-(((1-((benzyloxy)carbonyl)-4-methylpiperidin-4-yl)oxy)methyl)-6-(4-chloro-3-(4-(((*S*)-tetrahydrofuran-3-yl)oxy)benzyl)phenyl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (92)



Prepared according to the general procedure B with redox-active ester **RAE2** (339 mg, 0.75 mmol, **3.00 equiv.**), 4DPAIPN (9.96 mg, 12.5 μmol, 5 mol%), Cp₂TiCl₂ (6.22 mg, 25.0 μmol, 10 mol%), [ZnCO₃]₂·[Zn(OH)₂]₃ (68.6 mg, 125 μmol, 0.5 equiv.), [(2*R*,3*R*,4*R*,5*S*,6*S*)-4,5-diacetoxy-6-[4-

chloro-3-[[4-[(3*S*)-tetrahydrofuran-3-yl]oxyphenyl]methyl]phenyl]-2-(hydroxymethyl)tetrahydropyran-3-yl] acetate (144mg, 250 μ mol, **1.00 equiv.**), in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours in the **integrated photoreactor** using the 505 nm plate, 100% light intensity, full fan speed and a stir rate of 800 rpm, the crude reaction mixture was filtered through a syringe filter and the filter was subsequently flushed with DCM (2 x 3 mL). The solvent was removed under reduced pressure. The crude residue was dissolved in a minimal amount of DMSO and purified by preparative HPLC (RediSep C18 column, 30% to 100% MeCN in H₂O with 0.1% NH₄OH) to provide the product as a yellow solid (80.5 mg, 100 μ mol, 40% yield).

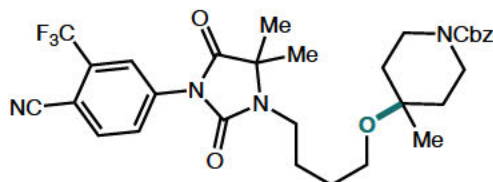
¹H NMR (500 MHz, CDCl₃) δ 7.38 – 7.30 (m, 8H), 7.06 (d, *J* = 8.3 Hz, 2H), 6.78 (d, *J* = 8.7, 2H), 5.52 – 5.36 (m, 1H), 5.34 – 5.05 (m, 5H), 5.01 – 4.71 (m, 2H), 4.45 – 4.11 (m, 4H), 4.09 – 4.00 (m, 2H), 3.99 – 3.92 (m, 4H), 3.92 – 3.83 (m, 2H), 2.20 – 2.08 (m, 5H), 2.06 (s, 2H), 2.02 – 1.96 (m, 2H), 1.93 (s, 1H), 1.86 (d, *J* = 7.7 Hz, 2H), 1.74 – 1.71 (m, 3H), 1.71 – 1.66 (m, 3H). (mixture of rotamers)

¹³C NMR (500 MHz, CDCl₃) δ 171.69, 171.39, 170.83, 170.71, 169.12, 169.00, 156.05, 156.02, 155.49, 155.47, 155.44, 155.38, 154.26, 139.56, 138.89, 138.81, 138.76, 137.02, 137.00, 136.92, 136.25, 136.15, 136.11, 135.97, 135.78, 135.75, 135.68, 134.54, 134.46, 131.81, 131.74, 130.05, 130.00, 129.94, 129.86, 129.81, 129.00, 128.97, 128.92, 128.77, 128.73, 128.68, 128.66, 128.62, 128.59, 128.58, 128.56, 128.40, 128.35, 128.23, 128.19, 128.15, 128.08, 128.03, 128.00, 127.96, 127.93, 126.22, 126.15, 115.50, 115.48, 79.47, 78.51, 73.22, 73.20, 72.65, 69.11, 67.92, 67.28, 67.12, 67.07, 63.34, 43.94, 42.51, 40.24, 38.36, 37.11, 33.09, 32.77, 29.69, 21.04, 20.95, 20.77, 20.59, 20.45, 20.43. (mixture of rotamers)

HRMS (ESI-TOF) *m/z* calcd. for C₄₃H₅₀ClNO₁₂Na [*M*+Na]⁺ 830.29192; found: 830.29131.

IR (film) ν_{max} 2950, 2872, 1748, 1697, 1637, 1609, 1508, 1425, 1364, 1225, 1101, 1033, 907, 825, 647 cm⁻¹

Benzyl 4-(4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-2,4-dioxoimidazolidin-1-yl)butoxy)-4-methylpiperidine-1-carboxylate (93)



Prepared according to the general procedure B with redox-active ester **RAE2** (113 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μmol , 5 mol%), Cp_2TiCl_2 (6.22 mg, 25.0 μmol , 10 mol%), $[\text{ZnCO}_3]_2 \cdot [\text{Zn}(\text{OH})_2]_3$ (68.6 mg, 125 μmol , 0.5 equiv.), 4-[3-(4-hydroxybutyl)-4,4-dimethyl-2,5-dioxo-imidazolidin-1-yl]-2-(trifluoromethyl)benzonitrile (277 mg, 750 μmol , 3.00 equiv.), in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the luminox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 10% to 80% EtOAc in hexanes. The fractions containing product were concentrated to provide the product as a colorless solid (87.9 mg, 146 μmol , 59% yield).

^1H NMR (500 MHz, CDCl_3) δ 8.16 (d, $J = 2.1$ Hz, 1H), 8.01 (dd, $J = 8.5, 2.1$ Hz, 1H), 7.90 (d, $J = 8.4$ Hz, 1H), 7.35 (d, $J = 3.9$ Hz, 4H), 7.33 – 7.28 (m, 1H), 5.12 (s, 2H), 3.88 – 3.73 (m, 2H), 3.42 – 3.33 (m, 4H), 3.22 – 3.09 (m, 2H), 1.84 – 1.67 (m, 4H), 1.65 – 1.58 (m, 2H), 1.53 (s, 6H), 1.48 – 1.39 (m, 2H), 1.16 (s, 3H).

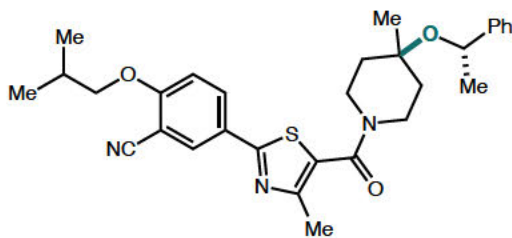
^{13}C NMR (126 MHz, CDCl_3) δ 174.76, 155.50, 152.92, 137.03, 136.63, 135.37, 133.73 (q, $J = 33.2$ Hz), 128.61, 128.11, 127.99, 123.10 (q, $J = 5.0$ Hz), 122.12 (d, $J = 274.2$ Hz), 115.17, 108.33 (q, $J = 2.1$ Hz), 71.33, 67.13, 61.97, 60.04, 40.48, 40.16, 35.92, 27.94, 26.95, 24.68, 23.67.

^{19}F NMR (376 MHz, CDCl_3) δ -62.01.

HRMS (ESI-TOF) m/z calcd. for $\text{C}_{31}\text{H}_{35}\text{F}_3\text{N}_4\text{O}_5\text{Na}$ $[\text{M}+\text{Na}]^+$ 623.24572; found: 623.24566.

IR (film) ν_{max} 2940, 2872, 1777, 1720, 1692, 1504, 1435, 1407, 1367, 1312, 1237, 1178, 1136, 1085, 909 cm^{-1}

(*S*)-2-isobutoxy-5-(4-methyl-5-(4-methyl-4-(1-phenylethoxy)piperidine-1-carbonyl)thiazol-2-yl)benzonitrile (94)



Prepared according to the general procedure B with redox-active ester **RAE25** (154 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μ mol, 5 mol%), Cp_2TiCl_2 (6.22 mg, 25.0 μ mol, 10 mol%), $[\text{ZnCO}_3]_2 \cdot [\text{Zn}(\text{OH})_2]_3$ (68.6 mg, 125 μ mol, 0.5 equiv.), (*S*)-1-phenylethanol (91.6 mg, 750 μ mol, 3.00 equiv.) in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the luminox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 10% to 80% EtOAc in hexanes. The fractions containing product were concentrated and further purified by preparative HPLC (RediSep C18 column, 40% to 100% MeCN in H_2O with 0.1% NH_4OH) to provide the product as a colorless oil (52.9 mg, 102 μ mol, 41% yield).

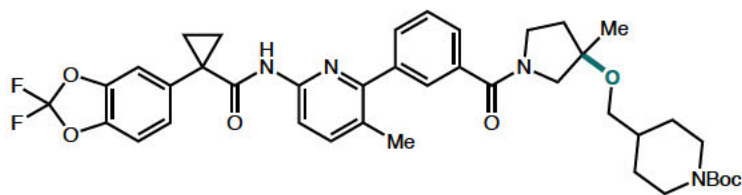
^1H NMR (500 MHz, CDCl_3) δ 8.10 (d, J = 2.3 Hz, 1H), 8.01 (dd, J = 8.8, 2.3 Hz, 1H), 7.34 – 7.29 (m, 4H), 7.25 – 7.21 (m, 1H), 6.99 (d, J = 8.9 Hz, 1H), 4.63 (q, J = 6.4 Hz, 1H), 4.50 – 3.92 (m, 1H), 3.89 (d, J = 6.5 Hz, 2H), 3.62 – 3.23 (m, 2H), 3.18 – 2.88 (m, 1H), 2.42 (s, 3H), 2.19 (*virt. dh*, J = 13.3, 6.7 Hz, 1H), 1.97 – 1.83 (m, 1H), 1.82 – 1.67 (m, 1H), 1.54 – 1.45 (m, 1H), 1.44 – 1.36 (m, 1H), 1.41 (d, J = 6.5 Hz, 3H), 1.14 (s, 3H), 1.09 (d, J = 6.7 Hz, 6H).

^{13}C NMR (126 MHz, CDCl_3) δ 164.83, 162.23, 162.09, 152.60, 146.68, 132.42, 131.91, 128.52, 127.19, 126.29, 125.81, 125.11, 115.65, 112.74, 103.03, 75.78, 73.13, 70.27, 44.20, 36.94, 28.30, 26.77, 26.08, 19.20, 16.57.

HRMS (ESI-TOF) m/z calcd. for $C_{30}H_{36}N_3O_3S$ $[M+H]^+$ 518.24774; found: 518.24771.

IR (film) $\nu_{\max}$ 2936, 2864, 1667, 1521, 1448, 1426, 1391, 1365, 1262, 1165, 1057, 962, 906, 727 cm^{-1}

***Tert*-butyl 4-(((1-(3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)cyclopropane-1-carboxamido)-3-methylpyridin-2-yl)benzoyl)-3-methylpyrrolidin-3-yl)oxy)methyl)piperidine-1-carboxylate (95)**



Prepared according to the general procedure B with redox-active ester **RAE** (185 mg, 0.25 mmol, 1.00 equiv.), 4DPAIPN (9.96 mg, 12.5 μmol , 5 mol%), Cp_2TiCl_2 (6.22 mg, 25.0 μmol , 10 mol%), $[\text{ZnCO}_3]_2 \cdot [\text{Zn}(\text{OH})_2]_3$ (68.6 mg, 125 μmol , 0.5 equiv.), *tert*-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (161 mg, 750 μmol , 3.00 equiv.) in DCE (0.2 M, 1.25 mL).

After irradiation for 20 hours at level 5 (8.4 W) in the lumidox setup, the solvent was removed under reduced pressure. The crude residue was loaded on a 25 g Biotage Sfär normal phase column and purified with eluents 15% to 100% EtOAc in hexanes. The fractions containing product were concentrated and further purified by preparative HPLC (RediSep C18 column, 40% to 100% MeCN in H_2O with 0.1% NH_4OH) to provide the product as a colorless solid (88.9 mg, 121 μmol , 49% yield).

^1H NMR (500 MHz, CDCl_3) δ 8.09 (d, J = 8.4 Hz, 1H), 7.68 – 7.56 (m, 3H), 7.56 – 7.42 (m, 3H), 7.23 (dd, J = 8.2, 1.8 Hz, 1H), 7.19 (d, J = 1.8 Hz, 1H), 7.07 (d, J = 8.1 Hz, 1H), 4.18 – 3.90 (m, 2H), 3.80 – 3.56 (m, 2H), 3.55 – 3.14 (m, 1H), 2.95 – 2.78 (m, 1H), 2.74 – 2.64 (m, 1H), 2.61 –

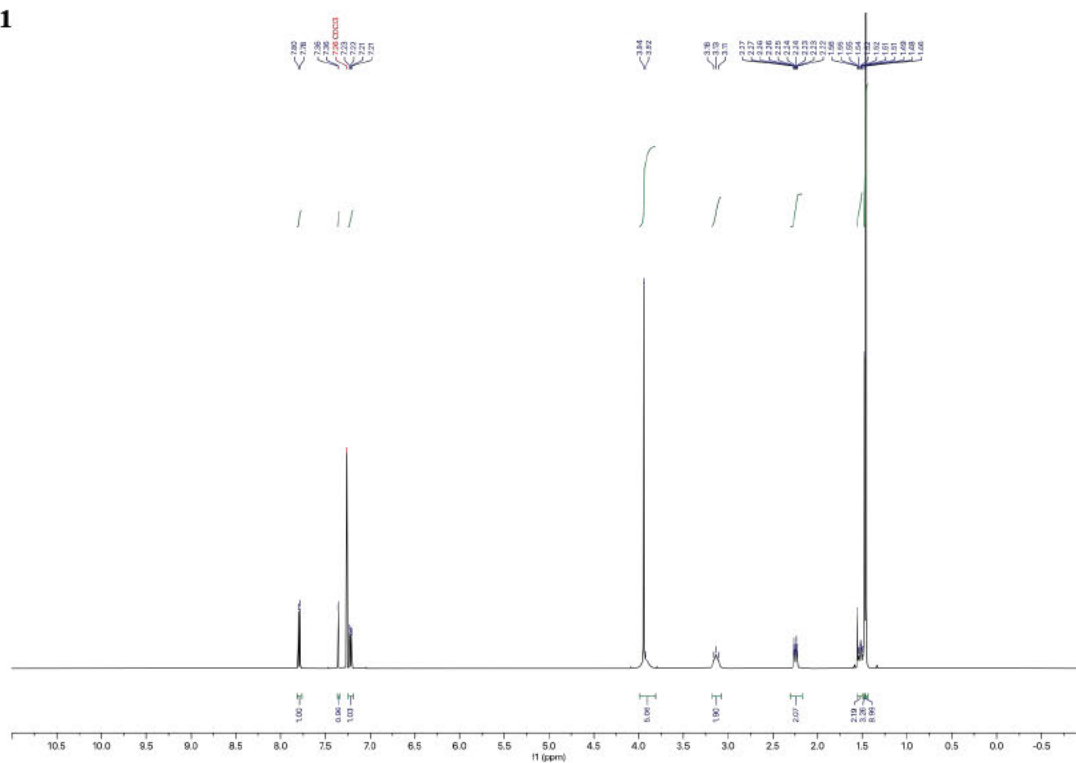
2.43 (m, 1H), 2.32 – 2.07 (m, 2H), 2.25 (s, 3H), 2.06 – 1.87 (m, 1H), 1.84 – 1.66 (m, 4H), 1.65 – 1.50 (m, 2H), 1.45 (d, $J = 4.3$ Hz, 9H), 1.18 – 1.12 (m, 3H), 1.11 – 0.92 (m, 3H), 0.84 (d, $J = 6.9$ Hz, 1H). (mixture of rotamers)

^{13}C NMR (126 MHz, CDCl_3) δ 171.83, 171.55, 171.06, 155.62, 155.05, 154.90, 149.01, 144.28, 143.75, 141.09, 140.05, 136.68, 135.07, 131.82 (t, $J = 256.8$ Hz), 130.92, 130.73, 130.62, 128.32, 127.10, 126.77, 112.96, 112.54, 110.30, 94.63, 79.51, 79.37, 71.26, 48.11, 44.06, 40.09, 38.68, 37.76, 37.06, 36.79, 36.50, 31.32, 29.18, 29.17, 28.61, 27.78, 19.37, 17.35, 17.16, 16.56. (mixture of rotamers)

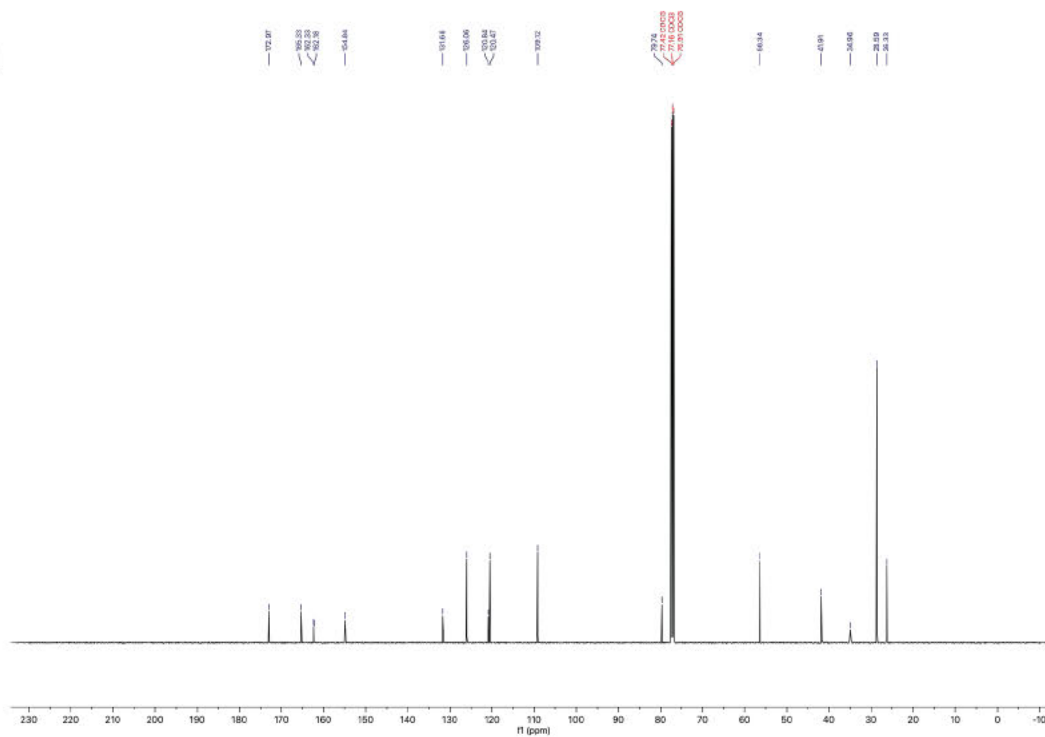
^{19}F NMR (471 MHz, CDCl_3) δ -49.53 – -49.64 (m).

HRMS (ESI-TOF) m/z calcd. for $\text{C}_{40}\text{H}_{47}\text{F}_2\text{N}_4\text{O}_7$ $[\text{M}+\text{H}]^+$ 733.34128; found: 733.34105.

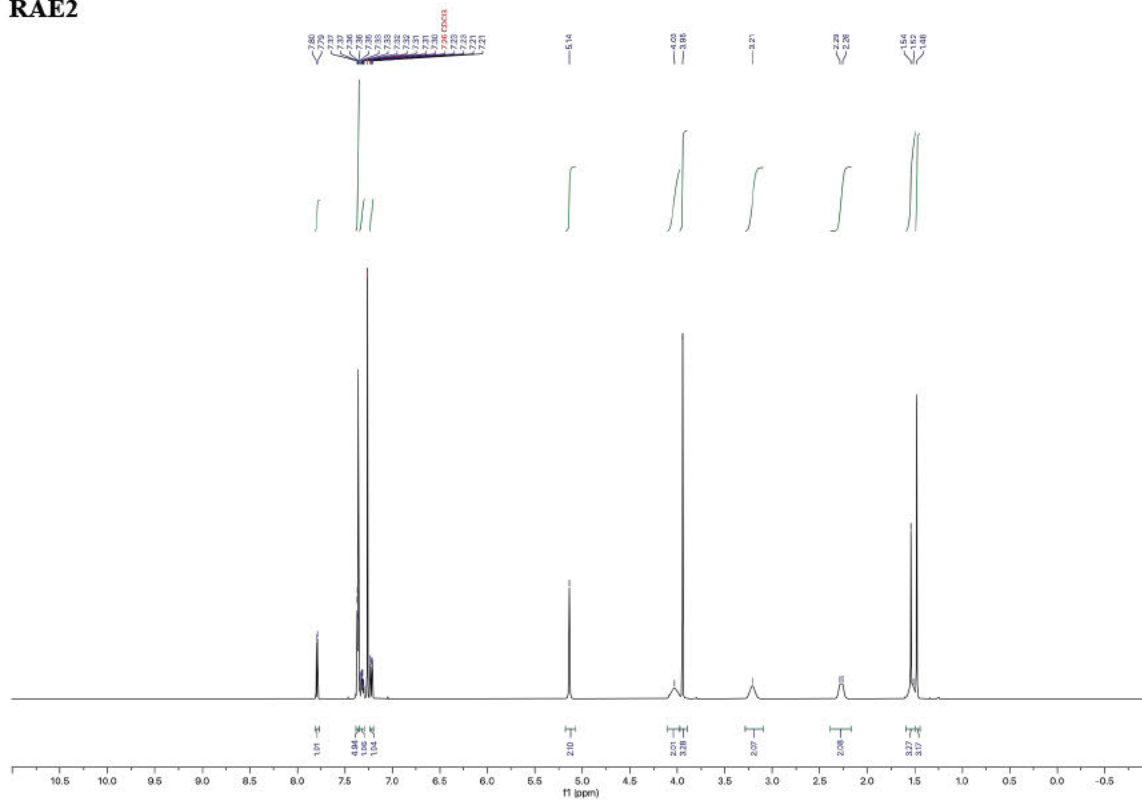
IR (film) ν_{max} 3404, 2931, 2243, 1924, 1677, 1632, 1589, 1495, 1424, 1366, 1236, 1154, 907, 727 cm^{-1}

RAE1

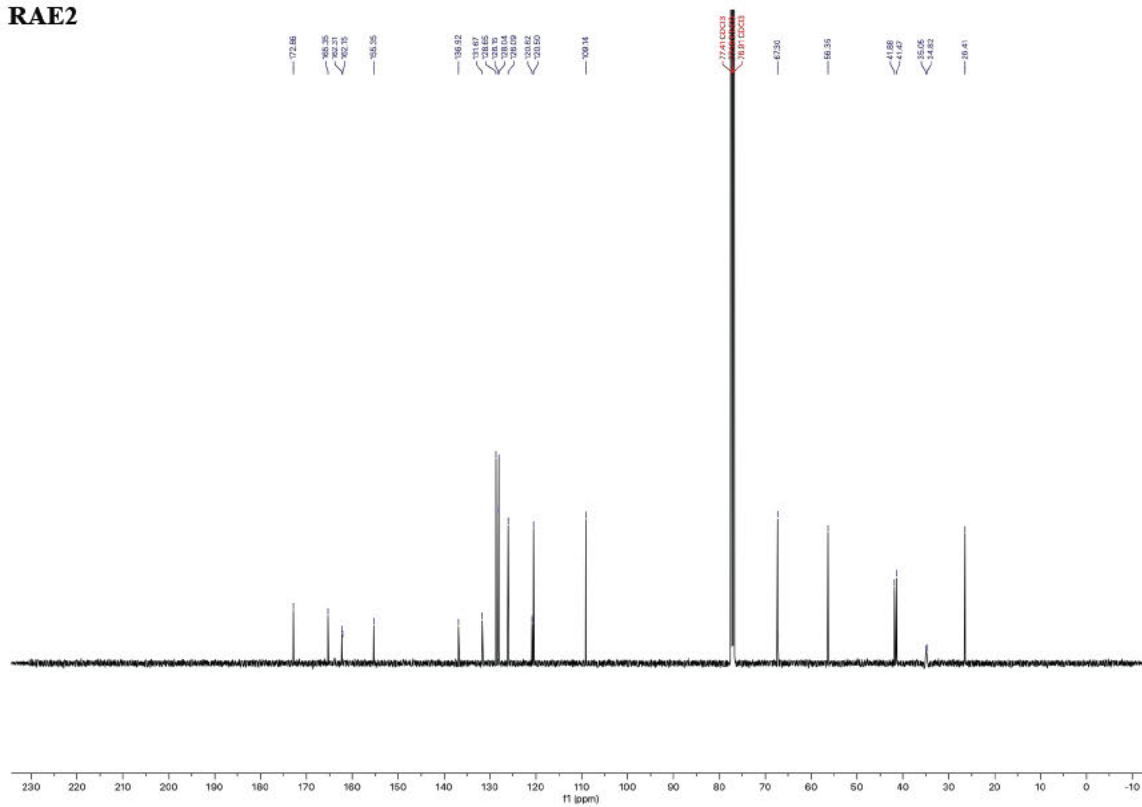
RAE1



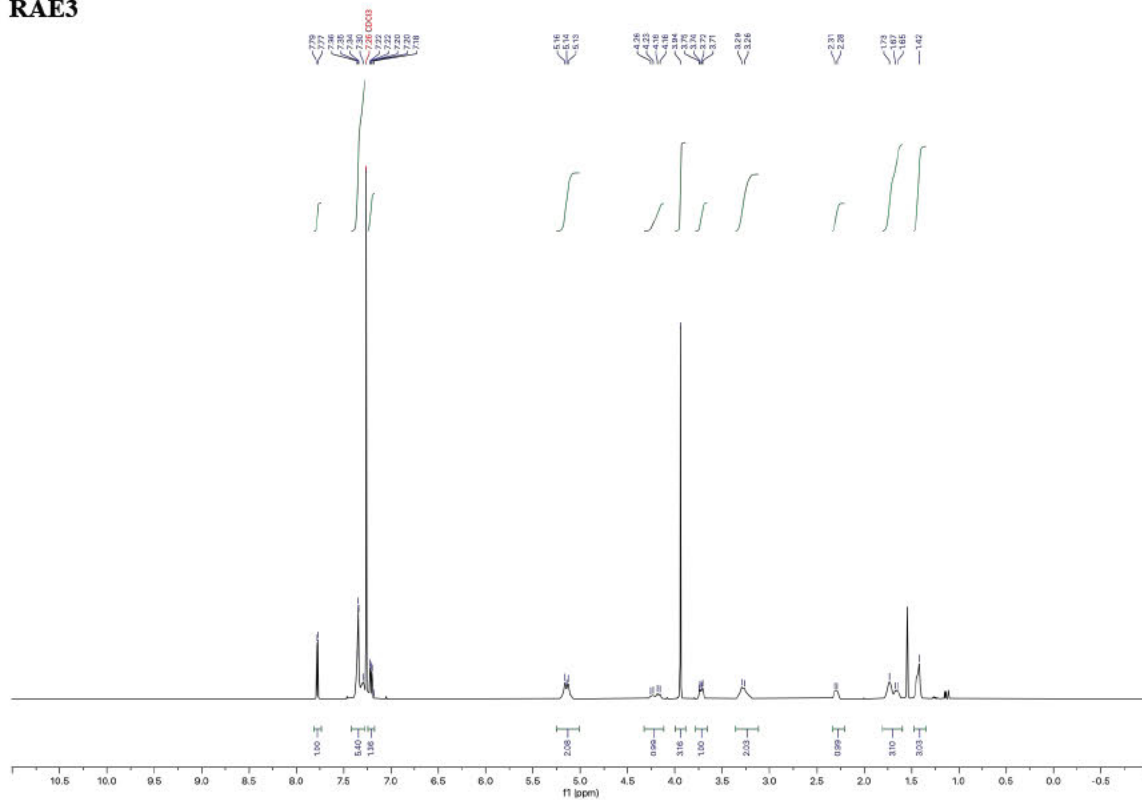
RAE2



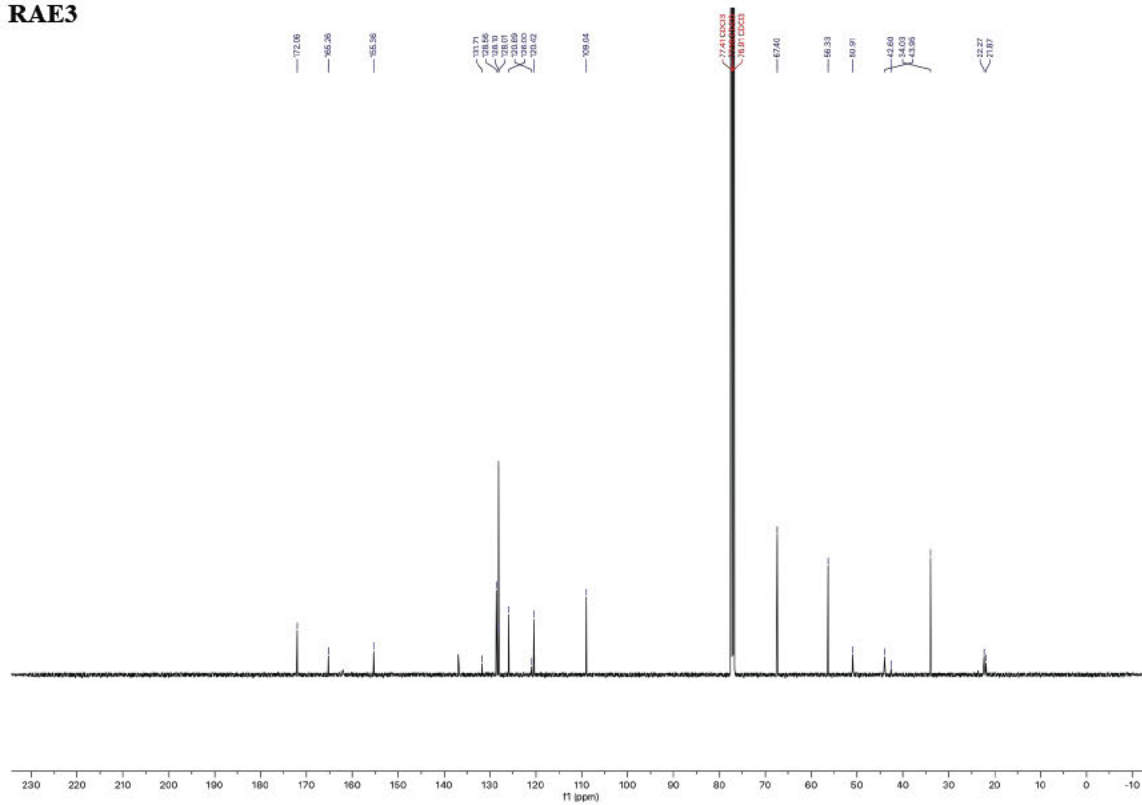
RAE2



RAE3



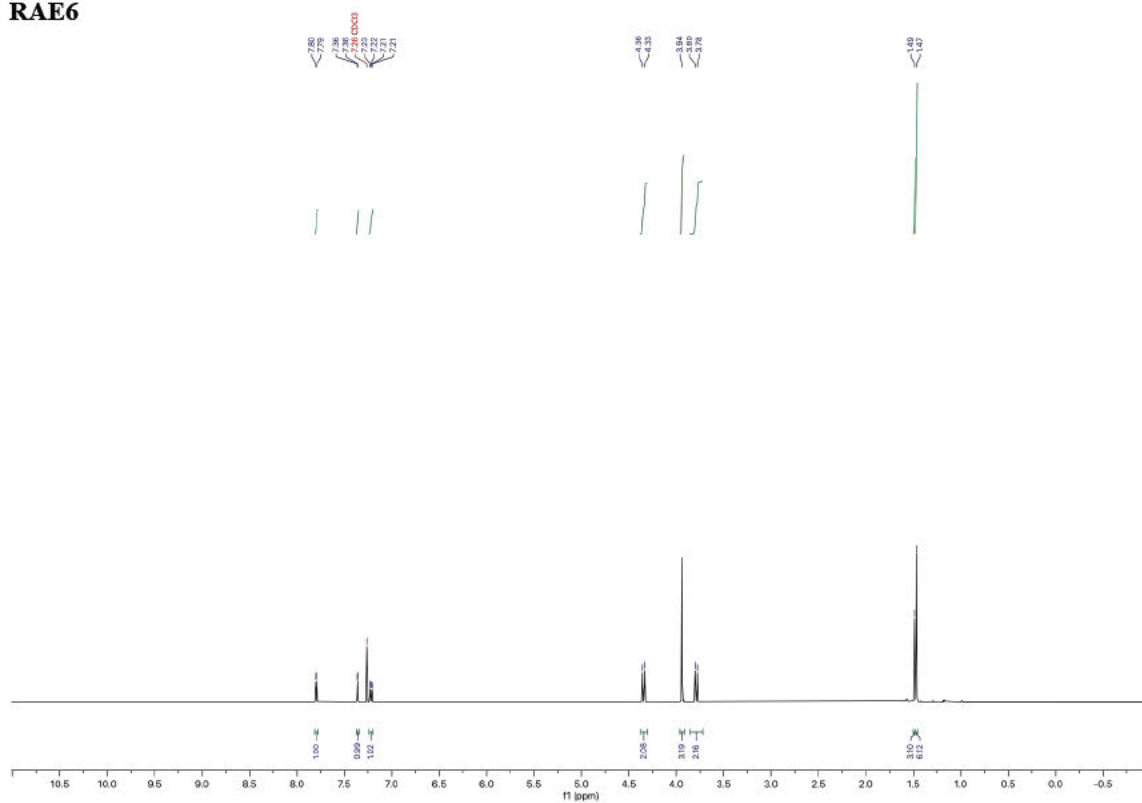
RAE3



10a

¹H NMR spectrum (CDCl₃) of compound **10a**. The spectrum displays peaks in the aromatic region (7.2-7.8 ppm), a methoxy singlet (3.8 ppm), and a methine doublet (1.5 ppm). Integration values are provided below the baseline. A chemical structure of **10a** is shown in the top right corner.

RAE6



RAE6

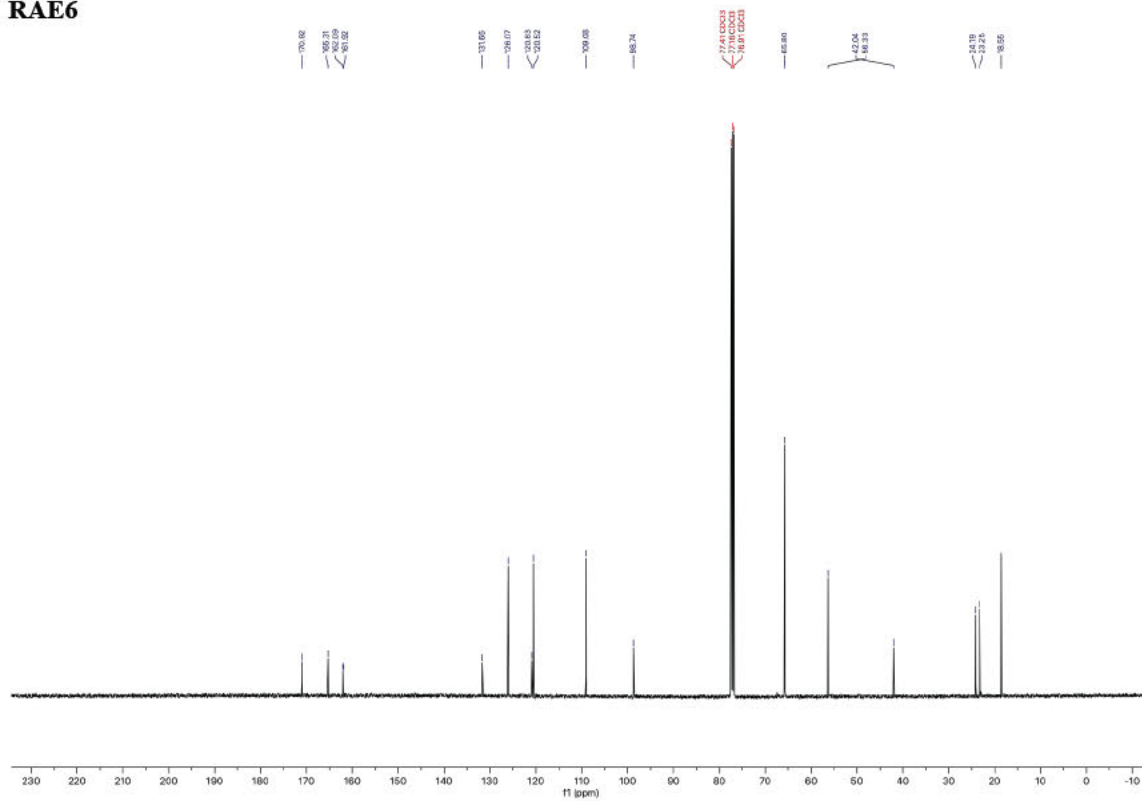
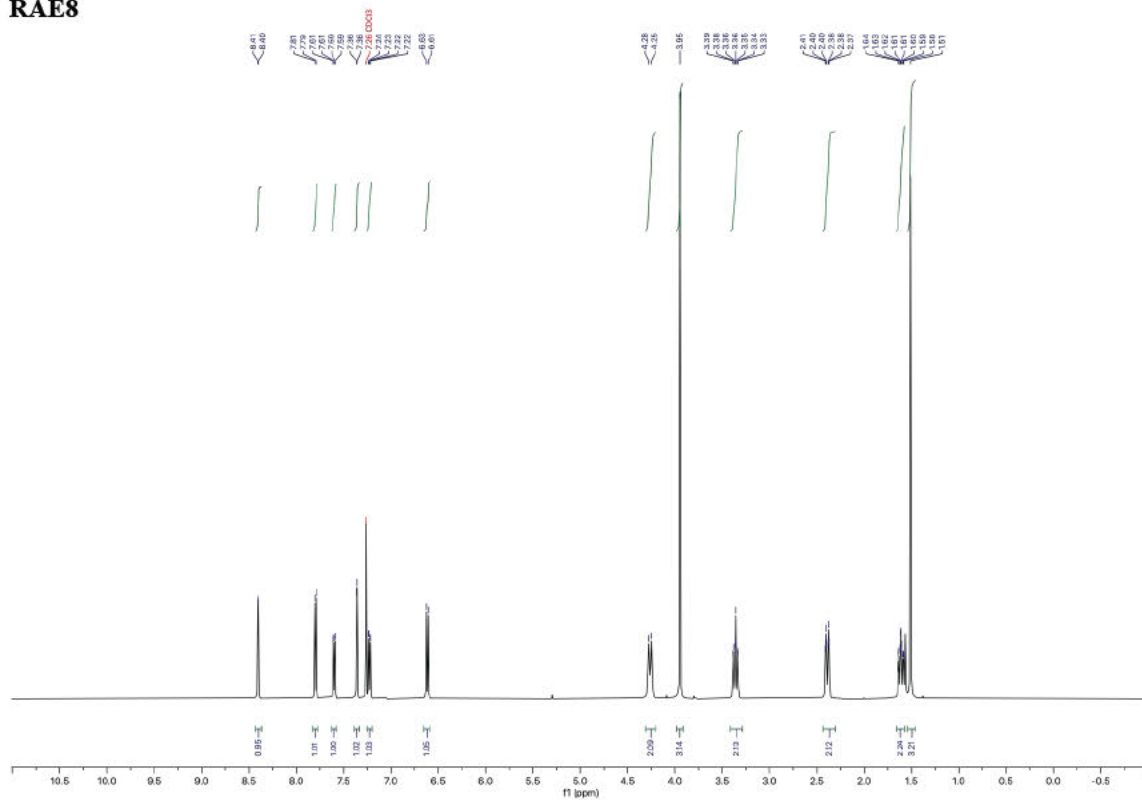


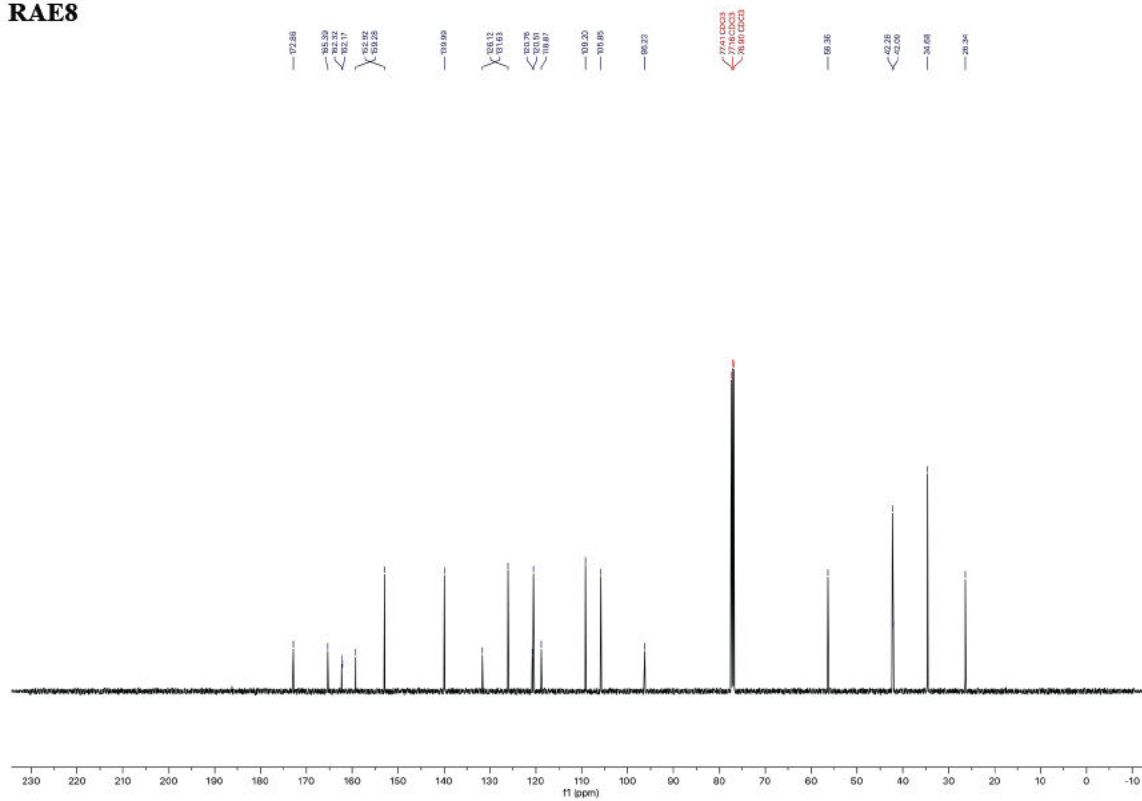
Figure 1: Phylogenetic tree of the 12S rDNA region. The tree shows relationships between various species, with bootstrap values indicated at the nodes. The tree is rooted at the bottom left and branches out to the right. The species names are listed at the tips of the branches. The tree is divided into several major clades, with some clades highlighted in red and others in blue. The red clade includes species like *C. (C. 12S)* and *C. (C. 12S)*. The blue clade includes species like *C. (C. 12S)* and *C. (C. 12S)*. The tree is a maximum likelihood tree based on 12S rDNA sequences.



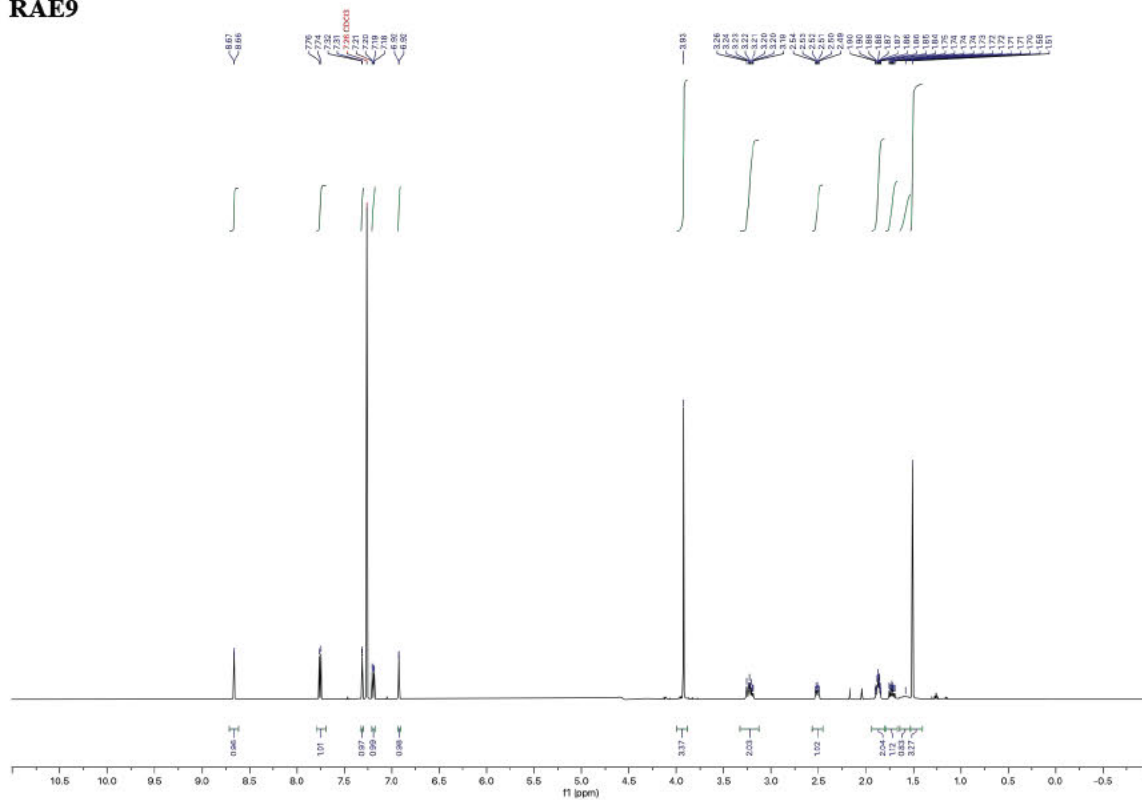
RAE8



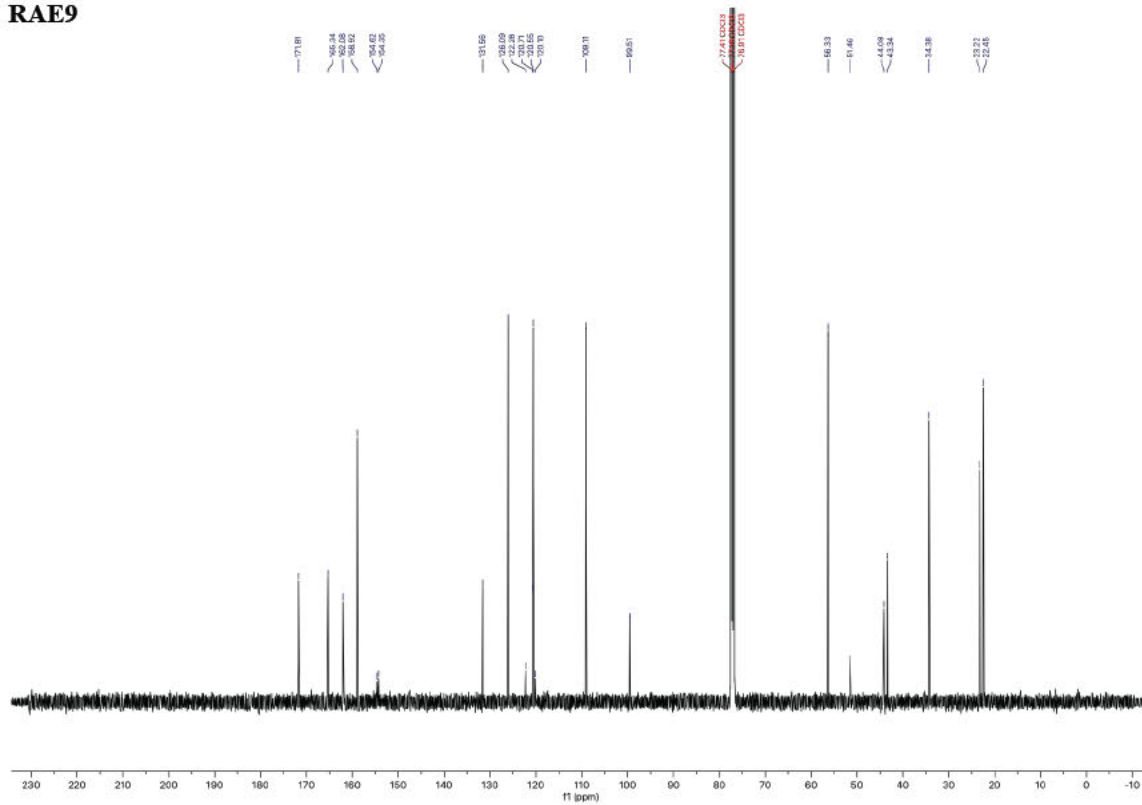
RAE8



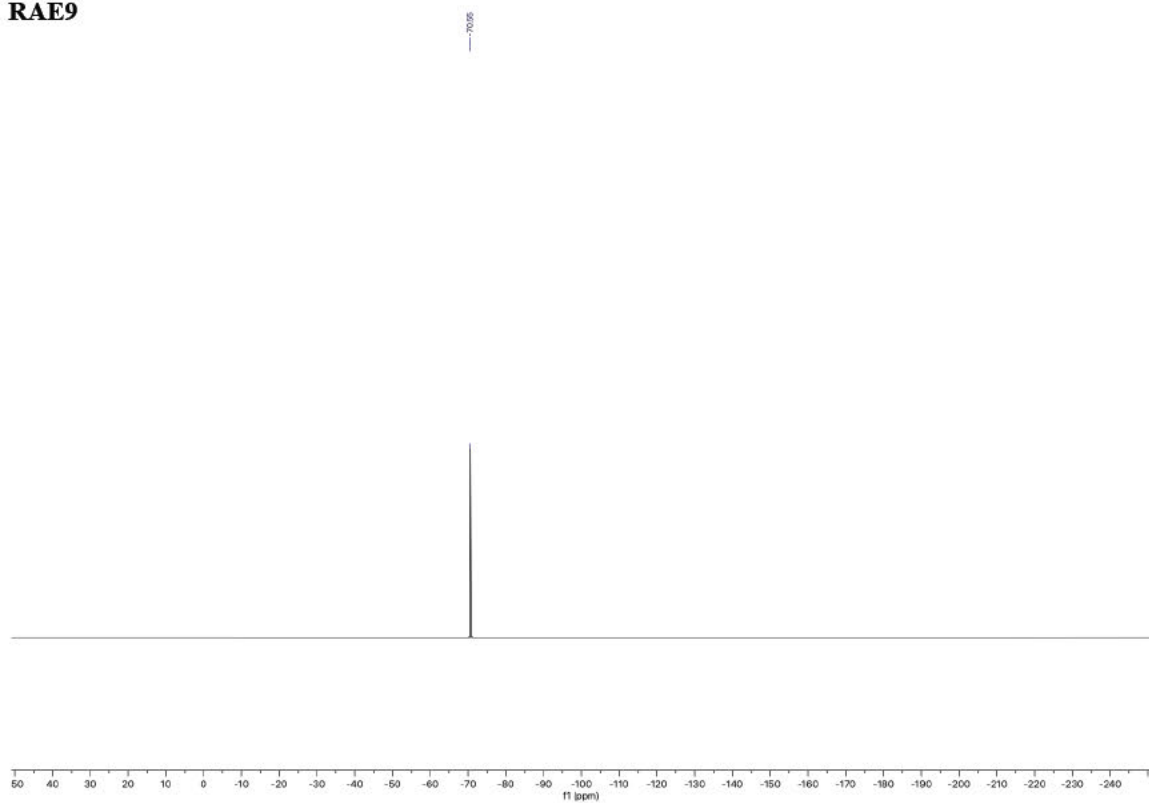
RAE9



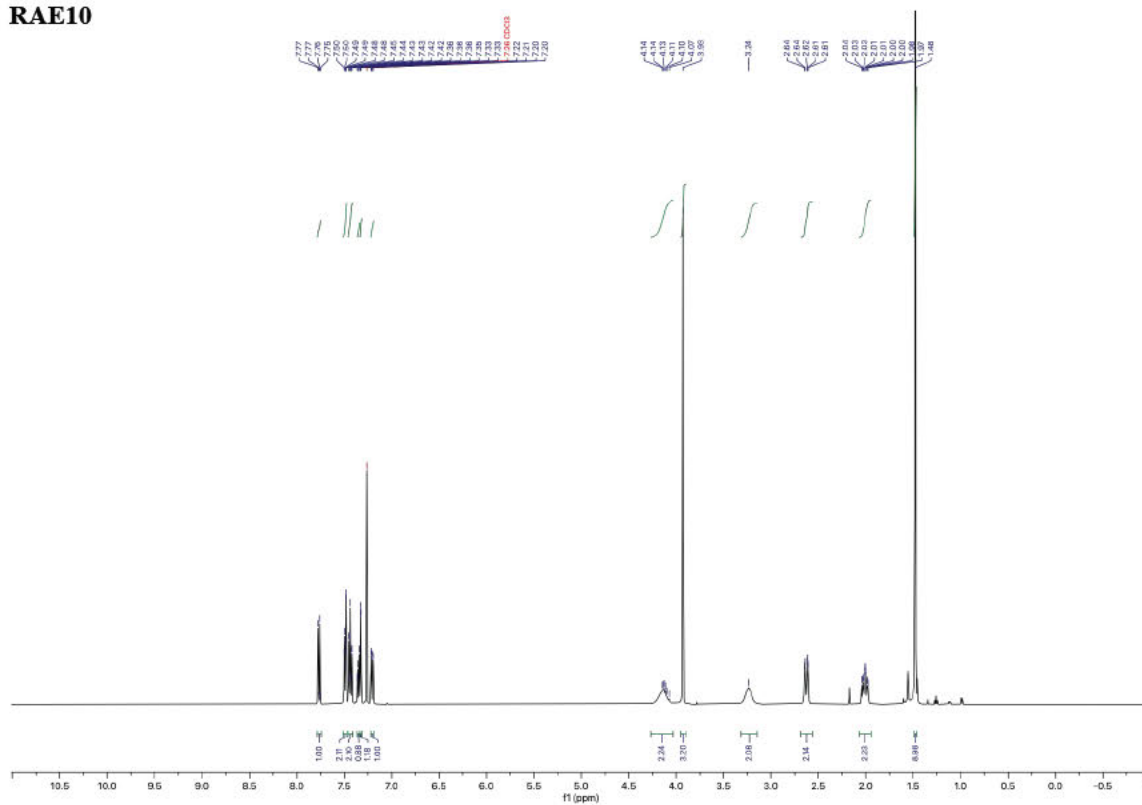
RAE9



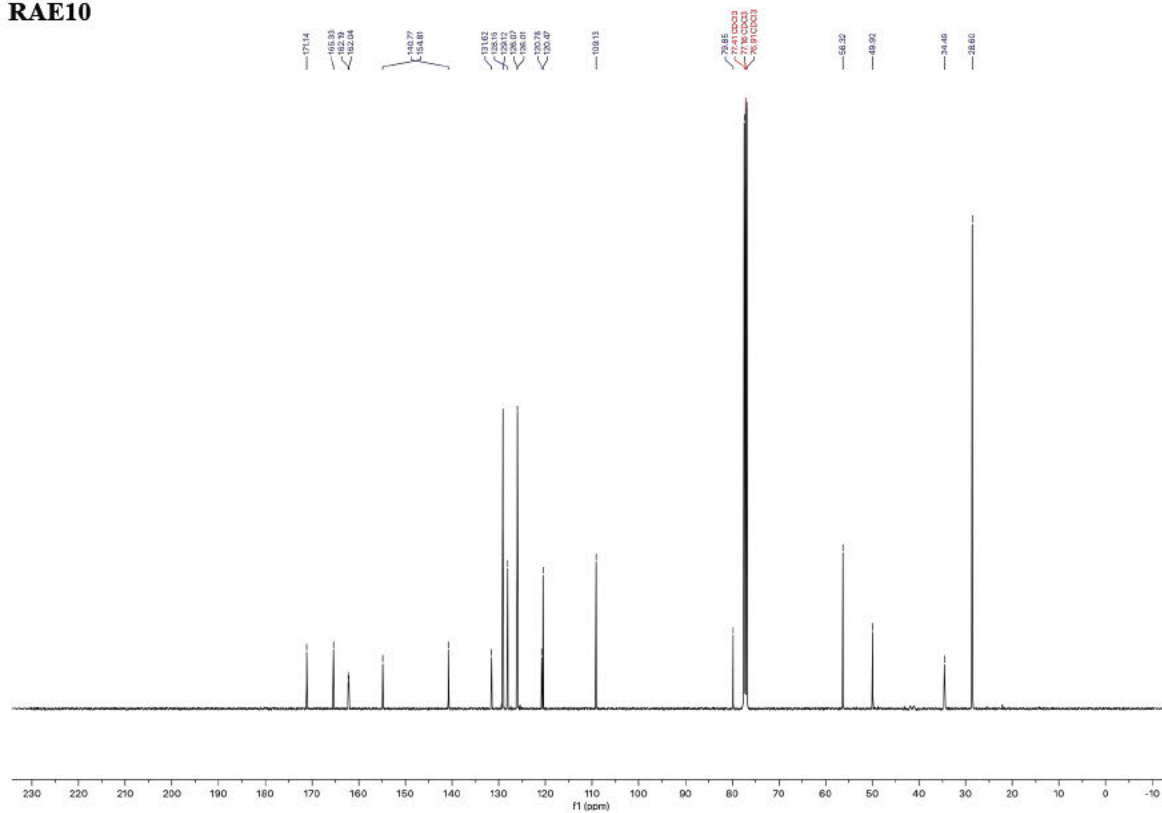
RAE9

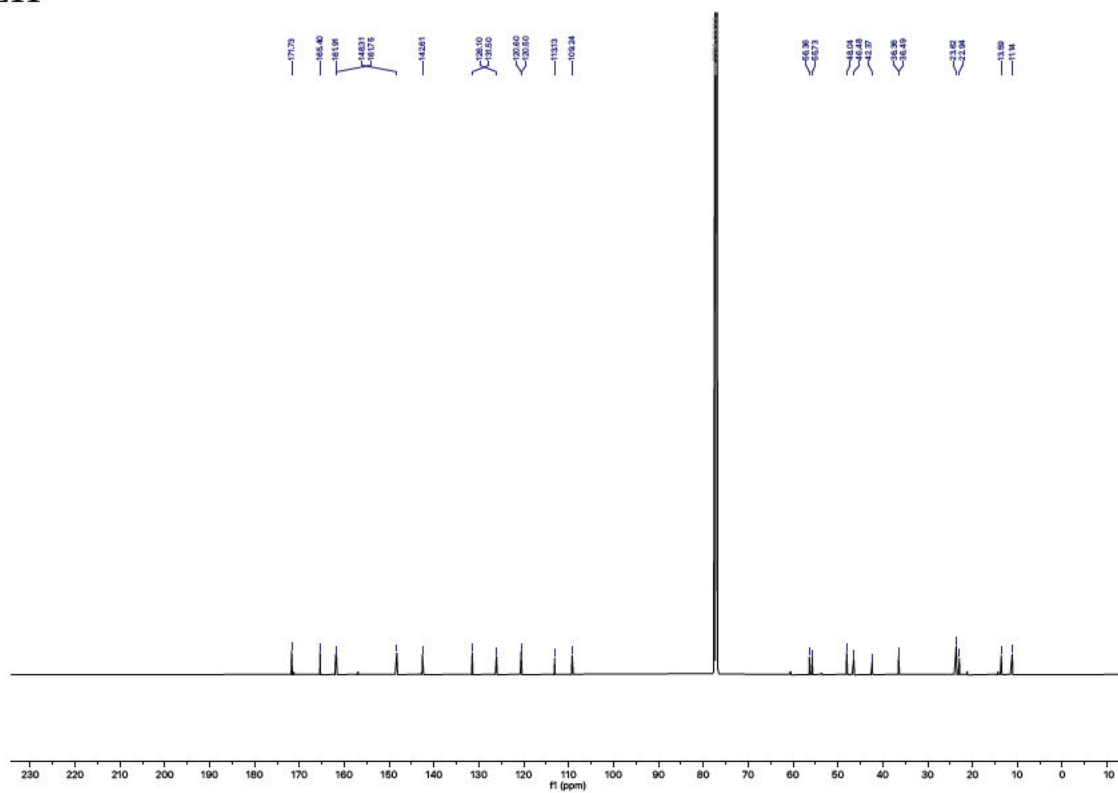


RAE10

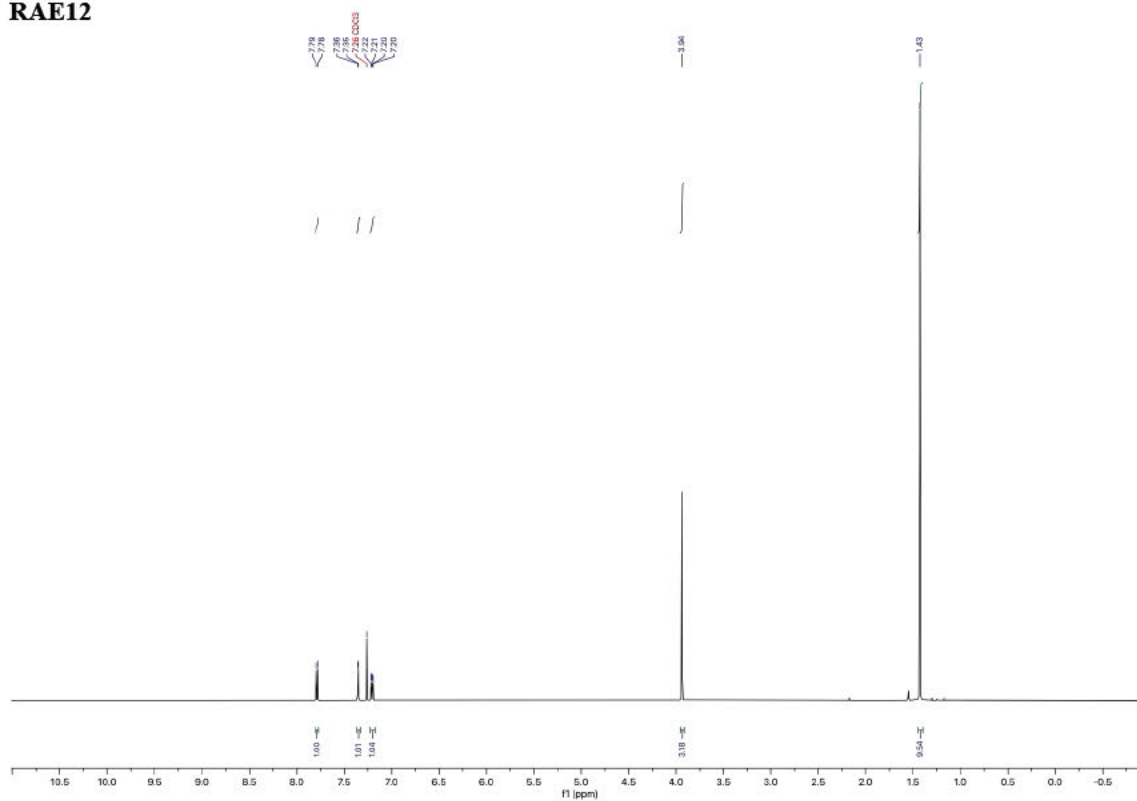


RAE10

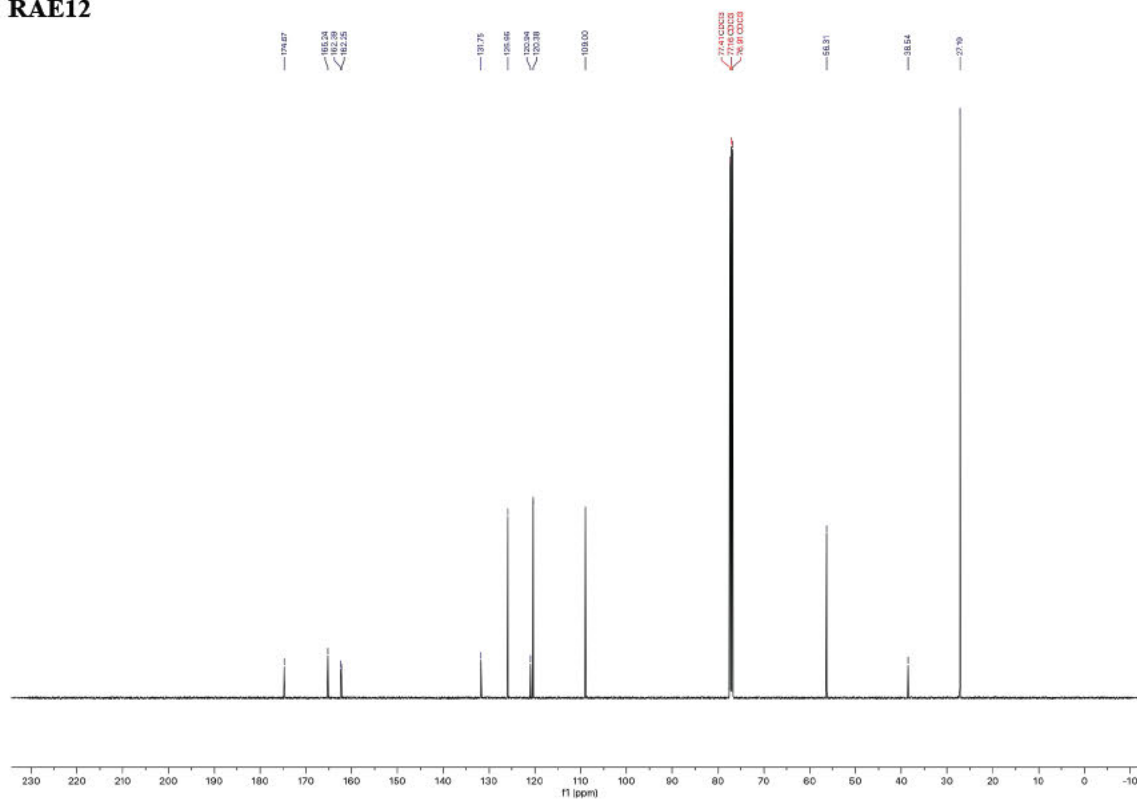


RAE11

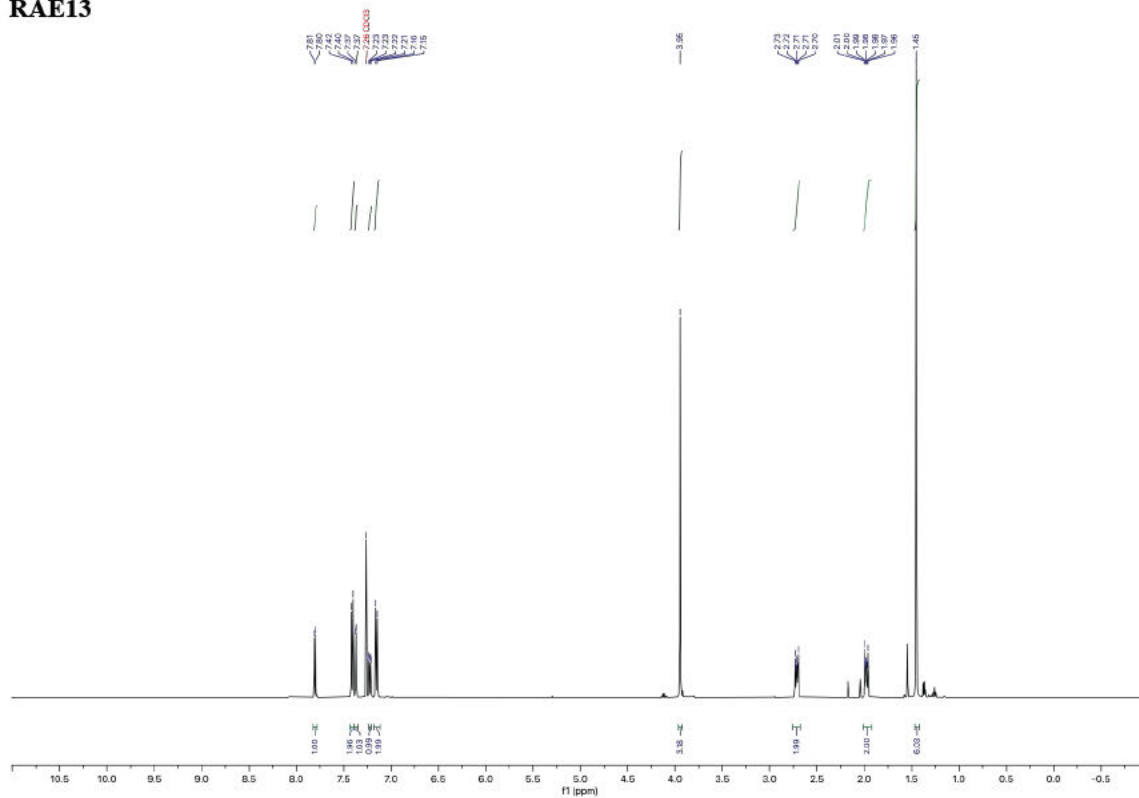
RAE12



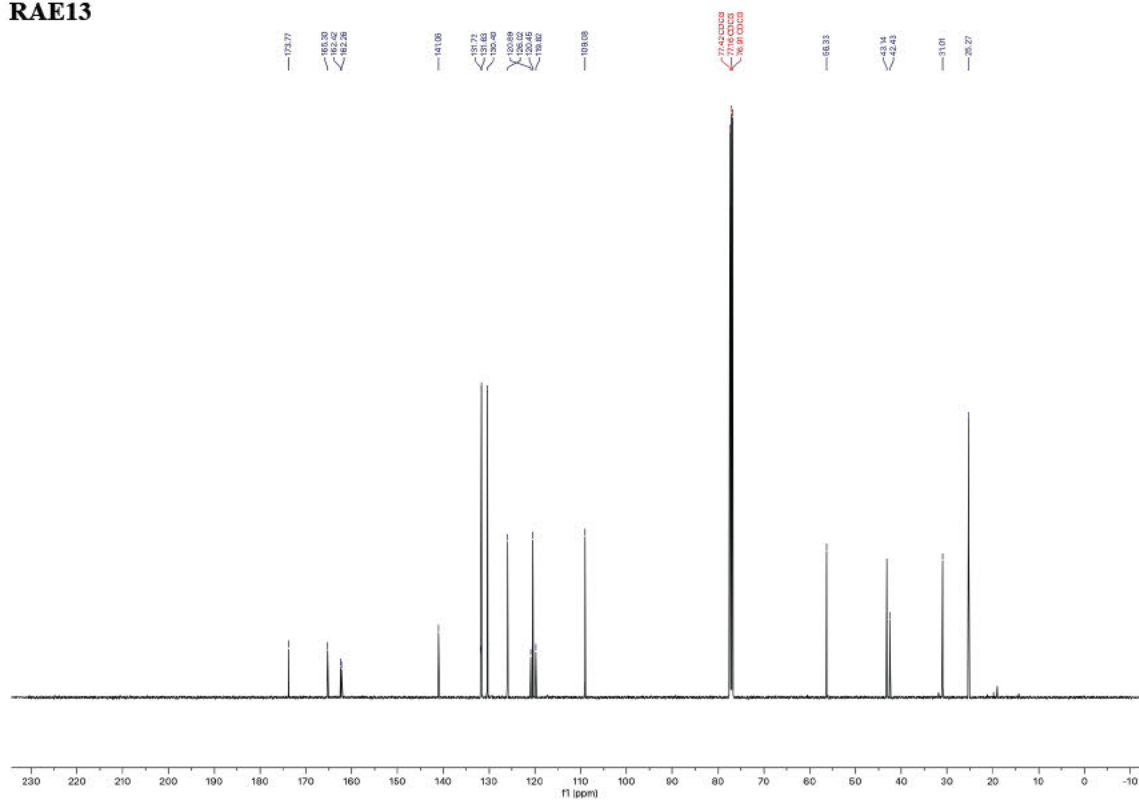
RAE12



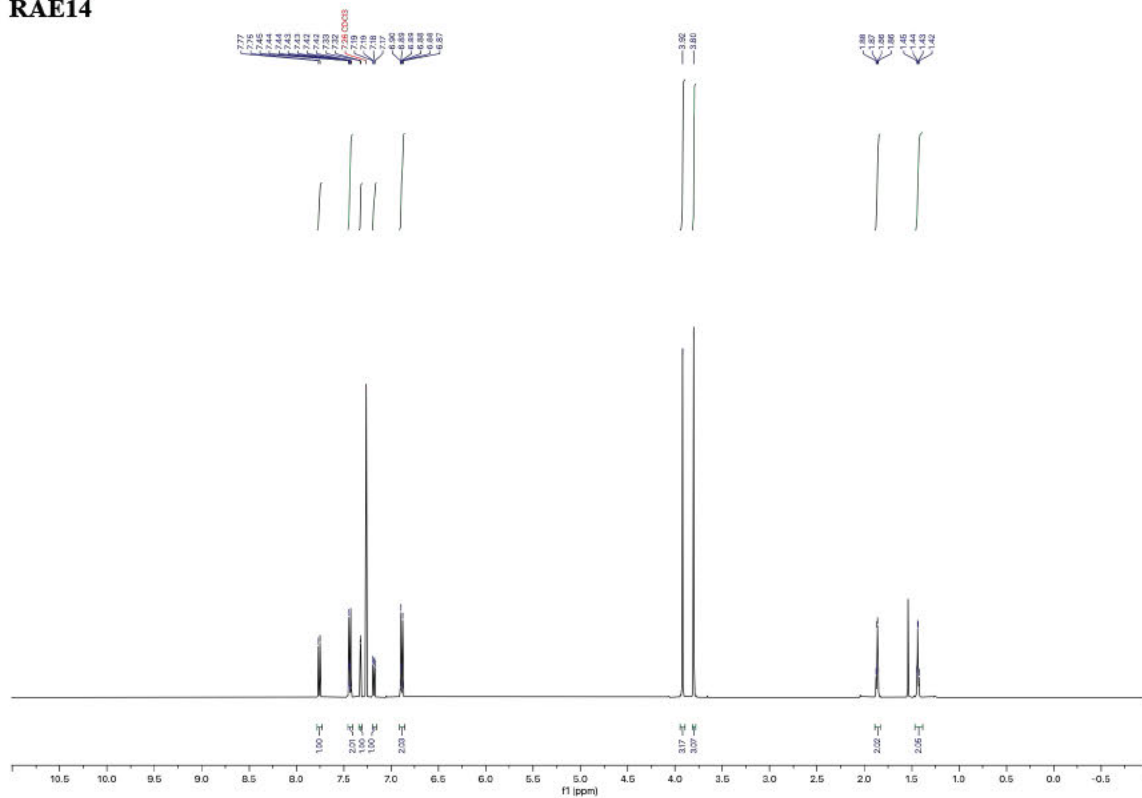
RAE13



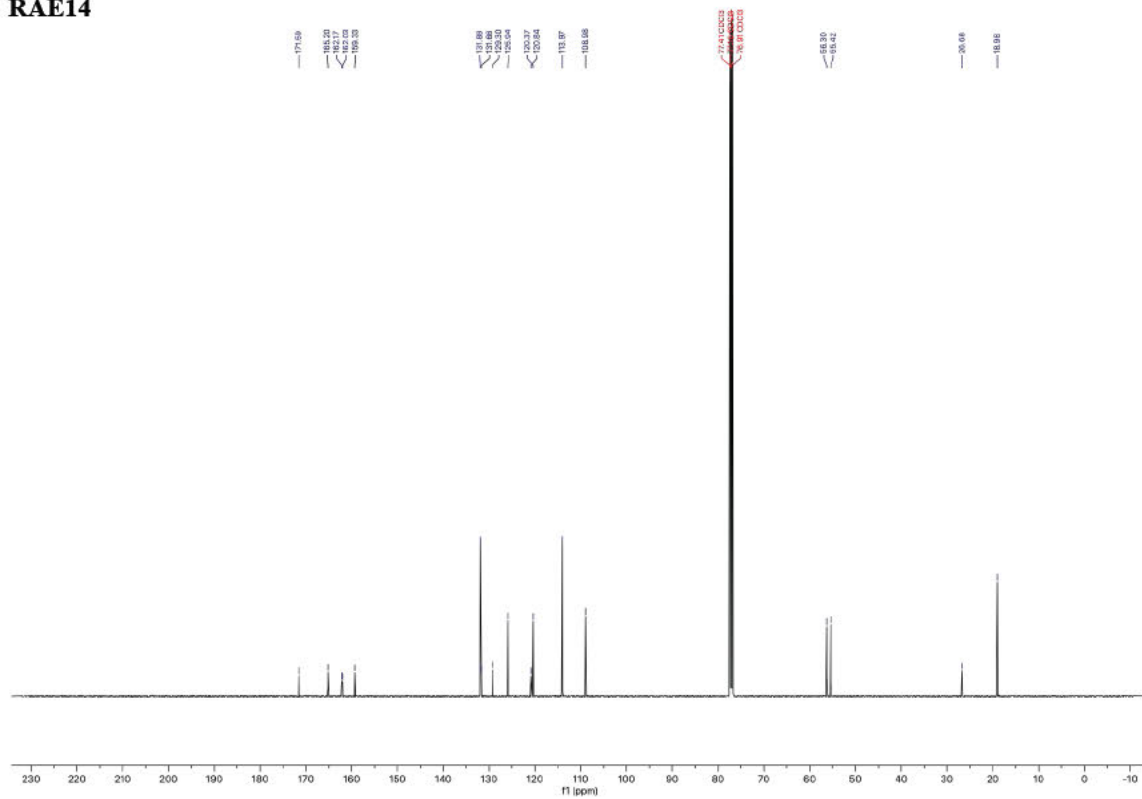
RAE13



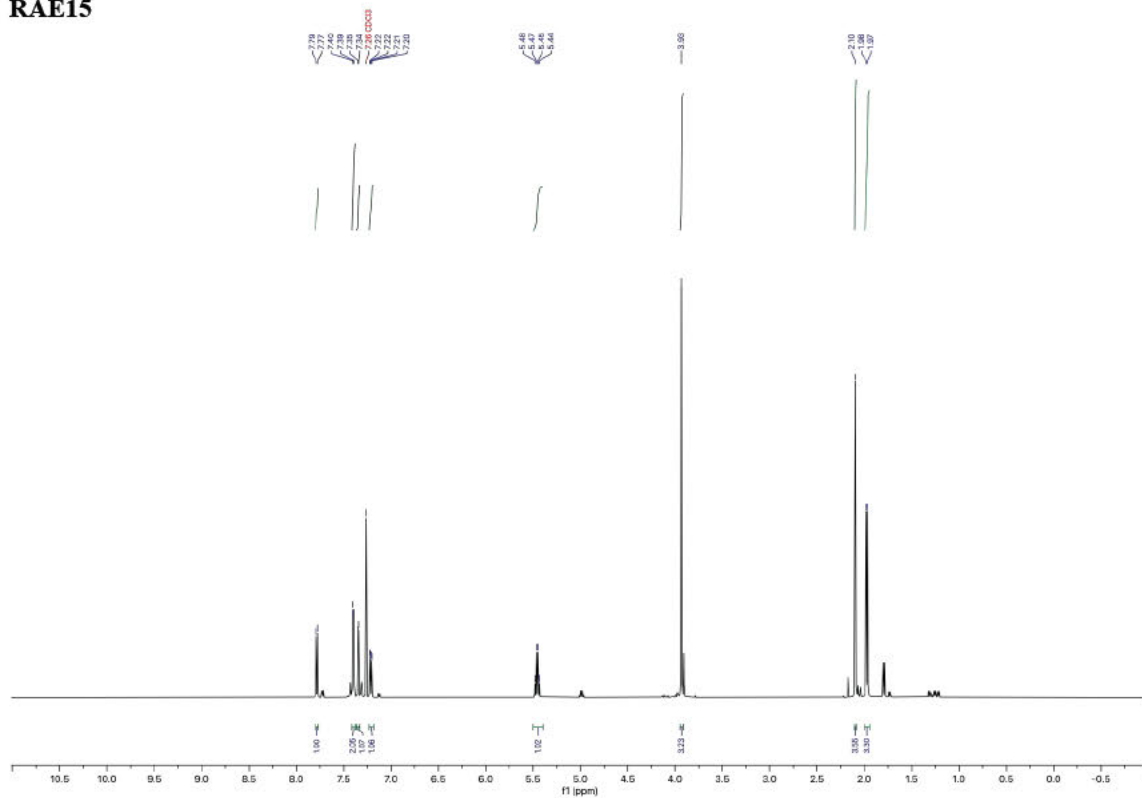
RAE14



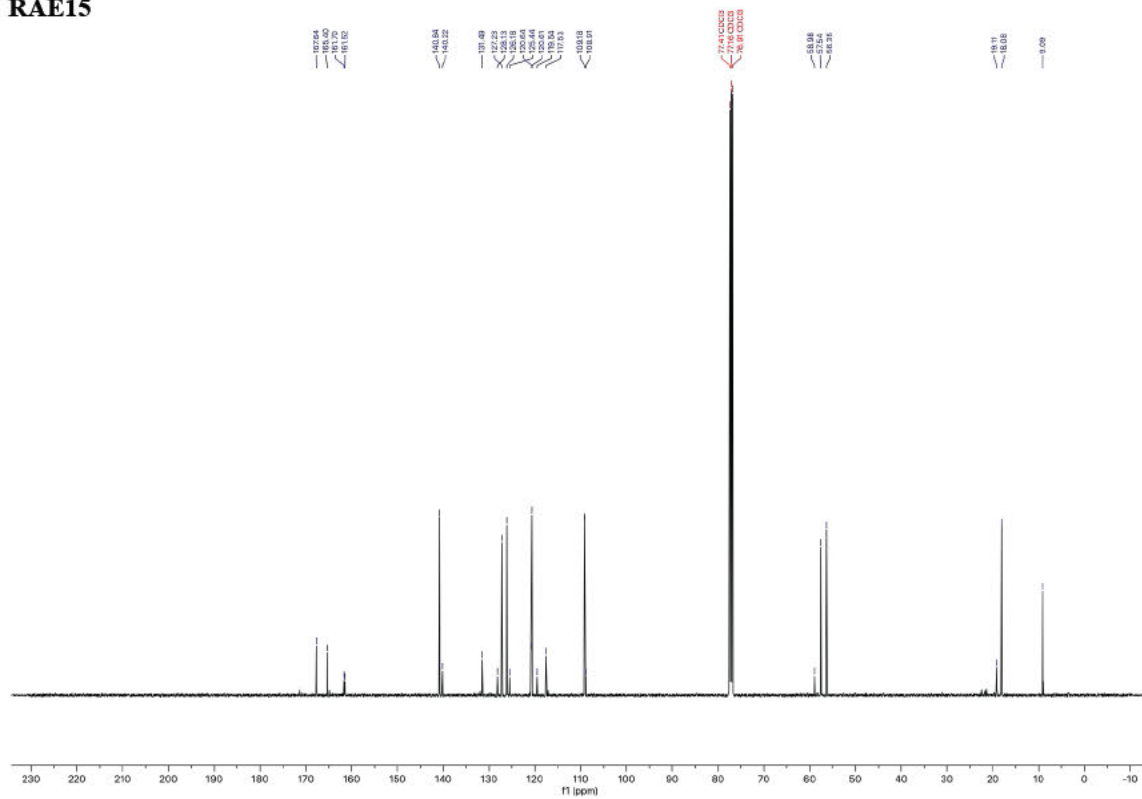
RAE14



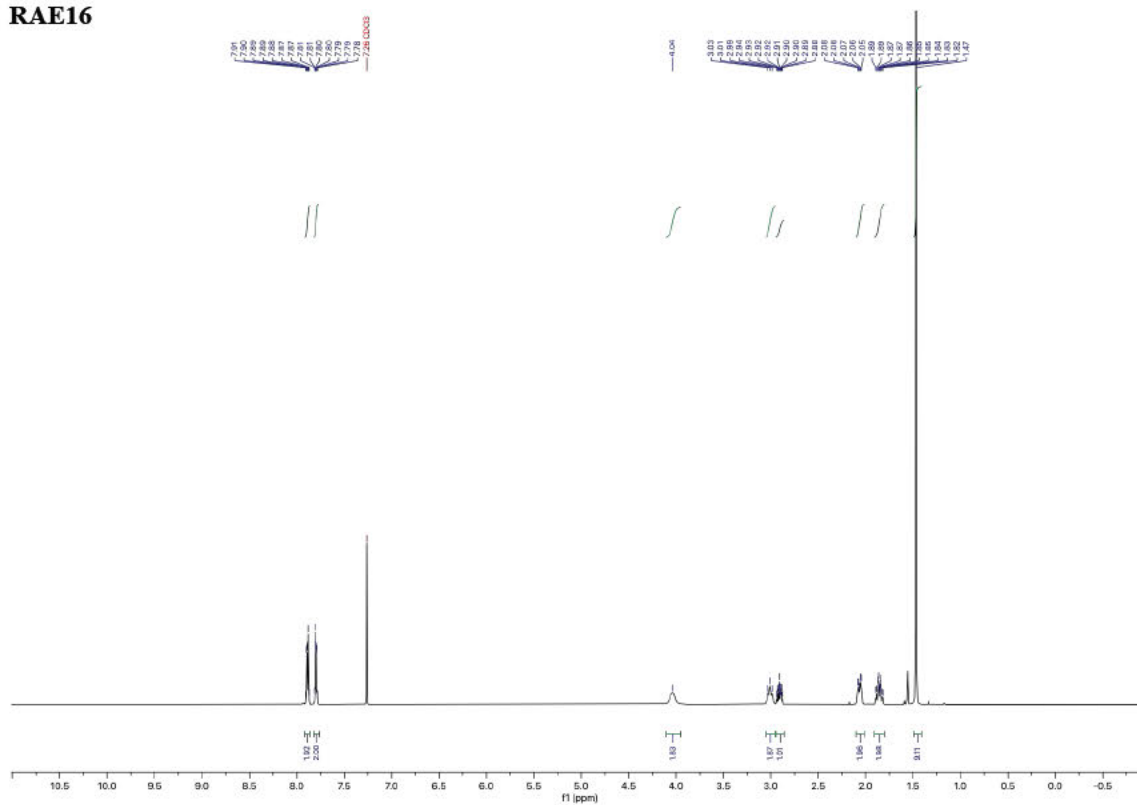
RAE15



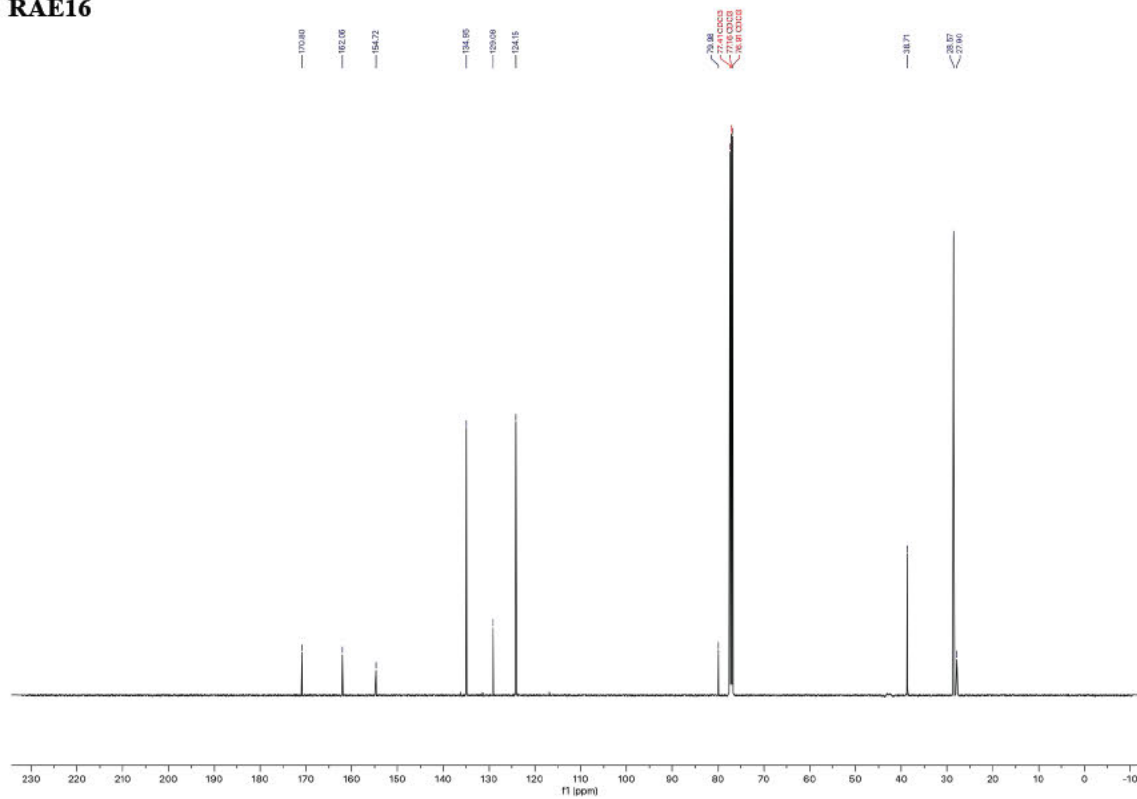
RAE15



RAE16



RAE16



[illegible][illegible]

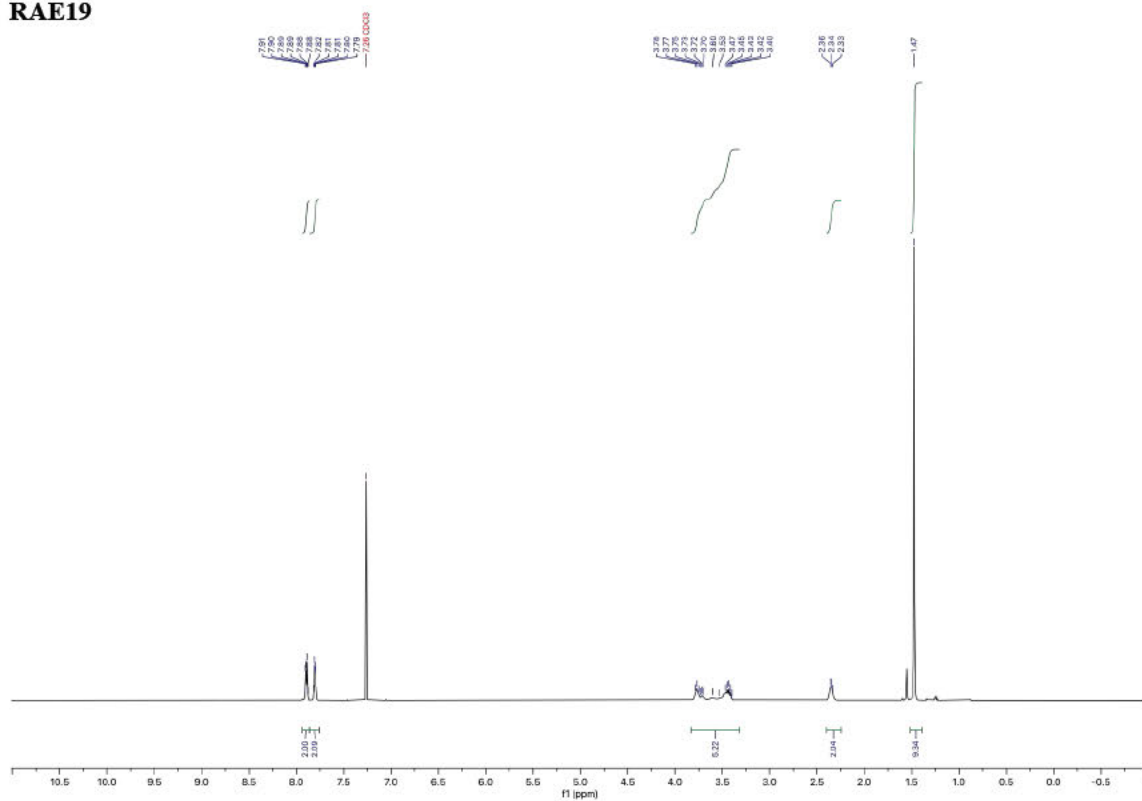
[illegible]

RAE18

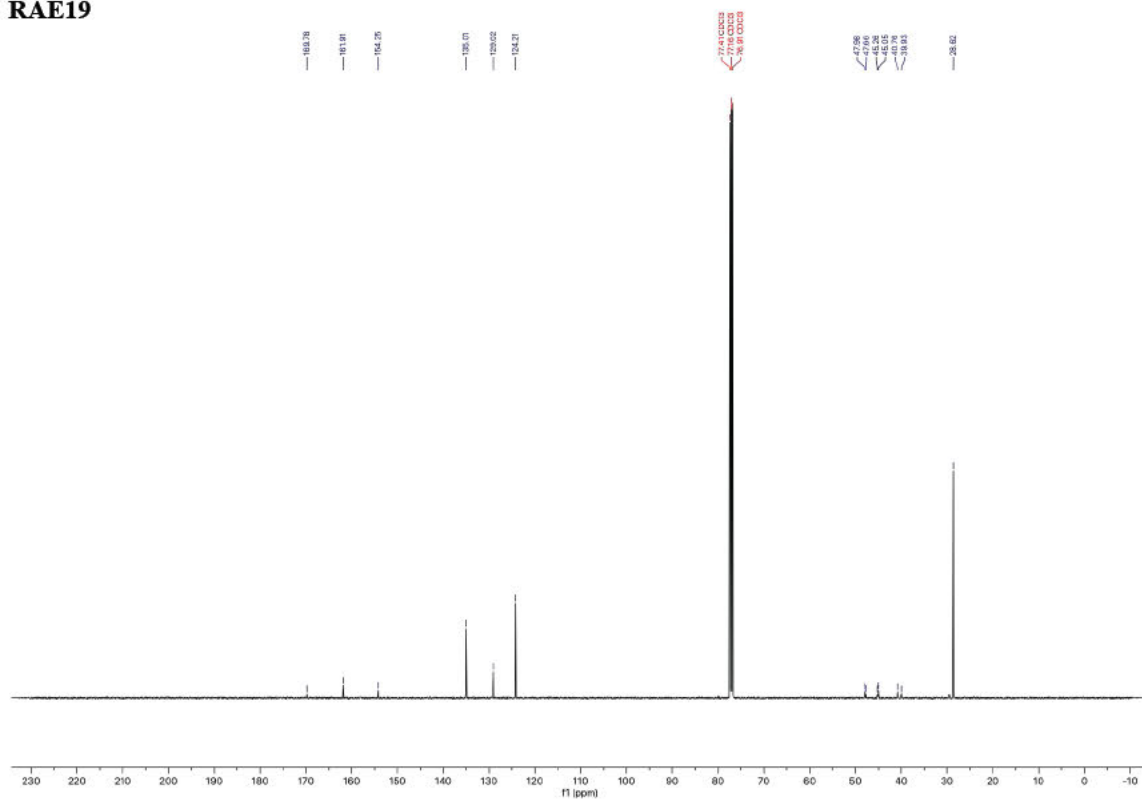
171.17
162.06
162.06
162.06
134.93
129.67
124.14
76.82
53.10
52.46
32.06
28.94

ppm

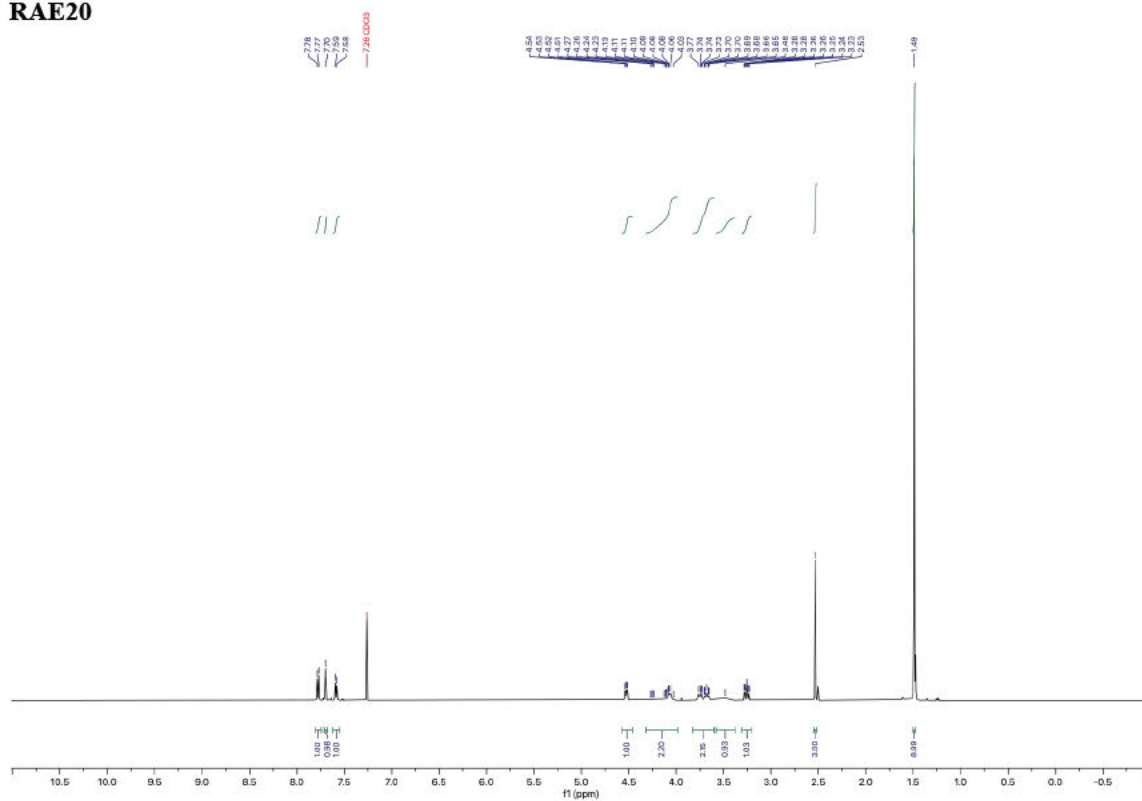
RAE19



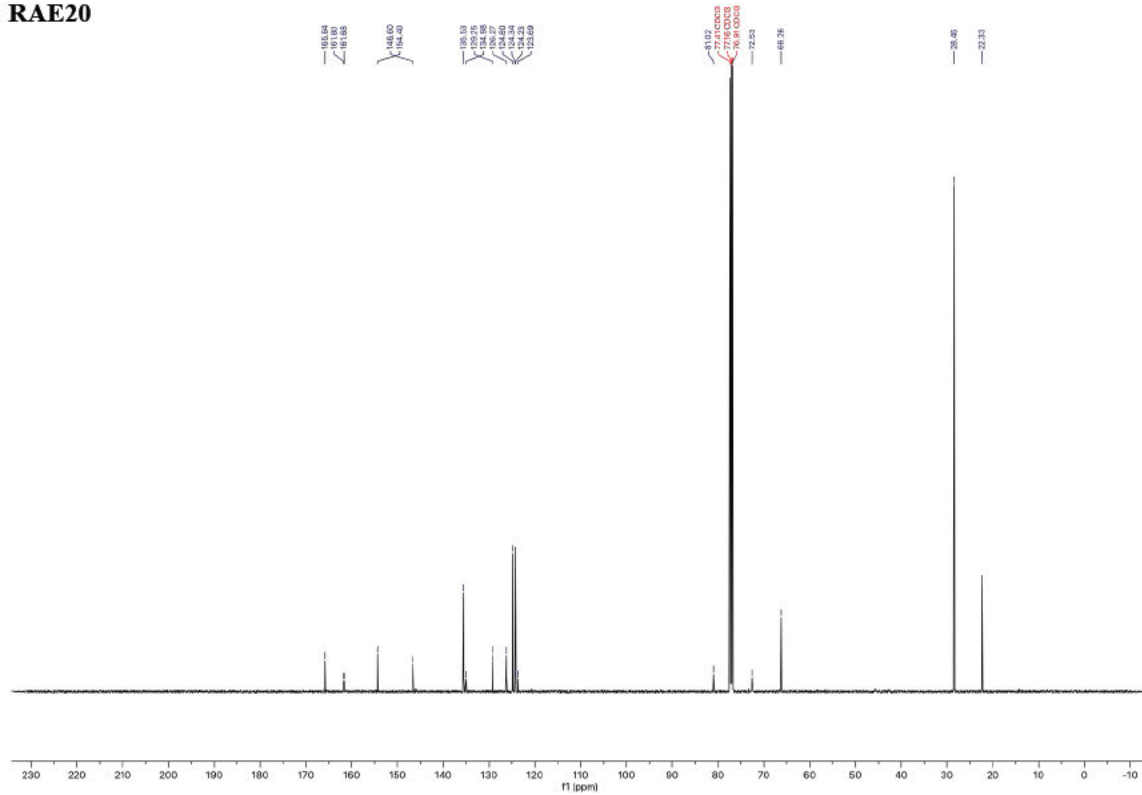
RAE19



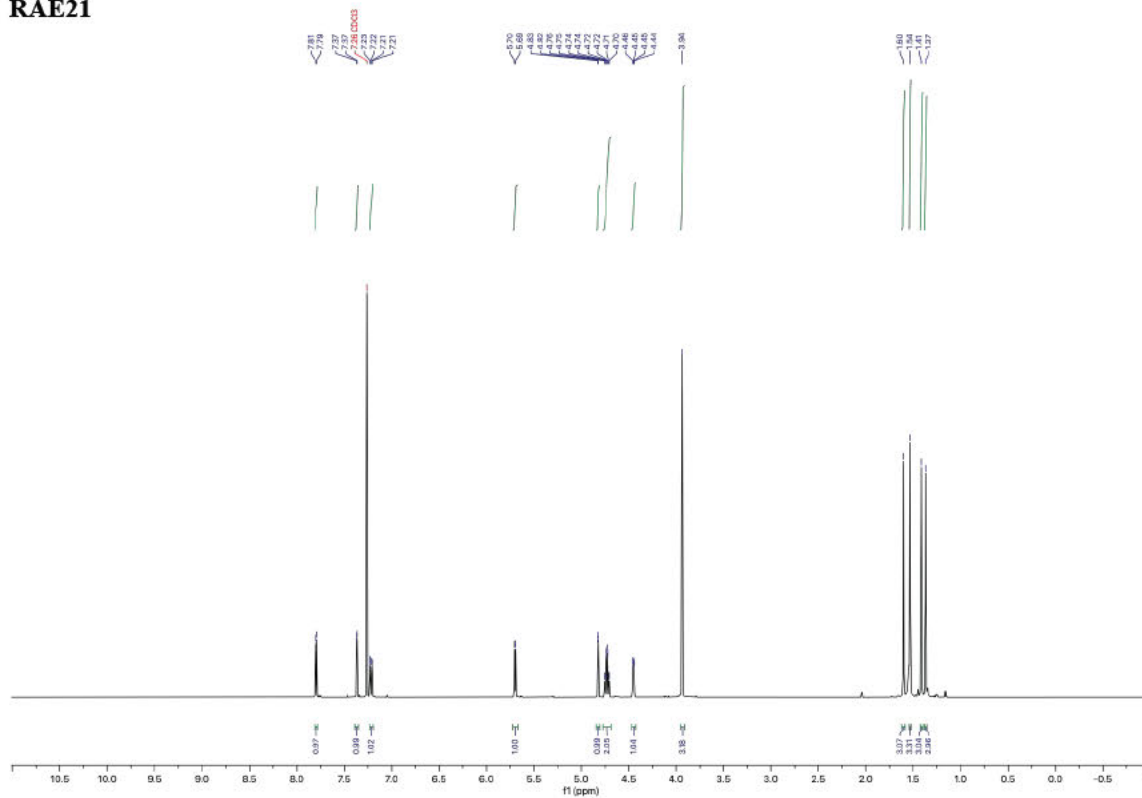
RAE20



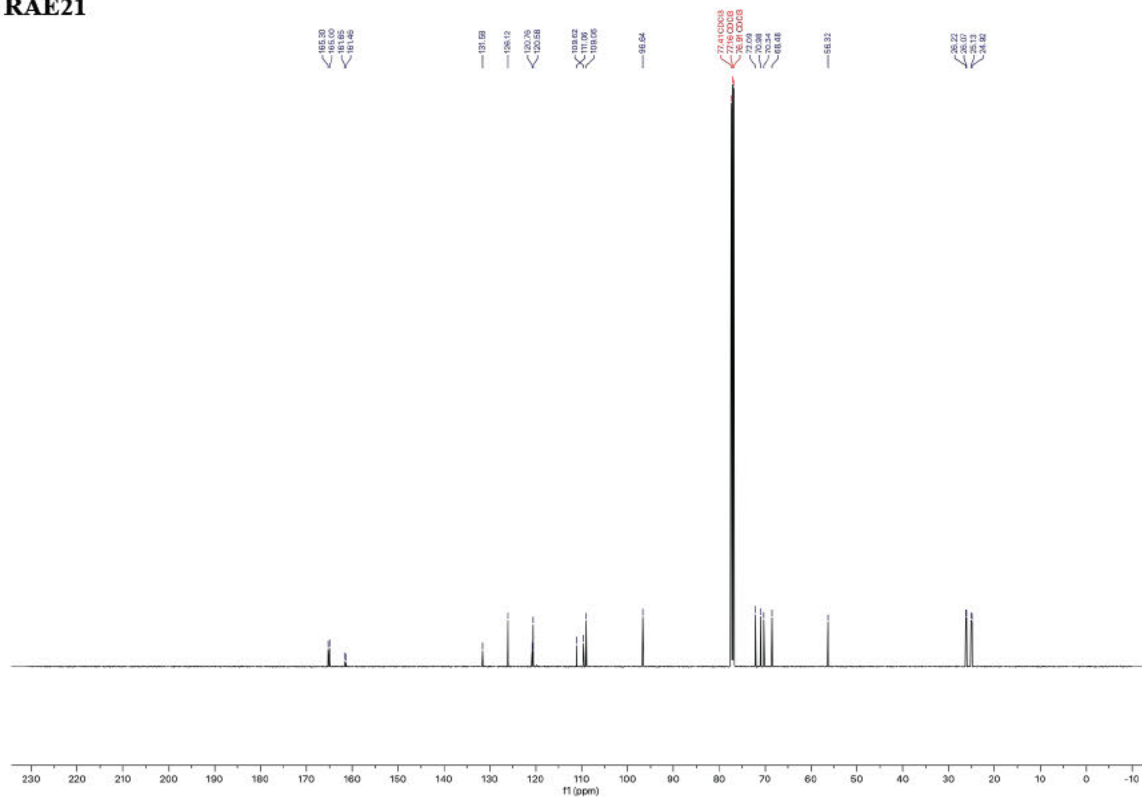
RAE20



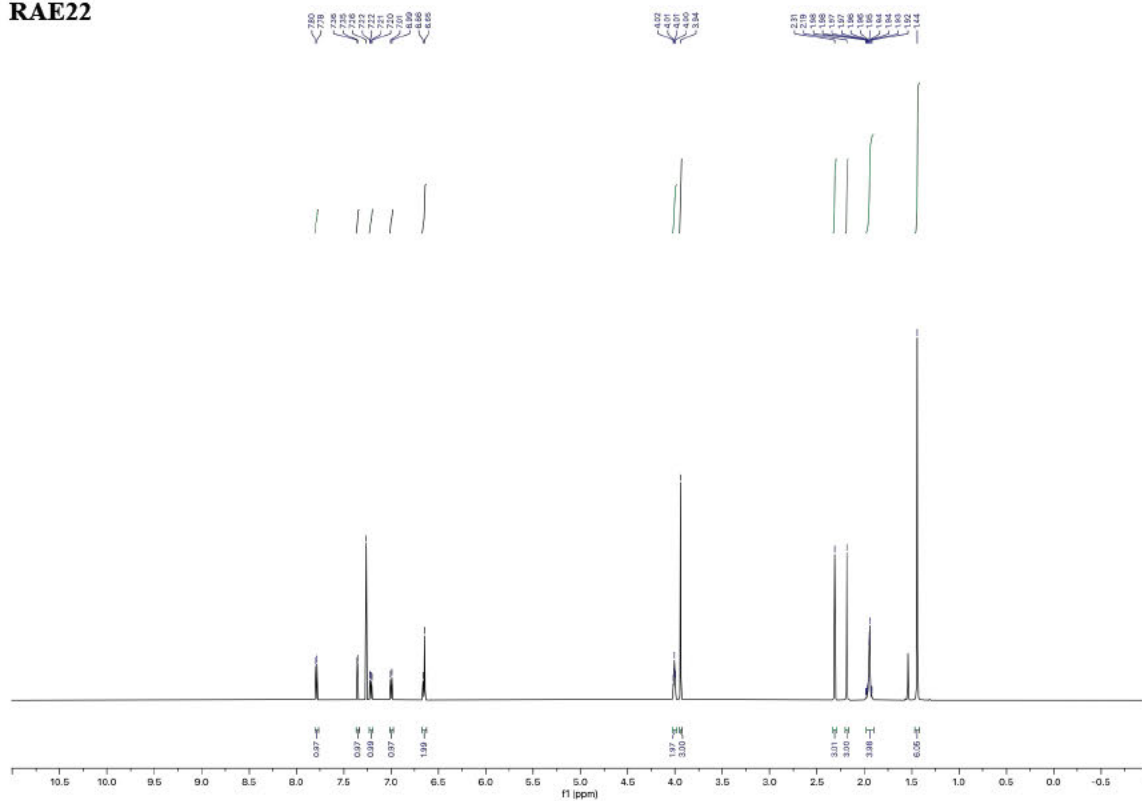
RAE21



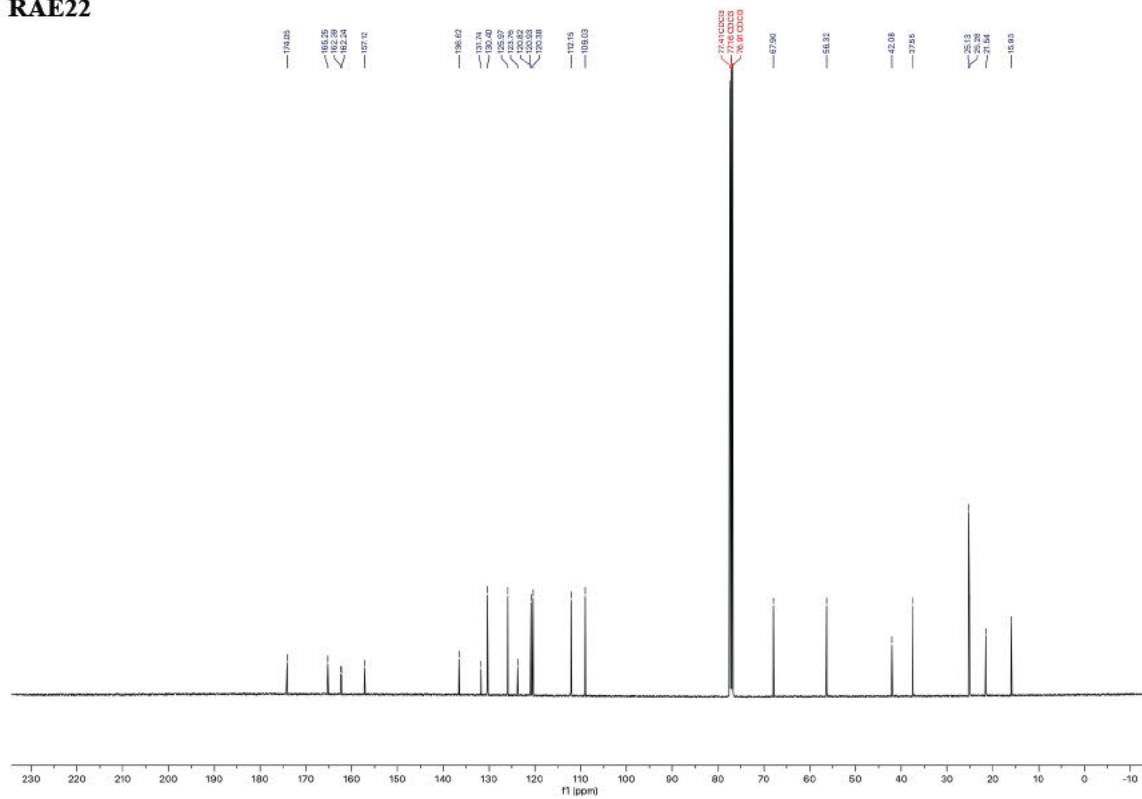
RAE21

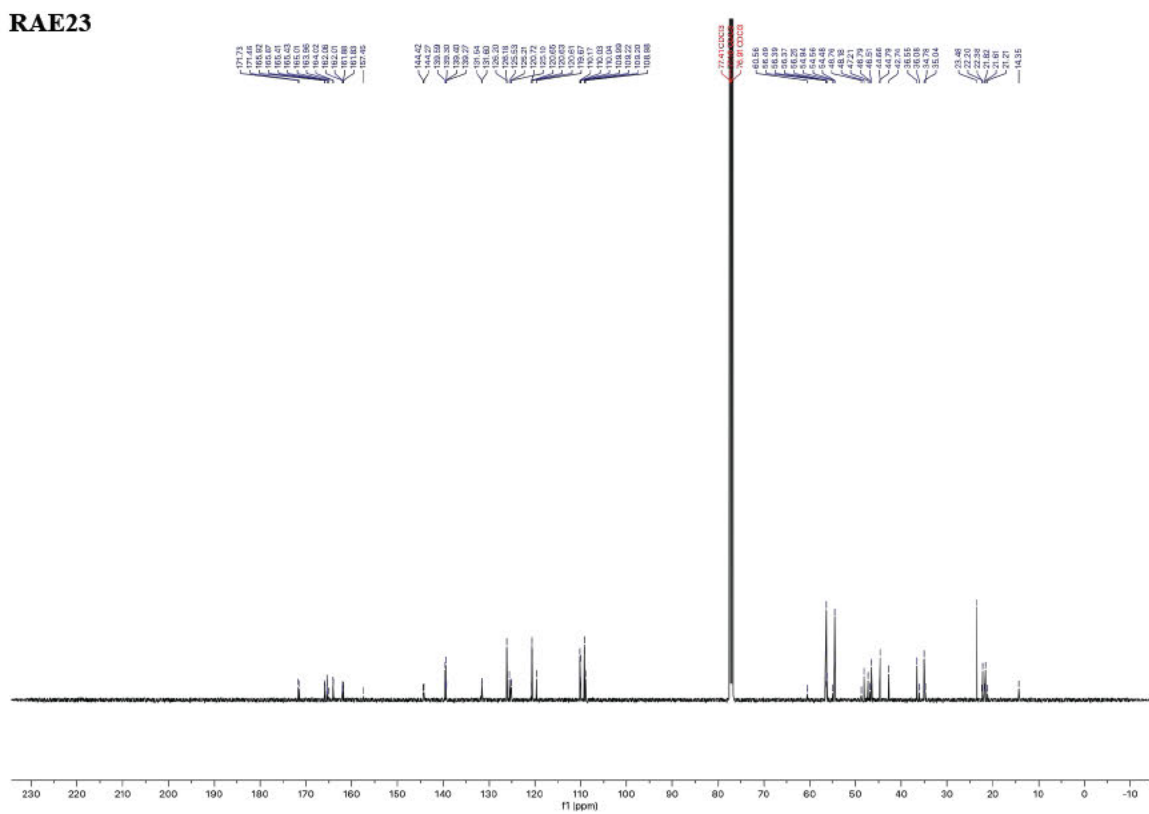
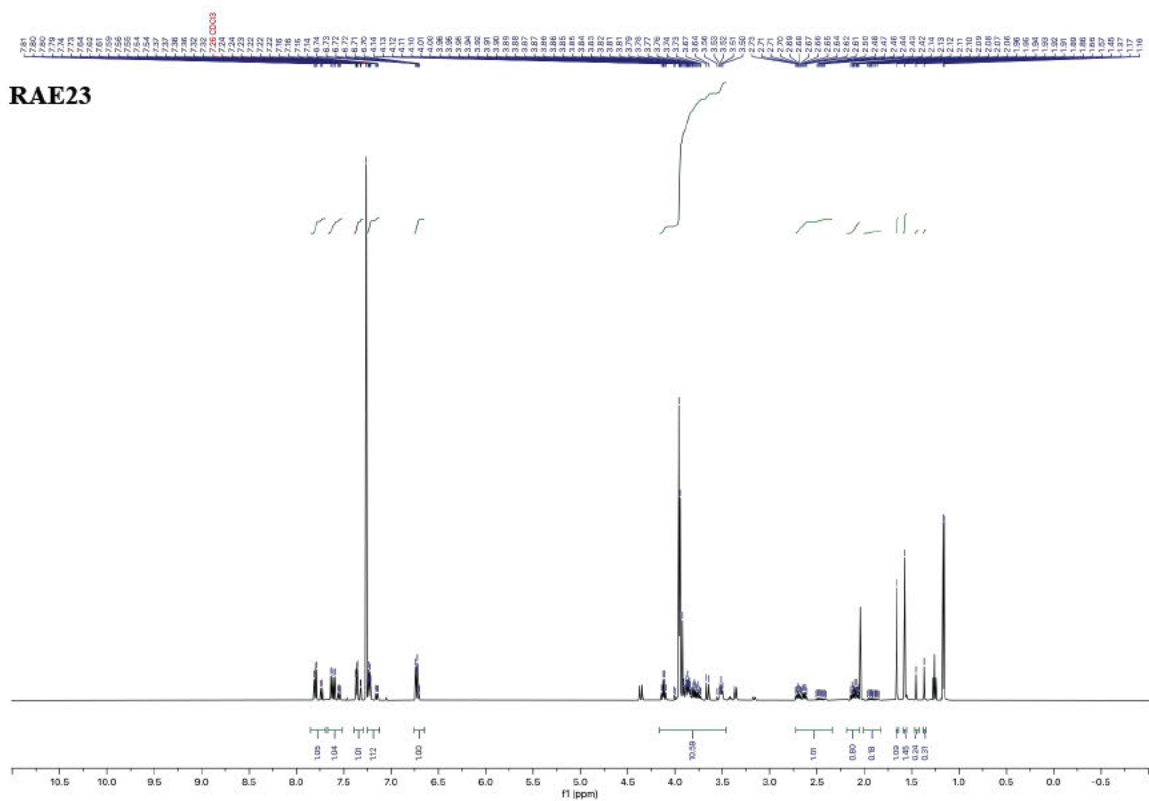


RAE22



RAE22





RAE24

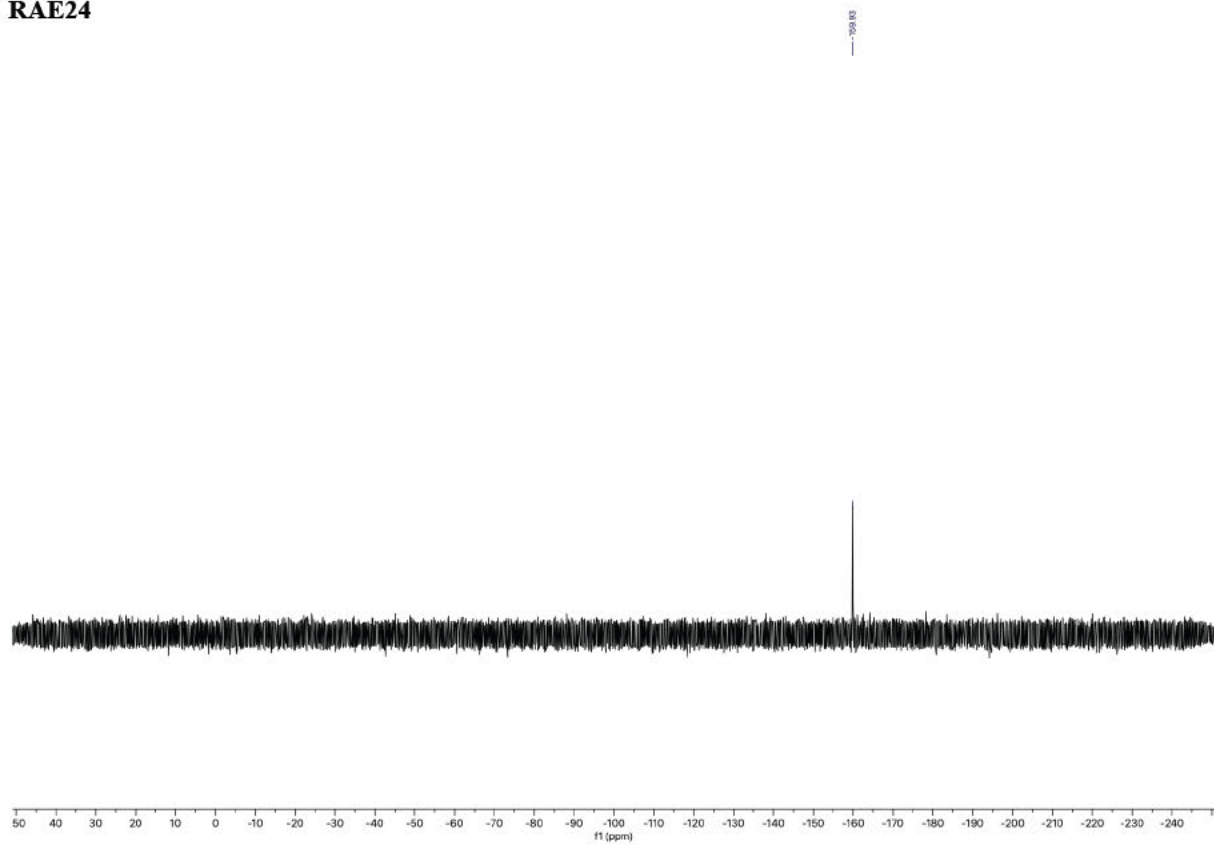
¹H NMR spectrum (CDCl₃) of compound 10a. The x-axis represents the chemical shift in ppm, ranging from -0.5 to 10.5. The spectrum shows several peaks with corresponding integration values and chemical shift labels.

Chemical Shift (ppm)	Integration
~1.5	3.00
~3.5	4.09
~4.1	1.05
7.0 - 8.0	1.98, 1.00, 1.32

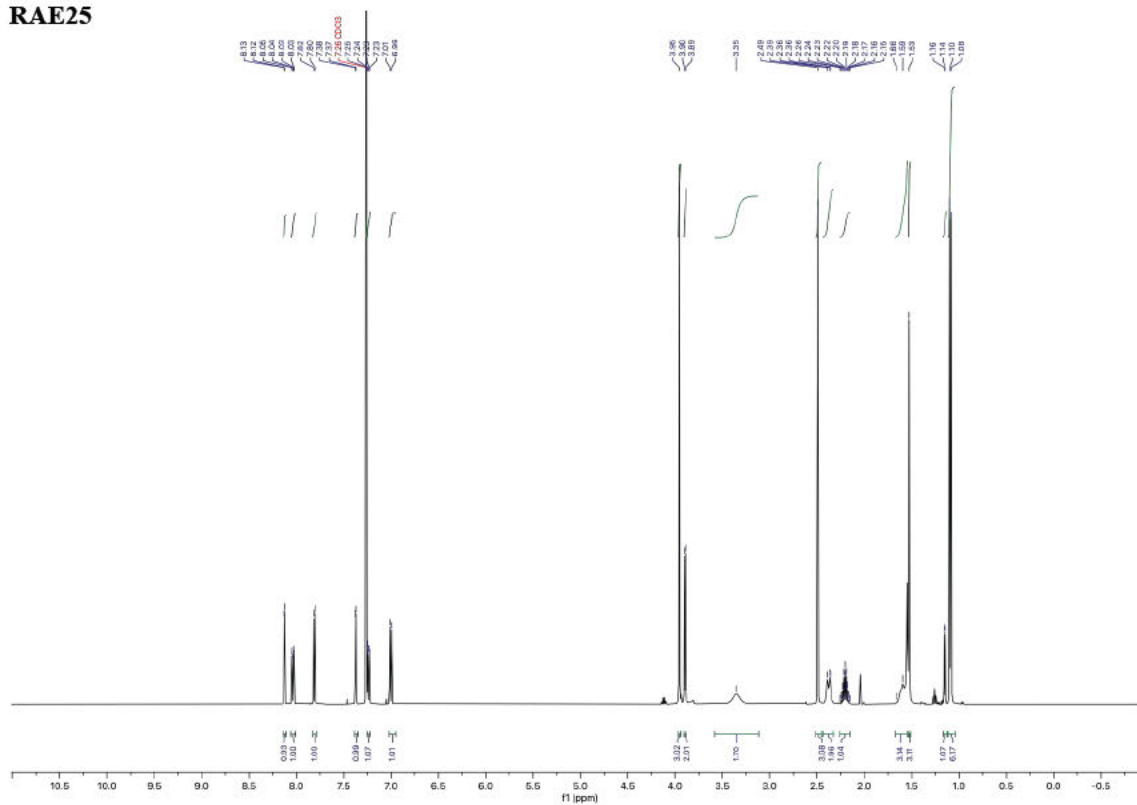
RAE24

Chemical shift labels (ppm): 173.04, 165.37, 162.16, 162.20, 155.03, 151.63, 131.67, 128.13, 120.71, 120.81, 118.17, 80.30, 77.41 (CDCl₃), 76.48 (CDCl₃), 55.36, 44.45, 43.94, 43.52, 42.71, 42.50, 28.69, 26.41.

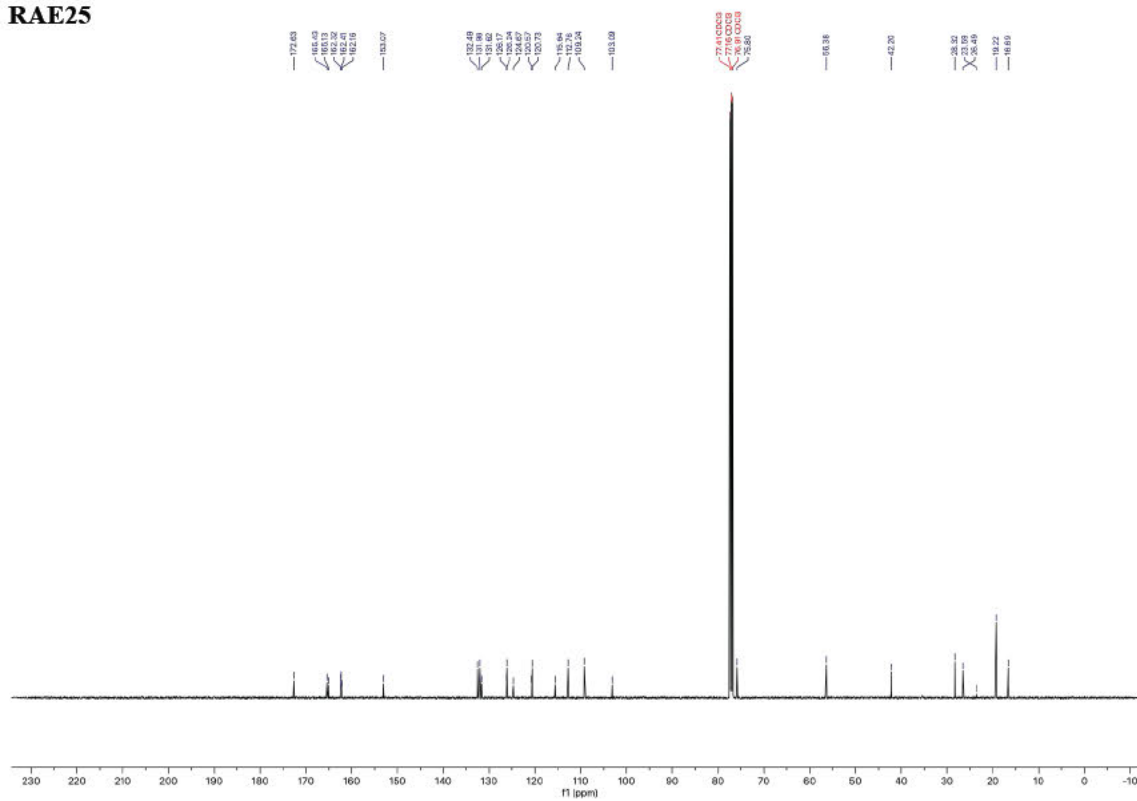
RAE24

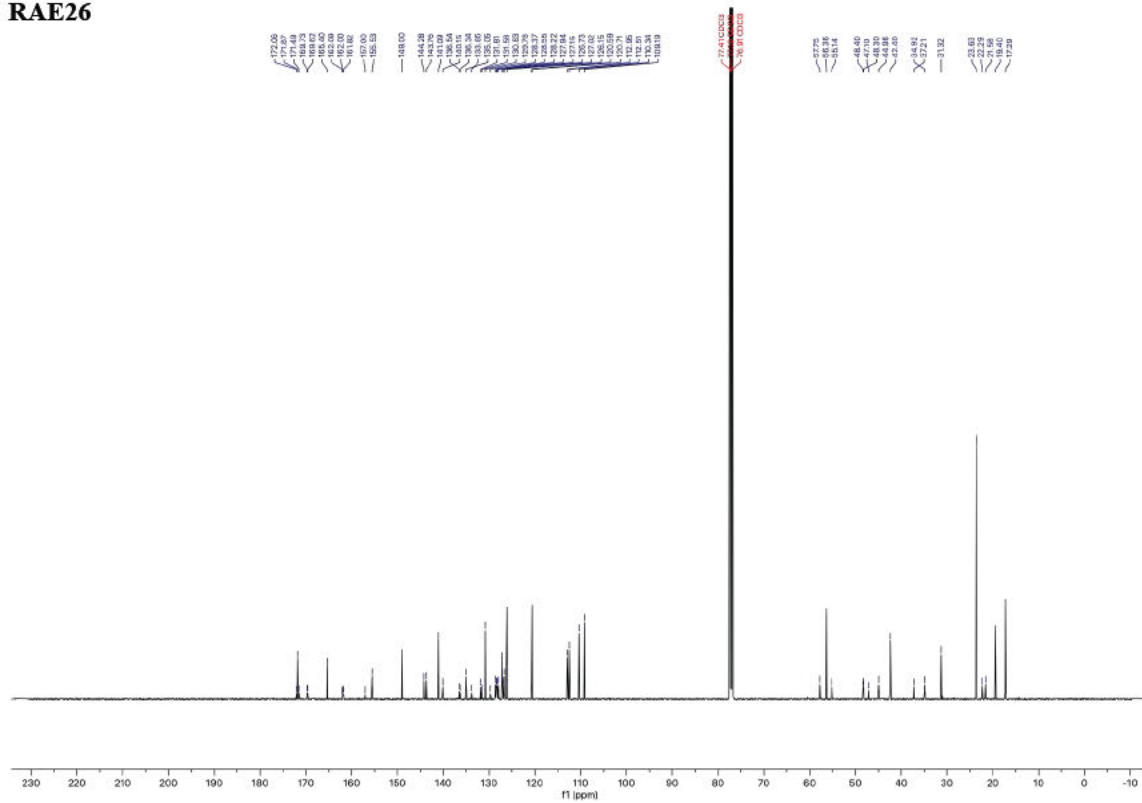
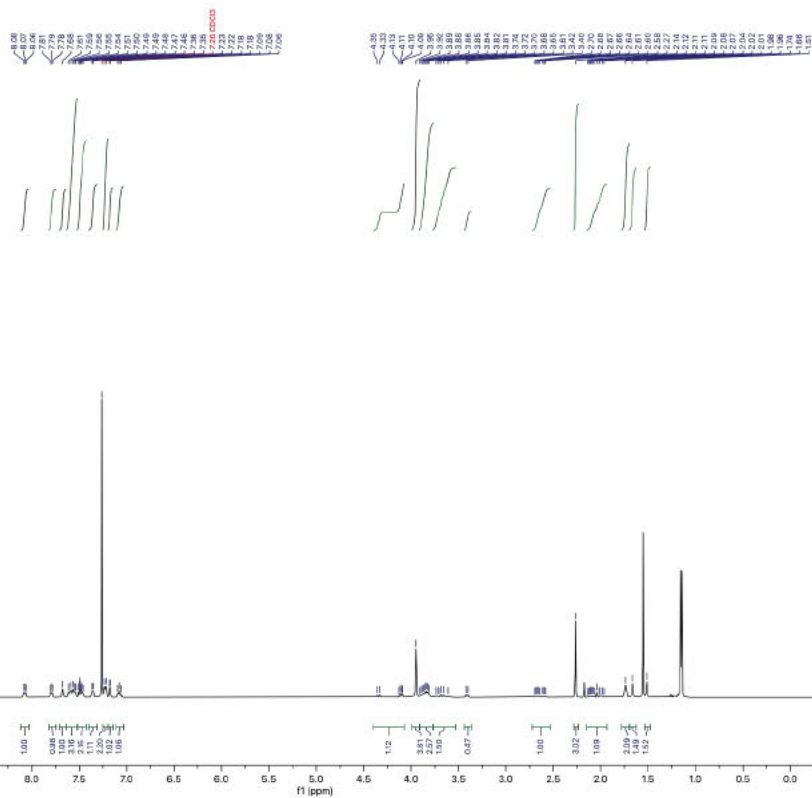


RAE25

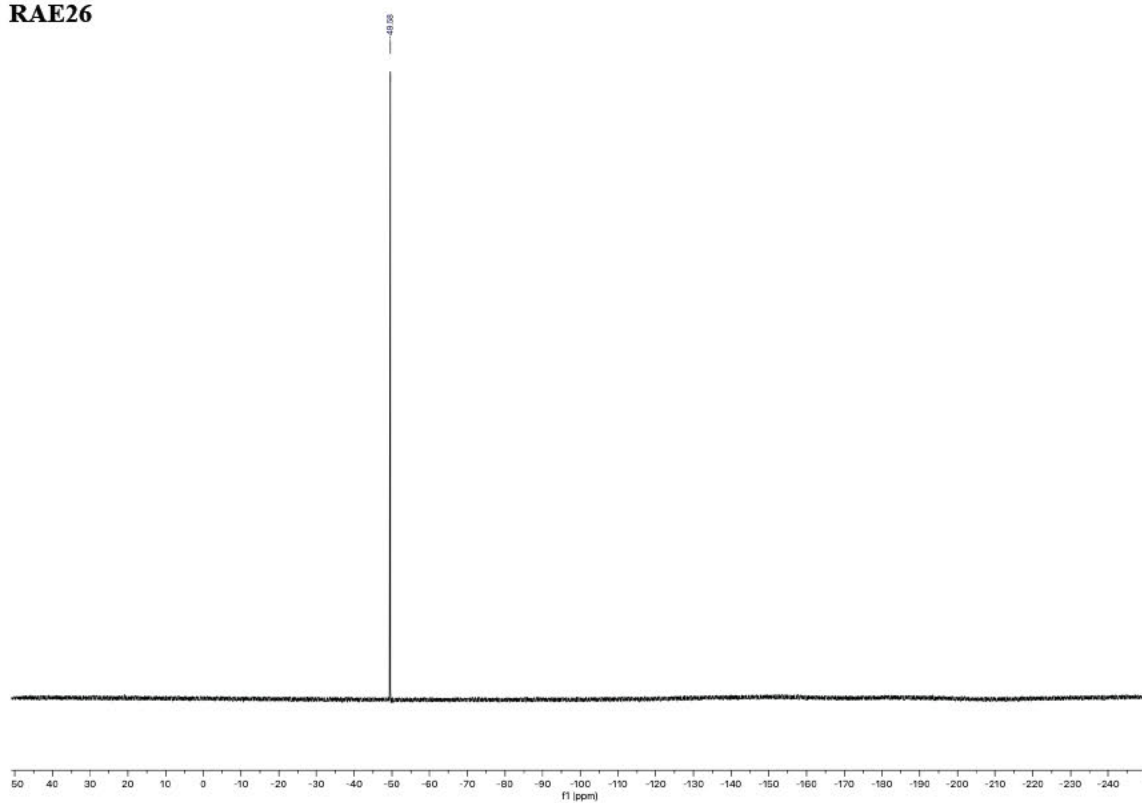


RAE25

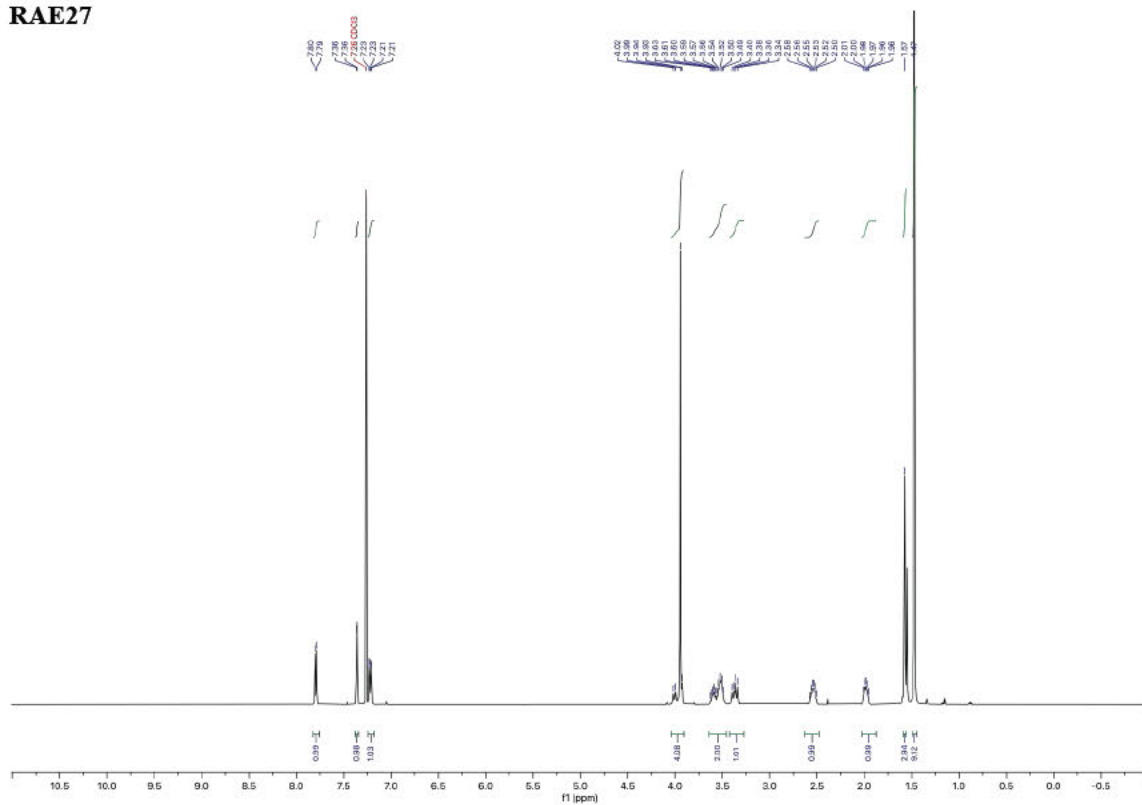




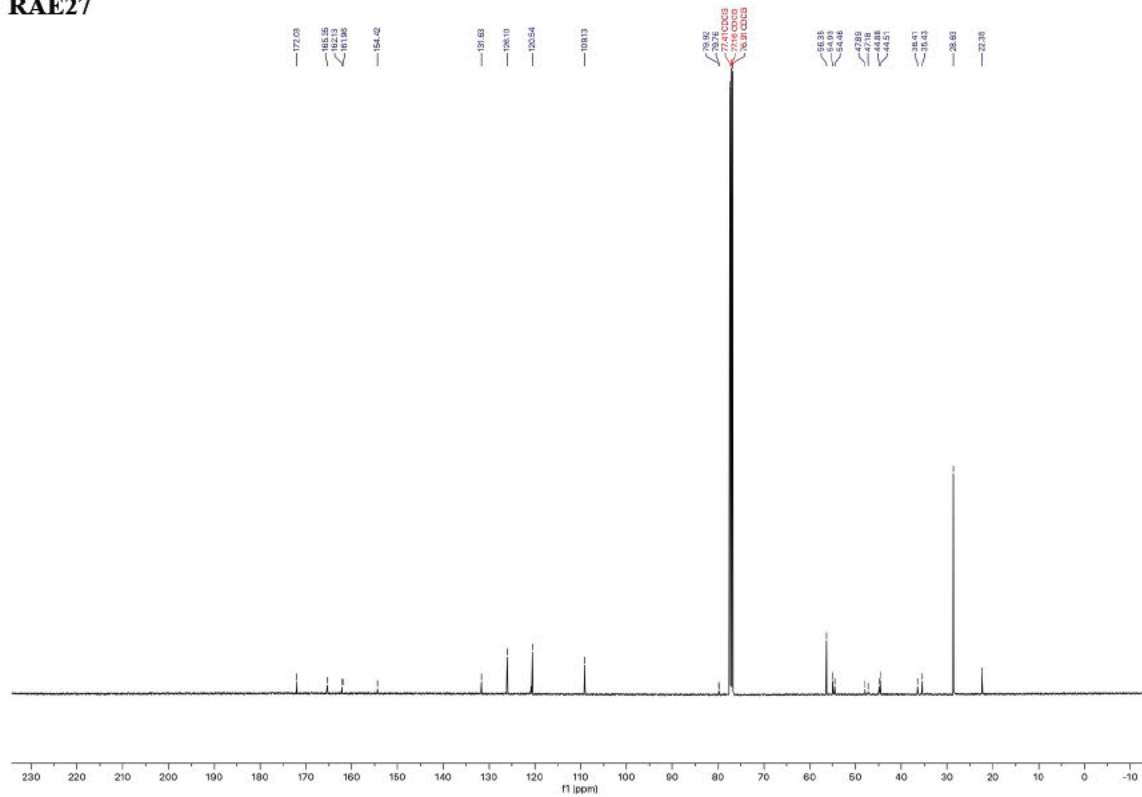
RAE26

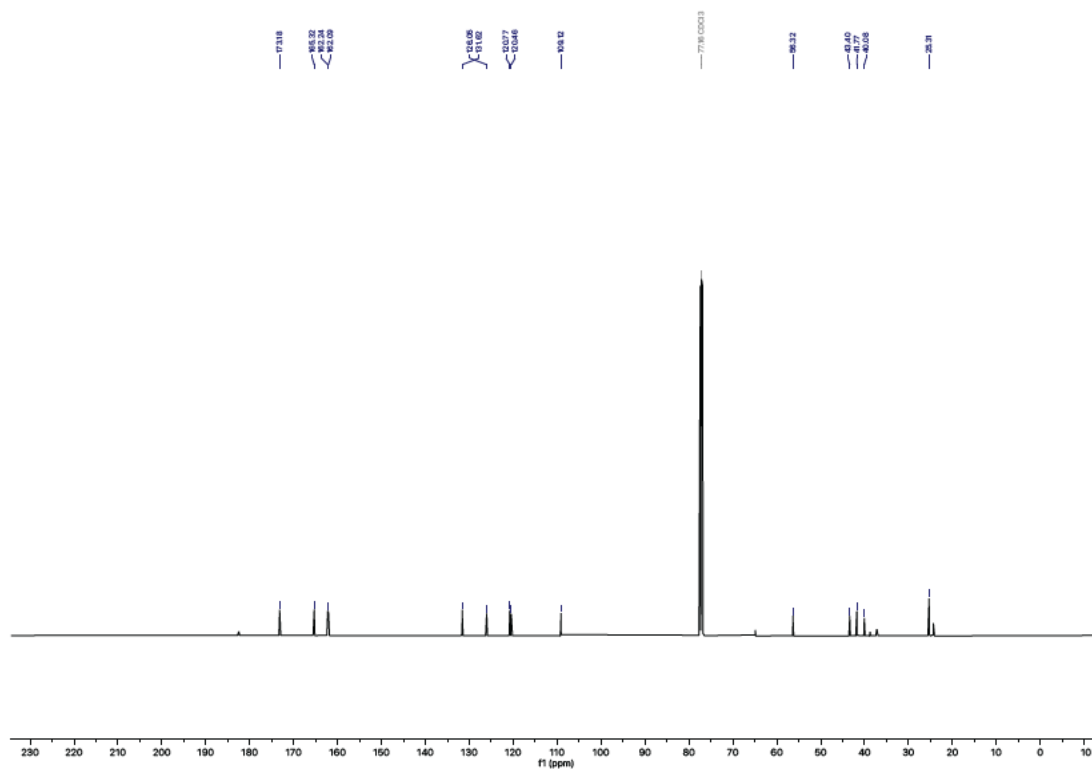


RAE27

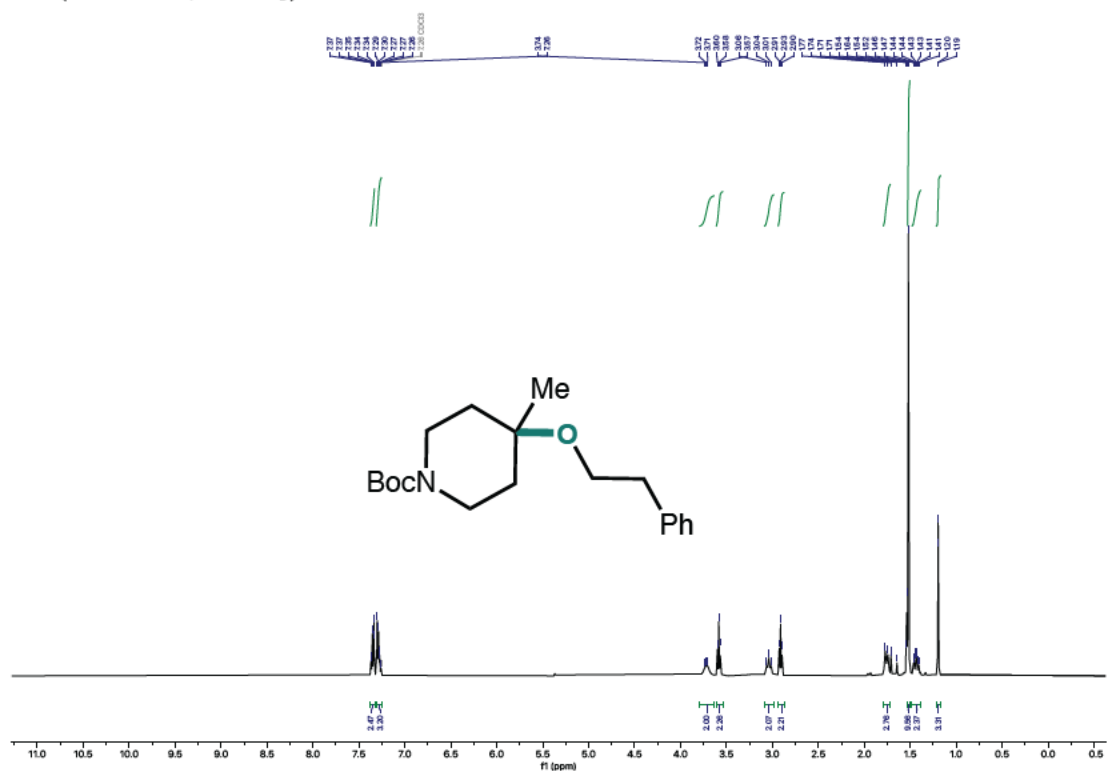
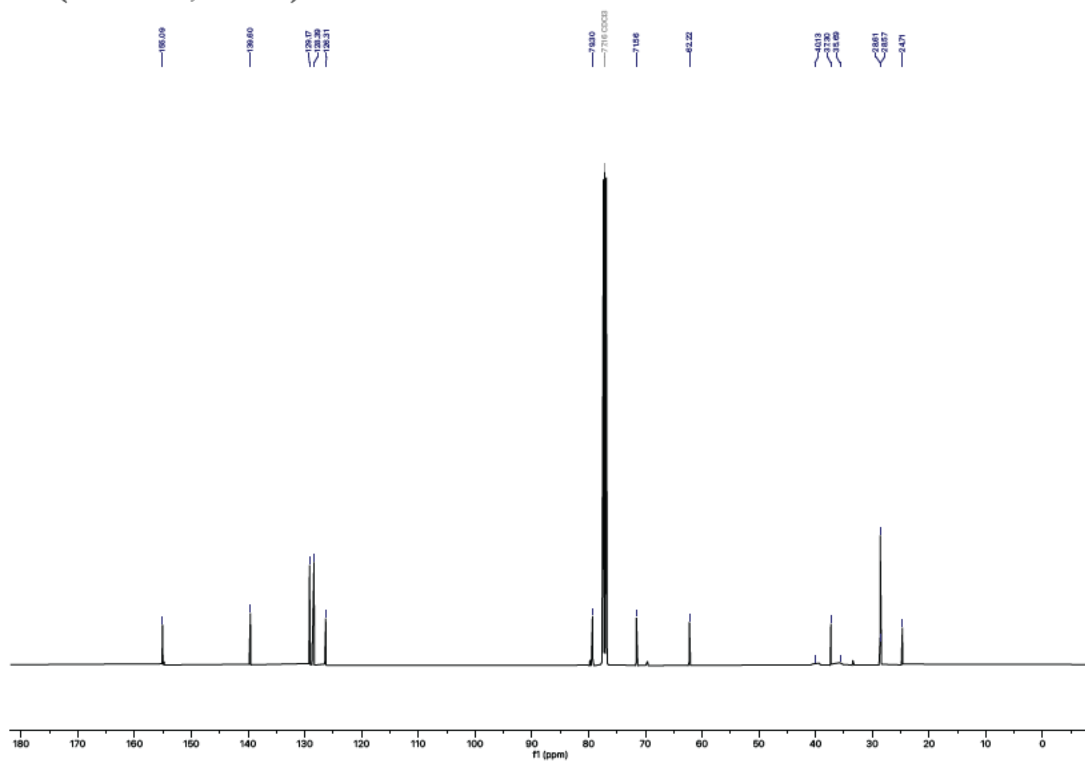


RAE27



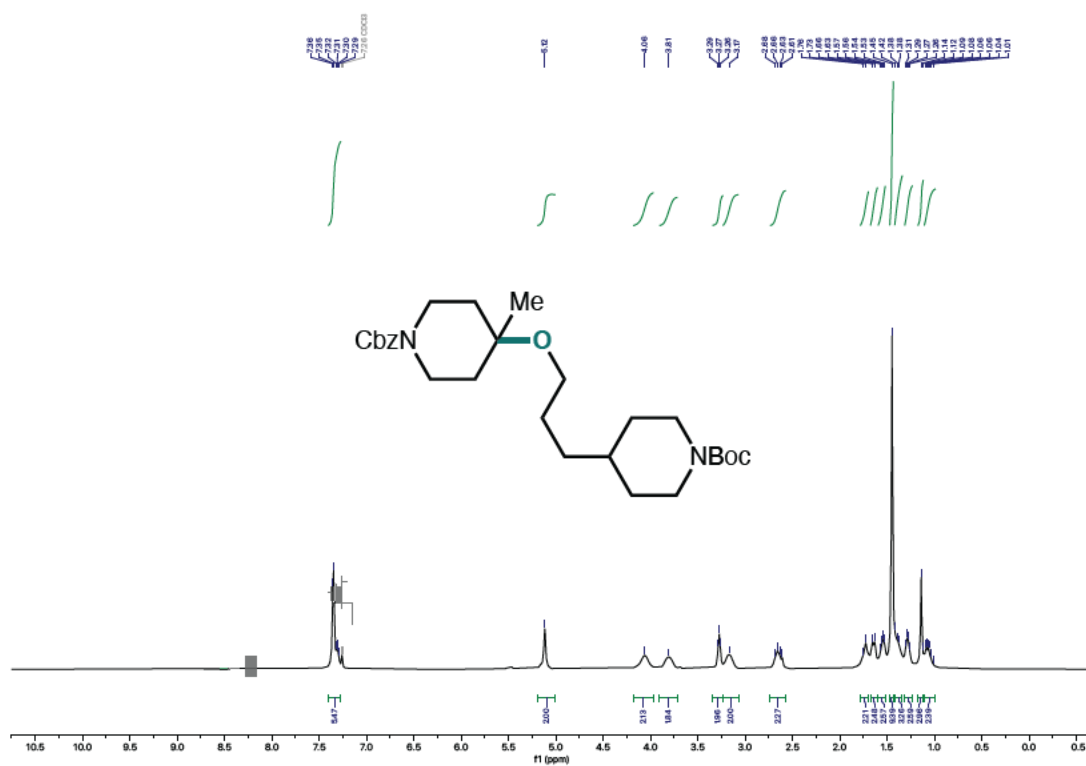
RAE28

***Tert*-butyl 4-methyl-4-phenethoxypiperidine-1-carboxylate (10)**

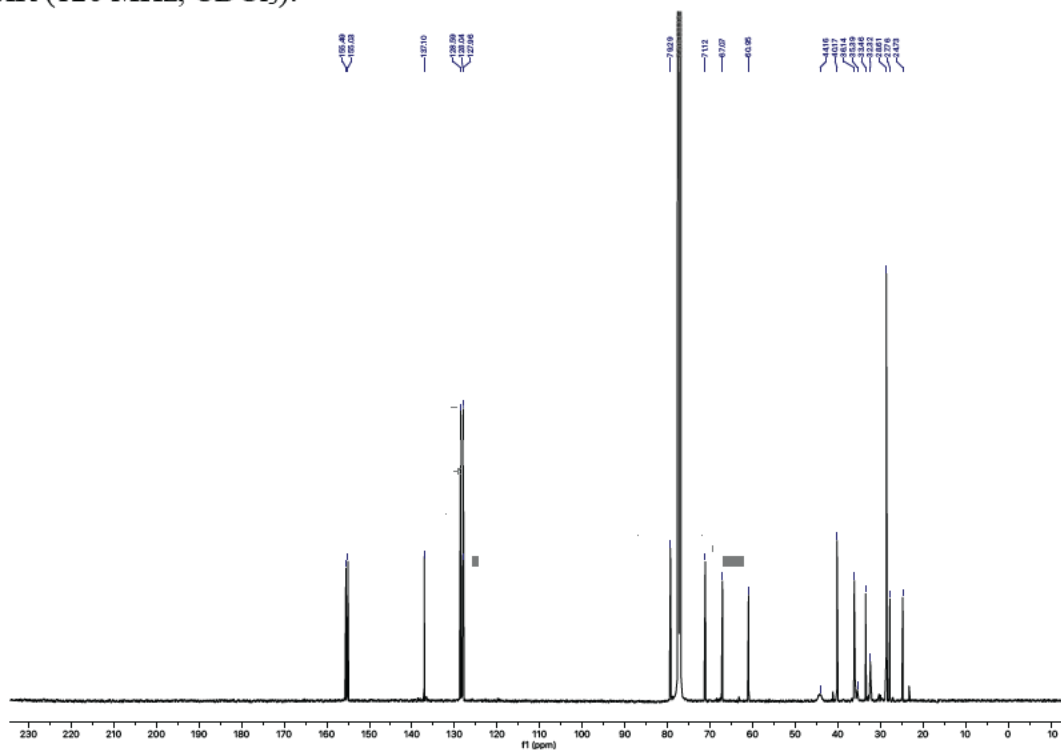
¹H NMR (500 MHz, CDCl₃):¹³C NMR (126 MHz, CDCl₃):

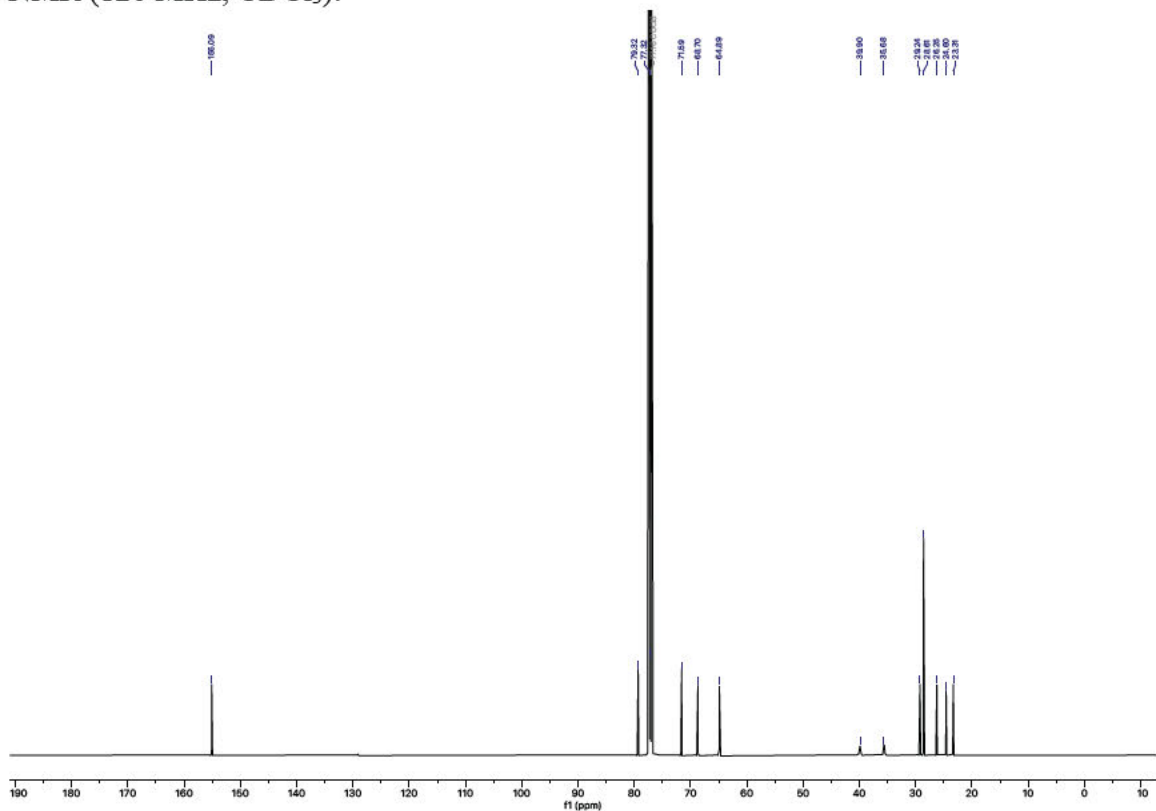
Benzyl 4-(3-(1-(tert-butoxycarbonyl)piperidin-4-yl)propoxy)-4-methylpiperidine-1-carboxylate (15)

^1H NMR (500 MHz, CDCl_3):



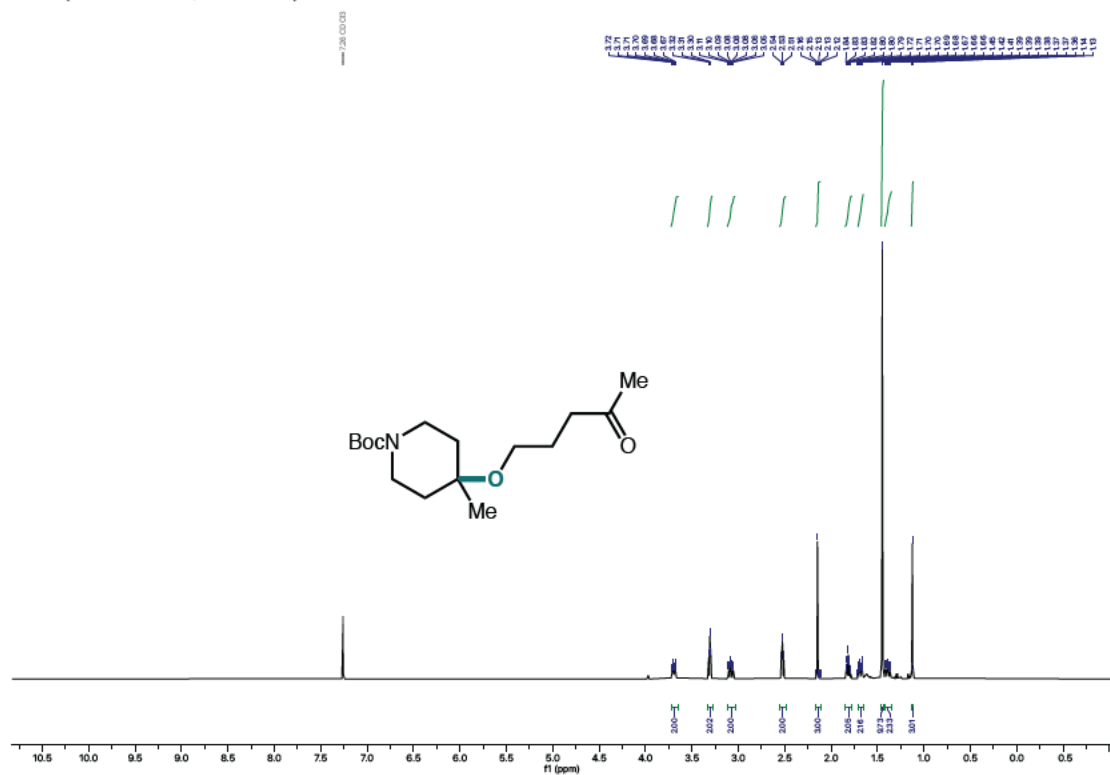
^{13}C NMR (126 MHz, CDCl_3):



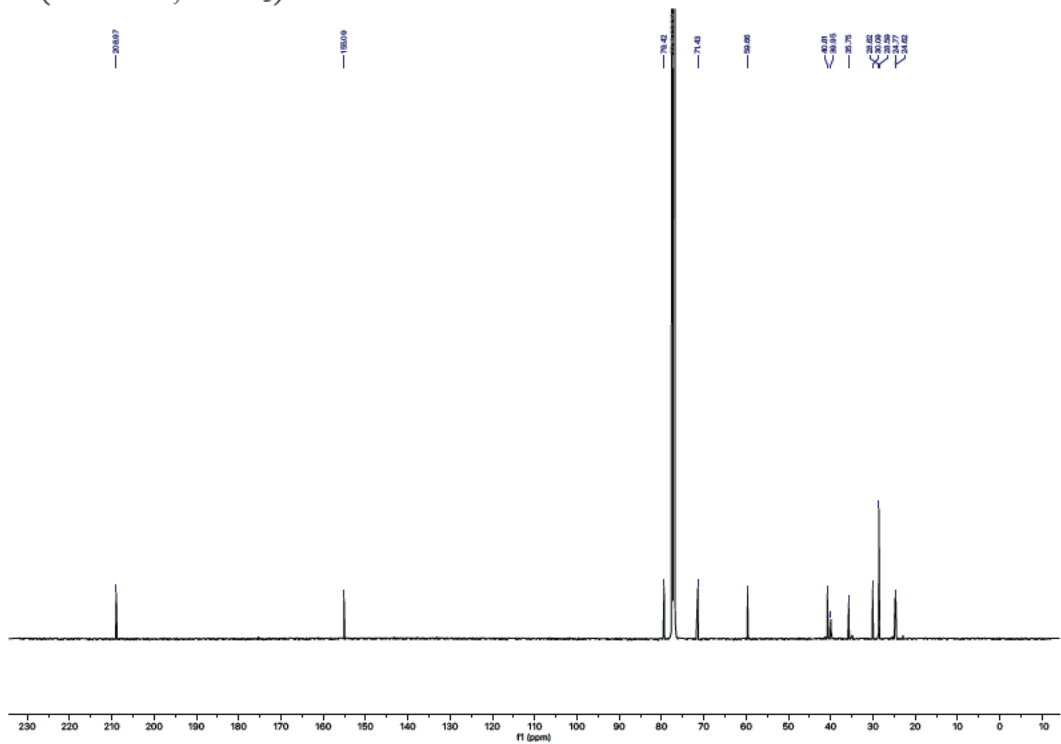
¹H NMR (500 MHz, CDCl₃):

***Tert*-butyl 4-methyl-4-(4-oxopentoxy)piperidine-1-carboxylate (17)**

^1H NMR (500 MHz, CDCl_3):

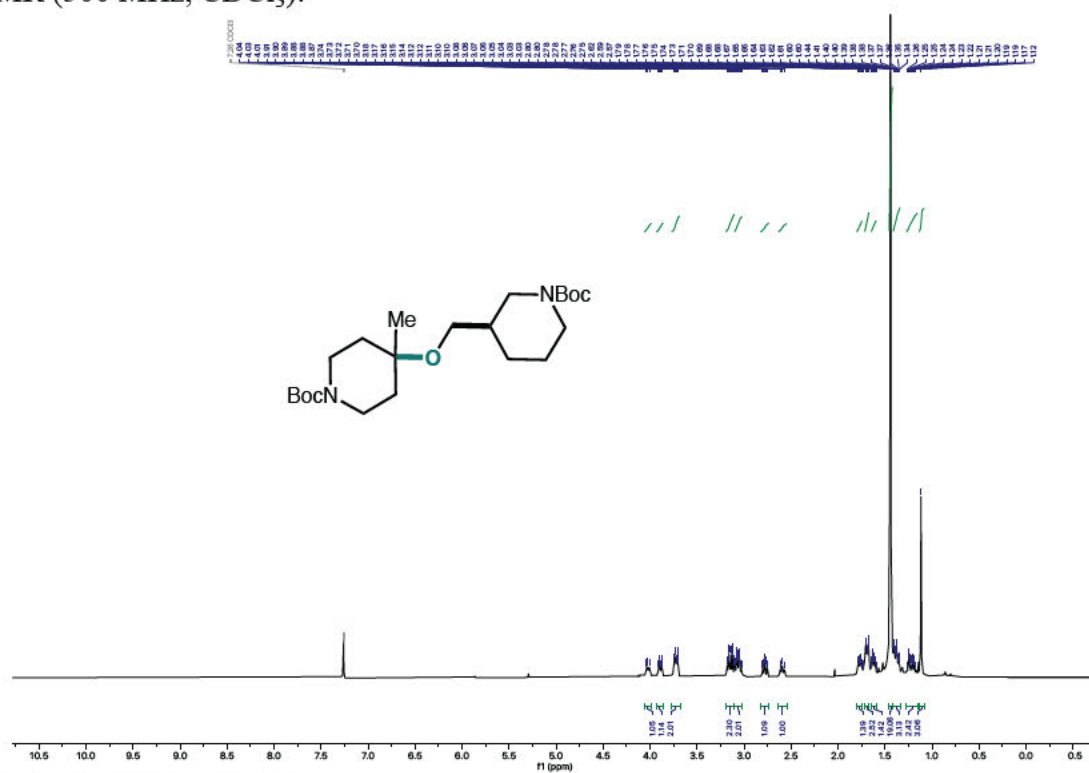


^{13}C NMR (126 MHz, CDCl_3):

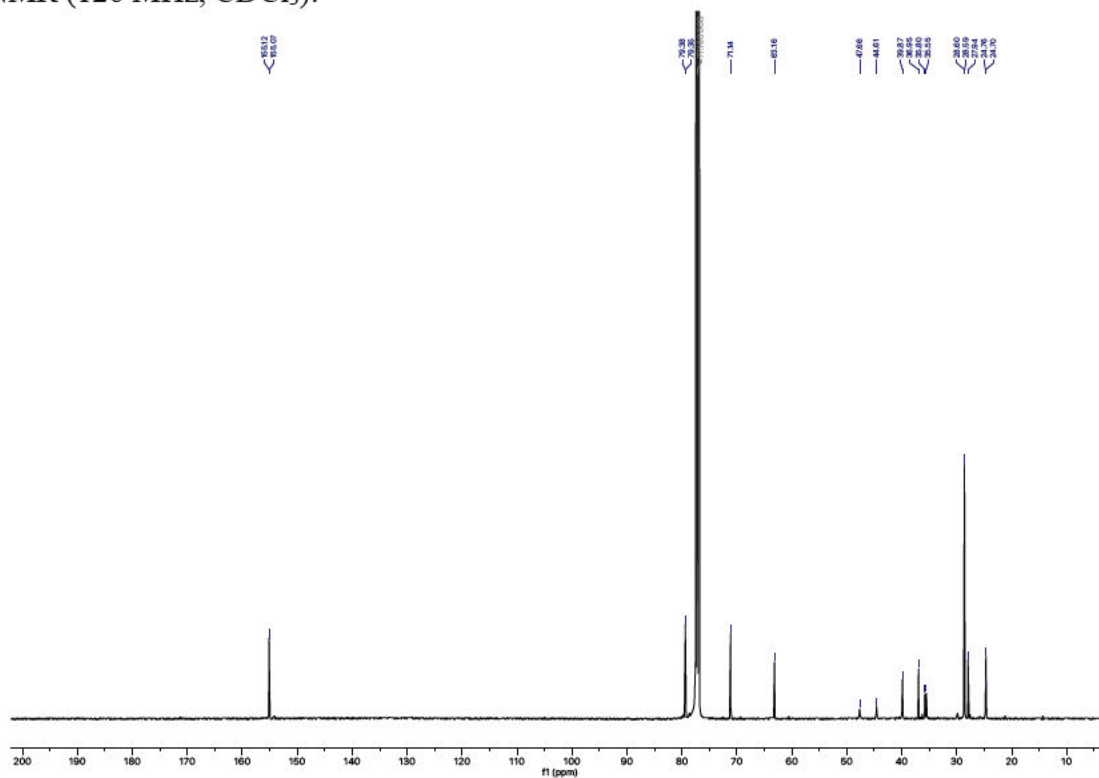


***Tert*-butyl (S)-4-((1-(*tert*-butoxycarbonyl)piperidin-3-yl)methoxy)-4-methylpiperidine-1-carboxylate (18)**

^1H NMR (500 MHz, CDCl_3):

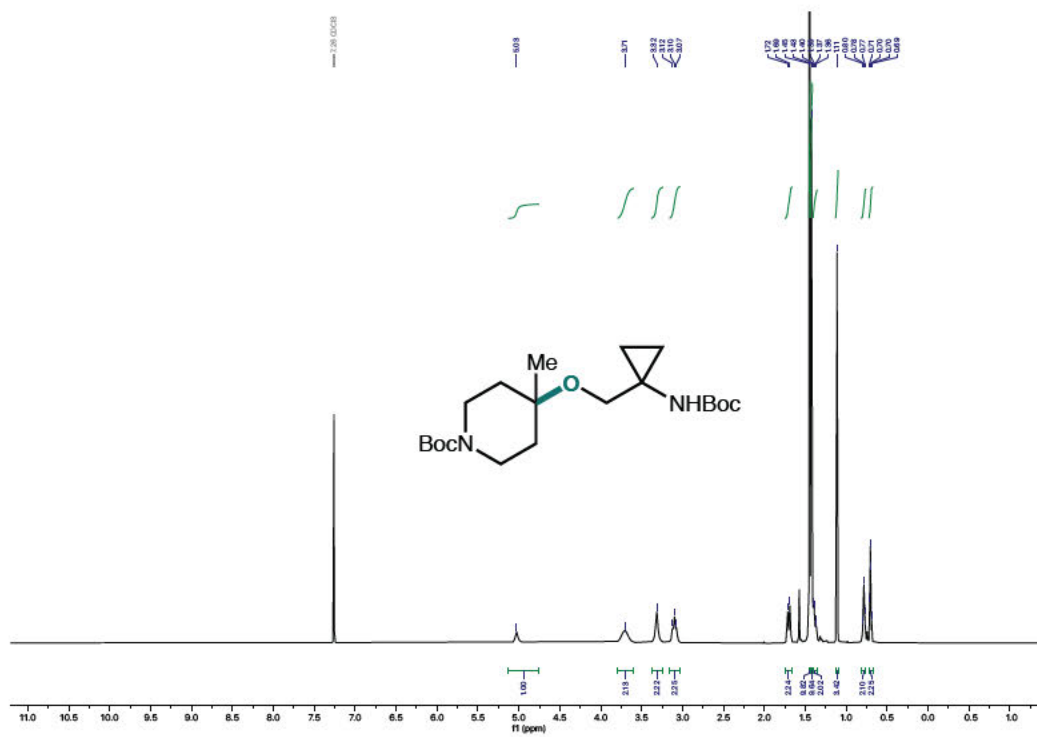


^{13}C NMR (126 MHz, CDCl_3):

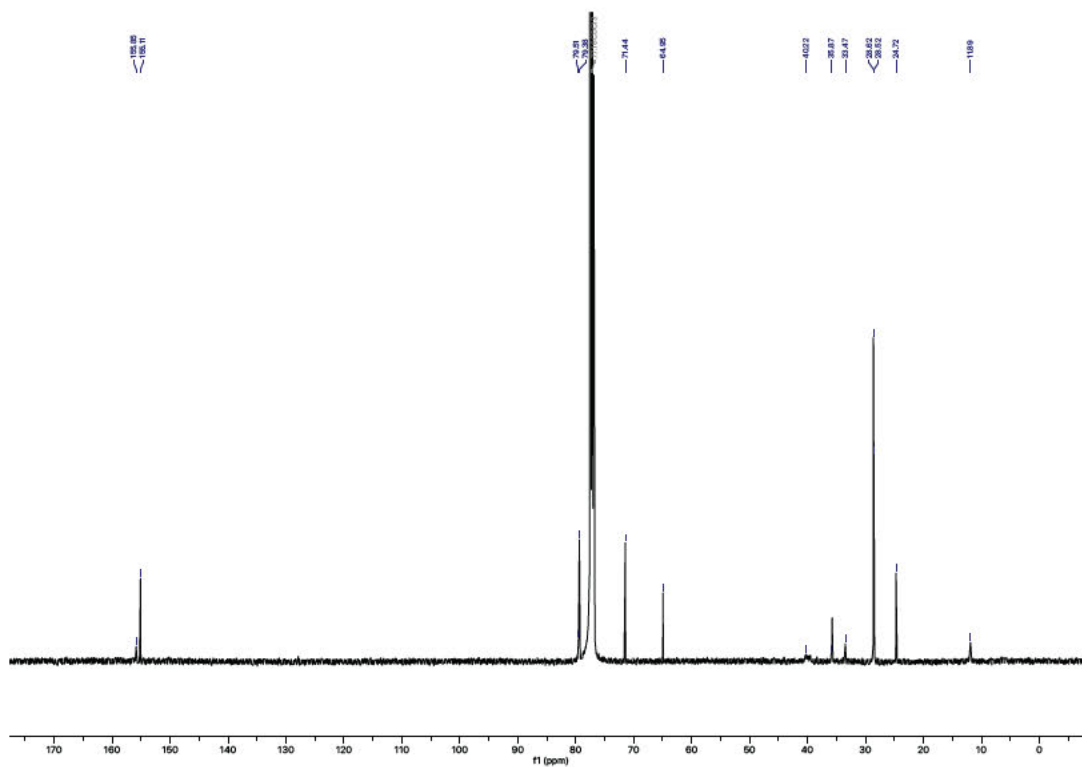


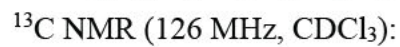
***Tert*-butyl 4-((1-((*tert*-butoxycarbonyl)amino)cyclopropyl)methoxy)-4-methylpiperidine-1-carboxylate (20)**

^1H NMR (500 MHz, CDCl_3):



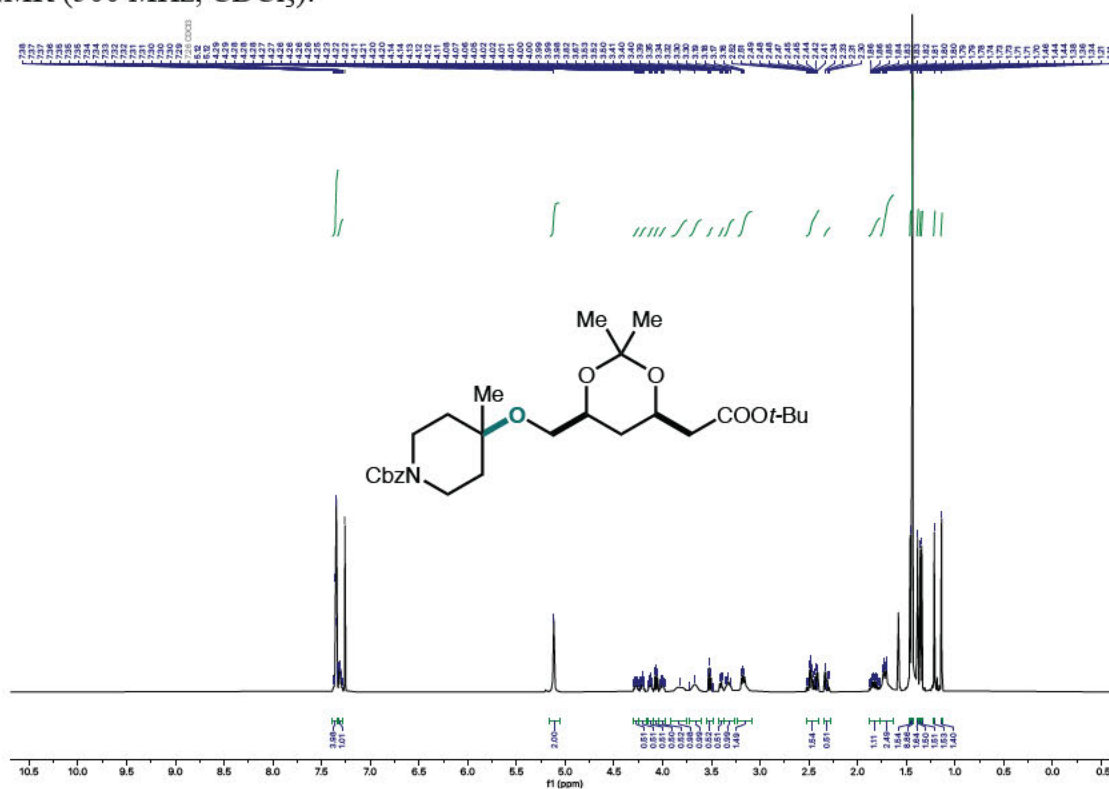
^{13}C NMR (126 MHz, CDCl_3):



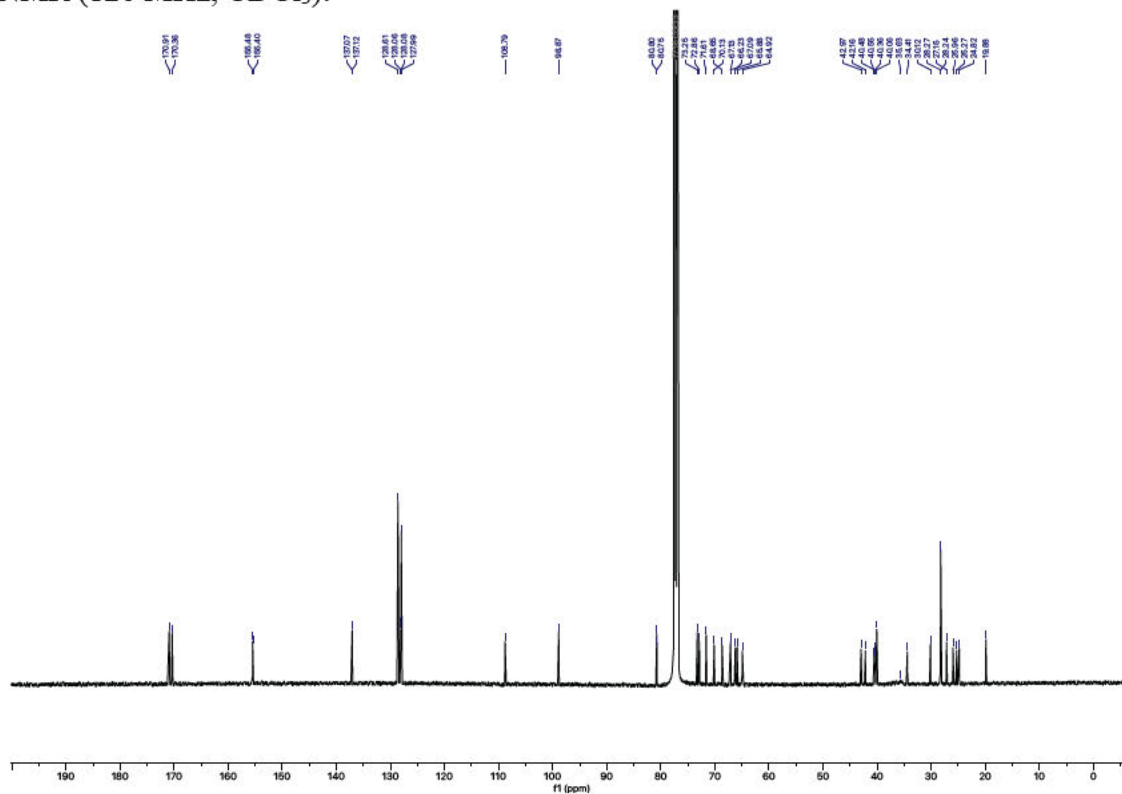
¹H NMR (500 MHz, CDCl₃):

Benzyl 4-(((4*S*,6*R*)-6-(2-(*tert*-butoxy)-2-oxoethyl)-2,2-dimethyl-1,3-dioxan-4-yl)methoxy)-4-methylpiperidine-1-carboxylate (22)

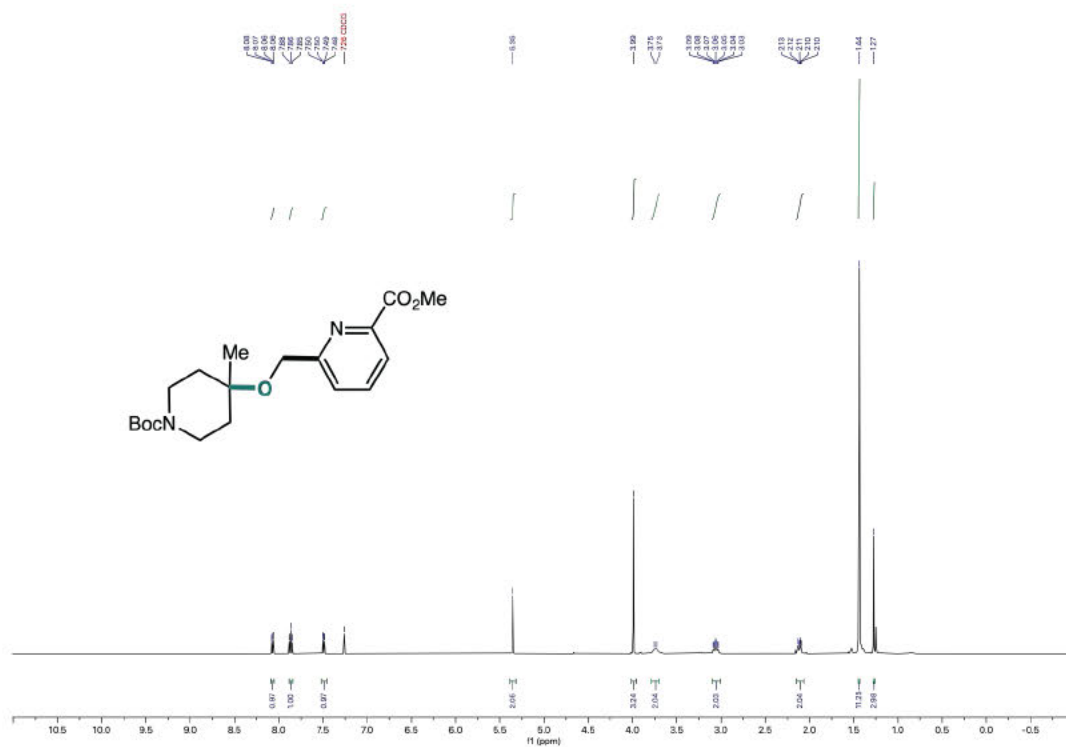
^1H NMR (500 MHz, CDCl_3):



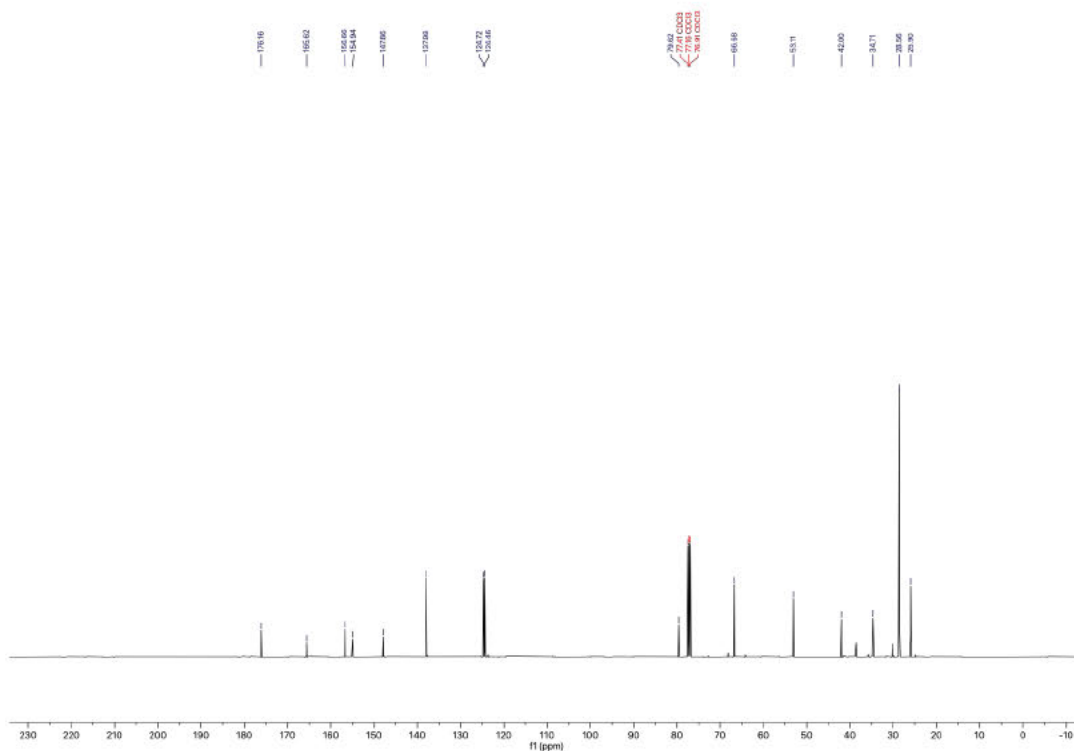
^{13}C NMR (126 MHz, CDCl_3):



23, ^1H NMR, 500 MHz, CDCl_3

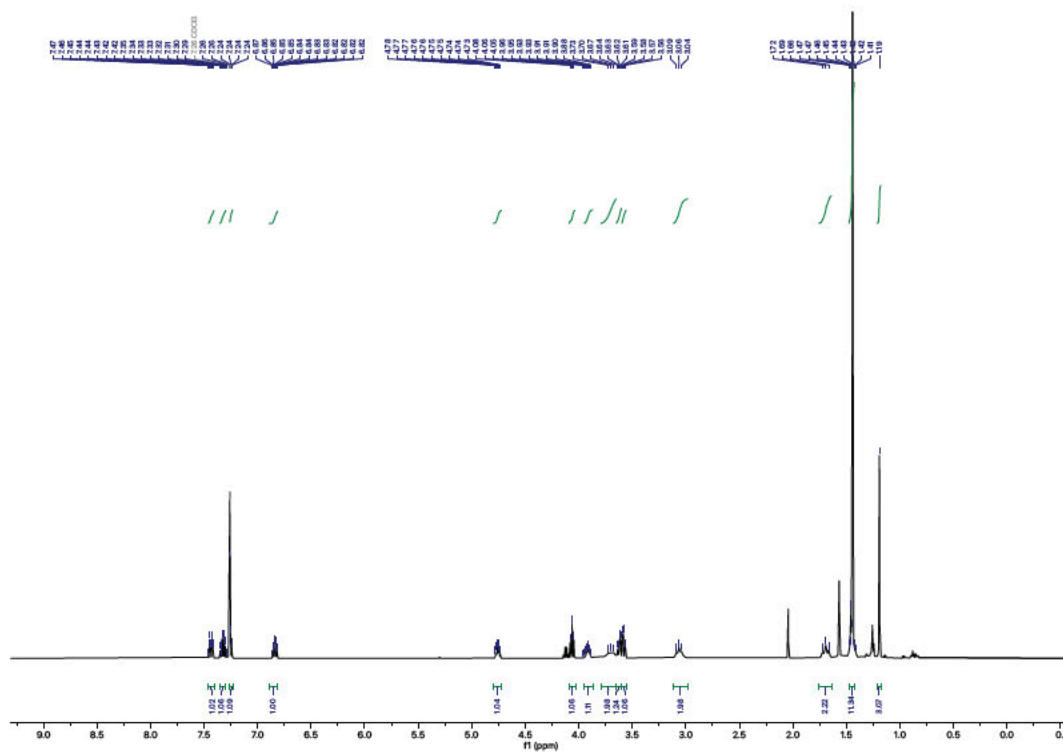


23, ^{13}C NMR, 126 MHz, CDCl_3

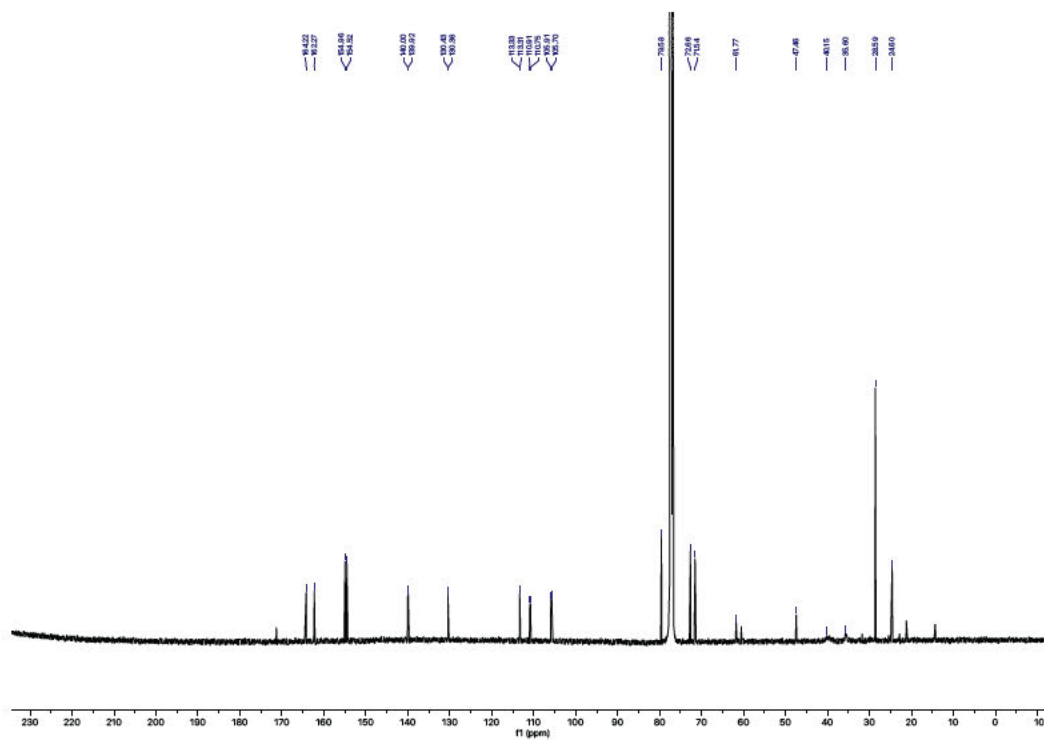


***Tert*-butyl (R)-4-((3-(3-fluorophenyl)-2-oxooxazolidin-5-yl)methoxy)-4-methylpiperidine-1-carboxylate (24)**

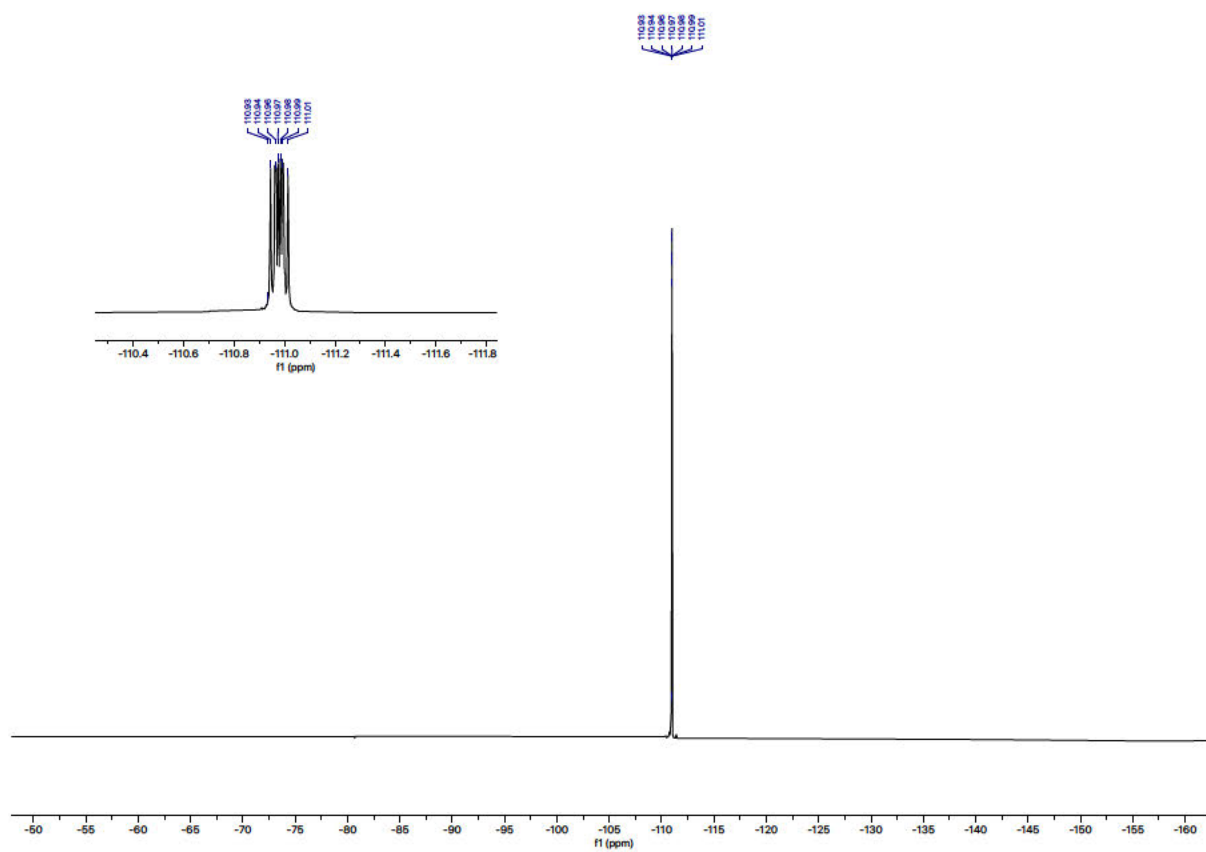
¹H NMR (500 MHz, CDCl₃):

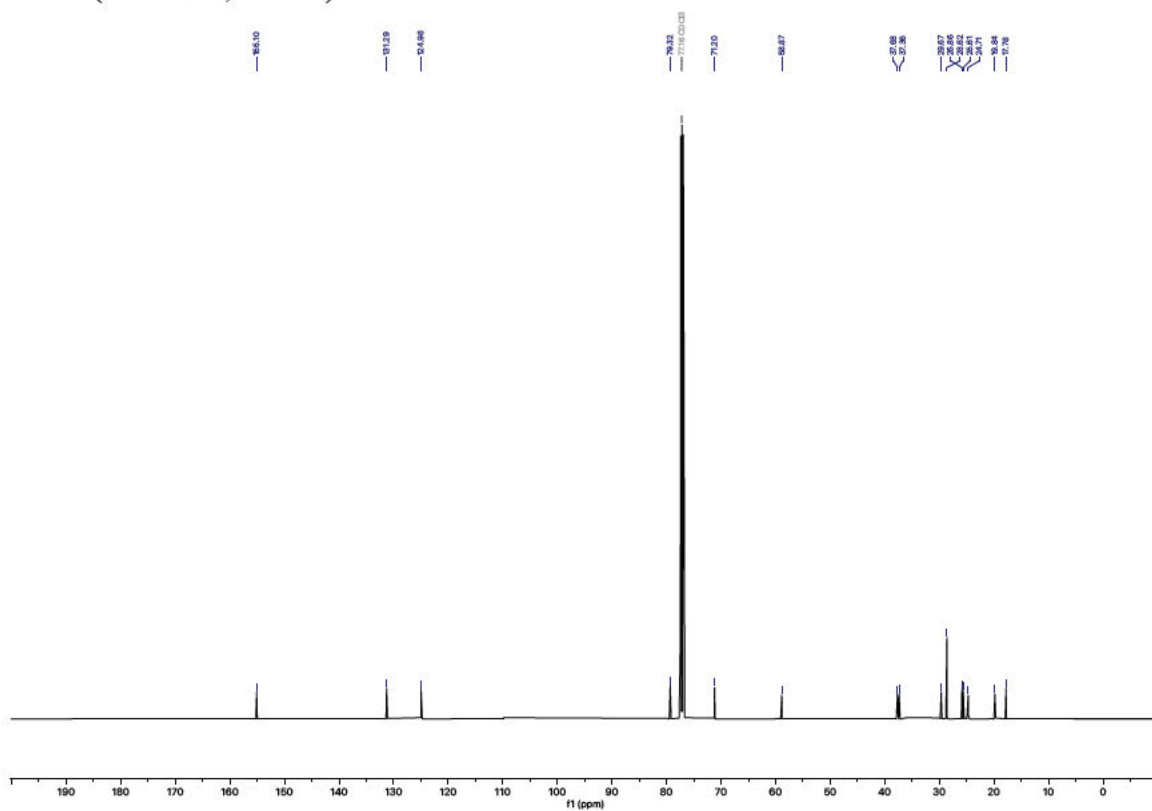


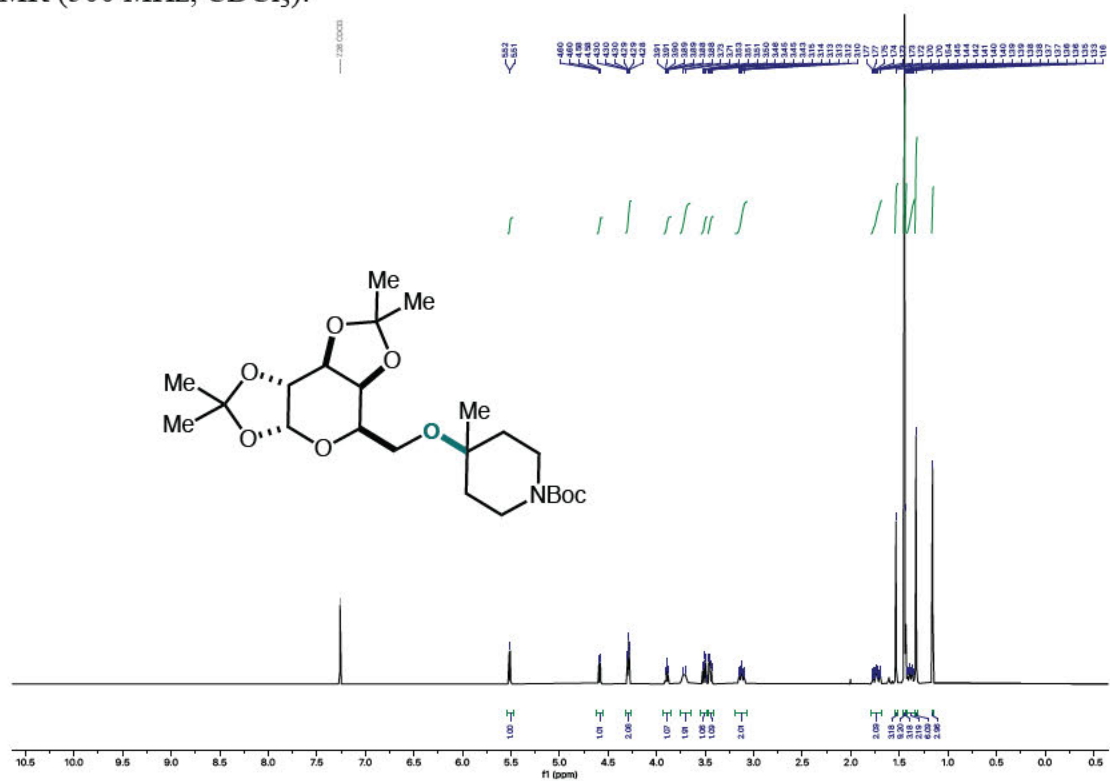
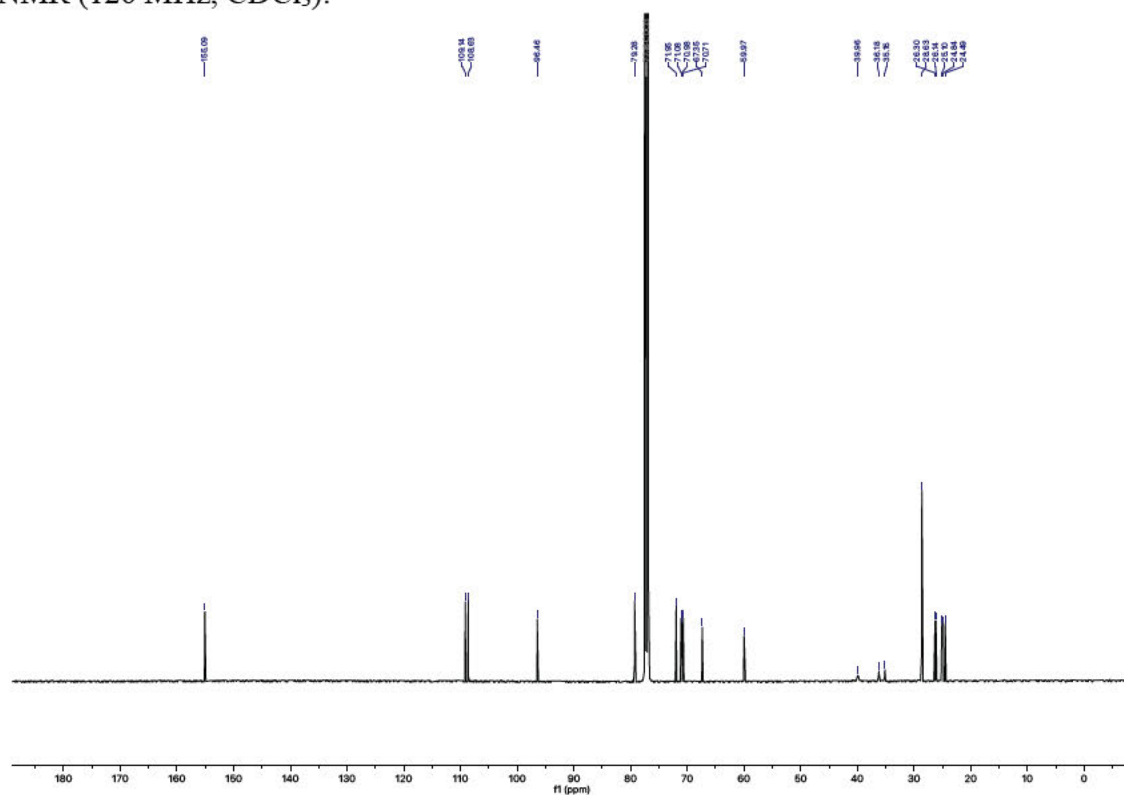
¹³C NMR (126 MHz, CDCl₃):

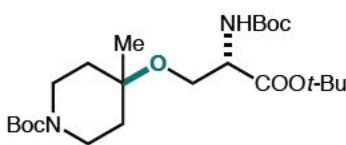
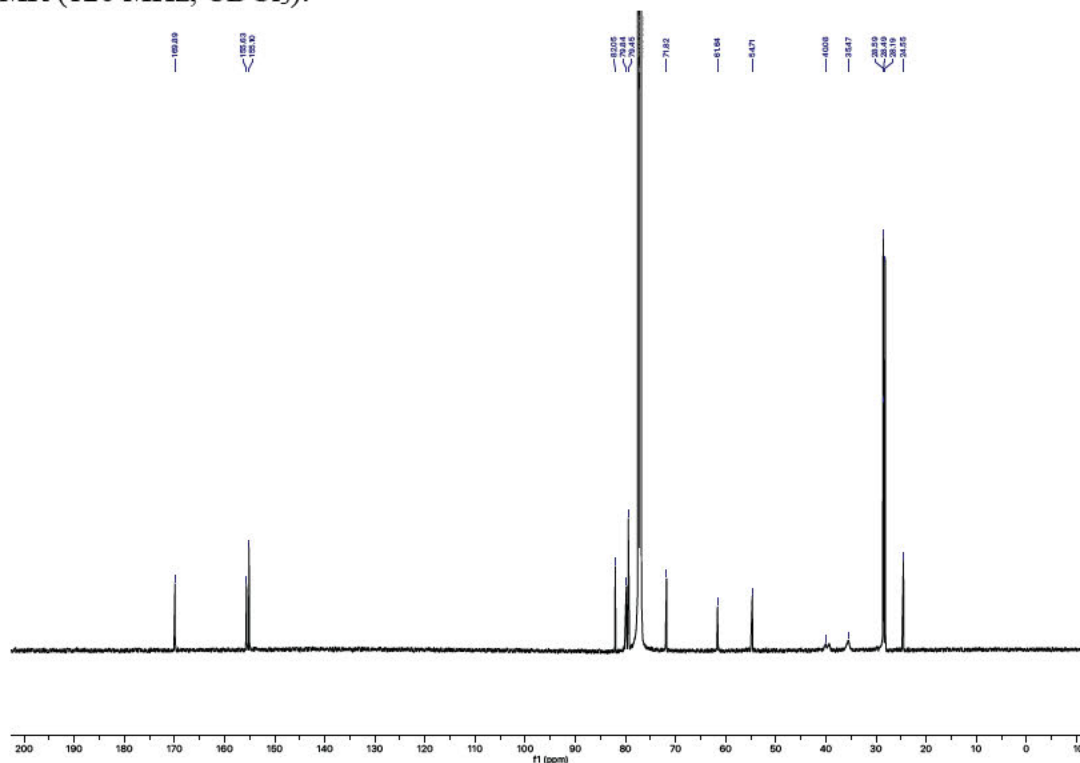


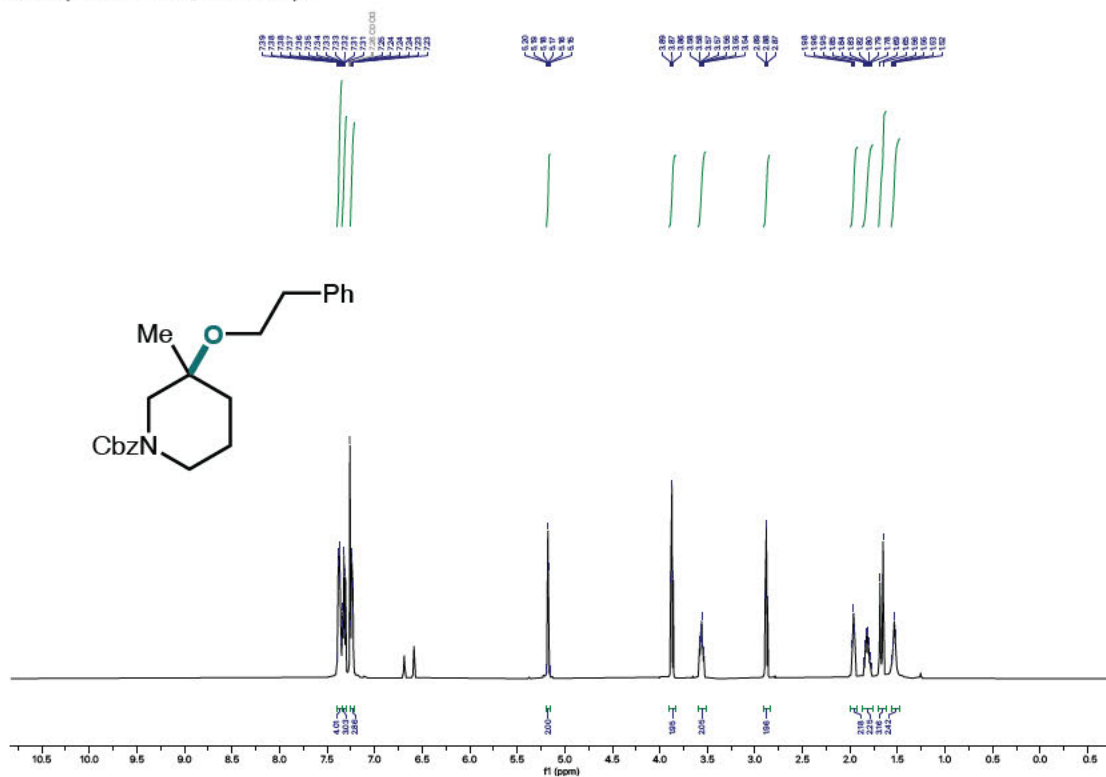
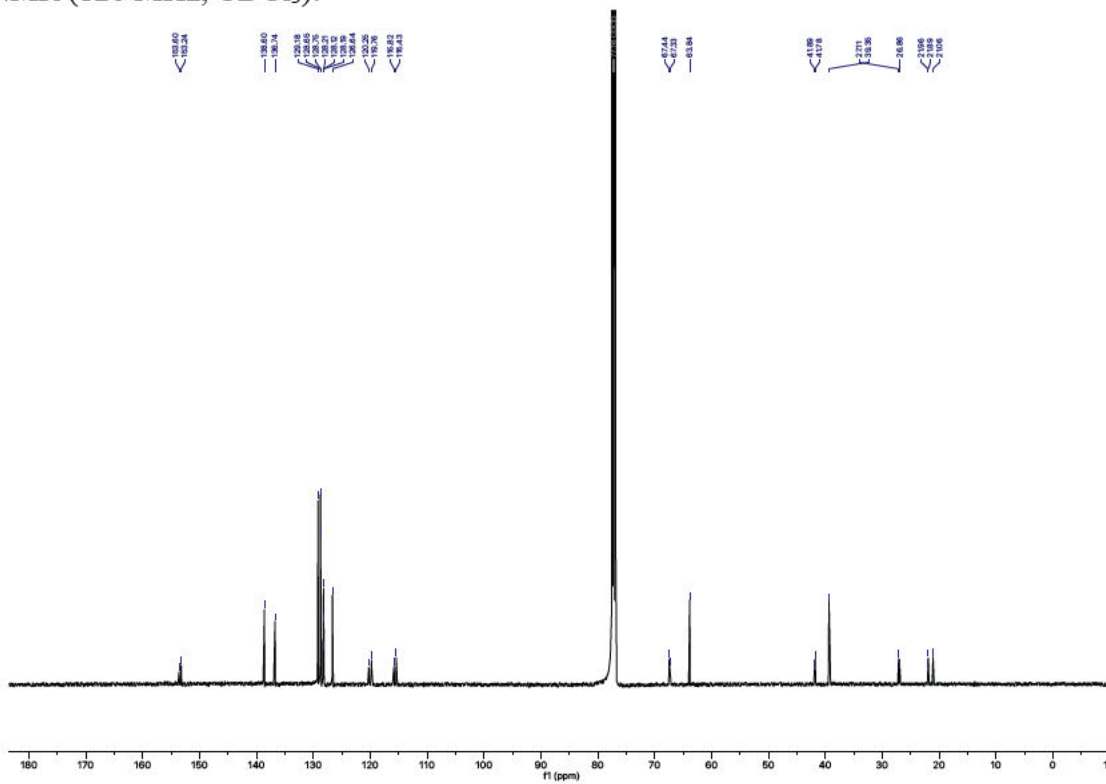
^{19}F NMR (376 MHz, CDCl_3)

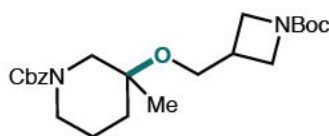
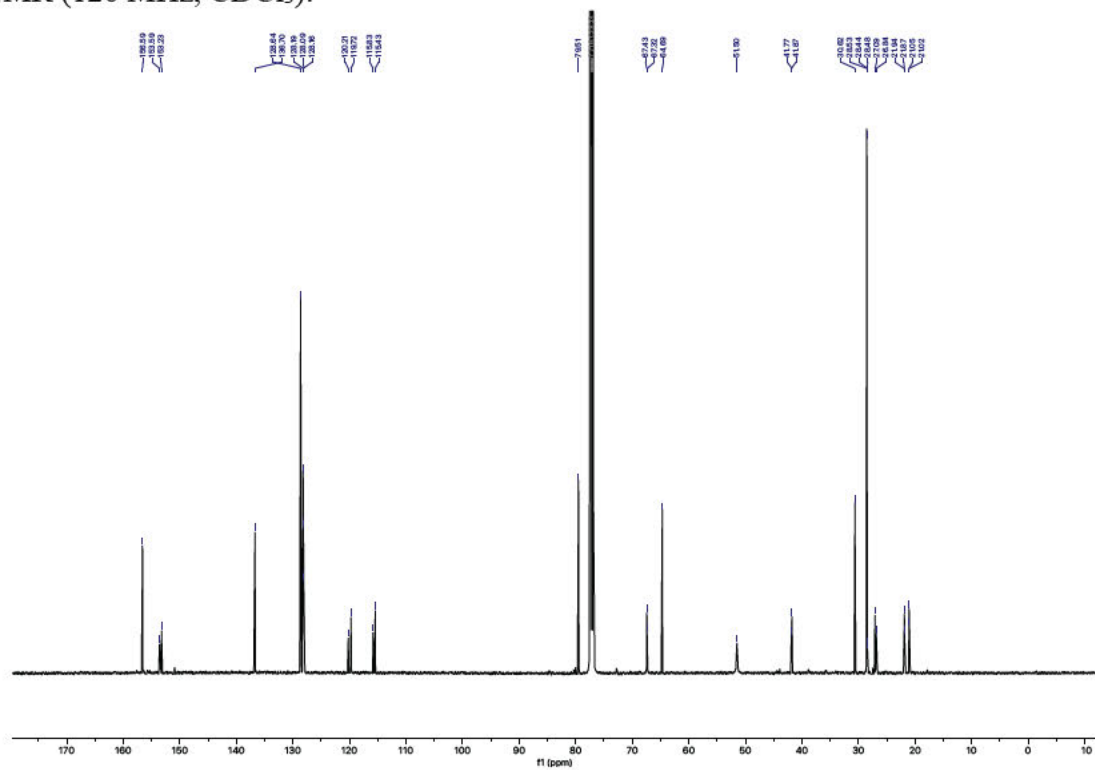


¹H NMR (500 MHz, CDCl₃):

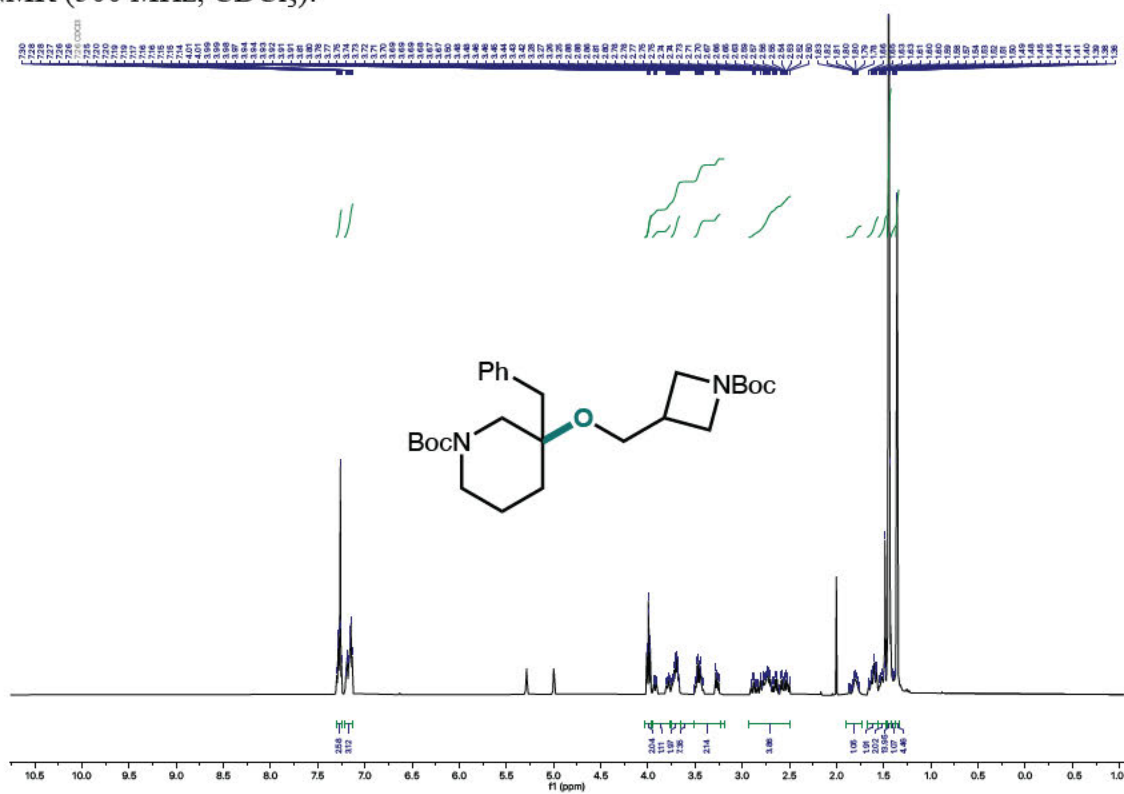
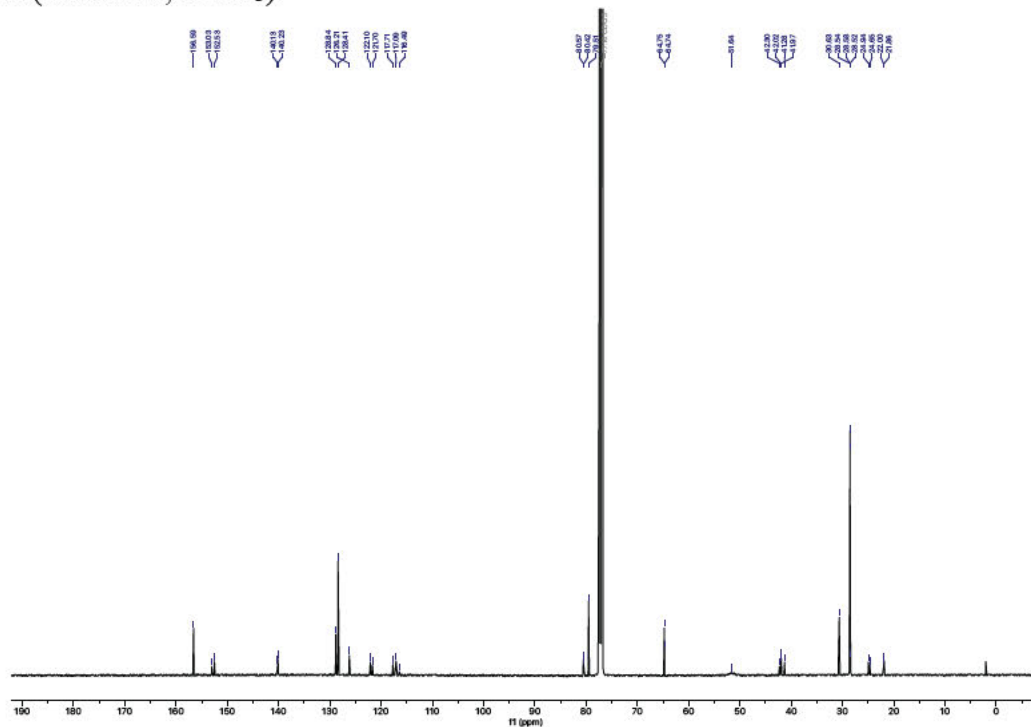
¹H NMR (500 MHz, CDCl₃): ^{13}C NMR (126 MHz, CDCl_3):

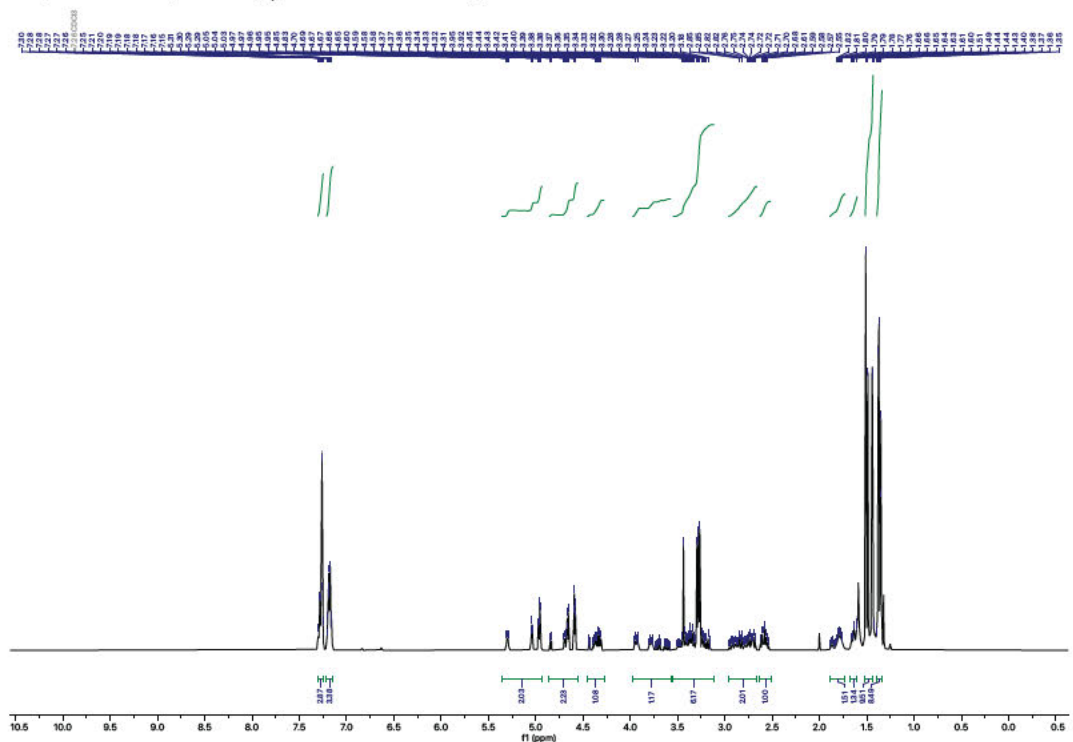
¹H NMR (500 MHz, CDCl₃):¹³C NMR (126 MHz, CDCl₃):

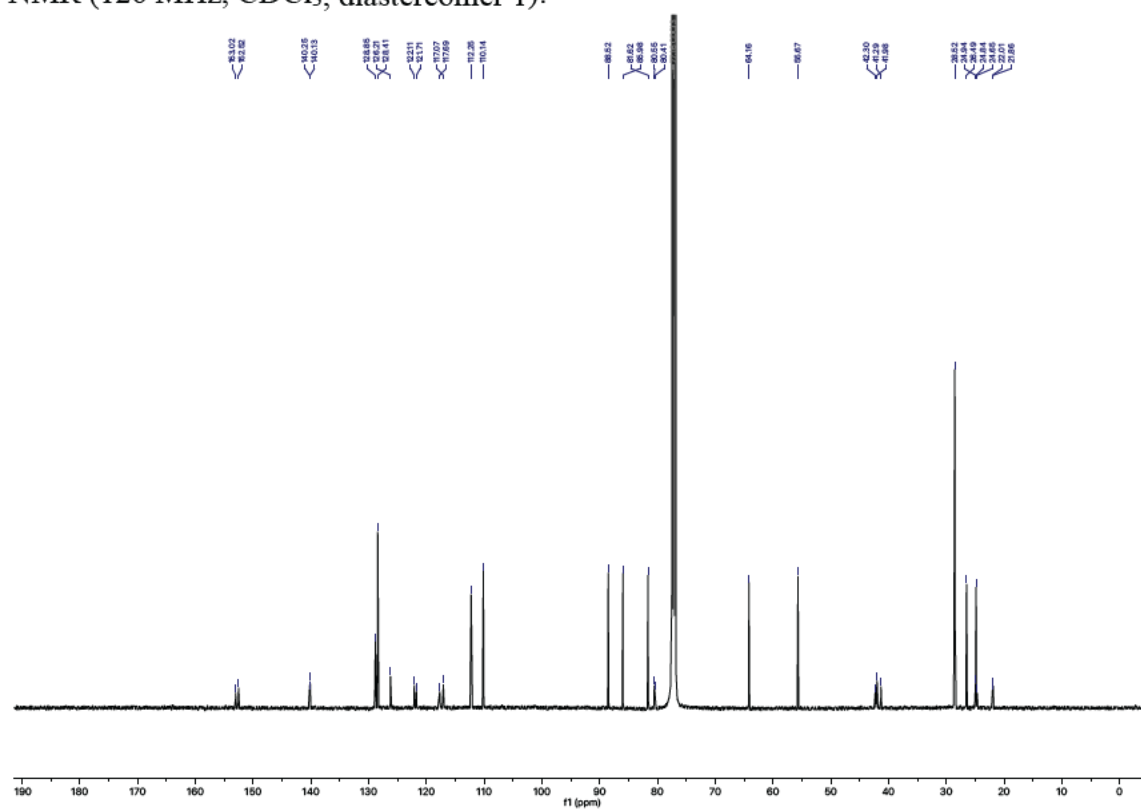
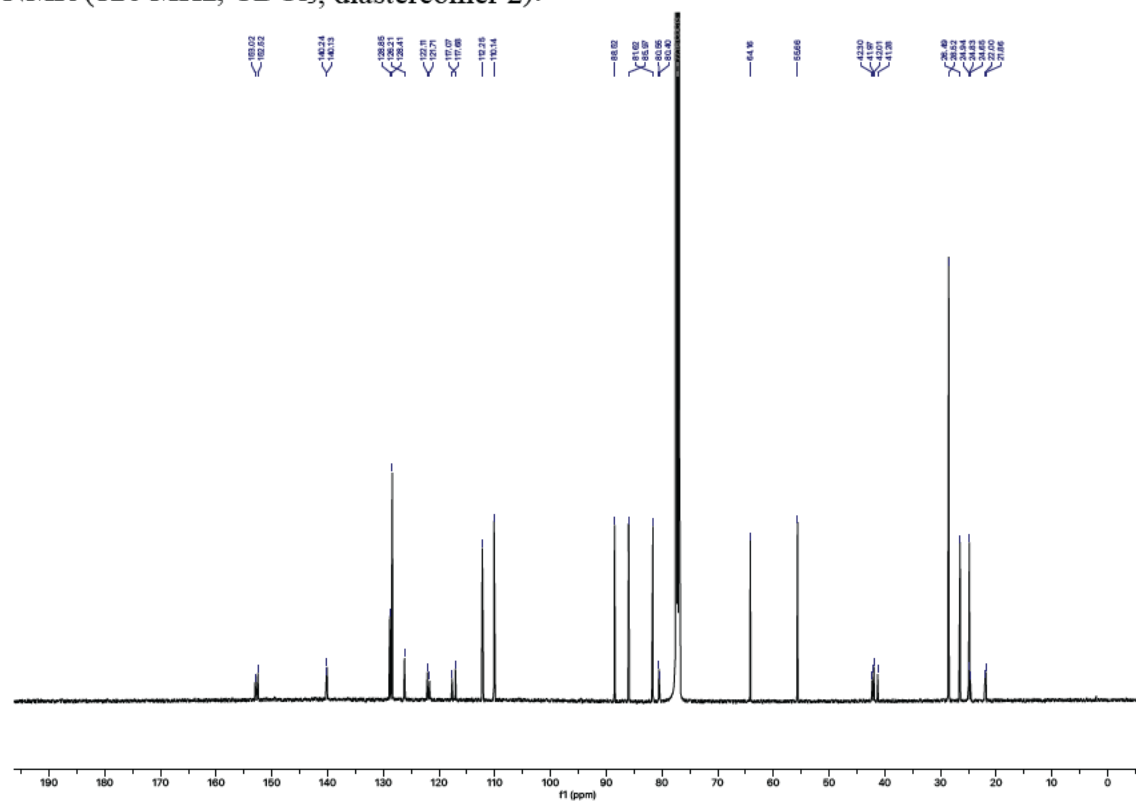
¹H NMR (500 MHz, CDCl₃): ^{13}C NMR (126 MHz, CDCl_3):

¹H NMR (500 MHz, CDCl₃): ^{13}C NMR (126 MHz, CDCl_3):

***Tert*-butyl 3-benzyl-3-((1-(*tert*-butoxycarbonyl)azetidin-3-yl)methoxy)piperidine-1-carboxylate (30)**

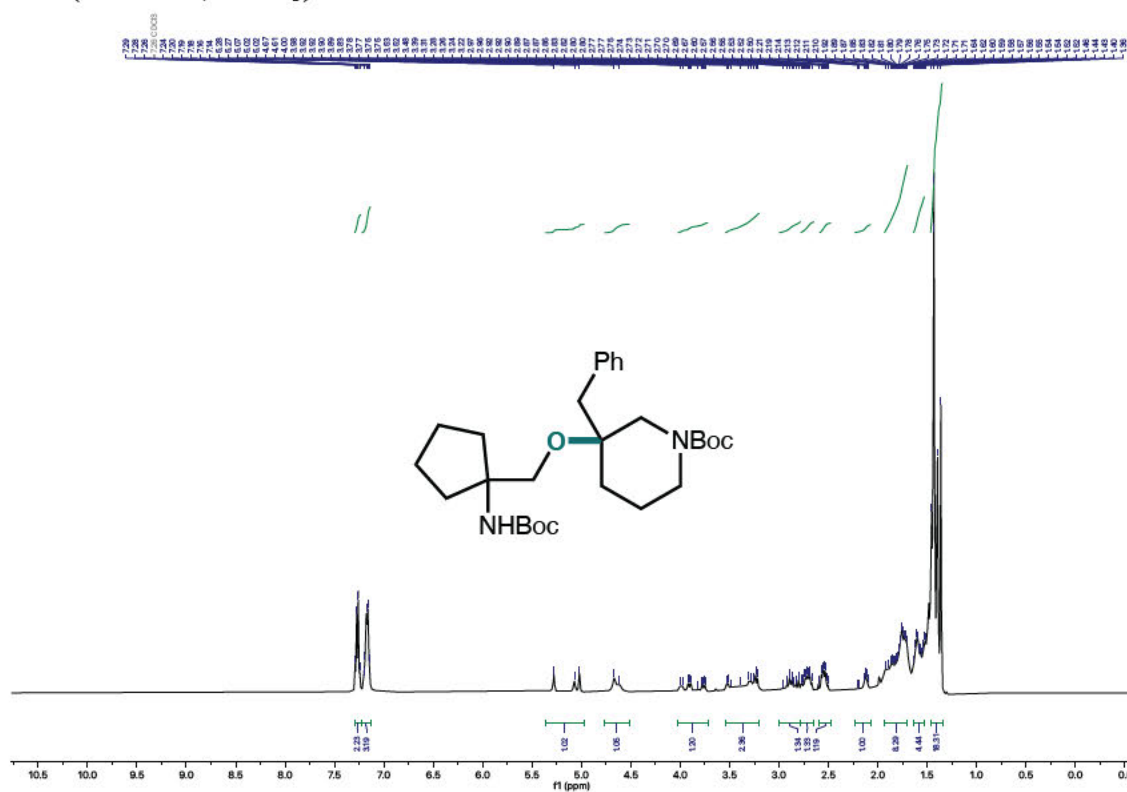
¹H NMR (500 MHz, CDCl₃): ^{13}C NMR (126 MHz, CDCl_3):

¹H NMR (500 MHz, CDCl₃, diastereomer 1):

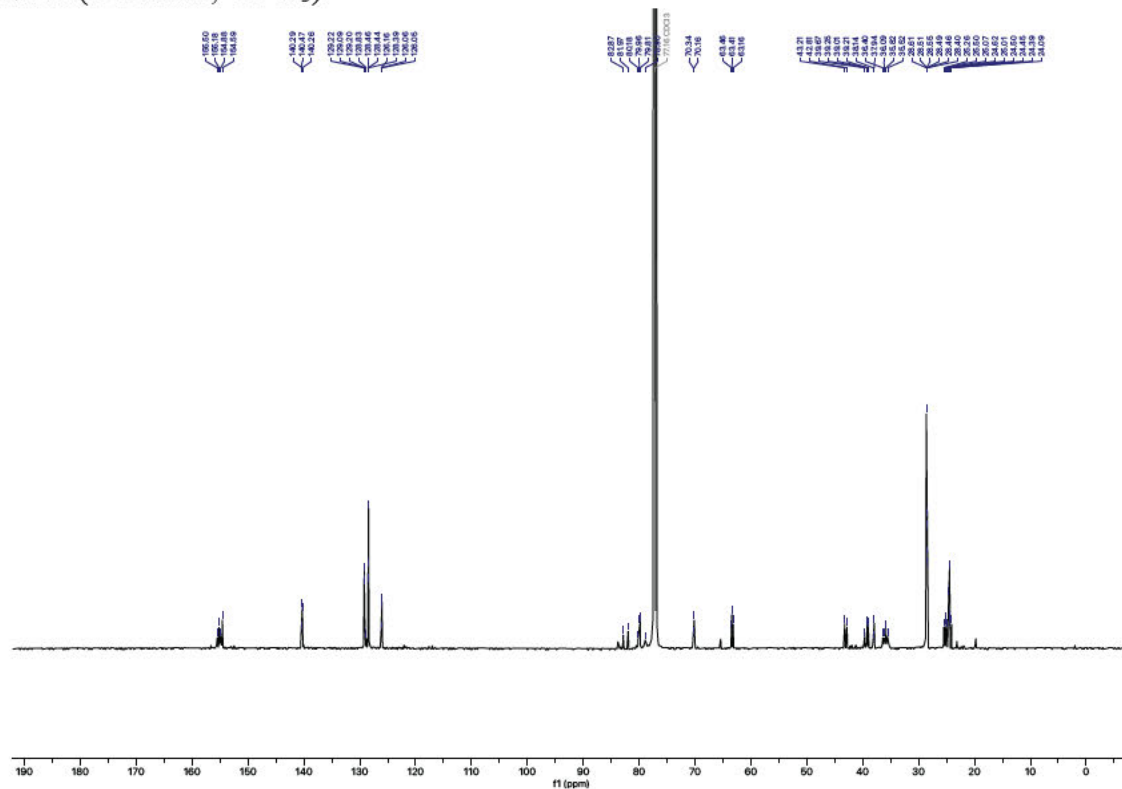
¹³C NMR (126 MHz, CDCl₃, diastereomer 1):¹³C NMR (126 MHz, CDCl₃, diastereomer 2):

***Tert*-butyl 3-benzyl-3-((1-(((*tert*-butoxycarbonyl)amino)cyclopentyl)methoxy)piperidine-1-carboxylate (32)**

^1H NMR (500 MHz, CDCl_3):

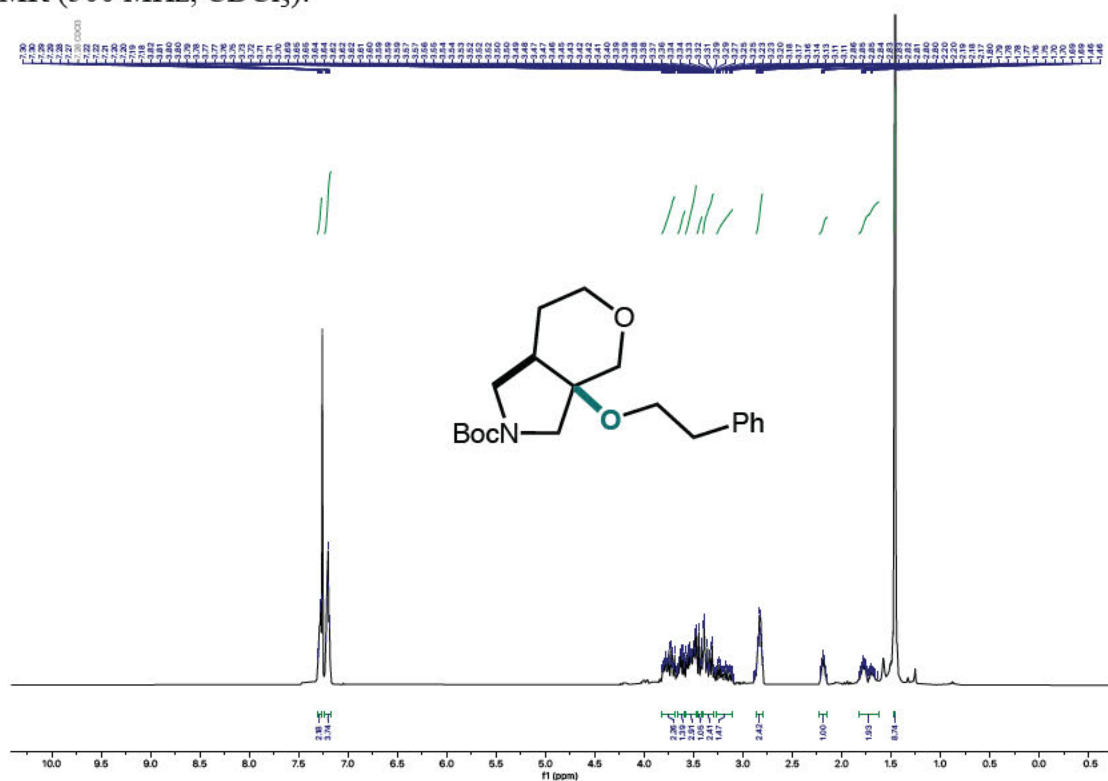


^{13}C NMR (126 MHz, CDCl_3):

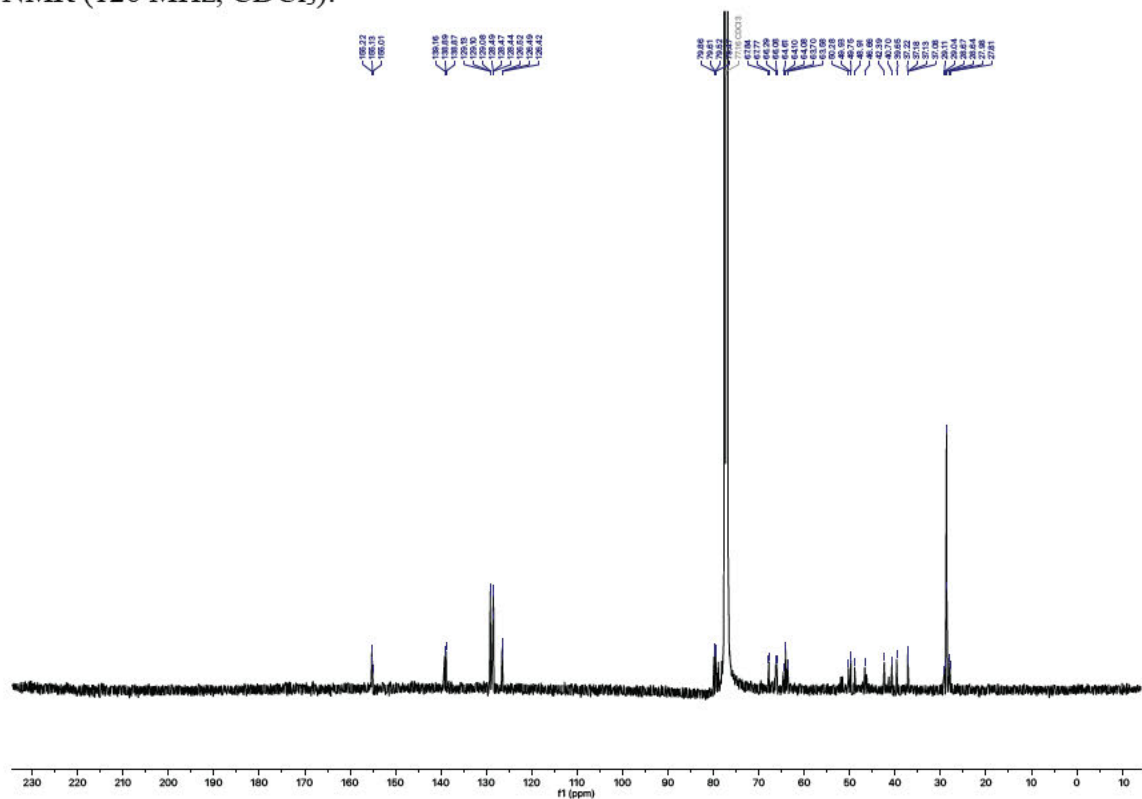


***Tert*-butyl (3aR/S,7aR)-3a-phenethoxyhexahydropyrano[3,4-c]pyrrole-2(3H)-carboxylate (33)**

¹H NMR (500 MHz, CDCl₃):

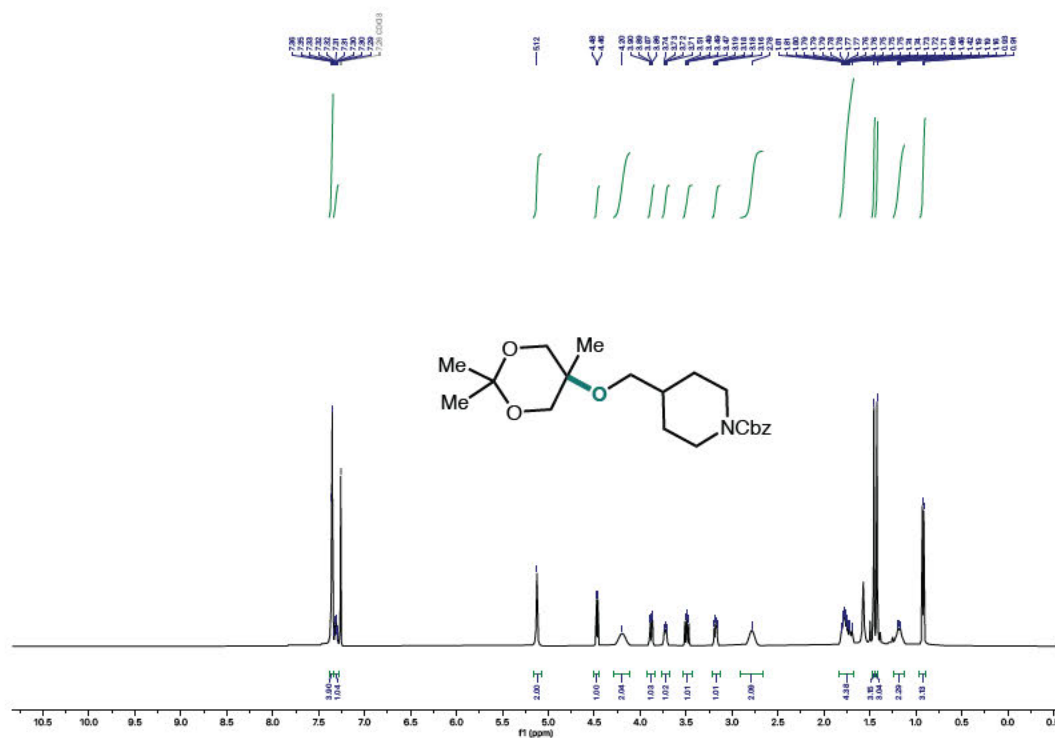


¹³C NMR (126 MHz, CDCl₃):

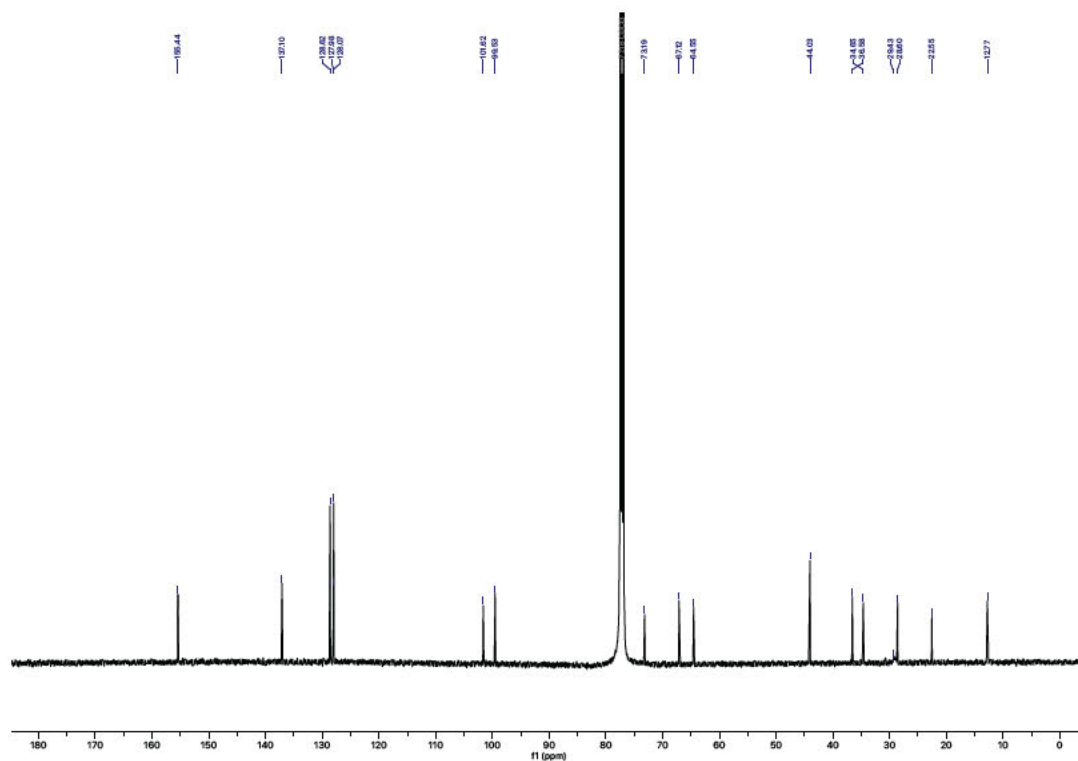


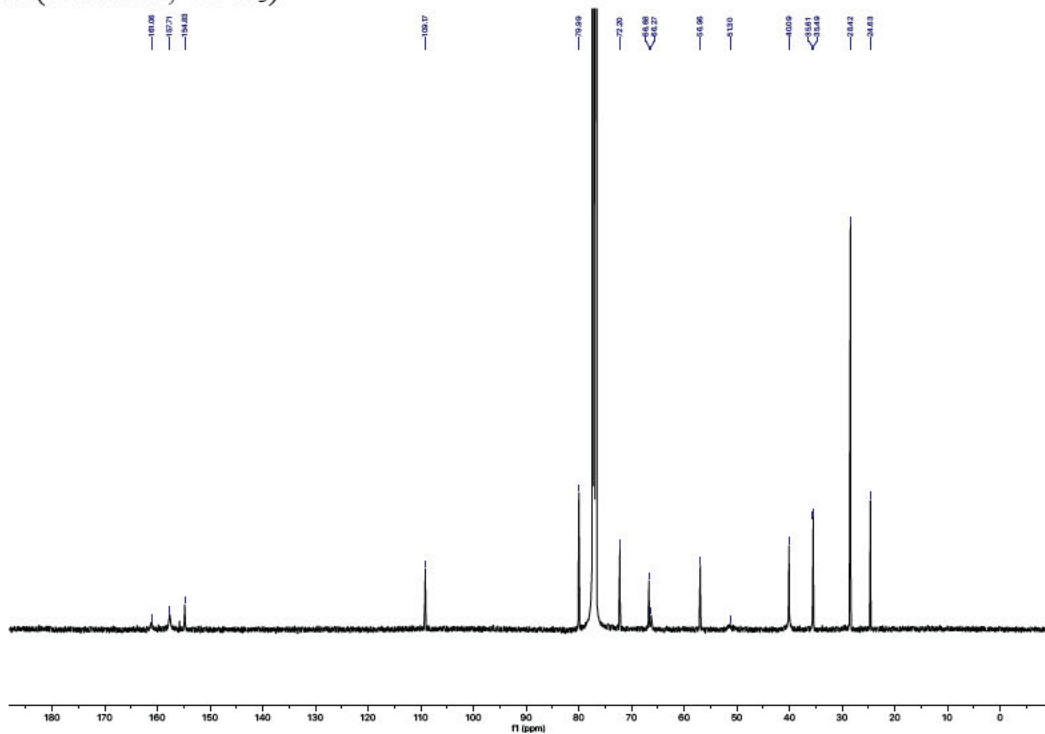
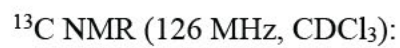
Benzyl 4-(((2,2,5-trimethyl-1,3-dioxan-5-yl)oxy)methyl)piperidine-1-carboxylate (34)

^1H NMR (500 MHz, CDCl_3):



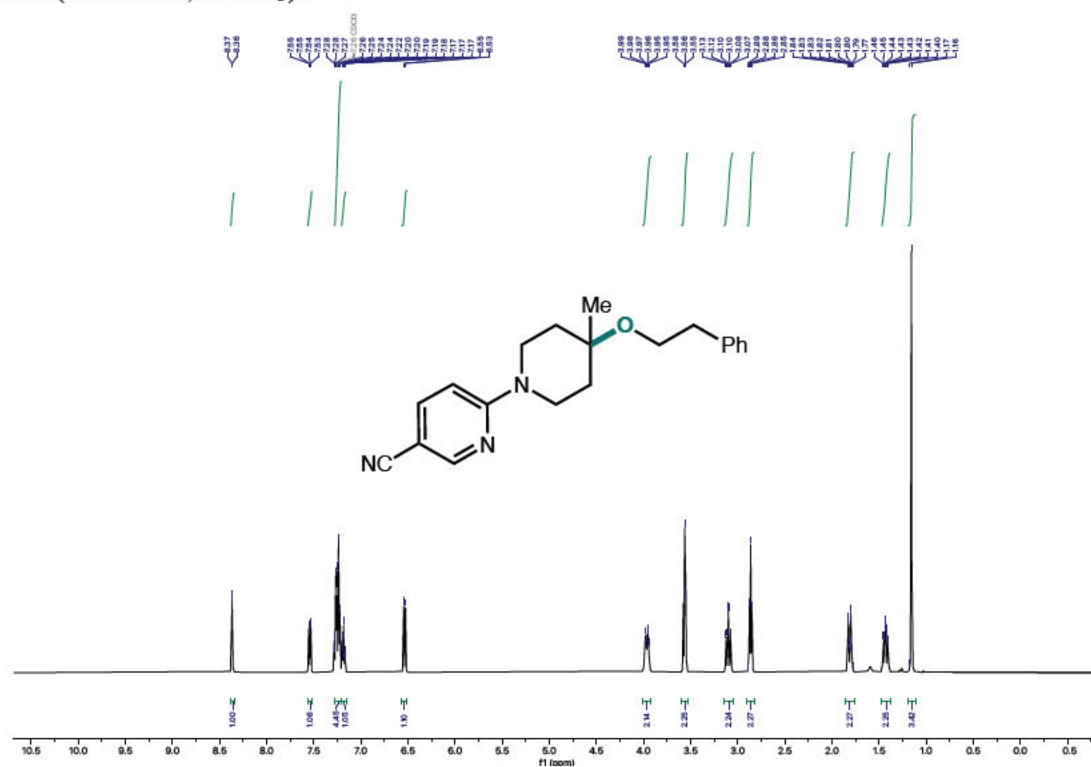
^{13}C NMR (126 MHz, CDCl_3):



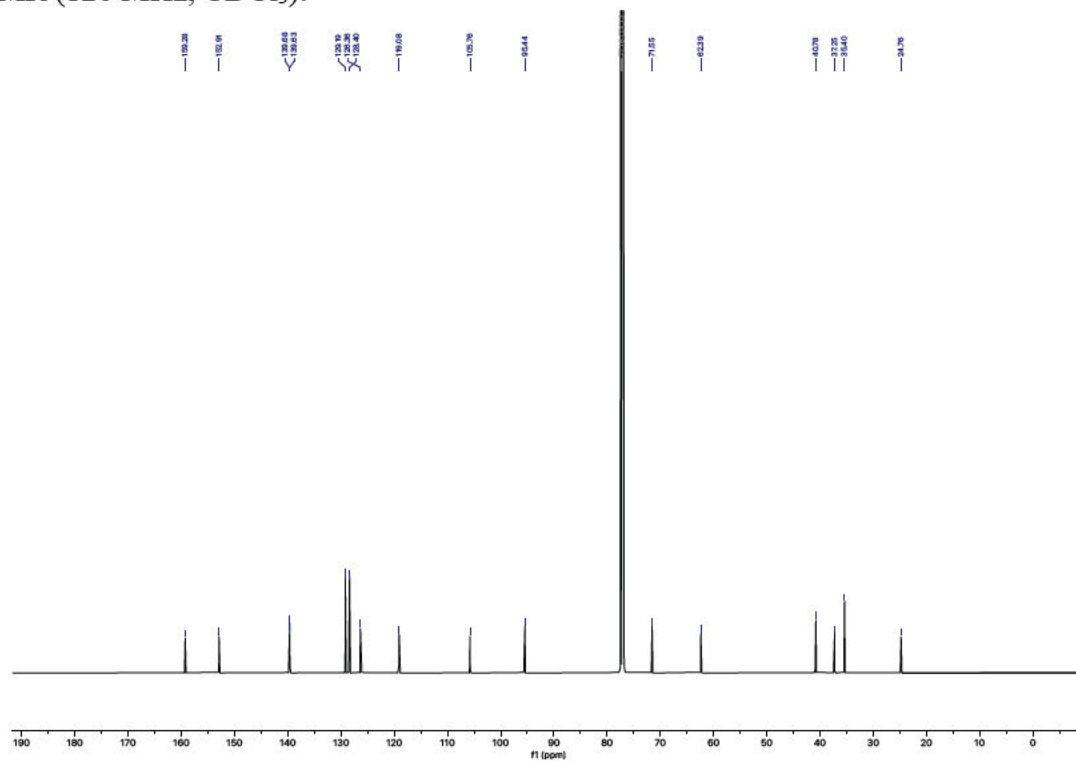
¹H NMR (500 MHz, CDCl₃):

6-(4-methyl-4-phenethoxypiperidin-1-yl)nicotinonitrile (36)

¹H NMR (500 MHz, CDCl₃):

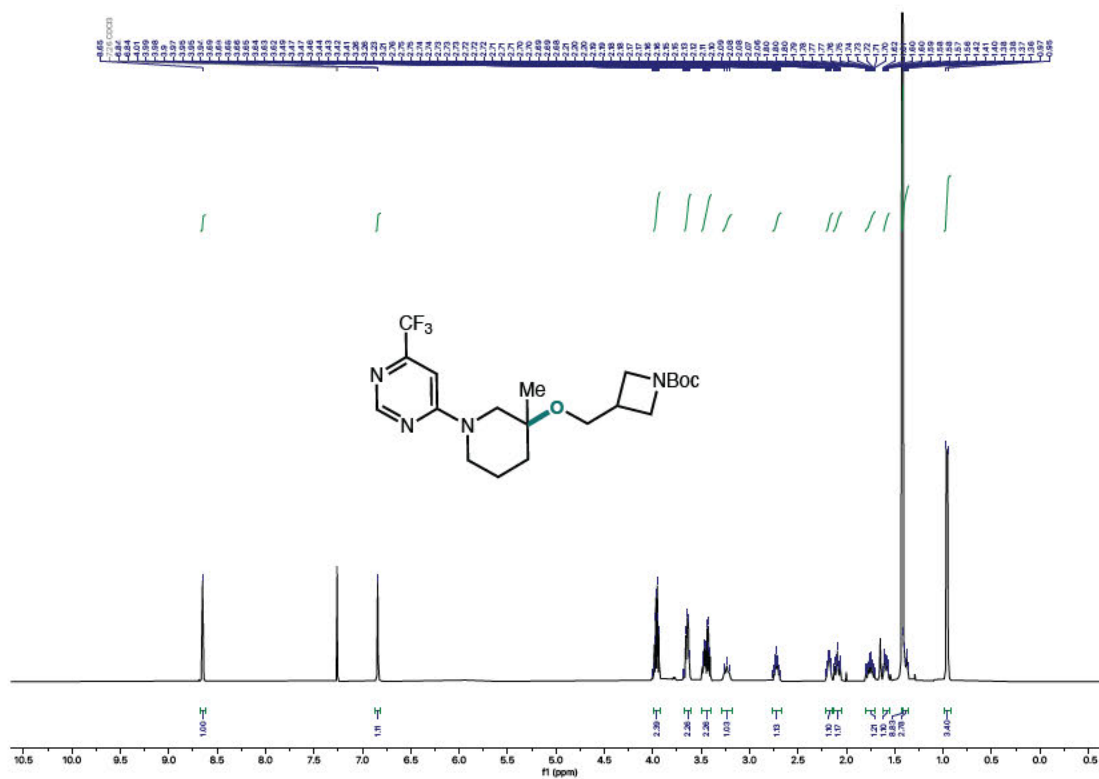


¹³C NMR (126 MHz, CDCl₃):

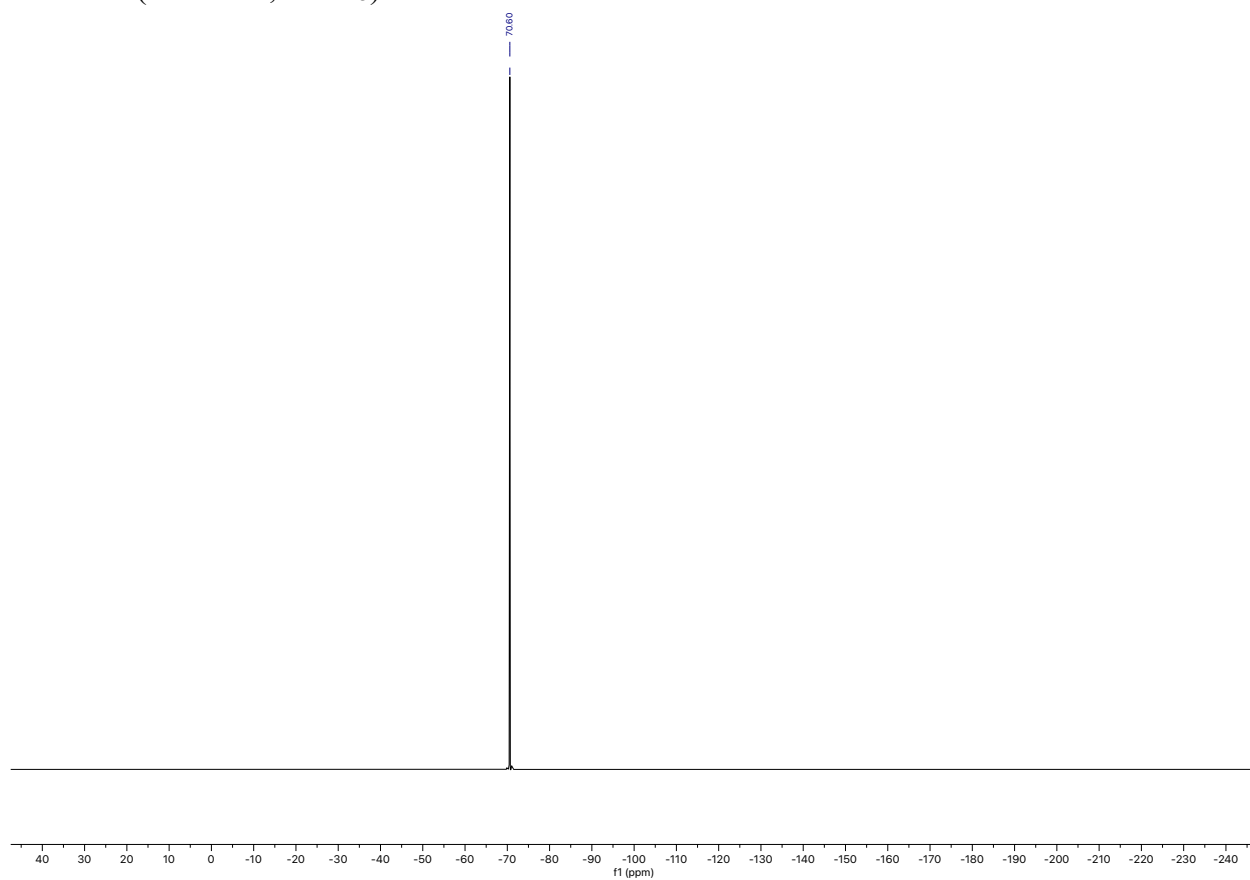


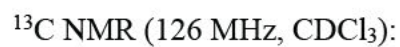
***Tert*-butyl 3-(((4-methyl-1-(6-(trifluoromethyl)pyrimidin-4-yl)piperidin-4-yl)oxy)methyl)azetidine-1-carboxylate (37)**

^1H NMR (500 MHz, CDCl_3):

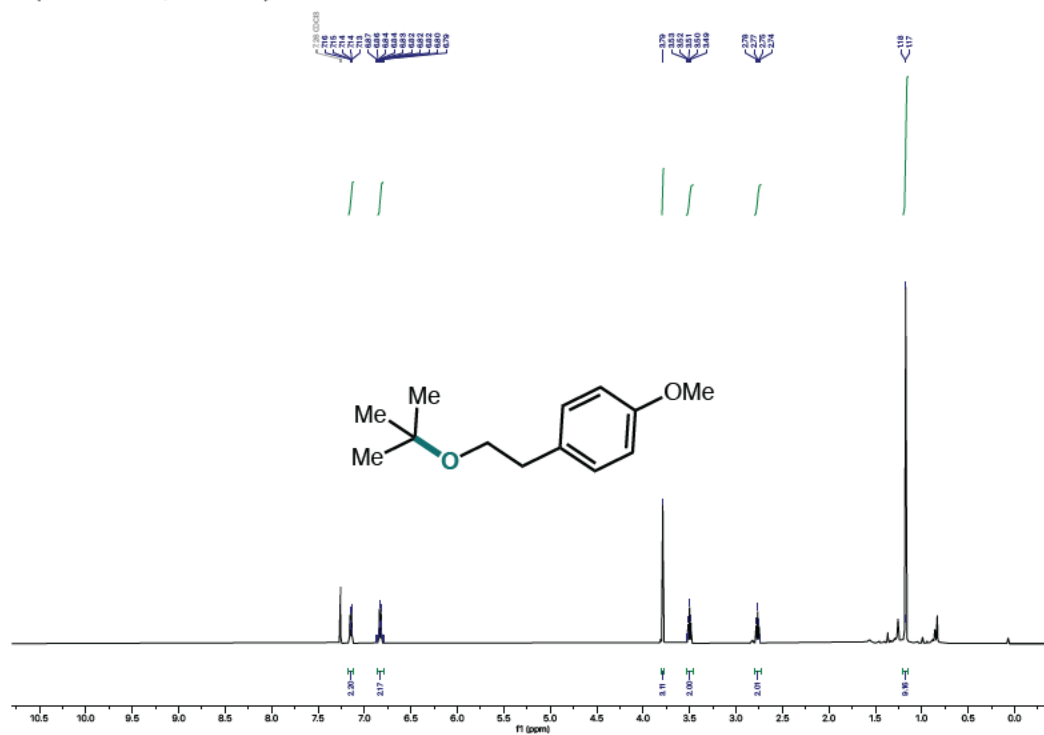
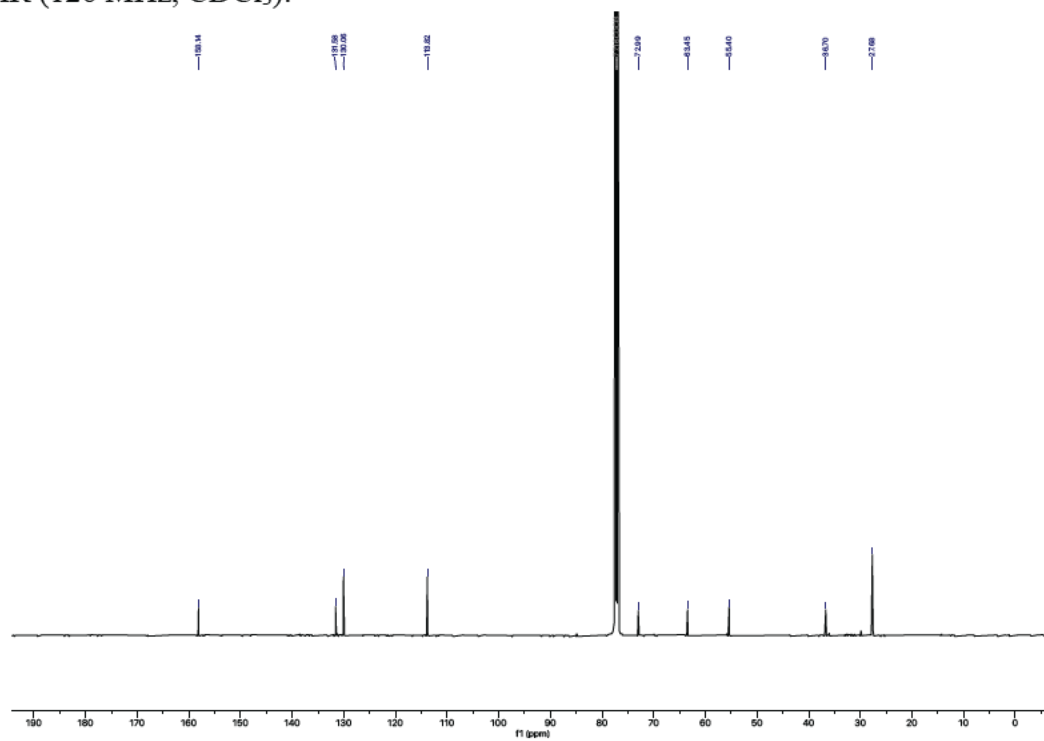


^{19}F NMR (471 MHz, CDCl_3)

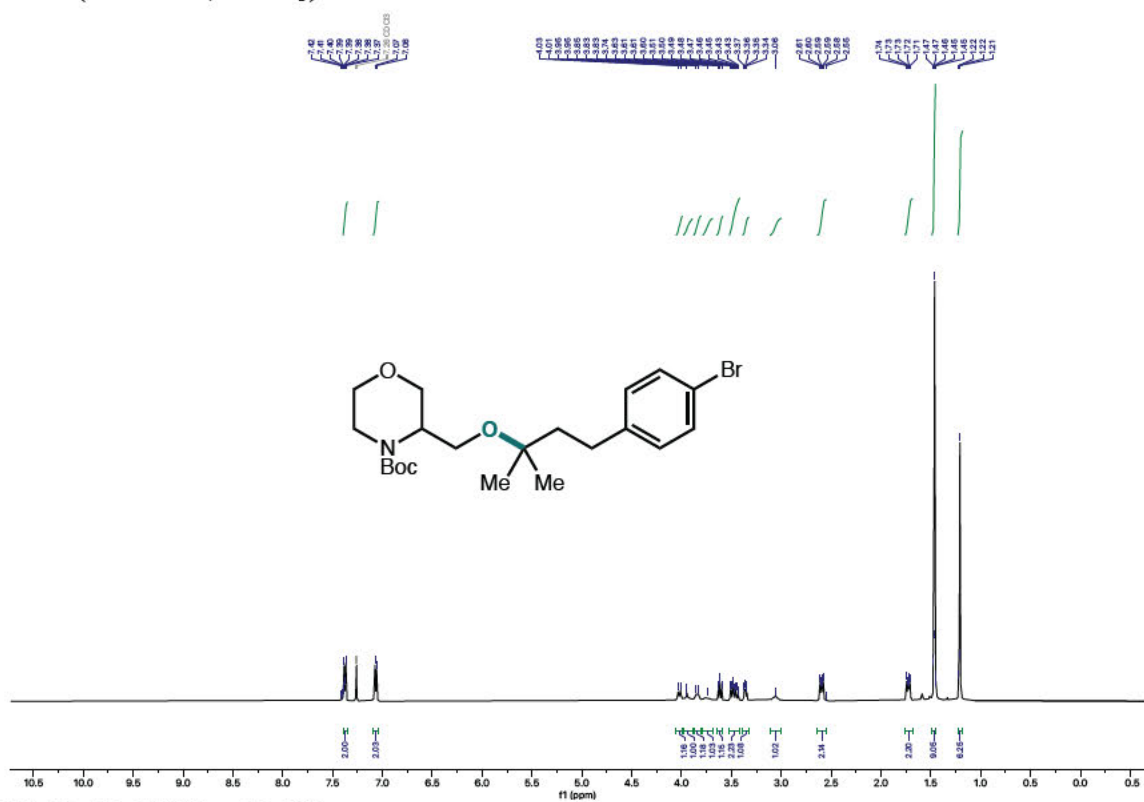
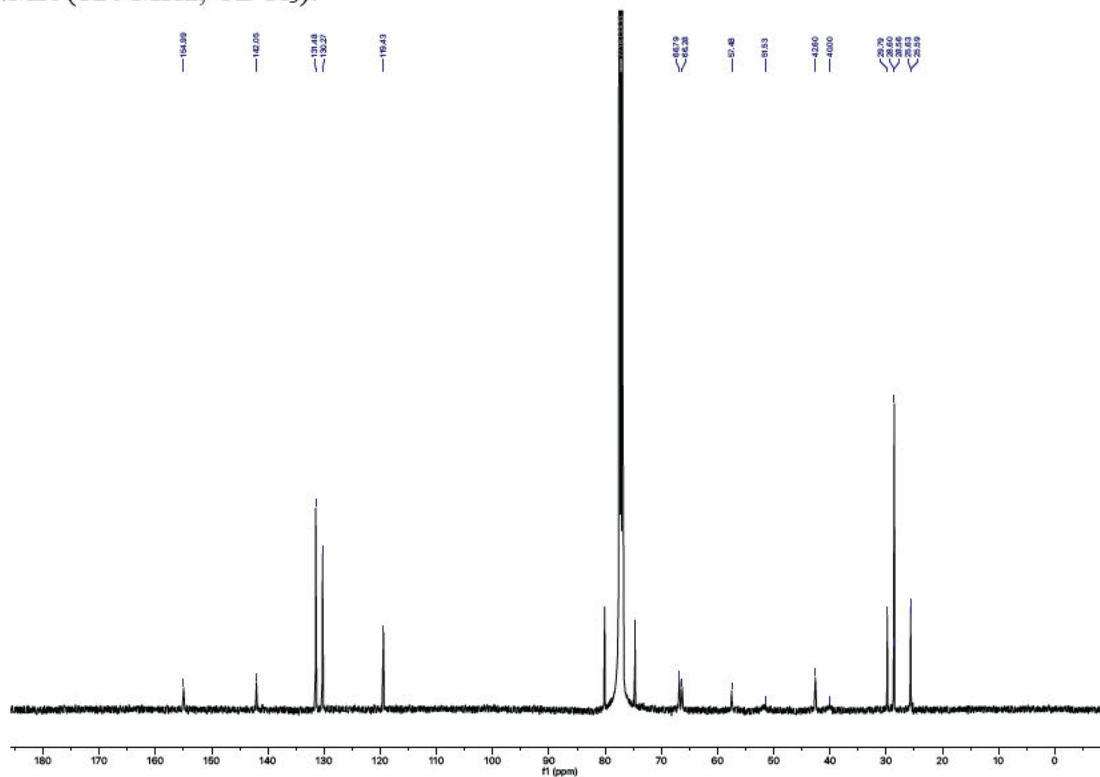


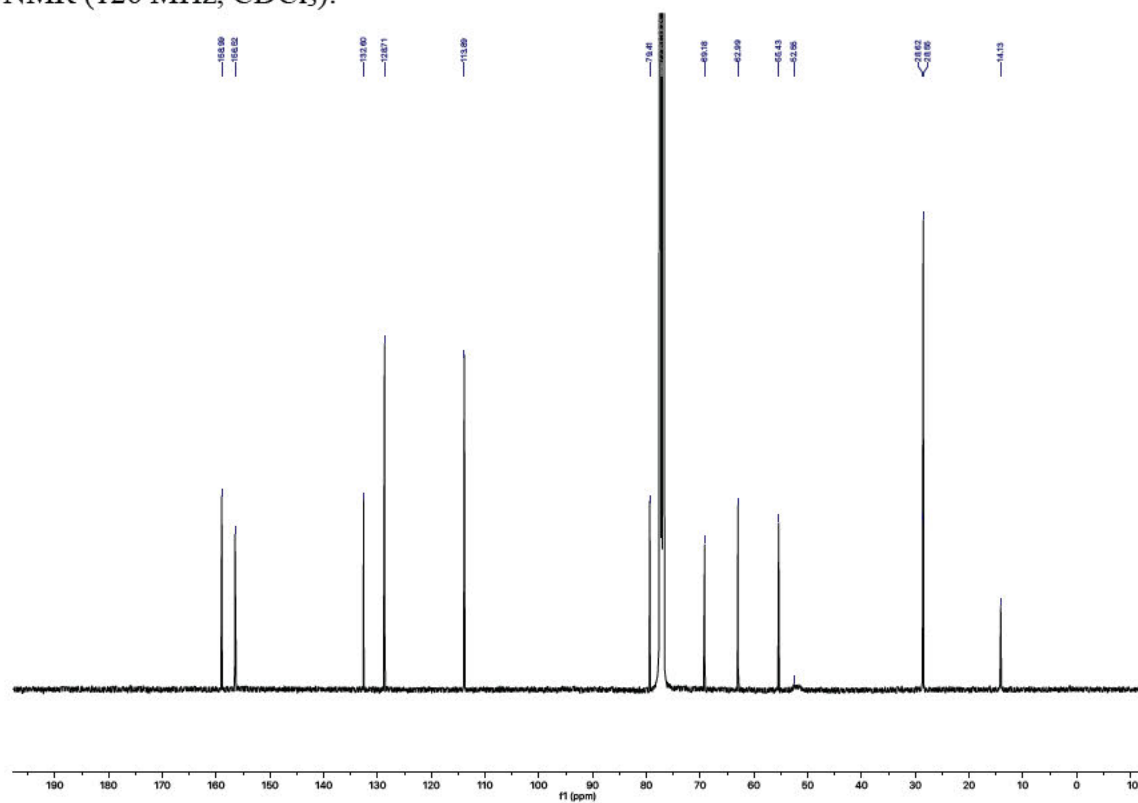
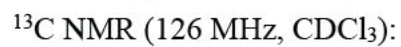
¹H NMR (500 MHz, CDCl₃):

¹H NMR (500 MHz, CDCl₃):

¹H NMR (500 MHz, CDCl₃):¹³C NMR (126 MHz, CDCl₃):

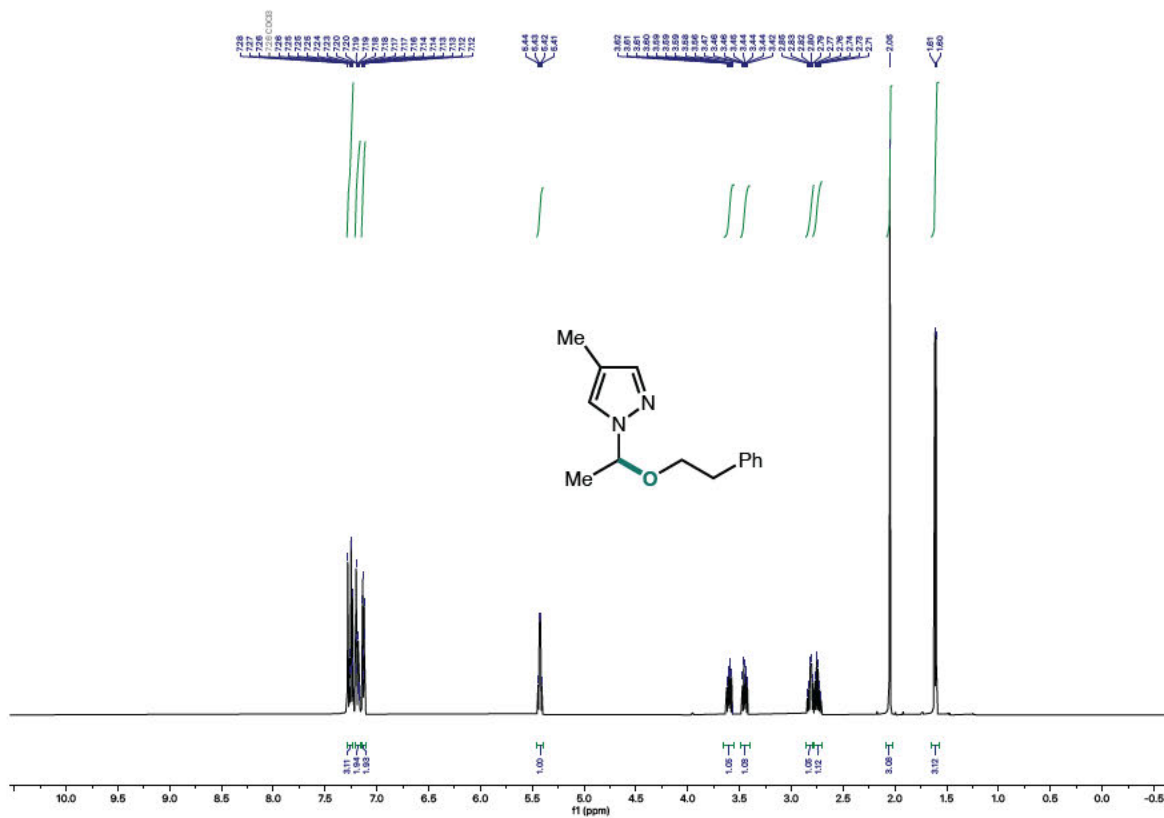
***Tert*-butyl 3-(((4-(4-bromophenyl)-2-methylbutan-2-yl)oxy)methyl)morpholine-4-carboxylate (41)**

¹H NMR (500 MHz, CDCl₃): ^{13}C NMR (126 MHz, CDCl_3):

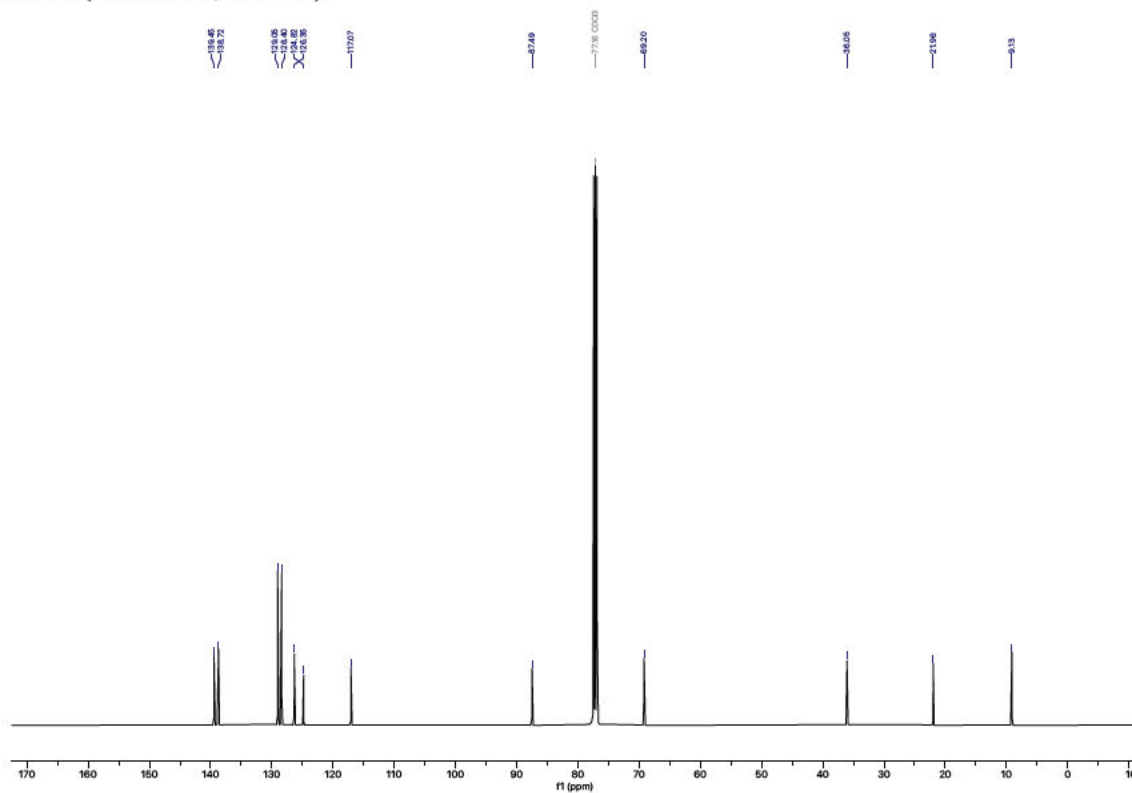
¹H NMR (500 MHz, CDCl₃):

4-Methyl-1-(1-phenethoxyethyl)-1H-pyrazole (43)

^1H NMR (500 MHz, CDCl_3):

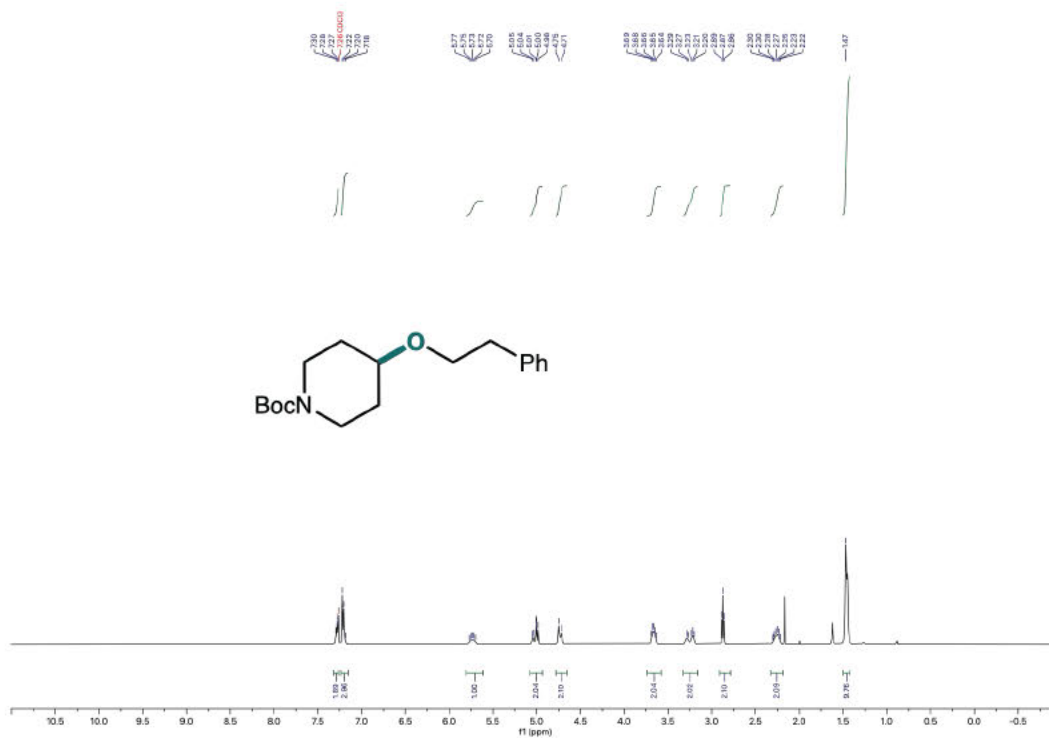


^{13}C NMR (126 MHz, CDCl_3):

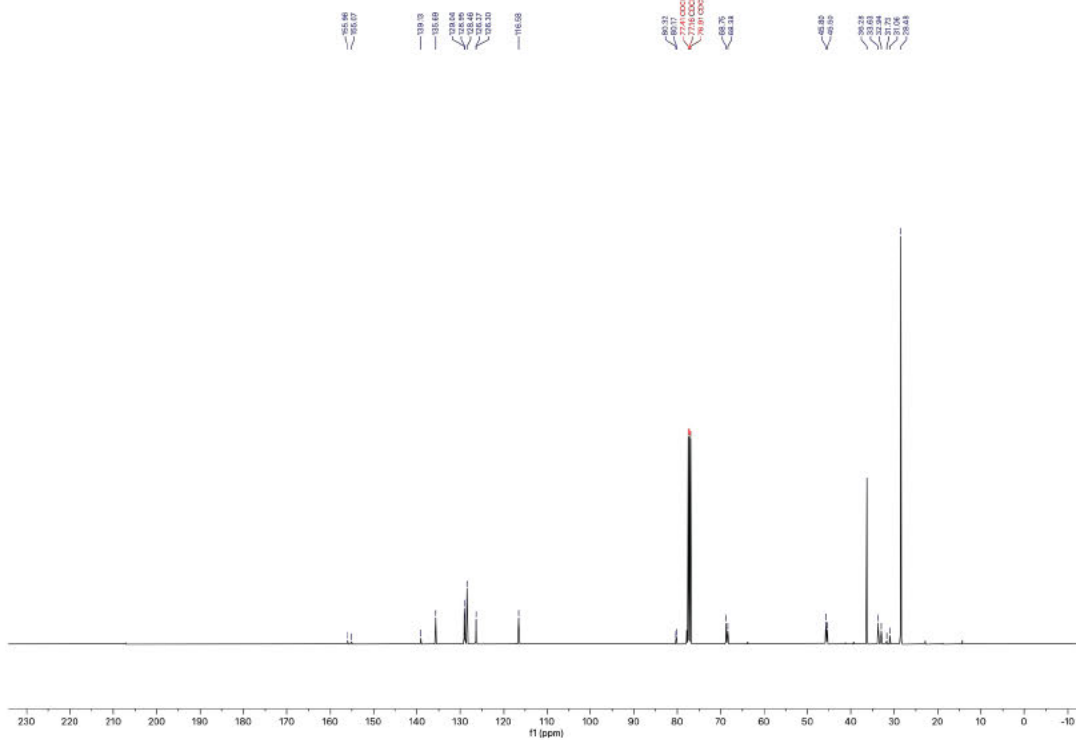


***Tert*-butyl 4-(2-phenylethoxy)piperidine-1-carboxylate**

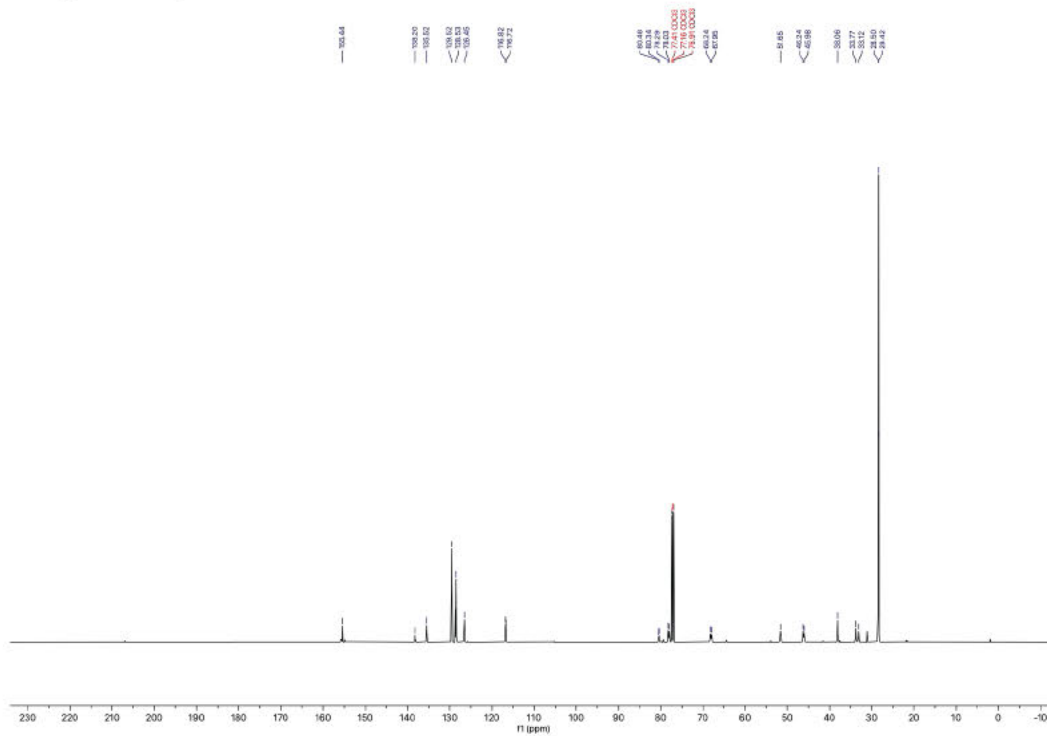
44, ^1H NMR, 500 MHz, CDCl_3



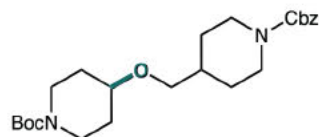
44, ^{13}C NMR, 126 MHz, CDCl_3



45, ^1H NMR, 500 MHz, CDCl_3



46, ^1H NMR, 500 MHz, CDCl_3



— 133.20

— 137.06
— 135.99

— 138.68
— 138.04
— 127.90

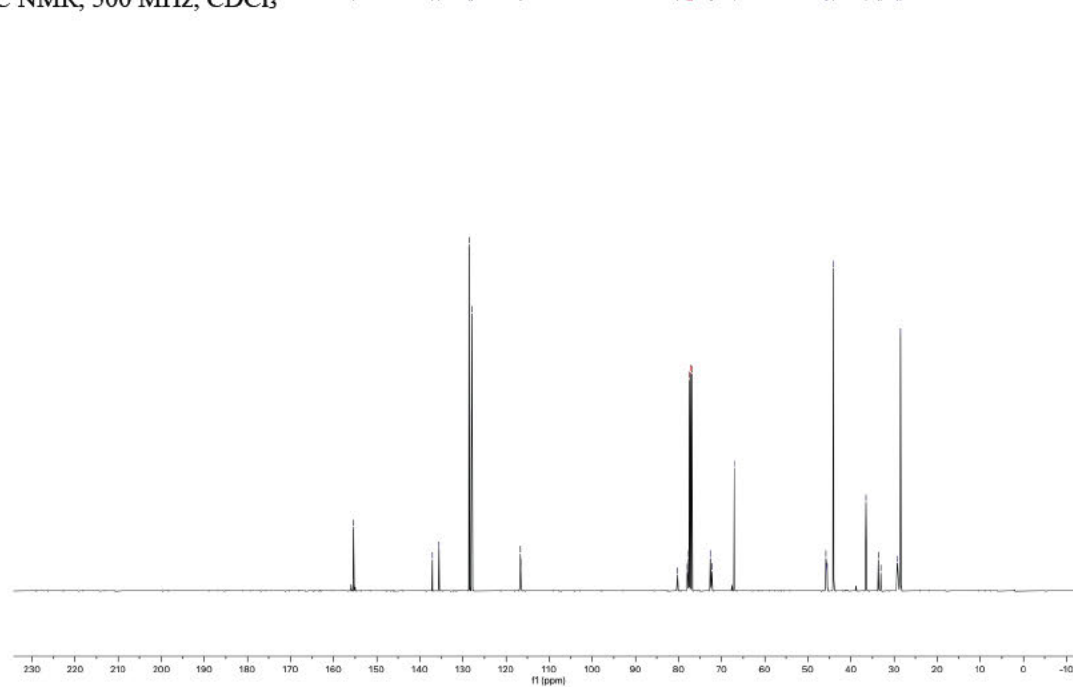
— 116.71
— 116.62

56.22
70.96
70.66
77.42
77.16
76.94
73.81
73.20

— 87.09

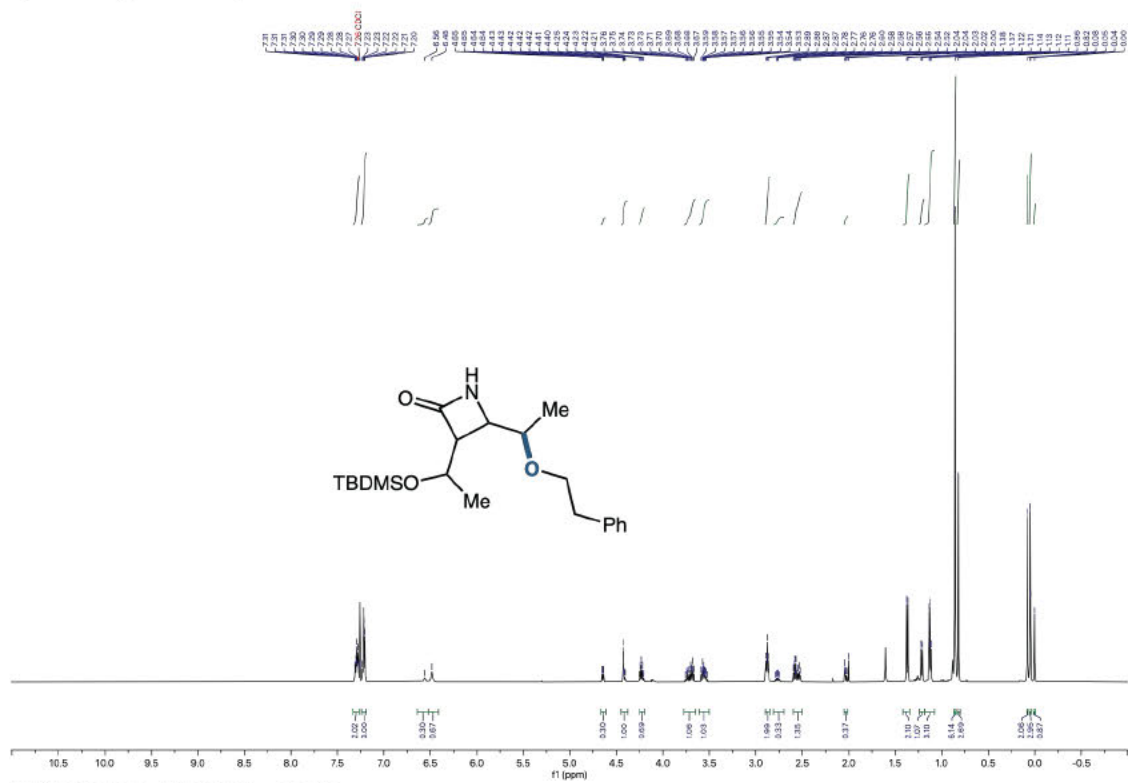
46.84
46.55
43.99

— 36.45
— 33.69
— 33.01
— 26.13
— 26.46

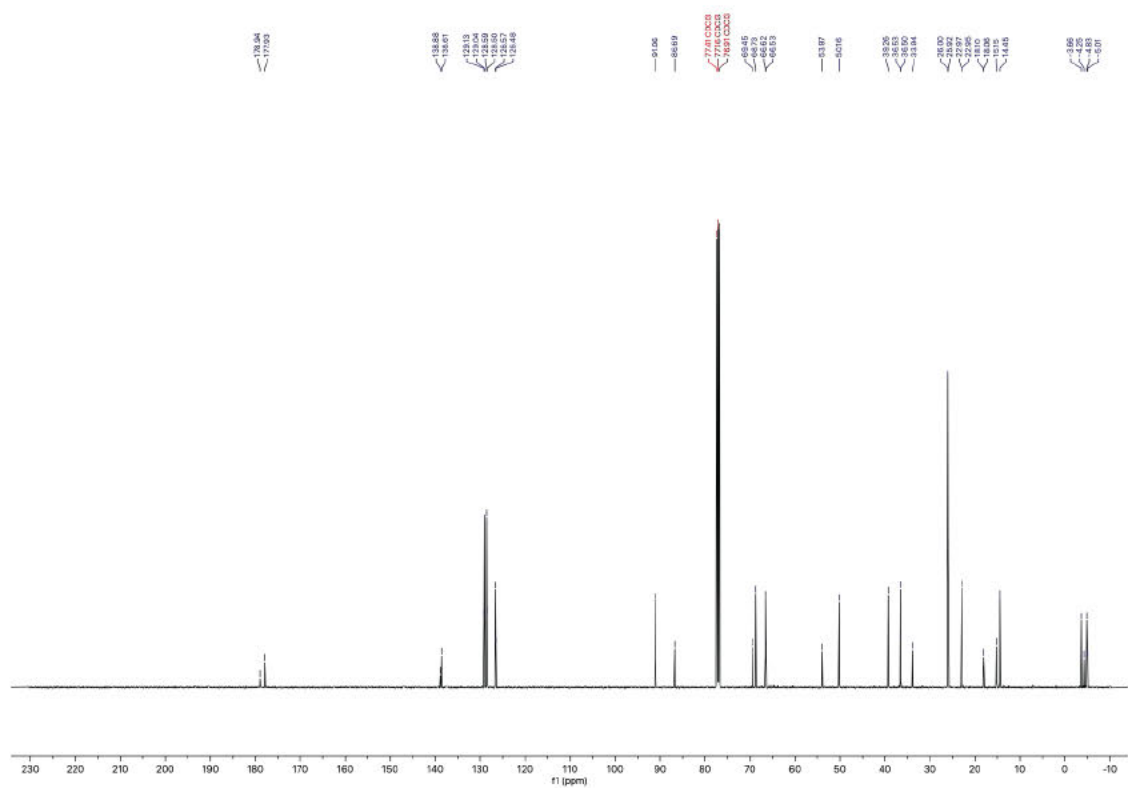


3-(1-((*Tert*-butyldimethylsilyl)oxy)ethyl)-4-(1-phenethoxyethyl)azetidin-2-one

47, ^1H NMR, 500 MHz, CDCl_3

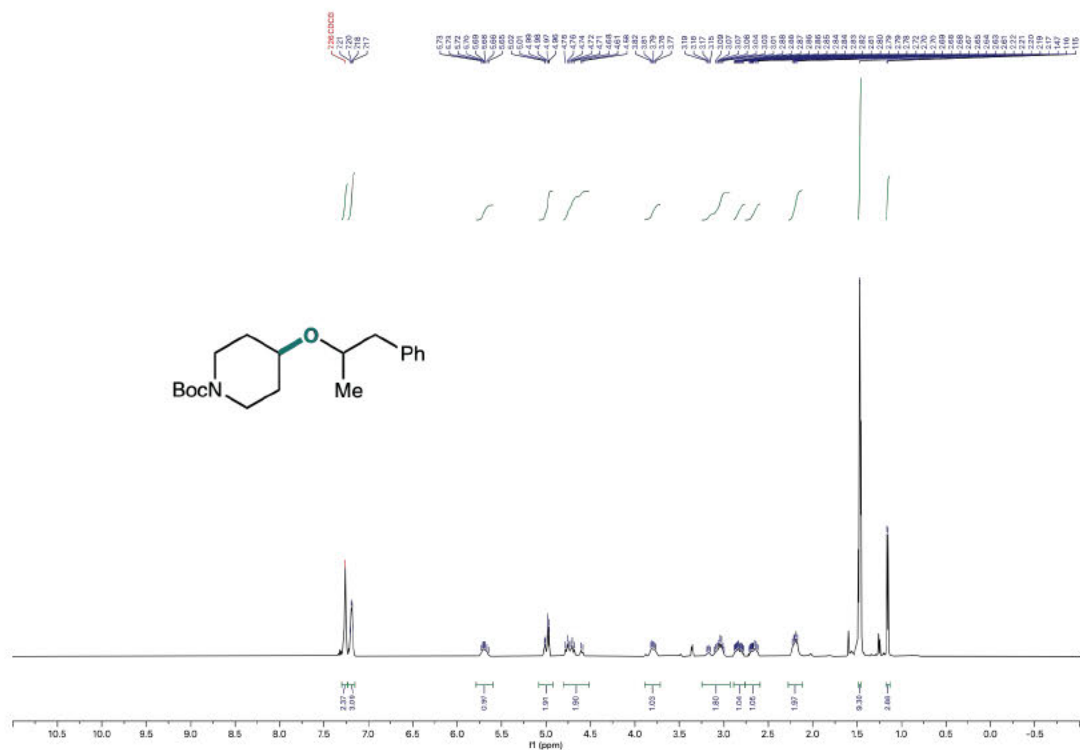


47, ^{13}C NMR, 500 MHz, CDCl_3

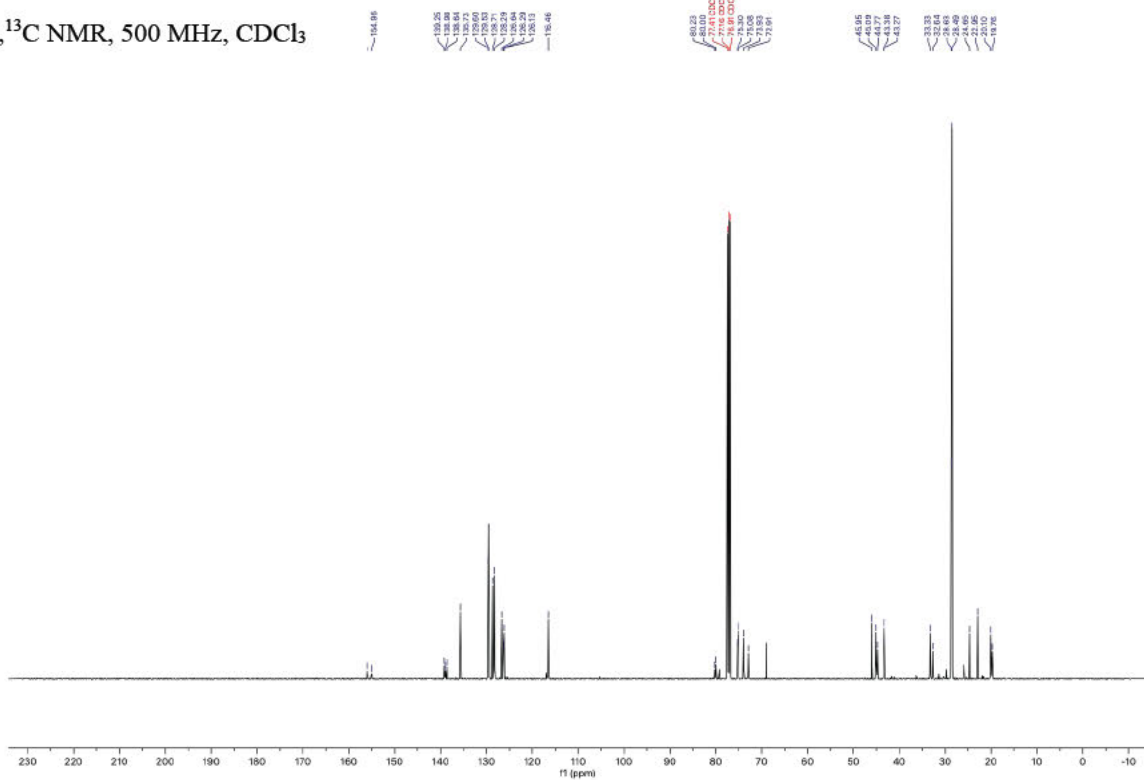


***Tert*-butyl 4-((1-phenylpropan-2-yl)oxy)piperidine-1-carboxylate**

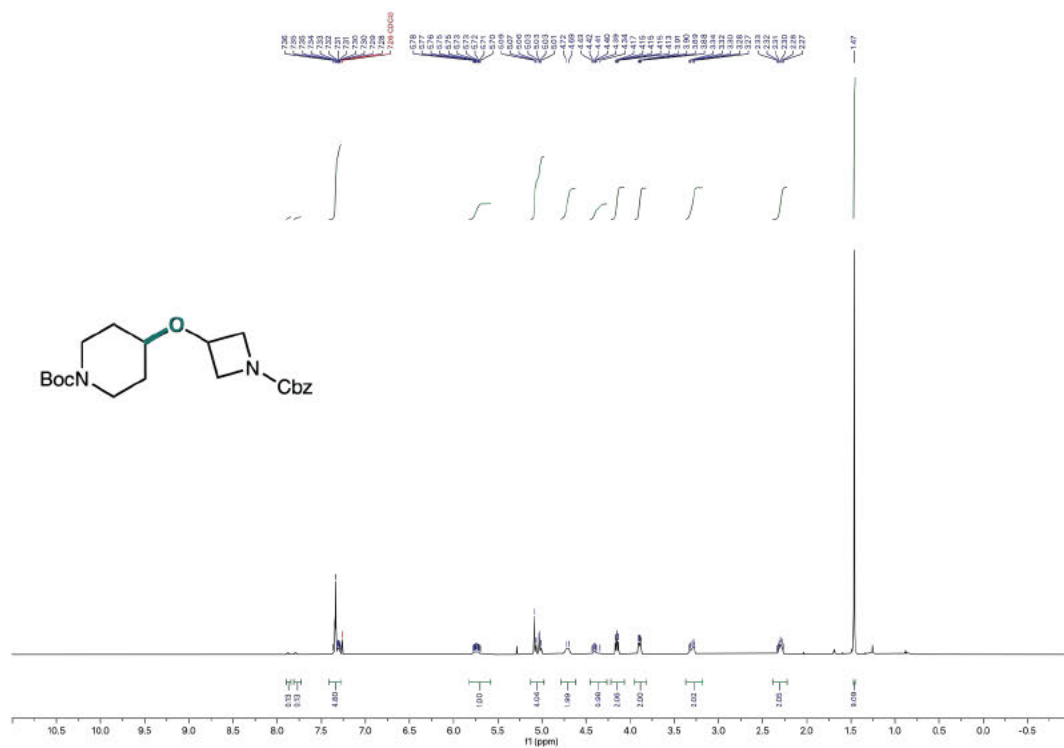
48, ^1H NMR, 500 MHz, CDCl_3



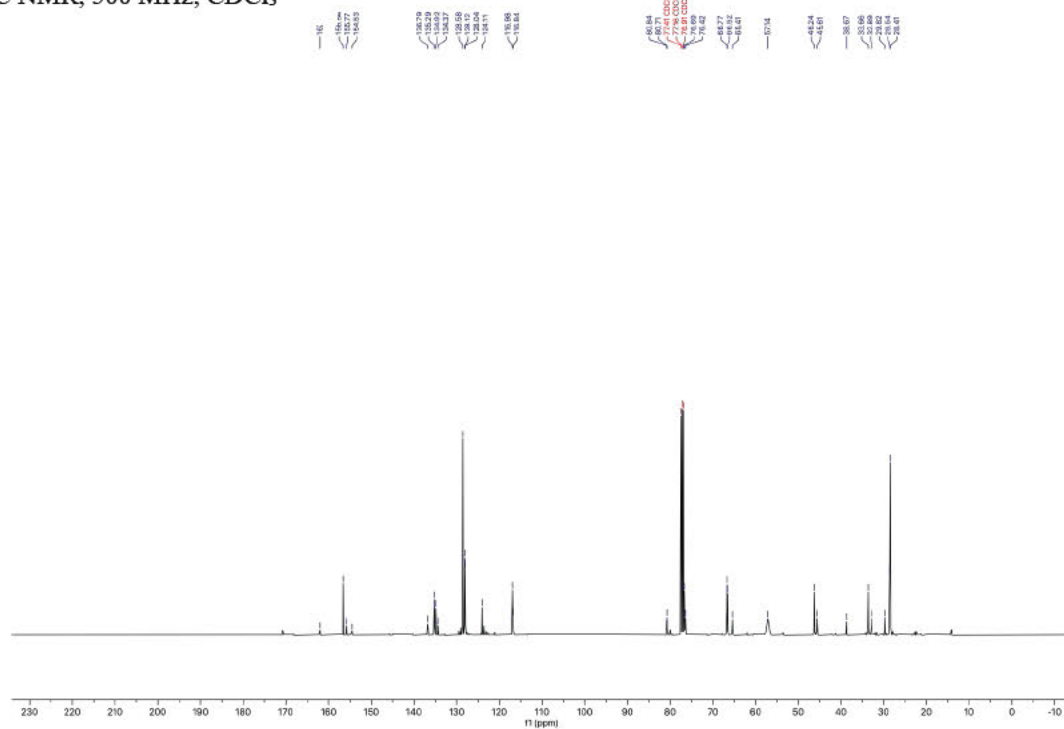
48, ^{13}C NMR, 500 MHz, CDCl_3



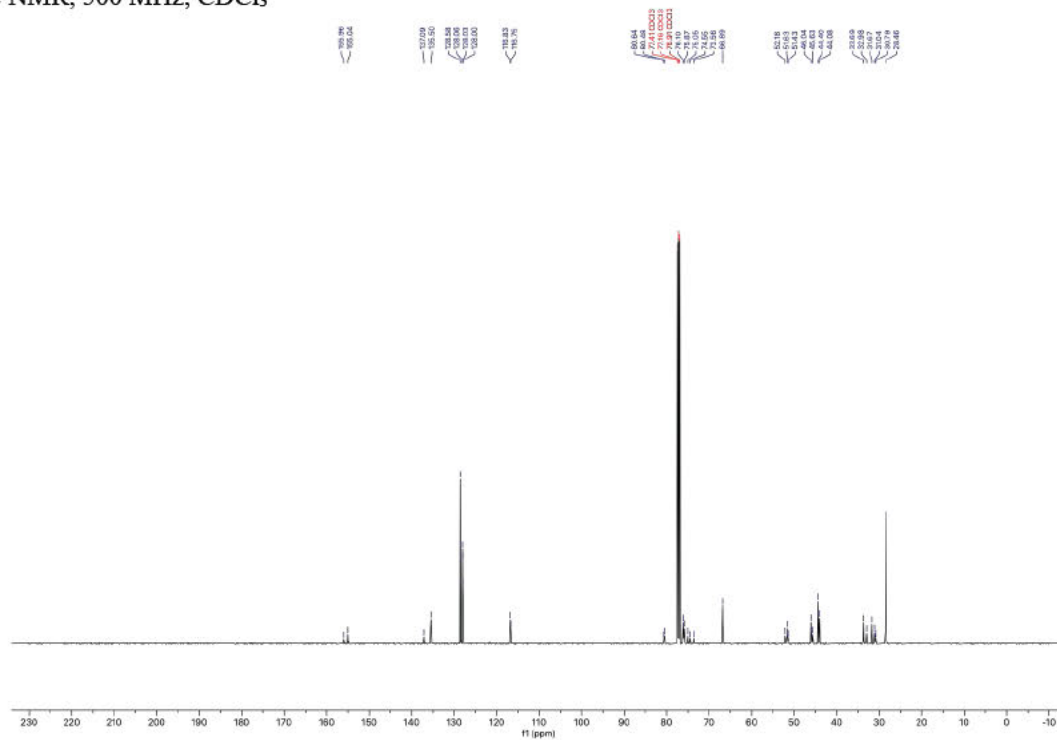
***Tert*-butyl 4-((1-((benzyloxy)carbonyl)azetidin-3-yl)oxy)piperidine-1-carboxylate**
49, ¹H NMR, 500 MHz, CDCl₃



49, ^{13}C NMR, 500 MHz, CDCl_3

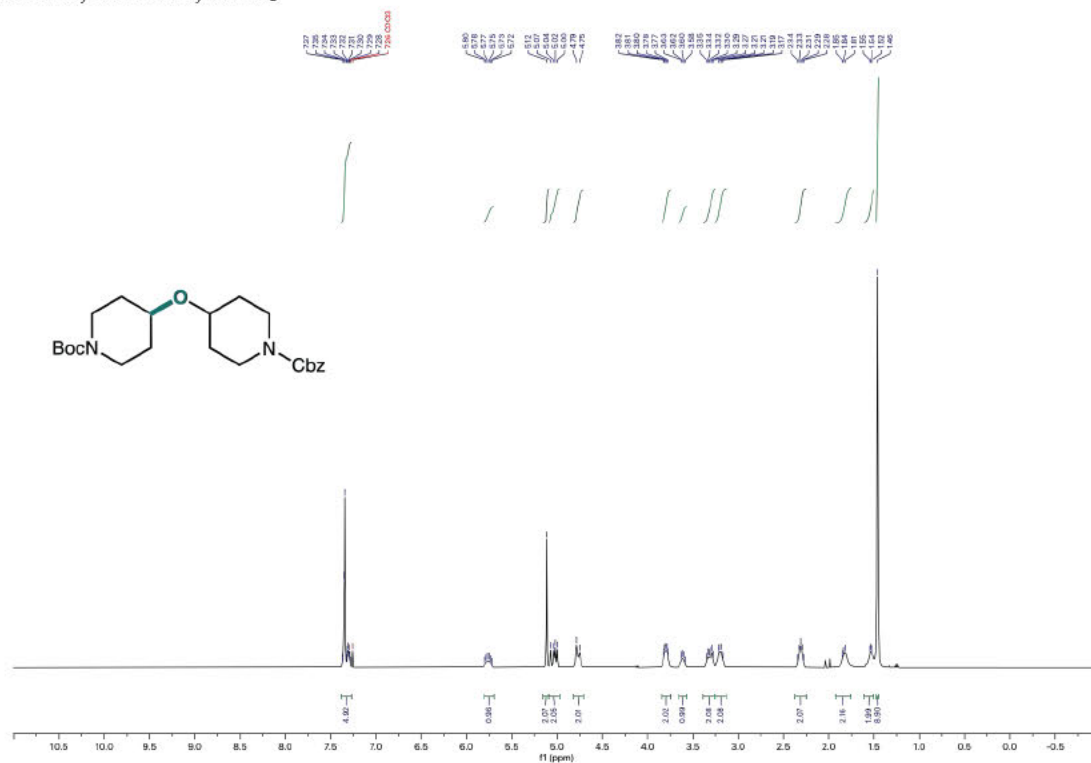


50, ¹H NMR, 500 MHz, CDCl₃

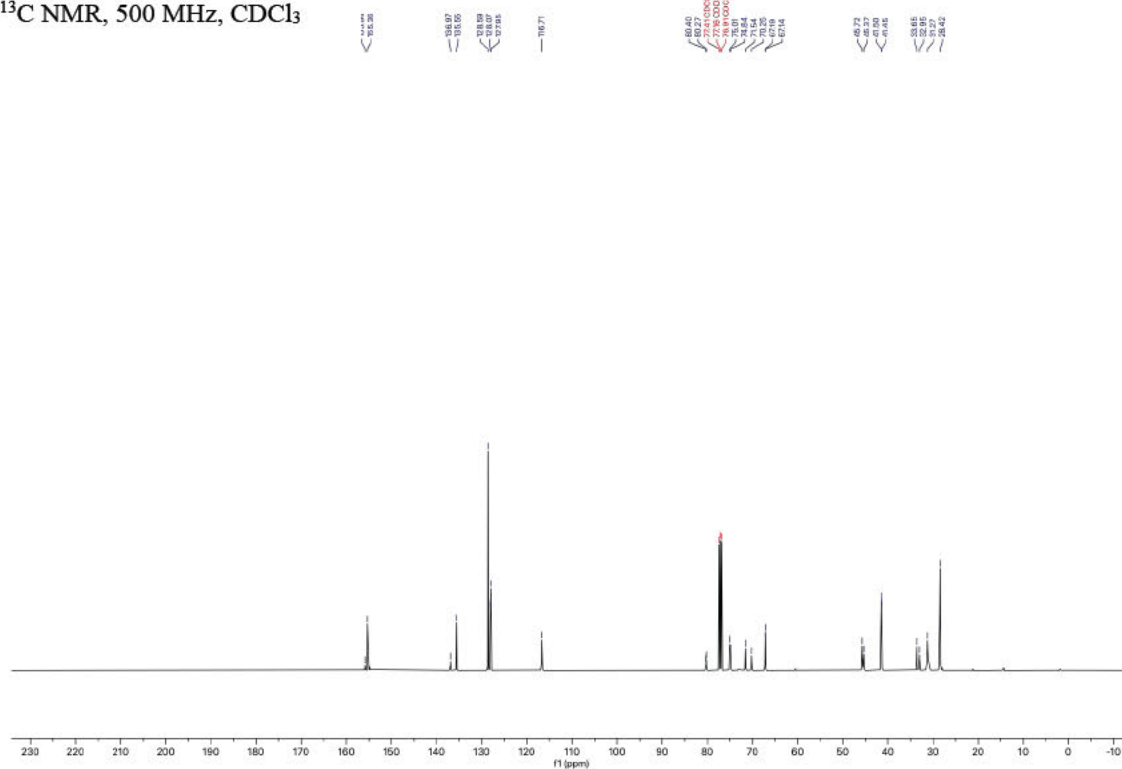


Benzyl 4-[(1-tert-butoxycarbonyl-4-piperidyl)oxy]piperidine-1-carboxylate

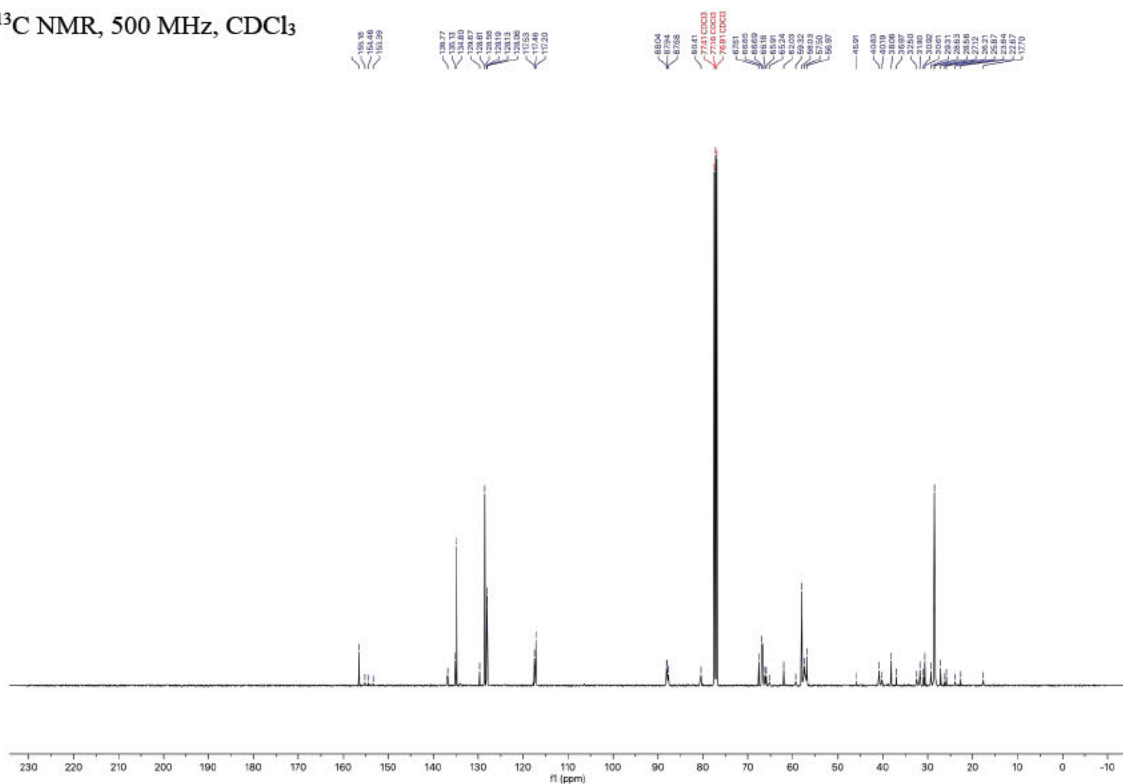
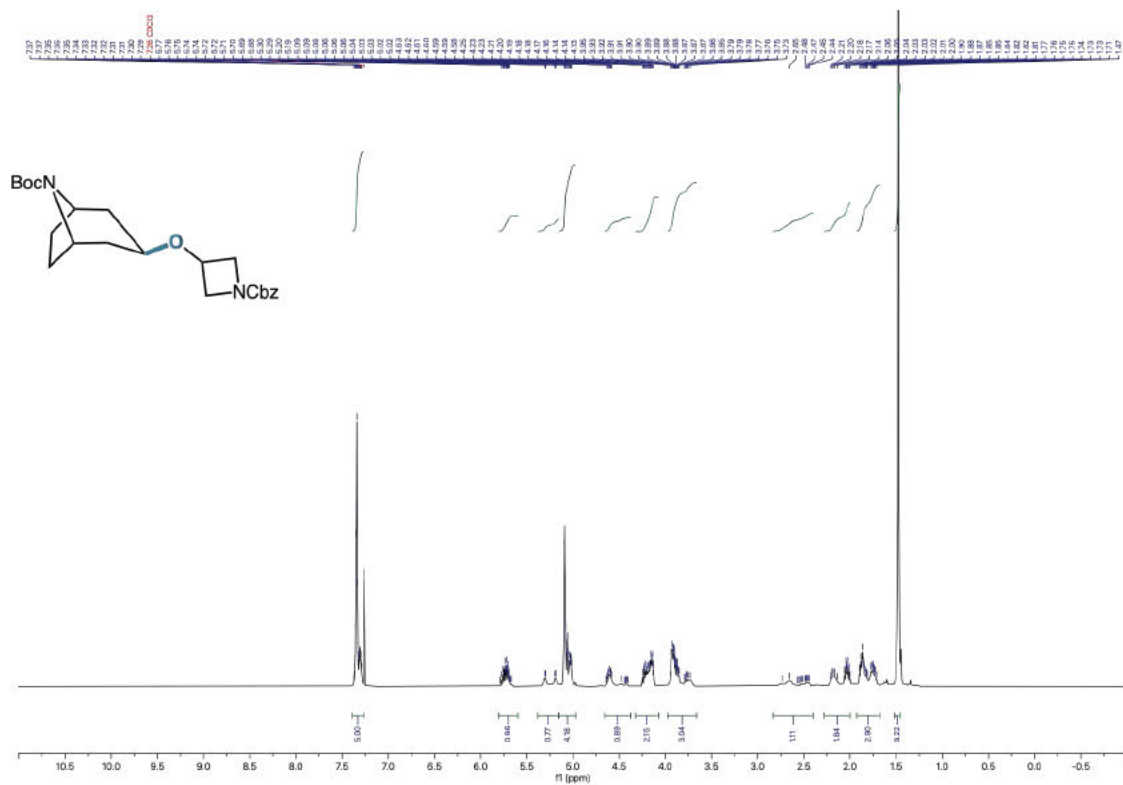
51, ^1H NMR, 500 MHz, CDCl_3



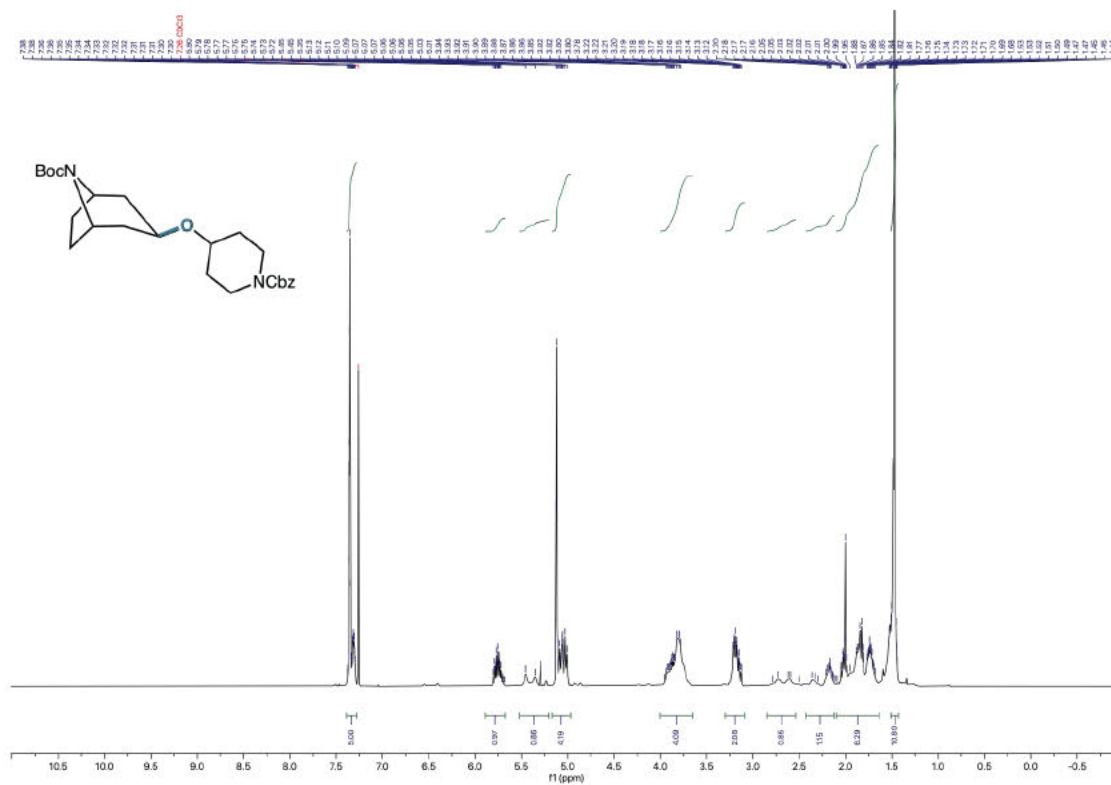
51, ^{13}C NMR, 500 MHz, CDCl_3



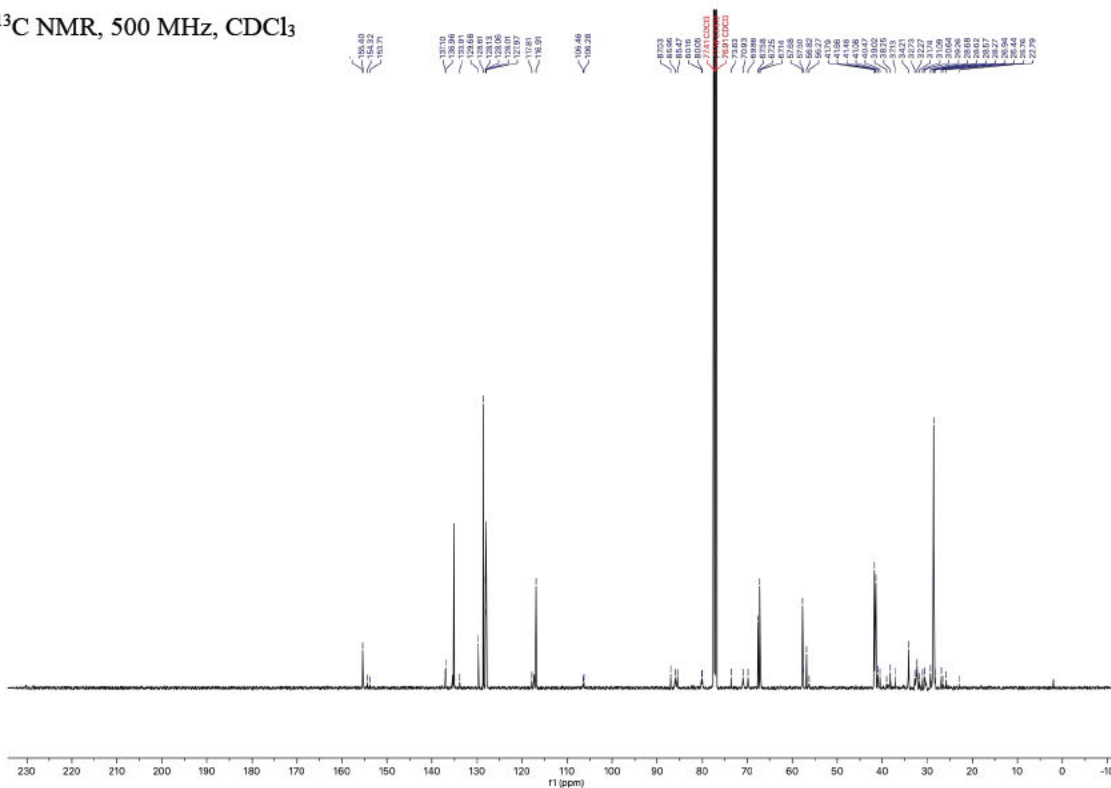
Benzyl 3-(1-tert-butoxycarbonylazetidin-3-yl)oxy-8-azabicyclo[3.2.1]octane-8-carboxylate
52, ¹H NMR, 500 MHz, CDCl₃



Benzyl 3-[(1-tert-butoxycarbonyl-4-piperidyl)oxy]-8-azabicyclo[3.2.1]octane-8-carboxylate
53, ^1H NMR, 500 MHz, CDCl_3

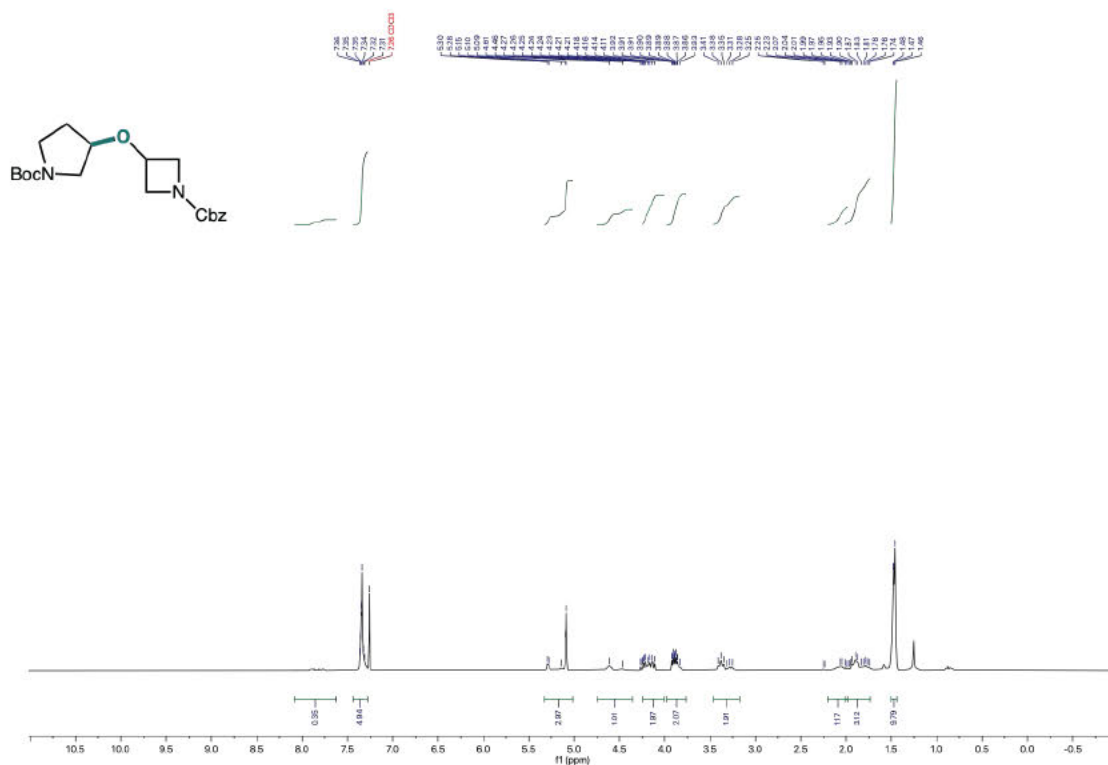


53, ^{13}C NMR, 500 MHz, CDCl_3

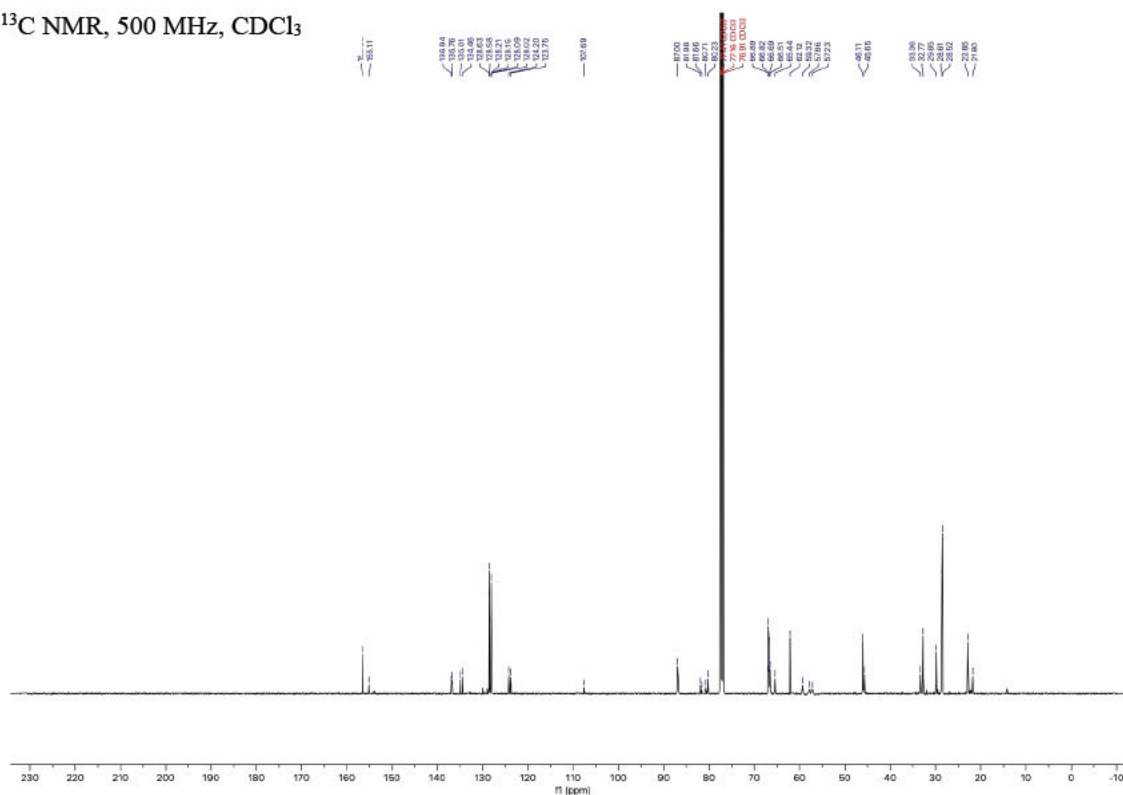


***Tert*-butyl 3-(1-benzoyloxycarbonylazetidin-3-yl)oxypyrrolidine-1-carboxylate**

54X, ^1H NMR, 500 MHz, CDCl_3

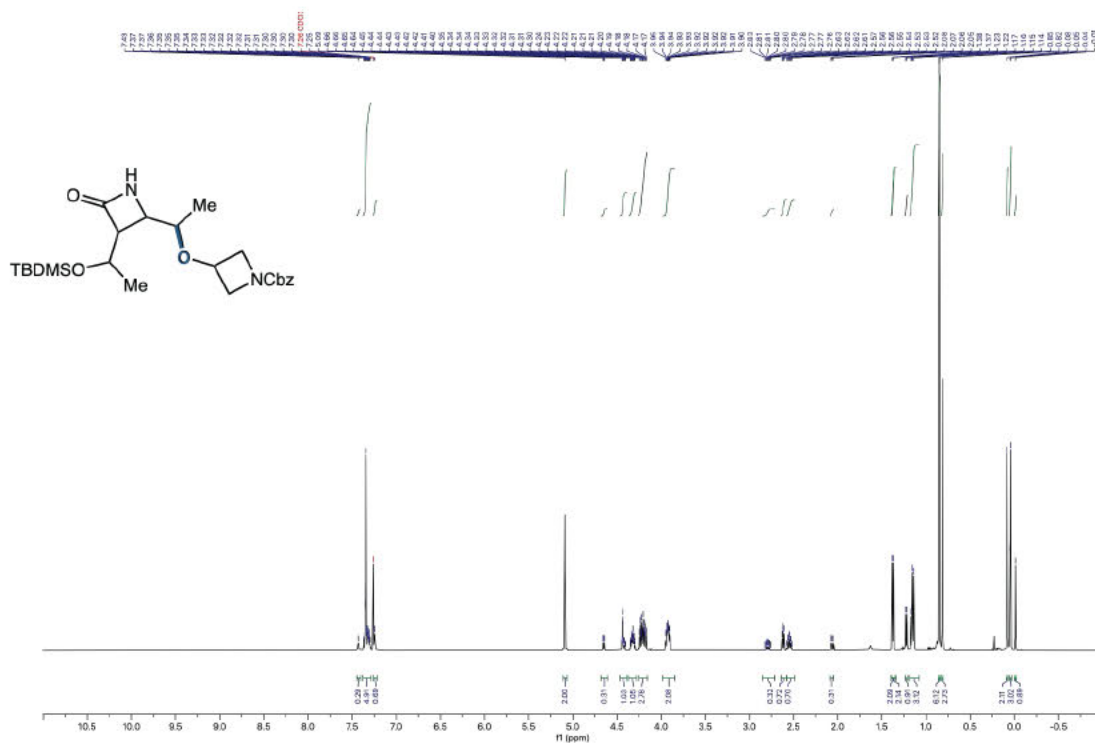


54, ^{13}C NMR, 500 MHz, CDCl_3



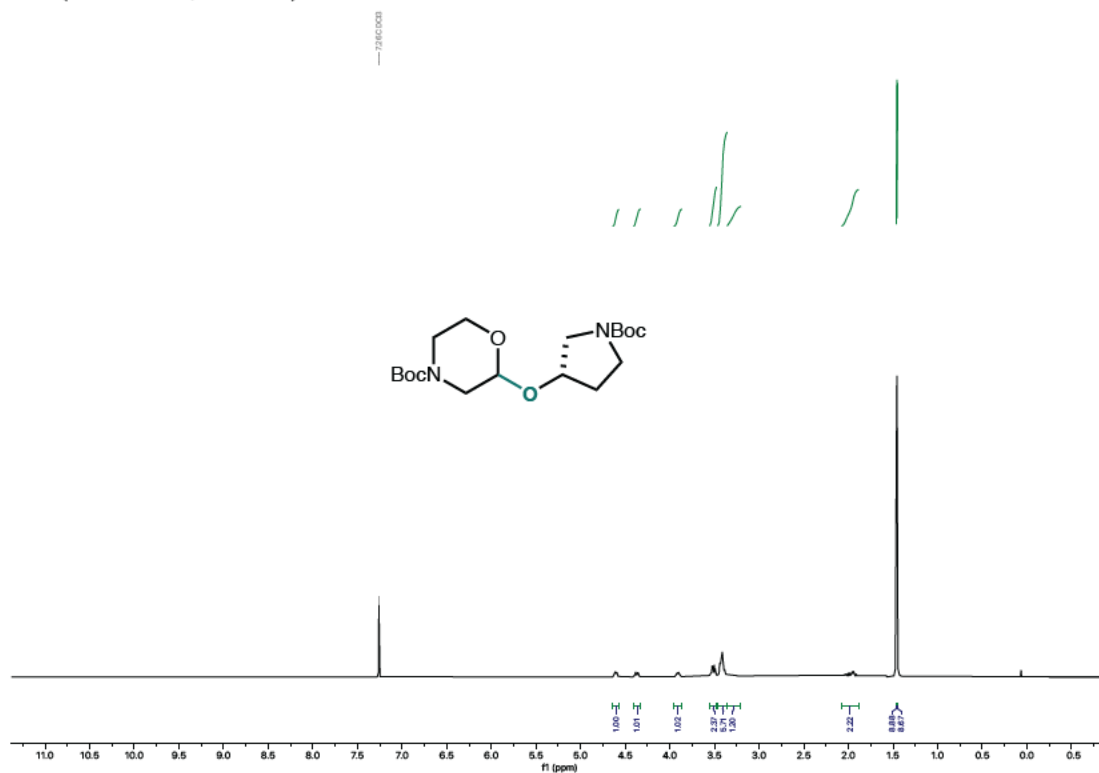
Benzyl 3-[1-[3-[1-[tert-butyl(dimethyl)silyl]oxyethyl]-4-oxo-azetidin-2-yl]ethoxy]azetidine-1-carboxylate

55, ^1H NMR, 500 MHz, CDCl_3

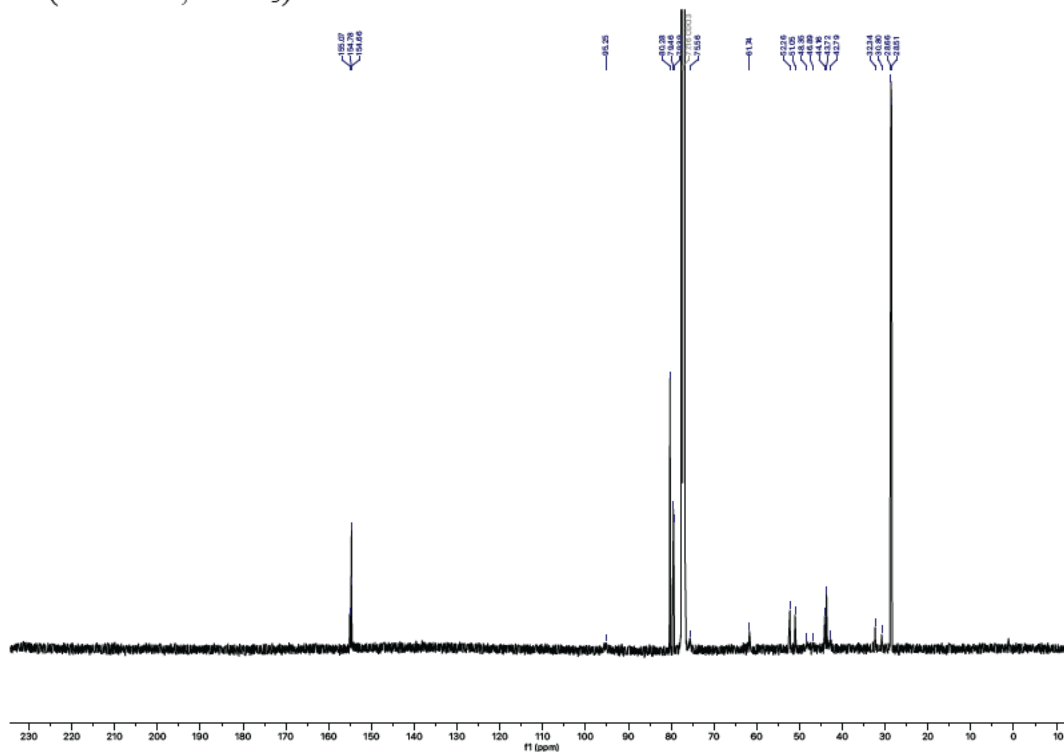


***Tert*-butyl 2-(((*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)oxy)morpholine-4-carboxylate (56)**

^1H NMR (500 MHz, CDCl_3):

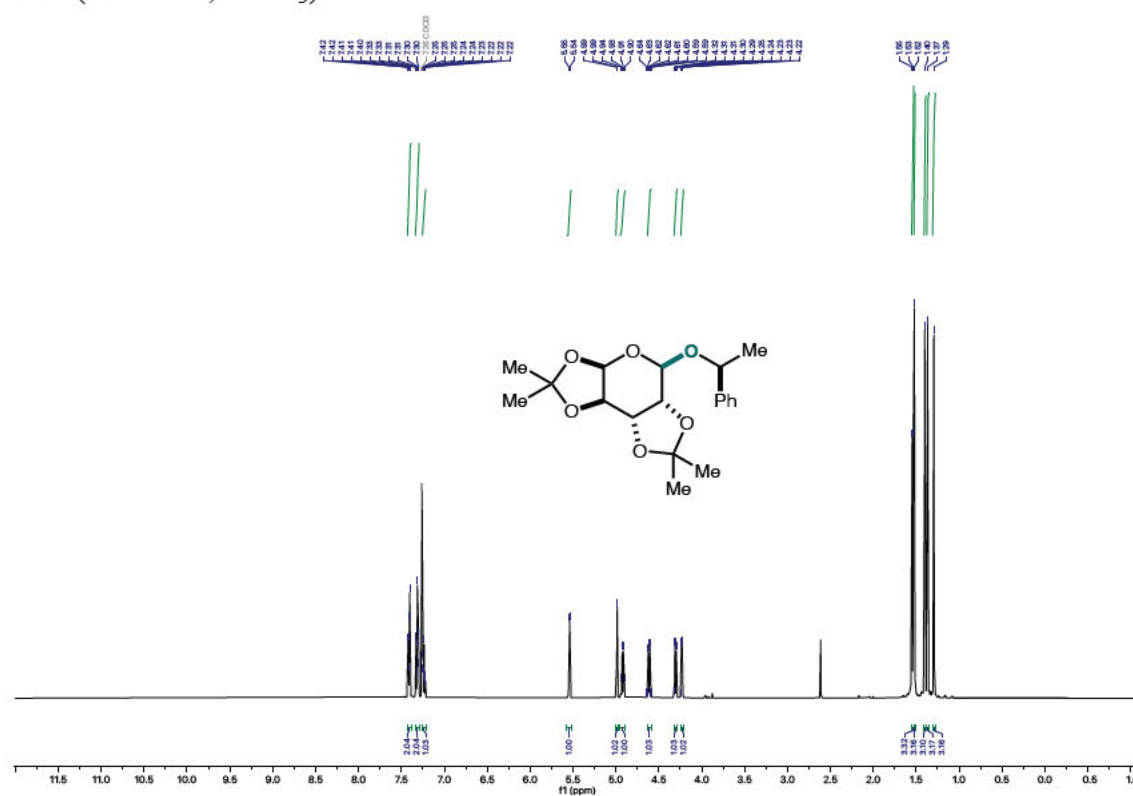


^{13}C NMR (126 MHz, CDCl_3):



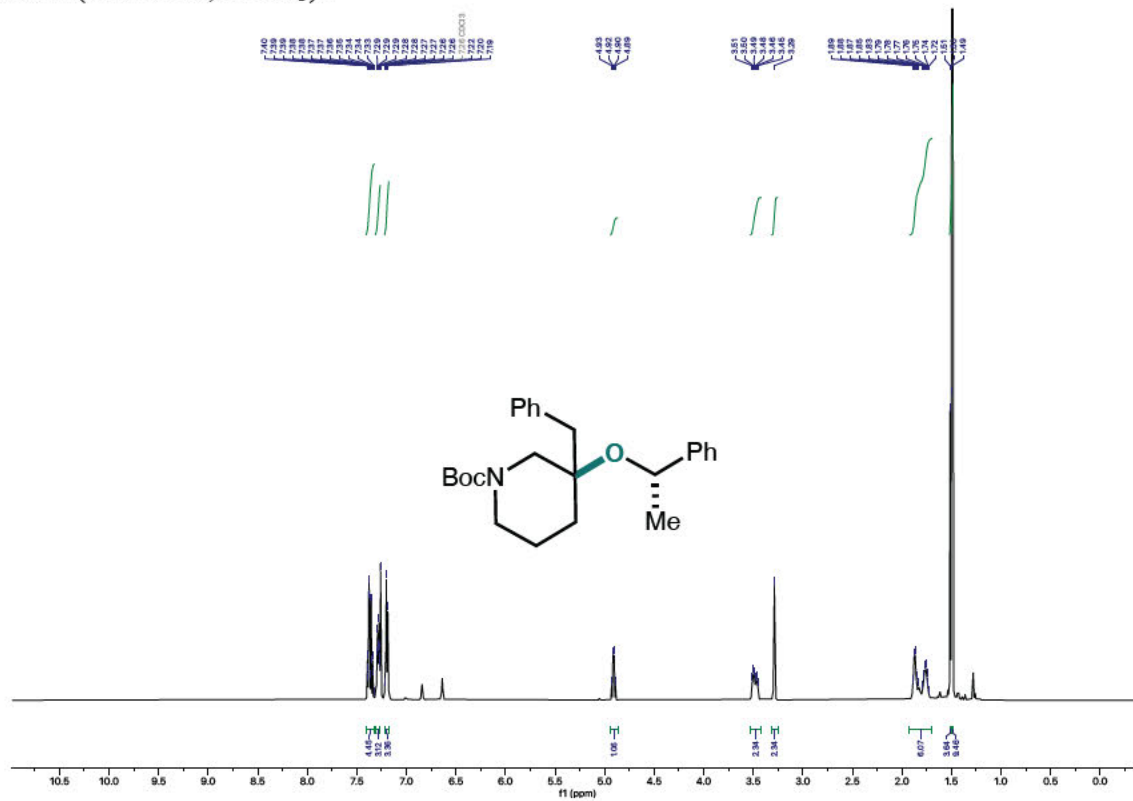
(3aR,5R,5aR,8aS,8bR)-2,2,7,7-tetramethyl-5-((S)-1-phenylethoxy)tetrahydro-5H-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran

^1H NMR (500 MHz, CDCl_3):



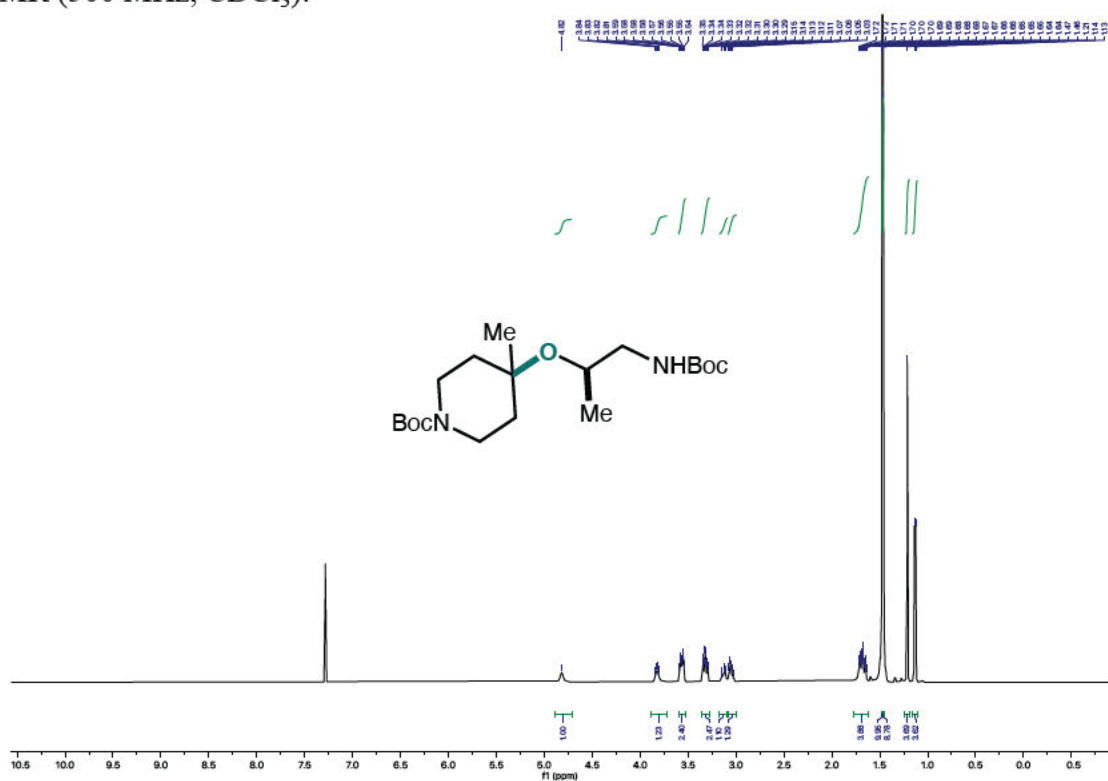
***Tert*-butyl 3-benzyl-3-((*S*)-1-phenylethoxy)piperidine-1-carboxylate (**58**)**

^1H NMR (500 MHz, CDCl_3):

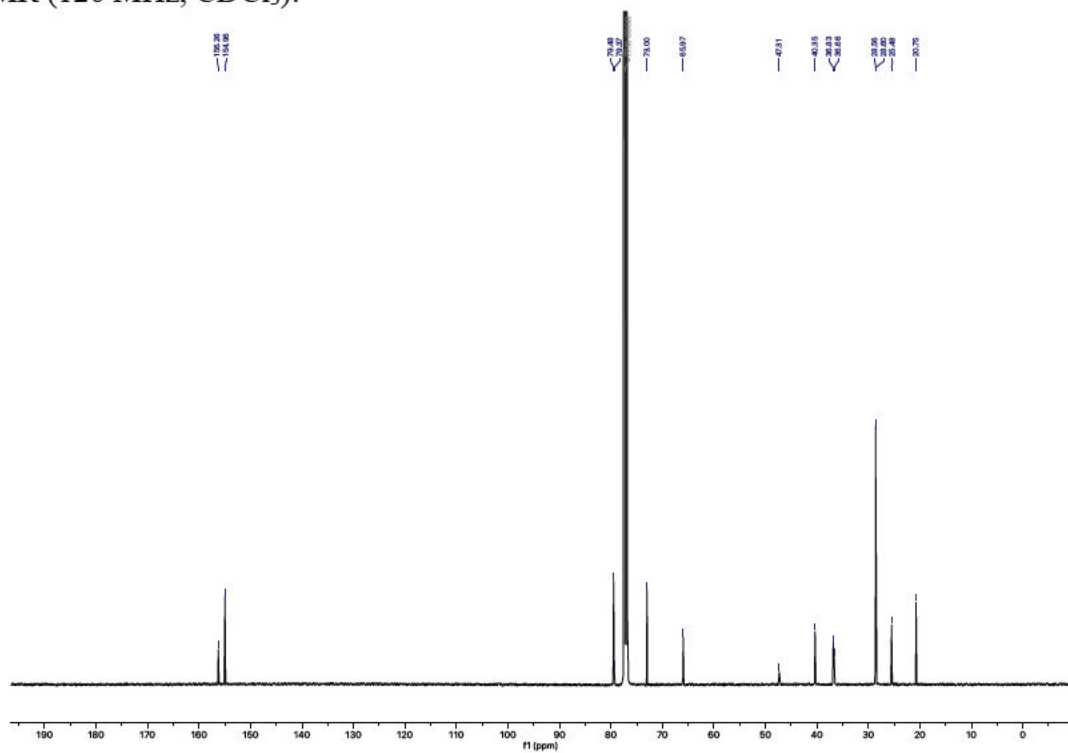


***Tert*-butyl (*R*)-4-((1-((*tert*-butoxycarbonyl)amino)propan-2-yl)oxy)-4-methylpiperidine-1-carboxylate (**59**)**

¹H NMR (500 MHz, CDCl₃):

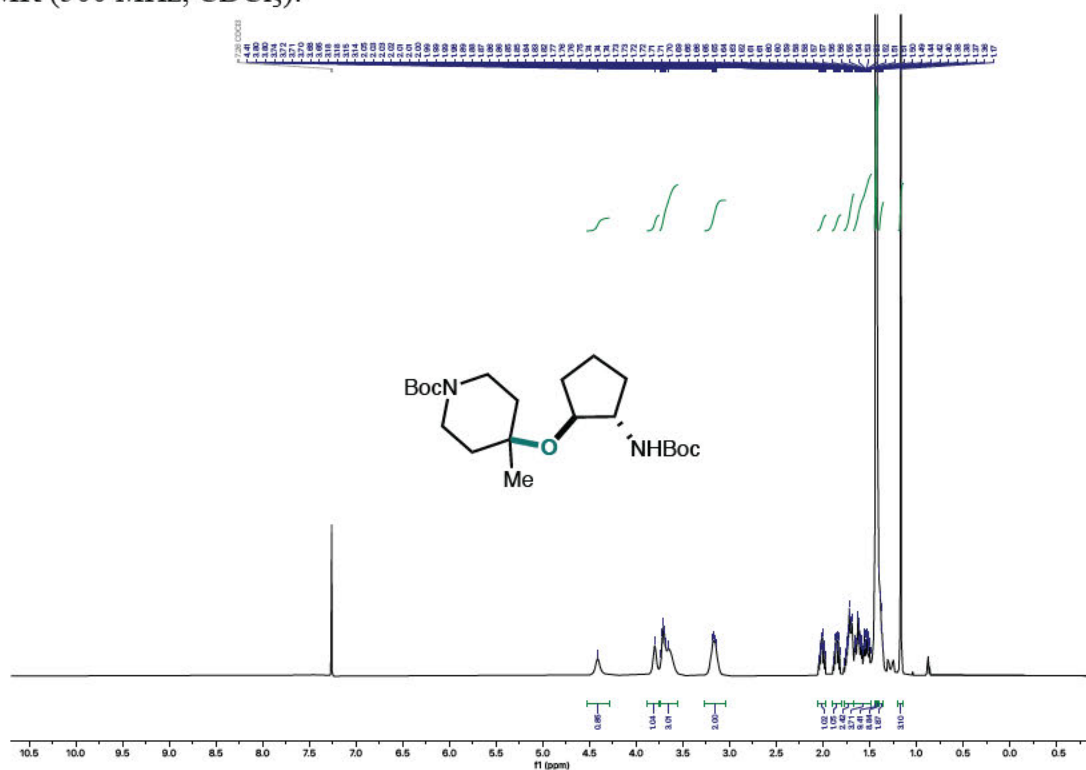


¹³C NMR (126 MHz, CDCl₃):

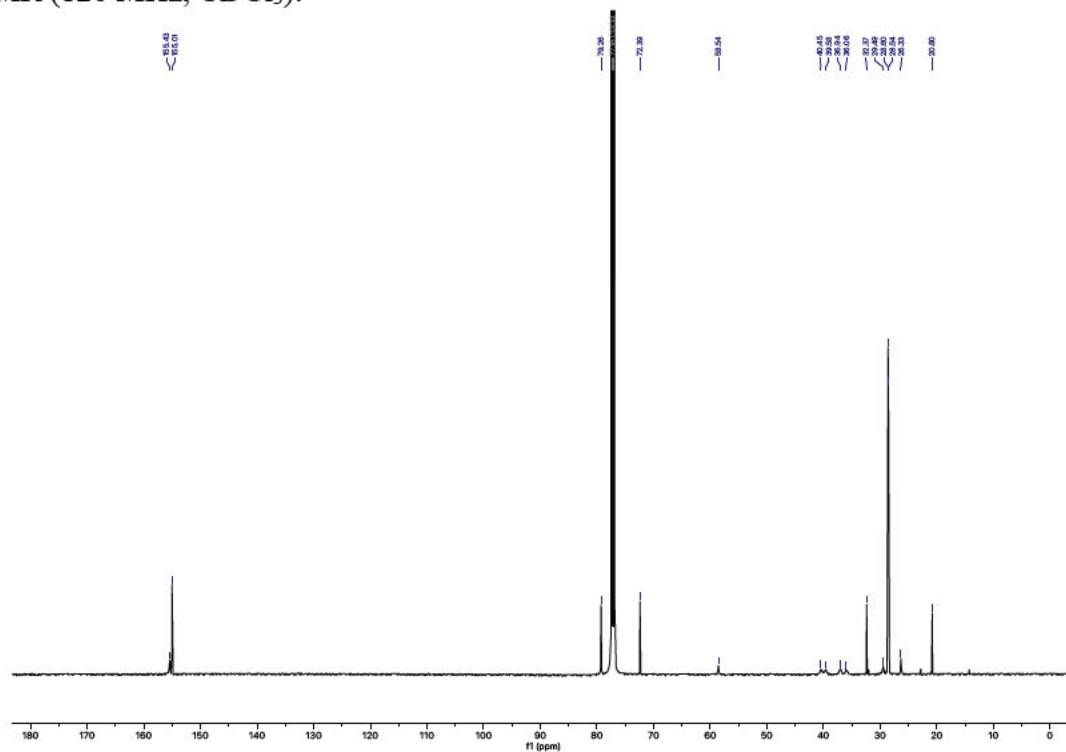


Tert-butyl 4-(((1*S*,2*S*)-2-((*tert*-butoxycarbonyl)amino)cyclopentyl)oxy)-4-methylpiperidine-1-carboxylate (60)

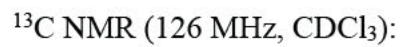
¹H NMR (500 MHz, CDCl₃):

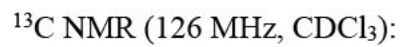


¹³C NMR (126 MHz, CDCl₃):

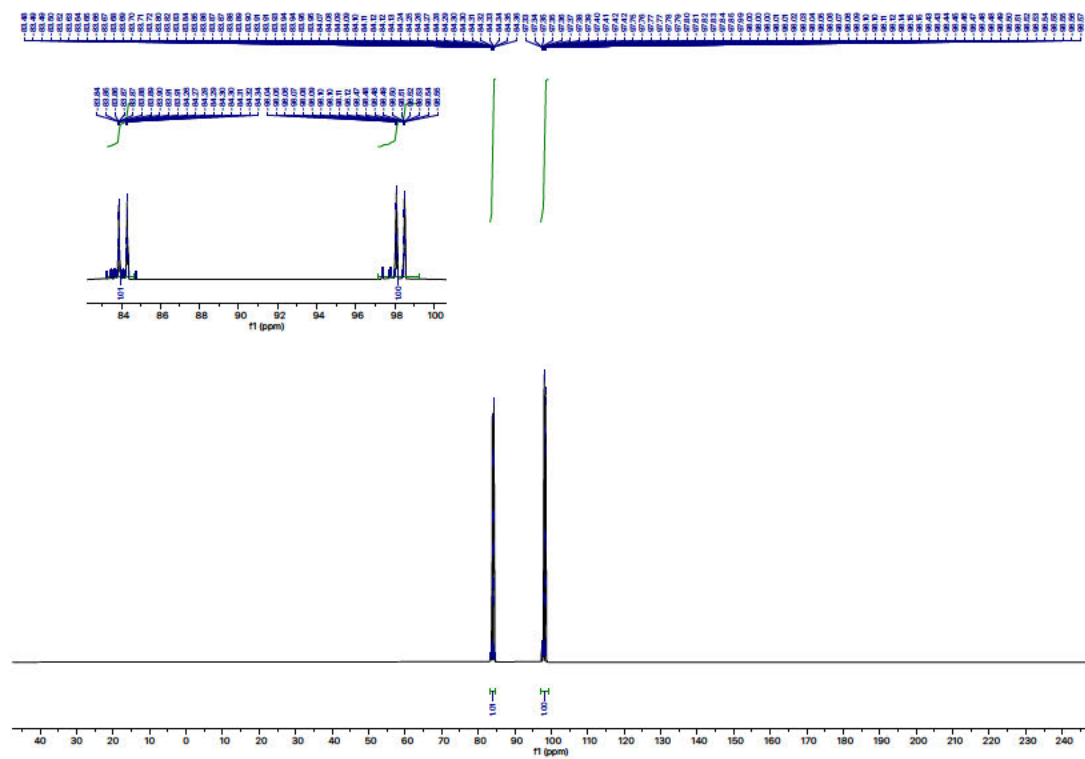


¹H NMR (500 MHz, CDCl₃):

¹H NMR (500 MHz, CDCl₃):

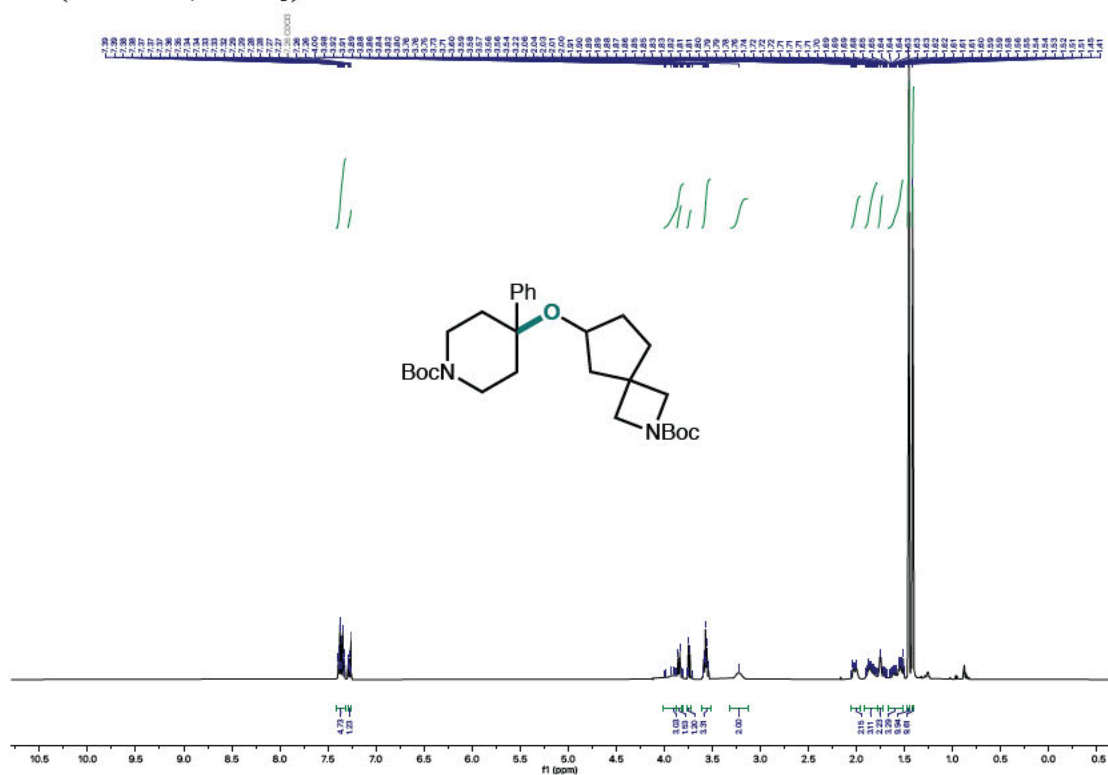
¹H NMR (500 MHz, CDCl₃):

^{19}F NMR (376 MHz, CDCl_3)

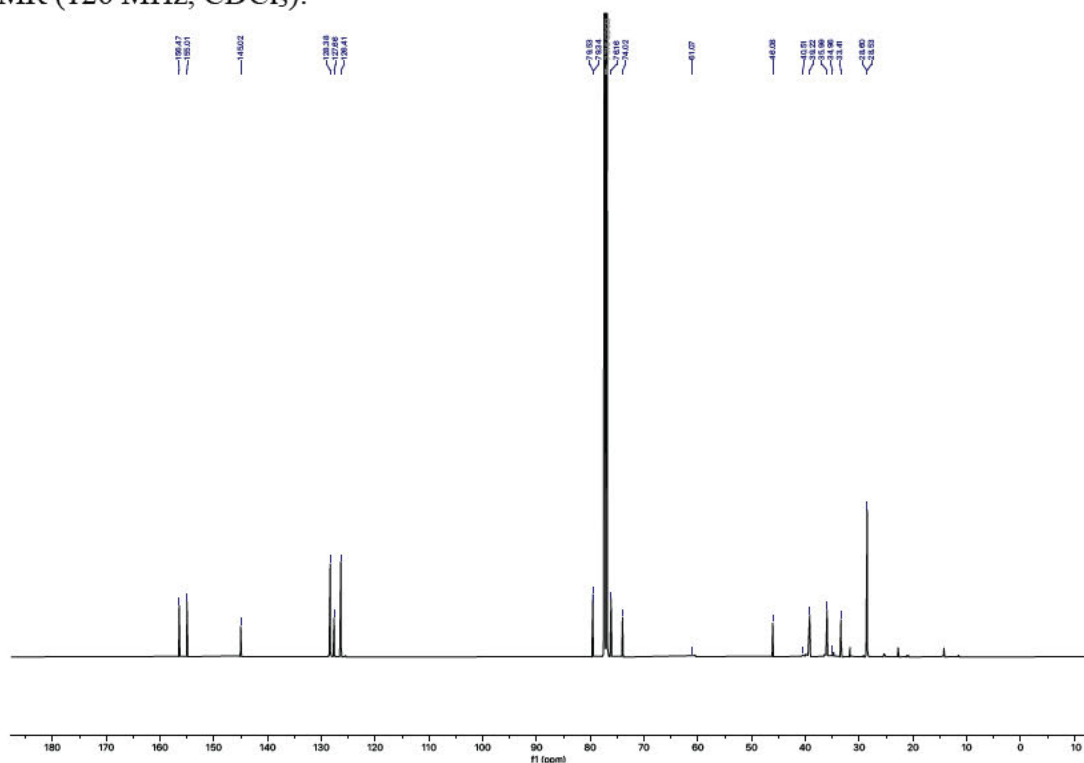


***Tert*-butyl 6-((1-(*tert*-butoxycarbonyl)-4-phenylpiperidin-4-yl)oxy)-2-azaspiro[3.4]octane-2-carboxylate (65)**

^1H NMR (500 MHz, CDCl_3):



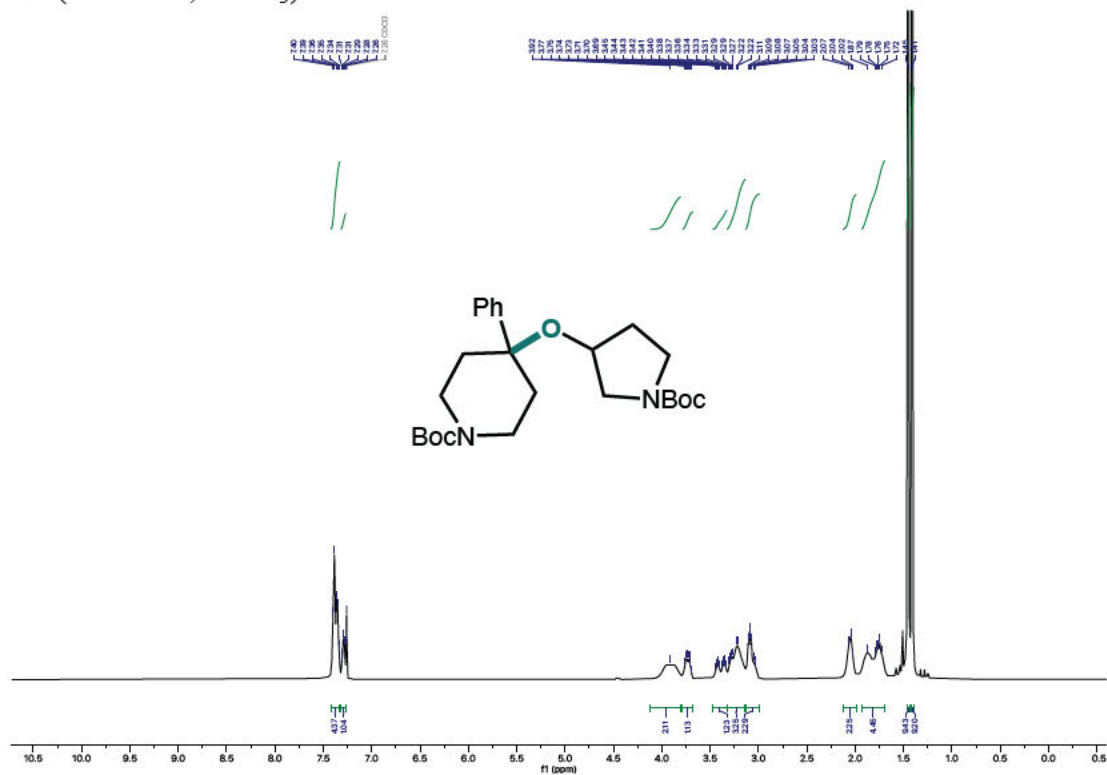
^{13}C NMR (126 MHz, CDCl_3):



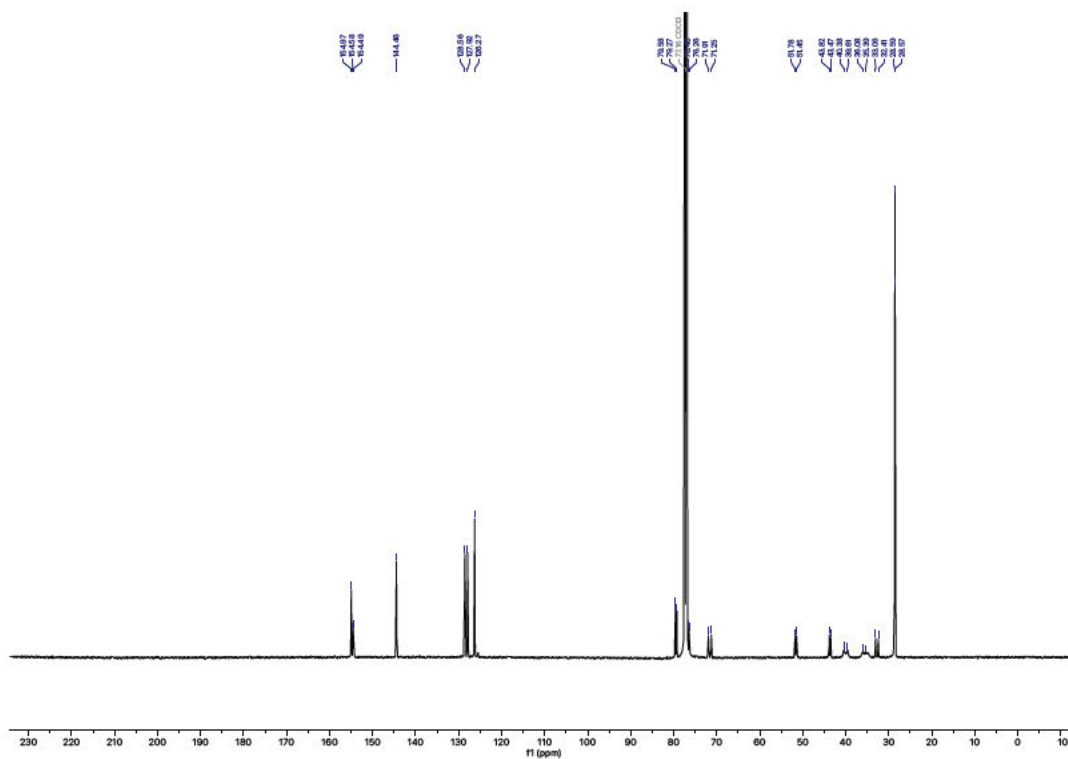
**Tert-butyl
carboxylate (66)**

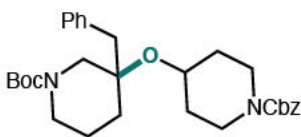
4-((1-(tert-butoxycarbonyl)pyrrolidin-3-yl)oxy)-4-phenylpiperidine-1-

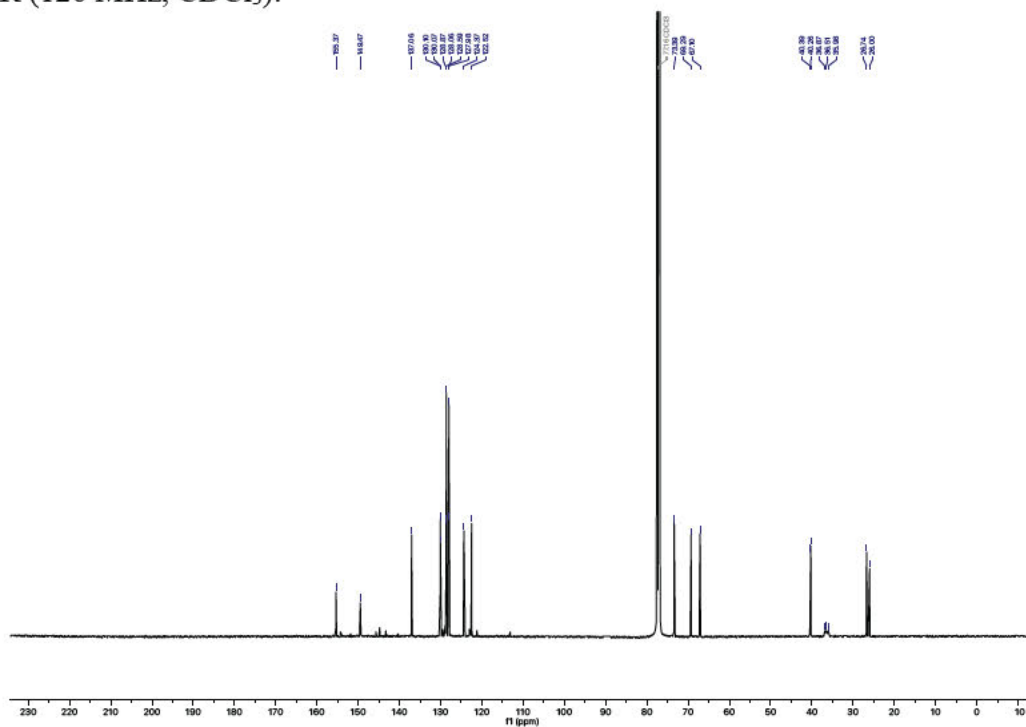
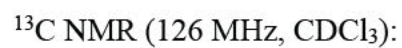
¹H NMR (500 MHz, CDCl₃):



¹³C NMR (126 MHz, CDCl₃):

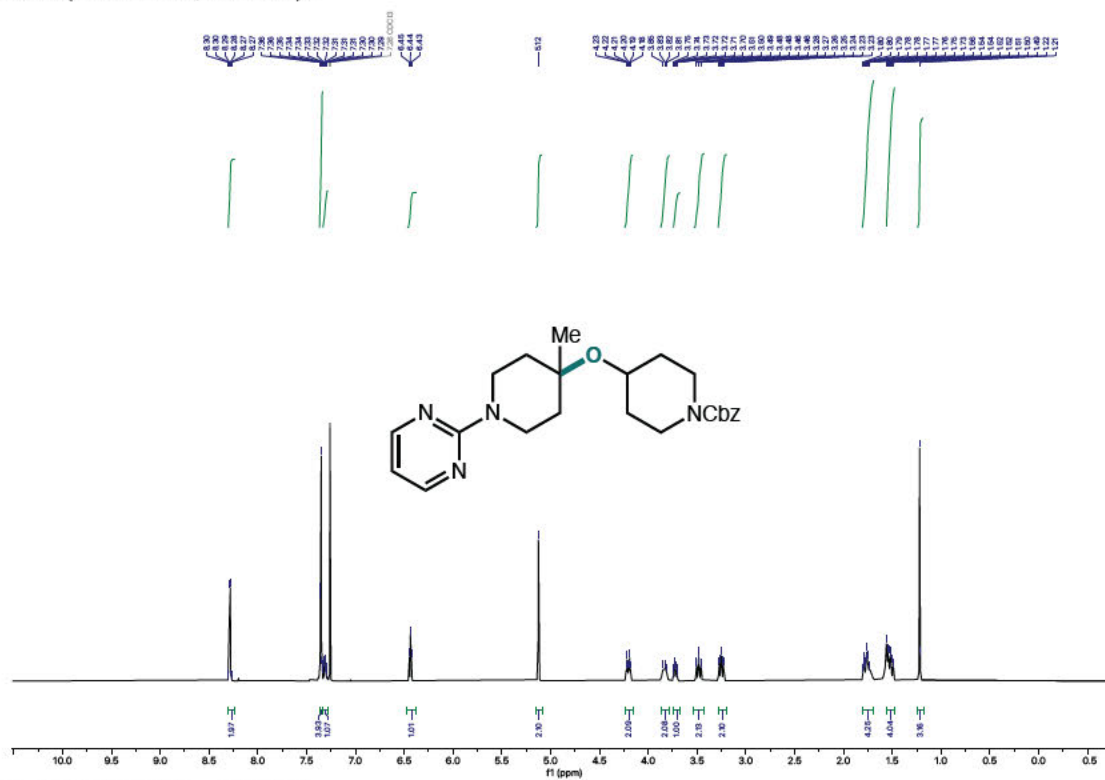


¹H NMR (500 MHz, CDCl₃):

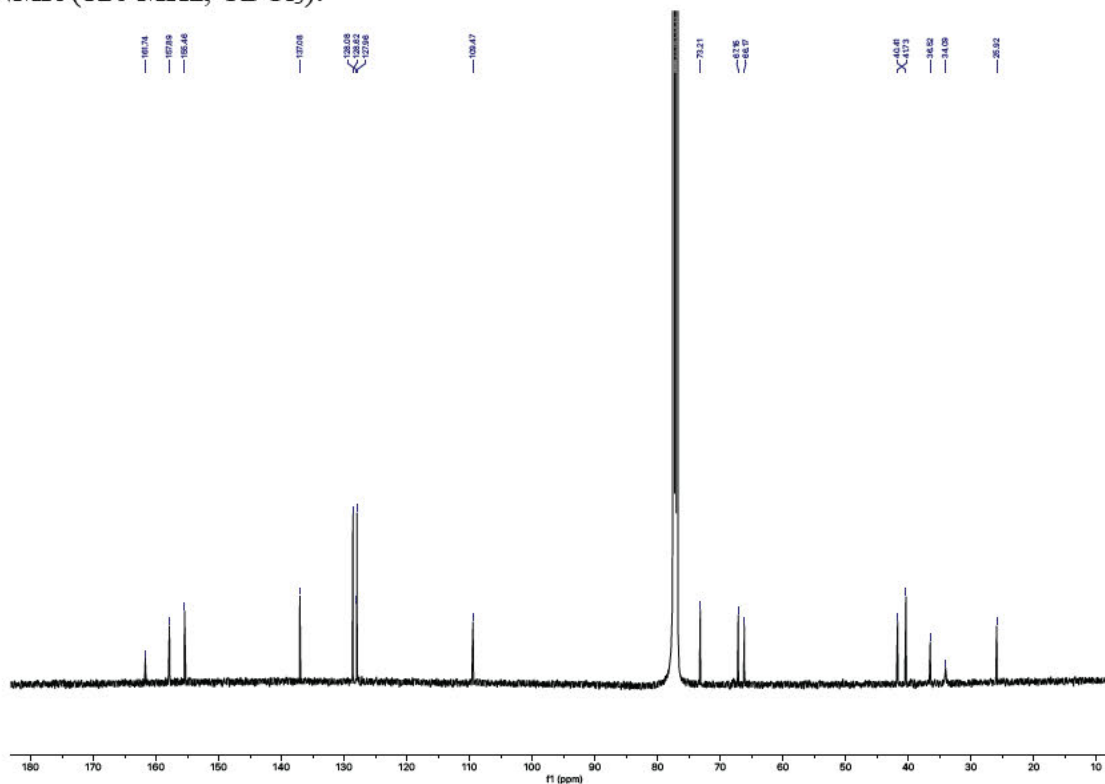
¹H NMR (500 MHz, CDCl₃):

Benzyl 4-((4-methyl-1-(pyrimidin-2-yl)piperidin-4-yl)oxy)piperidine-1-carboxylate (69)

^1H NMR (500 MHz, CDCl_3):

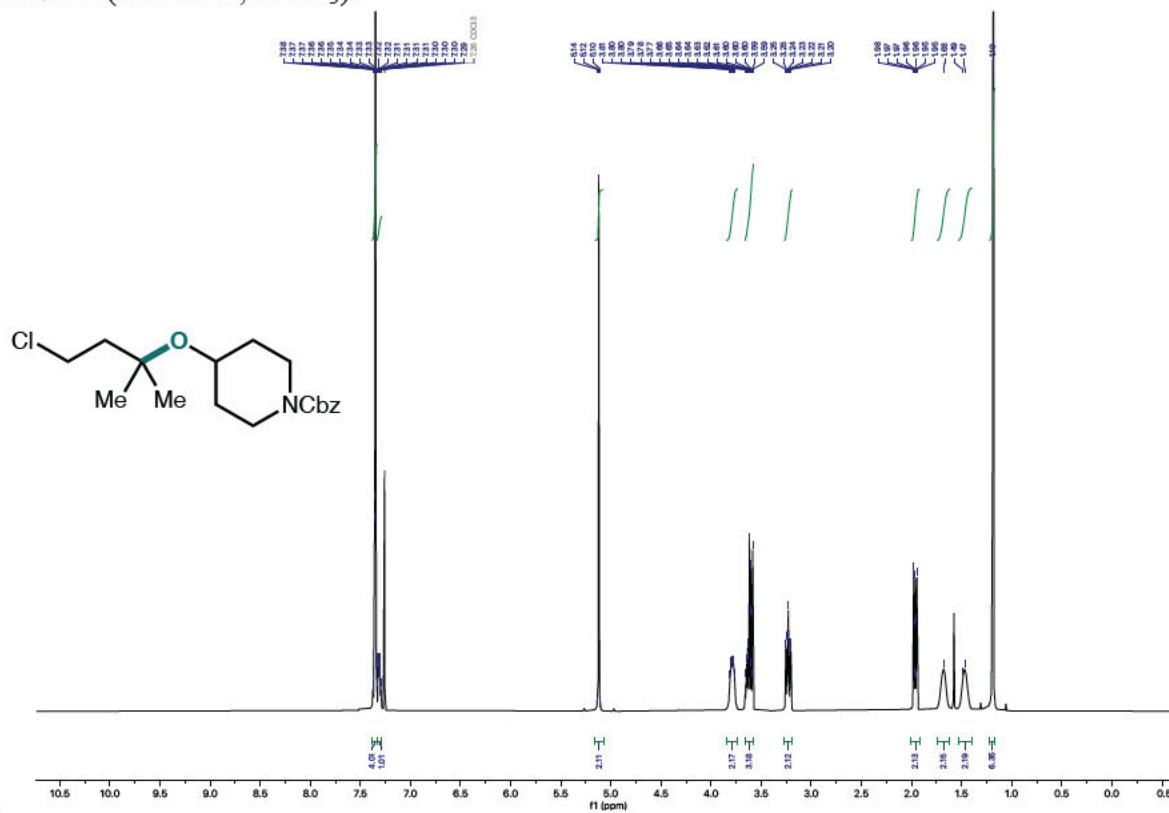


^{13}C NMR (126 MHz, CDCl_3):

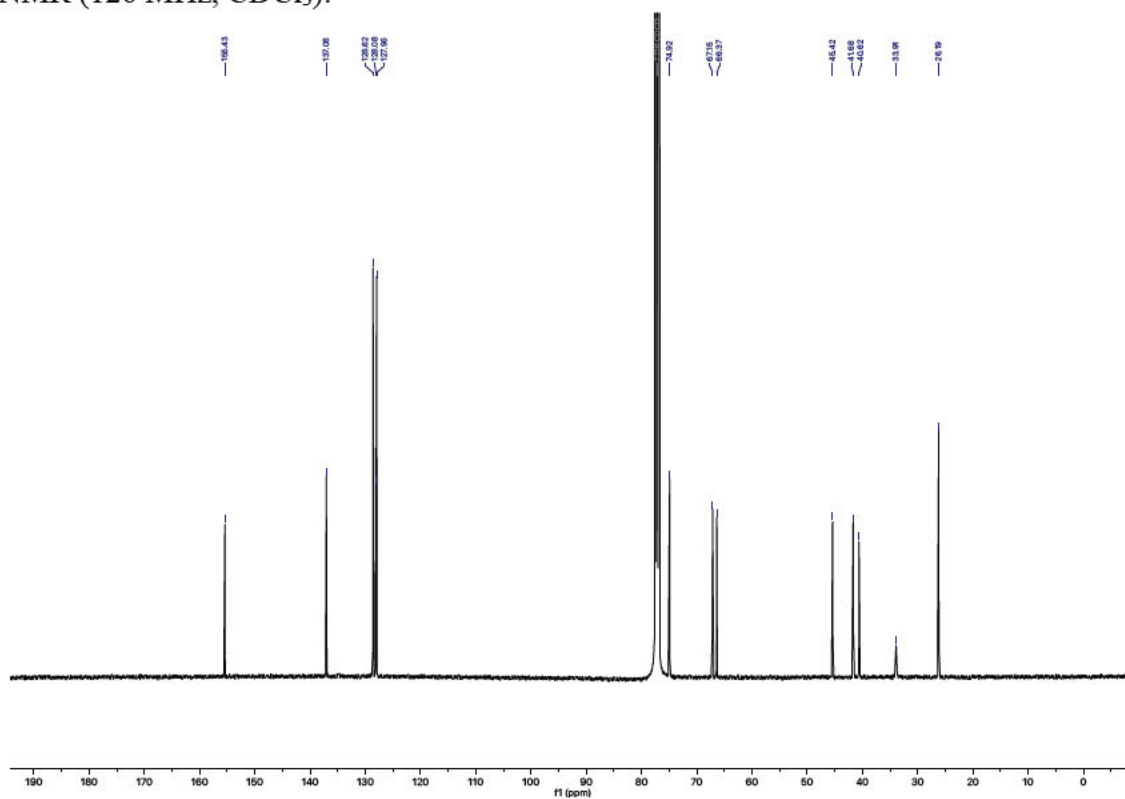


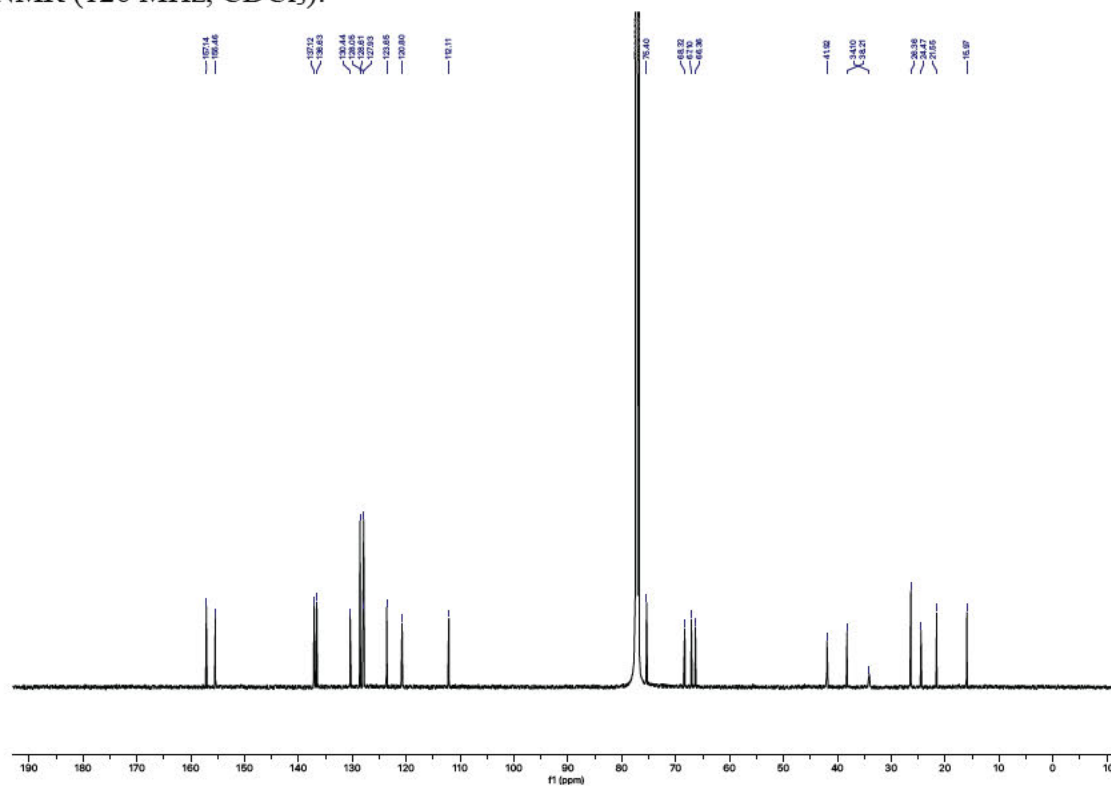
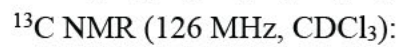
Benzyl 4-((4-chloro-2-methylbutan-2-yl)oxy)piperidine-1-carboxylate (70)

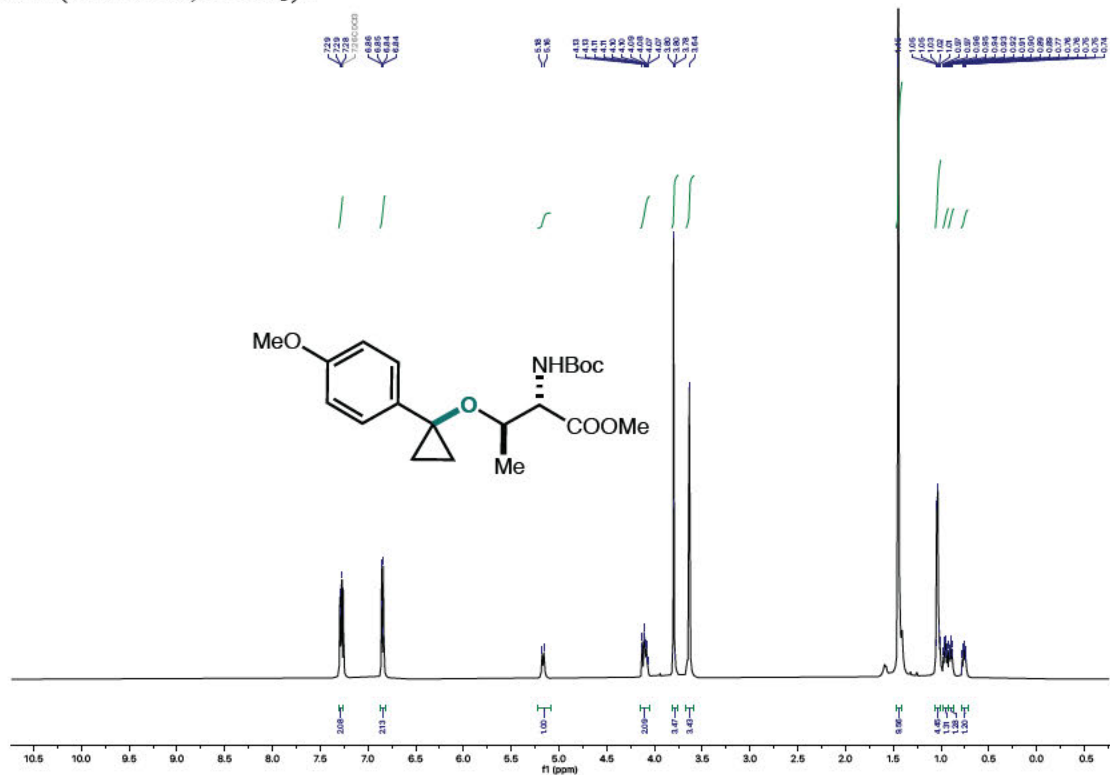
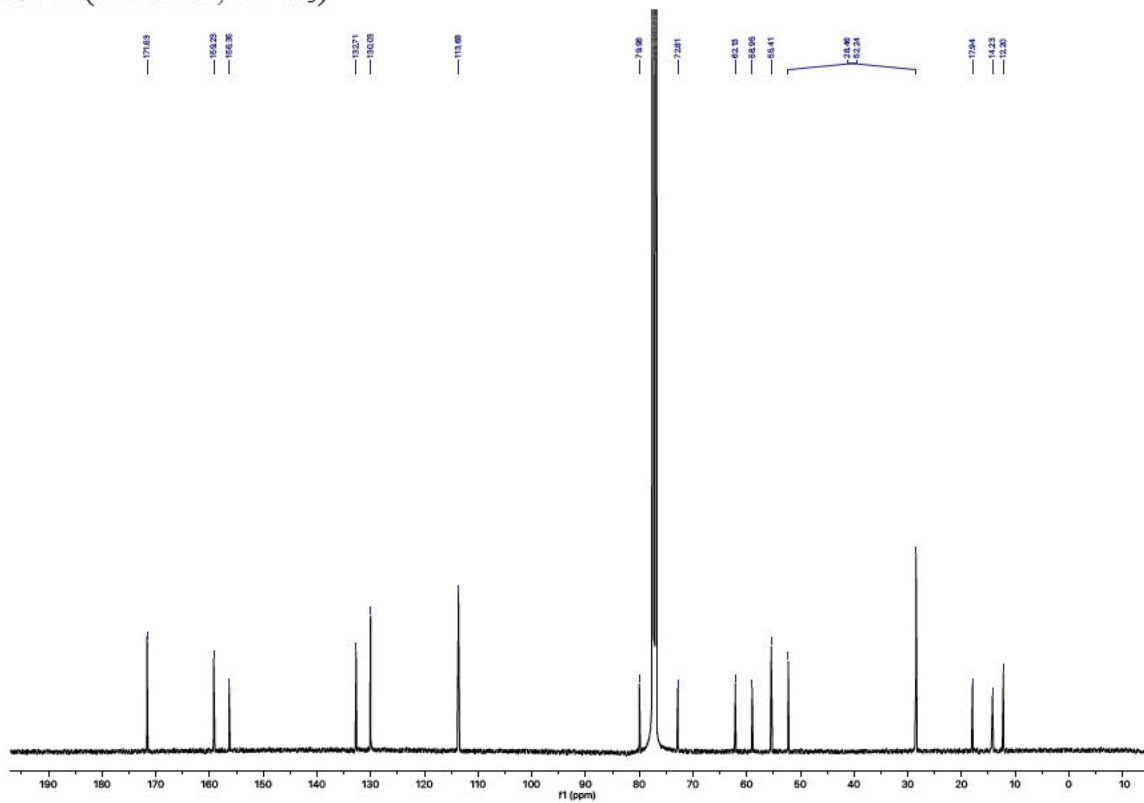
^1H NMR (500 MHz, CDCl_3):

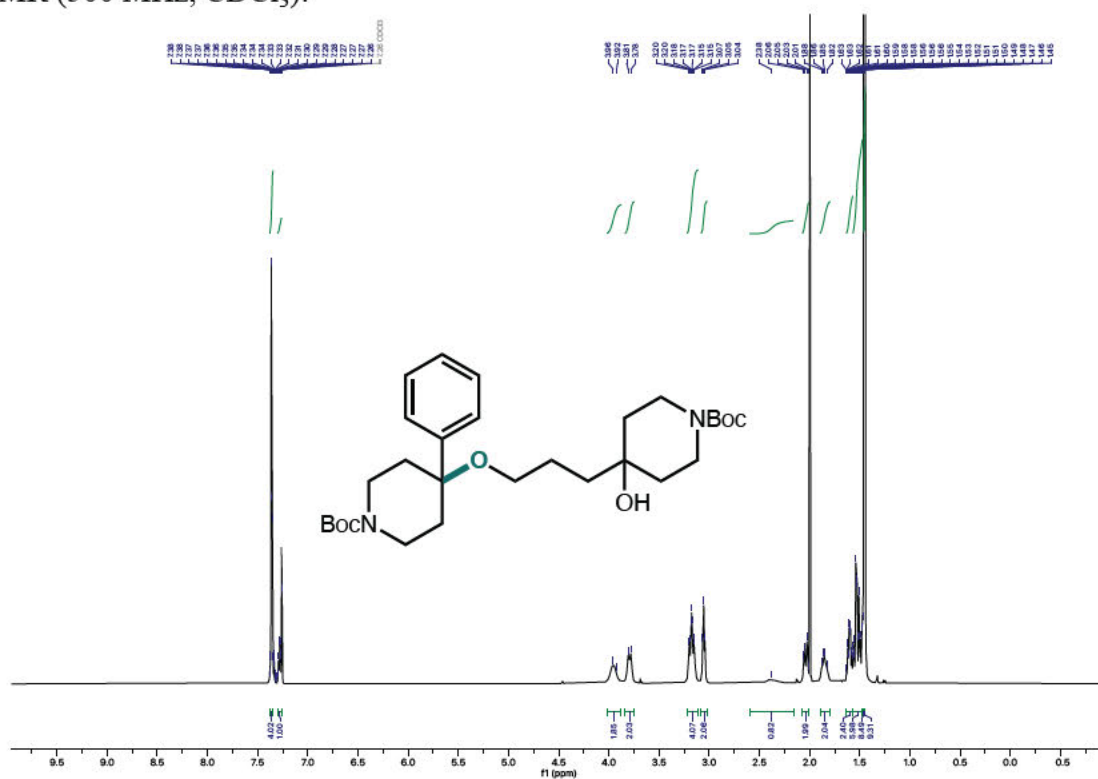
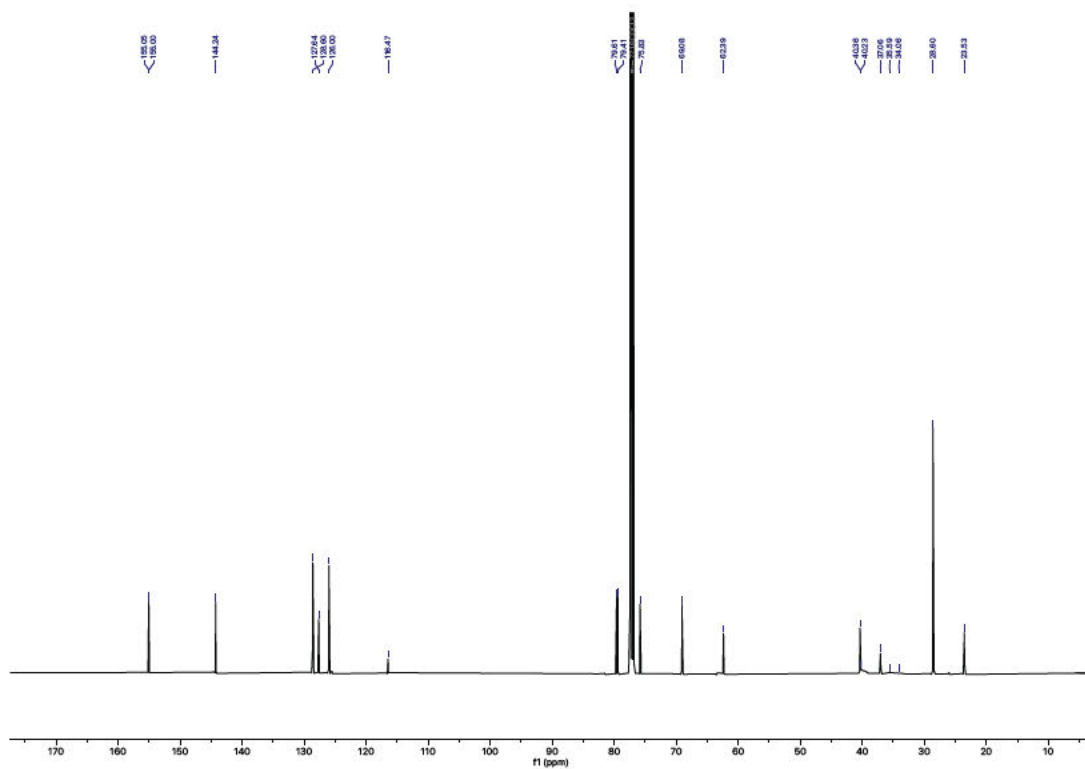


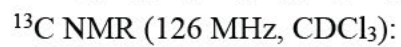
^{13}C NMR (126 MHz, CDCl_3):

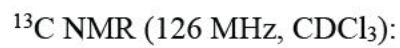


¹H NMR (500 MHz, CDCl₃):

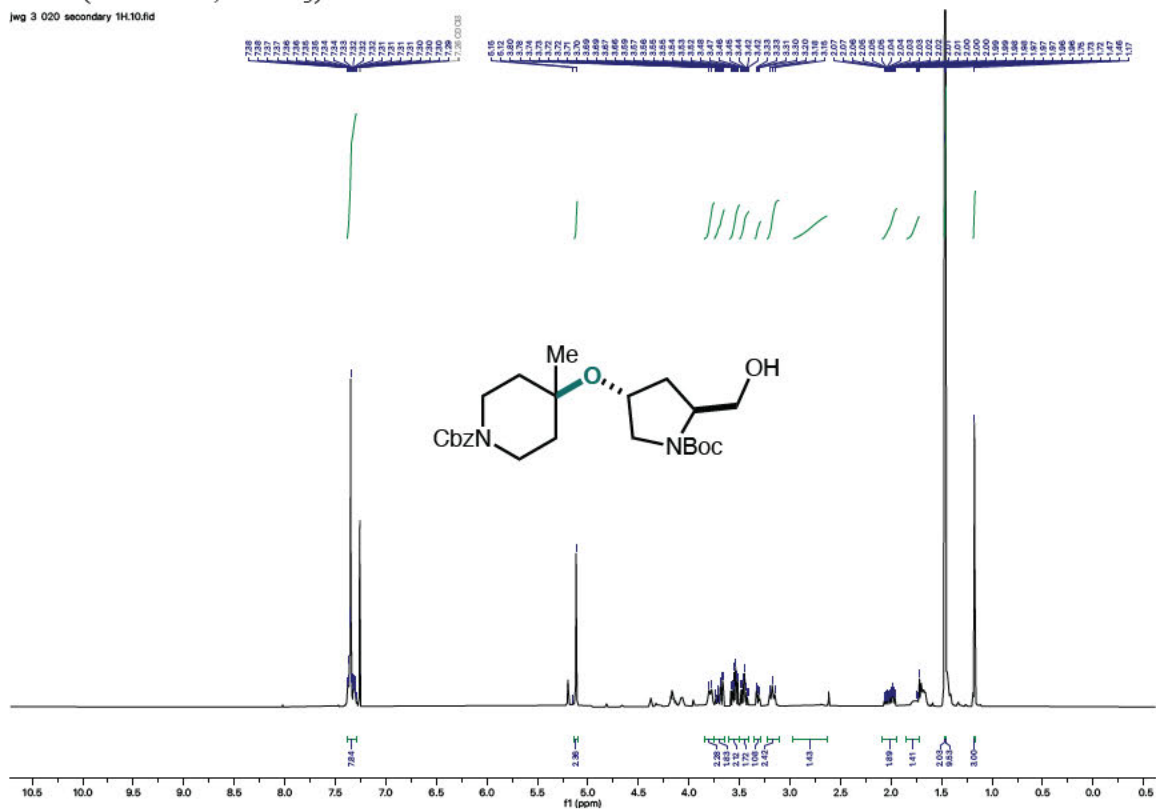
¹H NMR (500 MHz, CDCl₃): ^{13}C NMR (126 MHz, CDCl_3):

¹H NMR (500 MHz, CDCl₃): ^{13}C NMR (126 MHz, CDCl_3):

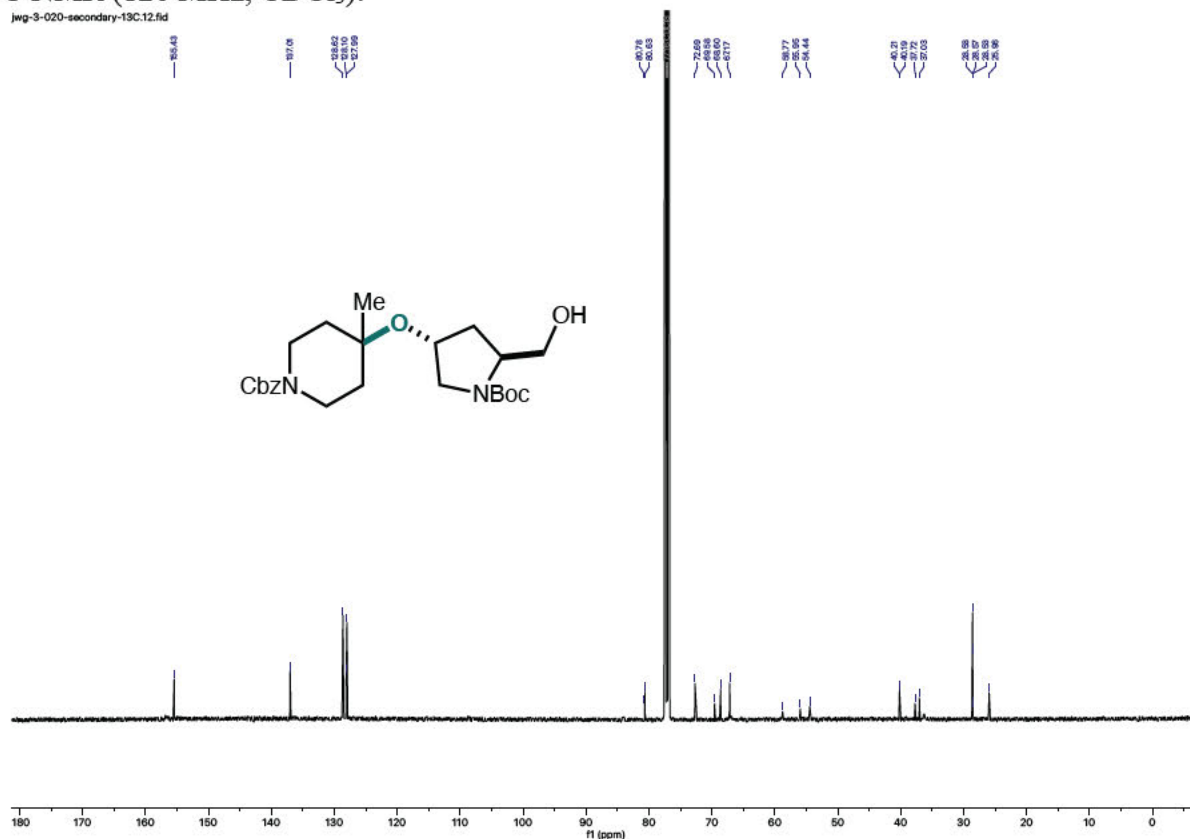
¹H NMR (500 MHz, CDCl₃):

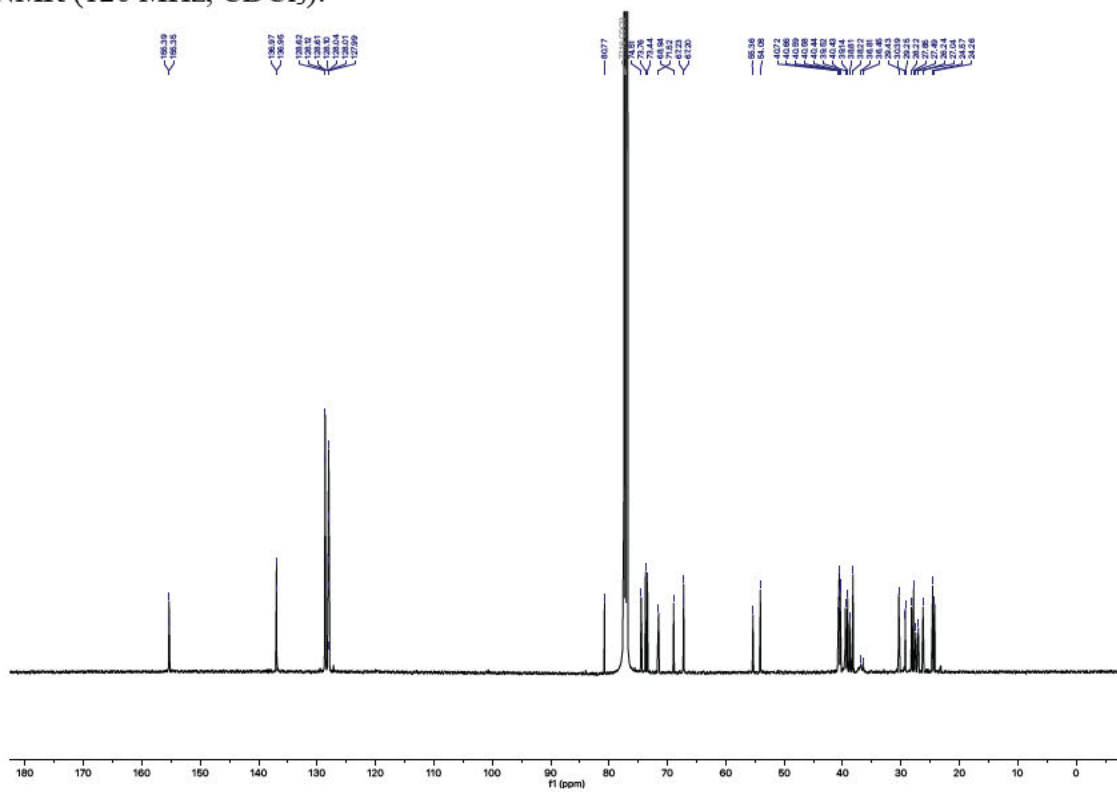
¹H NMR (500 MHz, CDCl₃):

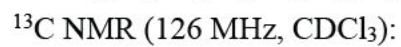
^1H NMR (500 MHz, CDCl_3):



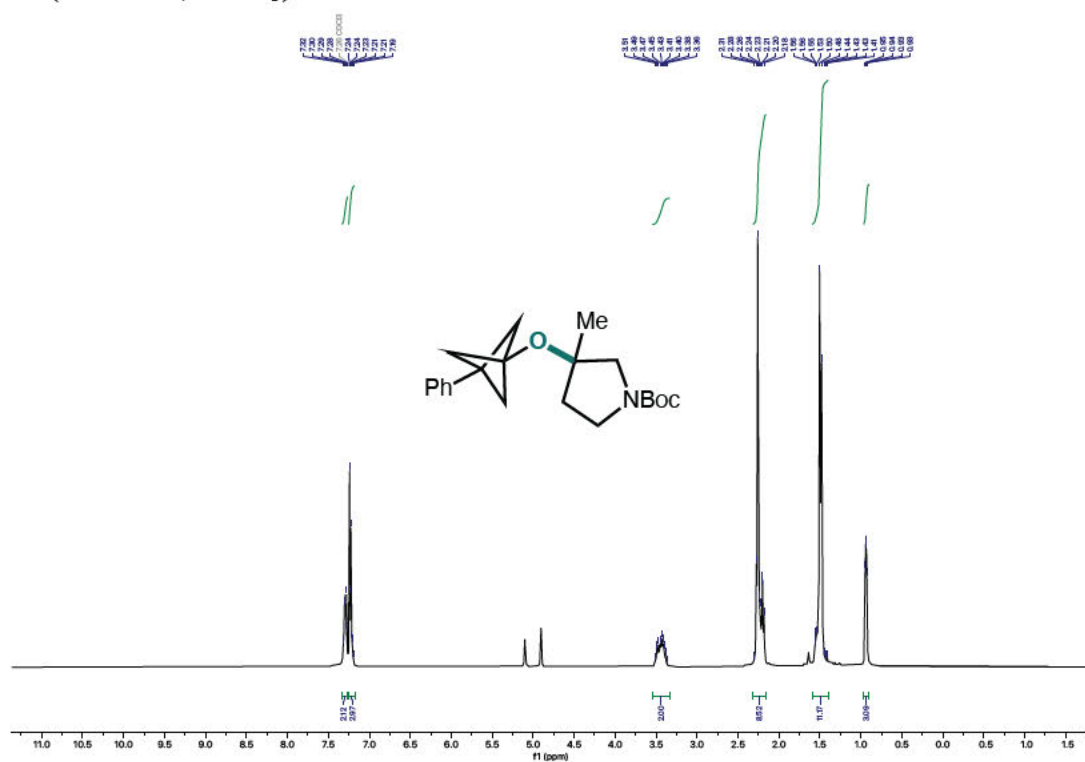
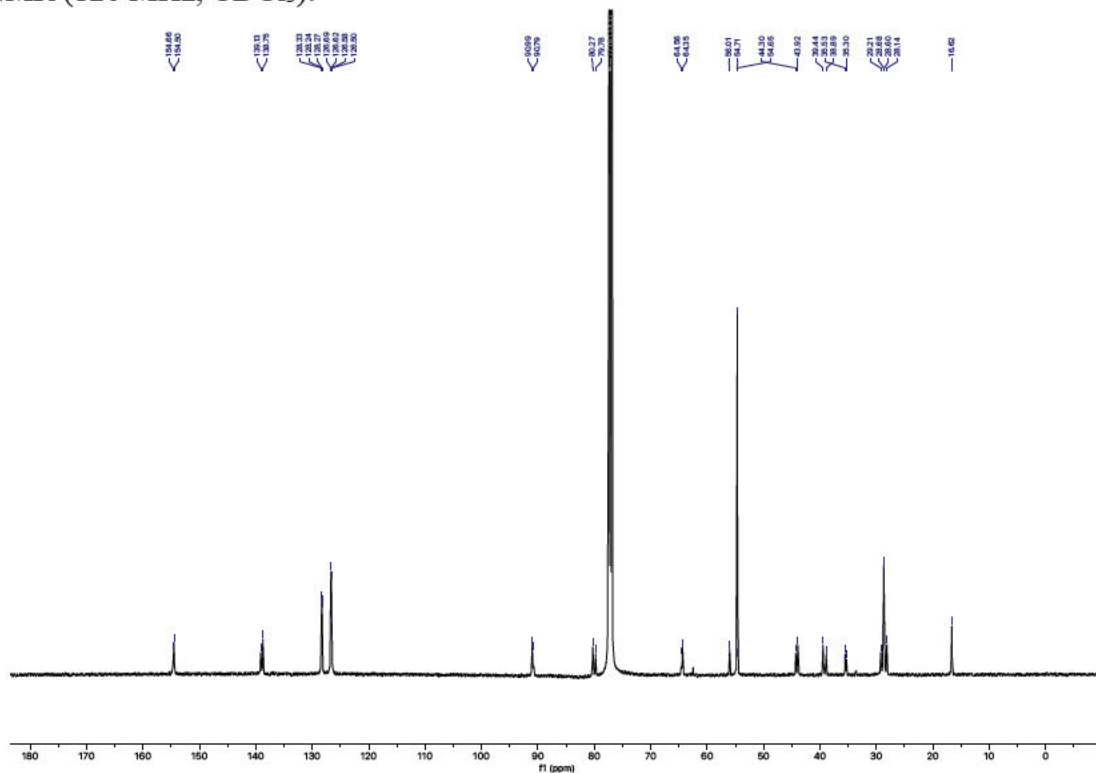
^{13}C NMR (126 MHz, CDCl_3):



¹H NMR (500 MHz, CDCl₃):

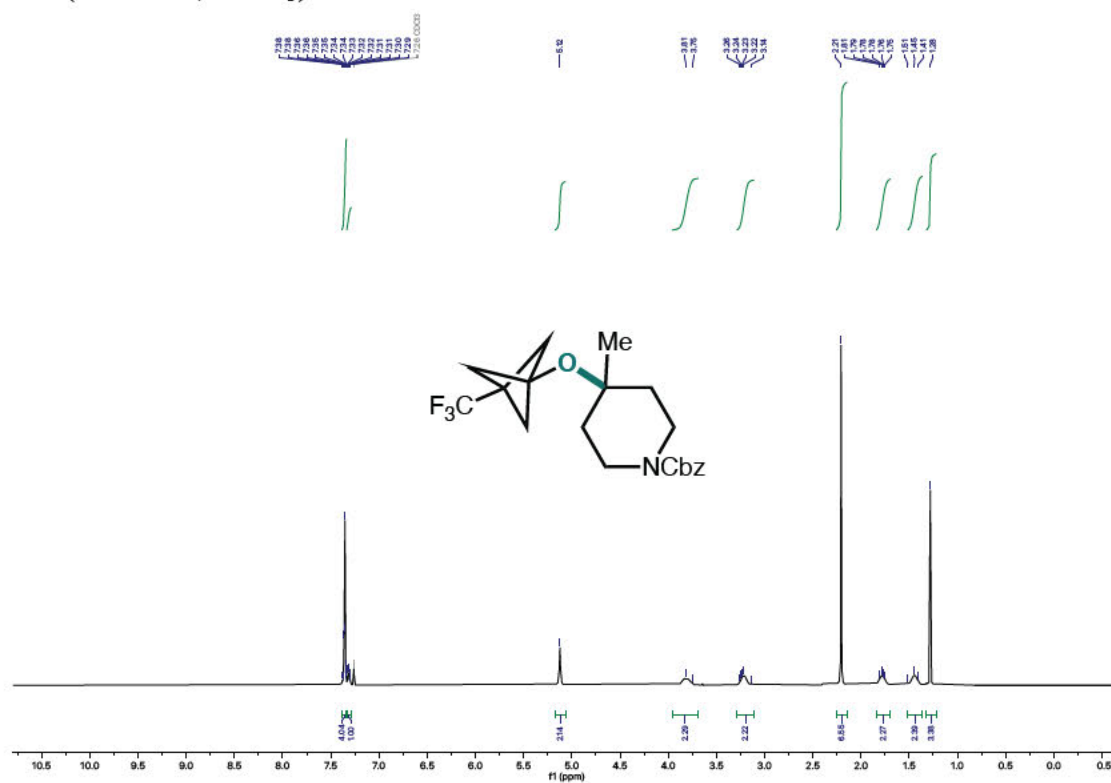
¹H NMR (500 MHz, CDCl₃):

***Tert*-butyl
carboxylate (78)** **(*R*)-3-methyl-3-((3-phenylbicyclo[1.1.1]pentan-1-yl)oxy)pyrrolidine-1-**

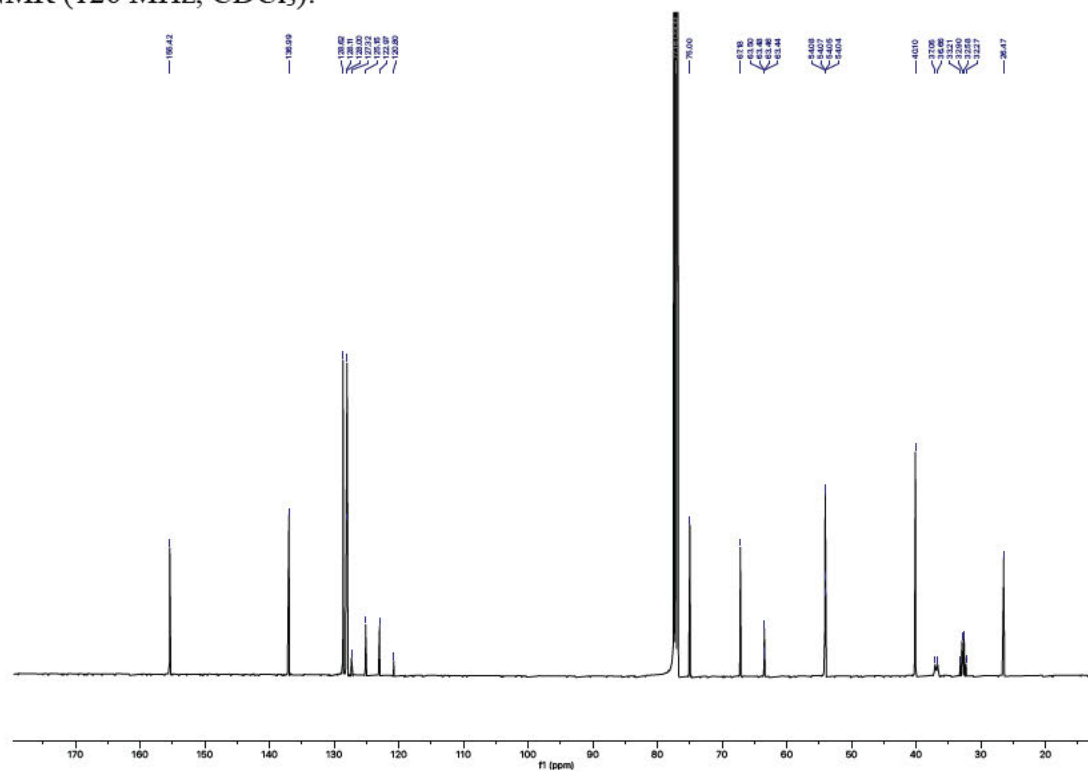
¹H NMR (500 MHz, CDCl₃): ^{13}C NMR (126 MHz, CDCl_3):

Benzyl 4-methyl-4-((3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)oxy)piperidine-1-carboxylate (79)

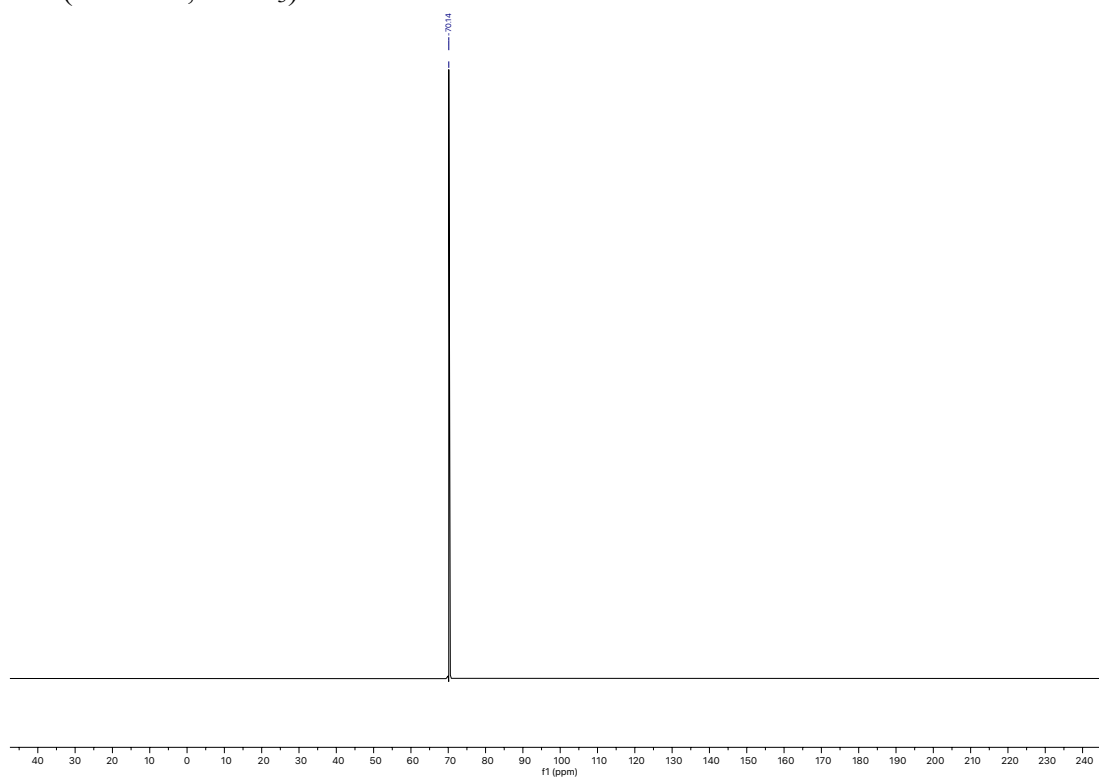
^1H NMR (500 MHz, CDCl_3):



^{13}C NMR (126 MHz, CDCl_3):

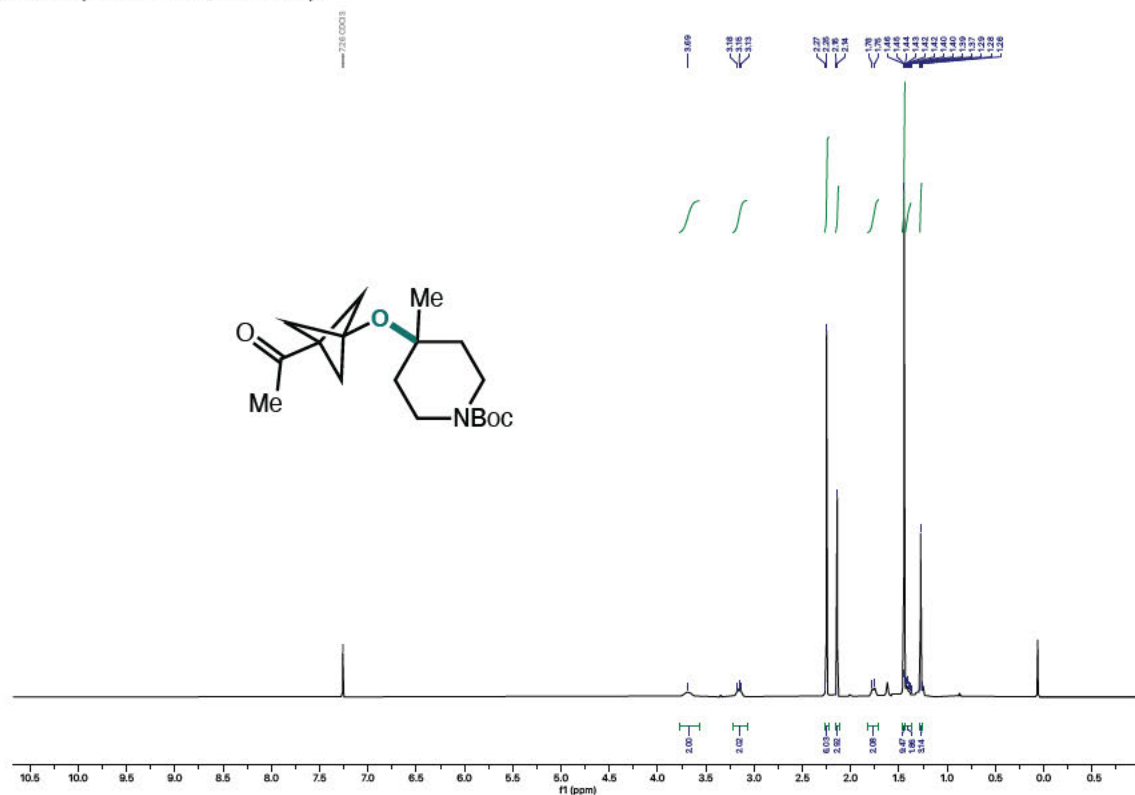


^{19}F NMR (471MHz, CDCl_3):

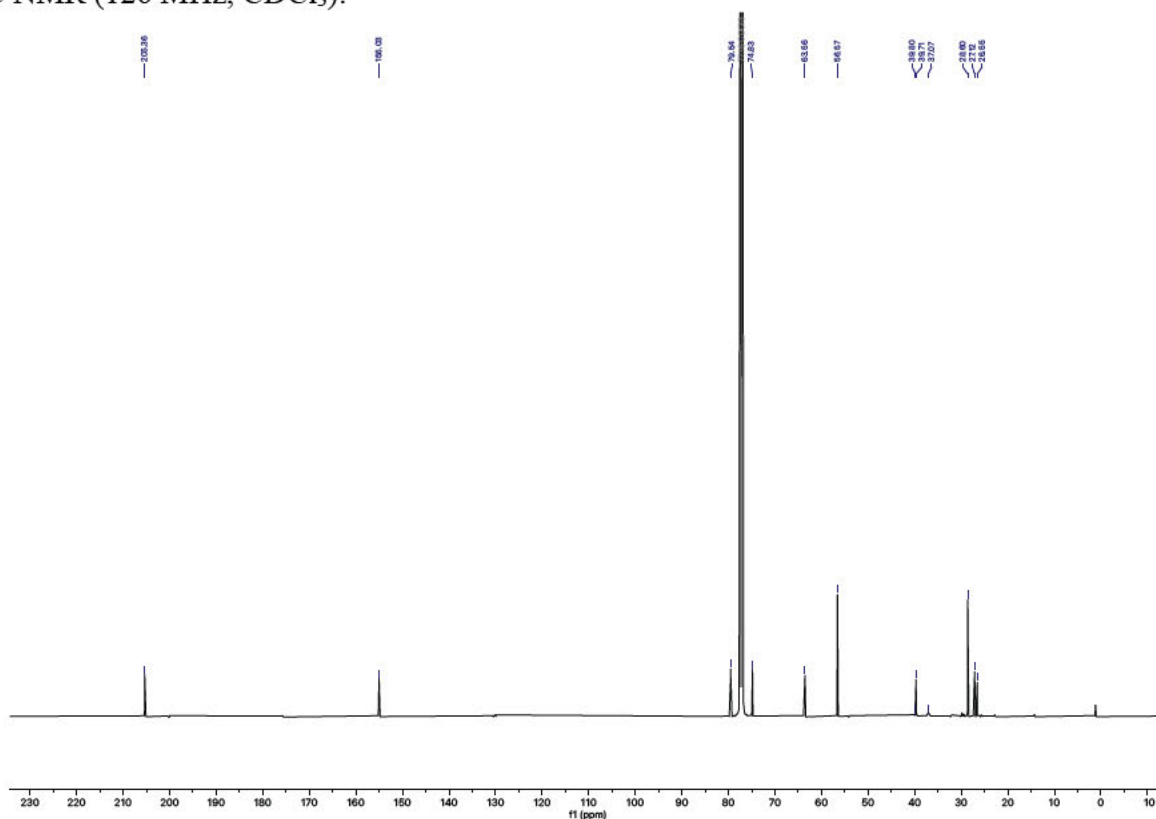


***Tert*-butyl 4-((3-acetylbicyclo[1.1.1]pentan-1-yl)oxy)-4-methylpiperidine-1-carboxylate (80)**

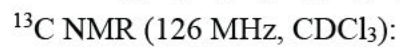
^1H NMR (500 MHz, CDCl_3):

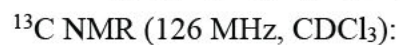


^{13}C NMR (126 MHz, CDCl_3):



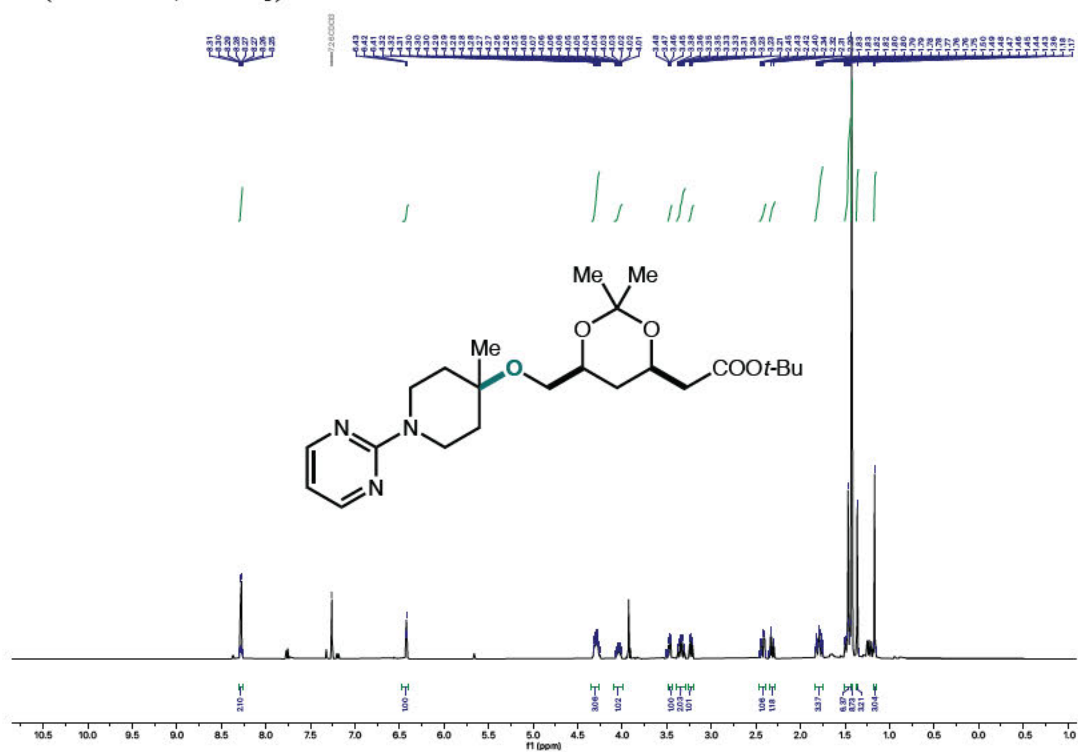
¹H NMR (500 MHz, CDCl₃):

¹H NMR (500 MHz, CDCl₃):

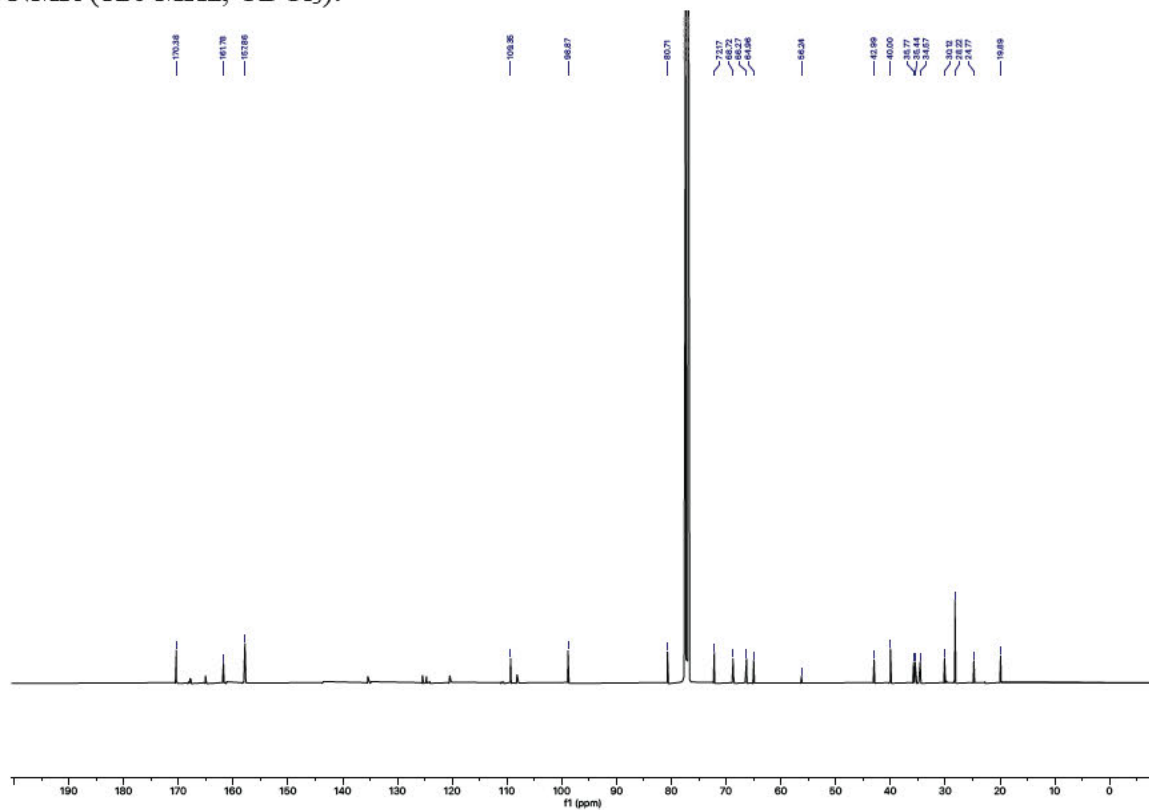
¹H NMR (500 MHz, CDCl₃):

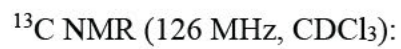
Tert-butyl 2-((4*R*,6*S*)-2,2-dimethyl-6-(((4-methyl-1-(pyrimidin-2-yl)piperidin-4-yl)oxy)methyl)-1,3-dioxan-4-yl)acetate (84)

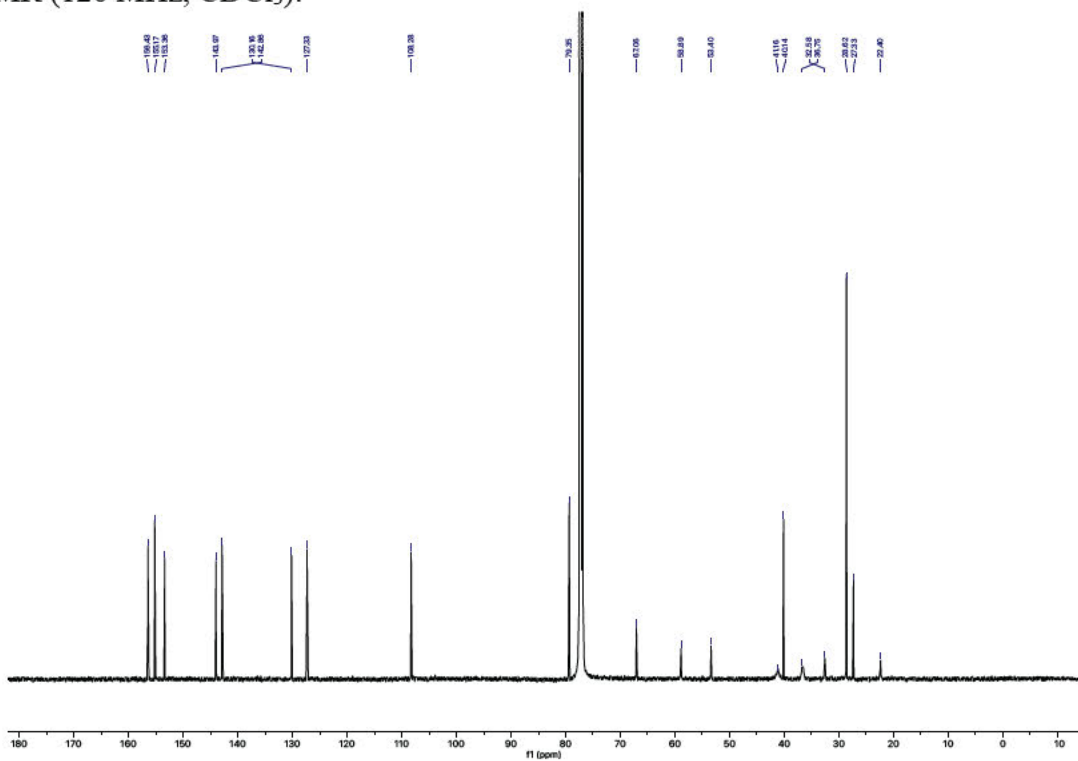
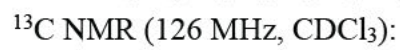
¹H NMR (500 MHz, CDCl₃):

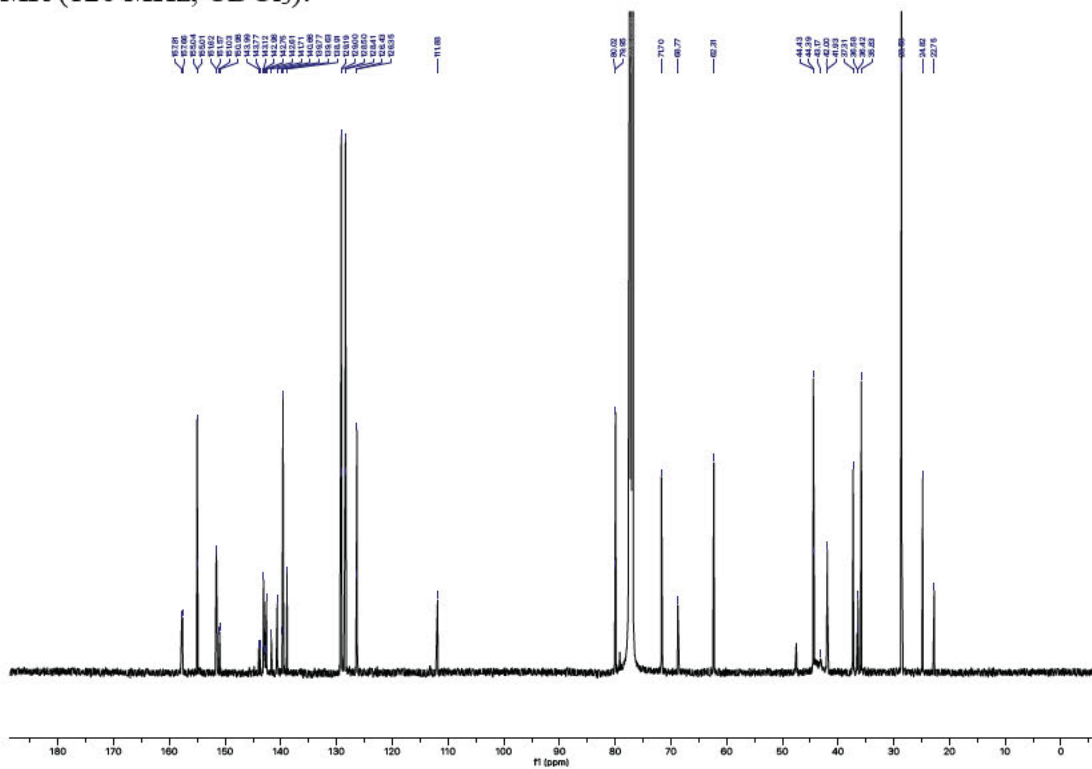


¹³C NMR (126 MHz, CDCl₃):

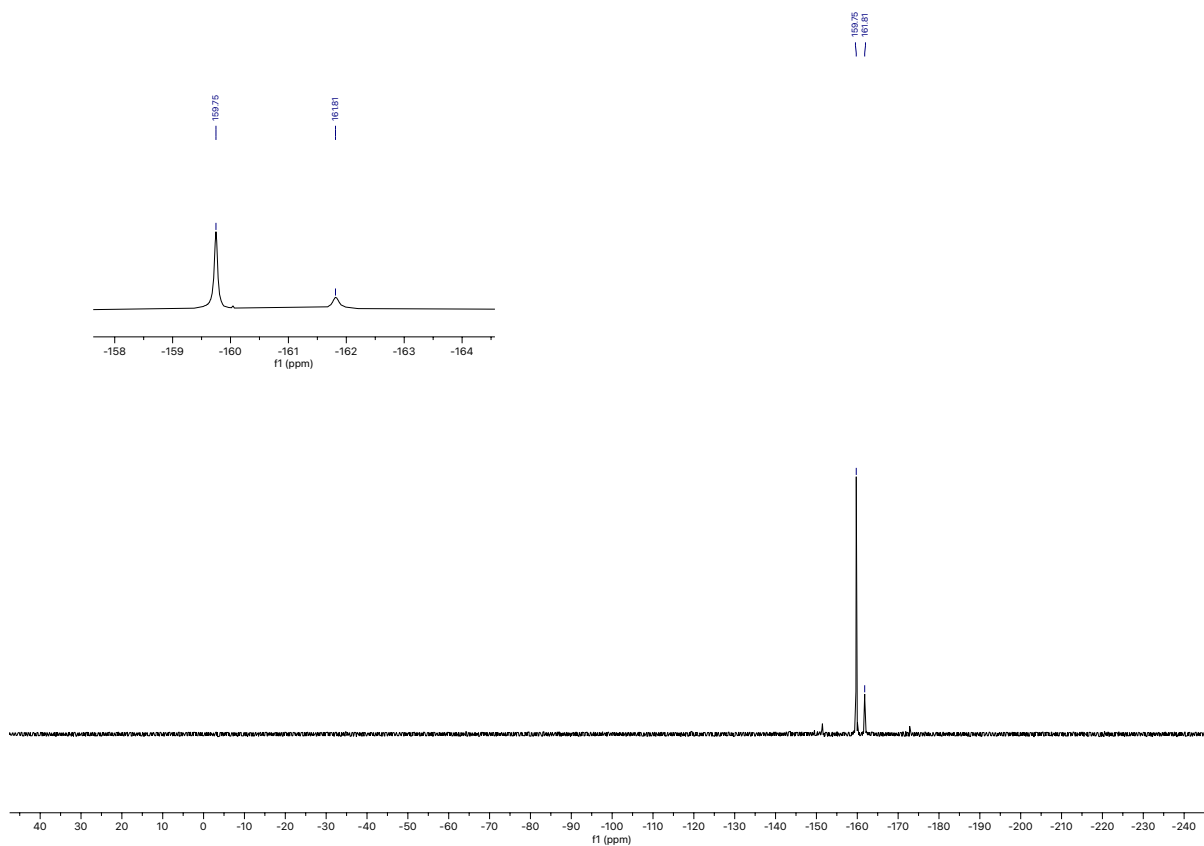


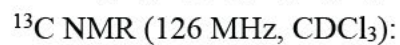
¹H NMR (500 MHz, CDCl₃):

¹H NMR (500 MHz, CDCl₃):

¹H NMR (500 MHz, CDCl₃):

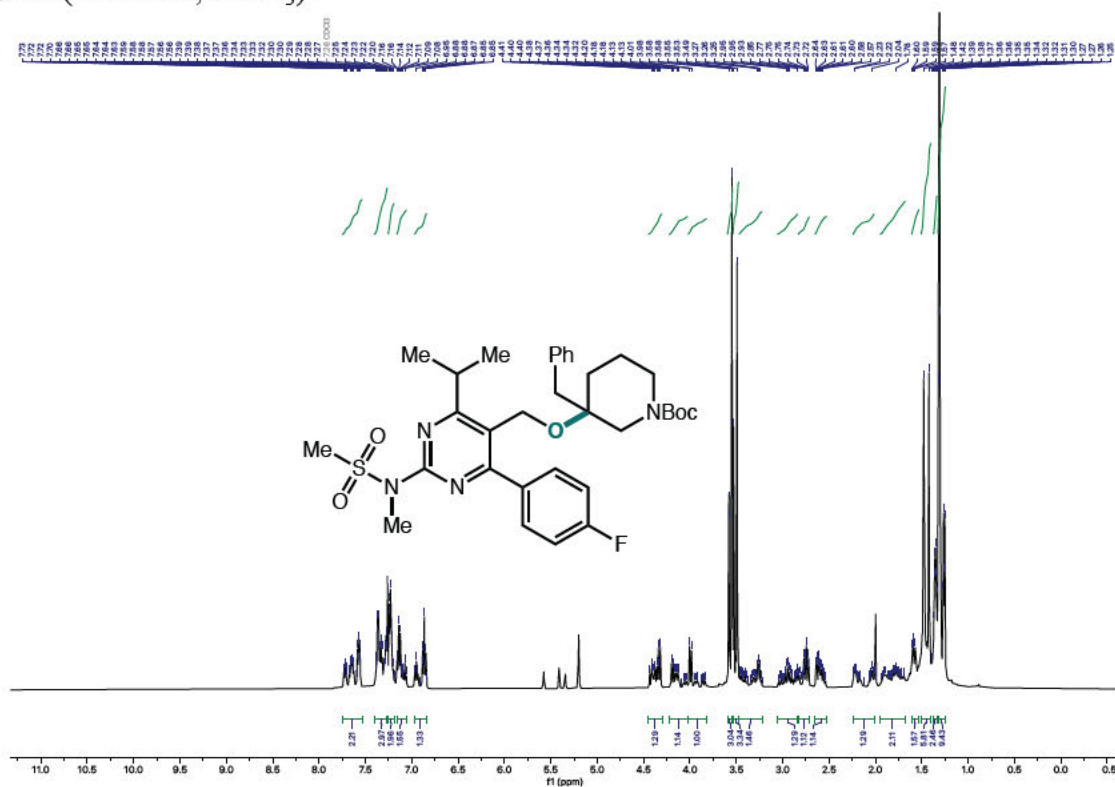
^{19}F NMR (471 MHz, CDCl_3)



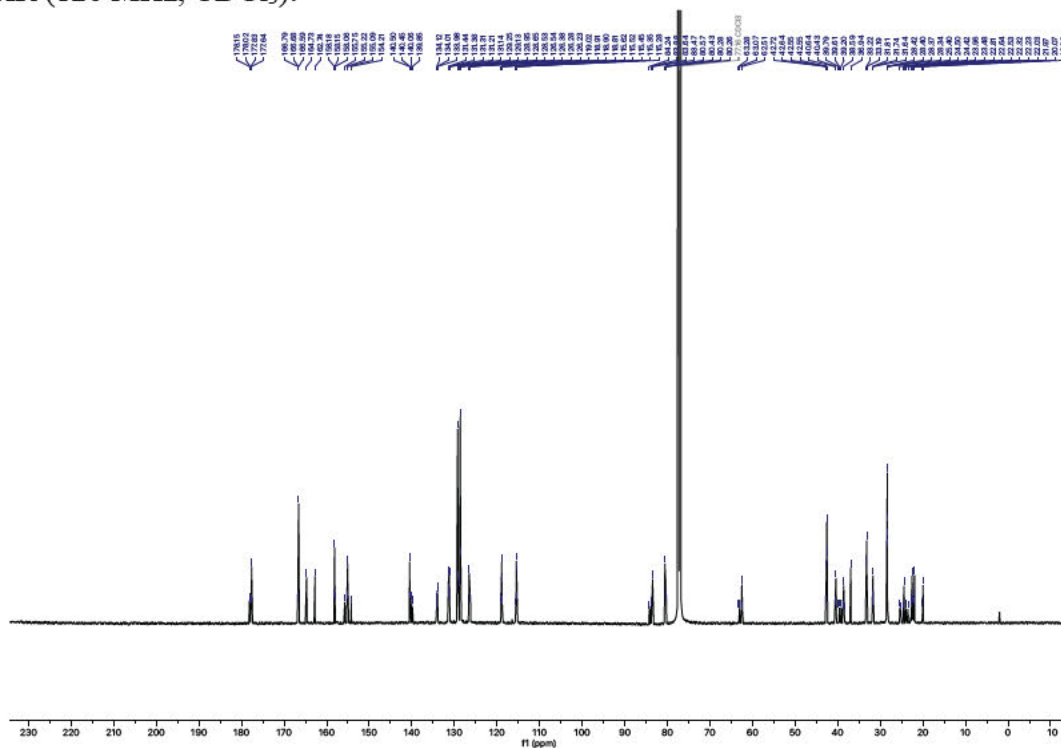
¹H NMR (500 MHz, CDCl₃):

Tert-butyl 3-benzyl-3-((4-(4-fluorophenyl)-6-isopropyl-2-(N-methylmethanesulfonamido)pyrimidin-5-yl)methoxy)piperidine-1-carboxylate (89)

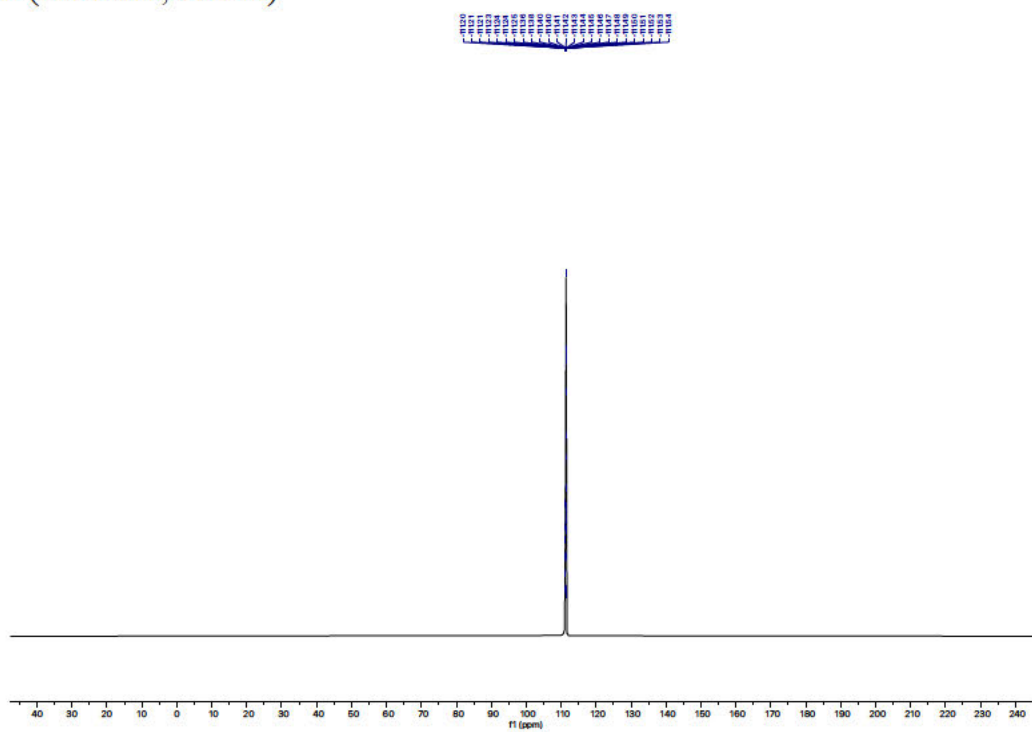
¹H NMR (500 MHz, CDCl₃):



¹³C NMR (126 MHz, CDCl₃):

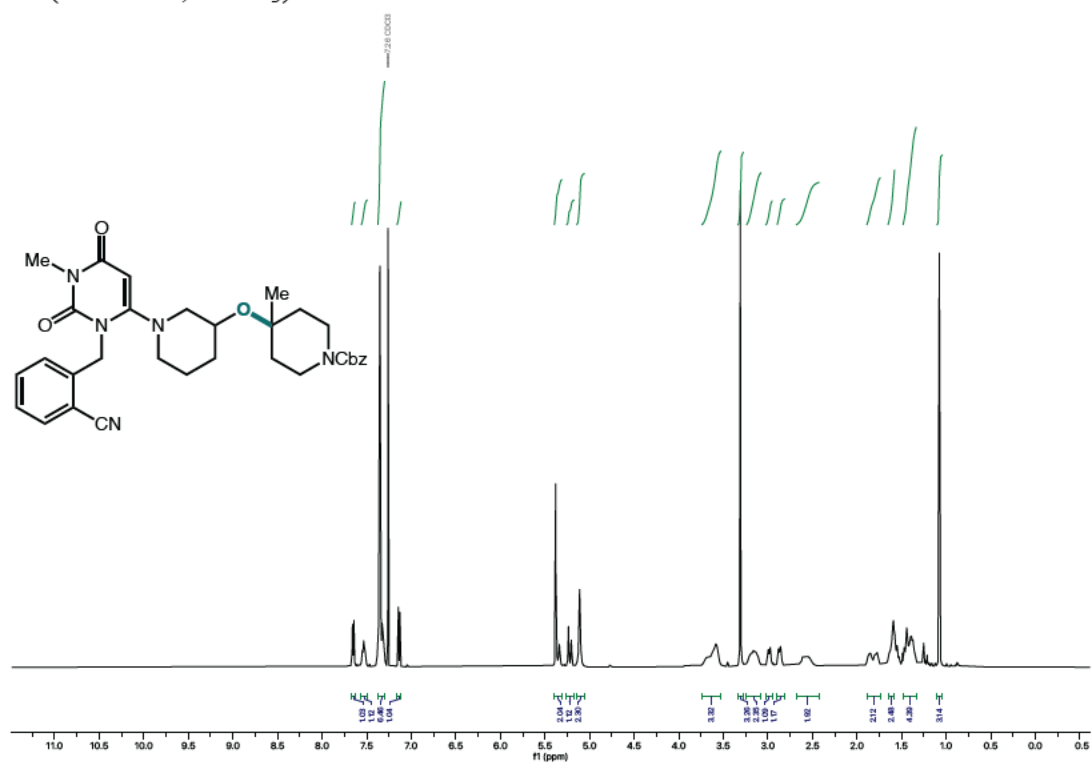


^{19}F NMR (471 MHz, CDCl_3)

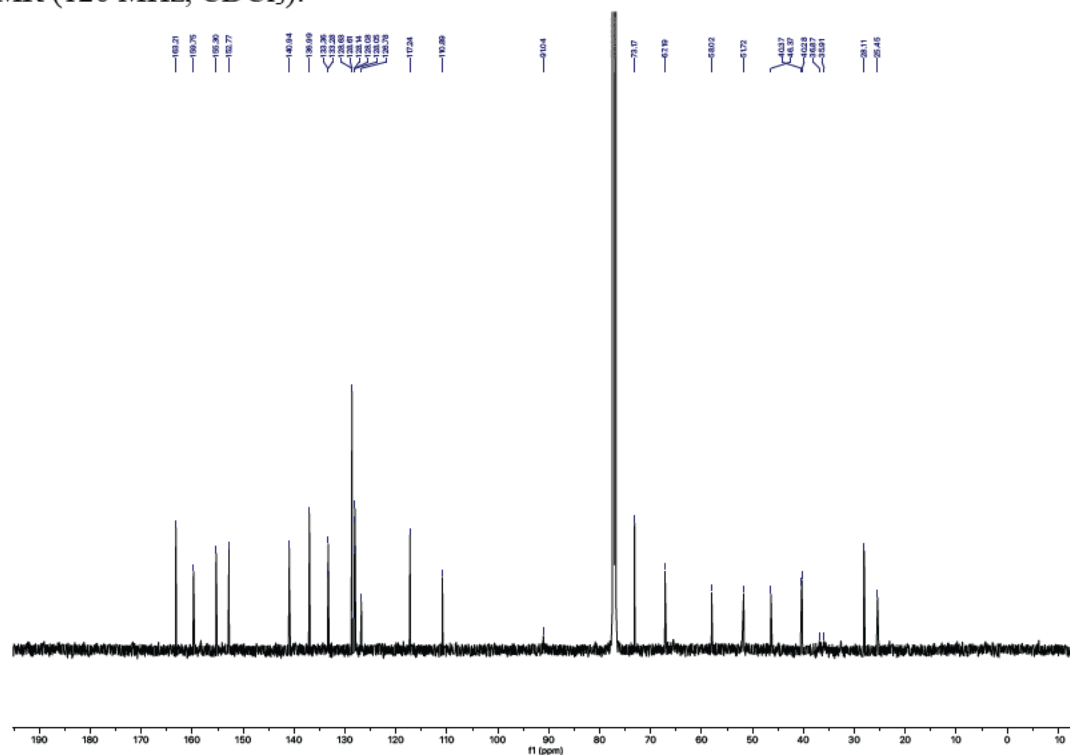


Benzyl 4-((1-(3-(2-cyanobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperidin-3-yl)oxy)-4-methylpiperidine-1-carboxylate (90)

¹H NMR (500 MHz, CDCl₃):

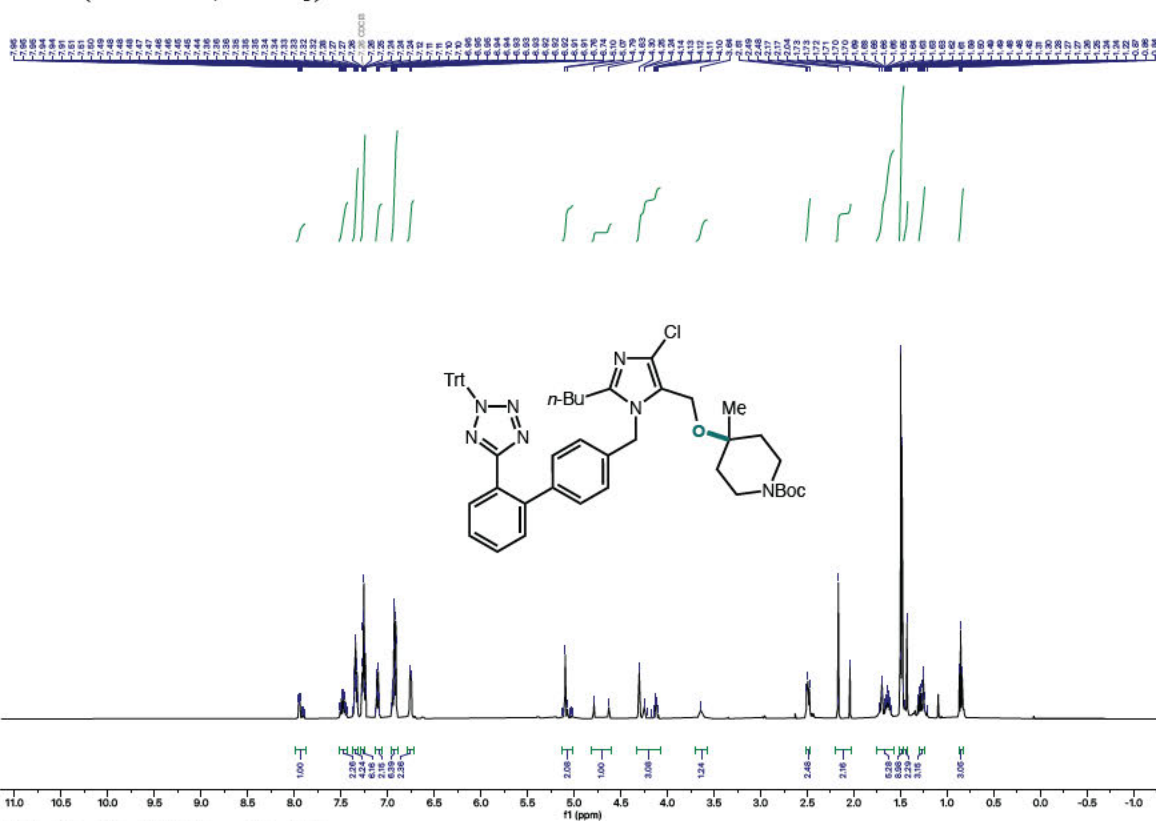


¹³C NMR (126 MHz, CDCl₃):



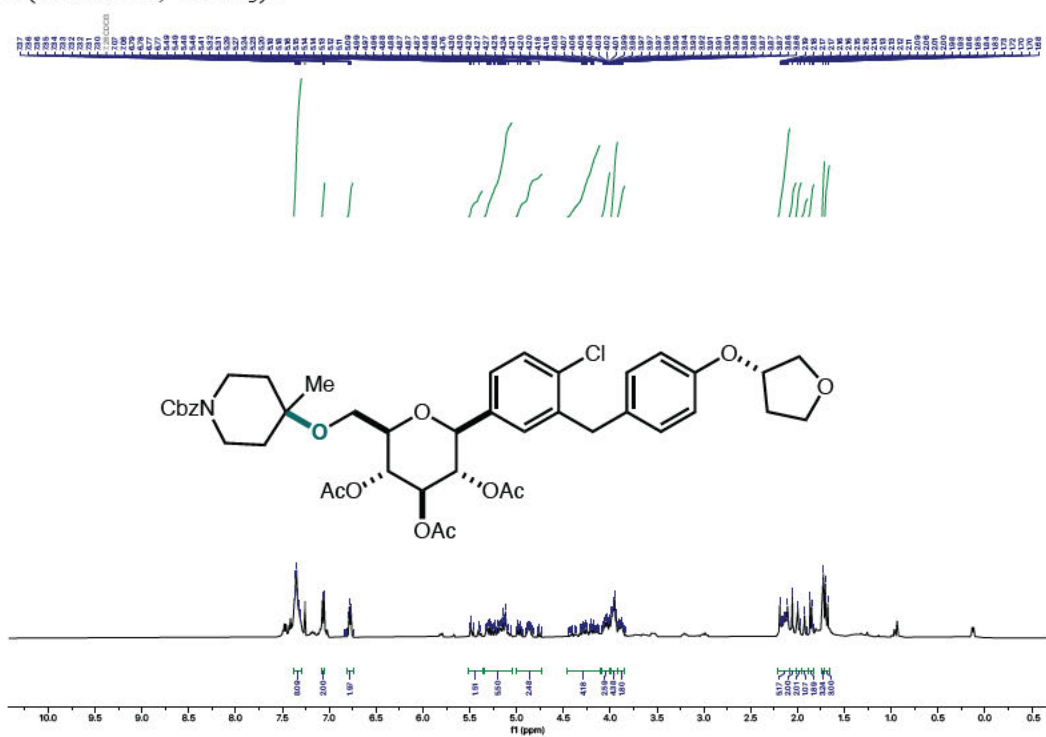
Tert-butyl 4-((2-butyl-4-chloro-1-((2'-(2-trityl-2*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-1*H*-imidazol-5-yl)methoxy)-4-methylpiperidine-1-carboxylate (91)

¹H NMR (500 MHz, CDCl₃):

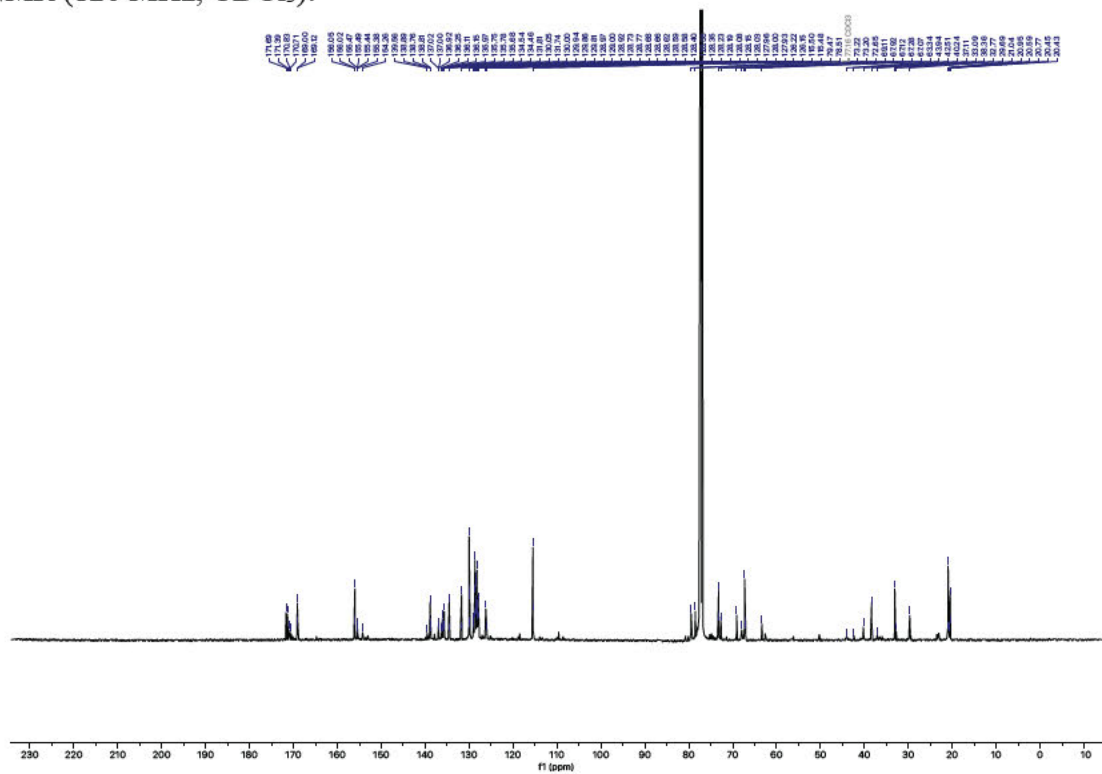


(2*R*,3*R*,4*R*,5*S*,6*S*)-2-(((1-((benzyloxy)carbonyl)-4-methylpiperidin-4-yl)oxy)methyl)-6-(4-chloro-3-(4-(((*S*)-tetrahydrofuran-3-yl)oxy)benzyl)phenyl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (92)

¹H NMR (500 MHz, CDCl₃):

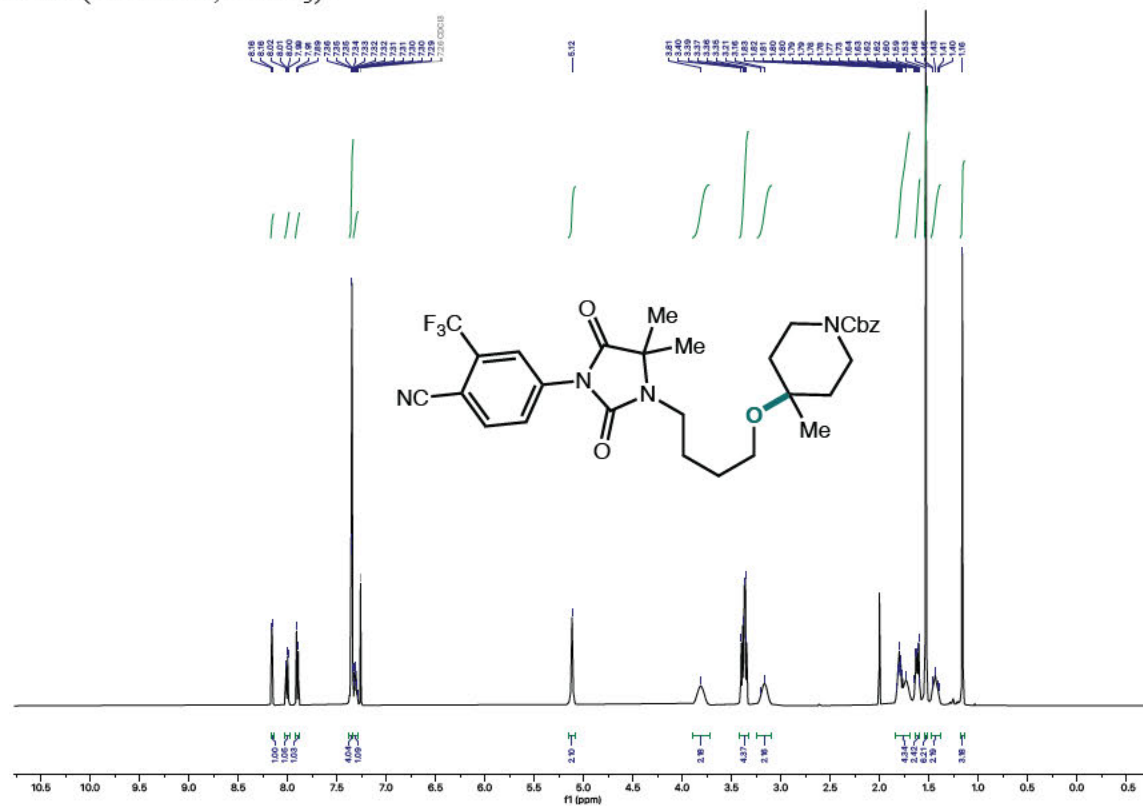


¹³C NMR (126 MHz, CDCl₃):

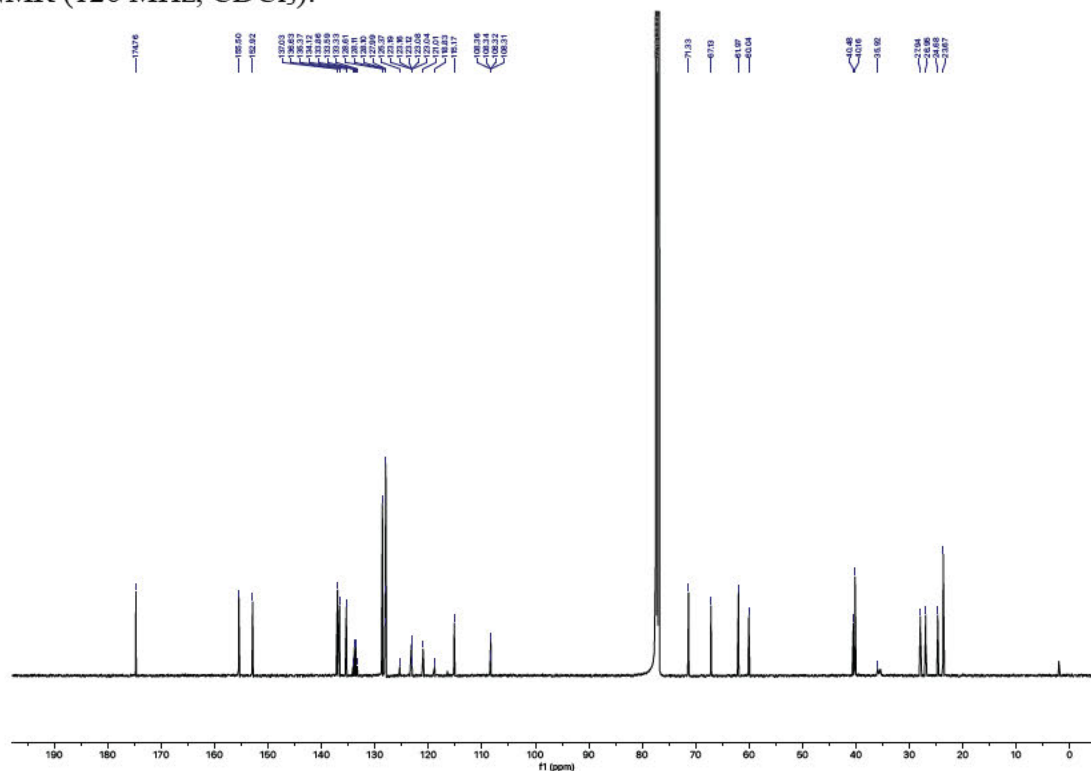


Benzyl 4-(4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-2,4-dioximidazolidin-1-yl)butoxy)-4-methylpiperidine-1-carboxylate (93)

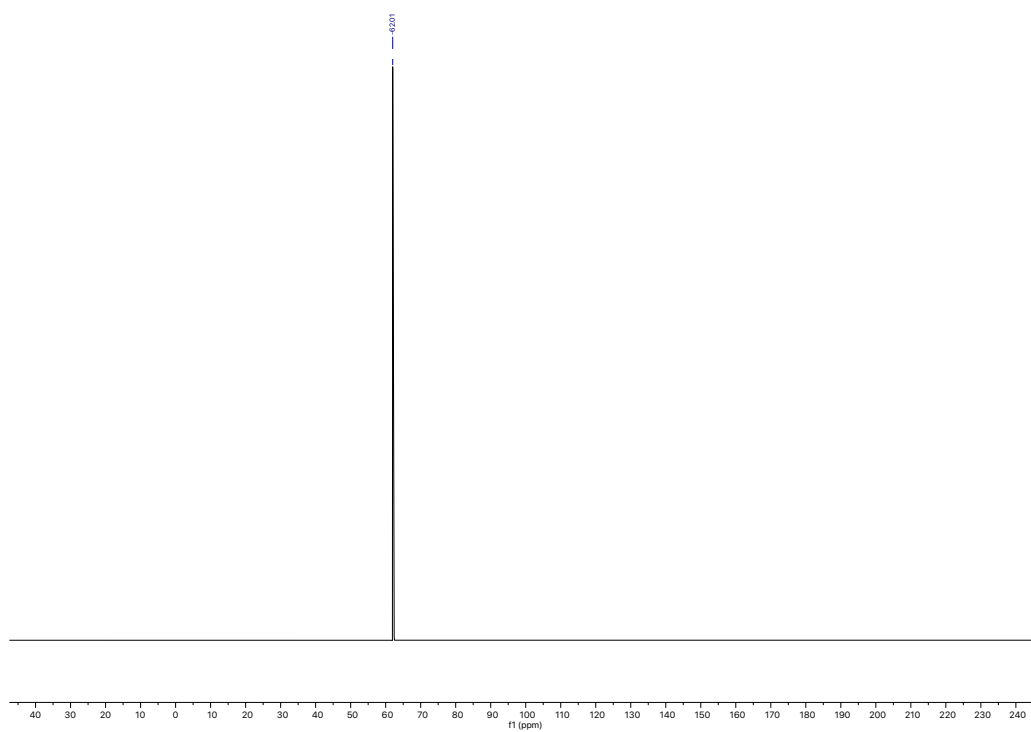
^1H NMR (500 MHz, CDCl_3):



^{13}C NMR (126 MHz, CDCl_3):

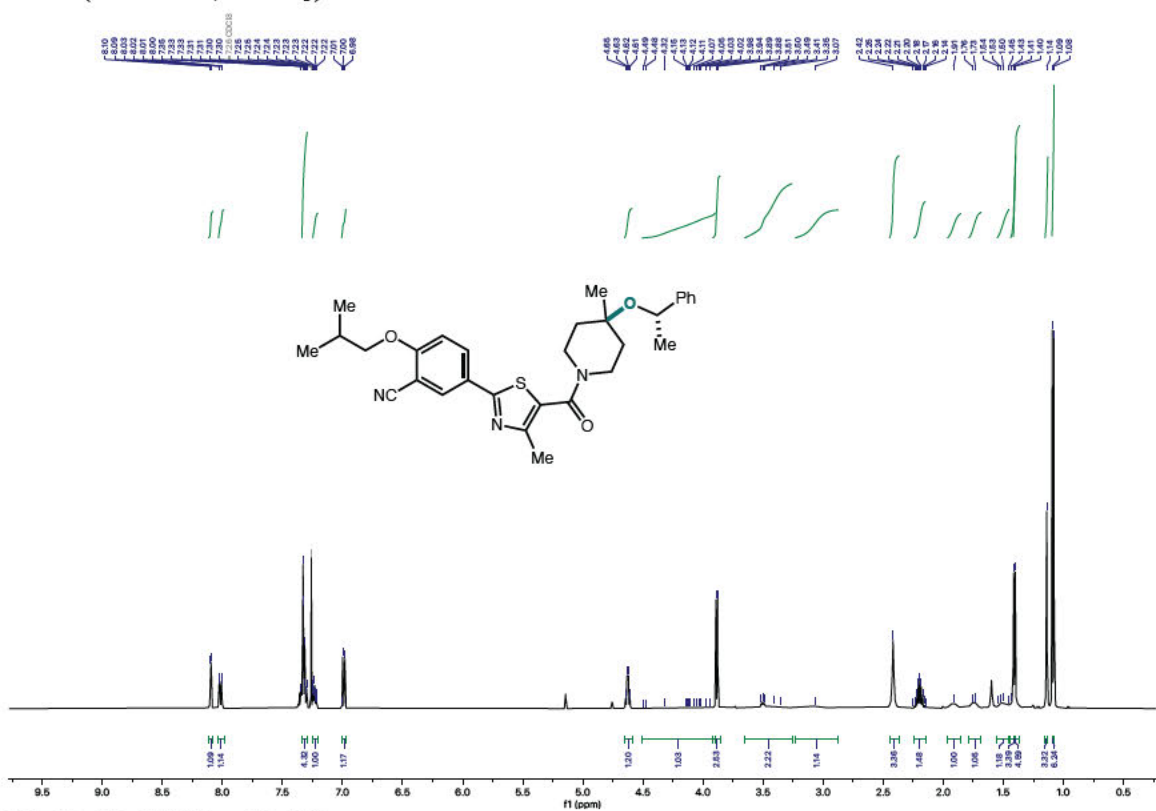


^{19}F NMR (376 MHz, CDCl_3)

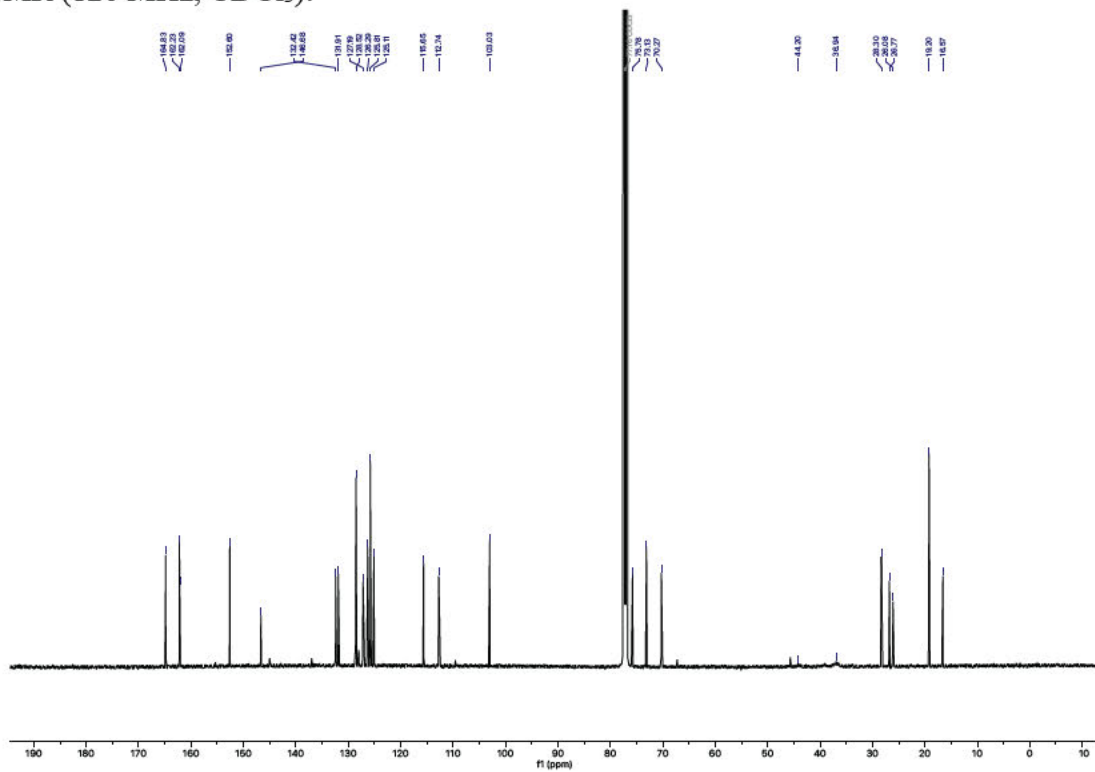


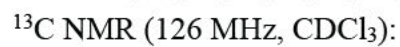
(S)-2-isobutoxy-5-(4-methyl-5-(4-methyl-4-(1-phenylethoxy)piperidine-1-carbonyl)thiazol-2-yl)benzonitrile (94)

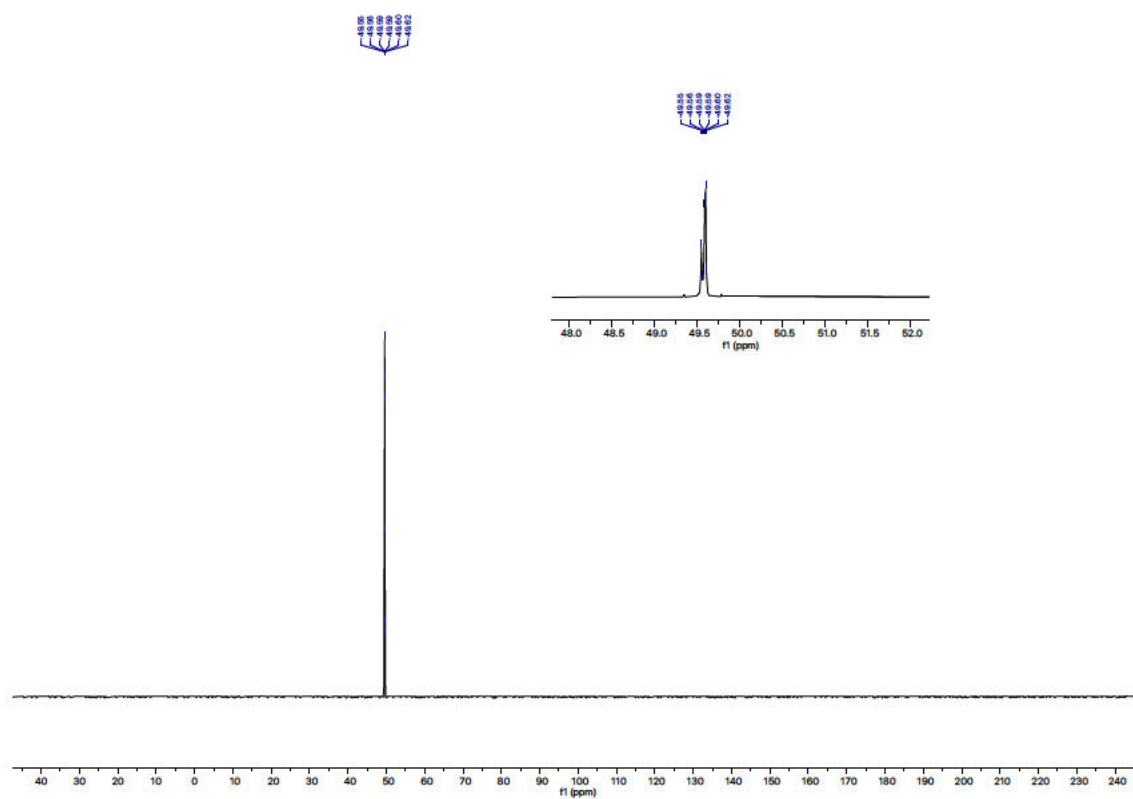
^1H NMR (500 MHz, CDCl_3):



^{13}C NMR (126 MHz, CDCl_3):



¹H NMR (500 MHz, CDCl₃):

¹⁹F NMR (126 MHz, CDCl₃)

15. References

1. M. S. Lowry, J. I. Goldsmith, J. D. Slinker, R. Rohl, R. A. Pascal, G. G. Malliaras, S. Bernhard, Single-Layer Electroluminescent Devices and Photoinduced Hydrogen Production from an Ionic Iridium(III) Complex. *Chem. Mater.* **17**, 5712–5719 (2005).
2. C. “Chip” Le, M. K. Wismer, Z.-C. Shi, R. Zhang, D. V. Conway, G. Li, P. Vachal, I. W. Davies, D. W. C. MacMillan, A General Small-Scale Reactor To Enable Standardization and Acceleration of Photocatalytic Reactions. *ACS Cent. Sci.* **3**, 647–653 (2017).
3. D. C. Salgueiro, B. K. Chi, I. A. Guzei, P. García-Reynaga, D. J. Weix, Control of Redox-Active Ester Reactivity Enables a General Cross-Electrophile Approach to Access Arylated Strained Rings. *Angew. Chem. Int. Ed.* **61**, e202205673 (2022).
4. J. Luo, J. Zhang, Donor–Acceptor Fluorophores for Visible-Light-Promoted Organic Synthesis: Photoredox/Ni Dual Catalytic C(sp³)–C(sp²) Cross-Coupling. *ACS Catal.* **6**, 873–877 (2016).
5. F. Toriyama, J. Cornella, L. Wimmer, T.-G. Chen, D. D. Dixon, G. Creech, P. S. Baran, Redox-Active Esters in Fe-Catalyzed C–C Coupling. *J. Am. Chem. Soc.* **138**, 11132–11135 (2016).
6. W. Liu, M. N. Lavagnino, C. A. Gould, J. Alcázar, D. W. C. MacMillan, A biomimetic S_H 2 cross-coupling mechanism for quaternary sp³-carbon formation. *Science* **374**, 1258–1263 (2021).
7. M. Parasram, B. J. Shields, O. Ahmad, T. Knauber, A. G. Doyle, Regioselective Cross-Electrophile Coupling of Epoxides and (Hetero)aryl Iodides via Ni/Ti/Photoredox Catalysis. *ACS Catal.* **10**, 5821–5827 (2020).
8. A. Gansäuer, M. Pierobon, H. Bluhm, Catalytic, Highly Regio- and Chemoselective Generation of Radicals from Epoxides: Titanocene Dichloride as an Electron Transfer Catalyst in Transition Metal Catalyzed Radical Reactions. *Angew. Chem. Int. Ed.* **37**, 101–103 (1998).
9. J. A. Shah, A. E. Lojko, Z. Tang, Y. Lin, E. H. Scher, C. A. Barefoot, J. M. Lipshultz, Degradative Alcohol Functionalization by Titanocene Photocatalysis. *ACS Catal.* **15**, 15315–15323 (2025).
10. M. Kubista, R. Sjöback, S. Eriksson, B. Albinsson, Experimental correction for the inner-filter effect in fluorescence spectra. *The Analyst* **119**, 417–419 (1994).
11. J. Xiang, M. Shang, Y. Kawamata, H. Lundberg, S. H. Reisberg, M. Chen, P. Mykhailiuk, G. Beutner, M. R. Collins, A. Davies, M. Del Bel, G. M. Gallego, J. E. Spangler, J. Starr, S. Yang, D. G. Blackmond, P. S. Baran, Hindered dialkyl ether synthesis with electrogenerated carbocations. *Nature* **573**, 398–402 (2019).

12. T. K. Salvador, C. H. Arnett, S. Kundu, N. G. Sapiezynski, J. A. Bertke, M. Raghibi Boroujeni, T. H. Warren, Copper Catalyzed sp^3 C–H Etherification with Acyl Protected Phenols. *J. Am. Chem. Soc.* **138**, 16580–16583 (2016).
13. Y. A. Almeahmadi, A. J. Passmore, P. Gabriel, D. J. Dixon, Iridium-Catalyzed Reductive Deoxygenation of Esters for the Synthesis of Sterically Hindered Ethers. *Angew. Chem. Int. Ed.* **64**, e202508301 (2025).
14. Gaussian 16, Revision A.03, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2016.
15. P. J. Stephens, F. J. Devlin, C. F. Chabalowski, M. J. Frisch, Ab Initio Calculation of Vibrational Absorption and Circular Dichroism Spectra Using Density Functional Force Fields. *J. Phys. Chem.* **98**, 11623–11627 (1994).
16. S. Grimme, J. Antony, S. Ehrlich, H. Krieg, A consistent and accurate *ab initio* parametrization of density functional dispersion correction (DFT-D) for the 94 elements H–Pu. *J. Chem. Phys.* **132**, 154104 (2010).
17. F. Weigend, R. Ahlrichs, Balanced basis sets of split valence, triple zeta valence and quadruple zeta valence quality for H to Rn: Design and assessment of accuracy. *Phys. Chem. Chem. Phys.* **7**, 3297 (2005).
18. M. Cossi, N. Rega, G. Scalmani, V. Barone, Energies, structures, and electronic properties of molecules in solution with the C-PCM solvation model. *J. Comput. Chem.* **24**, 669–681 (2003).
19. H. B. Schlegel, Optimization of equilibrium geometries and transition structures. *J. Comput. Chem.* **3**, 214–218 (1982).
20. C. Peng, H. Bernhard Schlegel, Combining Synchronous Transit and Quasi-Newton Methods to Find Transition States. *Isr. J. Chem.* **33**, 449–454 (1993).
21. G. B. Bacskay, A quadratically convergent Hartree–Fock (QC-SCF) method. Application to closed shell systems. *Chem. Phys.* **61**, 385–404 (1981).
22. C. Gonzalez, H. B. Schlegel, An improved algorithm for reaction path following. *J. Chem. Phys.* **90**, 2154–2161 (1989).

23. K. Fukui, The path of chemical reactions - the IRC approach. *Acc. Chem. Res.* **14**, 363–368 (1981).
24. J.-D. Chai, M. Head-Gordon, Long-range corrected hybrid density functionals with damped atom–atom dispersion corrections. *Phys. Chem. Chem. Phys.* **10**, 6615 (2008).
25. A. E. Reed, R. B. Weinstock, F. Weinhold, Natural population analysis. *J. Chem. Phys.* **83**, 735–746 (1985).