# Radical Redox Annulations: A General Light-Driven Method for the Synthesis of Saturated Heterocycles

## Supporting Information

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## 1. Collection of recently reported methods for the synthesis of saturated carbocycles and heterocycles through annulation with emphasis on photocatalysis

Methods are presented chronologically and by research group within each heterocycle type. Where reports detail access to more than one product class, we order by the class displayed in the majority of substrate scope examples.

### Three-membered ring systems

#### Cyclopropanes

- del Hoyo, A. M.; Herraiz, A. G.; Suero, M. G. A Stereoconvergent Cyclopropanation Reaction of Styrenes. *Angew. Chemie - Int. Ed.* **2017**, *56*, 1610–1613.
- del Hoyo, A. M.; García Suero, M. Photoredox-Catalyzed Cyclopropanation of Michael Acceptors. *European J. Org. Chem.* **2017**, 2122–2125.
- Herraiz, A. G.; Suero, M. G. A Transition-Metal-Free & Diazo-Free Styrene Cyclopropanation. *Chem. Sci.* **2019**, 10, 9374–9379.
- Phelan, J. P.; Lang, S. B.; Compton, J. S.; Kelly, C. B.; Dykstra, R.; Gutierrez, O.; Molander, G. A. Redox-Neutral Photocatalytic Cyclopropanation via Radical/Polar Crossover. *J. Am. Chem. Soc.* **2018**, *140*, 8037–8047.
- Milligan, J. A.; Phelan, J. P.; Polites, V. C.; Kelly, C. B.; Molander, G. A. Radical/Polar Annulation Reactions (RPARs) Enable the Modular Construction of Cyclopropanes. *Org. Lett.* **2018**, *20*, 6840–6844.
- Milligan, J. A.; Burns, K. L.; Le, A. V.; Polites, V. C.; Wang, Z. J.; Molander, G. A.; Kelly, C. B. Radical-Polar Crossover Annulation: A Platform for Accessing Polycyclic Cyclopropanes. *Adv. Synth. Catal.* **2020**, *362*, 242–247.
- Piou, T.; Romanov-Michailidis, F.; Ashley, M. A.; Romanova-Michaelides, M.; Rovis, T. Stereodivergent Rhodium(III)-Catalyzed Cis-Cyclopropanation Enabled by Multivariate Optimization. *J. Am. Chem. Soc.* **2018**, *140*, 9587–9593.
- Phipps, E. J. T.; Rovis, T. Rh(III)-Catalyzed C-H Activation-Initiated Directed Cyclopropanation of Allylic Alcohols. *J. Am. Chem. Soc.* **2019**, *141*, 6807–6811.
- Phipps, E. J. T.; Piou, T.; Rovis, T. Rhodium(III)-Catalyzed Cyclopropanation of Unactivated Olefins Initiated by C-H Activation. *Synlett* **2019**, *30*, 1787–1790.
- Shu, C.; Mega, R. S.; Andreassen, B. J.; Noble, A.; Aggarwal, V. K. Synthesis of Functionalized Cyclopropanes from Carboxylic Acids by a Radical Addition–Polar Cyclization Cascade. *Angew. Chemie - Int. Ed.* **2018**, *57*, 15430–15434.

#### Aziridines

- Jat, J. L.; Paudyal, M. P.; Gao, H.; Xu, Q. L.; Yousufuddin, M.; Devarajan, D.; Ess, D. H.; Kürti, L.; Falck, J. R. Direct Stereospecific Synthesis of Unprotected N-H and N-Me Aziridines from Olefins. *Science* **2014**, *343*, 61–65.
- Ma, Z.; Zhou, Z.; Kürti, L. Direct and Stereospecific Synthesis of N-H and N-Alkyl Aziridines from Unactivated Olefins Using Hydroxylamine-O-Sulfonic Acids. *Angew. Chemie - Int. Ed.* **2017**, *56*, 9886–9890.
- Cheng, Q. Q.; Zhou, Z.; Jiang, H.; Siitonen, J. H.; Ess, D. H.; Zhang, X.; Kürti, L. Organocatalytic Nitrogen Transfer to Unactivated Olefins via Transient Oxaziridines. *Nat. Catal.* **2020**, *3*, 386–392.
- Holst, D. E.; Wang, D. J.; Kim, M. J.; Guzei, I. A.; Wickens, Z. K. Aziridine Synthesis by Coupling Amines and Alkenes via an Electrogenerated Dication. *Nature* **2021**, *596*, 74–79.

### Four-membered ring systems

#### Cyclobutanes

- Ischay, M. A.; Anzovino, M. E.; Du, J.; Yoon, T. P. Efficient Visible Light Photocatalysis of [2+2] Enone Cycloadditions. *J. Am. Chem. Soc.* **2008**, *130*, 12886–12887.
- Du, J.; Yoon, T. P. Crossed Intermolecular [2+2] Cycloadditions of Acyclic Enones via Visible Light Photocatalysis. *J. Am. Chem. Soc.* **2009**, *131*, 14604–14605.
- Ischay, M. A.; Lu, Z.; Yoon, T. P. Cycloadditions by Oxidative Visible Light Photocatalysis. *J. Am. Chem. Soc.* **2010**, *132*, 8572–8574.
- Ischay, M. A.; Ament, M. S.; Yoon, T. P. Crossed Intermolecular [2+2] Cycloaddition of Styrenes by Visible Light Photocatalysis. *Chem. Sci.* **2012**, *3*, 2807–2811.
- Lu, Z.; Yoon, T. P. Visible Light Photocatalysis of [2+2] Styrene Cycloadditions by Energy Transfer. *Angew. Chemie - Int. Ed.* **2012**, *51*, 10329–10332.
- Du, J.; Skubi, K. L.; Schultz, D. M.; Yoon, T. P. A Dual-Catalysis Approach to Enantioselective [2+2] Photocycloadditions Using Visible Light. *Science* **2014**, *344*, 392–396.

- Hurtley, A. E.; Lu, Z.; Yoon, T. P. Cycloaddition of 1,3-Dienes by Visible Light Photocatalysis. *Angew. Chemie - Int. Ed.* **2014**, *53*, 8991–8994.
- Blum, T. R.; Miller, Z. D.; Bates, D. M.; Guzei, I. A.; Yoon, T. P. Enantioselective Photochemistry through Lewis Acid-Catalyzed Triplet Energy Transfer. *Science* **2016**, *354*, 1391–1395.
- Miller, Z. D.; Lee, B. J.; Yoon, T. P. Enantioselective Crossed Photocycloadditions of Styrenic Olefins by Lewis Acid Catalyzed Triplet Sensitization. *Angew. Chemie - Int. Ed.* **2017**, *56*, 11891–11895.
- Daub, M. E.; Jung, H.; Lee, B. J.; Won, J.; Baik, M. H.; Yoon, T. P. Enantioselective [2+2] Cycloadditions of Cinnamate Esters: Generalizing Lewis Acid Catalysis of Triplet Energy Transfer. *J. Am. Chem. Soc.* **2019**, *141*, 9543–9547.
- Zheng, J.; Swords, W. B.; Jung, H.; Skubi, K. L.; Kidd, J. B.; Meyer, G. J.; Baik, M. H.; Yoon, T. P. Enantioselective Intermolecular Excited-State Photoreactions Using a Chiral Ir Triplet Sensitizer: Separating Association from Energy Transfer in Asymmetric Photocatalysis. *J. Am. Chem. Soc.* **2019**, *141*, 13625–13634.
- Sherbrook, E. M.; Jung, H.; Cho, D.; Baik, M. H.; Yoon, T. P. Brønsted Acid Catalysis of Photosensitized Cycloadditions. *Chem. Sci.* **2020**, *11*, 856–861.
- Sherbrook, E. M.; Genzink, M. J.; Park, B.; Guzei, I. A.; Baik, M. H.; Yoon, T. P. Chiral Brønsted Acid-Controlled Intermolecular Asymmetric [2+2] Photocycloadditions. *Nat. Commun.* **2021**, *12*, 1–7.
- Gravatt, C. S.; Melecio-Zambrano, L.; Yoon, T. P. Olefin-Supported Cationic Copper Catalysts for Photochemical Synthesis of Structurally Complex Cyclobutanes. *Angew. Chemie - Int. Ed.* **2021**, *60*, 3989–3993.
- Chapman, S. J.; Swords, W. B.; Le, C. M.; Guzei, I. A.; Toste, F. D.; Yoon, T. P. Cooperative Stereoinduction in Asymmetric Photocatalysis. *J. Am. Chem. Soc.* **2022**, *144*, 4206–4213.
- Zou, Y. Q.; Duan, S. W.; Meng, X. G.; Hu, X. Q.; Gao, S.; Chen, J. R.; Xiao, W. J. Visible Light Induced Intermolecular [2+2]-Cycloaddition Reactions of 3-Ylideneoxindoles through Energy Transfer Pathway. *Tetrahedron* **2012**, *68*, 6914–6919.
- Renata, H.; Zhou, Q.; Baran, P. S. Strategic Redox Relay Enables a Scalable Synthesis of Ouabagenin, a Bioactive Cardenolide. *Science* **2013**, *339*, 59–63.
- Brimioulle, R.; Bach, T. Enantioselective Lewis Acid Catalysis of Intramolecular Enone [2+2] Photocycloaddition Reactions. *Science* **2013**, *342*, 840–843.
- Brimioulle, R.; Bach, T. [2+2] Photocycloaddition of 3-Alkenyloxy-2-Cycloalkenones: Enantioselective Lewis Acid Catalysis and Ring Expansion. *Angew. Chemie Int. Ed.* **2014**, *53*, 12921–12924.
- Maturi, M. M.; Bach, T. Enantioselective Catalysis of the Intermolecular [2+2] Photocycloaddition between 2-Pyridones and Acetylenedicarboxylates. *Angew. Chemie Int. Ed.* **2014**, *53*, 7661–7664.
- Alonso, R.; Bach, T. A Chiral Thioxanthone as an Organocatalyst for Enantioselective [2+2] Photocycloaddition Reactions Induced by Visible Light. Angew. Chemie Int. Ed. **2014**, *53*, 4368–4371.
- Brimioulle, R.; Bauer, A.; Bach, T. Enantioselective Lewis Acid Catalysis in Intramolecular [2+2] Photocycloaddition Reactions: A Mechanistic Comparison between Representative Coumarin and Enone Substrates. *J. Am. Chem. Soc.* **2015**, *137*, 5170–5176.
- Tröster, A.; Alonso, R.; Bauer, A.; Bach, T. Enantioselective Intermolecular [2+2] Photocycloaddition Reactions of 2(1H)-Quinolones Induced by Visible Light Irradiation. *J. Am. Chem. Soc.* **2016**, *138*, 7808–7811.
- Brenninger, C.; Pöthig, A.; Bach, T. Brønsted Acid Catalysis in Visible-Light-Induced [2+2] Photocycloaddition Reactions of Enone Dithianes. *Angew. Chemie Int. Ed.* **2017**, *56*, 4337–4341.
- Poplata, S.; Bach, T. Enantioselective Intermolecular [2+2] Photocycloaddition Reaction of Cyclic Enones and Its Application in a Synthesis of (−)-Grandisol. *J. Am. Chem. Soc.* **2018**, *140*, 3228–3231.
- Hörmann, F. M.; Chung, T. S.; Rodriguez, E.; Jakob, M.; Bach, T. Evidence for Triplet Sensitization in the Visible-Light-Induced [2+2] Photocycloaddition of Eniminium Ions. *Angew. Chemie - Int. Ed.* **2018**, *57*, 827–831.
- Hörmann, F. M.; Kerzig, C.; Chung, T. S.; Bauer, A.; Wenger, O. S.; Bach, T. Triplet Energy Transfer from Ruthenium Complexes to Chiral Eniminium Ions: Enantioselective Synthesis of Cyclobutanecarbaldehydes by [2+2] Photocycloaddition. *Angew. Chemie Int. Ed.* **2020**, *59*, 9659–9668.
- Pecho, F.; Sempere, Y.; Gramüller, J.; Hörmann, F. M.; Gschwind, R. M.; Bach, T. Enantioselective [2+2] Photocycloaddition via Iminium Ions: Catalysis by a Sensitizing Chiral Brønsted Acid. *J. Am. Chem. Soc.* **2021**, *143*, 9350–9354.
- Rigotti, T.; Schwinger, D. P.; Graßl, R.; Jandl, C.; Bach, T. Enantioselective Crossed Intramolecular [2+2] Photocycloaddition Reactions Mediated by a Chiral Chelating Lewis Acid. *Chem. Sci.* **2022**, *13*, 2378–2384.

- Shu, C.; Noble, A.; Aggarwal, V. K. Photoredox-Catalyzed Cyclobutane Synthesis by a Deboronative Radical Addition–Polar Cyclization Cascade. *Angew. Chemie Int. Ed.* **2019**, *58*, 3870–3874.
- James, M. J.; Schwarz, J. L.; Strieth-Kalthoff, F.; Wibbeling, B.; Glorius, F. Dearomative Cascade Photocatalysis: Divergent Synthesis through Catalyst Selective Energy Transfer. *J. Am. Chem. Soc.* **2018**, *140*, 8624–8628.
- Zhu, M.; Zheng, C.; Zhang, X.; You, S. L. Synthesis of Cyclobutane-Fused Angular Tetracyclic Spiroindolines via Visible-Light-Promoted Intramolecular Dearomatization of Indole Derivatives. *J. Am. Chem. Soc.* **2019**, *141*, 2636–2644.
- Oderinde, M. S.; Mao, E.; Ramirez, A.; Pawluczyk, J.; Jorge, C.; Cornelius, L. A. M.; Kempson, J.; Vetrichelvan, M.; Pitchai, M.; Gupta, A.; et al. Synthesis of Cyclobutane-Fused Tetracyclic Scaffolds via Visible-Light Photocatalysis for Building Molecular Complexity. *J. Am. Chem. Soc.* **2020**, *142*, 3094–3103.
- Oderinde, M. S.; Ramirez, A.; Dhar, T. G. M.; Cornelius, L. A. M.; Jorge, C.; Aulakh, D.; Sandhu, B.; Pawluczyk, J.; Sarjeant, A. A.; Meanwell, N. A.; et al. Photocatalytic Dearomative Intermolecular [2+2] Cycloaddition of Heterocycles for Building Molecular Complexity. *J. Org. Chem.* **2021**, *86*, 1730–1747.
- Murray, P. R. D.; Bussink, W. M. M.; Davies, G. H. M.; Van Der Mei, F. W.; Antropow, A. H.; Edwards, J. T.; D'Agostino, L. A.; Ellis, J. M.; Hamann, L. G.; Romanov-Michailidis, F.; et al. Intermolecular Crossed [2+2] Cycloaddition Promoted by Visible-Light Triplet Photosensitization: Expedient Access to Polysubstituted 2-Oxaspiro[3.3]Heptanes. *J. Am. Chem. Soc.* **2021**, *143*, 4055–4063.
- Zhu, M.; Huang, X. L.; Xu, H.; Zhang, X.; Zheng, C.; You, S. L. Visible-Light-Mediated Synthesis of Cyclobutene-Fused Indolizidines and Related Structural Analogs. *CCS Chem.* **2021**, *3*, 652–664.
- Liu, Y.; Ni, D.; Stevenson, B. G.; Tripathy, V.; Braley, S. E.; Raghavachari, K.; Swierk, J. R.; Brown, M. K. Photosensitized [2+2]-Cycloadditions of Alkenylboronates and Alkenes. *Angew. Chemie - Int. Ed.* **2022**, *61*.

Azetidines

- Kumarasamy, E.; Kandappa, S. K.; Raghunathan, R.; Jockusch, S.; Sivaguru, J. Realizing an Aza Paternò–Büchi Reaction. *Angew. Chemie Int. Ed.* **2017**, *56*, 7056–7061.
- Becker, M. R.; Richardson, A. D.; Schindler, C. S. Functionalized Azetidines via Visible Light-Enabled Aza Paternò-Büchi Reactions. *Nat. Commun.* **2019**, *10*, 5095.
- Becker, M. R.; Wearing, E. R.; Schindler, C. S. Synthesis of Azetidines via Visible-Light-Mediated Intermolecular [2+2] Photocycloadditions. *Nat. Chem.* **2020**, *12*, 898–905.
- Wearing, E. R.; Blackmun, D. E.; Becker, M. R.; Schindler, C. S. 1- and 2-Azetines via Visible Light-Mediated [2+2]-Cycloadditions of Alkynes and Oximes. *J. Am. Chem. Soc.* **2021**, *143*, 16235–16242.
- Blackmun, D. E.; Chamness, S. A.; Schindler, C. S. Intramolecular, Visible-Light-Mediated Aza Paternò-Büchi Reactions of Unactivated Alkenes. *Org. Lett.* **2022**, *24*, 3053–3057.
- Zhu, M.; Zhang, X.; Zheng, C.; You, S.-L. Visible-Light-Induced Dearomatization via [2+2] Cycloaddition or 1,5-Hydrogen Atom Transfer: Divergent Reaction Pathways of Transient Diradicals. *ACS Catal.* **2020**, *10*, 12618–12626.
- Li, X.; Großkopf, J.; Jandl, C.; Bach, T. Enantioselective, Visible Light Mediated Aza Paternò–Büchi Reactions of Quinoxalinones. *Angew. Chemie - Int. Ed.* **2021**, *60*, 2684–2688.
- Flores, D. M.; Neville, M. L.; Schmidt, V. A. Intermolecular 2+2 Imine-Olefin Photocycloadditions Enabled by Cu(I)-Alkene MLCT. *Nat. Commun.* **2022**, *13*, 1–6.

Oxetanes

- Flores, D. M.; Schmidt, V. A. Intermolecular 2 + 2 Carbonyl-Olefin Photocycloadditions Enabled by Cu(I)-Norbornene MLCT. *J. Am. Chem. Soc.* **2019**, *141*, 8741–8745.
- Rykaczewski, K. A.; Schindler, C. S. Visible-Light-Enabled Paternò–Büchi Reaction via Triplet Energy Transfer for the Synthesis of Oxetanes. *Org. Lett.* **2020**, *22*, 6516–6519.
- Zheng, J.; Dong, X.; Yoon, T. P. Divergent Photocatalytic Reactions of **α**-Ketoesters under Triplet Sensitization and Photoredox Conditions. *Org. Lett.* **2020**, *22*, 6520–6525.
- Mateos, J.; Vega-Peñaloza, A.; Franceschi, P.; Rigodanza, F.; Andreetta, P.; Companyó, X.; Pelosi, G.; Bonchio, M.; Dell'Amico, L. A Visible-Light Paternò–Büchi Dearomatisation Process towards the Construction of Oxeto-Indolinic Polycycles. *Chem. Sci.* **2020**, *11*, 6532–6538.
- Li, H.-F.; Cao, W.; Ma, X.; Xie, X.; Xia, Y.; Ouyang, Z. Visible-Light-Driven [2+2] Photocycloadditions between Benzophenone and C═C Bonds in Unsaturated Lipids. *J. Am. Chem. Soc.* **2020**, *142*, 3499–3505.

## Five-membered ring systems

### Cyclopentane and cyclopentene


- Maity, S.; Zhu, M.; Shinabery, R. S.; Zheng, N. Intermolecular [3+2] Cycloaddition of Cyclopropylamines with Olefins by Visible-Light Photocatalysis. *Angew. Chemie - Int. Ed.* **2012**, *51*, 222–226.
- Nguyen, T. H.; Morris, S. A.; Zheng, N. Intermolecular [3+2] Annulation of Cyclopropylanilines with Alkynes, Enynes, and Diynes via Visible Light Photocatalysis. *Adv. Synth. & Catal.* **2014**, *356*, 2831–2837.
- Hashimoto, T.; Kawamata, Y.; Maruoka, K. An Organic Thiyl Radical Catalyst for Enantioselective Cyclization. *Nat. Chem.* **2014**, *6*, 702–705.
- Zhang, F.; Das, S.; Walkinshaw, A. J.; Casitas, A.; Taylor, M.; Suero, M. G.; Gaunt, M. J. Cu-Catalyzed Cascades to Carbocycles: Union of Diaryliodonium Salts with Alkenes or Alkynes Exploiting Remote Carbocations. *J. Am. Chem. Soc.* **2014**, *136*, 8851–8854.
- Kohara, K.; Trowbridge, A.; Smith, M. A.; Gaunt, M. J. Thiol-Mediated **α**-Amino Radical Formation via Visible-Light-Activated Ion-Pair Charge-Transfer Complexes. *J. Am. Chem. Soc.* **2021**, *143*, 19268–19274.
- Amador, A. G.; Sherbrook, E. M.; Yoon, T. P. Enantioselective Photocatalytic [3 + 2] Cycloadditions of Aryl Cyclopropyl Ketones. *J. Am. Chem. Soc.* **2016**, *138*, 4722–4725.
- Amador, A. G.; Sherbrook, E. M.; Lu, Z.; Yoon, T. P. A General Protocol for Radical Anion [3+2] Cycloaddition Enabled by Tandem Lewis Acid Photoredox Catalysis. *Synth.* **2018**, *50*, 539–547.
- Bagal, D. B.; Park, S.-W.; Song, H.-J.; Chang, S. Visible Light Sensitization of Benzoyl Azides: Cascade Cyclization toward Oxindoles via a Non-Nitrene Pathway. *Chem. Commun.* **2017**, *53*, 8798–8801.
- Hao, W.; Harenberg, J. H.; Wu, X.; MacMillan, S. N.; Lin, S. Diastereo- and Enantioselective Formal [3+2] Cycloaddition of Cyclopropyl Ketones and Alkenes via Ti-Catalyzed Radical Redox Relay. *J. Am. Chem. Soc.* **2018**, *140*, 3514–3517.
- Zhu, M.; Zhou, K.; Zhang, X.; You, S. L. Visible-Light-Promoted Cascade Alkene Trifluoromethylation and Dearomatization of Indole Derivatives via Intermolecular Charge Transfer. *Org. Lett.* **2018**, *20*, 4379–4383.
- Zhao, Q.-Q.; Zhou, X.-S.; Xu, S.-H.; Wu, Y.-L.; Xiao, W.-J.; Chen, J.-R. Visible-Light-Driven Nitrogen Radical-Catalyzed [3 + 2] Cyclization of Vinylcyclopropanes and N-Tosyl Vinylaziridines with Alkenes. *Org. Lett.* **2020**, *22*, 2470–2475.
- Uraguchi, D.; Kimura, Y.; Ueoka, F.; Ooi, T. Urea as a Redox-Active Directing Group under Asymmetric Photocatalysis of Iridium-Chiral Borate Ion Pairs. *J. Am. Chem. Soc.* **2020**, *142*, 19462–19467.
- Ma, J.; Schäfers, F.; Daniliuc, C.; Bergander, K.; Strassert, C. A.; Glorius, F. Gadolinium Photocatalysis: Dearomative [2+2] Cycloaddition/Ring-Expansion Sequence with Indoles. *Angew. Chemie Int. Ed.* **2020**, *59*, 9639–9645.
- Clayman, P. D.; Hyster, T. K. Photoenzymatic Generation of Unstabilized Alkyl Radicals: An Asymmetric Reductive Cyclization. *J. Am. Chem. Soc.* **2020**, *142*, 15673–15677.
- White, D. H.; Noble, A.; Booker-Milburn, K. I.; Aggarwal, V. K. Diastereoselective Photoredox-Catalyzed [3+2] Cycloadditions of N-Sulfonyl Cyclopropylamines with Electron-Deficient Olefins. *Org. Lett.* **2021**, *23*, 3038–3042.
- Agasti, S.; Beattie, N. A.; McDouall, J. J. W.; Procter, D. J. $SmI_2$-Catalyzed Intermolecular Coupling of Cyclopropyl Ketones and Alkynes: A Link between Ketone Conformation and Reactivity. *J. Am. Chem. Soc.* **2021**, *143*, 3655–3661.
- Collins, J. L.; Staveness, D.; Sowden, M. J.; Stephenson, C. R. J. A One-Pot Photochemical Method for the Generation of Functionalized Aminocyclopentanes. *Org. Lett.* **2022**, *24*, 4344–4348.
- Kumar, M.; Verma, S.; Mishra, V.; Reiser, O.; Verma, A. K. Visible-Light-Accelerated Copper-Catalyzed [3+2] Cycloaddition of N-Tosylcyclopropylamines with Alkynes/Alkenes. *J. Org. Chem.* **2022**, *87*, 6263–6272.
- Le, S.; Li, J.; Feng, J.; Zhang, Z.; Bai, Y.; Yuan, Z.; Zhu, G. [3+2] Cycloaddition of Alkyl Aldehydes and Alkynes Enabled by Photoinduced Hydrogen Atom Transfer. *Nat. Commun.* **2022**, 1–8.
- Bellotti, P.; Rogge, T.; Paulus, F.; Laskar, R.; Rendel, N.; Ma, J.; Houk, K. N.; Glorius, F. Visible-Light Photocatalyzed Peri-(3+2) Cycloadditions of Quinolines. *J. Am. Chem. Soc.* **2022**.


### Pyrrolidine and indoline


- Musacchio, A. J.; Nguyen, L. Q.; Beard, G. H.; Knowles, R. R. Catalytic Olefin Hydroamination with Aminium Radical Cations: A Photoredox Method for Direct C-N Bond Formation. *J. Am. Chem. Soc.* **2014**, *136*, 12217–12220.
- Gentry, E. C.; Rono, L. J.; Hale, M. E.; Matsuura, R.; Knowles, R. R. Enantioselective Synthesis of Pyrroloindolines via Noncovalent Stabilization of Indole Radical Cations and Applications to the Synthesis of Alkaloid Natural Products. *J. Am. Chem. Soc.* **2018**, *140*, 3394–3402.
- Zhu, Q.; Graff, D. E.; Knowles, R. R. Intermolecular Anti-Markovnikov Hydroamination of Unactivated Alkenes with Sulfonamides Enabled by Proton-Coupled Electron Transfer. *J. Am. Chem. Soc.* **2018**, *140*, 741–747.

- Roos, C. B.; Demaerel, J.; Graff, D. E.; Knowles, R. R. Enantioselective Hydroamination of Alkenes with Sulfonamides Enabled by Proton-Coupled Electron Transfer. *J. Am. Chem. Soc.* **2020**, *142*, 5974–5979.
- Cludius-Brandt, S.; Kupracz, L.; Kirschning, A. [3+2]-Cycloadditions of Nitrile Ylides after Photoactivation of Vinyl Azides under Flow Conditions. *Beilstein J. Org. Chem.* **2013**, *9*, 1745–1750.
- Hashimoto, T.; Takino, K.; Hato, K.; Maruoka, K. A Bulky Thiyl-Radical Catalyst for the [3+2] Cyclization of N-Tosyl Vinylaziridines and Alkenes. *Angew. Chemie - Int. Ed.* **2016**, *55*, 8081–8085.
- Wappes, E. A.; Fosu, S. C.; Chopko, T. C.; Nagib, D. A. Triiodide-Mediated **δ**-Amination of Secondary C−H Bonds. *Angew. Chemie - Int. Ed.* **2016**, *55*, 9974–9978.
- Stateman, L. M.; Dare, R. M.; Paneque, A. N.; Nagib, D. A. Aza-Heterocycles via Copper-Catalyzed, Remote C–H Desaturation of Amines. *Chem* **2022**, *8*, 210–224.
- Hao, W.; Wu, X.; Sun, J. Z.; Siu, J. C.; MacMillan, S. N.; Lin, S. Radical Redox-Relay Catalysis: Formal [3+2] Cycloaddition of N-Acylaziridines and Alkenes. *J. Am. Chem. Soc.* **2017**, *139*, 12141–12144.
- Ye, K. Y.; Song, Z.; Sauer, G. S.; Harenberg, J. H.; Fu, N.; Lin, S. Synthesis of Chlorotrifluoromethylated Pyrrolidines by Electrocatalytic Radical Ene-Yne Cyclization. *Chem. - A Eur. J.* **2018**, *24*, 12274–12279.
- Herold, S.; Bafaluy, D.; Muñiz, K. Anodic Benzylic C(Sp3)-H Amination: Unified Access to Pyrrolidines and Piperidines. *Green Chem.* **2018**, *20*, 3191–3196.
- Hu, X.; Zhang, G.; Bu, F.; Nie, L.; Lei, A. Electrochemical-Oxidation-Induced Site-Selective Intramolecular C(Sp3)-H Amination. *ACS Catal.* **2018**, *8*, 9370–9375.
- Wang, Q.; Wang, P.; Gao, X.; Wang, D.; Wang, S.; Liang, X.; Wang, L.; Zhang, H.; Lei, A. Regioselective/Electro-Oxidative Intermolecular [3 + 2] Annulation for the Preparation of Indolines. *Chem. Sci.* **2020**, *11*, 2181–2186.
- Amador, A. G.; Sherbrook, E. M.; Yoon, T. P. A Redox Auxiliary Strategy for Pyrrolidine Synthesis via Photocatalytic [3+2] Cycloaddition. *Asian J. Org. Chem.* **2019**, *8*, 978–985.
- Boddy, A. J.; Affron, D. P.; Cordier, C. J.; Rivers, E. L.; Spivey, A. C.; Bull, J. A. Rapid Assembly of Saturated Nitrogen Heterocycles in One-Pot: Diazo-Heterocycle "Stitching" by N–H Insertion and Cyclization. *Angew. Chemie - Int. Ed.* **2019**, *58*, 1458–1462.
- Pantaine, L. R. E.; Milligan, J. A.; Matsui, J. K.; Kelly, C. B.; Molander, G. A. Photoredox Radical/Polar Crossover Enables Construction of Saturated Nitrogen Heterocycles. *Org. Lett.* **2019**, *21*, 2317–2321.
- Flodén, N. J.; Trowbridge, A.; Willcox, D.; Walton, S. M.; Kim, Y.; Gaunt, M. J. Streamlined Synthesis of C($sp^3$)-Rich N-Heterospirocycles Enabled by Visible-Light-Mediated Photocatalysis. *J. Am. Chem. Soc.* **2019**, *141*, 8426–8430.
- Lee, S.; Lei, H.; Rovis, T. A Rh(III)-Catalyzed Formal [4+1] Approach to Pyrrolidines from Unactivated Terminal Alkenes and Nitrene Sources. *J. Am. Chem. Soc.* **2019**, *141*, 12536–12540.
- Yamazaki, K.; Gabriel, P.; Di Carmine, G.; Pedroni, J.; Farizyan, M.; Hamlin, T. A.; Dixon, D. J. General Pyrrolidine Synthesis via Iridium-Catalyzed Reductive Azomethine Ylide Generation from Tertiary Amides and Lactams. *ACS Catal.* **2021**, *11*, 7489–7497.
- Rodríguez, R. I.; Mollari, L.; Alemán, J. Light-Driven Enantioselective Synthesis of Pyrroline Derivatives by a Radical/Polar Cascade Reaction. *Angew. Chemie - Int. Ed.* **2021**, *60*, 4555–4560.
- Hidasová, D.; Pohl, R.; Císařová, I.; Jahn, U. A Diastereoselective Catalytic Approach to Pentasubstituted Pyrrolidines by Tandem Anionic-Radical Cross-Over Reactions. *Adv. Synth. Catal.* **2022**, *364*, 671–678.

Pyrrolidinones, oxazolidinones, and five-membered cyclic ureas

- Gesmundo, N. J.; Grandjean, J. M. M.; Nicewicz, D. A. Amide and Amine Nucleophiles in Polar Radical Crossover Cycloadditions: Synthesis of **γ**-Lactams and Pyrrolidines. *Org. Lett.* **2015**, *17*, 1316–1319.
- Tarantino, K. T.; Miller, D. C.; Callon, T. A.; Knowles, R. R. Bond-Weakening Catalysis: Conjugate Aminations Enabled by the Soft Homolysis of Strong N-H Bonds. *J. Am. Chem. Soc.* **2015**, *137*, 6440–6443.
- Choi, G. J.; Knowles, R. R. Catalytic Alkene Carboaminations Enabled by Oxidative Proton-Coupled Electron Transfer. *J. Am. Chem. Soc.* **2015**, *137*, 9226–9229.
- Miller, D. C.; Choi, G. J.; Orbe, H. S.; Knowles, R. R. Catalytic Olefin Hydroamidation Enabled by Proton-Coupled Electron Transfer. *J. Am. Chem. Soc.* **2015**, *137*, 13492–13495.
- Nguyen, S. T.; Zhu, Q.; Knowles, R. R. PCET-Enabled Olefin Hydroamidation Reactions with N-Alkyl Amides. *ACS Catal.* **2019**, *9*, 4502–4507.
- Ye, J.; Kalvet, I.; Schoenebeck, F.; Rovis, T. Direct **α**-Alkylation of Primary Aliphatic Amines Enabled by CO2 and Electrostatics. *Nat. Chem.* **2018**, *10*, 1037–1041.

- Reed, N. L.; Herman, M. I.; Miltchev, V. P.; Yoon, T. P. Photocatalytic Oxyamination of Alkenes: Copper(II) Salts as Terminal Oxidants in Photoredox Catalysis. *Org. Lett.* **2018**, *20*, 7345–7350.
- Zheng, S.; Gutiérrez-Bonet, Á.; Molander, G. A. Merging Photoredox PCET with Ni-Catalyzed Cross-Coupling: Cascade Amidoarylation of Unactivated Olefins. *Chem* **2019**, *5*, 339–352.
- Zheng, S.; Zhang, S. Q.; Saeednia, B.; Zhou, J.; Anna, J. M.; Hong, X.; Molander, G. A. Diastereoselective Olefin Amidoacylationviaphotoredox PCET/Nickel-Dual Catalysis: Reaction Scope and Mechanistic Insights. *Chem. Sci.* **2020**, *11*, 4131–4137.
- Lei, H.; Conway, J. H.; Cook, C. C.; Rovis, T. Ligand Controlled Ir-Catalyzed Regiodivergent Oxyamination of Unactivated Alkenes. *J. Am. Chem. Soc.* **2019**, *141*, 11864–11869.
- Vasu, D.; Fuentes de Arriba, A. L.; Leitch, J. A.; De Gombert, A.; Dixon, D. J. Primary **α**-Tertiary Amine Synthesis via **α**-C-H Functionalization. *Chem. Sci.* **2019**, *10*, 3401–3407.
- Biegasiewicz, K. F.; Cooper, S. J.; Gao, X.; Oblinsky, D. G.; Kim, J. H.; Garfinkle, S. E.; Joyce, L. A.; Sandoval, B. A.; Scholes, G. D.; Hyster, T. K. Photoexcitation of Flavoenzymes Enables a Stereoselective Radical Cyclization. *Science* **2019**, *364*, 1166–1169.
- Black, M. J.; Biegasiewicz, K. F.; Meichan, A. J.; Oblinsky, D. G.; Kudisch, B.; Scholes, G. D.; Hyster, T. K. Asymmetric Redox-Neutral Radical Cyclization Catalysed by Flavin-Dependent 'Ene'-Reductases. *Nat. Chem.* **2020**, *12*, 71–75.
- Gao, X.; Turek-Herman, J. R.; Choi, Y. J.; Cohen, R. D.; Hyster, T. K. Photoenzymatic Synthesis of **α**-Tertiary Amines by Engineered Flavin-Dependent "Ene"-Reductases. *J. Am. Chem. Soc.* **2021**, *143*, 19643–19647.
- Nicholls, B. T.; Oblinsky, D. G.; Kurtoic, S. I.; Grosheva, D.; Ye, Y.; Scholes, G. D.; Hyster, T. K. Engineering a Non-Natural Photoenzyme for Improved Photon Efficiency. *Angew. Chemie Int. Ed.* **2022**, *61*, e202113842.
- Jung, H.; Keum, H.; Kweon, J.; Chang, S. Tuning Triplet Energy Transfer of Hydroxamates as the Nitrene Precursor for Intramolecular C($sp^3$)–H Amidation. *J. Am. Chem. Soc.* **2020**, *142*, 5811–5818.
- Lee, E.; Hwang, Y.; Kim, Y. B.; Kim, D.; Chang, S. Enantioselective Access to Spirolactams via Nitrenoid Transfer Enabled by Enhanced Noncovalent Interactions. *J. Am. Chem. Soc.* **2021**, *143*, 6363–6369.
- Cheng, Y.-Z.; Huang, X.-L.; Zhuang, W.-H.; Zhao, Q.-R.; Zhang, X.; Mei, T.-S.; You, S.-L. Intermolecular Dearomatization of Naphthalene Derivatives by Photoredox-Catalyzed 1,2-Hydroalkylation. *Angew. Chemie Int. Ed.* **2020**, *59*, 18062–18067.
- Huang, X.-L.; Cheng, Y.-Z.; Zhang, X.; You, S.-L. Photoredox-Catalyzed Intermolecular Hydroalkylative Dearomatization of Electron-Deficient Indole Derivatives. *Org. Lett.* **2020**, *22*, 9699–9705.
- Ryder, A. S. H.; Cunningham, W. B.; Ballantyne, G.; Mules, T.; Kinsella, A. G.; Turner-Dore, J.; Alder, C. M.; Edwards, L. J.; McKay, B. S. J.; Grayson, M. N.; et al. Photocatalytic **α**-Tertiary Amine Synthesis via C−H Alkylation of Unmasked Primary Amines. *Angew. Chemie - Int. Ed.* **2020**, *59*, 14986–14991.
- Zhao, H.; Leonori, D. Minimization of Back-Electron Transfer Enables the Elusive $sp^3$ C−H Functionalization of Secondary Anilines. *Angew. Chemie - Int. Ed.* **2021**, *60*, 7669–7674.
- McDaniel, K. A.; Blood, A. R.; Smith, G. C.; Jui, N. T. Dearomatization of Unactivated Arenes via Catalytic Hydroalkylation. *ACS Catal.* **2021**, *11*, 4968–4972.
- Hartley, W. C.; Schiel, F.; Ermini, E.; Melchiorre, P. Lewis Base-Catalysed Enantioselective Radical Conjugate Addition for the Synthesis of Enantioenriched Pyrrolidinones. *Angew. Chemie - Int. Ed.* **2022**, *61*, 1–5.
- del Río-Rodríguez, R.; Westwood, M. T.; Sicignano, M.; Juhl, M.; Fernández-Salas, J. A.; Alemán, J.; Smith, A. D. Isothiourea-Catalysed Enantioselective Radical Conjugate Addition under Batch and Flow Conditions. *Chem. Commun.* **2022**, 7277–7280.
- Richter, M. J. R.; Zécri, F. J.; Briner, K.; Schreiber, S. L. Modular Synthesis of Cyclopropane-Fused N-Heterocycles Enabled by Underexplored Diazo Reagents. *Angew. Chemie - Int. Ed.* **2022**.


Tetrahydrofurans and benzodihydrofurans


- Grandjean, J. M. M.; Nicewicz, D. A. Synthesis of Highly Substituted Tetrahydrofurans by Catalytic Polar-Radical-Crossover Cycloadditions of Alkenes and Alkenols. *Angew. Chemie - Int. Ed.* **2013**, *52*, 3967–3971.
- Blum, T. R.; Zhu, Y.; Nordeen, S. A.; Yoon, T. P. Photocatalytic Synthesis of Dihydrobenzofurans by Oxidative [3+2] Cycloaddition of Phenols. *Angew. Chemie - Int. Ed.* **2014**, *53*, 11056–11059.
- Wu, F.; Wang, L.; Ji, Y.; Zou, G.; Shen, H.; Nicewicz, D. A.; Chen, J.; Huang, Y. Direct Synthesis of Bicyclic Acetals via Visible Light Catalysis. *iScience* **2020**, *23*, 101395.

- Xiong, M.; Liang, X.; Liang, X.; Pan, Y.; Lei, A. Hexafluoro-2-Propanol-Promoted Electro-Oxidative [3+2] Annulation of 1,3-Dicarbonyl Compounds and Alkenes. *ChemElectroChem* **2019**, *6*, 3383–3386.
- Cheng, Y.-Z.; Zhao, Q.-R.; Zhang, X.; You, S.-L. Asymmetric Dearomatization of Indole Derivatives with N-Hydroxycarbamates Enabled by Photoredox Catalysis. *Angew. Chemie Int. Ed.* **2019**, *58*, 18069–18074.
- Tsui, E.; Metrano, A. J.; Tsuchiya, Y.; Knowles, R. R. Catalytic Hydroetherification of Unactivated Alkenes Enabled by Proton-Coupled Electron Transfer. *Angew. Chemie Int. Ed.* **2020**, *59*, 11845–11849.
- Krolo, T.; Bhattacharyya, A.; Reiser, O. Accessing HIV-1 Protease Inhibitors through Visible-Light-Mediated Sequential Photocatalytic Decarboxylative Radical Conjugate Addition-Elimination-Oxa-Michael Reactions. *Org. Lett.* **2021**, *23*, 6283–6287.
- Victoria-Miguel, J.; García-Santos, W. H.; Cordero-Vargas, A. A Visible Light Ru-Catalyzed Photoredox Access to Substituted Dihydrofurans. *J. Org. Chem.* **2022**.

### γ-Butyrolactones

- Zeller, M. A.; Riener, M.; Nicewicz, D. A. Butyrolactone Synthesis via Polar Radical Crossover Cycloaddition Reactions: Diastereoselective Syntheses of Methylenolactocin and Protolichesterinic Acid. *Org. Lett.* **2014**, *16*, 4810–4813.
- Cavanaugh, C. L.; Nicewicz, D. A. Synthesis of **α**-Benzyloxyamino-**γ**-Butyrolactones via a Polar Radical Crossover Cycloaddition Reaction. *Org. Lett.* **2015**, *17*, 6082–6085.
- Jeffrey, J. L.; Terrett, J. A.; MacMillant, D. W. C. O-H Hydrogen Bonding Promotes H-Atom Transfer from **α** C-H Bonds for C-Alkylation of Alcohols. *Science* **2015**, *349*, 1532–1536.
- Kaplaneris, N.; Bisticha, A.; Papadopoulos, G. N.; Limnios, D.; Kokotos, C. G. Photoorganocatalytic Synthesis of Lactones: Via a Selective C-H Activation-Alkylation of Alcohols. *Green Chem.* **2017**, 19, 4451–4456.
- Sha, W.; Ni, S.; Han, J.; Pan, Y. Access to Alkyl-Substituted Lactone via Photoredox-Catalyzed Alkylation/Lactonization of Unsaturated Carboxylic Acids. *Org. Lett.* **2017**, *19*, 5900–5903.

## Six-membered ring systems

### Cyclohexanes, cyclohexenes, and cyclohexadienes

- Jui, N. T.; Lee, E. C. Y.; MacMillan, D. W. C. Enantioselective Organo-SOMO Cascade Cycloadditions: A Rapid Approach to Molecular Complexity from Simple Aldehydes and Olefins. *J. Am. Chem. Soc.* **2010**, *132*, 10015–10017.
- Lin, S.; Ischay, M. A.; Fry, C. G.; Yoon, T. P. Radical Cation Diels-Alder Cycloadditions by Visible Light Photocatalysis. *J. Am. Chem. Soc.* **2011**, *133*, 19350–19353.
- Hurtley, A. E.; Cismesia, M. A.; Ischay, M. A.; Yoon, T. P. Visible Light Photocatalysis of Radical Anion Hetero-Diels-Alder Cycloadditions. *Tetrahedron* **2011**, *67*, 4442–4448.
- Lin, S.; Padilla, C. E.; Ischay, M. A.; Yoon, T. P. Visible Light Photocatalysis of Intramolecular Radical Cation Diels-Alder Cycloadditions. *Tetrahedron Lett.* **2012**, *53*, 3073–3076.
- Zhu, M.; Xu, H.; Zhang, X.; Zheng, C.; You, S.-L. Visible-Light-Induced Intramolecular Double Dearomative Cycloaddition of Arenes. *Angew. Chemie Int. Ed.* **2021**, *60*, 7036–7040.
- Wang, Y.; Zhang, W.-Y.; Yu, Z.-L.; Zheng, C.; You, S.-L. $SmI_2$-Mediated Enantioselective Reductive Dearomatization of Non-Activated Arenes. *Nat. Synth.* **2022**, *1*, 401–406.
- Flynn, A. R.; Mcdaniel, K. A.; Hughes, M. E.; Vogt, D. B.; Jui, N. T. Hydroarylation of Arenes via Reductive Radical-Polar Crossover. *J. Am. Chem. Soc.* **2020**, *142*, 9163–9168.

### Piperidines, 2-piperidinones, and tetrahydroisoquinolines

- Luescher, M. U.; Bode, J. W. SnAP-EX Reagents for the Synthesis of Exocyclic 3-Amino- and 3-Alkoxypyrrolidines and Piperidines from Aldehydes. *Org. Lett.* **2016**, *18*, 2652–2655.
- Petersen, W. F.; Taylor, R. J. K.; Donald, J. R. Photoredox-Catalyzed Reductive Carbamoyl Radical Generation: A Redox-Neutral Intermolecular Addition-Cyclization Approach to Functionalized 3,4-Dihydroquinolin-2-Ones. *Org. Lett.* **2017**, *19*, 874–877.
- Piou, T.; Romanov-Michailidis, F.; Romanova-Michaelides, M.; Jackson, K. E.; Semakul, N.; Taggart, T. D.; Newell, B. S.; Rithner, C. D.; Paton, R. S.; Rovis, T. Correlating Reactivity and Selectivity to Cyclopentadienyl Ligand Properties in Rh(III)-Catalyzed C–H Activation Reactions: An Experimental and Computational Study. *J. Am. Chem. Soc.* **2017**, *139*, 1296–1310.

- Conway, J. H.; Rovis, T. Regiodivergent Iridium(III)-Catalyzed Diamination of Alkenyl Amides with Secondary Amines: Complementary Access to **γ**- or **δ**-Lactams. *J. Am. Chem. Soc.* **2018**, *140*, 135–138.
- Hassan, I. S.; Ta, A. N.; Danneman, M. W.; Semakul, N.; Burns, M.; Basch, C. H.; Dippon, V. N.; McNaughton, B. R.; Rovis, T. Asymmetric **δ**-Lactam Synthesis with a Monomeric Streptavidin Artificial Metalloenzyme. *J. Am. Chem. Soc.* **2019**, *141*, 4815–4819.
- Leitch, J. A.; Fuentes De Arriba, A. L.; Tan, J.; Hoff, O.; Martínez, C. M.; Dixon, D. J. Photocatalytic Reverse Polarity Povarov Reaction. *Chem. Sci.* **2018**, *9*, 6653–6658.
- Zhang, Z.; Zhang, X.; Nagib, D. A. Chiral Piperidines from Acyclic Amines via Enantioselective, Radical-Mediated **δ** C–H Cyanation. *Chem* **2019**, *5*, 3127–3134.
- He, J.; Bai, Z. Q.; Yuan, P. F.; Wu, L. Z.; Liu, Q. Highly Efficient Iridium-Based Photosensitizers for Thia-Paternò-Büchi Reaction and Aza-Photocyclization. *ACS Catal.* **2021**, *11*, 446–455.
- Zhu, M.; Huang, X.-L.; Sun, S.; Zheng, C.; You, S.-L. Visible-Light-Induced Dearomatization of Indoles/Pyrroles with Vinylcyclopropanes: Expedient Synthesis of Structurally Diverse Polycyclic Indolines/Pyrrolines. *J. Am. Chem. Soc.* **2021**, *143*, 13441–13449.
- Keum, H.; Jung, H.; Jeong, J.; Kim, D.; Chang, S. Visible-Light Induced C($sp^2$)–H Amidation with an Aryl–Alkyl **σ**-Bond Relocation via Redox-Neutral Radical–Polar Crossover. *Angew. Chemie Int. Ed.* **2021**, *60*, 25235–25240.
- Spurlin, R. M.; Harris, A. L.; Pratt, C. J.; Jui, N. T. Synthesis of Spirocyclic Piperidines by Radical Hydroarylation. *Synlett* **2021**, *32*, 211–214.
- Maust, M. C.; Hendy, C. M.; Jui, N. T.; Blakey, S. B. Switchable Regioselective 6-Endo or 5-Exo Radical Cyclization via Photoredox Catalysis. *J. Am. Chem. Soc.* **2022**, *144*, 3776–3781.
- Ye, Y.; Cao, J.; Oblinsky, D. G.; Verma, D.; Prier, C. K.; Scholes, G. D.; Hyster, T. K. Using Enzymes to Tame Nitrogen-Centered Radicals for Enantioselective Hydroamination. *Chem RXIV* **2022**, 1–21.

Morpholines, thiomorpholines, and piperazines

- Vo, C.-V. T.; Mikutis, G.; Bode, J. W. SnAP Reagents for the Transformation of Aldehydes into Substituted Thiomorpholines—An Alternative to Cross-Coupling with Saturated Heterocycles. *Angew. Chemie Int. Ed.* **2013**, *52*, 1705–1708.
- Luescher, M. U.; Vo, C.-V. T.; Bode, J. W. SnAP Reagents for the Synthesis of Piperazines and Morpholines. *Org. Lett.* **2014**, *16*, 1236–1239.
- Vo, C.-V. T.; Luescher, M. U.; Bode, J. W. SnAP Reagents for the One-Step Synthesis of Medium-Ring Saturated N-Heterocycles from Aldehydes. *Nat. Chem.* **2014**, *6*, 310–314.
- Siau, W. Y.; Bode, J. W. One-Step Synthesis of Saturated Spirocyclic N-Heterocycles with Stannyl Amine Protocol (SnAP) Reagents and Ketones. *J. Am. Chem. Soc.* **2014**, *136*, 17726–17729.
- Geoghegan, K.; Bode, J. W. Bespoke SnAP Reagents for the Synthesis of C-Substituted Spirocyclic and Bicyclic Saturated N-Heterocycles. *Org. Lett.* **2015**, *17*, 1934–1937.
- Luescher, M. U.; Bode, J. W. Catalytic Synthesis of N-Unprotected Piperazines, Morpholines, and Thiomorpholines from Aldehydes and SnAP Reagents. *Angew. Chemie - Int. Ed.* **2015**, *54*, 10884–10888.
- Hsieh, S. Y.; Bode, J. W. Silicon Amine Reagents for the Photocatalytic Synthesis of Piperazines from Aldehydes and Ketones. *Org. Lett.* **2016**, *18*, 2098–2101.
- Hsieh, S. Y.; Bode, J. W. Lewis Acid Induced Toggle from Ir(II) to Ir(IV) Pathways in Photocatalytic Reactions: Synthesis of Thiomorpholines and Thiazepanes from Aldehydes and SLAP Reagents. *ACS Cent. Sci.* **2017**, *3*, 66–72.
- Jackl, M. K.; Legnani, L.; Morandi, B.; Bode, J. W. Continuous Flow Synthesis of Morpholines and Oxazepanes with Silicon Amine Protocol (SLAP) Reagents and Lewis Acid Facilitated Photoredox Catalysis. *Org. Lett.* **2017**, *19*, 4696–4699.
- Jindakun, C.; Hsieh, S. Y.; Bode, J. W. Iridium-Catalyzed Synthesis of Saturated N-Heterocycles from Aldehydes and SnAP Reagents with Continuous Flow Photochemistry. *Org. Lett.* **2018**, *20*, 2071–2075.
- Wang, Y.-Y.; Bode, J. W. Olefin Amine (OLA) Reagents for the Synthesis of Bridged Bicyclic and Spirocyclic Saturated N-Heterocycles by Catalytic Hydrogen Atom Transfer (HAT) Reactions. *J. Am. Chem. Soc.* **2019**, *141*, 9739–9745.
- Saito, F.; Trapp, N.; Bode, J. W. Iterative Assembly of Polycyclic Saturated Heterocycles from Monomeric Building Blocks. *J. Am. Chem. Soc.* **2019**, *141*, 5544–5554.
- Bissonnette, N. B.; Ellis, J. M.; Hamann, L. G.; Romanov-Michailidis, F. Expedient Access to Saturated Nitrogen Heterocycles by Photoredox Cyclization of Imino-Tethered Dihydropyridines. *Chem. Sci.* **2019**, *10*, 9591–9596.

- Cheng, Q.; Bai, Z.; Tewari, S.; Ritter, T. Bifunctional Sulfilimines Enable Synthesis of Multiple N-Heterocycles from Alkenes. *Nat. Chem.* **2022**.


Bridged bicyclic ring systems


- Zhao, J.; Brosmer, J. L.; Tang, Q.; Yang, Z.; Houk, K. N.; Diaconescu, P. L.; Kwon, O. Intramolecular Crossed [2+2] Photocycloaddition through Visible Light-Induced Energy Transfer. *J. Am. Chem. Soc.* **2017**, *139*, 9807–9810.
- Ma, J.; Strieth-Kalthoff, F.; Dalton, T.; Freitag, M.; Schwarz, J. L.; Bergander, K.; Daniliuc, C.; Glorius, F. Direct Dearomatization of Pyridines via an Energy-Transfer-Catalyzed Intramolecular [4+2] Cycloaddition. *Chem* **2019**, *5*, 2854–2864.
- Ma, J.; Chen, S.; Bellotti, P.; Guo, R.; Schäfer, F.; Heusler, A.; Zhang, X.; Daniliuc, C.; Brown, M. K.; Houk, K. N.; et al. Photochemical Intermolecular Dearomative Cycloaddition of Bicyclic Azaarenes with Alkenes. *Science* **2021**, *371*, 1338–1345.
- Leitch, J. A.; Rogova, T.; Duarte, F.; Dixon, D. J. Dearomative Photocatalytic Construction of Bridged 1,3-Diazepanes. *Angew. Chemie - Int. Ed.* **2020**, *59*, 4121–4130.
- Harmata, A. S.; Spiller, T. E.; Sowden, M. J.; Stephenson, C. R. J. Photochemical Formal (4 + 2)-Cycloaddition of Imine-Substituted Bicyclo[1.1.1]Pentanes and Alkenes. *J. Am. Chem. Soc.* **2021**, *143*, 21223–21228.
- Kleinmans, R.; Pinkert, T.; Dutta, S.; Paulisch, T. O.; Keum, H.; Daniliuc, C. G.; Glorius, F. Intermolecular [2π+2**σ**]-Photocycloaddition Enabled by Triplet Energy Transfer. *Nature* **2022**, *605*, 477–482.
- Guo, R.; Chang, Y.-C.; Herter, L.; Salome, C.; Braley, S. E.; Fessard, T. C.; Brown, M. K. Strain-Release [2π + 2**σ**] Cycloadditions for the Synthesis of Bicyclo[2.1.1]Hexanes Initiated by Energy Transfer. *J. Am. Chem. Soc.* **2022**, *144*, 7988–7994.
- Agasti, S.; Beltran, F.; Pye, E.; Kaltsoyannis, N.; Crisenza, G. E. M.; Procter, D. J. A Catalytic Alkene Insertion Approach to Bicyclo[2.1.1]Hexane Bioisosteres. *Chem RXIV* **2022**, 1–9.

## 2. General experimental information

### General reaction information

Unless otherwise noted, all reactions were performed in flame-dried glassware and carried out under an atmosphere of argon or nitrogen. Anhydrous solvents were purified according to the method of Grubbs,[1] with exception of acetone used for photochemical reactions, which was purified *via* distillation from calcium sulfate under an atmosphere of nitrogen, or purchased from Acros ('Extra-dry' grade in sure-seal container) and used as received. All reagents were purchased from commercial vendors such as Sigma Aldrich, VWR, Fisher Scientific, Strem, Alfa-Aesar, and Oakwood scientific, and used as received unless otherwise stated. Exceptions to this include styrene, all 4-substituted styrenes, α- and β-methyl styrenes, each of which were passed through a plug of basic alumina and sparged with argon or nitrogen for 15 min., then used immediately. Flash column chromatography was performed on silica (Merck silica gel 60) according to the method of Still,[2] or by using automated chromatography on a Biotage Isolera One instrument with cartridges containing Fluka 230–400 mesh silica gel. Thin-layer chromatography (TLC) was performed on Silicycle 250 µm silica gel plates. Visualization of the developed chromatogram was performed by irradiation with UV light or treatment with a solution of potassium permanganate followed by heating when necessary. Analytical supercritical fluid chromatography (SFC) was performed on a Berger Analytical SFC. Preparative scale SCF was performed on a Berger MG2 SFC. Analytical and preparative high-performance liquid chromatography (HPLC) were performed on an Agilent Infinity Series LC using ChiralPak/ChiralCel columns from Daicel Chemical Industries. All yields refer to purified compounds by flash column chromatography or recrystallization unless otherwise noted. Diastereoisomeric ratios (d.r.) of annulation products were determined by analysis of crude $^{1}$H NMR spectra, with exception of compounds **22** and **56** which were determined by analytical SFC.

### Photoredox reaction information

All photochemical reactions were performed in oven-dried vials (for 0.1 mmol scale reactions – Chemglass CG-4909, 4.0 mL total volume; for 0.5 mmol scale reactions – VWR 66011-085, 7.4 mL total volume; for 6.0 mmol scale reactions – Wheaton E-C sample vial, total volume 40 mL). Photochemical reactions were irradiated with Kessil PR160L 456 nm lamps (set to 50% lamp intensity), with fan cooling to 35±3 °C, with magnetic stirring provided by a Corning PC-410D stir plate.

### Instrumentation

All $^{1}$H and $^{13}$C nuclear magnetic resonance (NMR) experiments were performed on Bruker Avance II 500 (500 and 126 MHz for $^{1}$H and $^{13}$C respectively), and Bruker Avance III HD 800 (800 MHz for $^{1}$H) instruments. $^{19}$F NMR experiments were performed on a Bruker 300 AVANCE (282 MHz). Chemical shifts (δ) are reported in parts per million (ppm) relative to $CDCl_3$ ($^{1}$H: 7.26 ppm, $^{13}$C: 77.16 ppm), $C_6D_6$ ($^{1}$H: 7.16 ppm, $^{13}$C: 128.06 ppm), or DMSO-*d*6 ($^{1}$H: 3.33 ppm, $^{13}$C: 39.52 ppm) with multiplicity (*s* = singlet, br. *s* = broad singlet, *d* = doublet, *t* = triplet, *q* = quartet, *dd* = doublet of doublets, *dt* = doublet of triplets, *dq* = doublet of quartets, and *m* = multiplet). High-resolution mass spectra (HRMS) were obtained using an Agilent 6210 TOF LC/MS (Electrospray Ionization, ESI) or an Agilent 7200 Q-TOF GC/MS (Electron Ionization, EI). Δppm values were calculated according to $m/z_{(theoretical)}$-$m/z_{(experimental)}$. IR spectra were recorded on a Thermo Scientific Nicolet 6700 FT-IR spectrometer. Stern-Volmer experiments were performed on an Agilent Eclipse fluorescence spectrometer.

## 3. Photoreactor assembly

**Figure S.1**. Reactor cooling fan arrangement. Reactor shown equipped with 7.4 mL vial rack.
Front view Side view.

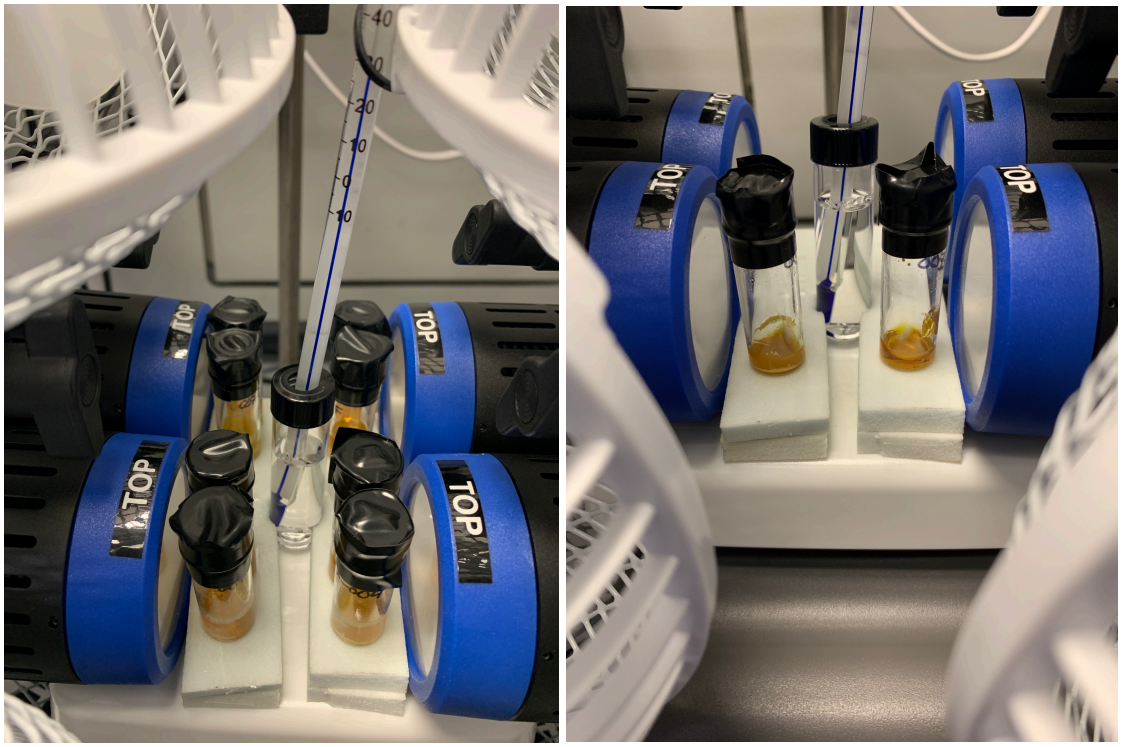
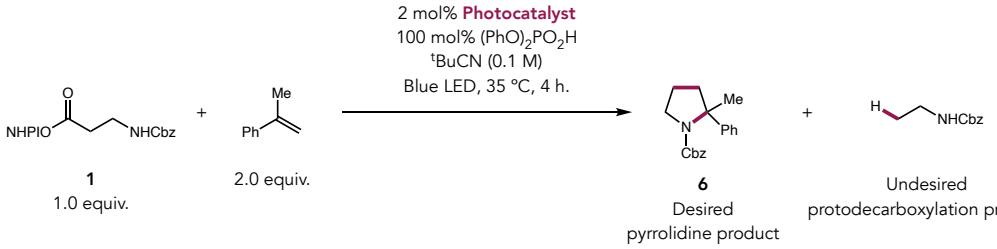



**Figure S.2**. Typical arrangement of 4 mL vials for 0.1 mmol scale reactions; reaction appearance post-irradiation.
Eight vial parallel experiment Two vial parallel experiment


**Figure S.3**. Arrangement of 60 mL vial for 6.0 mmol scale reactions; reaction appearance prior to irradiation.

## 4. Additional reaction optimization information

**Table S.1.** Photocatalyst identity dependence of the reaction between NHPI ester reagent **1** and α-methyl styrene.



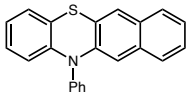

**1**
1.0 equiv.

2.0 equiv.

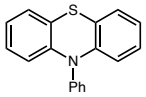
**6**
Desired pyrrolidine product

Undesired protodecarboxylation product

Ohmiya phenothiazine:



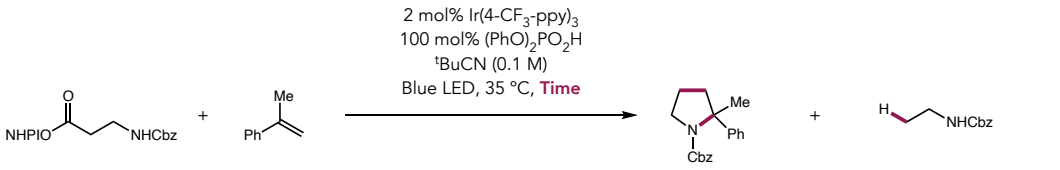

*N*-Ph phenothiazine:




| Entry | Photocatalyst | Pyrrolidine 6 /NMR% | Protodecarboxlation /NMR% | Remaining NHPI reagent 1 /NMR% |
|---|---|---|---|---|
| 1 | $Ir(4\text{-}F\text{-}ppy)_3$ | 57 | 7 | 29 |
| **2** | **$Ir(4\text{-}CF_3\text{-}ppy)_3$** | **68** | **3** | **28** |
| 3 | $Ir(ppy)_3$ | 51 | 11 | 26 |
| 4 | $[Ir(ppy)_2(dtbbpy)]PF_6$ | 43 | 15 | 27 |
| 5 | $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ | 0 | 0 | 100 |
| 6 | $[Ru(bpy)_3](PF_6)_2$ | 6 | 80 | 16 |
| 7 | Ohmiya phenothiazine | 40 | 23 | 22 |
| 8 | *N*-Ph phenothiazine | 4 | 77 | 14 |

0.1 mmol scale. Yields by analysis of the crude reaction mixture $^1$H NMR vs 1,3,5-trimethoxybenzene internal standard.

**Table S.2.** Time dependence of the reaction between NHPI ester reagent **1** and α-methyl styrene.




**1**
1.0 equiv.

2.0 equiv.

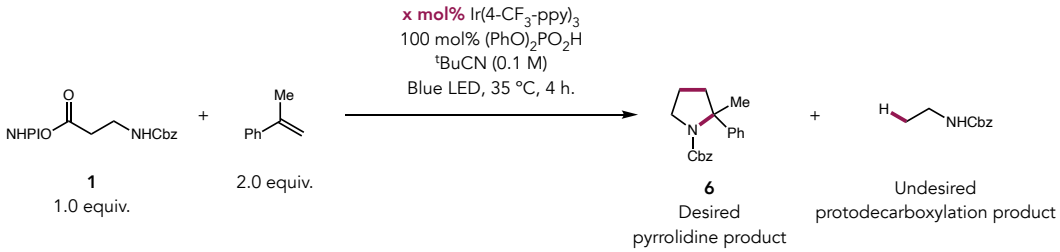
**6**
Desired pyrrolidine product

Undesired protodecarboxylation product

| Entry | Time /min. | Pyrrolidine 6 /NMR% | Protodecarboxlation /NMR% | Remaining NHPI reagent 1 /NMR% |
|---|---|---|---|---|
| 1 | 0 | 0 | 0 | 100 |
| 2 | 30 | 60 | 6 | 30 |
| 3 | 60 | 67 | 6 | 29 |
| 4 | 90 | 64 | 6 | 30 |
| 5 | 120 | 65 | 6 | 29 |
| 6 | 180 | 63 | 5 | 26 |
| 7 | 240 | 64 | 4 | 25 |

0.1 mmol scale. Yields by analysis of the crude reaction mixture $^1$H NMR vs 1,3,5-trimethoxybenzene internal standard.

**Table S.3.** Photocatalyst loading dependence of the reaction between NHPI ester reagent **1** and α-methyl styrene.




**1**
1.0 equiv.

2.0 equiv.

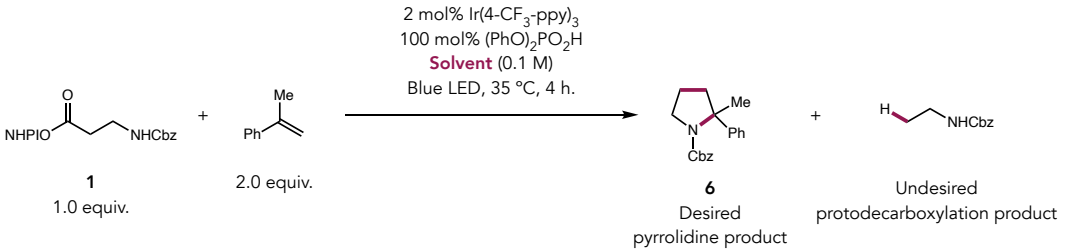
**6**
Desired
pyrrolidine product

Undesired
protodecarboxylation product

| Entry | Loading /mol% | Pyrrolidine 6 /NMR% |
|---|---|---|
| 1 | 2 | 75 |
| **2** | **1** | **78** |
| 3 | 0.5 | 81 |
| 4 | 0.25 | 64 |
| 5 | 0.125 | 52 |
| 6 | 0.0625 | 44 |
| 7 | 0.01 | 6 |

0.1 mmol scale. Yields by analysis of the crude reaction mixture $^1$H NMR vs 1,3,5-trimethoxybenzene internal standard.

**Table S.4.** Solvent identity dependence of the reaction between NHPI ester reagent **1** and α-methyl styrene.




**1**
1.0 equiv.

2.0 equiv.

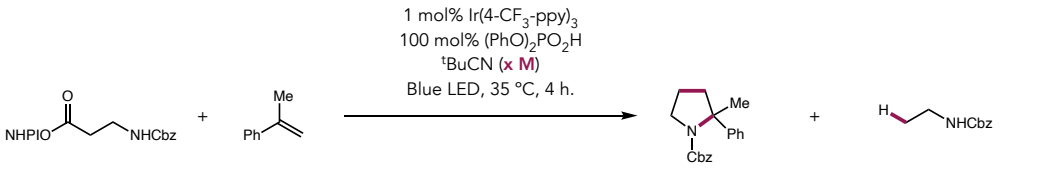
**6**
Desired
pyrrolidine product

Undesired
protodecarboxylation product

| Entry | Solvent | Pyrrolidine 6 /NMR% | Protodecarboxlation /NMR% | Remaining NHPI reagent 1 /NMR% |
|---|---|---|---|---|
| 1 | MeCN | 74 | 0 | 20 |
| 2 | Dioxane | 16 | 44 | 18 |
| 3 | PhF | 12 | 22 | 50 |
| 4 | $^t$BuCN | 75 | 0 | 25 |
| 5 | $PhCF_3$ | 59 | 17 | 38 |
| 6 | 1,2-DCE | 60 | 10 | 25 |
| 7 | 1,2-Difluorobenzene | 68 | 0 | 39 |
| 8 | Diethyl carbonate | 23 | 30 | 21 |
| 9 | PhH | 37 | 15 | 28 |
| 10 | $^t$BuOAc | 25 | 11 | 35 |
| 11 | Methyl pivalate | 19 | 50 | 21 |
| 12 | Acetone (non-dried) | 83 | 0 | 18 |
| **13** | **Acetone (anhydrous)** | **92** | **0** | 10 |
| 14 | 1,2-Dichlorobenzene | 49 | 13 | 32 |
| 15 | *N,N*-DMF | 63 | 40 | 15 |
| 16 | THF | 32 | 23 | 23 |
| 17 | $CH_2Cl_2$ | 46 | 10 | 30 |

0.1 mmol scale. Yields by analysis of the crude reaction mixture $^1$H NMR vs 1,3,5-trimethoxybenzene internal standard.

**Table S.5.** Solvent concentration dependence of the reaction between NHPI ester reagent **1** and α-methyl styrene.




**1**
1.0 equiv.

2.0 equiv.

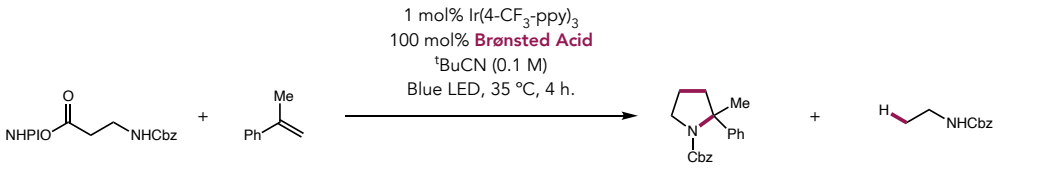
**6**
Desired
pyrrolidine product

Undesired
protodecarboxylation product

| Entry | Conc. /M | Pyrrolidine 6 /NMR% | Protodecarboxlation /NMR% | Remaining NHPI reagent 1 /NMR% |
|---|---|---|---|---|
| 1 | 0.05 | 77 | 0 | 35 |
| 2 | 0.10 | 74 | 0 | 31 |
| 3 | 0.20 | 72 | 0 | 32 |
| 4 | 0.30 | 77 | 0 | 33 |
| 5 | 0.40 | 74 | 0 | 34 |
| 6 | 0.50 | 78 | 0 | 17 |

0.1 mmol scale. Yields by analysis of the crude reaction mixture $^1$H NMR vs 1,3,5-trimethoxybenzene internal standard.

**Table S.6.** Brønsted acid identity dependence of the reaction between NHPI ester reagent **1** and α-methyl styrene.




**1**
1.0 equiv.

2.0 equiv.

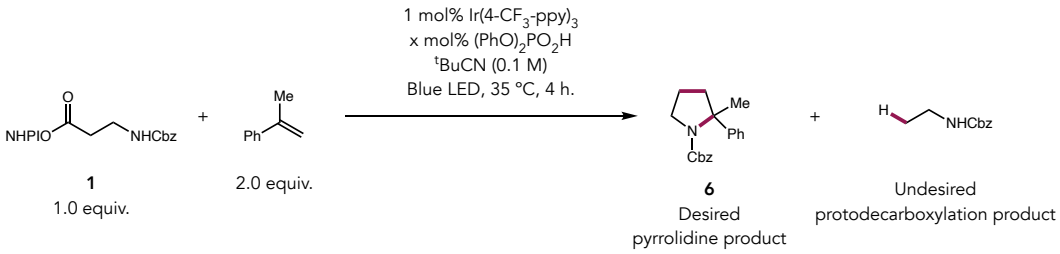
**6**
Desired
pyrrolidine product

Undesired
protodecarboxylation product

| Entry | Brønsted Acid | Pyrrolidine 6 /NMR% | Protodecarboxlation /NMR% | Remaining NHPI reagent 1 /NMR% |
|---|---|---|---|---|
| 1 | $(PhO)_2PO_2H$ | 71 | 0 | 24 |
| 2 | TFA | 75 | 0 | 13 |
| 3 | AcOH | 62 | 0 | 32 |
| 4 | $^t$BuCO$_2$H | 57 | 0 | 22 |
| 5 | BzOH | 61 | 0 | 23 |
| 6 | HCl, 4.0 M in dioxane | 35 | 0 | 52 |
| 7 | $H_2O$ | 53 | 0 | 22 |
| 8 | PPTS | 66 | 0 | 20 |

0.1 mmol scale. Yields by analysis of the crude reaction mixture $^1$H NMR vs 1,3,5-trimethoxybenzene internal standard.

**Table S.7.** Brønsted acid loading dependence of the reaction between NHPI ester reagent **1** and α-methyl styrene.




**1**
1.0 equiv.

2.0 equiv.

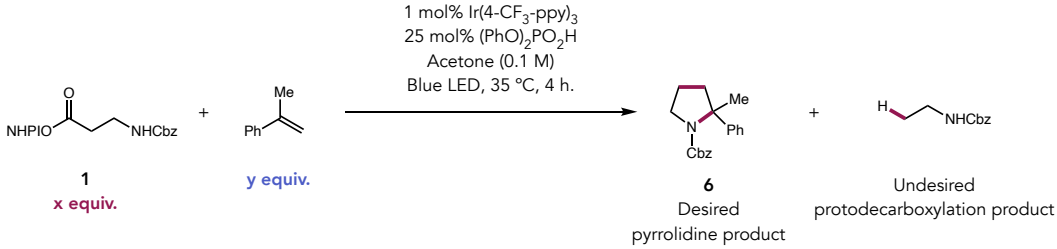
**6**
Desired pyrrolidine product

Undesired protodecarboxylation product

| Entry | Loading /mol% | Pyrrolidine 6 /NMR% | Protodecarboxlation /NMR% | Remaining NHPI reagent 1 /NMR% |
|---|---|---|---|---|
| 1 | 200 | 66 | 0 | 18 |
| 2 | 100 | 73 | 0 | 18 |
| 3 | 50 | 73 | 0 | 17 |
| **4** | **25** | **82** | **0** | **13** |
| 5 | 20 | 65 | 0 | 15 |
| 6 | 10 | 60 | 0 | 15 |
| 7 | 5 | 71 | 0 | 19 |

0.1 mmol scale. Yields by analysis of the crude reaction mixture $^1$H NMR vs 1,3,5-trimethoxybenzene internal standard.

**Table S.8.** Reagent stoichiometry dependence of the reaction between NHPI ester reagent **1** and α-methyl styrene.




**1**
x equiv.

y equiv.

**6**
Desired pyrrolidine product

Undesired protodecarboxylation product

**Excess α-methyl styrene regime (x = 1):**

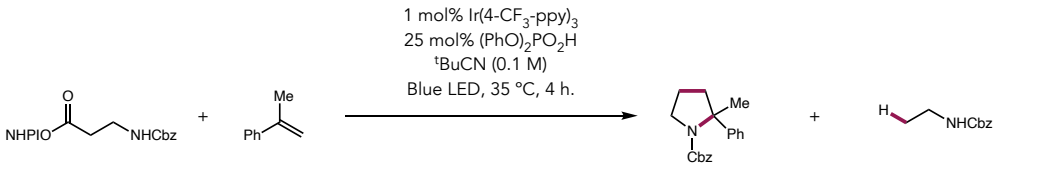
| Entry | Stoichiometry y /equiv. | Pyrrolidine 6 /NMR% |
|---|---|---|
| 1 | 1.0 | 84 |
| 2 | 1.1 | 79 |
| 3 | 1.3 | 89 |
| 4 | 1.5 | 92 |
| 5 | 2.0 | 95 |
| 6 | 3.0 | 99 |

**Excess NHPI ester regime (y = 1):**

| Entry | Stoichiometry y /equiv. | Pyrrolidine 6 /NMR% |
|---|---|---|
| 1 | 1.0 | 82 |
| 2 | 1.1 | 87 |
| 3 | 1.3 | 93 |
| 4 | 1.5 | 90 |
| 5 | 2.0 | 99 |
| 6 | 3.0 | 99 |

0.1 mmol scale. Yields by analysis of the crude reaction mixture $^1$H NMR vs 1,3,5-trimethoxybenzene internal standard.

**Table S.9.** Control reactions in the reaction between NHPI ester reagent **1** and α-methyl styrene.




**1**
1.0 equiv.

2.0 equiv.

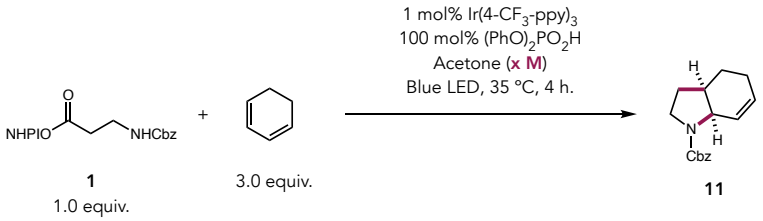
**6**
Desired pyrrolidine product

Undesired protodecarboxylation product

| Entry | Change | Pyrrolidine 6 /NMR% | Protodecarboxlation /NMR% | Remaining NHPI reagent 1 /NMR% |
|---|---|---|---|---|
| 1 | No change | 77 | 0 | 16 |
| 2 | No $(PhO)_2PO_2H$ | 53 | 15 | 15 |
| 3 | No $Ir(4\text{-}CF_3\text{-}ppy)_3$ | 0 | 0 | 100 |
| 4 | No irradiation | 0 | 0 | 100 |
| 5 | No α-methyl styrene | - | 0 | 50 |

0.1 mmol scale. Yields by analysis of the crude reaction mixture $^1H$ NMR vs 1,3,5-trimethoxybenzene internal standard.

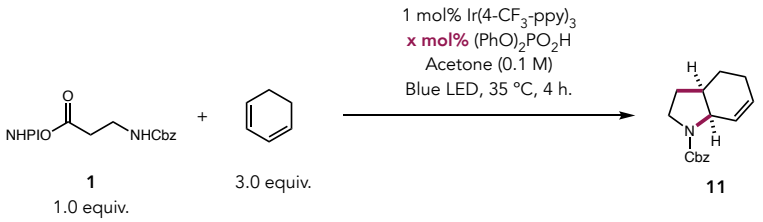
**Table S.10.** Solvent concentration dependence of the reaction between NHPI ester reagent **1** and 1,3-cyclohexadiene.




| Entry | Concentration /M | Pyrrolidine 11 /NMR% | Remaining NHPI reagent 1 /NMR% |
|---|---|---|---|
| **1** | **0.10** | **33** | **0** |
| 2 | 0.20 | 32 | 0 |
| 3 | 0.25 | 31 | 0 |
| 4 | 0.40 | 26 | 0 |
| 5 | 0.50 | 27 | 0 |
| 6 | 1.0 | 19 | 0 |

0.1 mmol scale. Yields by analysis of the crude reaction mixture $^1$H NMR vs 1,3,5-trimethoxybenzene internal standard.

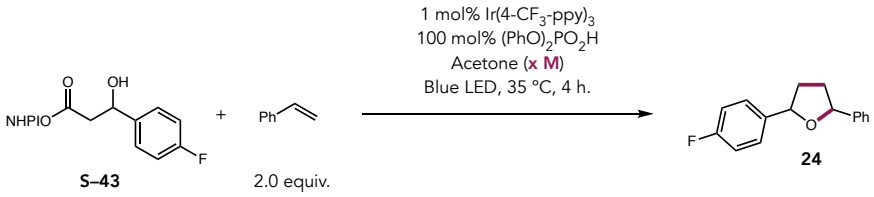
**Table S.11.** Brønsted acid loading dependence of the reaction between NHPI ester reagent **1** and 1,3-cyclohexadiene.




| Entry | Loading /mol% | Pyrrolidine 11 /NMR% | Remaining NHPI reagent 1 /NMR% |
|---|---|---|---|
| 1 | 0 | 0 | 0 |
| 2 | 5 | 16 | 0 |
| 3 | 10 | 26 | 0 |
| **4** | **25** | **32** | **0** |
| 5 | 50 | 32 | 0 |
| 6 | 100 | 32 | 0 |
| 7 | 200 | 30 | 0 |
| 8 | 300 | 27 | 0 |

0.1 mmol scale. Yields by analysis of the crude reaction mixture $^1$H NMR vs 1,3,5-trimethoxybenzene internal standard.

**Table S.12.** Solvent concentration dependence of the reaction between NHPI ester reagent **S–43** and styrene.

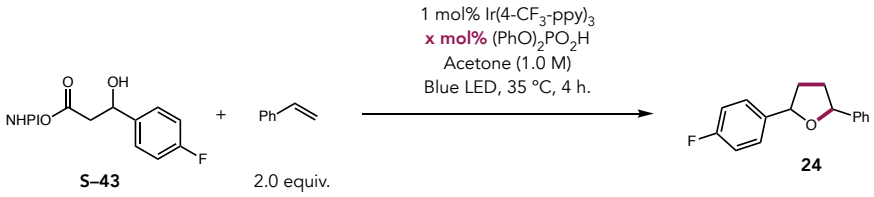



**S–43** 1.0 equiv. + Ph 2.0 equiv. → **24**

| Entry | Concentration /M | Tetrahydrofuran 24 /NMR% | d.r. |
|---|---|---|---|
| 1 | 0.10 | 45 | 1.9:1 |
| 2 | 0.20 | 53 | 1.6:1 |
| 3 | 0.25 | 51 | 1.6:1 |
| 4 | 0.40 | 63 | 1.2:1 |
| 5 | 0.50 | 68 | 1.2:1 |
| **6** | **1.0** | **75** | 1.1:1 |

0.1 mmol scale. Yields by analysis of the crude reaction mixture $^1$H NMR vs 1,3,5-trimethoxybenzene internal standard.

**Table S.13.** Brønsted acid loading dependence of the reaction between NHPI ester reagent **S–43** and styrene.

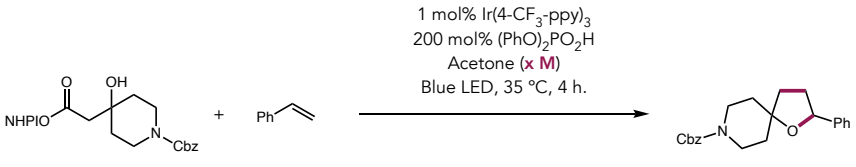



**S–43** 1.0 equiv. + Ph 2.0 equiv. → **24**

| Entry | Loading /mol% | Tetrahydrofuran 24 /NMR% | d.r. |
|---|---|---|---|
| 1 | 25 | 50 | 2.0:1 |
| 2 | 50 | 60 | 1.4:1 |
| 3 | 100 | 75 | 1.1:1 |
| **4** | **200** | **78** | 1.1:1 |

0.1 mmol scale. Yields by analysis of the crude reaction mixture $^1$H NMR vs 1,3,5-trimethoxybenzene internal standard.

**Table S.14.** Solvent concentration dependence of the reaction between NHPI ester reagent **S–46** and styrene.




**S–46**
1.0 equiv.

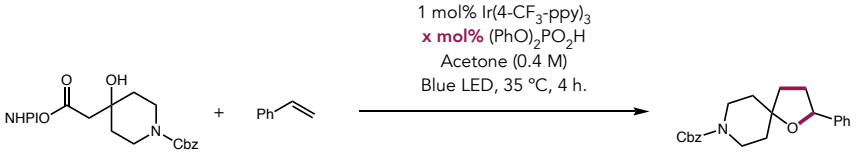
2.0 equiv.

**27**

| Entry | Concentration /M | Tetrahydrofuran 27 /NMR% |
|---|---|---|
| 1 | 0.10 | 40 |
| 2 | 0.20 | 44 |
| **3** | **0.25** | **52** |
| **4** | **0.40** | **52** |
| 5 | 0.50 | 47 |
| 6 | 1.0 | 44 |

0.1 mmol scale. Yields by analysis of the crude reaction mixture $^1$H NMR vs 1,3,5-trimethoxybenzene internal standard.

**Table S.15.** Brønsted acid loading dependence of the reaction between NHPI ester reagent **S–46** and styrene.




**S–46**
1.0 equiv.

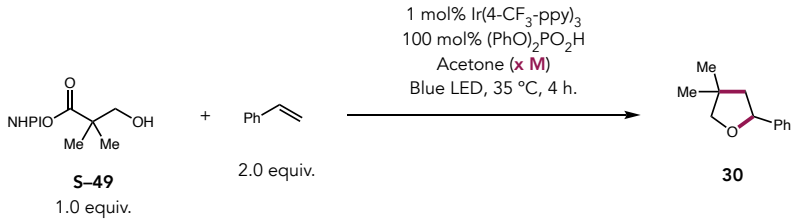
2.0 equiv.

**27**

| Entry | Loading /mol% | Tetrahydrofuran 27 /NMR% |
|---|---|---|
| **1** | **25** | **58** |
| 2 | 50 | 55 |
| 3 | 100 | 54 |
| 4 | 200 | 53 |

0.1 mmol scale. Yields by analysis of the crude reaction mixture $^1$H NMR vs 1,3,5-trimethoxybenzene internal standard.

**Table S.16.** Solvent concentration dependence of the reaction between NHPI ester reagent **S–49** and styrene.




**S–49**
1.0 equiv.

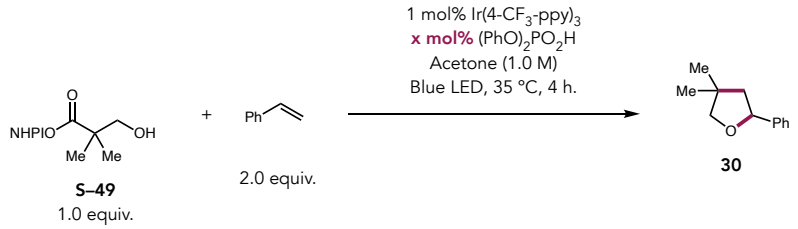
2.0 equiv.

**30**

| Entry | Concentration /M | Tetrahydrofuran 30 /NMR% |
|---|---|---|
| 1 | 0.10 | 28 |
| 2 | 0.20 | 34 |
| 3 | 0.25 | 37 |
| 4 | 0.40 | 42 |
| 5 | 0.50 | 40 |
| **6** | **1.0** | **53** |

0.1 mmol scale. Yields by analysis of the crude reaction mixture $^1$H NMR vs 1,3,5-trimethoxybenzene internal standard.

**Table S.17.** Brønsted acid loading dependence of the reaction between NHPI ester reagent **S–49** and styrene.




**S–49**
1.0 equiv.

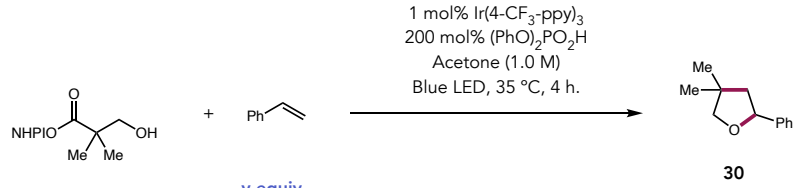
2.0 equiv.

**30**

| Entry | Loading /mol% | Tetrahydrofuran 30 /NMR% |
|---|---|---|
| 1 | 0 | 31 |
| 2 | 5 | 35 |
| 3 | 10 | 37 |
| 4 | 25 | 37 |
| 5 | 50 | 43 |
| 6 | 100 | 62 |
| **7** | **200** | **76** |
| 8 | 300 | 72 |

0.1 mmol scale. Yields by analysis of the crude reaction mixture $^1$H NMR vs 1,3,5-trimethoxybenzene internal standard.

**Table S.18.** Reagent stoichiometry dependence of the reaction between NHPI ester reagent **S–49** and styrene.




**S–49**
x equiv.

y equiv.

**30**

**Excess styrene regime (x = 1):**

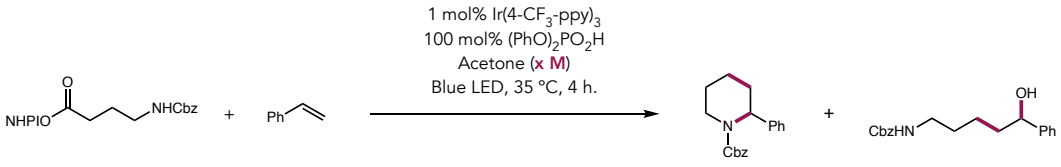
| Entry | Stoichiometry y /mol% | Tetrahydrofuran 30 /NMR% |
|---|---|---|
| 1 | 1.0 | 66 |
| **2** | **1.5** | **73** |
| 3 | 2.0 | 73 |
| 4 | 2.5 | 74 |
| 5 | 3.0 | 68 |

**Excess NHPI regime (y = 1):**

| Entry | Stoichiometry x /mol% | Tetrahydrofuran 30 /NMR% |
|---|---|---|
| 1 | 1.0 | 66 |
| **2** | **1.5** | **89** |
| 3 | 2.0 | 78 |
| 4 | 2.5 | 77 |

0.1 mmol scale. Yields by analysis of the crude reaction mixture $^1$H NMR vs 1,3,5-trimethoxybenzene internal standard.

**Table S.19.** Solvent concentration dependence of the reaction between NHPI ester reagent **31** and styrene.




**31**
1.0 equiv.

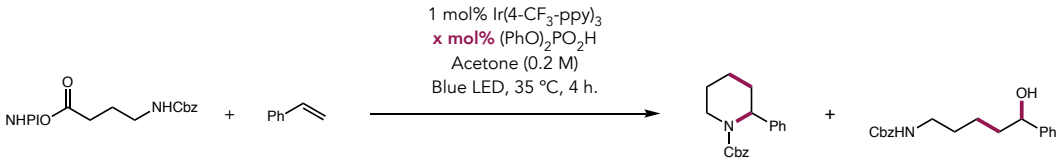
2.0 equiv.

**S–53**

| Entry | Concentration /M | Piperidine S–53 /NMR% | Hydration product /NMR% |
|---|---|---|---|
| 1 | 0.10 | 20 | 3 |
| **2** | **0.20** | **21** | **2** |
| 3 | 0.25 | 18 | 2 |
| 4 | 0.40 | 19 | 1 |
| 5 | 0.50 | 18 | 1 |
| 6 | 1.0 | 20 | 1 |

0.1 mmol scale. Yields by analysis of the crude reaction mixture $^1$H NMR vs 1,3,5-trimethoxybenzene internal standard.

**Table S.20.** Brønsted acid loading dependence of the reaction between NHPI ester reagent **31** and styrene.




**31**
1.0 equiv.

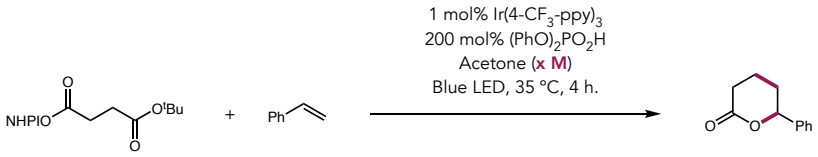
2.0 equiv.

**S–53**

| Entry | Loading /mol% | Piperidine S–53 /NMR% | Hydration product /NMR% |
|---|---|---|---|
| 1 | 0 | 0 | 35 |
| 2 | 25 | 11 | 20 |
| 3 | 50 | 13 | 4 |
| 4 | 100 | 16 | 2 |
| 5 | 200 | 25 | 3 |
| **6** | **300** | **32** | **5** |

0.1 mmol scale. Yields by analysis of the crude reaction mixture $^1$H NMR vs 1,3,5-trimethoxybenzene internal standard.

**Table S.21.** Solvent concentration dependence of the reaction between NHPI ester reagent **32** and styrene.




**32**
1.0 equiv.

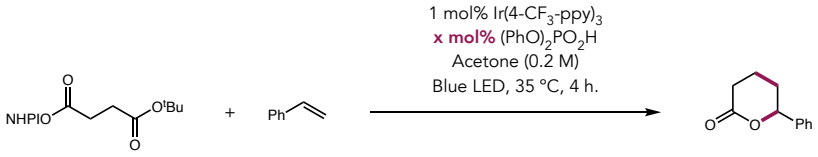
2.0 equiv.

**37**

| Entry | Concentration /M | Lactone 37 /NMR% |
|---|---|---|
| 1 | 0.10 | 51 |
| **2** | **0.20** | **59** |
| **3** | **0.25** | **59** |
| 4 | 0.40 | 56 |
| 5 | 0.50 | 58 |
| 6 | 1.0 | 53 |

0.1 mmol scale. Yields by analysis of the crude reaction mixture $^1$H NMR vs 1,3,5-trimethoxybenzene internal standard.

**Table S.22.** Brønsted acid loading dependence of the reaction between NHPI ester reagent **32** and styrene.




**32**
1.0 equiv.

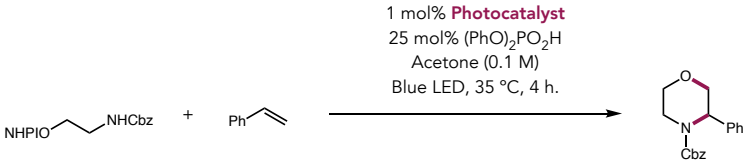
2.0 equiv.

**37**

| Entry | Loading /mol% | Lactone 37 /NMR% |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 5 | 9 |
| 3 | 10 | 13 |
| 4 | 25 | 27 |
| 5 | 50 | 42 |
| 6 | 100 | 51 |
| 7 | 150 | 57 |
| **8** | **200** | **61** |

0.1 mmol scale. Yields by analysis of the crude reaction mixture $^1$H NMR vs 1,3,5-trimethoxybenzene internal standard.

**Table S.23.** Photocatalyst identity dependence of the reaction between NHPI ether reagent **33** and styrene.

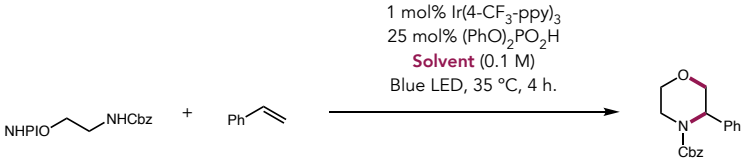



**33** 1.0 equiv. | 2.0 equiv. | **38**

| Entry | Photocatalyst | Morpholine 38 /NMR% | Remaining NHPI reagent 33 /NMR% |
|---|---|---|---|
| 1 | $Ir(4\text{-}F\text{-}ppy)_3$ | 22 | 0 |
| **2** | **$Ir(4\text{-}CF_3\text{-}ppy)_3$** | **30** | **0** |
| 3 | $Ir(ppy)_3$ | 12 | 0 |
| 4 | $Ir(dFppy)_3$ | 29 | 0 |
| 5 | $[Ir(ppy)_2(dtbbpy)]PF_6$ | 22 | 36 |
| 6 | $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ | 0 | 93 |
| 7 | $[Ru(bpy)_3](PF_6)_2$ | 0 | 97 |
| 8 | *N*-Ph phenothiazine | 0 | 93 |

0.1 mmol scale. Yields by analysis of the crude reaction mixture $^1$H NMR vs 1,3,5-trimethoxybenzene internal standard.

**Table S.24.** Solvent identity dependence of the reaction between NHPI ether reagent **33** and styrene.

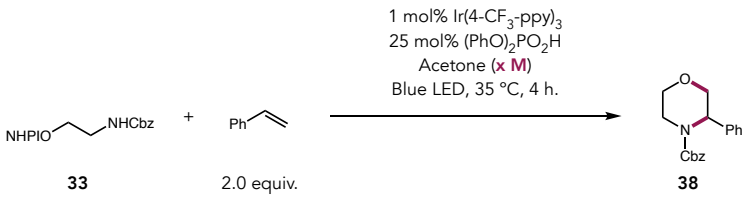



**33** 1.0 equiv. | 2.0 equiv. | **38**

| Entry | Solvent | Morpholine 38 /NMR% | Remaining NHPI reagent 33 /NMR% |
|---|---|---|---|
| 1 | MeCN | 7 | 0 |
| 2 | $^t$BuCN | 9 | 0 |
| **3** | **Acetone** | **29** | **0** |
| 4 | PhH | 0 | 94 |
| 5 | PhF | 0 | 100 |
| 6 | $PhCF_3$ | 2 | 83 |
| 7 | 1,2-Difluorobenzene | 8 | 31 |
| 8 | 1,2-DCE | 7 | 33 |
| 9 | *N*,*N*-DMF | 16 | 0 |
| 10 | DMSO | 19 | 0 |
| 11 | $CH_2Cl_2$ | 6 | 39 |
| 12 | Methyl ethyl ketone | 25 | 0 |

0.1 mmol scale. Yields by analysis of the crude reaction mixture $^1$H NMR vs 1,3,5-trimethoxybenzene internal standard.

**Table S.25.** Solvent concentration dependence of the reaction between NHPI ether reagent **33** and styrene.

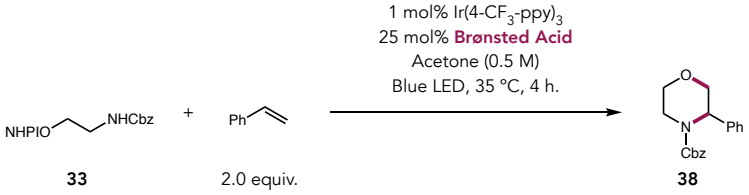



**33** 1.0 equiv. | 2.0 equiv. | **38**

| Entry | Concentration /M | Morpholine 38 /NMR% | Remaining NHPI reagent 33 /NMR% |
|---|---|---|---|
| 1 | 1.0 | 39 | 4 |
| **2** | **0.5** | **39** | **7** |
| 3 | 0.25 | 37 | 2 |
| 4 | 0.20 | 31 | 4 |
| 5 | 0.10 | 30 | 4 |
| 6 | 0.05 | 22 | 5 |
| 7 | 0.033 | 15 | 5 |
| 8 | 0.025 | 15 | 5 |

0.1 mmol scale. Yields by analysis of the crude reaction mixture $^1$H NMR vs 1,3,5-trimethoxybenzene internal standard.

**Table S.26.** Brønsted acid identity dependence of the reaction between NHPI ether reagent **33** and styrene.

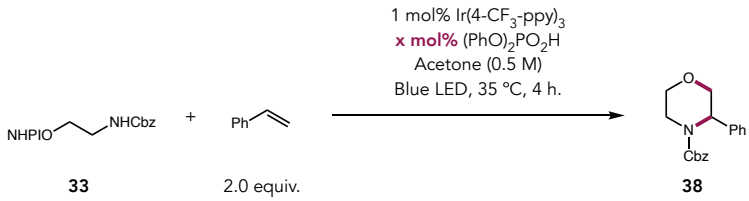



**33** 1.0 equiv. | 2.0 equiv. | **38**

| Entry | Brønsted Acid | Morpholine 38 /NMR% | Remaining NHPI reagent 33 /NMR% |
|---|---|---|---|
| **1** | **$(PhO)_2PO_2H$** | **39** | **0** |
| 2 | TFA | 30 | 0 |
| 3 | AcOH | 1 | 77 |
| 4 | $^t$BuCO$_2$H | 1 | 38 |
| 5 | BzOH | 0 | 61 |
| 6 | HCl, 4.0 M in dioxane | 0 | 18 |
| 7 | $H_2O$ | 0 | 63 |
| 8 | PPTS | 7 | 2 |

0.1 mmol scale. Yields by analysis of the crude reaction mixture $^1$H NMR vs 1,3,5-trimethoxybenzene internal standard.

**Table S.27.** Brønsted acid loading dependence of the reaction between NHPI ether reagent **33** and styrene.

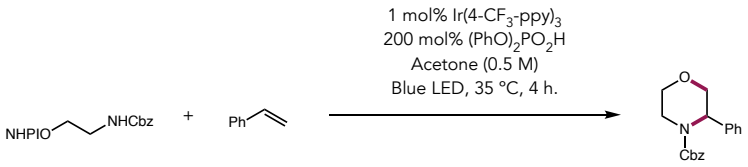



**33** 1.0 equiv. | 2.0 equiv. | **38**

| Entry | Loading /mol% | Morpholine 38 /NMR% | Remaining NHPI reagent 33 /NMR% |
|---|---|---|---|
| 1 | 0 | 0 | 65 |
| 2 | 5 | 2 | 64 |
| 3 | 10 | 4 | 4 |
| 4 | 25 | 40 | 0 |
| 5 | 50 | 47 | 0 |
| 6 | 100 | 48 | 0 |
| **7** | **200** | **54** | 0 |
| 8 | 300 | 55 | 0 |

0.1 mmol scale. Yields by analysis of the crude reaction mixture $^1$H NMR vs 1,3,5-trimethoxybenzene internal standard.

**Table S.28.** Reagent stoichiometry dependence of the reaction between NHPI ether reagent **33** and styrene.




**33** (x equiv.) + (y equiv.) → **38**

**Excess styrene regime (x = 1):**

| Entry | Stoichiometry y /equiv. | Morpholine 38 /NMR% |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 1.0 | 45 |
| 3 | 1.1 | 49 |
| 4 | 1.3 | 47 |
| 5 | 1.5 | 49 |
| **6** | **2.0** | **54** |
| 7 | 3.0 | 54 |
| 8 | 4.0 | 57 |

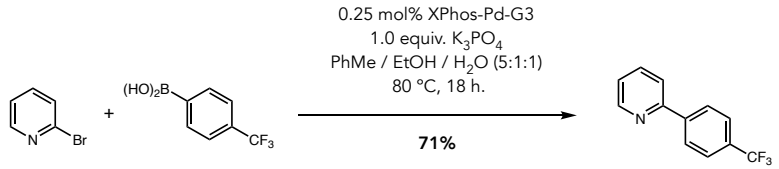
**Excess NHPI regime (y = 1):**

| Entry | Stoichiometry x /equiv. | Morpholine 38 /NMR% |
|---|---|---|
| 1 | 1.0 | 41 |
| 2 | 1.1 | 49 |
| 3 | 1.3 | 50 |
| 4 | 1.5 | 71 |
| **5** | **2.0** | **76** |

0.1 mmol scale. Yields by analysis of the crude reaction mixture $^1$H NMR vs 1,3,5-trimethoxybenzene internal standard.

## 5. Procedures for Ir(4-$CF_3$-ppy)$_3$ photocatalyst synthesis

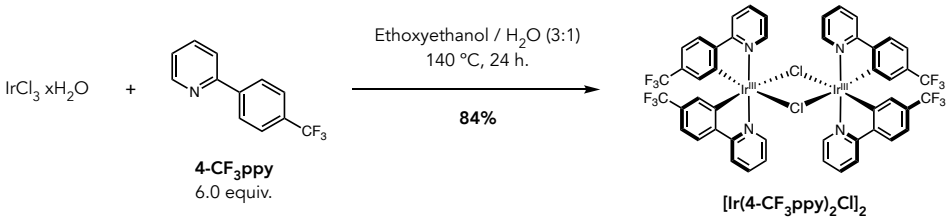
### 2-(4-Trifluoromethylphenyl)pyridine (4-$CF_3$-ppy)




A 500 mL single-necked was charged a teflon-coated stir bar, toluene (300 mL), ethanol (60 mL), and water (60 mL), and degassed via sparging with nitrogen for 1 h. To the mixture was added 2-bromopyridine (9.54 mL, 100 mmol, 1.0 equiv.), 4-(trifluoromethyl)phenylboronic acid (28.5 g, 150 mmol, 1.5 equiv.), $K_3PO_4$ (21.3 g, 100 mmol, 1.0 equiv.), and XPhos-Pd-G3 (220 mg, 0.25 mmol, 0.25 mol%). The flask was fitted with a reflux condenser and placed under a nitrogen atmosphere. The mixture was heated to an 80 °C setpoint temperature with stirring for 18 h. The reaction was cooled, and the mixture partitioned between EtOAc (300 mL) and water (300 mL). Phases were separated, and the aqueous phase extracted with EtOAc (2 x 100 mL). Combined organic phases were washed with brine (100 mL) and dried over sodium sulfate. Filtration of drying agents and evaporation of all volatiles *in vacuo* gave a yellow solid, which was purified via flash column chromatography on silica (5% EtOAc / hexanes) to afford pure **4-$CF_3$-ppy** as a white solid (15.8 g, 70.9 mmol, 71%).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 8.73 (1H, d, $^3J_{HH}$ = 4.8 Hz), 8.11 (2H, d, $^3J_{HH}$ = 8.0 Hz), 7.79 (1H, qd, $^3J_{HH}$ = 7.2 Hz, $^4J_{HH}$ = 1.5 Hz), 7.76 (1H, d, $^3J_{HH}$ = 7.8 Hz),7.73 (2H, d, $^3J_{HH}$ = 8.0 Hz).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 156.0, 150.1, 142.8, 137.1, 130.9 (q, $^2J_{CF}$ = 32.5 Hz), 127.3, 125.8 (q, $^3J_{CF}$ = 3.9 Hz), 124.3 (q, $^1J_{CF}$ = 272 Hz), 123.1, 121.0.
**$^{19}$F-NMR (δ, 376 MHz, $CDCl_3$):** -62.6.
**HRMS (ESI-TOF):** Calc. for $C_{12}H_9F_3N^+$ ([M+H]$^+$): 224.06816, found: 224.06838, Δ 0.93 ppm.
**FTIR (ATR, cm$^{-1}$):** 1328s, 1314m, 1167w, 1108s, 1071w, 783m.
Characterization data is consistent with that reported by Zheng and co-workers.[3]

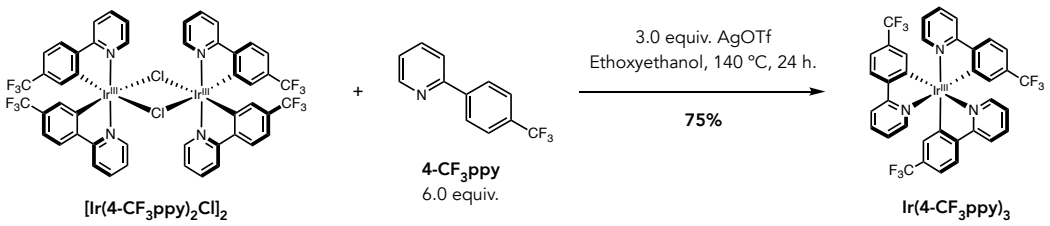
### [(4-$CF_3$ppy)$_2$Ir(μ-Cl)]$_2$




A 200 mL single-necked round bottomed flask was charged with a teflon-coated stir bar, iridium(III) chloride hydrate (assume monohydrate and treat this as limiting reagent, 1.58 g, 5.0 mmol, 1.0 equiv.) and 2-(4-(trifluoromethyl)phenyl)pyridine (**4-$CF_3$-ppy**, 3.35 g, 15.0 mmol, 3.0 equiv.). The flask was fitted with a reflux condenser and nitrogen inlet and placed under a nitrogen atmosphere through 5 x 1 min. cycles of vacuum and purge. To the flask was added sequentially ethoxyethanol (25 mL, degassed through sparging) and water (8 mL, degassed through sparging), and the mixture was heated to 140 °C setpoint temperature with stirring for 24 h. During this time a yellow precipitate formed from solution. The mixture was cooled, and water (170 mL) was added with stirring. The mixture was filtered, and the resultant yellow solid washed with water (3 x 100 mL). The solid was collected and azeotropically dried with toluene (3 x 50 mL), before redissolving in a minimal volume of $CH_2Cl_2$ (*ca.* 20 mL). With stirring, hexanes (400 mL) were slowly added to reprecipitate a yellow solid. This was collected via filtration, washed with hexanes (3 x 50 mL) and dried *in vacuo*, to afford pure **[Ir(4-$CF_3$-ppy)$_2$Cl]$_2$** as a yellow solid (2.82 g, 2.10 mmol, 84%).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 9.23 (4H, dd, $^3J_{HH}$ = 5.9 Hz, $^4J_{HH}$ = 0.6 Hz), 7.99 (4H, d, $^3J_{HH}$ = 8.1 Hz), 7.88 (4H, td, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.1 Hz), 7.60 (4H, d, $^3J_{HH}$ = 8.2 Hz), 7.05 (4H, d, $^3J_{HH}$ = 8.5 Hz), 6.93 (4H, td, $^3J_{HH}$ = 6.6 Hz, $^4J_{HH}$ = 1.2 Hz), 6.09 (4H, s).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 167.3, 151.8, 147.3, 144.2, 137.4, 130.3 (q, $^2J_{CF}$ = 30.6 Hz), 126.5 (q, $^3J_{CF}$ = 3.8 Hz), 123.8, 123.7 (q, $^1J_{CF}$ = 272 Hz), 123.6, 119.9, 119.0 (q, $^2J_{CF}$ = 3.7 Hz).
**$^{19}$F-NMR (δ, 376 MHz, $CDCl_3$):** -63.0.
**FTIR (ATR, cm$^{-1}$):** 1609w, 1480w, 1394w, 1317s, 1159m, 1120m, 1074m, 781m.
Characterization data is consistent with that reported by Shavaleev, Armaroli, Nazeeruddin and co-workers.[4]

**Ir(4-$CF_3$-ppy)$_3$**



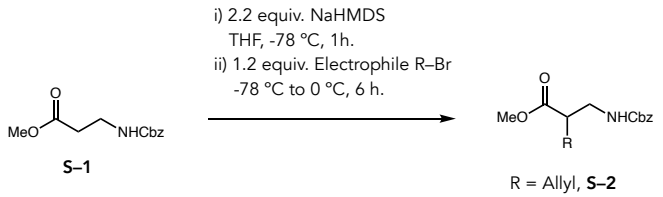

A 200 mL single-necked round bottomed flask was charged a teflon-coated stir bar, **[Ir(4-$CF_3$-ppy)$_2$Cl]$_2$** (1.47 g, 1.09 mmol, 1.0 equiv.) and 2-(4-(trifluoromethyl)phenyl)pyridine (**4-$CF_3$-ppy**, 1.46 g, 6.56 mmol, 6.0 equiv.), and silver triflate (840 mg, 3.27 mmol, 3.0 equiv.). The flask was fitted with a reflux condenser and placed under a nitrogen atmosphere through 5 x 1 min. cycles of vacuum and purge. To the flask was added ethoxyethanol (110 mL, degassed through sparging) and the mixture was heated to 140 °C setpoint temperature with stirring for 24 h. The mixture was cooled and partitioned between $CH_2Cl_2$ (100 mL) and water (400 mL). Phases were separated, and the aqueous phase extracted with further $CH_2Cl_2$ (4 x 100 mL). Combined organic phases were washed with brine (100 mL) and dried over magnesium sulfate. Filtration of drying agents and evaporation of all volatiles *in vacuo* gave a dark yellow solid, which was purified via flash column chromatography on silica (0-2-4-6% acetone / $CH_2Cl_2$) to afford yield a bright yellow solid. This was dissolved in a minimal volume of acetone (*ca.* 40 mL) and slowly treated with hexanes (400 mL) with stirring to reprecipitate the pure photocatalyst **Ir(4-$CF_3$ppy)$_3$** as a bright yellow solid (1.45 g, 1.69 mmol, 78%).

**$^1$H-NMR (δ, 500 MHz, DMSO-$d_6$):** 8.32 (1H, d, $^3J_{HH}$ = 8.2 Hz), 7.99 (1H, d, $^3J_{HH}$ = 8.2 Hz), 7.92 (1H, td, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.4 Hz), 7.55 (1H, d, $^3J_{HH}$ = 5.3 Hz), 7.28 (1H, t, $^3J_{HH}$ = 6.4 Hz), 7.14 (1H, d, $^3J_{HH}$ = 8.0 Hz), 6.77 (1H, d, $^4J_{HH}$ = 1.2 Hz).
**$^{13}$C-NMR (δ, 126 MHz, DMSO-$d_6$):** 163.7, 159.2, 148.2, 147.4, 138.1, 131.3 (q, $^3J_{CF}$ = 3.8 Hz), 129.0 (q, $^2J_{CF}$ = 29.9 Hz), 124.7, 124.6, 124.4 (q, $^1J_{CF}$ = 272 Hz), 120.6, 116.8 (q, $^3J_{CF}$ = 3.8 Hz).
**$^{19}$F-NMR (δ, 376 MHz, DMSO-$d_6$):** -61.3.
**FTIR (ATR, cm$^{-1}$):** 3211w, 1603w, 1474m, 1321s, 1159m, 1106m, 1073m, 781m.

## 6. Procedures for substrate synthesis

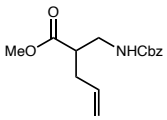
### 6.1. Precursors to NHPI reagents

**General procedure A – α-Alkylation of Cbz-β-Ala-OMe (S–1) with allyl and propargyl bromides**




To a flame-dried flask equipped with stir bar was added Cbz-β-alanine methyl ester[5] (**S–1**, 4.75 g, 20.0 mmol, 1.0 equiv.) and anhydrous THF (60 mL), and the solution cooled to -78 °C. To this was added dropwise over a 15 min. period NaHMDS solution in THF (44.0 mL of a 1.0 M solution in THF, 44.0 mmol, 2.2 equiv.), followed by continued stirring for a further 45 min. Then, a solution of electrophile (24.0 mmol, 1.2 equiv.) in THF (10 mL) was added dropwise over 10 min. The solution was stirred for a further 6 h., as it slowly warmed to ca. 0 °C, where the mixture was then quenched with sat. aq. ammonium chloride solution (100 mL). Phases were separated and the aqueous phase extracted with ethyl acetate (3 x 100 mL). Combined organic phases were washed with brine and dried over magnesium sulfate. Filtration of drying agents and evaporation of solvents gave a yellow oil, which was purified via flash column chromatography on silica to afford pure enolate alkylation products **S–2** and **S–3**.

**Methyl 2-((((benzyloxy)carbonyl)amino)methyl)pent-4-enoate (S-2)**

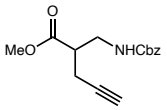



S–2

Prepared according to general procedure **A** using allyl bromide (2.07 mL, 24.0 mmol, 1.2 equiv.) as electrophile. Purification of crude product by flash column chromatography on silica (1–25% EtOAc / hexanes) gave pure α-allyl ester **S–2** as a colorless oil (4.53 g, 16.3 mmol, 82%).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.31–7.38 (5H, m), 5.74 (1H, m), 5.05–5.13 (5H, m), 3.68 (3H, s), 3.44-3.49 (1H, m), 3.30–3.36 (1H, m), 2.70–2.76 (1H, m), 2.37–2.43 (1H, m), 2.26–2.32 (1H, m).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 174.6, 156.3, 136.5, 134.3, 128.6, 128.2, 128.2, 117.7, 66.8, 51.9, 45.1, 41.6, 34.0.
**HRMS (ESI-TOF):** Calc. for $C_{15}H_{19}NO_4Na^+$ ([M+Na]$^+$): 300.12063, found: 300.12086, Δ 0.85 ppm.
**FTIR (ATR, cm$^{-1}$):** 3350w br, 2951w, 1725s, 1527m, 1441w, 1245m, 993w, 697w.

**Methyl 2-((((benzyloxy)carbonyl)amino)methyl)pent-4-ynoate (S-3)**

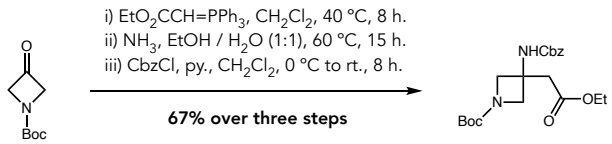



S–3

Prepared according to general procedure **A** using propargyl bromide (1.82 mL, 24.0 mmol, 1.2 equiv.) as electrophile. Purification of crude product by flash column chromatography on silica (10–50% $Et_2O$ / hexanes) gave pure α-propargyl ester **S–3** as a colorless oil (3.43 g, 12.5 mmol, 62%).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.30–7.37 (5H, m), 5.19 (1H, br s), 5.09 (2H, s), 3.72 (3H, s), 3.48–3.60 (2H, m), 2.83 (1H, t, $^3J_{HH}$ = 6.6 Hz), 2.54 (2H, d $^3J_{HH}$ = 6.7 Hz), 2.03 (1H, s).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 173.3, 156.5, 136.5, 128.7, 128.3, 128.3, 80.2 71.0, 67.0, 52.3, 44.0, 41.3, 19.1.
**HRMS (ESI-TOF):** Calc. for $C_{15}H_{17}NO_4Na^+$ ([M+Na]$^+$): 298.10498, found: 298.10516, Δ 0.65 ppm.
**FTIR (ATR, cm$^{-1}$):** 3294 w br, 2952w, 1708s, 1521m, 1438m, 1242s, 1173m, 1145m, 993w, 697m, 644m.

*Tert*-butyl 3-(((benzyloxy)carbonyl)amino)-3-(2-ethoxy-2-oxoethyl)azetidine-1-carboxylate (S–5)



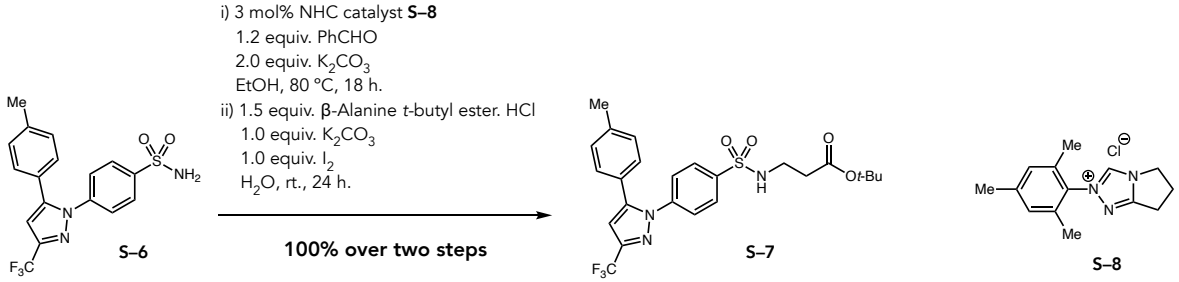

To a solution of *N*-Boc 3-azetidinone (**S–4**, 5.14 g, 30.0 mmol, 1.0 equiv.) in $CH_2Cl_2$ (120 mL) was added (carbethoxymethylene)triphenylphosphorane (12.5 g, 36.0 mmol, 1.2 equiv.). The solution was heated to reflux under a nitrogen atmosphere and stirred at this temperature for 8 h. Then, the solution was cooled, and solvents removed *in vacuo*. The residual yellow oil was triturated with $Et_2O$, filtered through silica, and the silica plug rinsed with further $Et_2O$. Combined solvents were removed *in vacuo* to yield a yellow oil, which was used directly in the subsequent preparation without further purification, assuming quantitative yield.

To the crude enoate ester as prepared above was added ethanol (45 mL) and 30% aq. $NH_3$ solution (45 mL). The mixture was heated to 60 °C with stirring for 16 h. The solution was cooled, and ethanol removed *in vacuo*. The resulting mixture was partitioned between $CH_2Cl_2$ (200 mL) and water (100 mL). Phases were separated, and the aqueous phase extracted with further $CH_2Cl_2$ (2 x 50 mL). Combined organic phases were washed with brine (50 mL) and dried over sodium sulfate. Filtration of drying agents and evaporation of solvents gave a yellow oil, which was used directly in the subsequent preparation without further purification, assuming quantitative yield.

The crude amine as prepared above was taken up in $CH_2Cl_2$ (150 mL) and cooled to 0 °C. To this solution was added pyridine (7.25 mL, 90.0 mmol, 3.0 equiv.) and benzyl chloroformate (5.14 mL, 36.0 mmol, 1.2 equiv.). The solution was stirred at 0 °C for 1 h., then rt. for 6 h. The solution was diluted with $CH_2Cl_2$ and washed with sat. aq. $NaHCO_3$ solution (100 mL) and brine (100 mL) and dried over magnesium sulfate. Filtration of drying agents and evaporation of solvents gave a yellow oil, which was purified by flash column chromatography on silica (5 – 40% Acetone / Hexanes) to afford pure Cbz-protected β-amino ester **S–5** as a colorless oil which slowly solidifies to a white solid (7.84 g, 19.98 mmol, 67% over three steps).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.31–7.38 (5H, m), 5.51 (1H, br s), 5.08 (2H, s), 4.13 (2H, q, $^3J_{HH}$ = 7.2 Hz), 4.03 (2H, br d, $^2J_{HH}$ = 9.0 Hz), 3.90 (2H, d, $^2J_{HH}$ = 9.0 Hz), 3.00 (2H, s), 1.43 (9H, s), 1.24 (3H, t, $^3J_{HH}$ = 7.2 Hz).
**$^{13}$C-NMR (126 MHz, $CDCl_3$):** 170.8, 156.3, 154.8, 136.2, 128.7, 128.4, 128.2, 80.0, 66.9, 59.5, 49.4, 40.7, 28.5, 14.3.
**HRMS (ESI-TOF):** Calc. for $C_{20}H_{28}N_2O_6Na^+$ ([M+Na]$^+$): 415.18396, found: 415.18445, Δ 0.97 ppm.
**FTIR (ATR, cm$^{-1}$):** 3324br w, 2977w, 1699s, 1518m, 1392m, 1367m, 1256m, 1148s, 1053s, 772m, 738m, 697m.

*Tert*-butyl 3-((4-(5-(*p*-tolyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)sulfonamido)propanoate (S–7)

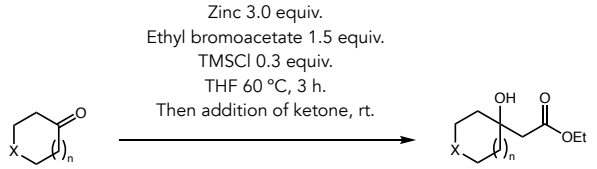



According to the method Fier and Maloney,[6] celecoxib (**S–6**, 1.91 g, 5.00 mmol, 1.0 equiv.), $K_2CO_3$ (1.38 g, 10.0 mmol, 2.0 equiv.), and NHC pre-catalyst **S–8** (40.0 mg, 0.15 mmol, 3 mol%) were added to a 25 mL round bottomed flask equipped with a magnetic stir bar. Ethanol (5 mL) was added, followed by benzaldehyde (610 µL, 6.0 mmol, 1.2 equiv.) and the mixture was heated to 80 °C under an atmosphere of nitrogen for 18 h. The reaction mixture was cooled, and solvents removed *in vacuo*. To the resulting mixture was added water (10 mL), *tert*-butyl β-alanine hydrochloride (1.36 g, 7.5 mmol, 1.0 equiv.),

$K_2CO_3$ (0.69 g, 5.0 mmol, 1.0 equiv.), and iodine (1.27 g, 5.0 mmol, 1.0 equiv.), each as a solid in one portion. The heterogeneous mixture was stirred vigorously at room temperature for 24 h. The mixture was partitioned between water (50 mL) and $CH_2Cl_2$ (100 mL). Phases were separated, and the aqueous phase extracted with further $CH_2Cl_2$ (2 x 30 mL). The combined organic phase was washed with freshly-prepared 10% aq. $Na_2SO_3$ solution (30 mL) and brine (30 mL) and dried over magnesium sulfate. Filtration of drying agents and evaporation of solvents, then purification by flash column chromatography on silica (5 – 35% EtOAc / hexanes) gave pure *N*-alkylation product **S–7** (2.54 g, 5.00 mmol, 100% over two steps) as a viscous foaming oil.

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.85 (2H, d, $^3J_{HH}$ = 8.7 Hz), 4.48 (2H, d, $^3J_{HH}$ = 8.7 Hz), 7.18 (2H, d, $^3J_{HH}$ = 8.0 Hz), 7.10 (2H, d, $^3J_{HH}$ = 8.0 Hz), 6.74 (1H, s), 5.34 (1H, t, $^3J_{HH}$ = 6.5 Hz), 3.14 (2H, app q, $^3J_{HH}$ = 6.2 Hz), 2.44 (2H, t, $^3J_{HH}$ = 6.2 Hz), 2.38 (3H, s), 1.42 (9H, s).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 171.6, 145.4, 144.2 (q, $^2J_{CF}$ = 38.4 Hz), 142.7, 139.9, 139.6, 129.9, 128.9, 128.2, 125.8, 125.8, 121.2 (q, $^1J_{CF}$ = 268.4 Hz), 106.4, 82.0, 39.1, 34.9, 28.2, 21.5.
**$^{19}$F-NMR (δ, 376 MHz, $CDCl_3$):** -62.5.
**HRMS (ESI-TOF):** Calc. for $C_{24}H_{26}F_3N_3O_4SNa^+$ ([M+Na]$^+$): 532.14883, found: 532.14864, Δ 0.12 ppm.
**FTIR (ATR, cm$^{-1}$):** 3286br w, 2980w, 1726m, 1472m, 1370w, 1237m, 1160s, 1131m, 1097m, 976m, 626m.

General procedure B – Reformatsky reaction of cycloalkanones S–9, S–10, and S–4 with ethyl bromoacetate

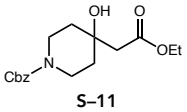



X = NCbz, n = 1, **S–9**
X = O, n = 1, **S–10**
X = NBoc, n= -1, **S–4**

X = NCbz, n = 1, **S–11**
X = O, n = 1, **S–12**
X = NBoc, n= -1, **S–13**

Elemental zinc (activated according to the method of Kishi and stored in a dessicator,[7] 3.92 g, 60.0 mmol, 3.0 equiv.) was charged to a 250 mL flame-dried round bottomed flask equipped with stir bar. To this was added anhydrous THF (60 mL), followed by chlorotrimethylsilane (760 µL, 6.0 mmol, 0.3 equiv.) and the mixture heated to 60 °C. Then, neat ethyl bromoacetate (3.33 mL, 30.0 mmol, 1.5 equiv.) was added dropwise at such a rate to maintain a gentle reflux (*ca.* 10 min. addition time). The solution takes on a characteristic green-orange coloration in this step. Stirring is maintained at this temperature for a total of 3 h. Then, the solution of zinc enolate is allowed to cool to room temperature, before addition of ketone substrate (20.0 mmol, 1.0 equiv.) as a solution in anhydrous THF (20 mL) dropwise. The solution was then stirred for the indicated time. Sat. aq. ammonium chloride solution (100 mL) was added and the mixture stirred vigorously for 15 min. The phases were separated, and the aqueous phase extracted with ethyl acetate (3 x 50 mL). Combined organic phases were washed with water (100 mL) and brine (100 mL) and dried over magnesium sulfate. Filtration of drying agents and evaporation of solvents gave a yellow oil, which was purified by flash column chromatography on silica (conditions given alongside each example below) to afford pure Reformatsky products **S–11**, **S–12**, and **S–13**.

### Benzyl 4-(2-ethoxy-2-oxoethyl)-4-hydroxypiperidine-1-carboxylate (S–11)

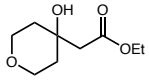


**S–11**

According to general procedure **B**, using *N*-Cbz 4-piperidinone (**S–9**, 3.50 g, 15.0 mmol, 1.0 equiv.), with a 6 h. reaction time after addition of ketone substrate. Purification by flash column chromatography on silica (10–60% EtOAc / hexanes) gave pure β-hydroxyester **S–11** as a colorless oil (4.77 g, 14.9 mmol, 99%).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.30–7.36 (5H, m), 5.12 (2H, s), 4.18 (2H, q, $^3J_{HH}$ = 7.2 Hz), 3.85–4.00 (2H, br m), 3.62 (1H, s), 3.20–3.33 (2H, br m), 2.45 (2H, s), 1.62–1.74 (2H, br m), 1.41–1.55 (2H, br m), 1.29 (3H, t, $^3J_{HH}$ = 7.2 Hz).
**$^{13}$C-NMR (126 MHz, $CDCl_3$):** 172.7, 155.4, 137.0, 128.6, 128.1, 128.0, 68.1, 67.2, 61.0, 45.5, 39.8, 36.8, 36.6, 14.3.
**FTIR (ATR, cm$^{-1}$):** 3394br w, 2938w, 2838w, 1592s, 1458m, 1426m, 1203s, 1147s, 1066m, 819m.

### Ethyl 2-(4-hydroxytetrahydro-2H-pyran-4-yl)acetate (S–12)

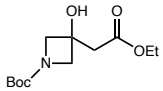


S–12

According to general procedure **B**, using tetrahydro-4H-pyran-4-one (**S–10**, 1.85 mL, 20.0 mmol, 1.0 equiv.), with a 24 h. reaction time after addition of ketone substrate. Purification by flash column chromatography on silica (30–80% $Et_2O$ / hexanes) gave pure β-hydroxyester **S–12** as a colorless oil (3.12 g, 16.6 mmol, 83%).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 4.19 (2H, q, $^3J_{HH}$ = 7.1 Hz), 3.80-3.85 (2H, m), 3.74 (1H, t, $^3J_{HH}$ = 3.9 Hz), 3.72 (1H, t, $^3J_{HH}$ = 3.8 Hz), 2.49 (2H, s), 1.63-1.66 (4H, m), 1.29 (3H, t, $^3J_{HH}$ = 7.1 Hz).
**$^{13}$C-NMR (126 MHz, $CDCl_3$):** 172.8, 67.4, 63.7, 61.0, 45.8, 37.6, 14.3.
**FTIR (ATR, cm$^{-1}$):** 3347br w, 2923s, 2854m, 1734m, 1664m, 1464m, 1260m, 1026m, 800m.

### *Tert*-butyl 3-(2-ethoxy-2-oxoethyl)-3-hydroxyazetidine-1-carboxylate (S–13)

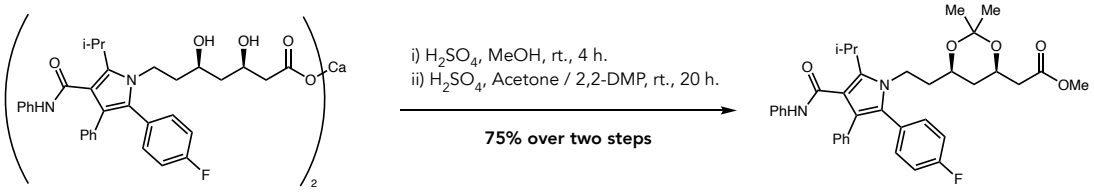


S–13

According to general procedure **B**, using *N*-Boc 3-oxoazetidine (**S–4**, 3.43 g, 20.0 mmol, 1.0 equiv.), with a 2 h. reaction time after addition of ketone substrate. Purification by flash column chromatography on silica (40–90% $Et_2O$ / hexanes) gave pure β-hydroxyester **S–13** as a white solid (4.68 g, 18.0 mmol, 90%).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 4.19 (2H, q, $^3J_{HH}$ = 7.1 Hz), 3.92 (2H, d, $^3J_{HH}$ = 9.2 Hz), 3.88 (1H, br s), 3.80 (2H, d, $^3J_{HH}$ = 9.2 Hz), 2.80 (2H, s), 1.43 (9H, s), 1.28 (3H, t, $^3J_{HH}$ = 7.1 Hz).
**$^{13}$C-NMR (126 MHz, $CDCl_3$):** 172.2, 156.5, 79.9, 67.8, 61.6, 61.4, 42.7, 28.5, 14.3.
**FTIR (ATR, cm$^{-1}$):** 3400br w, 2978w, 1734m, 1701s, 1674s, 1392s, 1366s, 1231m, 1149s, 1085s, 1031m.

### Methyl 2-((4*R*,6*R*)-6-(2-(2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1*H*-pyrrol-1-yl)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (S–15)




S–14 S–15

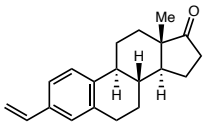
To anhydrous methanol (50 mL) was added conc. $H_2SO_4$ (10 drops) at 0 °C, followed by atorvastatin calcium salt (**S–14**, 1.16 g, 1.0 mmol, 1.0 equiv.), added as a solid in one portion. The reaction mixture was stirred at 0 °C for 10 min., then warmed to room temperature and stirred for a further 4 h. After this time, solvents were removed *in vacuo* to approximately 10 mL remaining volume. Then, acetone (20 mL) and 2,2-dimethoxypropane (20 mL) were added and the resulting solution stirred at room temperature for 20 h. The reaction mixture was partitioned between EtOAc (100 mL) and sat. aq. $NaHCO_3$ solution (50 mL). Phases were separated, and the aqueous phase was extracted with further EtOAc (3 x 30 mL). Combined organic phases were washed with brine (30 mL) and dried over $MgSO_4$. Filtration of drying agents, evaporation of solvents, and purification of the residue via flash column chromatography on silica (5 – 25% acetone / hexanes) gave pure atorvastatin acetonide methyl ester (**S–15**, 0.92 g, 1.50 mmol, 75% over two steps) as a colorless viscous oil.

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.14–7.21 (9H, m), 7.07 (2H, d, $^3J_{HH}$ = 8.1 Hz), 6.97–7.01 (3H, m), 6.86 (1H, br s), 4.18–4.23 (1H, m), 4.04–4.10 (1H, m), 3.79–3.85 (1H, m), 3.67–3.72 (4H, m), 3.54–3.60 (1H, m), 2.52 (1H, dd, $^2J_{HH}$ = 15.9 Hz, $^3J_{HH}$ = 6.7 Hz), 2.32 (1H, dd, $^2J_{HH}$ = 15.9 Hz, $^3J_{HH}$ = 6.4 Hz), 2.19 (1H, d, $^3J_{HH}$ = 9.2 Hz), 1.64–1.70 (2H, m), 1.54 (3H, s), 1.52 (3H, s), 1.35–1.38 (4H, m), 1.30 (3H, s).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 171.4, 164.9, 163.4, 161.4, 141.6, 138.5, 134.8, 133.4, 133.3, 130.6, 128.9, 128.8, 128.5, 128.4, 128.4, 126.7, 123.6, 121.9, 119.7, 115.6, 115.5, 115.4, 98.9, 66.6, 65.7, 51.8, 41.1, 41.0, 38.2, 36.1, 30.0, 26.2, 21.9, 21.7, 19.8.
**$^{19}$F-NMR (δ, 376 MHz, $CDCl_3$):** -113.72.
**HRMS (ESI-TOF):** Calc. for $C_{37}H_{41}FN_2O_5Na^+$ ([M+Na]$^+$): 635.28917, found: 635.28909, Δ 0.58 ppm.

**FTIR (ATR, $cm^{-1}$):** 3407w, 2954w, 1737m, 1666m, 1595m, 1526s, 1509s, 1436s, 1381m, 1312m, 1222m, 1200m, 1157m, 753m, 735m, 693m.
Characterization data is consistent with that reported by Hosokawa and co-workers.[8]

## 6.2. Preparation of alkene substrates

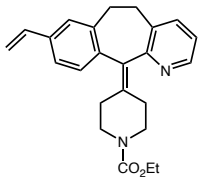
### Vinyl estrone (40)



**40**

Vinyl estrone (**40**) was prepared according to the method of Echavarren and coworkers.[9]

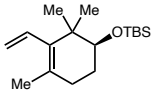
### Vinyl loratadine (S–16)



**S–16**

Vinyl loratadine (**S–16**) was prepared according to the method of Buchwald and coworkers.[10]

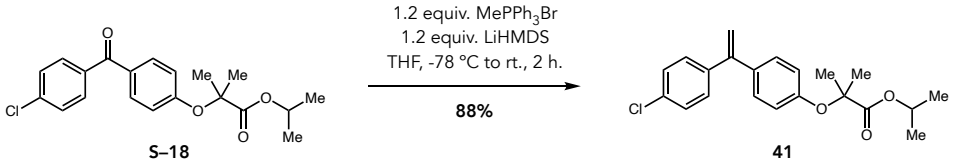
### Diene S–17



**S–17**

Diene **S–17** was prepared according to the method of Mori and Watanabe.[11] We kindly thank Professor Erik J. Sorensen for providing us with this material.

### Fenofibrate 1,1-diaryl ethylene (41)

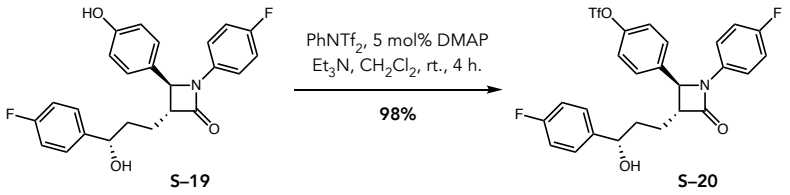



**S–18** **41**

In a flame-dried flask, a suspension of methyl triphenylphosphonium bromide (azeotropically dried with toluene, then placed under high vacuum for 1 h. prior to reaction, 1.29 g, 3.6 mmol, 1.2 equiv.) in anhydrous THF (20 mL) was cooled to -78 °C and treated with LiHMDS (3.6 mL of a 1.0 M solution in THF, 3.6 mmol, 1.2 equiv.). The resulting yellow suspension was stirred at this temperature for 1 h. Then, a solution of fenofibrate (**S–18**, 1.08 g, 3.0 mmol, 1.0 equiv.) in THF (10 mL) was added dropwise over 5 min. The reaction was allowed to stir at -78 °C for 1 h., then the cooling bath was removed, and the reaction allowed to warm to rt., and stirred for a further 1 h. Sat. aq. $NH_4Cl$ solution (10 mL) and water (10 mL) were added to the reaction. Phases were separated, and the aqueous phase extracted with diethyl ether (3 x 30 mL). Combined organic phases were washed with brine (30 mL) and dried over magnesium sulfate. Filtration of drying agents and evaporation of solvents gave a yellow oil, which was purified by flash column chromatography on silica (0 – 5% $Et_2O$ / Hexanes) to afford pure fenofibrate 1,1-diaryl ethylene **41** as a colorless oil (944 mg, 2.63 mmol, 88%).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.29 (2H, dt, $^3J_{HH}$ = 8.4 Hz, $^5J_{HH}$ = 2.0 Hz), 7.26 (2H, dt, $^3J_{HH}$ = 8.4 Hz, $^5J_{HH}$ = 2.0 Hz) , 7.17 (2H, app dt, $^3J_{HH}$ = 8.8 Hz, $^5J_{HH}$ = 2.1 Hz), 6.79 (2H, app dt, $^3J_{HH}$ = 8.8 Hz, $^5J_{HH}$ = 2.1 Hz), 5.39 (1H, d, $^5J_{HH}$ = 1.0 Hz), 5.33 (1H, d, $^5J_{HH}$ = 1.0 Hz), 5.09 (1H, sept, $^3J_{HH}$ = 6.3 Hz), 1.61 (6H, s), 1.23 (6H, d, $^3J_{HH}$ = 6.3 Hz).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 173.8, 155.6, 148.5, 140.3, 134.6, 133.6, 129.8, 129.0, 128.4, 118.5, 113.7, 79.2, 69.1, 25.5, 21.7.
**HRMS (ESI-TOF):** Calc. for $C_{21}H_{23}ClO_3Na^+$ ([M+Na]$^+$): 381.12279, found: 381.12309, Δ 1.38 ppm.
**FTIR (ATR, cm$^{-1}$):** 2982w, 2938w, 1727m, 1655m, 1598m, 1506m, 1285m, 1248m, 1174s, 1145s, 1100s, 1014m, 927m, 852w.

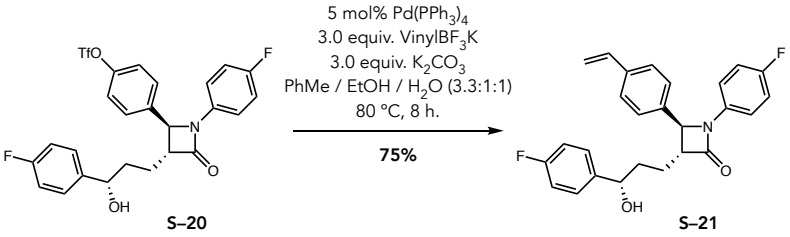
### Ezetimibe triflate (S–20)




To a solution of ezetimibe (**S–19**, 2.05 g, 5.0 mmol, 1.0 equiv.) in $CH_2Cl_2$ (50 mL) at room temperature was added DMAP (122 mg, 1.0 mmol, 20 mol%), triethylamine (1.40 mL, 10.0 mmol, 2.0 equiv.), and $PhNTf_2$ (1.96 g, 5.5 mmol, 1.1 equiv.) as a solid in one portion. The homogeneous solution was stirred at room temperature for 4 h. The mixture was diluted with ethyl acetate (200 mL) and washed with 0.5 M aq. HCl solution (50 mL) and brine (50 mL) and dried over sodium sulfate. Filtration of drying agents and evaporation of solvents gave a yellow oil, which was purified by flash column chromatography on silica (10 – 50% EtOAc / hexanes) to afford pure ezetimibe triflate (**S–20**) as a white foam (2.65 g, 4.89 mmol, 98%).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.41 (2H, d, $^3J_{HH}$ = 8.8 Hz), 7.31 (2H, t, $^3J_{HH}$ = 2.8 Hz), 7.28 (2H, t, $^3J_{HH}$ = 2.9 Hz), 7.17–7.22 (2H, m), 7.02 (2H, t, $^3J_{HH}$ = 8.6 Hz), 6.95 (2H, t, $^3J_{HH}$ = 8.6 Hz), 4.72 (1H, t, $^3J_{HH}$ = 5.9 Hz), 4.67 (1H, d, $^4J_{HH}$ = 2.2 Hz), 3.08 (1H, td, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 2.2 Hz), 1.87–2.06 (4H, m).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 169.7, 162.4 (d, $^1J_{CF}$ = 247 Hz), 159.3 (d, $^1J_{CF}$ = 244 Hz), 149.5, 140.0 (d, $^4J_{CF}$ = 3.2 Hz), 138.4, 133.6 (d, $^4J_{CF}$ = 2.8 Hz), 127.8, 127.5 (d, $^3J_{CF}$ = 8.1 Hz) 122.5, 118.7 (q, $^1J_{CF}$ = 320 Hz), 118.4 (d, $^3J_{CF}$ = 8.0 Hz), 116.2 (d, $^2J_{CF}$ = 22.6 Hz), 115.6 (d, $^2J_{CF}$ = 21.8 Hz), 73.3, 60.7, 60.5, 36.7, 25.3.
**$^{19}$F-NMR (δ, 376 MHz, $CDCl_3$):** -72.8, -114.7, -117.4.
**HRMS (ESI-TOF):** Calc. for $C_{25}H_{21}F_5NO_5S^+$ ([M+H]$^+$): 542.10551, found: 542.10620, Δ 0.89 ppm.
**FTIR (ATR, cm$^{-1}$):** 3432br w, 2927w, 1744m, 1509s, 1421m, 1387w, 1215s, 1138s, 888m, 834m, 608w.

### Vinyl ezetimibe (S–21)

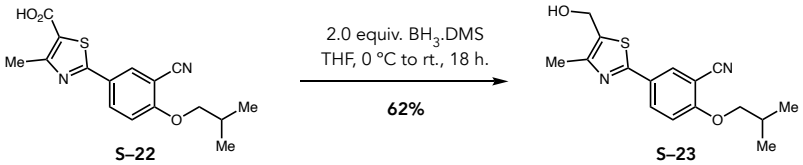



A 50 mL round bottomed flask was charged with stir bar, $vinylBF_3K$ (402 mg, 3.0 mmol, 3.0 equiv.), $K_2CO_3$ (415 mg, 3.0 mmol, 3.0 equiv.), and ezetimibe triflate (**S–20**, 541 mg, 1.0 mmol, 1.0 equiv.). The flask was brought into a nitrogen-filled glovebox, and $Pd(PPh_3)_4$ (58 mg, 0.05 mmol, 5 mol%) was added. The flask was sealed and brought out of the glovebox and connected to a nitrogen-filled Schlenk line. Toluene (degassed by sparging with nitrogen, 10 mL), ethanol (degassed by sparging with nitrogen, 3 mL), and water (degassed by sparging with nitrogen, 3 mL) were added via syringe, and the homogeneous mixture was heated to 80 °C with stirring for 8 h. The solution was cooled to room temperature and partitioned between EtOAc (50 mL) and water (20 mL). Phases were separated and the aqueous phase extracted with further EtOAc (2 x 30 mL). The combined organic phase was washed with brine (30 mL) and dried over sodium sulfate. Filtration of drying agents and evaporation of solvents gave a yellow oil, which was purified by flash column chromatography on silica (30 – 90% $Et_2O$ / Hexanes) to afford pure vinyl ezetimibe (**S–21**) as a white foam (314 mg, 0.75 mmol, 75%).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.41 (2H, d, $^3J_{HH}$ = 8.1 Hz), 7.27-7.31 (6H, m), 7.23 (2H, dd, $^3J_{HH}$ = 8.9, 4.7 Hz), 7.02 (2H, t, $^3J_{HH}$ = 8.6 Hz), 6.93 (2H, t, $^3J_{HH}$ = 8.6 Hz), 6.70 (1H, dd, $^2J_{HH}$ = 16.9 Hz, $^3J_{HH}$ = 10.3 Hz), 5.75 (1H, d, $^3J_{HH}$ = 16.9 Hz), 5.28 (1H, d, $^3J_{HH}$ = 10.3 Hz), 4.72 (1H, t, $^3J_{HH}$ = 5.5 Hz), 4.61 (1H, d, $^4J_{HH}$ = 1.9 Hz), 3.09 (1H, td, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.9 Hz), 2.16 (1H, br s), 1.86-2.03 (4H, m).

**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 167.6, 162.3 (d, $^1J_{CF}$ = 246 Hz), 159.1 (d, $^1J_{CF}$ = 244 Hz), 140.1 (d, $^4J_{CF}$ = 3.0 Hz), 138.2, 137.1, 136.1, 134.0 (d, $^4J_{CF}$ = 2.6 Hz), 127.5 (d, $^3J_{CF}$ = 8.1 Hz), 127.2, 126.2, 118.5 (d, $^3J_{CF}$ = 8.0 Hz), 116.0 (d, $^2J_{CF}$ = 22.7 Hz), 115.5 (d, $^2J_{CF}$ = 21.3 Hz), 114.9, 73.3, 61.4, 60.5, 36.8, 25.2.
**$^{19}$F-NMR (δ, 376 MHz, $CDCl_3$):** -114.8, -117.8.
**HRMS (ESI-TOF):** Calc. for $C_{26}H_{24}F_2NO_2^+$ ([M+H]$^+$): 420.17696, found: 420.17710, Δ 0.24 ppm.
**FTIR (ATR, cm$^{-1}$):** 3423br w, 2925w, 1732m, 1507s, 1386m, 1219m, 1104w, 1015w, 832m, 514w.

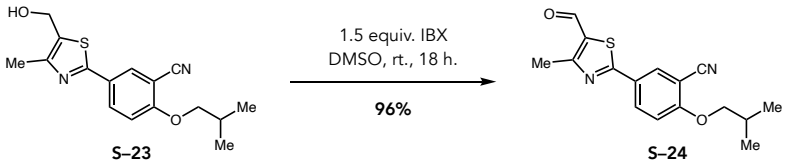
### Febuxostat alcohol (S–23)




A stirring solution of febuxostat (**S–22**, 1.97 g, 6.23 mmol, 1.0 equiv.) in anhydrous THF (15 mL) under a nitrogen atmosphere was treated dropwise with borane dimethylsulfide complex (1.18 mL, 12.46 mmol, 2.0 equiv.) at 0 °C. the solution was allowed to stir at 0 °C for 2 h., then warmed to room temperature and stirrer for a further 16 h. Methanol (10 mL) was added dropwise to the yellow solution (Warning: evolution of gas!) and the resulting orange solution stirrer at room temperature for 0.5 h. All volatiles were removed *in vacuo*. The residual yellow oil was taken up in methanol (50 mL), which was also removed *in vacuo*. This evaporation process was repeated a total of three times. The crude product was purified by flash column chromatography on silica (20–60% acetone / hexanes) to afford pure febuxostat alcohol **S–23** as a pale-yellow oil (1.16 g, 3.84 mmol, 62%).

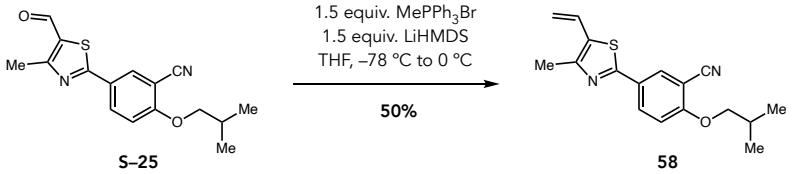
**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 8.10 (1H, d, $^4J_{HH}$ = 2.3 Hz), 8.03 (1H, dd, $^3J_{HH}$ = 9.0 Hz, $^4J_{HH}$ = 2.3 Hz), 6.99 (1H, d, $^3J_{HH}$ = 9.0 Hz), 4.83 (2H, s), 3.88 (2H, d, $^3J_{HH}$ = 6.8 Hz), 2.45 (3H, s), 2.20 (1H, hept, $^3J_{HH}$ = 6.8 Hz), 1.09 (3H, s), 1.08 (3H, s).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 163.7, 162.0, 150.6, 132.2, 131.7, 131.3, 126.8, 115.8, 112.7, 102.9, 75.7, 57.0, 28.3, 19.2, 15.2.
**HRMS (ESI-TOF):** Calc. for $C_{16}H_{19}N_2O_2S^+$ ([M+H]$^+$): 303.11617, found: 303.11579, Δ 0.86 ppm.
**FTIR (ATR, cm$^{-1}$):** 3353w br, 2961m, 2929m, 2874w, 2228w, 1606m, 1508s, 1446m, 1392w, 1282s, 1128w, 1012s, 819m.

### Febuxostat aldehyde (S–24)




A stirring solution of febuxostat alcohol (**S–23**, 1.42 g, 4.70 mmol, 1.0 equiv.) in DMSO (15 mL) was treated with IBX (1.97 g, 7.05 mmol, 1.5 equiv.). The yellow solution was stirred at room temperature overnight, forming a white precipitate within the first hour. The mixture was filtered through a sintered funnel, and the collected solids washed with EtOAc (60 mL). The combined organic solution was washed with water (3 x 30 mL), and brine (2 x 30 mL) and dried over sodium sulfate. Filtration of drying agents and evaporation of solvents gave a yellow solid, which was purified by flash column chromatography on silica (5–35% Acetone / Hexanes) to afford pure febuxostat aldehyde **S–24** as a pale-yellow solid (1.35 g, 4.49 mmol, 96%).
**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 10.09 (1H, s), 8.25 (1H, d, $^4J_{HH}$ = 2.3 Hz), 8.11 (1H, dd, $^3J_{HH}$ = 8.9 Hz, $^4J_{HH}$ = 2.3 Hz), 7.03 (1H, d, $^3J_{HH}$ = 8.9 Hz), 3.92 (2H, d, $^3J_{HH}$ = 6.6 Hz), 2.78 (3H, s), 2.21 (1H, sept, $^3J_{HH}$ = 6.6 Hz), 1.10 (6H, d, $^3J_{HH}$ = 6.8 Hz).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 182.1, 171.1, 163.1, 162.7, 133.1, 132.8, 132.7, 125.8, 115.4, 112.8, 103.3, 75.9, 28.3, 19.2, 16.4.
**HRMS (ESI-TOF):** Calc. for $C_{16}H_{17}N_2O_2S^+$ ([M+H]$^+$): 301.10052, found: 301.09930, Δ 4.54 ppm.
**FTIR (ATR, cm$^{-1}$):** 2926w, 2227w, 1651s, 1506w, 1381w, 1328m, 1276m, 1166w, 1115m, 1011m, 835w.

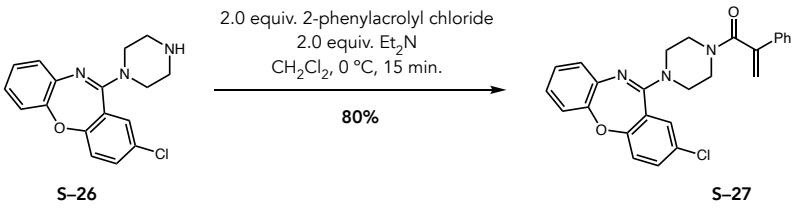
### Vinyl febuxostat (58)




In a flame-dried flask, a suspension of methyl triphenylphosphonium bromide (azeotropically dried with toluene, then placed under high vacuum for 1 h. prior to reaction, 2.41 g, 6.75 mmol, 1.5 equiv.) in anhydrous THF (25 mL) was cooled to 0°C and treated with LiHMDS (6.75 mL of a 1.0 M solution in THF, 6.75 mmol, 1.5 equiv.). The resulting yellow suspension was stirred at this temperature for 0.5 h, then cooled to -78 °C. Then, a solution of febuxostat aldehyde (**S–25**, 1.35 g, 4.49 mmol, 1.0 equiv.) in anhydrous THF (10 mL + 5 mL rinse) was added dropwise. The solution was stirred at -78 °C for 2 h., then allowed to warm to 0 °C and stirred for a further 0.5 h. at this temperature. The reaction was quenched with sat. aq. $NH_4Cl$ solution (20 mL). The reaction mixture was partitioned between EtOAc (100 mL) and water (50 mL). Phases were separated, and the aqueous phase extracted with further EtOAc (2 x 30 mL). Combined organic phases were washed with brine (30 mL) and dried over $MgSO_4$. Filtration of drying agents and evaporation of solvents gave a yellow solid, which was purified by flash column chromatography on silica (2–20% Acetone / Hexanes) to afford pure vinyl febuxostat **58** as a pale-yellow solid (0.68 g, 2.26 mmol, 50%).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 8.10 (1H, d, $^4J_{HH}$ = 2.3 Hz), 8.02 (1H, dd, $^3J_{HH}$ = 8.9 Hz, $^4J_{HH}$ = 2.3 Hz), 6.98 (1H, d, $^3J_{HH}$ = 8.9 Hz), 6.79 (1H, dd, $^2J_{HH}$ = 16.9 Hz, $^3J_{HH}$ = 10.9 Hz), 5.47 (1H, d, $^2J_{HH}$ = 16.9 Hz), 5.26 (1H, d, $^3J_{HH}$ = 10.9 Hz), 3.88 (2H, d, $^3J_{HH}$ = 6.5 Hz), 2.45 (3H, s), 2.19 (1H, hept, $^3J_{HH}$ = 6.5 Hz), 1.09 (3H, s), 1.08 (3H, s).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 161.8, 161.7, 150.9, 132.1, 131.6, 131.5, 126.7, 126.6, 116.0, 115.7, 112.5, 102.7, 75.6, 28.2, 19.1, 15.3.
**HRMS (ESI-TOF):** Calc. for $C_{17}H_{19}N_2OS^+$ ([M+H]$^+$): 299.12126, found: 299.12153, Δ 0.98 ppm.
**FTIR (ATR, cm$^{-1}$):** 2961w, 2875w, 2228w, 1662w, 1605m, 1507m, 1446m, 1392m, 1280s, 1118m, 1010s, 818m, 734sm.

### Amoxapine α-phenyl acrylamide (S–27)

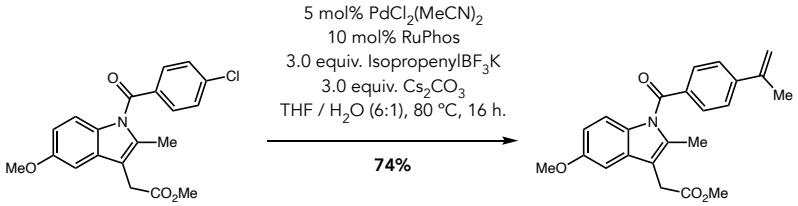



2-Phenylacrylic acid (0.69 g, 4.66 mmol, 2.0 equiv.) in anhydrous $CH_2Cl_2$ (20 mL) was treated at room temperature with thionyl chloride (1.02 mL, 13.98 mmol, 6.0 equiv.). The pale-yellow reaction solution was stirred for 2 h., then all volatiles removed *in vacuo*. The resulting yellow oil was taken up in anhydrous $CH_2Cl_2$ (20 mL) and added dropwise to a stirring solution of amoxapine (**S–26**, 0.73 g, 2.33 mmol, 1.0 equiv.) and $Et_3N$ (0.65 mL, 4.66 mmol, 2.0 equiv.) in $CH_2Cl_2$ (25 mL) at 0 °C. The resulting homogeneous brown solution was stirred at 0 °C for 15 min., then partitioned between $CH_2Cl$ (100 mL) and sat. aq. $NaHCO_3$ (30 mL). Phases were separated, the organic phase was washed with brine (30 mL) and then dried over sodium sulfate. Filtration of drying agents and evaporation of solvents gave a brown oil, which was purified by flash column chromatography on silica (10–50% EtOAc / hexanes) to afford pure amoxapine α-phenyl acrylamide **S–27** as a yellow foaming oil (0.83 g, 1.87 mmol, 80%).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.73–7.45 (2H, m), 7.31–7.41 (4H, m), 7.29 (1H, d, $^4J_{HH}$ = 2.5 Hz), 7.19 (1H, d, $^3J_{HH}$ = 8.7 Hz), 7.07–7.12 (3H, m), 6.99–7.03 (1H, m), 5.78 (1H, s), 5.42 (1H, s), 3.89 (2H, br s), 3.57 (2H, br s), 3.51 (2H, br s), 3.35 (2H, br s).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 169.7, 159.5, 158.9, 151.9, 144.8, 135.5, 133.1, 130.6, 129.1, 129.0, 129.0, 127.2, 126.0, 125.8, 125.3, 124.8, 123.0, 120.3, 114.8, 47.8, 46.6, 41.4.
**HRMS (ESI-TOF):** Calc. for $C_{26}H_{23}ClN_3O_2^+$ ([M+H]$^+$): 444.14733, found: 444.14753, Δ 0.47 ppm.

**FTIR (ATR, cm$^{-1}$):** 3057w, 2921w, 2853w, 1639s, 1601s, 1587s, 158s, 1469s, 1434m, 1402m, 1260m, 1211m, 1186m, 1102m, 1013s, 911w, 854m, 774m, 701m.

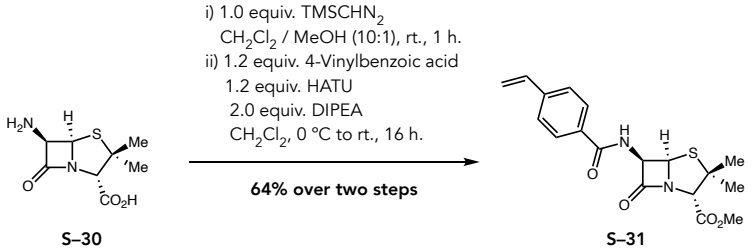
### Isopropenyl indomethacin methyl ester (S–29)




A 50 mL round bottomed flask was equipped with magnetic stir bar, indomethacin methyl ester[8] (**S–28**, 1.0 g, 2.69 mmol, 1.0 equiv.), $PdCl_2(MeCN)_2$ (34.9 mg, 0.135 mmol, 5 mol%), RuPhos (126 mg, 0.269 mmol, 10 mol%), potassium isopropenyltrifluoroborate (797 mg, 5.38, 2.0 equiv.), and cesium carbonate (2.63 g, 8.07 mmol, 3.0 equiv.). The flask was fitted with a reflux condenser and septum and placed under a nitrogen atmosphere. THF (12 mL) and water (degassed, 2 mL) were added, and the mixture was heated to reflux with stirring for 16 h. the mixture was cooled and passed through a plug of silica, rinsing with ethyl acetate. Evaporation of solvents gave a brown oil, which was purified by flash column chromatography on silica (2 – 20% EtOAc / Hexanes) to afford pure isopropenyl indomethacin methyl ester (**S–29**) as a viscous yellow oil (749 mg, 1.98 mmol, 74%).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.69 (2H, d, $^3J_{HH}$ = 8.5 Hz), 7.57 (1H, d, $^3J_{HH}$ = 8.5 Hz), 6.96 (1H, d, $^4J_{HH}$ = 2.5 Hz), 6.92 (1H, d, $^3J_{HH}$ = 9.0 Hz), 6.66 (1H, dd, $^3J_{HH}$ = 9.0 Hz, $^4J_{HH}$ = 2.5 Hz), 5.53 (1H, s), 5.24 (1H, t, $^4J_{HH}$ = 1.4 Hz), 3.84 (3H, s), 3.71 (3H, s), 3.68 (2H, s), 2.39 (3H, s, 2.20 (3H, s).
**$^{13}$C-NMR (125 MHz, $CDCl_3$):** 171.6, 169.3, 156.0, 145.8, 142.3, 136.2, 134.3, 131.1, 130.7, 130.1, 125.9, 115.1, 112.2, 111.6, 101.3, 55.9, 52.3, 30.3, 21.8, 13.5.
**HRMS (ESI-TOF):** Calc. for $C_{23}H_{23}NO_4Na^+$ ([M+Na]$^+$): 400.15193, found: 400.15199, Δ 0.37 ppm.
**FTIR (ATR, cm$^{-1}$):** 2950w, 1736m, 1678s, 1605m, 1477m, 1456m, 1355m, 1312s, 1263m, 1224s, 1166m, 1068m, 1036m, 854w.

### *N*-(4-Vinylbenzamido)Penicillin methyl ester (S–31)

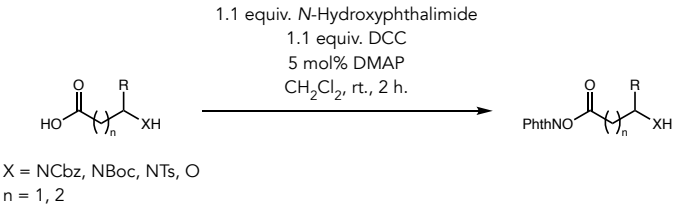



In a 250 mL round-bottomed flask open to air, 6-aminopenacillanic acid (6-APA, **S–30**, 1.30 g, 6.0 mmol, 1.0 equiv.) in $CH_2Cl_2$ (50 mL) and MeOH (5 mL) was treated with $TMSCHN_2$ (3.0 mL of a 2.0 M solution in hexanes, 6.0 mmol, 1.0 equiv.) at room temperature. The yellow solution was stirred for 1 h., as the yellow coloration faded to a colorless solution with evolution of gas. All volatiles were removed *in vacuo*, and the resulting off-white solid was redissolved in $CH_2Cl_2$ (100 mL) and cooled to 0 °C. The homogeneous solution was treated with 4-vinylbenzoic acid (1.07 g, 7.2 mmol, 1.2 equiv.), DIPEA (2.09 mL, 12.0 mmol, 2.0 equiv.), and HATU (2.74 g, 7.2 mmol, 1.2 equiv.). The yellow solution was allowed to warm to room temperature and stir for a total of 16 h. Then, the mixture was diluted with further $CH_2Cl_2$ (200 mL) and washed with sat. aq. $NH_4Cl$ solution (100 mL), sat. aq. $NaHCO_3$ solution (100 mL) and brine (50 mL), and dried over sodium sulfate. Filtration of drying agents and evaporation of solvents gave an orange oil, which was purified by flash column chromatography on silica (5 – 40% EtOAc / hexanes) to afford pure penicillin 4-vinylbenzamide methyl ester **S–31** as an off-white foam (1.39 g, 3.86 mmol, 64% over two steps).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.75 (2H, d, $^3J_{HH}$ = 8.3 Hz), 7.48 (2H, d, $^3J_{HH}$ = 8.3 Hz), 6.71-6.80 (2H, m), 5.91 (1H, dd, $^3J_{HH}$ = 8.9, 4.2 Hz), 5.84 (1H, d, $^2J_{HH}$ = 17.7 Hz), 5.64 (1H, d, $^3J_{HH}$ = 4.2 Hz), 5.38 (1H, d, $^3J_{HH}$ = 10.9 Hz), 4.48 (1H, s), 3.79 (3H, s), 1.69 (3H, s), 1.52 (3H, s).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 174.1, 168.3, 166.3, 141.6, 135.9, 132.1, 127.7, 126.6, 116.6, 70.8, 68.3, 65.0, 59.0, 52.6, 31.5, 27.3.
**HRMS (ESI-TOF):** Calc. for $C_{18}H_{20}N_2O_4SNa^+$ ([M+Na]$^+$): 383.10360, found: 383.10324, Δ 0.89 ppm.
**FTIR (ATR, cm$^{-1}$):** 3342br w, 2956w, 2927w, 1783m, 1741s, 1651s, 1527m, 1498m, 1272m, 1211s, 855w, 735m.

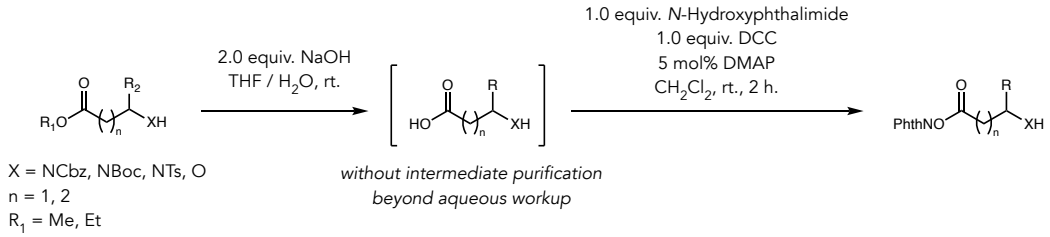
## 6.3. General procedures for the preparation of NHPI ester and ether annulation reagents

### General Procedure C – Preparation of NHPI ester reagents from isolated carboxylic acid precursors.




Carboxylic acid substrate (1.0 equiv.) was dissolved in $CH_2Cl_2$ (0.2 M) at room temperature. This was treated sequentially with *N*-hydroxyphthalimide (1.1 equiv.), DMAP (5 mol%), and DCC (1.1 equiv.), each added as solids in one portion. The thick white-to-orange mixture was stirred at room temperature for 2 h. The heterogeneous mixture was then diluted with EtOAc (1 volume wrt. $CH_2Cl_2$), and the mixture filtered through a 1 inch x 3 inch ⌀ plug of silica. This plug was rinsed with further EtOAc (4 volumes). Combined organic solvents were removed *in vacuo*, and the crude reaction product triturated with solvent as indicated for each entry below. The solids (residual DCU) were filtered, and the filtrate evaporated *in vacuo.* This trituration step was repeated if residual DCU was still observed after evaporation. The product NHPI ester reagent was then purified as indicated for each entry below.

### General Procedure D – Preparation of NHPI ester reagents *via* two-step telescoped transesterification.



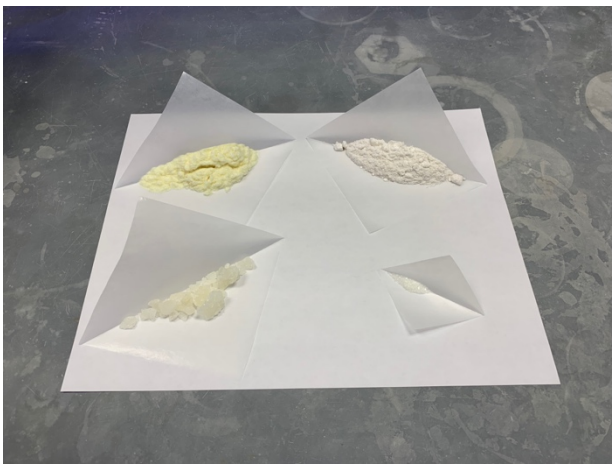

To a stirring solution of ester substrate (1.0 equiv.) in THF (0.5 M) was added dropwise at room temperature over 5 min. a 1.0 M aq. sodium hydroxide solution (2.0 equiv.). The solution was stirred at room temperature for the indicated time until full conversion of ester substrate was observed *via* TLC. The reaction mixture was poured into diethyl ether (100 mL). Phases were separated, and the organic phase extracted with water (20 mL). The combined aqueous phase was acidified with 1.0 M aq. HCl solution (2.2 equiv.). The aqueous phase was extracted with ethyl acetate (3 x 100 mL). Combined organic phases were washed with brine (50 mL) and dried over sodium sulfate. Filtration of drying agent and evaporation of all volatiles yielded crude carboxylic acid, which was used directly and immediately in the next step without further purification.

Crude carboxylic acid substrate as prepared above was dissolved in $CH_2Cl_2$ (0.2 M) at room temperature. This was treated sequentially with *N*-hydroxyphthalimide (1.0 equiv.), DMAP (5 mol%), and DCC (1.0 equiv.), each added as solids in one portion. The thick mixture was stirred at room temperature for 2 h. The heterogeneous mixture was then diluted with EtOAc (1 volume wrt. $CH_2Cl_2$), and the mixture filtered through a 1 inch think plug of silica. This plug was rinsed with further EtOAc (3 volumes). Combined organic solvents were removed *in vacuo*, and the crude reaction product triturated with solvent as indicated for each entry below. The solids (residual DCU) were filtered, and the filtrate evaporated *in vacuo.* This trituration step was repeated if residual DCU was still observed after evaporation. The product NHPI ester was then purified as indicated for each entry below.

## 6.4. Step-by-step photographic guide to the preparation of parent *N*-Cbz pyrrolidine [3+2] reagent (1)

Reagent appearance (Clockwise from top left):

*N*-Hydroxyphthalimide, 3.59 g, 22.0 mmol, 1.1 equiv.
Cbz-**β**-Ala-OH, 4.46 g, 20.0 mmol, 1.0 equiv.
DMAP, 122 mg, 1.0 mmol, 5 mol%
DCC, 4.54 g, 22.0 mmol, 1.1 equiv.

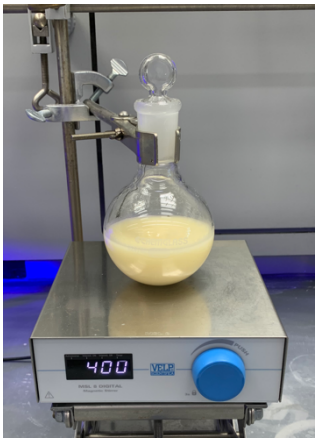


**1.** A 250 mL round bottomed flask is equipped with stir bar, to which is added *N*-Hydroxyphthalimide, Cbz-**β**-Ala-OH, and DMAP as solids, followed by $CH_2Cl_2$ (100 mL). Then, with stirring, DCC is added as a solid in one portion. Order of addition of the first three reagents is unimportant, but DCC should be the last addition. Small additional volumes of $CH_2Cl_2$ (up to ca. 10 mL) can be used to rinse the inner walls of the flask to bring reagents into solution if required. There is no requirement to use anhydrous solvent, and reaction is run under air. Appearance of reaction at time points prior to (t = 0 min.) and following addition of DCC:

At t = 0 min.

At t = 1 min.

At t = 10 min

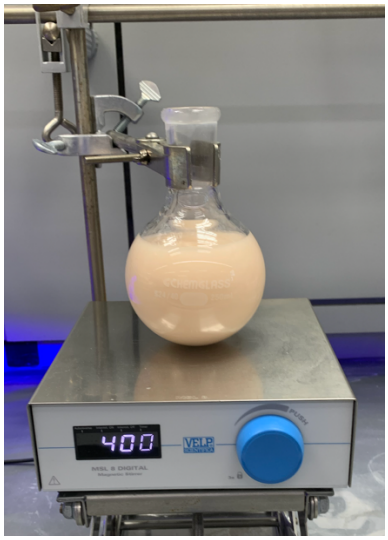


At t = 0.5 h.

At t = 1 h.

At t = 2 h.

**2.** After stirring for 2 h., the reaction mixture is diluted with EtOAc (100 mL):



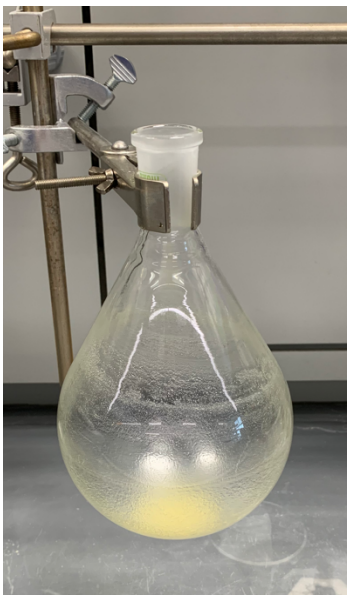

**3.** A silica gel filter plug is prepared by slurrying silica in EtOAc and pouring into a *ca.* 3 inch ⌀ sintered funnel with a medium porosity frit to a height of approx. 1 inch. Excess solvent is removed by applying vacuum to flask, then a layer of sand is added on top of silica:


**4.** While applying vacuum to the flask, the reaction mixture is poured through the silica filter plug. The plug is not allowed to go dry at any stage of the transfer. Small volumes of EtOAc (*ca.* 30 mL) are used to rinse the flask and assist transfer of total contents onto the filter. Appearance after filtration of reaction mixture:

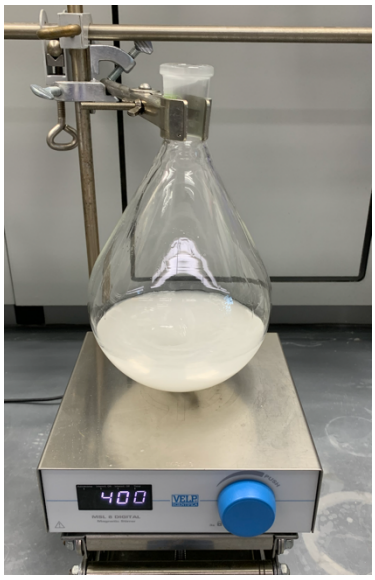
**5.** While applying vacuum to the flask, the filter plug and collected solids (DCU) are rinsed with EtOAc (400 mL). During the rinsing process, the filter plug is not allowed to go dry. Appearance after rinsing:

**6.** Finally, full removal of solvent by applying continued vacuum:

**7.** Solvents are removed *in vacuo*, bath temp 30-35 °C.
Crude product after removal of solvents:

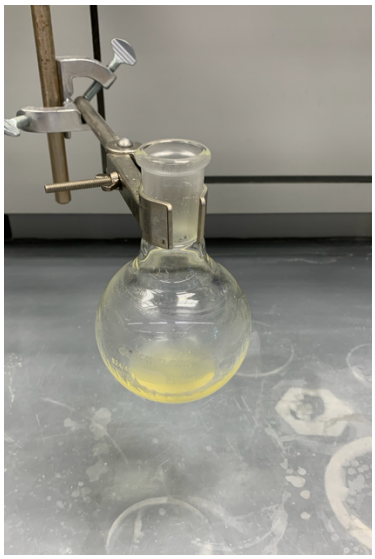


**8.** Trituration of crude product with 3:1 mixture of $Et_2O$ / EtOAc (200 mL):




**9.** Filtration of solids (DCU) through a medium porosity sintered funnel:


**10.** Removal of solvents:

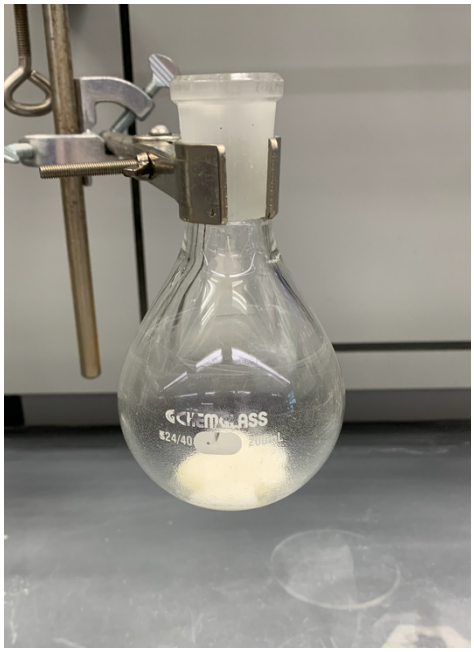


**11.** Second trituration of product with 3:1 mixture of $Et_2O$ / EtOAc (100 mL):


**12.** Filtration of precipitated solids:

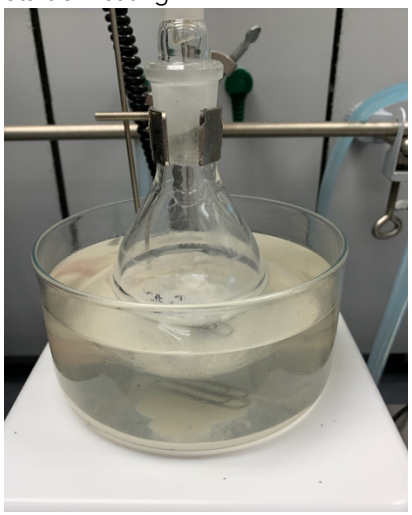
**13.** Appearance immediately after removal of solvents:

Appearance after standing for ca. 1 h.:



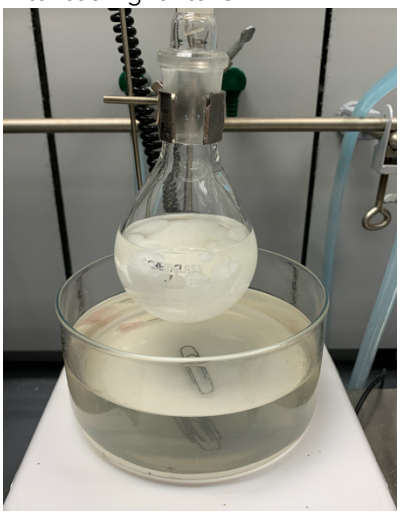
**14.** Recrystallization is carried out by suspending crude reaction product in a mixture of hexane (100 mL) and EtOAc (20 mL). Flask is equipped with a reflux condenser and brought to reflux under air. Then, EtOAc is added in 10 mL portions down the condenser until a fully homogeneous solution forms. Total time under reflux ca. 5–8 min., total solvent volumes required: hexanes (100 mL), EtOAc (50 mL). Then, heating bath is lowered, and the flask allowed to cool without stirring. Product begins to precipitate typically within 1–2 hours:

Start of heating:



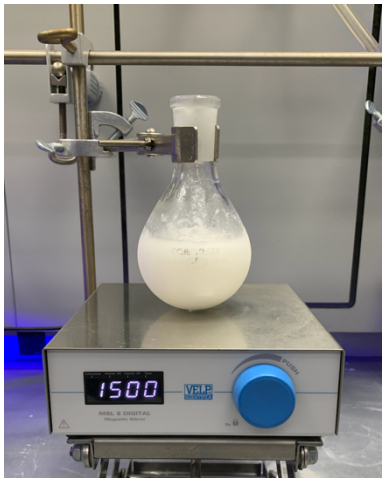
After full dissolution:

After cooling for ca. 3 h.:



**15.** After cooling to room temperature and standing under product precipitation is observed and appears to be complete, flask is stoppered and placed into a -20°C freezer overnight. Appearance after cooling:

**16.** Whilst the flask is still cold, the mixture is stirred vigorously for *ca.* 2–3 min. to break up the solid mass:

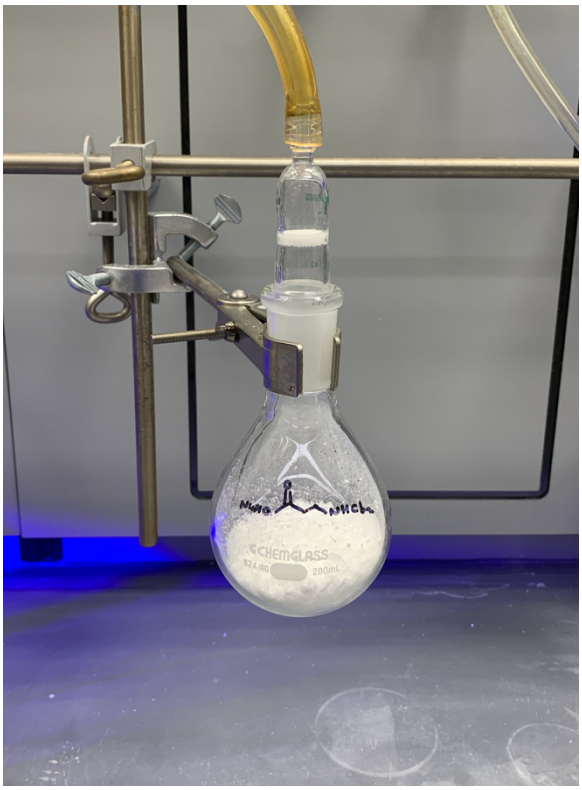



**17.** Precipitated solids (NHPI reagent) are collected via filtration through a medium porosity sintered funnel by applying vacuum to the collection flask. Small volumes of hexane (*ca.* 20 mL) are used to assist in rinsing of the flask after removal of solvents from collected solids, to ensure complete transfer of all material into sintered funnel:

**18.** The vacuum is disconnected, and the collected solids are stirred for *ca.* 3 min. in the sintered funnel with hexanes (100 mL):

**19.** Rinsings are removed by applying vacuum, and air is pulled through the sintered funnel for *ca.* 15 min.:

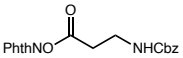
**20.** Solids are transferred to a tared flask and dried fully under high vacuum (<0.1 torr) at room temperature overnight to constant weight. Product NHPI ester **1** collected as a white solid (6.59 g, 17.9 mmol, 89%). In our experience, attempting to recover a second crop through removal of solvents and repeated recrystallization of the residue provides only minimal additional product recovery, of lower quality. When this procedure is carried out on >20 mmol scale, we found that a third trituration step was necessary to fully remove DCU prior to recrystallization.



## 6.5. Characterization of NHPI ester and ether annulation reagents

### 6.5.1. Pyrrolidine reagents

#### Parent *N*-Cbz pyrrolidine [3+2] reagent (1)

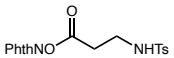



**1**

Prepared according to general procedure **C** from Cbz-β-alanine (4.46 g, 20.0 mmol, 1.0 equiv.). Trituration of crude esterification product was carried out using $Et_2O$ / EtOAc (3:1). Purification was achieved *via* recrystallization from EtOAc / hexanes. NHPI ester **1** was isolated as a white solid (6.59 g, 17.9 mmol, 89%).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.88-7.91 (2H, m), 7.79-7.82 (2H, m), 7.29-7.38 (5H, m), 5.40 (1H, br t, $^3J_{HH}$ = 6.3 Hz), 5.13 (2H, s), 3.65 (2H, app q, $^3J_{HH}$ = 6.3 Hz), 2.93 (2H, t, $^3J_{HH}$ = 6.0 Hz).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 168.6, 162.0, 156.4, 136.5, 135.1, 129.0, 128.7, 128.3, 128.2, 124.2, 67.1, 36.8, 32.2.
**HRMS (ESI-TOF):** Calc. for $C_{19}H_{16}N_2O_6Na^+$ ([M+Na]$^+$): 391.09006, found: 391.09012, Δ 0.11 ppm.
**FTIR (ATR, cm$^{-1}$):** 3392br w, 2949w, 1787m, 1738s, 1521m, 1363m, 1246m, 1186m, 1136m, 1081m, 1064m, 877m, 695s, 518w.

#### Parent *N*-Ts pyrrolidine [3+2] reagent (S–32)

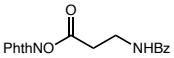



**S–32**

Prepared according to general procedure **C** from Ts-β-alanine (2.43 g, 10.0 mmol, 1.0 equiv.). Trituration of crude esterification product was carried out using EtOAc. Purification was achieved *via* flash column chromatography on silica (10–50% EtOAc / hexanes). NHPI ester **S–32** was isolated as a white solid (2.42 g, 6.23 mmol, 62%).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.89–7.91 (2H, m), 7.80–7.82 (2H, m), 7.77 (2H, d, $^3J_{HH}$ = 8.2 Hz), 7.33 (2H, d, $^3J_{HH}$ = 8.2 Hz), 3.40 (2H, app q, $^3J_{HH}$ = 6.3 Hz), 2.86 (2H, t, $^3J_{HH}$ = 6.3 Hz), 2.43 (3H, s).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 168.2, 161.9, 143.9, 137.1, 135.1, 130.1, 128.9, 127.2, 124.3, 38.8, 32.2, 21.7.
**HRMS (ESI-TOF):** Calc. for $C_{18}H_{16}N_2O_6SNa^+$ ([M+Na]$^+$): 411.06213, found: 411.06225, Δ 0.35 ppm.
**FTIR (ATR, cm$^{-1}$):** 3293br w, 1815w, 1787w, 1740s, 1329w, 1158m, 1082w, 697m.

#### Parent *N*-Bz pyrrolidine [3+2] reagent (S–33)

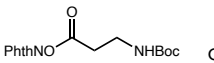



**S–33**

Prepared according to general procedure **C** from Bz-β-alanine (3.86 g, 20.0 mmol, 1.0 equiv.). Trituration of crude esterification product was carried out using EtOAc. Purification was achieved *via* recrystallization from EtOAc / hexanes. NHPI ester **S–33** was isolated as a white solid (5.91 g, 17.5 mmol, 87%). A trace contaminant of DCU was present in this sample but did not affect viability in the annulation reaction.

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.89–7.92 (2H, m), 7.80–7.85 (4H, m), 7.50 (1H, t, $^3J_{HH}$ = 7.4 Hz), 7.44 (2H, t, $^3J_{HH}$ = 7.4 Hz), 6.96 (1H, br s), 3.93 (2H, app q, $^3J_{HH}$ = 5.9 Hz), 3.02 (2H, t, $^3J_{HH}$ = 5.9 Hz).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 168.9, 167.8, 162.1, 135.1, 134.1, 131.8, 128.9, 128.7, 127.2, 124.3, 35.8, 32.2.
**HRMS (ESI-TOF):** Calc. for $C_{18}H_{14}N_2O_5Na^+$ ([M+Na]$^+$): 361.07949, found: 361.07975, Δ 0.66 ppm.
**FTIR (ATR, cm$^{-1}$):** 3339w br, 2979w, 1788m, 1742s, 1646m, 1535m, 1370w, 1081w, 696m.

#### Parent *N*-Boc pyrrolidine [3+2] reagent (S–34)



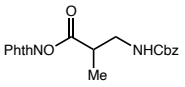

**S–34**

Prepared according to general procedure **C** from Boc-β-alanine (3.78 g, 20.0 mmol, 1.0 equiv.). Trituration of crude esterification product was carried out using $Et_2O$ / EtOAc (1:1). Purification was achieved *via* recrystallization from EtOAc / hexanes. NHPI ester **S–34** was isolated as a white solid (4.87 g, 14.6 mmol, 72%).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.89–7.91 (2H, m), 7.80–7.81 (2H, m), 5.13 (1H, br t, $^3J_{HH}$ = 5.9 Hz), 3.56 (2H, app q, $^3J_{HH}$ = 6.0 Hz), 2.91 (2H, app t, $^3J_{HH}$ = 5.9 Hz), 1.45 (9H, s).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 168.8, 162.0, 155.9, 135.0, 129.0, 124.2, 80.0, 36.3, 32.3, 28.5.
**HRMS (ESI-TOF):** Calc. for $C_{16}H_{18}N_2O_6Na^+$ ([M+Na]$^+$): 357.10571, found: 357.10614, Δ 1.01 ppm.

**FTIR (ATR, cm$^{-1}$):** 3388w br, 2978w, 1788m, 1742s, 1711m, 1512m, 1366m, 1251w, 1168m, 1082m, 970m, 878m, 697m.

### α-Methyl *N*-Cbz pyrrolidine [3+2] reagent (S–35)

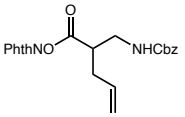


S–35

Prepared according to general procedure **C** from corresponding carboxylic acid[12] (2.78 g, 11.70 mmol, 1.0 equiv.). Trituration of crude esterification product was carried out with EtOAc. Purification was achieved *via* recrystallization from EtOAc / hexanes. NHPI ester **S–35** was isolated as a white solid (3.06 g, 8.00 mmol, 68%).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.89–7.90 (2H, m), 7.80–7.81 (2H, m), 7.28–7.38 (5H, m), 5.58 (1H, br t, $^3J_{HH}$ = 6.0 Hz), 5.14 (2H, s), 3.67 (1H, ddd, $^2J_{HH}$ = 14.4 Hz, $^3J_{HH}$ = 7.0, 4.6 Hz), 3.42 (1H, ddd, $^2J_{HH}$ = 14.4 Hz, $^3J_{HH}$ = 7.6, 6.3 Hz), 3.14 (1H, td, $^3J_{HH}$ = 7.0, 4.6 Hz), 1.37 (3H, d, $^3J_{HH}$ = 7.2 Hz).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 171.6, 162.1, 156.8, 136.7, 135.0, 129.0, 128.6, 128.2, 128.1, 124.3, 67.0, 44.0, 38.5, 14.3.
**HRMS (ESI-TOF):** Calc. for $C_{20}H_{18}N_2O_6Na^+$ ([M+Na]$^+$): 405.10571, found: 405.10598, Δ 0.48 ppm.
**FTIR (ATR, cm$^{-1}$):** 3395br w, 2941w, 1785m, 1738s, 1521m, 1467m, 1455m, 1370m, 1237m, 1186m, 1137m, 1044m, 696s.

### α-Allyl *N*-Cbz pyrrolidine [3+2] reagent (S–36)

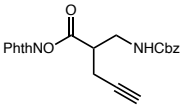


S–36

Prepared according to general procedure **D** from corresponding methyl ester (**S–2**, 4.52 g, 16.3 mmol, 1.0 equiv.). Saponification was complete in 2 h. Trituration of crude esterification product was carried out with $CH_2Cl_2$ / EtOAc (1:1). Purification was achieved *via* recrystallization from EtOAc / Hexanes. NHPI ester **S–36** was isolated as a white solid (6.18 g, 15.1 mmol, 93% over two steps). A trace contaminant of DCU was present in this sample but did not affect viability in the annulation reaction.

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.87–7.90 (2H, m), 7.79–7.82 (2H, m), 7.28–7.38 (5H, m), 5.83–5.91 (1H, m), 5.59 (1H, t, $^3J_{HH}$ = 6.4 Hz), 5.11–5.25 (4H, m), 3.70–3.75 (1H, m), 3.39–3.45 (1H, m), 3.11–3.16 (1H, m), 2.54–2.60 (1H, m), 2.41–2.47 (1H, m).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 170.8, 162.4, 156.9, 136.9, 135.3, 133.5, 129.2, 128.9, 128.4, 128.4, 124.7, 124.5, 119.1, 67.2, 44.1, 42.6, 33.6.
**HRMS (ESI-TOF):** Calc. for $C_{22}H_{20}N_2O_6Na^+$ ([M+Na]$^+$): 431.12136, found: 431.12119, Δ 0.48 ppm.
**FTIR (ATR, cm$^{-1}$):** 3397br w, 2932w, 1785w, 1742s, 1523m, 1371w, 1252w, 696m.

### α-Propargyl *N*-Cbz pyrrolidine [3+2] reagent (S–37)

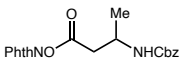


S–37

Prepared according to a modification of general procedure **D** from corresponding methyl ester (**S–3**, 3.38 g, 12.3 mmol, 1.0 equiv.) involving addition of EtOH (1.0 mL) to reaction mixture of THF (25 mL) and 1.0 M aq. NaOH solution (25 mL). Saponification was complete in 2 h. Trituration of crude esterification product was carried out with $CH_2Cl_2$ / EtOAc (1:1) then a second trituration with EtOAc. Purification was achieved *via* recrystallization from EtOAc / Hexanes. NHPI ester **S–37** was isolated as a white solid (3.75 g, 9.23 mmol, 75% over two steps).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.89–7.91 (2H, m), 7.80–7.82 (2H, m), 7.28–7.38 (5H, m), 5.60 (1H, br t, $^3J_{HH}$ = 6.5 Hz), 5.15 (2H, s), 3.80–3.86 (1H, m), 3.61–3.66 (1H, m), 3.27–3.30 (1H, m), 2.73 (1H, ddd, $^2J_{HH}$ = 17.2 Hz, $^3J_{HH}$ = 6.3 Hz, $^4J_{HH}$ = 2.2 Hz), 2.64 (1H, ddd, $^2J_{HH}$ = 17.2 Hz, $^3J_{HH}$ = 7.3 Hz, $^4J_{HH}$ = 2.0 Hz), 2.14 (1H, s).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 169.5, 156.7, 136.6, 135.1, 128.9, 128.6, 128.2, 128.2, 124.3, 79.2, 71.6, 67.1, 43.0, 41.9, 18.8.
**HRMS (ESI-TOF):** Calc. for $C_{22}H_{18}N_2O_6Na^+$ ([M+Na]$^+$): 429.10571, found: 429.10608, Δ 0.65 ppm.
**FTIR (ATR, cm$^{-1}$):** 3291br w, 2929w, 1786m, 1742s, 1523m, 1254m, 878m, 696m.

### β-Me *N*-Cbz pyrrolidine [3+2] reagent (S–38)



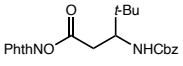
S–38

Prepared according to general procedure **C** from corresponding carboxylic acid[13] (2.89 g, 12.2 mmol, 1.0 equiv.). Trituration of crude esterification product was carried out with EtOAc. Purification was achieved

*via* recrystallization from EtOAc / hexanes. NHPI ester **S–38** was isolated as a white solid (4.18 g, 10.9 mmol, 90%).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.87–7.89 (2H, m), 7.78–7.80 (2H, m), 7.29–7.37 (5H, m), 5.23 (1H, d, $^3J_{HH}$ = 7.3 Hz), 5.08–5.15 (2H, m), 4.24–4.28 (1H, m), 2.89–2.94 (2H, m), 1.37 (3H, d, $^3J_{HH}$ = 6.8 Hz).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 167.4, 162.0, 155.6, 136.5, 135.0, 129.0, 128.6, 128.2, 128.2, 124.2, 66.9, 44.1, 37.6, 19.8.
**HRMS (ESI-TOF):** Calc. for $C_{20}H_{18}N_2O_6Na^+$ ([M+Na]$^+$): 405.10571, found: 405.10631, Δ 1.43 ppm.
**FTIR (ATR, cm$^{-1}$):** 3331 br w, 2977w, 1787m, 1740s, 1522m, 1371w, 1292w, 1059m, 972w, 878w, 696m.

### β-$^t$Bu *N*-Cbz pyrrolidine [3+2] reagent (S–39)

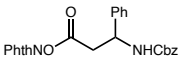


**S–39**

Prepared according to general procedure **C** from corresponding carboxylic acid[14] (1.30 g, 4.66 mmol, 1.0 equiv.). Trituration of crude esterification product was carried out with EtOAc. Purification was achieved *via* recrystallization from EtOAc / $Et_2O$. NHPI ester **S–39** was isolated as a white solid (1.28 g, 3.02 mmol, 65%).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.87–7.89 (2H, m), 7.78–7.80 (2H, m), 7.29–7.40 (5H, m), 5.13–5.18 (2H, m), 4.97 (1H, d, $^3J_{HH}$ = 10.5 Hz), 4.16 (1H, td, $^3J_{HH}$ = 10.1, 4.3 Hz), 2.97 (1H, dd, $^2J_{HH}$ = 15.8 Hz, $^3J_{HH}$ = 4.3 Hz), 2.71 (1H, dd, $^2J_{HH}$ = 15.8 Hz, $^3J_{HH}$ = 9.7 Hz), 0.99 (9H, s).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 168.0, 161.8, 156.2, 136.7, 134.9, 129.1, 128.6, 128.4, 128.2, 124.1, 67.1, 56.3, 35.3, 33.0, 26.3.
**HRMS (ESI-TOF):** Calc. for $C_{23}H_{24}N_2O_6Na^+$ ([M+Na]$^+$): 447.15266, found: 447.15294, Δ 0.47 ppm.
**FTIR (ATR, cm$^{-1}$):** 3333br w, 2964w, 1789m, 1743s, 1532m, 1370m, 1239m, 1057m, 878m, 696m.

### β-Ph *N*-Cbz pyrrolidine [3+2] reagent (S–40)

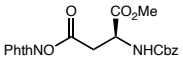


**S–40**

Prepared according to general procedure **C** from corresponding carboxylic acid[15] (2.82 g, 9.42 mmol, 1.0 equiv.). Trituration of crude esterification product was carried out with EtOAc. Purification was achieved *via* recrystallization from EtOAc / hexanes. NHPI ester **S–40** was isolated as a white solid (3.85 g, 8.67 mmol, 92%).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.85–7.87 (2H, m), 7.77–7.78 (2H, m), 7.30–7.40 (10H, m), 5.65 (1H, br s), 5.33–5.37 (1H, m), 5.12–5.17 (2H, m), 3.21–3.34 (2H, m).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 167.0, 161.7, 155.7, 139.4, 136.4, 134.9, 129.1, 128.9, 128.6, 128.3, 128.3, 126.4, 124.2, 67.2, 51.6, 37.6.
**HRMS (ESI-TOF):** Calc. for $C_{25}H_{20}N_2O_6Na^+$ ([M+Na]$^+$): 467.12136, found: 467.12189, Δ 0.73 ppm.
**FTIR (ATR, cm$^{-1}$):** 3325 br w, 3033w, 1788m, 1743s, 1527m, 1371m, 1076m, 696m.

### (*S*)-β-$CO_2$Me *N*-Cbz pyrrolidine [3+2] reagent (S–41)

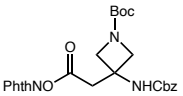


**S–41**

Prepared according to general procedure **C** from Z-Asp-OMe (2.81 g, 10.0 mmol, 1.0 equiv.). Trituration of crude esterification product was carried out with EtOAc. Purification was achieved *via* recrystallization from EtOAc / hexanes. NHPI ester **S–41** was isolated as a white solid (3.78 g, 8.87 mmol, 89%).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.86–7.89 (2H, m), 7.30–7.39 (5H, m), 5.83 (1H, d, $^3J_{HH}$ = 7.9 Hz), 5.13–5.16 (2H, m), 4.78–4.82 (1H, m), 3.81 (3H, s), 3.38 (1H, dd, $^2J_{HH}$ = 16.9 Hz, $^3J_{HH}$ = 4.6 Hz), 3.27 (1H, dd, $^2J_{HH}$ = 16.9 Hz, $^3J_{HH}$ = 4.8 Hz).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 170.1, 167.3, 161.7, 155.9, 136.1, 135.0, 128.9, 128.7, 128.3, 128.2, 124.2, 67.5, 53.3, 50.4, 34.3.
**HRMS (ESI-TOF):** Calc. for $C_{21}H_{18}N_3O_8Na^+$ ([M+Na]$^+$): 449.09554, found: 449.09577, Δ 0.42 ppm.
**FTIR (ATR, cm$^{-1}$):** 3372 br w, 2954w, 1789w, 1744s, 1521w, 1218w, 1083w, 697w.

**β-Spiro *N*-Cbz pyrrolidine / *N*-Boc azetidine reagent (S–42)**

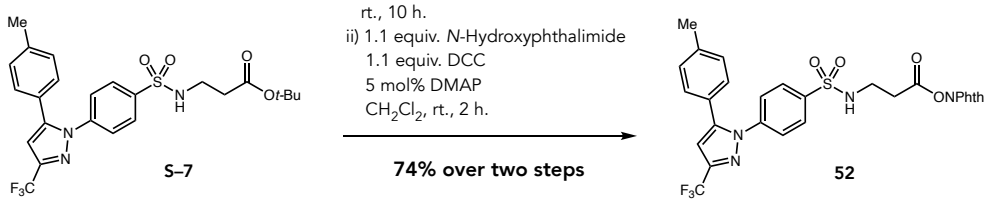


S–42

Prepared according to general procedure **D** from corresponding ethyl ester (**S–5**, 7.84 g, 19.97 mmol, 1.0 equiv.). Saponification was complete in 2 h. Trituration of crude esterification product was carried out with $CH_2Cl_2$ / EtOAc (1:1). Purification was achieved *via* recrystallization from EtOAc / Hexanes (*ca.* 4:1). NHPI ester **S–42** was isolated as a white solid (7.57 g, 14.9 mmol, 74%).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.87–7.91 (2H, m), 7.79-7.83 (2H, m), 7.29–7.35 (5H, m), 5.68 (1H, br s), 5.12 (2H, s), 4.05 (4H, s), 3.39 (2H, s), 1.44 (9H, s).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 166.8, 161.9, 156.2, 154.9, 136.2, 135.1, 128.9, 128.7, 128.3, 128.1, 124.3, 80.3, 67.1, 59.6, 49.7, 38.2, 28.5.
**HRMS (ESI-TOF):** Calc. for $C_{26}H_{27}N_3O_8Na^+$ ([M+Na]$^+$): 532.16904, found: 532.16877, Δ 0.98 ppm.
**FTIR (ATR, cm$^{-1}$):** 3315 br w, 2976w, 1744s, 1701m, 1406m, 1367m, 1261m, 1159m, 1063m, 696m.

**Celecoxib β-alanine NHPI reagent (52)**

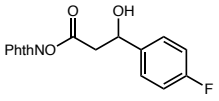



*Tert*-butyl ester **S–7** (2.54 g, 5.0 mmol, 1.0 equiv.) was dissolved in $CH_2Cl_2$ (50 mL) and treated dropwise at room temperature with TFA (5.0 mL). The homogeneous pale-yellow solution was stirred at room temperature for 10 h., after which time TLC indicated full substrate conversion. The reaction mixture was diluted with toluene (50 mL), and all volatiles were removed *in vacuo*. The residue was taken up in toluene (50 mL) and volatiles once again removed *in vacuo*. This evaporation process was repeated for a total of three times. Then, the residual yellow oil was taken up in $CH_2Cl_2$ (50 mL) and treated sequentially with *N*-hydroxyphthalimide (897 mg, 5.5 mmol, 1.1 equiv.), DMAP (31.0 mg, 0.25 mmol, 5 mol%), and DCC (1.14 g, 5.5 mmol, 1.1 equiv.), each added as a solid on one portion. The heterogeneous reaction mixture was stirred at room temperature for 2 h., then diluted with EtOAc (50 mL). The mixture was filtered through a 1 inch x 3 inch ⌀ plug of silica, which was then rinsed with EtOAc (200 mL). Combined filtrate and rinsings were evaporated *in vacuo*. The residue was triturated with $Et_2O$ (100 mL), filtered to remove precipitated solids (DCU), and filtrate evaporated *in vacuo*. Purification of the resulting viscous oil was achieved via flash column chromatography on silica (10 – 50% EtOAc / hexanes) to afford pure celecoxib β-alanine NHPI ester reagent **52** (2.25 g, 3.76 mmol, 74% over two steps) as a colorless foaming oil.

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.87–7.90 (4H, m), 7.80–7.82 (2H, m), 7.49 (2H, d, $^3J_{HH}$ = 8.6 Hz), 7.17 (2H, d, $^3J_{HH}$ = 8.0 Hz), 7.11 (2H, d, $^3J_{HH}$ = 8.0 Hz), 6.73 (1H, s), 5.45 (1H, t, $^3J_{HH}$ = 6.5 Hz), 3.44 (2H, app q, $^3J_{HH}$ = 6.3 Hz), 2.87 (2H, t, $^3J_{HH}$ = 6.3 Hz), 2.36 (3H, s).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 168.0, 161.9, 145.4, 144.2 (q, $^2J_{CF}$ = 38.5 Hz), 142.8, 139.9, 139.7, 135.2, 129.9, 128.9, 128.8, 128.2, 125.8, 124.4, 121.2 (q, $^1J_{CF}$ = 268.6 Hz), 106.4, 38.9, 32.3, 21.5.
**$^{19}$F-NMR (δ, 376 MHz, $CDCl_3$):** -62.5.
**HRMS (ESI-TOF):** Calc. for $C_{28}H_{22}F_3N_4O_6S^+$ ([M+H]$^+$): 599.12067, found: 599.11976, Δ 0.93 ppm.
**FTIR (ATR, cm$^{-1}$):** 3297br w, 2962w, 1816w, 1743s, 1471m, 1237m, 1160s, 1132m, 1096m, 975m, 806m, 697m.

### 6.5.2. Tetrahydrofuran reagents

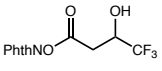
#### β-4-F-Ph tetrahydrofuran [3+2] reagent (S–43)


S–43

Prepared according to general procedure **C** from corresponding carboxylic acid[16] (3.61 g, 19.6 mmol, 1.0 equiv.). Trituration of crude esterification product was carried out with EtOAc. A second trituration was then carried out with $Et_2O$. Purification was achieved *via* trituration from a mixture of $Et_2O$ (40 mL), $CH_2Cl_2$ (10 mL), and hexanes (50 mL). NHPI ester **S–43** was isolated as a white solid (4.95 g, 15.0 mmol, 77%).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.89–7.91 (2H, m), 7.80–7.82 (2H, m), 7.41–7.44 (2H, m), 7.08 (2H, t, $^3J_{HH}$ = 8.4 Hz), 5.29 (1H, br d, $^3J_{HH}$ = 8.0 Hz), 3.00–3.13 (3H, m).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 167.9, 163.7, 162.0, 161.7, 137.6 (d, $^3J_{CF}$ = 3.2 Hz), 135.1, 128.9, 127.6 (d, $^2J_{CF}$ = 8.3 Hz), 124.3, 115.8 (d, $^1J_{CF}$ = 21.4 Hz), 69.8, 41.4.
**$^{19}$F-NMR (δ, 376 MHz, $CDCl_3$):** -113.9.
**HRMS (ESI-TOF):** Calc. for $C_{17}H_{12}FNO_5Na^+$ ([M+Na]$^+$): 352.05917, found: 352.05990, Δ 2.90 ppm.
**FTIR (ATR, cm$^{-1}$):** 3517br w, 2980w, 1787m, 1741s, 1510m, 1081m, 697m.

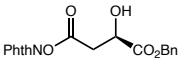
#### β-$CF_3$ tetrahydrofuran [3+2] reagent (S–44)


S–44

Prepared according to general procedure **C** from the freshly-prepared corresponding carboxylic acid[17] (3.16 g, 20.0 mmol, 1.0 equiv.). Trituration of crude esterification product was carried out with EtOAc. Purification was achieved *via* flash column chromatography on silica (5–50% EtOAc / hexanes), followed by trituration of the material collected from combined product-containing fractions (5% $Et_2O$ / hexanes). NHPI ester **S–44** was isolated as a white solid (4.65 g, 15.3 mmol, 75%).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.88–7.92 (2H, m), 7.80–7.85 (2H, m), 4.55–4.68 (1H, m), 3.23–3.30 (1H, m), 3.01–3.14 (2H, m).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 166.6, 161.8, 135.2, 128.8, 124.4, 124.0 (q, $^1J_{CF}$ = 281.1 Hz), 67.1 (q, $^2J_{CF}$ = 33.5 Hz), 33.1 (q, $^3J_{CF}$ = 1.9 Hz).
**$^{19}$F-NMR (δ, 376 MHz, $CDCl_3$):** -79.8.
**FTIR (ATR, cm$^{-1}$):** 3458m, 3090br w, 1734m, 1450w, 1411w, 1377w, 1335w, 1275w, 1236w, 1183s, 1123s, 656m.
With a variety of ionization techniques, we were not able to obtain accurate high-resolution mass spectrometry data. An accurate high resolution mass spectrum was obtained for the annulation product of this NHPI ester reagent with styrene (compound **25**, *vide infra*).

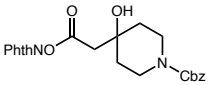
#### (*R*)-β-$CO_2$Bn tetrahydrofuran [3+2] reagent (S–45)


S–45

Prepared according to general procedure **C** from corresponding malic acid-derived monocarboxylic acid[18] (4.48 g, 20.0 mmol, 1.0 equiv.). Trituration of crude esterification product was carried out with $Et_2O$. Purification was achieved *via* flash column chromatography on silica (10–60% EtOAc / hexanes). NHPI ester **S–45** was isolated as a pale-yellow oil which solidified on prolonged storage at -20 °C (4.01 g, 10.8 mmol, 54%).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.87–7.89 (2H, m), 7.79–7.81 (2H, m), 7.32–7.39 (5H, m), 5.29 (1H, d, $^2J_{HH}$ = 10.6 Hz), 5.24 (1H, d, $^2J_{HH}$ = 10.6 Hz), 4.67 (1H, app t, $^3J_{HH}$ = 5.4 Hz), 3.38 (1h, br s), 3.24 (1H, dd, $^2J_{HH}$ = 16.6 Hz, $^3J_{HH}$ =4.7 Hz), 3.15 (1H, dd, $^2J_{HH}$ = 16.6 Hz, $^3J_{HH}$ = 6.1 Hz).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 172.4, 166.8, 161.7, 135.0, 134.8, 128.9, 128.9, 128.8, 128.8, 124.2, 68.3, 66.9, 36.1.
**HRMS (ESI-TOF):** Calc. for $C_{19}H_{15}NO_7Na^+$ ([M+Na]$^+$): 392.07407, found: 392.0744, Δ 0.48 ppm
**FTIR (ATR, cm$^{-1}$):** 3515 br w, 3030w, 2926w, 1818w, 1788m, 1741s, 1371w, 1187w, 1113w, 1082w, 968w, 878w, 696w.

***Spiro*-*N*-Cbz piperidine / tetrahydrofuran [3+2] reagent (S–46)**

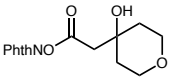


**S–46**

Prepared according to general procedure **D** from corresponding ethyl ester (**S–11**, 4.76 g, 14.8 mmol, 1.0 equiv.). Saponification was complete in 8 h. Trituration of crude esterification product was carried out with EtOAc. Purification was achieved *via* flash column chromatography on silica (20–60% EtOAc / hexanes). NHPI ester **S–46** was isolated as a white solid (3.05 g, 6.96 mmol, 47% over two steps).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.88-7.92 (2H, m), 7.80-7.83 (2H, m), 7.32-7.38 (4H, m), 7.30-7.32 (1H, m), 5.14 (2H, s), 3.91-4.10 (2H, br m), 3.21-3.34 (2H, br m), 2.82 (2H, s), 2.76 (1H, br s), 1.81-1.84 (2H, m), 1.64-1.67 (2H, m).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 167.7, 162.0, 155.3, 136.9, 135.2, 128.9, 128.6, 128.2, 128.0, 124.3, 68.8, 67.3, 44.2, 39.8, 36.6.
**HRMS (ESI-TOF):** Calc. for $C_{23}H_{22}N_2O_7Na^+$ ([M+Na]$^+$): 461.13192, found: 461.13187, Δ 0.34 ppm.
**FTIR (ATR, cm$^{-1}$):** 3424br w, 2928w, 1786m, 1740s, 1693m, 1468m, 1360m, 1245m, 1082m, 971m, 878m, 696m.

***Spiro*-tetrahydropyran / tetrahydrofuran [3+2] reagent (S–47)**

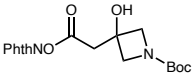


**S–47**

Prepared according to general procedure **D** from corresponding ethyl ester (**S–12**, 3.12 g, 16.6 mmol, 1.0 equiv.). Saponification was complete in 1.5 h. Trituration of crude esterification product was carried out with $Et_2O$. Purification was achieved *via* trituration from $Et_2O$ / Hexanes (2:1) at room temperature. NHPI ester **S–47** was isolated as a white solid (2.63 g, 8.61 mmol, 52% over two steps).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.88-7.91 (2H, m), 7.81-7.82 (2H, m), 3.85 (2H, td, $^2J_{HH}$ = 11.4 Hz, $^3J_{HH}$ = 2.8 Hz), 3.79 (2H, ddd, $^2J_{HH}$ = 11.4 Hz, $^3J_{HH}$ = 4.9, 2.8 Hz), 2.85 (2H, s), 2.74 (1H, br s), 1.83 (2H, td, $^2J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 5.3 Hz), 1.76 (2H, app dq, $^2J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 2.5 Hz).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 167.7, 162.1, 135.1, 128.9, 124.3, 68.1, 63.6, 44.4, 37.5.
**HRMS (ESI-TOF):** Calc. for $C_{15}H_{15}NO_6Na^+$ ([M+Na]$^+$): 328.07916, found: 328.07990, Δ 2.34 ppm.
**FTIR (ATR, cm$^{-1}$):** 3413br w, 2953w, 2866w, 1786m, 1741s, 1467w, 1361w, 1140w, 970w, 697w.

***Spiro*-*N*-Boc azetidine / tetrahydrofuran [3+2] reagent (S–48)**

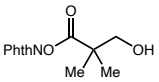


**S–48**

Prepared according to general procedure **D** from corresponding ethyl ester (**S–13**, 4.67 g, 18.0 mmol, 1.0 equiv.). Saponification was complete in 1 h. Trituration of crude esterification product was carried out with $Et_2O$ / EtOAc (1:1). Purification was achieved *via* trituration from $Et_2O$ / Hexanes (2:1) at room temperature. NHPI ester **S–48** was isolated as a white solid (5.41 g, 14.4 mmol, 80% over two steps).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.88-7.91 (2H, m), 7.81-7.83 (2H, m), 3.98-4.02 (4H, m), 3.49 (1H, br s), 3.18 (2H, s), 1.44 (9H, s).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 167.5, 161.9, 156.4, 135.2, 128.8, 124.4, 80.2, 68.0, 61.6, 40.8, 28.5.
**HRMS (ESI-TOF):** Calc. for $C_{18}H_{20}N_2O_7Na^+$ ([M+Na]$^+$): 399.11627, found: 399.11635, Δ 0.26 ppm.
**FTIR (ATR, cm$^{-1}$):** 3390br w, 2977w, 1789w, 1744s, 1676m, 1417m, 1367m, 1160m, 1097m, 698m.

**α,α-Dimethyl tetrahydrofuran [3+2] reagent (S–49)**

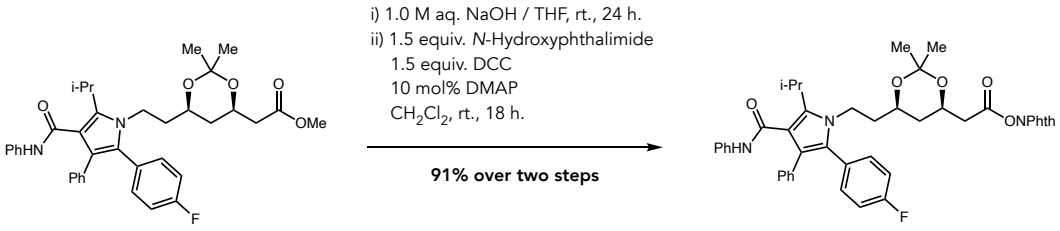


**S–49**

Prepared according to general procedure **C** from hydroxypivalic acid (2.36 g, 20.0 mmol, 1.0 equiv.). Trituration of crude esterification product was carried out with EtOAc. Purification was achieved *via* flash column chromatography on silica (10–50% EtOAc / hexanes). NHPI ester **S–49** was isolated as a viscous colorless oil, which solidified to a white solid upon storage at -20 °C (5.26 g, 19.9 mmol, 99%).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.88–7.90 (2H, m), 7.79–7.82 (2H, m), 3.76 (2H, s), 2.71 (1H, br s), 1.42 (6H, s).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 173.1, 162.4, 135.0, 129.0, 124.2, 70.3, 45.2, 21.7.
**HRMS (ESI-TOF):** Calc. for $C_{13}H_{13}NO_5Na^+$ ([M+Na]$^+$): 286.06859, found: 286.06880, Δ 1.02 ppm.
**FTIR (ATR, cm$^{-1}$):** 3518br w, 2979w, 1782m, 1732s, 1467m, 1186m, 1039s, 878m, 696s.
Characterization data is consistent with that reported by Aggarwal and co-workers.[19]

Atorvastatin acetonide NHPI ester reagent (54)




**S–15** **54**

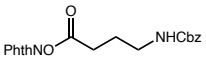
Methyl ester **S–15** (0.89 g, 1.45 mmol, 1.0 equiv.) was dissolved in THF (15 mL) and treated with 1.0 M aq. NaOH solution (3.0 mL). The reaction mixture was stirred at room temperature for 24 h. A 10% w/v citric acid solution (10 mL) was then added, and the resulting mixture extracted with EtOAc (3 x 20 mL). Combined organic phases were washed with brine (10 mL) and dried over sodium sulfate. Removal of all volatiles gave a viscous oil, which was used immediately in the subsequent preparation, assuming quantitative yield.

The crude carboxylic acid as prepared above was taken up in $CH_2Cl_2$ (15 mL) and treated sequentially with *N*-hydroxyphthalimide (0.36 g, 2.18 mmol, 1.5 equiv.), DMAP (18.0 mg, 0.15 mmol, 10 mol%), and DCC (0.45 g, 2.18 mmol, 1.5 equiv.), each added as a solid in one portion. The resulting heterogeneous mixture was stirred at room temperature for 18 h. The mixture was diluted with EtOAc (30 mL) and filtered through a 0.5 inch x 1 inch ⌀ plug of silica, rinsing with further EtOAc (100 mL). All solvents were removed *in vacuo*, and the resulting crude product triturated with $Et_2O$ (50 mL). Filtration of solids (DCU) and evaporation of solvents gave a viscous oil, which was purified *via* flash column chromatography on silica (5–40% EtOAc / hexanes) to afford pure atorvastatin acetonide NHPI ester reagent **54** (0.98 g, 1.32 mmol, 91% over two steps) as a colorless foaming oil.

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.88–7.89 (2H, m), 7.79–7.80 (2H, m), 7.15–7.20 (9H, m), 7.07 (2H, d, $^3J_{HH}$ = 8.1 Hz), 6.97–7.02 (3H, m), 6.87 (1H, br s), 4.28–4.33 (1H, m), 4.06–4.13 (1H, m), 3.82–3.88 (1H, m), 3.70–3.76 (1H, m), 3.56–3.61 (1H, m), 2.85 (1H, dd, $^2J_{HH}$ = 15.4 Hz, $^3J_{HH}$ = 6.8 Hz), 2.69 (1H, dd, $^3J_{HH}$ = 15.4 Hz, $^3J_{HH}$ = 6.5 Hz), 1.67–1.74 (2H, m), 1.55 (3H, s), 1.53 (3H, s), 1.54–1.55 (1H, m), 1.40 (3H, s), 1.35 (3H, s).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 166.9, 164.9, 163.4, 161.9, 161.4, 141.7, 138.5, 135.0, 134.8, 133.4, 133.3, 130.6, 129.0, 128.9, 128.8, 128.5, 128.4, 128.4, 126.7, 124.1, 123.6, 121.9, 119.7, 115.6, 115.5, 99.3, 66.4, 65.6, 40.9, 38.4, 38.1, 35.9, 29.9, 26.2, 21.9, 21.7, 19.7.
**$^{19}$F-NMR (δ, 376 MHz, $CDCl_3$): –**113.7.
**HRMS (ESI-TOF):** Calc. for $C_{44}H_{43}FN_3O_7^+$ ([M+H]$^+$): 744.30796, found: 744.30781, Δ 0.62 ppm.
**FTIR (ATR, cm$^{-1}$):** 2982w, 1735s, 1372m, 1238s, 1109m, 1045m, 698m.

### 6.5.3. Piperidine reagents

#### Parent *N*-Cbz piperidine [4+2] reagent (31)

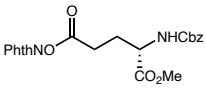



**31**

Prepared according to general procedure **C** from Z-ɣ-aminobutyric acid[20] (4.75 g, 20.0 mmol, 1.0 equiv.). Trituration of crude esterification product was carried out with EtOAc. Purification was achieved *via* recrystallization from EtOAc / hexanes. NHPI ester **31** was isolated as a white solid (7.24 g, 18.9 mmol, 95%).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.87-7.88 (2H, m), 7.78-7.80 (2H, m), 7.29-7.35 (5H, m), 5.11 (2H, s), 5.06 (1H, br s), 3.35 (2H, app q, $^3J_{HH}$ = 6.3 Hz), 2.73 (2H, t, $^3J_{HH}$ = 7.2 Hz), 2.02 (2H, t, $^3J_{HH}$ = 6.8 Hz).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 169.4, 162.0, 156.6, 136.6, 134.9, 129.0, 128.6, 128.2, 124.1, 66.9, 40.0, 28.5, 25.2.
**HRMS (ESI-TOF):** Calc. for $C_{20}H_{18}N_2O_6Na^+$ ([M+Na]$^+$): 405.10571, found: 405.10586, Δ 0.25 ppm.
**FTIR (ATR, cm$^{-1}$):** 3345br w, 2943w, 1814m, 1739s, 1522m, 1370m, 1245m, 1062m, 878m, 695s.

#### Glutamic acid-derived piperidine [4+2] reagent (S–50)

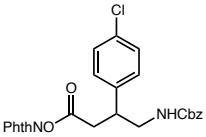



**S–50**

Prepared according to general procedure **C** from Z-Glu-OMe (4.99 g, 16.9 mmol, 1.0 equiv.). Trituration of crude esterification product was carried out with EtOAc. Purification was achieved *via* recrystallization from EtOAc / hexanes. NHPI ester **S–50** was isolated as a white solid (6.97 g, 15.8 mmol, 94%).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.87–7.88 (2H, m), 7.78–7.80 (2H, m), 7.29–7.37 (5H, m), 5.54 (1H, d, $J_{HH}$ = 8.0 Hz), 5.13 (2H, s), 4.48–4.53 (1H, m), 3.78 (3H, s), 2.72–2.86 (2H, m), 2.35–2.42 (1H, m), 2.12–2.20 (1H, m).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 171.9, 168.9, 161.9, 156.1, 136.2, 135.0, 129.0, 128.7, 128.7, 128.4, 128.3, 128.3, 124.2, 67.4, 53.2, 53.0, 27.7, 27.5.
**HRMS (ESI-TOF):** Calc. for $C_{22}H_{20}N_2O_8Na^+$ ([M+Na]$^+$): 463.11119, found: 463.11178, Δ 1.12 ppm.
**FTIR (ATR, cm$^{-1}$):** 3365br w, 2954w, 1788w, 1740s, 1523m, 1214m, 1056m, 878w, 697w.

#### Baclofen-derived piperidine [4+2] reagent (53)

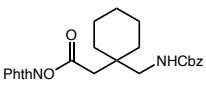



**53**

Prepared according to general procedure **C** from corresponding carboxylic acid (3.32 g, 9.54 mmol, 1.0 equiv.). Trituration of crude esterification product was carried out with EtOAc. Purification was achieved *via* recrystallization from EtOAc / hexanes. NHPI ester **53** was isolated as a white solid (4.24 g, 8.60 mmol, 90%).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.83–7.86 (2H, m), 7.76–7.79 (2H, m), 7.29–7.34 (7H, m), 7.21 (2H, d, $^3J_{HH}$ = 8.2 Hz), 5.06–5.11 (2H, m), 4.98 (1H, br s), 3.60–3.64 (1H, m), 3.43–3.49 (2H, m), 3.05 (1H, dd, $^2J_{HH}$ = 15.7 Hz, $^3J_{HH}$ = 6.2 Hz), 2.95 (1H, dd, $^2J_{HH}$ = 15.7 Hz, $^3J_{HH}$ = 7.6 Hz).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 167.9, 161.8, 156.5, 138.4, 136.4, 134.9, 133.5, 129.3, 129.1, 128.9, 128.6, 128.3, 128.2, 124.1, 67.0, 45.9, 41.9, 35.3.
**HRMS (ESI-TOF):** Calc. for $C_{26}H_{21}ClN_2O_6Na^+$ ([M+Na]$^+$): 515.09804, found: 515.09767, Δ 1.04 ppm.
**FTIR (ATR, cm$^{-1}$):** 3357br w, 2930w, 1815m, 1741s, 1521w, 1369w, 1249m, 1090m, 877m, 733m, 695s, 518w.

#### Gabapentin-derived piperidine [4+2] reagent (S–51)




**S–51**

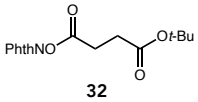
Prepared according to general procedure **C** from corresponding carboxylic acid (6.11 g, 20.0 mmol, 1.0 equiv.). Trituration of crude esterification product was carried out with $Et_2O$. Purification was achieved *via* flash column chromatography on silica (10–50 % $Et_2O$ / Hexanes). NHPI ester **S–51** was isolated as a viscous colorless oil (9.05 g, 20.0 mmol, 100%).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.86–7.89 (2H, m), 7.77–7.81 (2H, m), 7.28–7.37 (5H, m), 5.24 (1H, t, $^3J_{HH}$ = 6.9 Hz), 5.10 (2H, s), 3.36 (2H, d, $^3J_{HH}$ = 6.9 Hz), 2.63 (2H, s), 1.45–1.64 (10H, m).

**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 168.3, 162.1, 157.2, 136.7, 135.0, 129.0, 128.6, 128.2, 128.2, 124.2, 66.9, 47.4, 39.1, 37.9, 34.0, 25.9, 21.6.
**HRMS (ESI-TOF):** Calc. for $C_{25}H_{27}N_2O_6Na^+$ ([M+H]$^+$): 451.18636, found: 451.18616, Δ 0.93 ppm.
**FTIR (ATR, cm$^{-1}$):** 3402br w, 2928w, 2860w, 1785w, 1810m, 1740s, 1518m, 1467m, 1362m, 1235m, 1137m, 1061m, 972m, 878m, 696m.

## 6.5.4. Other NHPI reagents – Morpholine, valerolactone, and dioxanone reagents

### Parent valerolactone [4+2] reagent (32)

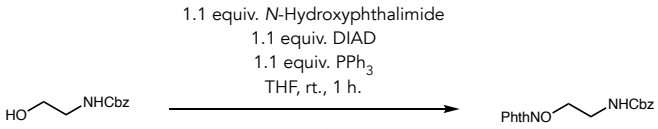


**32**

Prepared according to general procedure **C** from mono-*tert*-butyl succinate (3.48 g, 20.0 mmol, 1.0 equiv.). Trituration of crude esterification product was carried out using EtOAc. Purification was achieved *via* recrystallization from EtOAc / hexanes. NHPI ester **32** was isolated as a white solid (5.84 g, 18.3 mmol, 91%).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** δ 7.88-7.89 (2H, m), 7.78-7.79 (2H, m), 2.96 (2H, t, $^3J_{HH}$ = 7.1 Hz), 2.69 (2H, t, $^3J_{HH}$ = 7.1 Hz), 1.47 (9H, s).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** δ 170.2, 168.9, 161.9, 134.9, 129.0, 124.1, 81.6, 30.1, 28.1, 26.7.
**HRMS (ESI-TOF):** Calc. for $C_{16}H_{17}NO_6Na^+$ ([M+Na]$^+$): 342.09481, found: 342.09480, Δ 0.01 ppm.
**FTIR (ATR, cm$^{-1}$):** 2944w, 1787m, 1726s, 1376m, 1186m, 878m, 700m.

### Parent *N*–Cbz morpholine [4+2] reagent (33)

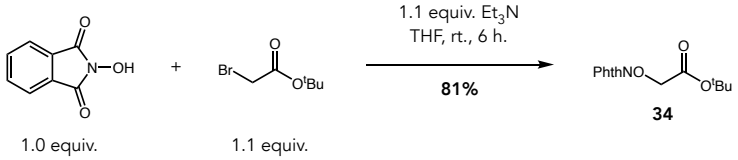


**S–52** **33**

*N*-Cbz glycinol (**S–52**, 4.18 g, 20.0 mmol, 1.0 equiv.), $PPh_3$ (5.77 g, 22.0 mmol, 1.1 equiv.), and *N*-hydroxyphthalimide (3.59 g, 22.0 mmol, 1.1 equiv.) were dissolved in anhydrous THF (100 mL). The resulting homogeneous solution was treated dropwise with DIAD (4.33 mL, 22.0 mmol, 1.1 equiv.) at room temperature. The resulting orange solution was stirred at room temperature for 1 h, becoming pale yellow over the course of reaction. After this time, silica (40 g) was added directly to the flask, and all volatiles were removed *in vacuo*. The resulting dry powder was loaded onto the top of a silica column, and product NHPI ether was purified via flash column chromatography (20–30–40–50% EtOAc / hexanes) to yield a white solid. This material was further purified *via* recrystallization (EtOAc / hexanes) to afford pure morpholine NHPI ether reagent **33** (6.65 g, 19.5 mmol, 98%) as a white solid.

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** δ 7.84–7.86 (2H, m), 7.76–7.78 (2H, m), 7.30–7.40 (5H, m), 5.97 (1H, br s), 5.14 (2H, s), 4.27 (2H, t, $^3J_{HH}$ = 4.3 Hz), 3.52 (2H, app q, $^3J_{HH}$ = 4.3 Hz).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** δ 164.2, 156.6, 136.7, 134.9, 128.9, 128.6, 128.2, 123.9, 77.8, 66.9, 39.4.
**HRMS (ESI-TOF):** Calc. for $C_{18}H_{16}N_2O_5Na^+$ ([M+Na]$^+$): 363.09514, found: 363.09517, Δ 0.27 ppm.
**FTIR (ATR, cm$^{-1}$):** 3406br w, 2949w, 1728s, 1514m, 1245m, 1186m, 1130m, 1025m, 907m, 878m, 777s, 699s, 518w.
Characterization data is consistent with reported by Player and co-workers.[21]

### Parent dioxanone [4+2] reagent (34)



1.0 equiv. 1.1 equiv. **34**

A stirring solution of *N*-hydroxyphthalimide (4.89 g, 30.0 mmol, 1.0 equiv.) and *tert*-butyl bromoacetate (4.87 mL, 33.0 mmol, 1.1 equiv.) in anhydrous THF (90 mL) was treated dropwise with triethylamine (4.60 mL, 33.0 mmol, 1.1 equiv.) at room temperature. On addition, the pale-yellow solution turned dark red, and stirring was continued for 6 h., after which time the pale yellow color had returned. The mixture was poured into EtOAc (200 mL) and washed with water (50 mL), sat. aq. $NaHCO_3$ solution (50 mL), and brine (50 mL). The organic phase was dried over magnesium sulfate. Filtration of drying agents and

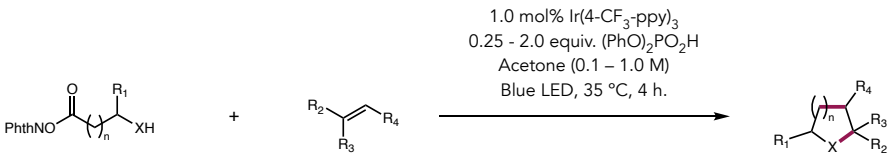
evaporation of solvents gave a pale yellow solid, which was purified *via* recrystallization (EtOAc / hexanes) to afford pure dioxanone NHPI ether reagent **34** (6.74 g, 24.3 mmol, 81%) as a white solid.

**$^{1}$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.84–7.86 (2H, m), 7.75–7.77 (2H, m), 4.71 (2H, s), 1.48 (9H, s).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 166.1, 163.2, 134.8, 129.0, 123.8, 83.2, 73.6, 28.2.
**HRMS (ESI-TOF):** Calc. for $C_{14}H_{15}NO_5Na^+$ ([M+Na]$^+$): 300.08424, found: 300.08410, Δ 0.31 ppm.
**FTIR (ATR, cm$^{-1}$):** 2976w, 2931w, 1788w, 1752m, 1732s, 1368m, 1241m, 1186m, 1165m, 1143m, 1054m, 878m, 701m.

## 7. Preparation of annulation products from NHPI reagents and alkenes

### 7.1. General procedure for 0.1 and 0.5 mmol scale annulation reactions of NHPI reagents and alkenes

**General Procedure E. Preparation of annulation products from NHPI reagents and alkenes at 0.10 or 0.50 mmol scale.**




**For volatile liquid alkenes:**

An oven-dried vial (for 0.10 mmol scale, Chemglass CG-4909, 4.0 mL total volume; for 0.50 mmol scale, VWR 66011-085, 7.4 mL total volume) was charged with Teflon-coated magnetic stir bar, Ir(4-$CF_3$-ppy)$_3$ photocatalyst, diphenylphosphoric acid co-catalyst, and NHPI ester or NHPI ether reagent (quantities indicated for each entry below). The vial was brought into a nitrogen-filled glovebox. Acetone (Acros, 99.8%, Extra-Dry, AcroSeal) was added to the open vial whilst stirring, and the reaction vial sealed with a septum and cap, then electrical tape around the neck of the vial. The reaction vial was taken out of the glovebox, and a nitrogen-flushed inlet needle was inserted through the septum seal. The neat liquid alkene was added *via* microsyringe with stirring, the nitrogen line was removed, and the pierced septum sealed with electrical tape. The vial was placed on a stir plate in front of a blue LED light source (Kessil PRL160L 456 nm, 50 W max, set to 50% lamp intensity) at a distance of 1 cm from the lamp face. The reaction vial was stirred and irradiated for 4 h. with cooling provided by overhead fans to maintain a reaction temperature of 35 ± 3 °C. The septum and cap were removed, and the crude reaction mixture purified directly by the indicated method in each entry below to yield the pure annulation product.

**For non-volatile liquid and solid alkenes:**

An oven-dried vial (for 0.10 mmol scale, Chemglass CG-4909, 4.0 mL total volume; for 0.50 mmol scale, VWR 66011-085, 7.4 mL total volume) was charged with Teflon-coated magnetic stir bar, Ir(4-$CF_3$-ppy)$_3$ photocatalyst, diphenylphosphoric acid co-catalyst, NHPI ester or NHPI ether reagent, and alkene substrate (quantities indicated for each entry below). The reaction vial was brought into a nitrogen-filled glovebox. Acetone (Acros, 99.8%, Extra-Dry, AcroSeal) was added to the open vial whilst stirring, and the vial sealed with a septum and cap, then electrical tape around the neck of the vial. The reaction vial was taken out of the glovebox and placed on a stir plate in front of a blue LED light source (Kessil PRL160L 456 nm, 50 W max, set to 50% lamp intensity) at a distance of 1 cm from the lamp face. The reaction vial was stirred and irradiated for 4 h. with cooling provided by overhead fans to maintain a reaction temperature of 35 ± 3 °C. The septum and cap were removed, and the crude reaction mixture purified directly by the indicated method in each entry below to yield the pure annulation product.

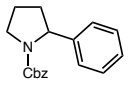
**Notes:**

- Comparable reaction yields were realized without the use of a glovebox by sealing the vial as described above, then purging the headspace with a nitrogen line inlet and needle outlet for 15 min.
- Comparable reaction yields were realized when acetone was distilled from calcium sulfate (Drierite) which was used immediately, or stored in an oven-dried Schlenk bomb in a nitrogen-flushed glovebox, and used as indicated above. Lower reaction yields were realized if non-dried acetone was used.
- Comparable reaction yields were realized using Kessil PRL160L 440 nm and Kessil PRL160L 427 nm lamps.
- We noted no dependence of overall reaction yield on light intensity, but at higher lamp intensities efficient cooling was more difficult to achieve.
- We noted no deterioration in annulation product yield when NHPI ester or ether reagent contained minor contamination (<5%) by DCU byproduct from the Steglich esterification.
- Lower reaction yields were realized if reaction temperature was <32 °C or <38 °C.
- On this reaction scale, phthalimide could typically be removed through chromatographic procedures as described. On larger scale, or if phthalimide contamination after chromatography was apparent, this contaminant could be removed by washing a $CH_2Cl_2$ solution of the annulation reaction product with 1.0 M aqueous NaOH solution.
- In the case of NHPI ester reagents, an audible outgassing ($CO_2$) is heard upon opening of the reaction vial after irradiation.

## 7.2. Characterization of annulation products

### 7.2.1. Pyrrolidine products

#### Benzyl 2-phenylpyrrolidine-1-carboxylate (2)

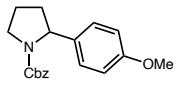



**2**

The title compound was prepared according to general procedure **E** from phthalimide ester **1** (184 mg, 0.50 mmol, 1.0 equiv.), styrene (115 µL, 1.0 mmol, 2.0 equiv.), Ir(4-$CF_3$ppy)$_3$ (4.3 mg, 0.005 mmol, 1.0 mol%), and $(PhO)_2PO_2H$ (31.3 mg, 0.125 mmol, 25 mol%) in acetone (5.0 mL, 0.1 M). Purification was carried out by flash column chromatography on silica (10% EtOAc / hexanes), and the product pyrrolidine **2** was isolated as a colorless oil (73% yield, average of two runs; run 1: 102 mg, 0.36 mmol, 72% yield; run 2: 105 mg, 0.37 mmol, 74% yield). Product appears as a rotameric mixture in NMR analysis.

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.15–7.38 (9H, m), 6.88 (1H, d, $^3J_{HH}$ = 7.1 Hz), 4.92–5.18 (3H, m), 3.59–3.72 (2H, m), 2.28–2.36 (1H, m), 1.84–1.97 (3H, m).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 155.2, 155.0, 144.5, 143.6, 137.2, 136.9, 128.6, 128.5, 128.3, 128.1, 127.6, 127.3, 126.9, 126.8, 125.6, 66.9, 66.7, 61.4, 61.2, 47.8, 47.3, 36.0, 34.9, 23.7, 23.0.
**HRMS (ESI-TOF):** Calc. for $C_{18}H_{20}NO_2^+$ ([M+H]$^+$): 282.14886, found: 282.14886, Δ 0 ppm.
**FTIR (ATR, cm$^{-1}$):** 3030w, 2951w, 2878w, 1697s, 1450m, 1408s, 1350m, 1108m, 770m, 751m, 698m.
Characterization data is consistent with that reported by Hashmi and co-workers.[22]

#### Benzyl 2-(4-methoxyphenyl)pyrrolidine-1-carboxylate (3)

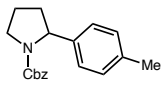



**3**

The title compound was prepared according to general procedure **E** from phthalimide ester **1** (184 mg, 0.50 mmol, 1.0 equiv.), 4-vinylanisole (133 µL, 1.0 mmol, 2.0 equiv.), Ir(4-$CF_3$ppy)$_3$ (4.3 mg, 0.005 mmol, 1.0 mol%), and $(PhO)_2PO_2H$ (31.3 mg, 0.125 mmol, 25 mol%) in acetone (5.0 mL, 0.1 M). Purification was carried out by flash column chromatography on silica (10% EtOAc / hexanes), and the product pyrrolidine **3** was isolated as a colorless oil (72% yield, average of two runs; run 1: 111 mg, 0.36 mmol, 72% yield; run 2: 110 mg, 0.36 mmol, 71% yield). Product appears as a rotameric mixture in NMR analysis.

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.31–7.40 (2H, m), 7.08–7.21 (4H, m), 6.95 (1H, d, $^3J_{HH}$ = 5.1 Hz), 6.84–6.87 (2H, m), 4.89–5.19 (3H, m), 3.79–3.81 (3H, m), 3.62–3.72 (2H, m), 2.25–2.33 (1H, m), 1.82–1.97 (3H, m).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 158.5, 155.1, 154.9, 137.1, 136.9, 136.5, 135.7, 128.6, 128.5, 128.2, 128.0, 127.5, 127.4, 126.7, 113.9, 113.8, 113.8, 66.7, 66.6, 60.8, 60.6, 55.4, 47.6, 47.1, 36.0, 34.8, 23.7, 22.9.
**HRMS (ESI-TOF):** Calc. for $C_{19}H_{22}NO_3^+$ ([M+H]$^+$): 312.15942, found: 312.15972, Δ 0.96 ppm.
**FTIR (ATR, cm$^{-1}$):** 2951w, 2876w, 1693s, 1610m, 1511s, 1446m, 1405s, 1349m, 1242s, 1172m, 1102m, 1027m, 826m, 697m.
Characterization data is consistent with that reported by Chemler and co-workers.[23]

#### Benzyl 2-(p-tolyl)pyrrolidine-1-carboxylate (4)



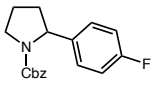

**4**

The title compound was prepared according to general procedure **E** from phthalimide ester **1** (184 mg, 0.50 mmol, 1.0 equiv.), 4-methylstyrene (132 µL, 1.0 mmol, 2.0 equiv.), Ir(4-$CF_3$ppy)$_3$ (4.3 mg, 0.005 mmol, 1.0 mol%), and $(PhO)_2PO_2H$ (31.3 mg, 0.125 mmol, 25 mol%) in acetone (5.0 mL, 0.1 M). Purification was carried out by flash column chromatography on silica (10% EtOAc / hexanes), and the product pyrrolidine **4** was isolated as a colorless oil (80% yield, average of two runs; run 1: 118 mg, 0.40 mmol, 80% yield; run 2: 117 mg, 0.40 mmol, 80% yield). Product appears as a rotameric mixture in NMR analysis.

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.06–7.39 (8H, m), 6.93 (1H, d, $^3J_{HH}$ = 6.7 Hz), 4.91–5.20 (3H, m), 3.62–3.74 (2H, m), 2.30–2.37 (4H, m), 1.84–1.98 (3H, m).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 155.1, 154.9, 141.4, 140.6, 137.2, 136.9, 136.4, 136.3, 129.2, 129.1, 128.5, 128.2, 128.0, 128.0, 127.5, 127.3, 125.5, 66.8, 66.5, 61.2, 60.9, 47.7, 47.2, 36.0, 34.9, 23.7, 22.9, 21.1.
**HRMS (ESI-TOF):** Calc. for $C_{19}H_{22}NO_2^+$ ([M+H]$^+$): 296.16451, found: 296.16468, Δ 0.57 ppm.
**FTIR (ATR, cm$^{-1}$):** 2949w, 2874w, 1696s, 1446m, 1405s, 1348s, 1171m, 1102s, 1076m, 812m, 770m, 733m, 696m.

Characterization data is consistent with that reported by Chemler and co-workers.[23]

### Benzyl 2-(4-fluorophenyl)pyrrolidine-1-carboxylate (5)

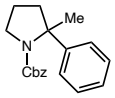


5

The title compound was prepared according to general procedure **E** from phthalimide ester **1** (184 mg, 0.50 mmol, 1.0 equiv.), 4-fluorostyrene (119 µL, 1.0 mmol, 2.0 equiv.), Ir(4-$CF_3$ppy)$_3$ (4.3 mg, 0.005 mmol, 1.0 mol%), and $(PhO)_2PO_2H$ (31.3 mg, 0.125 mmol, 25 mol%) in acetone (5.0 mL, 0.1 M). Purification was carried out by flash column chromatography on silica (10% EtOAc / hexanes), and the product pyrrolidine **5** was isolated as a colorless oil (73% yield, average of two runs; run 1: 105 mg, 0.35 mmol, 70% yield; run 2: 110 mg, 0.37 mmol, 76% yield). Product appears as a rotameric mixture in NMR analysis.

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.09–7.38 (6H, m), 6.91–7.01 (3H, m), 4.89–5.18 (3H, m), 3.61–3.70 (2H, m), 2.27–2.35 (1H, m), 1.80–1.95 (3H, m).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 162.8, 160.9, 155.1, 140.2, 139.3, 137.0, 136.7, 128.6, 128.3, 128.1, 127.7, 127.5, 127.2, 127.1, 115.4, 115.3, 115.2, 115.2, 66.9, 66.8, 60.9, 60.6, 47.7, 47.3, 36.1, 34.9, 23.7, 23.0.
**$^{19}$F-NMR (δ, 376 MHz, $CDCl_3$):** -116.56
**HRMS (ESI-TOF):** Calc. for $C_{18}H_{19}FNO_2^+$ ([M+H]$^+$): 300.13943, found:300.13990, Δ 1.57 ppm.
**FTIR (ATR, cm$^{-1}$):** 2951w, 2878w, 1702s, 1509m, 1410m, 1353m, 1220w, 1110w.
Characterization data is consistent with that reported by Chemler and co-workers.[23]

### Benzyl 2-methyl-2-phenylpyrrolidine-1-carboxylate (6)

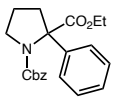


6

The title compound was prepared according to general procedure **E** from phthalimide ester **1** (184 mg, 0.50 mmol, 1.0 equiv.), α-methylstyrene (130 µL, 1.0 mmol, 2.0 equiv.), Ir(4-$CF_3$ppy)$_3$ (4.3 mg, 0.005 mmol, 1.0 mol%), and $(PhO)_2PO_2H$ (31.3 mg, 0.125 mmol, 25 mol%) in acetone (5.0 mL, 0.1 M). Purification was carried out by flash column chromatography on silica (20% EtOAc / hexanes), and the product pyrrolidine **6** was isolated as a colorless oil (90% yield, average of two runs; run 1: 133 mg, 0.45 mmol, 90% yield; run 2: 133 mg, 0.45 mmol, 90% yield). Product appears as a rotameric mixture in NMR analysis.

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.13–7.40 (9H, m), 6.78 (1H, d, $^3J_{HH}$ = 7.3 Hz), 5.07–5.15 (1H, m), 4.97 (0.5H, d, $^2J_{HH}$ = 12.5 Hz), 4.90 (0.5H, d, $^2J_{HH}$ = 12.5 Hz), 3.67–3.81 (2H, m), 2.02–2.11 (2H, m), 1.89 (1H, s), 1.70–1.88 (4H, m).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 155.1, 154.0, 147.8, 146.6, 137.4, 136.7, 128.6, 128.4, 128.2, 127.9, 127.5, 127.5, 126.4, 126.4, 125.1, 125.0, 66.6, 66.4, 66.3, 65.6, 49.5, 48.6, 46.1, 44.7, 26.0, 25.7, 22.2, 22.1.
**HRMS (ESI-TOF):** Calc. for $C_{19}H_{22}NO_2^+$ ([M+H]$^+$): 296.16451, found: 296.16465, Δ 0.47 ppm.
**FTIR (ATR, cm$^{-1}$):** 2972w, 2876w, 1691s, 1404s, 1351s, 761m, 698m.
Characterization data is consistent with that reported by Chemler and co-workers.[20]

### 1-Benzyl 2-ethyl 2-phenylpyrrolidine-1,2-dicarboxylate (7)



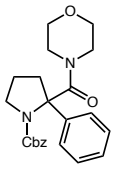
7

The title compound was prepared according to general procedure **E** from phthalimide ester **1** (184 mg, 0.50 mmol, 1.0 equiv.), ethyl 2-phenylacrylate (176 mg, 1.0 mmol, 2.0 equiv.), Ir(4-$CF_3$ppy)$_3$ (4.3 mg, 0.005 mmol, 1.0 mol%), and $(PhO)_2PO_2H$ (31.3 mg, 0.125 mmol, 25 mol%) in acetone (5.0 mL, 0.1 M). Purification was carried out by flash column chromatography on silica (20% EtOAc / hexanes), and the product pyrrolidine **7** was isolated as a colorless oil (42% yield, average of two runs; run 1: 71 mg, 0.20 mmol, 40% yield; run 2: 77 mg, 0.22 mmol, 44% yield).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.11–7.34 (9H, m), 6.95–6.97 (1H, m), 4.88–5.14 (2H, m), 4.07–4.17 (1H, m), 3.76–3.95 (1H, m), 3.63–3.73 (2H, m), 2.49–2.57 (1H, m), 2.20–2.26 (1H, m), 1.80–1.88 (1H, m), 1.58–1.67 (1H, m), 1.11 (1.4H, t, $^3J_{HH}$ = 7.1 Hz), 0.99 (1.6H, t, $^3J_{HH}$ = 7.1 Hz).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 172.4, 172.3, 154.8, 154.7, 140.1, 139.4, 137.1, 136.2, 128.5, 128.3, 128.1, 128.1, 128.0, 127.9, 127.7, 127.7, 127.2, 127.2, 127.2, 127.2, 72.3, 71.8, 67.1, 67.0, 61.7, 61.6, 48.7, 48.0, 43.9, 42.1, 23.5, 22.7, 14.1, 14.0.
**HRMS (ESI-TOF):** Calc. for $C_{21}H_{24}NO_4^+$ ([M+H]$^+$): 354.16998, found: 354.17119, Δ 3.42 ppm.
**FTIR (ATR, cm$^{-1}$):** 2980w, 2879w, 1741m, 1703s, 1446m, 1405s, 1352m, 1243m, 1171m, 1132m, 1026w, 697s.

Characterization data is consistent with that reported by Bull and co-workers.[24]

### Benzyl 2-(morpholine-4-carbonyl)-2-phenylpyrrolidine-1-carboxylate (8)

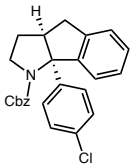



**8**

The title compound was prepared according to general procedure **E** from phthalimide ester **1** (184 mg, 0.50 mmol, 1.0 equiv.), 1-morpholino-2-phenylprop-2-en-1-one[24] (217 mg, 1.0 mmol, 2.0 equiv.), Ir(4-$CF_3$ppy)$_3$ (4.3 mg, 0.005 mmol, 1.0 mol%), and $(PhO)_2PO_2H$ (31.3 mg, 0.125 mmol, 25 mol%) in acetone (5.0 mL, 0.1 M). Purification was carried out by flash column chromatography on silica (75% EtOAc / hexanes), and the product pyrrolidine **8** was isolated as a white solid (60% yield, average of two runs; run 1: 113 mg, 0.29 mmol, 58% yield; run 2: 120 mg, 0.31 mmol, 62% yield).

**$^1$H-NMR (δ, 500 MHz, $C_6D_6$, 343 K):** 7.29 (2H, d, $^3J_{HH}$ = 7.7 Hz), 7.14–7.16 (2H, m), 7.01–7.11 (6H, m), 5.03 (2H, s), 3.60–3.64 (2H, m), 3.12–3.30 (8H, m), 2.43 (1H, br m), 2.07–2.12 (1H, m), 1.44–1.56 (2H, m).
**$^{13}$C-NMR (δ, 126 MHz, $C_6D_6$, 343 K):** 170.8, 155.2, 142.5, 137.7, 128.5, 128.4, 128.3, 127.3, 73.3, 67.1, 66.5, 48.8, 46.7, 42.4, 23.4.
**HRMS (ESI-TOF):** Calc. for $C_{23}H_{27}N_2O_4^+$ ([M+H]$^+$): 395.19653, found: 395.19695, Δ 1.06 ppm.
**FTIR (ATR, cm$^{-1}$):** 2960w, 2857w, 1693s, 1646s, 1402s, 1350m, 1222m, 1115s, 1038m, 979m, 764m, 749m, 698s.

### Benzyl (3a*R*,8b*R*)-8b-(4-chlorophenyl)-3,3a,4,8b-tetrahydroindeno[1,2-*b*]pyrrole-1(2*H*)-carboxylate (9)

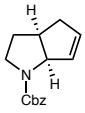



**9**

The title compound was prepared according to general procedure **E** from phthalimide ester **1** (36.8 mg, 0.1 mmol, 1.0 equiv.), 3-(4-chlorophenyl)-1*H*-indene (45.2 mg, 0.2 mmol, 2.0 equiv.), Ir(4-$CF_3$ppy)$_3$ (0.9 mg, 0.001 mmol, 1.0 mol%), and $(PhO)_2PO_2H$ (6.3 mg, 0.025 mmol, 25 mol%) in acetone (500 µL, 0.2 M). Purification was carried out by flash column chromatography on silica (10% EtOAc / Hexanes), and the product pyrrolidine **9** was isolated as a brown oil (53% yield, average of two runs; Run 1: 22.0 mg, 0.056 mmol, 56% yield; Run 2: 20.0 mg, 0.050 mmol, 50% yield).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.78 (0.5H, d, $^3J_{HH}$ = 7.5 Hz), 7.17–7.79 (9H, m), 7.08 (0.5H, t, $^3J_{HH}$ = 7.3 Hz), 6.94 (1H, d, $^3J_{HH}$ = 8.3 Hz), 6.91 (1H, d, $^3J_{HH}$ = 8.4 Hz), 6.84 (1H, d, $^3J_{HH}$ = 7.3 Hz), 5.13 (0.5H, d, $^2J_{HH}$ = 12.4 Hz), 5.10 (0.5 H, d, $^2J_{HH}$ = 12.2 Hz), 5.02 (0.5H, d, $^2J_{HH}$ = 12.5 Hz), 4.84 (0.5 H, d, $^3J_{HH}$ = 12.2 Hz), 3.80–3.98 (2H, m), 3.01–3.11 (1H, m), 2.90–2.98 (1H, m), 2.82 (1H, dd, $^2J_{HH}$ = 15.9 Hz, $^3J_{HH}$ = 4.0 Hz), 2.09–2.16 (1H, m), 1.73–1.79 (1H, m).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 154.6, 153.9, 144.5, 144.1, 143.8, 143.6, 143.3, 143.1, 137.1, 136.1, 132.5, 132.5, 129.0, 128.6, 128.6, 128.6, 128.4, 128.3, 128.3, 128.2, 128.1, 128.0, 128.0, 127.9, 127.5, 127.4, 127.1, 126.9, 125.0, 124.8, 80.1, 79.6, 67.0, 66.7, 57.6, 56.2, 49.2, 48.6, 35.3, 35.0, 28.2, 27.4.
**HRMS (ESI-TOF):** Calc. for $C_{25}H_{23}ClNO_2^+$ ([M+H]$^+$): 404.14118, found: 404.14213, Δ 2.35 ppm.
**FTIR (ATR, cm$^{-1}$):** 2947w, 1697s, 1491m, 1403m, 1352m, 1128w, 1093m, 757m.

### Benzyl (3aR,6aS)-3,3a,4,6a-tetrahydrocyclopenta[*b*]pyrrole-1(2*H*)-carboxylate (10)



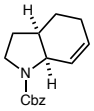

**10**

The title compound was prepared according to general procedure **E** from phthalimide ester **1** (184 mg, 0.50 mmol, 1.0 equiv.), cyclopentadiene (freshly cracked from dicyclopentadiene, 206 µL, 2.5 mmol, 5.0 equiv.), Ir(4-$CF_3$ppy)$_3$ (4.3 mg, 0.005 mmol, 1.0 mol%), and $(PhO)_2PO_2H$ (31.3 mg, 0.125 mmol, 25 mol%) in acetone (5.0 mL, 0.1 M). Purification was carried out by flash column chromatography on silica (20% EtOAc / hexanes), and the product pyrrolidine **10** as a single diastereoisomer was isolated as a yellow oil (60% yield, average of two runs; run 1: 67 mg, 0.28 mmol, 56% yield; run 2: 78 mg, 0.33 mmol, 65% yield).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.34–7.39 (4H, m), 7.29–7.32 (1H, m), 5.93–5.95 (0.5H, m), 5.72–5.79 (1.5H, m), 5.10–5.20 (2H, m), 4.79 (0.5H, d, $^3J_{HH}$ = 7.8 Hz), 4.74 (0.5H, d, $^3J_{HH}$ = 7.8 Hz), 3.38–3.50 (2H, m), 2.82–2.92 (1H, m), 2.53–2.61 (1H, m), 2.16–2.18 (0.5H, m), 2.12–2.14 (0.5H, m), 2.01–2.07 (1H, m), 1.54–1.62 (1H, m).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 156.4, 154.8, 154.6, 137.1, 136.7, 132.0, 131.8, 130.9, 130.6, 128.6, 128.6, 128.5, 128.5, 128.3, 128.2, 128.1, 128.0, 127.9, 127.9, 127.8, 68.4, 67.7, 66.7, 66.6, 66.6, 45.9, 45.6, 40.3, 39.2, 38.1, 36.0, 32.2, 31.4.
**HRMS (ESI-TOF):** Calc. for $C_{15}H_{18}NO_2^+$ ([M+H]$^+$): 244.13321, found: 244.13323, Δ 0.08 ppm.

**FTIR (ATR, cm$^{-1}$):** 3034w, 2945w, 1694s, 1446m, 1409s, 1352s, 1198m, 1112s, 733m, 695s.

### Benzyl (3a*R*,7a*S*)-2,3,3a,4,5,7a-hexahydro-1*H*-indole-1-carboxylate (11)

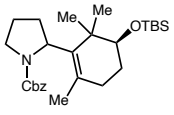



**11**

The title compound was prepared according to general procedure **E** from phthalimide ester **1** (184 mg, 0.50 mmol, 1.0 equiv.), 1,3-cyclohexadiene (95 µL, 1.0 mmol, 2.0 equiv.), Ir(4-$CF_3$ppy)$_3$ (4.3 mg, 0.005 mmol, 1.0 mol%), and $(PhO)_2PO_2H$ (31.3 mg, 0.125 mmol, 25 mol%) in acetone (5.0 mL, 0.1 M). Purification was carried out by flash column chromatography on silica (20% EtOAc / hexanes), and the product pyrrolidine **11** as a single diastereoisomer was isolated as a colorless oil (33% yield, average of two runs; run 1: 39.0 mg, 0.15 mmol, 30% yield; run 2: 45 mg, 0.17 mmol, 35% yield). Product appears as a rotameric mixture in NMR analysis.

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.34–7.39 (4H, m), 7.29–7.32 (1H, m), 5.93 (0.5H, br d, $^3J_{HH}$ = 10.3 Hz), 5.69–5.76 (1.5H, m), 5.10–5.19 (2H, m), 4.24–4.29 (1H, m), 3.38–3.53 (2H, m), 2.36–2.42 (1H, m), 1.93–2.07 (2H, m), 1.73–1.84 (3H, m), 1.63–1.70 (1H, m).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 155.1, 155.1, 137.2, 137.1, 128.6, 128.5, 128.5, 128.4, 128.3, 128.1, 127.9, 127.9, 127.9, 127.7, 126.6, 126.1, 66.7, 66.7, 66.5, 55.5, 55.1, 45.5, 45.1, 36.5, 35.8, 27.3, 26.3, 22.7, 22.6, 20.9, 20.6.
**HRMS (ESI-TOF):** Calc. for $C_{16}H_{20}NO_2^+$ ([M+H]$^+$): 258.14886, found: 258.14914, Δ 1.09 ppm.
**FTIR (ATR, cm$^{-1}$):** 2924w, 1700s, 1450w, 1415m, 1357m, 1111m, 698w.

### Benzyl 2-((*S*)-5-((*tert*-butyldimethylsilyl)oxy)-2,6,6-trimethylcyclohex-1-en-1-yl)pyrrolidine-1-carboxylate (12)

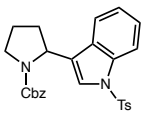



**12**

The title compound was prepared according to general procedure **E** from phthalimide ester **1** (36.8 mg, 0.1 mmol, 1.0 equiv.), diene **S–17**[11] (56.0 mg, 0.2 mmol, 2.0 equiv.), Ir(4-$CF_3$ppy)$_3$ (0.9 mg, 0.001 mmol, 1.0 mol%), and $(PhO)_2PO_2H$ (6.3 mg, 0.025 mmol, 25 mol%) in acetone (1.0 mL, 0.1 M). Purification was carried out by flash column chromatography on silica (10% EtOAc / petroleum ether), and the product pyrrolidine **12** was isolated as a colorless oil (62% yield, d.r. 1:1, average of two runs; Run 1: 28 mg, 0.028 mmol, 61% yield, d.r. 1:1; Run 2: 29 mg, 0.029 mmol, 63% yield, d.r. 1:1).

**Mixture of diastereoisomers:**
**$^1$H-NMR (δ, 500 MHz, $C_6D_6$, 323 K):** 7.26–7.30 (2H, m), 7.11–7.15 (2H, m), 7.04–7.09 (1H, m), 5.27 (1H, m), 4.94 (1H, d, $^2J_{HH}$ = 12.7 Hz), 4.20 (0.5H, app t, $^2J_{HH}$ = 8.6 Hz), 4.17 (0.5 H, app t, $^3J_{HH}$ = 8.7 Hz), 3.60–3.66 (1H, m), 3.48 (0.5H, d, $^3J_{HH}$ = 7.8 Hz), 3.42 (0.5H, dd, $^2J_{HH}$ = 11.5 Hz, $^3J_{HH}$ = 3.5 Hz), 3.28–3.34 (1H, m), 1.80–2.03 (3H, m), 1.55–1.75 (3H, m), 1.47–1.53 (1H, m), 1.47 (3H, s), 0.96–1.03 (12H, m), 0.06–0.09 (6H, m).
**$^{13}$C-NMR (δ, 126 MHz, $C_6D_6$, 323 K):** 153.4, 137.3, 137.3, 137.3, 137.2, 136.9, 135.7, 125.1, 124.6, 76.7, 76.0, 65.4, 65.3, 57.2, 57.0, 46.7, 46.5, 40.3, 39.7, 34.1, 34.0, 32.1, 30.4, 27.0, 26.2, 25.9, 25.3, 25.1, 25.1, 25.1, 25.0, 25.0, 25.0, 23.7, 23.6, 23.0, 19.9, 18.5, 18.4, 17.4, 17.3, -4.8, -5.0, -5.7, -5.7.
**HRMS (ESI-TOF):** Calc. for $C_{27}H_{44}NO_3Si^+$ ([M+H]$^+$): 458.30850, found:458.30910, Δ 1.31 ppm.
**FTIR (ATR, cm$^{-1}$):** 2954m, 2857m, 1696s, 1412m, 1355m, 1253m, 1113m, 1076m, 836m, 772m.

### Benzyl 2-(1-tosyl-1*H*-indol-3-yl)pyrrolidine-1-carboxylate (13)



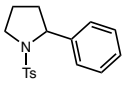

**13**

The title compound was prepared according to general procedure **E** from phthalimide ester **1** (184 mg, 0.50 mmol, 1.0 equiv.), 3-vinyl-1-tosyl-1H-indole[25] (297 mg, 1.0 mmol, 2.0 equiv.), Ir(4-$CF_3$ppy)$_3$ (4.3 mg, 0.005 mmol, 1.0 mol%), and $(PhO)_2PO_2H$ (31.3 mg, 0.125 mmol, 25 mol%) in acetone (5.0 mL, 0.1 M). Purification was carried out by flash column chromatography on silica (10–50% EtOAc / hexanes), and the product pyrrolidine **13** was isolated as a yellow oil (53% yield, average of two runs; run 1: 117 mg, 0.25 mmol, 49% yield; run 2: 134 mg, 0.28 mmol, 56% yield). Product appears as a rotameric mixture in NMR analysis.

**$^1$H-NMR (δ, 500 MHz, $C_6D_6$):** 8.23–8.28 (1H, br s), 7.52–7.65 (3H, br m), 7.32 (1H, br s), 7.11–7.21 (4H, m), 6.98 (1H, t, $^3J_{HH}$ = 7.6 Hz), 6.79–6.90 (2H, br d), 6.40–6.50 (2H, br d), 4.99–5.22 (2H, br m), 4.84–4.91 (1H, m), 3.49 (1H, br s), 3.16–3.29 (1H, br d), 1.57 (4H, m), 1.32–1.46 (2H, m), 1.19–1.24 (1H, m).

**$^{13}$C-NMR (δ, 126 MHz, $C_6D_6$):** 154.7, 144.4, 138.1, 137.3, 136.7, 136.4, 135.9, 135.7, 129.8, 128.4, 128.2, 128.0, 126.9, 126.3, 125.3, 125.0, 123.8, 123.5, 123.0, 120.1, 120.0, 114.6, 66.7, 54.8, 54.2, 47.3, 46.5, 33.3, 31.7, 23.8, 23.2, 21.0.
**HRMS (ESI-TOF):** Calc. for $C_{27}H_{26}N_2O_4SNa^+$ ([M+Na]$^+$): 497.15055, found: 497.15078, Δ 0.32 ppm.
**FTIR (ATR, cm$^{-1}$):** 2951w, 2280w, 1700s, 1447m, 1408m, 1355m, 1173s, 1122m, 1095m, 812m, 745m, 673m, 606m, 498m.

### 2-Phenyl-1-tosylpyrrolidine (14)

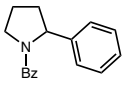


**14**

The title compound was prepared according to general procedure **E** from phthalimide ester **S–32** (194 mg, 0.50 mmol, 1.0 equiv.), styrene (115 µL, 1.0 mmol, 2.0 equiv.), Ir(4-$CF_3$ppy)$_3$ (4.3 mg, 0.005 mmol, 1.0 mol%), and $(PhO)_2PO_2H$ (31.3 mg, 0.125 mmol, 25 mol%) in acetone (5.0 mL, 0.1 M). Purification was carried out by flash column chromatography on silica (10% EtOAc / hexanes), and the product pyrrolidine **14** was isolated as an off-white solid (54% yield, average of two runs; run 1: 82 mg, 0.27 mmol, 54% yield; run 2: 81 mg, 0.27 mmol, 54% yield).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.63 (2H, d, $^3J_{HH}$ = 8.3 Hz), 7.28 – 7.21 (6H, m), 7.21 – 7.16 (1H, m), 4.74 (1H, dd, $^3J_{HH}$ = 8.0 Hz, 3.7 Hz), 3.61 – 3.54 (1H, m), 3.42 – 3.32 (1H, m), 2.38 (3H, s), 1.99 – 1.88 (1H, m), 1.85 – 1.73 (2H, m), 1.65 – 1.57 (1H, m).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 143.4, 143.2, 135.2, 129.7, 128.4, 127.6, 127.1, 126.3, 63.4, 49.5, 35.9, 24.1, 21.6.
Characterization data is consistent with that reported by Chen, Hu, Zhang, and co-workers.[26]

### Phenyl(2-phenylpyrrolidin-1-yl)methanone (15)

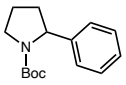


**15**

The title compound was prepared according to general procedure **E** from phthalimide ester **S–33** (169 mg, 0.50 mmol, 1.0 equiv.), styrene (115 µL, 1.0 mmol, 2.0 equiv.), Ir(4-$CF_3$ppy)$_3$ (4.3 mg, 0.005 mmol, 1.0 mol%), and $(PhO)_2PO_2H$ (31.3 mg, 0.125 mmol, 25 mol%) in acetone (5.0 mL, 0.1 M). Purification was carried out by flash column chromatography on silica (10% EtOAc / hexanes), and the product pyrrolidine **15** was isolated as a colorless oil (58% yield, average of two runs; run 1: 70 mg, 0.28 mmol, 56% yield; run 2: 74 mg, 0.29 mmol, 59% yield). Product appears as a rotameric mixture in NMR analysis.

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.55 – 7.48 (1H, m), 7.36 – 7.30 (1H, m), 7.27 – 7.22 (2H, m), 7.20 – 7.10 (3H, m), 7.08 – 7.04 (2H, m), 6.96 – 6.90 (1H, m), 5.27 – 5.25 (0.5H, m), 4.80 – 4.78 (0.5H, m), 3.93 – 3.87 (0.5H, m), 3.80 – 3.75 (0.5H, m), 3.68 – 3.63 (0.5H, m), 3.56 – 3.51 (0.5H, m), 2.38 – 2.31 (0.5H, m), 2.23 – 2.16 (0.5H, m), 1.94 – 1.72 (3H, m).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 171.1, 170.0, 143.9, 143.3, 137.2, 137.1, 130.2, 129.5, 128.6, 128.4, 128.0, 127.5, 127.1, 126.9, 126.7, 125.8, 125.7, 63.6, 61.0, 51.2, 47.2, 35.9, 34.9, 25.3, 21.8.
Characterization data is consistent with that reported by Lei and co-workers.[22]

### *Tert*-butyl 2-phenylpyrrolidine-1-carboxylate (16)

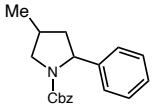


**16**

The title compound was prepared according to general procedure **E** from phthalimide ester **S–34** (167 mg, 0.50 mmol, 1.0 equiv.), styrene (115 µL, 1.0 mmol, 2.0 equiv.), Ir(4-$CF_3$ppy)$_3$ (4.3 mg, 0.005 mmol, 1.0 mol%), and $(PhO)_2PO_2H$ (31.3 mg, 0.125 mmol, 25 mol%) in acetone (5.0 mL, 0.1 M). Purification was carried out by flash column chromatography on silica (5% EtOAc / hexanes), and the product pyrrolidine **16** was isolated as a colorless oil (60% yield, average of two runs; run 1: 78 mg, 0.32 mmol, 64% yield; run 2: 70 mg, 0.28 mmol, 56% yield).

**$^1$H-NMR (δ, 500 MHz, $C_6D_6$, 343 K):** 7.03–7.14 (5H, m), 4.74 (1H, br s), 3.49 (2H, br s), 1.83–1.89 (1H, m), 1.48–1.55 (2H, m), 1.32–1.39 (10H, m).
**$^{13}$C-NMR (δ, 126 MHz, $C_6D_6$, 343 K):** 154.4, 128.4, 126.7, 126.0, 78.7, 61.5, 47.5, 35.7, 28.5, 23.5.
**HRMS (ESI-TOF):** Calc. for $C_{15}H_{21}NO_2Na^+$ ([M+Na]$^+$): 270.1465, found: 270.1465, Δ 0 ppm.
**FTIR (ATR, cm$^{-1}$):** 2973w, 2875w, 1691s, 1390s, 1364m, 1159m, 1113m, 700m.

### Benzyl 4-methyl-2-phenylpyrrolidine-1-carboxylate (17)



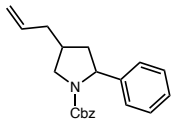
**17**

The title compound was prepared according to general procedure **E** from phthalimide ester **S–35** (191 mg, 0.50 mmol, 1.0 equiv.), styrene (115 µL, 1.0 mmol, 2.0 equiv.), Ir(4-$CF_3$ppy)$_3$ (4.3 mg, 0.005 mmol, 1.0 mol%), and $(PhO)_2PO_2H$ (31.3 mg, 0.125 mmol, 25 mol%) in acetone (5.0 mL, 0.1 M). Purification was carried out by flash column chromatography on silica (30% EtOAc / hexanes), and the product pyrrolidines **17** as a mixture of diastereoisomers were isolated as a colorless oil (75% yield, 1.1:1 d.r., average of two runs; run 1: 118 mg, 0.40 mmol, 80% yield, 1.1:1 d.r.; run 2: 102 mg, 0.35 mmol, 70% yield, 1.1:1 d.r.). Product appears as a rotameric mixture in NMR analysis.

**Mixture of diastereoisomers:**
**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.15–7.38 (9H, m), 6.89 (0.5H, d, $^3J_{HH}$ = 6.4 Hz), 6.75 (1H, d, $^3J_{HH}$ = 6.4 Hz), 4.95–5.17 (2.2H, m), 4.75–4.86 (0.8H, m), 3.96–4.06 (0.5H, m), 3.80–3.87 (0.5H, m), 3.20 (0.3H, t, $^3J_{HH}$ = 9.8 Hz), 3.10–3.15 (0.7H, m), 2.51 (0.5H, dt, $^2J_{HH}$ = 12.7 Hz, $^3J_{HH}$ = 6.4 Hz), 2.34–2.41 (0.5H, m), 2.24–2.29 (0.5H, m), 1.93–2.00 (1H, m), 1.46–1.52 (0.5H, m), 1.03–1.08 (3H, m).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 155.1, 145.0, 144.4, 143.6, 136.9, 136.7, 128.6, 128.5, 128.5, 128.3, 128.2, 128.1, 128.1, 127.6, 127.5, 127.3, 127.3, 127.0, 126.8, 125.7, 125.6, 66.9, 66.9, 66.7, 66.6, 62.8, 62.5, 61.6, 61.3, 55.4, 55.0, 54.5, 54.1, 46.1, 45.1, 43.6, 42.7, 33.6, 33.2, 31.1, 30.2, 29.9, 17.5, 17.4, 16.9.
**HRMS (ESI-TOF):** Calc. for $C_{19}H_{22}NO_2^+$ ([M+H]$^+$): 296.16451, found: 296.16555, Δ 3.5 ppm.
**FTIR (ATR, cm$^{-1}$):** 3031w, 2972w, 2876w, 1691s, 1404s, 1352s, 1161w, 1106w, 1082w, 1028w, 761w, 698m.

Major diastereoisomer was assigned as 2,4-*syn*-**S–N** by conversion of **S–N** to the corresponding *N*–Ts pyrrolidine (i. $H_2$, Pd/C, MeOH, rt.; ii. TsCl, $Et_3N$, $CH_2Cl_2$, rt.), and comparison to data for this compound as reported by Mūniz and co-workers.[27]

### Benzyl 4-allyl-2-phenylpyrrolidine-1-carboxylate (18)

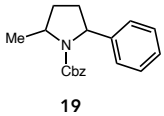


**18**

The title compound was prepared according to general procedure **E** from phthalimide ester **S–36** (204 mg, 0.50 mmol, 1.0 equiv.), styrene (115 µL, 1.0 mmol, 2.0 equiv.), Ir(4-$CF_3$ppy)$_3$ (4.3 mg, 0.005 mmol, 1.0 mol%), and $(PhO)_2PO_2H$ (31.3 mg, 0.125 mmol, 25 mol%) in acetone (5.0 mL, 0.1 M). Purification was carried out by flash column chromatography on silica (50% $Et_2O$ / hexanes), and the product pyrrolidines **18** as a mixture of diastereoisomers were isolated as a colorless oil (67% yield, 1.3:1 d.r., average of two runs; run 1: 100 mg, 0.31 mmol, 62% yield, 1.3:1 d.r.; run 2: 111 mg, 0.35 mmol, 70% yield, 1.3:1 d.r.). Product appears as a rotameric mixture in NMR analysis.

**Mixture of diastereoisomers:**
**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.26–7.39 (5H, m), 7.15–7.26 (4H, m), 6.91 (0.5H, d, $^3J_{HH}$ = 6.4 Hz), 6.77 (0.7H, d, $^3J_{HH}$ = 7.0 Hz), 5.70–5.81 (1H, m), 4.97–5.19 (5H, m), 4.77–4.89 (1H, m), 3.98–4.10 (0.5H, m), 3.80–3.88 (0.35H, m),3.18–3.31 (1H, m), 2.53 (0.7H, dt, $^2J_{HH}$ = 12.6 Hz, $^3J_{HH}$ = 6.5 Hz), 2.34–2.40 (0.35H, m), 2.24–2.31 (0.7H, m), 2.13–2.20 (2H, m), 1.96–1.99 (1H, m), 1.51–1.59 (0.7H, m).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 155.2, 155.0, 154.9, 154.8, 144.8, 144.2, 144.0, 143.4, 137.1, 137.0, 136.8, 136.6, 136.2, 136.2, 136.1, 128.6, 128.6, 128.5, 128.5, 128.3, 128.2, 128.1, 128.1, 127.6, 127.5, 127.3, 127.0, 126.9, 126.9, 126.8, 126.8, 125.7, 125.5, 116.5, 116.5, 116.4, 66.9, 66.9, 66.8, 66.6, 62.4, 62.1, 61.3, 61.0, 53.7, 53.2, 52.6, 52.2, 43.8, 42.7, 41.3, 40.4, 38.5, 38.0, 37.3, 37.0, 37.0, 36.2, 35.2.
**HRMS (ESI-TOF):** Calc. for $C_{21}H_{24}NO_2^+$ ([M+H]$^+$): 322.18016, found: 322.18044, Δ 0.87 ppm.
**FTIR (ATR, cm$^{-1}$):** 3030w, 2925w, 1702s, 1411m, 1352m, 1114w, 757w, 698m.

### Benzyl 2-methyl-5-phenylpyrrolidine-1-carboxylate (19)



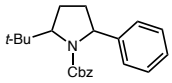
**19**

The title compound was prepared according to general procedure **E** from phthalimide ester **S–38** (191 mg, 0.50 mmol, 1.0 equiv.), styrene (115 µL, 1.0 mmol, 2.0 equiv.), Ir(4-$CF_3$ppy)$_3$ (4.3 mg, 0.005 mmol, 1.0 mol%), and $(PhO)_2PO_2H$ (31.3 mg, 0.125 mmol, 25 mol%) in acetone (5.0 mL, 0.1 M). Purification was carried out by flash column chromatography on silica (30% EtOAc / hexanes), and the product pyrrolidines **19** as a mixture

of diastereoisomers were isolated as a colorless oil (75% yield, 1.9:1 d.r., average of two runs; run 1: 122 mg, 0.41 mmol, 82% yield, 1.9:1 d.r.; run 2: 101 mg, 0.34 mmol, 68% yield, 1.9:1 d.r.). Product appears as a rotameric mixture in NMR analysis.

Mixture of diastereoisomers:
**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.09–7.39 (10H, m), 6.77 (1H, d, $^3J_{HH}$ = 7.2 Hz), 5.17 (0.35H, d, $^2J_{HH}$ = 12.4 Hz), 5.09 (0.35H, d, $^2J_{HH}$ = 12.4 Hz), 4.99–5.06 (1.65H, m), 4.86 (0.65H, d, $^2J_{HH}$ = 12.7 Hz), 4.30–4.36 (0.65H, m), 4.24–4.29 (0.35H, m), 2.38–2.50 (1H, m), 2.10–2.18 (1H, m), 1.71–1.77 (1H, m), 1.51–1.55 (1H, m), 1.32 (2H, d, $^3J_{HH}$ = 6.4 Hz), 1.25 (1H, d, $^3J_{HH}$ = 6.2 Hz).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 154.6, 144.8, 143.7, 136.9, 128.6, 128.5, 128.5, 128.2, 128.2, 128.0, 127.5, 127.3, 126.8, 126.7, 125.4, 125.4, 66.9, 66.4, 61.7, 61.6, 54.6, 54.0, 32.8, 31.9, 30.0, 29.1, 21.0, 19.9.
**HRMS (ESI-TOF):** Calc. for $C_{19}H_{22}NO_2^+$ ([M+H]$^+$): 296.16451, found: 296.16462, Δ 0.37 ppm.
**FTIR (ATR, cm$^{-1}$):** 3031w, 2965w, 1701s, 1404m, 1349m, 1088w, 698m.

Benzyl 2-(*tert*-butyl)-5-phenylpyrrolidine-1-carboxylate (20)



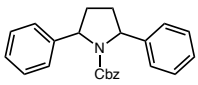
20

The title compound was prepared according to general procedure **E** from phthalimide ester **S–39** (212 mg, 0.50 mmol, 1.0 equiv.), styrene (115 µL, 1.0 mmol, 2.0 equiv.), Ir(4-$CF_3$ppy)$_3$ (4.3 mg, 0.005 mmol, 1.0 mol%), and $(PhO)_2PO_2H$ (31.3 mg, 0.125 mmol, 25 mol%) in acetone (5.0 mL, 0.1 M). Purification was carried out by flash column chromatography on silica (30% $Et_2O$ / hexanes), and the product pyrrolidines **20** as a mixture of diastereoisomers were isolated as a pale yellow oil (65% yield, 1.1:1 d.r., average of two runs; run 1: 116 mg, 0.34 mmol, 68% yield, 1.1:1 d.r.; run 2: 105 mg, 0.31 mmol, 70% yield, 1.1:1 d.r.). An analytical sample was further separated into component diastereoisomers using preparative TLC on silica (10% $Et_2O$ / hexanes).

Diastereoisomer 1:
**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.05–7.29 (8.5H, m), 6.66–6.68 (1.5H, m), 4.98 (1H, d, $^3J_{HH}$ = 8.6 Hz), 4.79 (1H, br d, $^2J_{HH}$ = 11.2 Hz), 4.65 (1H, br d, $^2J_{HH}$ = 11.2 Hz), 4.21 (1H, d, $^3J_{HH}$ = 8.3 Hz), 2.41–2.50 (1H, m), 2.07–2.16 (1H, m), 1.81–1.85 (1H, m), 1.64 (1H, app dd, $^2J_{HH}$ = 13.1 Hz, $^3J_{HH}$ = 8.0 Hz), 0.99 (9H, s).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 157.2, 146.9, 136.3, 128.7, 128.2, 128.1, 127.6, 126.6, 124.6, 67.1, 67.0, 63.7, 37.6, 34.6, 27.9, 24.0.
**HRMS (ESI-TOF):** Calc. for $C_{22}H_{28}NO_2^+$ ([M+H]$^+$): 338.21146, found: 338.21146, Δ 0.02 ppm.
**FTIR (ATR, cm$^{-1}$):** 2955w, 1704s, 1394m, 1337m, 1321m, 1110m, 698m.

Diastereoisomer 2:
**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.12–7.37 (8.5H, m), 6.99–7.12 (1.5H, br s), 4.99–5.14 (3H, m), 4.05 (1H, d, $^3J_{HH}$ = 7.6 Hz), 2.38–2.43 (1H, m), 1.89–1.98 (3H, m), 0.95 (9H, s).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 158.3, 144.2, 136.8, 128.4, 128.3, 127.7, 127.5, 126.3, 125.5, 68.4, 67.1, 63.9, 36.2, 34.7, 27.9, 26.9.
**HRMS (ESI-TOF):** Calc. for $C_{22}H_{28}NO_2^+$ ([M+H]$^+$): 338.21146, found: 338.21150, Δ 0.09 ppm.
**FTIR (ATR, cm$^{-1}$):** 2955w, 1703s, 1391m, 1336m, 1295m, 1105w, 698m.

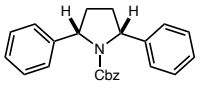
Benzyl 2,5-diphenylpyrrolidine-1-carboxylate (21)



21

The title compound was prepared according to general procedure **E** from phthalimide ester **S–40** (222 mg, 0.50 mmol, 1.0 equiv.), styrene (115 µL, 1.0 mmol, 2.0 equiv.), Ir(4-$CF_3$ppy)$_3$ (4.3 mg, 0.005 mmol, 1.0 mol%), and $(PhO)_2PO_2H$ (31.3 mg, 0.125 mmol, 25 mol%) in acetone (5.0 mL, 0.1 M). Purification was carried out by flash column chromatography on silica (50% $Et_2O$ / hexanes), and the product pyrrolidines **21** as a mixture of diastereoisomers were isolated as a yellow oil (70% yield, 1.6:1 d.r., average of two runs; run 1: 128 mg, 0.36 mmol, 72% yield, 1.6:1 d.r.; run 2: 121 mg, 0.34 mmol, 68% yield, 1.6:1 d.r.). An analytical sample was further separated into component diastereoisomers using preparative SFC (Whelk-O1 (R,R) (2 x 25 cm) 60 mL/min @ 40% isopropanol (0.1% DEA) / 60% $CO_2$ (100 bar); 2.0 mL injection @ ~20 mg/mL; detection at 220 nm).

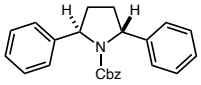
2,5-*Syn*-diastereoisomer (Major diastereoisomer):



*syn*-**21**

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.12–7.35 (13H, m), 6.78 (2H, d, $^3J_{HH}$ = 7.4 Hz), 5.35 (1H, d, $^3J_{HH}$ = 7.2 Hz), 5.28 (1H, d, $^3J_{HH}$ = 7.4 Hz), 5.01 (1H, d, $^2J_{HH}$ = 12.7 Hz), 4.87 (1H, d, $^2J_{HH}$ = 12.7 Hz), 2.46–2.51 (2H, m), 1.77 (2H, app t, $^3J_{HH}$ = 5.2 Hz).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 154.7, 144.6, 143.5, 136.7, 128.6, 128.6, 128.2, 127.6, 127.5, 127.0, 127.0, 126.9, 125.4, 125.4, 66.8, 62.4, 62.2, 32.4, 31.4.
**HRMS (ESI-TOF):** Calc. for $C_{24}H_{24}NO_2^+$ ([M+H]$^+$): 358.18016, found: 358.18040, Δ 0.74 ppm.
**FTIR (ATR, cm$^{-1}$):** 3064w, 3029w, 2975w, 1701s, 1528w, 1496m, 1454w, 1402m, 1340m, 1238w, 757w, 698s.

2,5-*Anti*-diastereoisomer (Minor diastereoisomer):

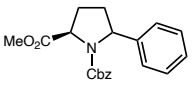


*anti*-**21**

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.30–7.39 (8H, m), 7.24–7.28 (2H, m), 7.19–7.23 (3H, m), 6.97 (2H, dd, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 2.3 Hz), 5.04–5.15 (2H, m), 5.02 (2H, s), 2.33–2.40 (2H, m), 2.10–2.17 (2H, m).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 156.5, 143.1, 136.6, 128.5, 128.3, 127.7, 127.6, 127.0, 126.7, 67.0, 63.5, 34.6, 33.0.
**HRMS (ESI-TOF):** Calc. for $C_{24}H_{24}NO_2^+$ ([M+H]$^+$): 358.18016, found: 358.18030, Δ 0.88 ppm.
**FTIR (ATR, cm$^{-1}$):** 3062w, 3029w, 2946w, 1704s, 1495w, 1451m, 1403m, 1346m, 1112m, 750w, 699s.

Assignment of relative stereochemical identity of these two diastereoisomers, and of 2,5-*syn*-**21** as the major isomer, were carried out by conversion of the two separated isomers to the corresponding N–H compounds ($H_2$, Pd/C, MeOH, rt.) and comparison to data for the *anti*-isomer of this compound as reported by Dauban and co-workers.[28]

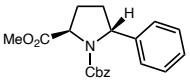
1-Benzyl 2-methyl (2*R*)-5-phenylpyrrolidine-1,2-dicarboxylate (22)



**22**

The title compound was prepared according to general procedure **E** from phthalimide ester **S–41** (213 mg, 0.50 mmol, 1.0 equiv.), styrene (115 μL, 1.0 mmol, 2.0 equiv.), Ir(4-$CF_3$ppy)$_3$ (4.3 mg, 0.005 mmol, 1.0 mol%), and $(PhO)_2PO_2H$ (31.3 mg, 0.125 mmol, 25 mol%) in acetone (5.0 mL, 0.1 M). Purification was carried out by flash column chromatography on silica (50–60% $Et_2O$ / hexanes), and the product pyrrolidines **22** as a mixture of diastereoisomers were isolated as a white solid (70% yield, 1.2:1 d.r., average of two runs; run 1: 113 mg, 0.33 mmol, 68% yield, 1.2:1 d.r.; run 2: 120 mg, 0.35 mmol, 71% yield, 1.2:1 d.r.). An analytical sample was further separated into component diastereoisomers using preparative HPLC (Whelk-O1 column, 20% iPrOH / hexanes eluent, 220 nm detection wavelength).

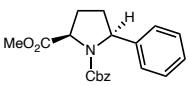
2,5-*Anti*-diastereoisomer (Major diastereoisomer):



*anti*-**22**

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.29–7.36 (4H, m), 7.21–7.26 (1H, m), 7.12–7.19 (4H, m), 6.85 (1H, d, $^3J_{HH}$ = 7.4 Hz), 5.23–5.25 (0.6H, m), 5.17–5.20 (0.8H, m), 5.08 (0.6H, d, $^2J_{HH}$ = 12.6 Hz), 4.98 (0.4H, d, $^2J_{HH}$ = 12.4 Hz), 4.94 (0.6H, d, $^2J_{HH}$ = 12.6 Hz), 4.69 (0.6H, dd, $^3J_{HH}$ = 9.0 Hz, $^4J_{HH}$ = 1.1 Hz), 4.62 (0.4H, dd, $^3J_{HH}$ = 9.0 Hz, $^4J_{HH}$ = 0.9 Hz), 3.78 (1.8H, s), 3.57 (1.2H, s), 2.42–2.55 (1H, m), 2.27–2.37 (1H, m), 1.96–2.00 (1H, m), 1.80–1.86 (1H, m).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 173.3, 173.0, 155.0, 154.3, 143.8, 143.0, 136.6, 136.5, 128.7, 128.6, 128.6, 128.3, 128.2, 128.2, 127.7, 127.3, 127.2, 127.1, 125.5, 67.3, 67.0, 61.9, 61.6, 60.3, 60.2, 52.5, 52.3, 33.6, 32.6, 28.4, 27.2.
**HRMS (ESI-TOF):** Calc. for $C_{20}H_{21}NO_4Na^+$ ([M+Na]$^+$): 362.1363, found: 362.1363, Δ 0.16 ppm.
**FTIR (ATR, cm$^{-1}$):** 3032w, 2953w, 1746m, 1705s, 1408s, 1349m, 1213m, 1118m, 700w.

2,5-*Syn* diastereoisomer (Minor diastereoisomer):



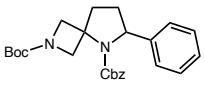
*syn*-**22**

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.54–7.56 (2H, m), 7.17–7.36 (7H, m), 6.86 (1H, d, $^3J_{HH}$ = 7.0 Hz), 5.06–5.12 (0.8H, m), 4.95–5.02 (1.6H, m), 4.91 (0.6H, t, $^3J_{HH}$ = 6.6 Hz), 4.55 (0.6H, t, $^3J_{HH}$ = 6.9 Hz), 4.48 (0.4H, t, $^3J_{HH}$ = 7.1 Hz), 3.83 (1.8H, s), 3.68 (1.2H, s), 2.23–2.38 (1H, m), 2.20–2.27 (1H, m), 2.07–2.14 (1H, m), 1.95–2.01 (1H, m).

**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 173.4, 173.3, 155.4, 154.6, 143.4, 142.6, 136.6, 136.3, 128.5, 128.3, 128.1, 128.0, 127.7, 127.4, 127.1, 127.0, 126.4, 126.3, 67.4, 67.2, 63.2, 62.9, 61.0, 60.6, 52.5, 52.3, 35.7, 34.6, 29.4, 28.7.
**HRMS (ESI-TOF):** Calc. for $C_{20}H_{21}NO_4Na^+$ ([M+Na]$^+$): 362.1363, found: 362.1363, Δ 0.19 ppm.
**FTIR (ATR, cm$^{-1}$):** 2950w, 1750m, 1704s, 1408m, 1345m, 1197m, 1174m, 701m.

Characterization data for 2,5-*syn*-**22** is consistent with that reported by Larchevêque and co-workers.[29] Relative stereochemical identity of these two diastereoisomers were assigned by comparison to this report.

### 5-Benzyl 2-(*tert*-butyl) 6-phenyl-2,5-diazaspiro[3.4]octane-2,5-dicarboxylate (23)

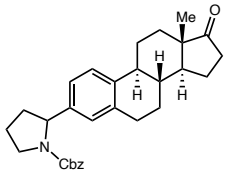


**23**

The title compound was prepared according to general procedure **E** from phthalimide ester **S–42** (255 mg, 0.50 mmol, 1.0 equiv.), styrene (115 µL, 1.0 mmol, 2.0 equiv.), Ir(4-$CF_3$ppy)$_3$ (4.3 mg, 0.005 mmol, 1.0 mol%), and $(PhO)_2PO_2H$ (31.3 mg, 0.125 mmol, 25 mol%) in acetone (5.0 mL, 0.1 M). Purification was carried out by flash column chromatography on silica (30% EtOAc / hexanes), and the product pyrrolidine **23** was isolated as a colorless oil (54% yield, average of two runs; run 1: 118 mg, 0.28 mmol, 56% yield; run 2: 110 mg, 0.26 mmol, 52% yield).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.15–7.41 (7H, m), 7.06 (2H, d, $^3J_{HH}$ = 7.3 Hz), 6.88 (1H, d, $^3J_{HH}$ = 7.3 Hz), 4.96–5.22 (4H, m), 4.40–4.78 (1H, m), 3.91 (1H, d, $^3J_{HH}$ = 8.1 Hz), 3.73 (1H, d, $^3J_{HH}$ = 7.8 Hz), 2.18–2.24 (3H, m), 1.76–1.78 (1H, m), 1.47 (9H, s).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 156.7, 154.1, 143.3, 136.5, 128.6, 128.3, 127.7, 127.4, 127.1, 125.3, 79.6, 67.7, 66.6, 63.6, 63.0, 59.7, 59.4, 58.6, 38.0, 36.8, 32.1, 31.5, 28.6.
**HRMS (ESI-TOF):** Calc. for $C_{25}H_{30}N_2O_4Na^+$ ([M+Na]$^+$): 445.2098, found: 445.2097, Δ 0.22 ppm
**FTIR (ATR, cm$^{-1}$):** 2939w, 1702s, 1401m, 1345w, 1128w, 699w.

### Benzyl 2-((8*R*,9*S*,13*S*,14*S*)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl)pyrrolidine-1-carboxylate (42)

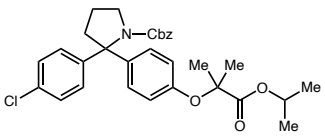


**42**

The title compound was prepared according to general procedure **E** from phthalimide ester **1** (36.8 mg, 0.1 mmol, 1.0 equiv.), vinyl estrone[9] (**40**, 28.0 mg, 0.1 mmol, 1.0 equiv.), Ir(4-$CF_3$ppy)$_3$ (0.9 mg, 0.001 mmol, 1.0 mol%), and $(PhO)_2PO_2H$ (6.3 mg, 0.025 mmol, 25 mol%) in acetone (1.0 mL, 0.1 M). Purification was carried out by flash column chromatography on silica (25% EtOAc / hexanes), and the product pyrrolidine **42** as a mixture of diastereoisomers was isolated as a colorless oil (72% yield, d.r. 1:1, average of two runs; Run 1: 34 mg, 0.074 mmol, 74% yield, d.r. 1:1; Run 2: 32 mg, 0.070 mmol, 70% yield, d.r. 1:1).

Mixture of diastereoisomers:
**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.30–7.39 (2.5H, m), 7.16–7.26 (2.5H, m), 6.86–6.99 (3H, m), 5.05–5.17 (1.5H, m), 4.87–4.97 (1.5H, m), 3.61–3.70 (2H, m), 2.83–2.91 (2H, m), 2.48–2.54 (1H, m), 2.39–2.44 (1H, m), 2.26–2.36 (2H, m), 1.85–2.17 (7H, m), 1.43–1.68 (7H, m), 1.25–1.29 (2H, m), 0.87–0.93 (3H, m).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 221.2, 221.1, 155.2, 155.0, 141.9, 141.2, 138.3, 138.2, 137.2, 137.1, 137.0, 136.5, 128.7, 128.6, 128.4, 128.2, 128.0, 127.5, 127.4, 127.3, 126.3, 126.2, 126.1, 125.6, 125.6, 125.5, 125.4, 123.3, 123.1, 123.1, 123.0, 67.2, 66.8, 66.6, 66.5, 61.2, 61.2, 60.9, 60.8, 50.6, 48.1, 47.7, 47.3, 44.5, 38.4, 38.2, 36.0, 35.9, 34.9, 31.7, 29.8, 29.8, 29.7, 29.6, 29.6, 26.7, 25.9, 25.8, 25.8, 23.8, 23.1, 22.8, 21.7, 14.3, 14.0.
**HRMS (ESI-TOF):** Calc. for $C_{30}H_{36}NO_3^+$ ([M+H]$^+$): 458.26897, found: 458.26971, Δ 1.61 ppm.
**FTIR (ATR, cm$^{-1}$):** 2927w, 2872w, 1737s, 1702s, 1411m, 1354w, 1110w.

**Benzyl 2-(4-chlorophenyl)-2-(4-((1-isopropoxy-2-methyl-1-oxopropan-2-yl)oxy)phenyl)pyrrolidine-1-carboxylate (45)**

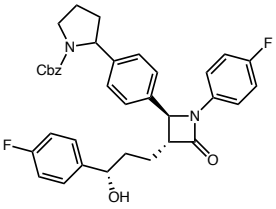



**45**

The title compound was prepared according to general procedure **E** from phthalimide ester **1** (36.8 mg, 0.1 mmol, 1.0 equiv.), fenofibrate 1,1-diaryl ethylene (**41**, 35.9 mg, 0.1 mmol, 1.0 equiv.), Ir(4-$CF_3$ppy)$_3$ (0.9 mg, 0.001 mmol, 1.0 mol%), and $(PhO)_2PO_2H$ (6.3 mg, 0.025 mmol, 25 mol%) in acetone (1.0 mL, 0.1 M). Purification was carried out by flash column chromatography on silica (10% EtOAc / petroleum ether), and the product pyrrolidine **45** was isolated as a brown oil (66% yield, average of two runs; Run 1: 33 mg, 0.062 mmol, 62% yield; Run 2: 37 mg, 0.069 mmol, 69% yield).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.31–7.36 (2H, m), 7.05–7.24 (8H, m), 6.70–6.78 (3H, m), 5.08 (1H, hept, $^3J_{HH}$ = 6.3 Hz), 5.02 (1H, br t, $^2J_{HH}$ = 12.3 Hz), 4.82 (0.5H, d, $^2J_{HH}$ = 12.3 Hz), 4.61 (0.5H, d, $^2J_{HH}$ = 12.3 Hz), 3.78–3.82 (2H, m), 2.50–2.60 (2H, m), 1.70–1.79 (2H, m), 1.59 (6H, s), 1.22 (6H, d, $^3J_{HH}$ = 6.3 Hz).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 173.8, 155.1, 154.5, 154.0, 143.0, 142.8, 137.3, 136.0, 135.6, 132.5, 129.3, 128.7, 128.5, 128.1, 128.0, 127.9, 127.8, 118.1, 79.2, 72.3, 72.2, 69.1, 69.1, 69.0, 66.8, 66.6, 49.2, 48.6, 47.7, 46.0, 25.6, 25.5, 25.5, 22.8, 22.1, 21.7.
**HRMS (ESI-TOF):** Calc. for $C_{31}H_{35}ClNO_5^+$ ([M+H]$^+$): 536.21983, found: 536.22029, Δ 0.86 ppm.
**FTIR (ATR, cm$^{-1}$):** 2981m, 2878w, 1724s, 1689s, 1507m, 1402m, 1349m, 1287w, 1179m, 1148m, 1101s, 1012m, 912m, 817m, 698m.

**Benzyl 2-(4-((2*S*,3*R*)-1-(4-fluorophenyl)-3-((*S*)-3-(4-fluorophenyl)-3-hydroxypropyl)-4-oxoazetidin-2-yl)phenyl)pyrrolidine-1-carboxylate (47)**

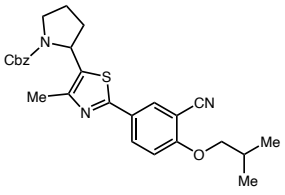



**47**

The title compound was prepared according to general procedure **E** from phthalimide ester **1** (36.8 mg, 0.10 mmol, 1.0 equiv.), vinyl ezetimibe (***S*–21**, 41.9 mg, 0.1 mmol, 1.0 equiv.), Ir(4-$CF_3$ppy)$_3$ (0.9 mg, 0.001 mmol, 1.0 mol%), and $(PhO)_2PO_2H$ (6.3 mg, 0.025 mmol, 25 mol%) in acetone (1.0 mL, 0.1 M). Purification was carried out by Flash column chromatography on silica (50–100% $Et_2O$ / hexanes), and the product pyrrolidine **47** as a mixture of diastereoisomers was isolated as a white solid (61% yield, d.r. 1:1 average of two runs; Run 1: 38.0 mg, 0.064 mmol, 64% yield, d.r. 1:1; Run 2: 34.0 mg, 0.057 mmol, 57% yield, d.r. 1:1).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.15–7.39 (10H, m), 6.87–7.13 (7H, m), 5.05–5.18 (1H, m), 4.91–5.01 (2H, m), 4.69–4.73 (1H, m), 4.58–4.62 (1H, m), 3.60–3.69 (2H, m), 3.06–3.12 (1H, m), 2.26–2.36 (1H, m), 1.83–2.02 (7H, m).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 167.8, 167.6, 163.3, 163.3, 161.3, 161.3, 160.1, 160.1, 158.1, 158.1, 155.1, 155.1, 145.0, 145.0, 144.2, 144.2, 140.2, 140.2, 137.0, 136.9, 136.7, 136.7, 136.1, 136.0, 136.0, 134.0, 133.9, 129.9, 129.8, 129.7, 129.6, 128.7, 128.6, 128.6, 128.3, 128.2, 128.2, 128.2, 128.1, 128.0, 128.0, 127.7, 127.5, 127.5, 127.5, 127.3, 127.2, 126.6, 126.6, 126.5, 126.0, 126.0, 126.0, 118.6, 118.5, 118.4, 116.1, 115.9, 115.5, 115.4, 73.4, 73.2, 73.2, 67.0, 66.7, 66.7, 61.3, 61.3, 61.2, 61.1, 61.1, 60.8, 60.4, 60.4, 60.3, 60.3, 47.7, 47.3, 36.8, 36.6, 35.8, 34.8, 29.6, 29.5, 25.2, 25.2, 25.2, 25.2, 25.1, 23.7, 23.7, 23.1.
**$^{19}$F-NMR (δ, 228 MHz, $CDCl_3$):** -115.0 – -114.8 (m), -118.1 – -118.0 (m).
**HRMS (ESI-TOF):** Calc. for $C_{36}H_{34}F_2N_2O_4Na^+$ ([M+Na]$^+$): 619.23789, found: 619.23927, Δ 2.23 ppm.
**FTIR (ATR, cm$^{-1}$):** 3441br w, 2948w, 1744m, 1700m, 1509s, 1417m, 1388m, 1353m, 1219m, 834m, 733m.

**Benzyl 2-(2-(3-cyano-4-isobutoxyphenyl)-4-methylthiazol-5-yl)pyrrolidine-1-carboxylate (48)**

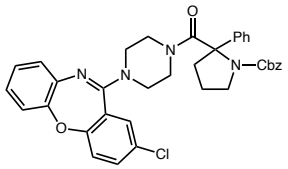



**48**

The title compound was prepared according to general procedure **E** from phthalimide ester **1** (36.8 mg, 0.10 mmol, 1.0 equiv.), vinyl febuxostat (**58**, 29.8 mg, 0.1 mmol, 1.0 equiv.), Ir(4-$CF_3$ppy)$_3$ (0.9 mg, 0.001 mmol, 1.0 mol%), and $(PhO)_2PO_2H$ (6.3 mg, 0.025 mmol, 25 mol%) in acetone (1.0 mL, 0.1 M). Purification was carried out by flash column chromatography on silica (10% EtOAc / hexanes), and the product pyrrolidine **48** was isolated as a colorless oil (77% yield, average of two runs; Run 1: 38.0 mg, 0.080 mmol, 80% yield; Run 2: 35.0 mg, 0.074 mmol, 74% yield).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$, 323 K):** 8.04–8.08 (1H, m), 7.93–7.98 (1H, m), 7.07–7.39 (5H, m), 6.96 (1H, d, $^3J_{HH}$ = 8.8 Hz), 4.88–5.29 (3H, m), 3.89 (1H, d, $^3J_{HH}$ = 6.4 Hz), 3.54–3.70 (2H, m), 2.32–2.52 (4H, m), 2.08–2.24 (3H, m), 1.90–2.03 (2H, m), 1.10 (6H, d, $^3J_{HH}$ = 6.6 Hz).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$, 323 K):** 161.8, 161.7, 154.9, 148.8, 136.8, 132.0, 131.6, 128.6, 128.1, 128.1, 127.4, 115.8, 112.8, 103.1, 75.9, 67.3, 54.9, 46.9, 35.2, 28.4, 23.9, 19.2, 15.4
**HRMS (ESI-TOF):** Calc. for $C_{27}H_{30}N_3O_3S^+$ ([M+H]$^+$): 476.2002, found 476.2001, Δ 0.21 ppm.
**FTIR (ATR, cm$^{-1}$):** 2960w, 2875w, 2228w, 1695m, 1607w, 1508m, 1448w, 1407m, 1354w, 1274m, 1114m, 1012m, 906s, 724s, 696m, 646m.

### Benzyl 2-(4-(2-chlorodibenzo[*b*,*f*][1,4]oxazepin-11-yl)piperazine-1-carbonyl)-2-phenylpyrrolidine-1-carboxylate (49)

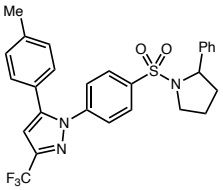


**49**

The title compound was prepared according to general procedure **E** from phthalimide ester **1** (36.8 mg, 0.10 mmol, 1.0 equiv), amoxapine α-phenyl acrylamide (**S–27**, 44.4 mg, 0.1 mmol, 1.0 equiv.), Ir(4-$CF_3$ppy)$_3$ (0.9 mg, 0.001 mmol, 1.0 mol%), and $(PhO)_2PO_2H$ (25.0 mg, 0.1 mmol, 1.0 equiv.) in acetonitrile (2.0 mL, 0.05 M). Purification was carried out by flash column chromatography on silica (30% EtOAc / hexanes), and the product pyrrolidine **49** was isolated as a yellow oil (38% yield, average of two runs; Run 1: 22 mg, 0.035 mmol, 35% yield; Run 2: 25 mg, 0.040 mmol, 40% yield).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.24–7.40 (12H, m), 7.06–7.18 (4H, m), 6.99–7.02 (1H, m), 5.08–5.10 (2H, m), 3.78–3.83 (1H, m), 3.66–3.71 (1H, m), 3.14–3.86 (8H, br m), 2.53–2.65 (2H, m), 1.89–2.04 (2H, m).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 171.1, 170.3, 159.5, 158.9, 154.9, 151.9, 141.2, 140.9, 139.9, 136.9, 136.2, 133.0, 130.6, 129.5, 129.4, 129.0, 128.5, 128.2, 127.9, 127.6, 127.2, 126.0, 125.9, 125.8, 125.1, 124.9, 123.0, 120.3, 72.9, 66.9, 48.5, 47.3, 46.7, 43.4, 41.9, 41.3, 23.9, 23.1.
**HRMS (ESI-TOF):** Calc. for $C_{36}H_{34}ClN_4O_4^+$ ([M+H]$^+$): 621.2263, found: 621.2268, Δ 0.87 ppm.
**FTIR (ATR, cm$^{-1}$):** 2926w, 2855w, 1697m, 1652m, 1602m, 1588m, 1559m, 1470m, 1404s, 1352m, 1234m, 1184m, 1010w, 699w.

### 1-(4-((2-Phenylpyrrolidin-1-yl)sulfonyl)phenyl)-5-(*p*-tolyl)-3-(trifluoromethyl)-1*H*-pyrazole (55)

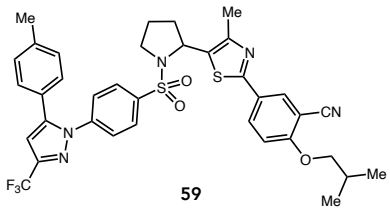


**55**

The title compound was prepared according to general procedure **E** from phthalimide ester **52** (59.9 mg, 0.1 mmol, 1.0 equiv.), styrene (25.0 µL, 0.2 mmol, 2.0 equiv.), Ir(4-$CF_3$ppy)$_3$ (0.9 mg, 0.001 mmol, 1.0 mol%), and $(PhO)_2PO_2H$ (25.0 mg, 0.1 mmol, 1.0 equiv.) in acetone (250 µL, 0.4 M). Purification was carried out by preparative thin layer chromatography on silica (35% EtOAc / Hexanes), and the product pyrrolidine **55** was isolated as a colorless oil (77% yield, average of two runs; Run 1: 41.0 mg, 0.080 mmol, 80% yield; Run 2: 37.5 mg, 0.073 mmol, 73% yield).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.74 (2H, d, $^3J_{HH}$ = 8.6 Hz), 7.43 (2H, m, $^3J_{HH}$ = 8.6 Hz), 7.21–7.31 (5H, m), 7.16 (2H, d, $^3J_{HH}$ = 8.1 Hz), 7.09 (2H, d, $^3J_{HH}$ = 8.1 Hz), 6.75 (1H, s), 4.79 (1H, dd, $^3J_{HH}$ = 8.1, 3.8 Hz), 3.61 (1H, ddd, $^2J_{HH}$ = 10.4 Hz, $^3J_{HH}$ = 4.7, 2.5 Hz), 4.34 (1H, dt, $^2J_{HH}$ = 10.4 Hz, $^3J_{HH}$ = 7.1 Hz), 2.38 (3H, s), 2.00–2.06 (1H, m), 1.82–1.94 (2H, m), 1.69–1.75 (1H, m).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 145.4, 144.2 (q, $^2J_{CF}$ = 38.5 Hz), 142.6, 142.5, 139.9, 138.0, 129.9, 128.8, 128.5, 128.5, 127.4, 126.3, 125.8, 125.6, 121.2 (q, $^1J_{CF}$ = 269.4 Hz), 106.3, 63.7, 49.5, 36.0, 24.2, 21.5.
**$^{19}$F-NMR (δ, 376 MHz, $CDCl_3$):** -62.4.
**HRMS (ESI-TOF):** Calc. for $C_{27}H_{25}F_3N_3O_2S^+$ ([M+H]$^+$): 512.16141, found: 512.16148, Δ 0.21 ppm.
**FTIR (ATR, cm$^{-1}$):** 2976w, 1497w, 1471w, 1350w, 1236m, 1159s, 1132m, 1097m, 976m, 844m, 808m, 743m, 616m.

**2-Isobutoxy-5-(4-methyl-5-(1-((4-(5-(*p*-tolyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)sulfonyl)pyrrolidin-2-yl)thiazol-2-yl)benzonitrile (59)**



**59**

**With 1:1 NHPI to styrene stoichiometry:**

The title compound was prepared according to general procedure **E** from phthalimide ester **52** (59.9 mg, 0.1 mmol, 1.0 equiv.), vinyl febuxostat **58** (29.8 mg, 0.1 mmol, 1.0 equiv.), Ir(4-$CF_3$ppy)$_3$ (0.9 mg, 0.001 mmol, 1.0 mol%), and $(PhO)_2PO_2H$ (25.0 mg, 0.1 mmol, 1.0 equiv.) in acetone (250 µL, 0.4 M). Purification was carried out by preparative thin layer chromatography on silica (50% $Et_2O$ / Hexanes) and the product pyrrolidine **59** was isolated as a colorless oil (61% yield, average of two runs; Run 1: 44.5 mg, 0.063 mmol, 63% yield; Run 2: 41.7 mg, 0.059 mmol, 59% yield).

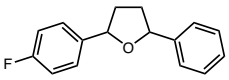
**With 1.2:1 NHPI to styrene stoichiometry:**

The title compound was prepared according to general procedure **E** from phthalimide ester **52** (72.0 mg, 0.12 mmol, 1.2 equiv.), vinyl febuxostat **58** (29.8 mg, 0.1 mmol, 1.0 equiv.), Ir(4-$CF_3$ppy)$_3$ (0.9 mg, 0.001 mmol, 1.0 mol%), and $(PhO)_2PO_2H$ (25.0 mg, 0.1 mmol, 1.0 equiv.) in acetone (250 µL, 0.4 M). Purification was carried out by preparative thin layer chromatography on silica (50% $Et_2O$ / Hexanes) and the product pyrrolidine **59** was isolated as a colorless oil (68% yield, average of two runs; Run 1: 49.4 mg, 0.070 mmol, 70% yield; Run 2: 46.5 mg, 0.066 mmol, 66% yield).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 8.01 (1H, d, $^4J_{HH}$ = 2.1 Hz), 7.79 (1H, dd, $^3J_{HH}$ = 9.0 Hz, $^3J_{HH}$ = 2.1 Hz), 7.64 (2H, d, $^3J_{HH}$ = 8.7 Hz), 7.34 (2H, d, $^3J_{HH}$ = 8.7 Hz), 7.15 (2H, d, $^3J_{HH}$ = 8.0 Hz), 7.03 (2H, d, $^3J_{HH}$ = 8.0 Hz), 6.90 (1H, d, $^3J_{HH}$ = 8.9 Hz), 6.69 (1H, s), 5.08 (1H, dd, $^3J_{HH}$ = 7.8, 4.1 Hz), 3.86 (2H, d, $^3J_{HH}$ = 6.4 Hz), 3.52 (2H, t, $^3J_{HH}$ = 6.5 Hz), 2.45 (3H, s), 2.37 (3H, s), 2.16–2.28 (2H, m), 2.05–2.11 (1H, m), 1.86–1.95 (2H, m).1.09 (6H, d, $^3J_{HH}$ = 6.7 Hz).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 163.2, 161.9, 149.5, 145.3, 144.1 (q, $^2J_{CF}$ = 38.7 Hz), 142.5, 140.0, 138.0, 134.9, 132.2, 131.4, 129.9, 128.8, 128.2, 126.5, 125.7, 125.4, 121.2 (q, $^1J_{CF}$ = 268.8 Hz), 115.8, 112.5, 106.4, 106.4, 102.8, 75.6, 56.7, 48.8, 35.7, 28.3, 24.6, 21.5, 19.2, 15.6.
**$^{19}$F-NMR (δ, 376 MHz, $CDCl_3$):** -62.3.
**HRMS (ESI-TOF):** Calc. for $C_{36}H_{35}F_3N_5O_3S_2^+$ ($[M+H]^+$): 706.21279, found: 706.2123, Δ 0.82 ppm.
**FTIR (ATR, cm$^{-1}$):** 2961w, 2228w, 1607w, 1508w, 1471m, 1448w, 1351m, 1272m, 1236m, 1161s, 1132m, 1097m, 1013m, 732m, 629m.

## 7.2.2. Tetrahydrofuran products

### 2-(4-Fluorophenyl)-5-phenyltetrahydrofuran (24)



**24**

The title compound was prepared according to general procedure **E** from phthalimide ester **S–43** (165 mg, 0.50 mmol, 1.0 equiv.), styrene (115 µL, 1.0 mmol, 2.0 equiv.), Ir(4-$CF_3$ppy)$_3$ (4.3 mg, 0.005 mmol, 1.0 mol%), and $(PhO)_2PO_2H$ (250 mg, 1.0 mmol, 2.0 equiv.) in acetone (0.5 mL, 1.0 M). Purification was carried out by flash column chromatography on silica (3% EtOAc / hexanes), and the product tetrahydrofurans **24** as a mixture of diastereoisomers were isolated as a colorless oil (79% yield 1.1:1 d.r., average of two runs; run 1: 97 mg, 0.40 mmol, 80% yield, 1.1:1 d.r.; run 2: 94 mg, 0.39 mmol, 78% yield, 1.1:1 d.r.). An analytical sample was further separated into component diastereoisomers using preparative TLC on silica (3% EtOAc / hexanes).

Diastereoisomer 1:

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.35–7.44 (6H, m), 7.27–7.31 (1H, m), 7.02–7.08 (2H, m), 5.00–5.07 (2H, m), 2.39–2.48 (2H, m), 1.90–2.02 (2H, m).

**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 162.2 (d, $^1J_{CF}$ = 245 Hz), 142.9, 138.7 (d, $^4J_{CF}$ = 3.2 Hz), 128.5, 127.8 (d, $^3J_{CF}$ = 8.0 Hz), 127.5, 126.1, 115.3 (d, $^2J_{C\text{-}F}$ = 21.3 Hz), 81.4, 80.8, 34.6, 34.4.

**$^{19}$F-NMR (δ, 228 MHz, $CDCl_3$):** -115.6 – -115.7 (m).

**HRMS (EI-Q-TOF):** Calc. for $C_{16}H_{15}FO^+$ ([M]$^+$): 242.11014, found: 242.11069, Δ 3.37 ppm.

**FTIR (ATR, cm$^{-1}$):** 3033w, 2930w, 2868w, 1605w, 1509s, 1222s, 1055s, 830s, 754s, 700s, 535m.

Diastereoisomer 2:

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.34–7.44 (6H, m), 7.27–7.31 (1H, m), 7.02–7.08 (2H, m), 5.22–5.29 (2H, m), 2.42–2.54 (2H, m), 1.91–2.08 (2H, m).

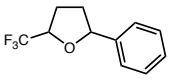
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 162.2 (d, $^1J_{CF}$ = 245 Hz), 143.6, 139.4 (d, $^4J_{CF}$ = 3.1 Hz), 128.5, 127.4 (d, $^3J_{CF}$ = 2.3 Hz), 127.3, 125.7, 115.3 (d, $^2J_{CF}$ = 21.3 Hz), 81.5, 80.9, 35.9, 35.7.

**$^{19}$F-NMR (δ, 228 MHz, $CDCl_3$):** -115.8 – -115.9 (m).

**HRMS (EI-Q-TOF):** Calc. for $C_{16}H_{15}FO^+$ ([M]$^+$): 242.11014, found: 242.11029, Δ 1.67 ppm.

**FTIR (ATR, cm$^{-1}$):** 3031w, 2936w, 2868w, 1604w, 1505m, 1219s, 1049s, 826s, 750s, 607s, 522m.

### 2-Phenyl-5-(trifluoromethyl)tetrahydrofuran (25)



**25**

The title compound was prepared according to general procedure **E** from phthalimide ester **S–44** (152 mg, 0.50 mmol, 1.0 equiv.), styrene (115 µL, 1.0 mmol, 2.0 equiv.), Ir(4-$CF_3$ppy)$_3$ (4.3 mg, 0.005 mmol, 1.0 mol%), and $(PhO)_2PO_2H$ (250 mg, 1.0 mmol, 2.0 equiv.) in acetone (0.5 mL, 1.0 M). Purification was carried out by flash column chromatography on silica (3% $Et_2O$ / hexanes), and the product tetrahydrofurans **25** as a mixture of diastereoisomers were isolated as a colorless oil (64% yield 1.3:1 d.r., average of two runs; run 1: 70 mg, 0.33 mmol, 65% yield, 1.3:1 d.r.; run 2: 67 mg, 0.31 mmol, 62% yield, 1.3:1 d.r.).

Mixture of diastereoisomers:

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.32–7.39 (4H, m), 7.27–7.31 (1H, m), 5.13 (0.45H, dd, $^3J_{HH}$ = 8.3 Hz, $^3J_{HH}$ = 6.0 Hz), 5.01 (0.55H, dd, $^3J_{HH}$ = 10.0 Hz, $^3J_{HH}$ = 5.1 Hz), 4.55 (0.45H, hept, $^3J_{HH}$ = 7.2 Hz), 4.43 (0.55H, pd, *J* = 7.3, 4.1 Hz). 2.41–2.50 (0.45H, m), 2.24–2.36 (2H, m), 2.14–2.23 (0.55H, m), 1.88–1.98 (1H, m).

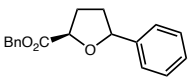
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 141.3, 140.8, 128.6, 128.0, 127.9, 127.3 – 121.8 (m), 126.0, 125.8, 83.5, 82.7, 77.0 – 76.2 (m), 34.3, 34.1, 27.2, 26.3.

**$^{19}$F-NMR (δ, 228 MHz, $CDCl_3$):** -78.2 (d, $^3J_{HF}$ = 7.2 Hz), -78.5 (d, $^3J_{HF}$ = 7.3 Hz).

**HRMS (EI-Q-TOF):** Calc. for $C_{11}H_{11}F_3O^+$ ([M]$^+$): 216.07565, found: 216.07537, Δ 3.85 ppm.

**FTIR (ATR, cm$^{-1}$):** 2918m, 2850w, 1287m, 1184m, 1156s, 1134s, 1075s, 757m, 699s.

### Benzyl (2*R*)-5-phenyltetrahydrofuran-2-carboxylate (26)



**26**

The title compound was prepared according to general procedure **E** from phthalimide ester **S–45** (185 mg, 0.50 mmol, 1.0 equiv.), styrene (115 µL, 1.0 mmol, 2.0 equiv.), $Ir(4\text{-}CF_3ppy)_3$ (4.3 mg, 0.005 mmol, 1.0 mol%), and $(PhO)_2PO_2H$ (250 mg, 1.0 mmol, 2.0 equiv.) in acetone (0.5 mL, 1.0 M). Purification was carried out by flash column chromatography on silica (10% $Et_2O$ / hexanes), and the product tetrahydrofurans **26** as a mixture of diastereoisomers were isolated as a colorless oil (59% yield, 1:1 d.r., average of two runs; run 1: 83 mg, 0.29 mmol, 58% yield, 1:1 d.r.; run 2: 84 mg, 0.30 mmol, 59% yield, 1:1 d.r.). An analytical sample was further separated into component diastereoisomers using preparative SFC (A2S-5 (CHIRALPAK AY-H) (2 x 25 cm) 60 mL/min @ 15% EtOH / 85% $CO_2$ (100 bar), ~8 mg/mL, 1.0 mL inj.; 220 nm detection).

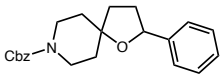
Diastereoisomer 1:

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.47–7.52 (2H, m), 7.23–7.41 (8H, m), 5.26 (1H, d, $^2J_{HH}$ = 12.2 Hz), 5.21 (1H, d, $^2J_{HH}$ = 12.2 Hz), 5.02 (1H, dd, $^3J_{HH}$ = 9.1 Hz, $^3J_{HH}$ = 5.7 Hz), 4.69 (1H, dd, $^3J_{HH}$ = 8.7 Hz, $^3J_{HH}$ = 4.1 Hz), 2.23–2.43 (3H, m), 1.86–1.95 (1H, m).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 173.1, 141.9, 135.7, 128.7, 128.5, 128.5, 128.4, 127.7, 126.3, 83.4, 77.6, 66.9, 34.5, 31.1.
**HRMS (ESI-TOF):** Calc. for $C_{18}H_{18}O_3^+$ ([M+Na]$^+$): 305.1148, found: 305.1147, Δ 0.33 ppm.
**FTIR (ATR, cm$^{-1}$):** 3031w, 2947w, 1746m, 1495w, 1454w, 1266w, 1192m, 1167m, 1072s, 1028m, 974m, 911w, 749m, 696s.

Diastereoisomer 2:

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.31–7.40 (9H, m), 7.24–7.29 (1H, m), 5.19–5.26 (3H, m), 4.80 (1H, dd, $^3J_{HH}$ = 7.7 Hz, $^3J_{HH}$ = 6.0 Hz), 2.34–2.45 (2H, m), 2.10–2.18 (1H, m), 1.81–1.92 (1H, m).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 173.4, 142.2, 135.8, 128.7, 128.5, 128.5, 128.4, 127.6, 125.8, 82.1, 77.4, 66.8, 34.3, 30.4.
**HRMS (ESI-TOF):** Calc. for $C_{18}H_{19}O_3^+$ ([M+H]$^+$): 283.1329, found: 283.1330, Δ 0.35 ppm.
**FTIR (ATR, cm$^{-1}$):** 3031w, 2944w, 1745m, 1495w, 1454w, 1277w, 1184m, 1158m, 1083m, 748m, 697s.

### Benzyl 2-phenyl-1-oxa-8-azaspiro[4.5]decane-8-carboxylate (27)

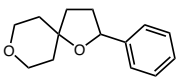


**27**

The title compound was prepared according to general procedure **E** from phthalimide ester **S–46** (219 mg, 0.50 mmol, 1.0 equiv.), styrene (115 µL, 1.0 mmol, 2.0 equiv.), $Ir(4\text{-}CF_3ppy)_3$ (4.3 mg, 0.005 mmol, 1.0 mol%), and $(PhO)_2PO_2H$ (31.3 mg, 0.125 mmol, 25 mol%) in acetone (1.25 mL, 0.4 M). Purification was carried out by flash column chromatography on silica (10% EtOAc / hexanes), and the product tetrahydrofuran **27** was isolated as a yellow oil (63% yield, average of two runs; run 1: 113 mg, 0.32 mmol, 64% yield.; run 2: 108 mg, 0.31 mmol, 62% yield).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.31–7.37 (9H, m), 7.24–7.27 (1H, m), 5.14 (2H, s), 4.98 (1H, t, $^3J_{HH}$ = 6.8 Hz), 3.78 (2H, br s), 3.44–3.53 (2H, m), 2.30–2.38 (1H, m), 1.57–1.92 (7H, m).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 155.4, 143.3, 137.1, 128.6, 128.4, 128.0, 127.9, 127.4, 125.7, 80.6, 80.4, 67.1, 41.5, 37.5, 37.4, 36.8, 36.6, 34.8.
**HRMS (ESI-TOF):** Calc. for $C_{22}H_{26}NO_3^+$ ([M+H]$^+$): 352.1907, found 352.1910, Δ 0.85 ppm.
**FTIR (ATR, cm$^{-1}$):** 2940w, 2869w, 1693s, 1427m, 1233s, 1149m, 1075m, 1020m, 732s, 695s.

### 2-Phenyl-1,8-dioxaspiro[4.5]decane (28)



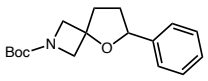
**28**

The title compound was prepared according to general procedure **E** from phthalimide ester **S–47** (152 mg, 0.50 mmol, 1.0 equiv.), styrene (115 µL, 1.0 mmol, 2.0 equiv.), $Ir(4\text{-}CF_3ppy)_3$ (4.3 mg, 0.005 mmol, 1.0 mol%), and $(PhO)_2PO_2H$ (31.3 mg, 0.125 mmol, 25 mol%) in acetone (1.25 mL, 0.4 M). Purification was carried out by flash column chromatography on silica (5% $Et_2O$ / hexanes), and the product tetrahydrofuran **28** was isolated as a pale-yellow oil (56% yield, average of two runs; run 1: 60 mg, 0.27 mmol, 55% yield.; run 2: 62 mg, 0.28 mmol, 57% yield).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.31–7.39 (4H, m), 7.22–7.28 (1H, m), 4.97–5.02 (1H, m), 3.85–3.97 (2H, m), 3.66–3.77 (2H, m), 2.29–2.39 (1H, m), 1.71–1.98 (7H, m).

**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 143.5, 128.4, 127.4, 125.8, 80.2, 80.1, 65.6, 65.6, 38.7, 38.0, 37.5, 34.9.
**HRMS (EI-Q-TOF):** Calc. for $C_{14}H_{18}O_2^+$ ([M]$^+$): 218.13068, found 218.13160, Δ 4.22 ppm.
**FTIR (ATR, cm$^{-1}$):** 2941w, 2859w, 1449w, 1225m, 1101m, 1042m, 1009m, 841m, 741m, 698s.

*Tert*-butyl 6-phenyl-5-oxa-2-azaspiro[3.4]octane-2-carboxylate (29)

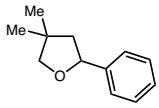


29

The title compound was prepared according to general procedure **E** from phthalimide ester **S–48** (188 mg, 0.50 mmol, 1.0 equiv.), styrene (115 µL, 1.0 mmol, 2.0 equiv.), Ir(4-$CF_3$ppy)$_3$ (4.3 mg, 0.005 mmol, 1.0 mol%), and $(PhO)_2PO_2H$ (31.3 mg, 0.125 mmol, 25 mol%) in acetone (1.25 mL, 0.4 M). Purification was carried out by flash column chromatography on silica (10% EtOAc / hexanes), and the product tetrahydrofuran **29** was isolated as a pale-yellow oil (40% yield, average of two runs; run 1: 60 mg, 0.21 mmol, 41% yield.; run 2: 57 mg, 0.20 mmol, 39% yield).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.14–7.28 (5H, m), 4.91 (1H, dd, $^3J_{HH}$= 8.2 Hz, $^3J_{HH}$ = 6.3 Hz), 4.10 (1H, d, $^3J_{HH}$ = 8.9 Hz), 4.05 (1H, d, $^3J_{HH}$ = 9.0 Hz), 3.84 (2H, dd, $^3J_{HH}$ = 9.0 Hz, $^3J_{HH}$ = 4.2 Hz), 2.05–2.30 (3H, m), 1.69–1.82 (1H, m), 1.35 (9H, s).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 156.6, 142.4, 128.6, 127.7, 125.7, 81.7, 79.7, 78.7, 62.7 (br), 36.6, 34.5, 28.5.
**HRMS (ESI-TOF):** Calc. for $C_{17}H_{23}NO_3Na^+$ ([M+Na]$^+$): 312.1276, found 312.1269, Δ 2.24 ppm
**FTIR (ATR, cm$^{-1}$):** 2973w, 2874w, 1697s, 1391s, 1365s, 1151m, 1084s, 1019m, 757m, 698s, 500m.

4,4-Dimethyl-2-phenyltetrahydrofuran (30)

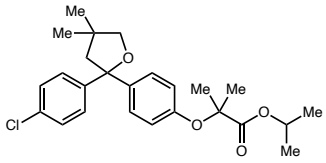


30

The title compound was prepared according to general procedure **E** from phthalimide ester **S–49** (132 mg, 0.50 mmol, 1.0 equiv.), styrene (115 µL, 1.0 mmol, 2.0 equiv.), Ir(4-$CF_3$ppy)$_3$ (4.3 mg, 0.005 mmol, 1.0 mol%), and $(PhO)_2PO_2H$ (31.3 mg, 0.125 mmol, 25 mol%) in acetone (1.25 mL, 0.4 M). Purification was carried out by flash column chromatography on silica (3% $Et_2O$ / hexanes), and the product tetrahydrofuran **30** was isolated as a colorless oil (81% yield, average of two runs; run 1: 73 mg, 0.41 mmol, 83% yield.; run 2: 70 mg, 0.40 mmol, 79% yield).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.30–7.37 (4H, m), 7.22–7.28 (1H, m), 5.06 (1H, dd, $^3J_{HH}$ = 9.4 Hz, $^3J_{HH}$ = 6.8 Hz), 3.76 (1H, d, $^2J_{HH}$ = 8.1 Hz), 3.67 (1H, d, $^2J_{HH}$ = 8.0 Hz), 2.13 (1H, dd, $^2J_{HH}$ = 12.4 Hz, $^3J_{HH}$ = 6.8 Hz), 1.69 (1H, dd, $^2J_{HH}$ = 12.4, $^3J_{HH}$ = 9.5 Hz), 1.21 (3H, s), 1.15 (3H, s).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 143.9, 128.5, 127.2, 125.6, 81.1, 80.9, 50.0, 40.3, 26.7, 26.6.
**FTIR (ATR, cm$^{-1}$):** 2956w, 2927w, 2868w, 1450w, 1368w, 1056s, 751m, 698s.
Characterization data is consistent with that reported by Hong and co-workers.[30]

Isopropyl 2-(4-(2-(4-chlorophenyl)tetrahydrofuran-2-yl)phenoxy)-2-methylpropanoate (46)



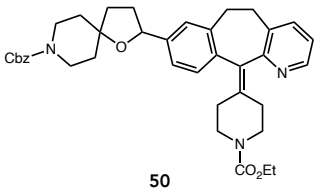
46

The title compound was prepared according to general procedure **E** from phthalimide ester **S–49** (39.5 mg, 0.15 mmol, 1.5 equiv.), fenofibrate 1,1-diarylethylene (**41**, 35.9 mg, 0.1 mmol, 1.0 equiv.), Ir(4-$CF_3$ppy)$_3$ (0.9 mg, 0.001 mmol, 1.0 mol%), and $(PhO)_2PO_2H$ (50.0 mg, 0.20 mmol, 2.0 equiv.) in acetone (100 µL, 1.0 M). Purification was carried out by flash column chromatography on silica (5% $Et_2O$ / hexanes), and the product tetrahydrofuran **46** was isolated as a colorless oil (85% yield, average of two runs; run 1: 38 mg, 0.088 mmol, 88% yield.; run 2: 35 mg, 0.081 mmol, 81% yield).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.39 (2H, dt, $^3J_{HH}$ = 8.7 Hz, $^4J_{HH}$ = 2.0 Hz), 7.24–7.30 (4H, m), 6.77 (2H, dt, $^3J_{HH}$ = 8.7 Hz, $^4J_{HH}$ = 2.0 Hz), 5.07 (1H, hept, $^3J_{HH}$ = 6.2 Hz), 3.69 (2H, m), 2.54 (1H, d, $^2J_{HH}$ = 12.7 Hz), 2.44 (1H, d, $^2J_{HH}$ = 12.7 Hz), 1.57 (6H, s), 1.20 (6H, d, $^3J_{HH}$ = 6.3 Hz)), 1.04 (6H, d, $^3J_{HH}$ = 6.4 Hz).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 173.8, 154.4, 146.7, 140.7, 132.2, 128.3, 127.1, 126.4, 118.6, 88.0, 79.8, 79.2, 69.0, 53.9, 40.7, 27.7, 27.5, 25.5, 25.5, 21.6.
**HRMS (ESI-TOF):** Calc. for $C_{25}H_{32}ClO_4^+$ ([M+H]$^+$): 431.1984, found: 431.1986, Δ 0.23 ppm.

**FTIR (ATR, cm$^{-1}$):** 2959m, 2868w, 1727m, 1607w, 1505m, 1488m, 1383w, 1285m, 1234m, 1176m, 1146m, 1102s, 1013m, 836m, 545w.

### Benzyl 2-(11-(1-(ethoxycarbonyl)piperidin-4-ylidene)-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-8-yl)-1-oxa-8-azaspiro[4.5]decane-8-carboxylate (50)

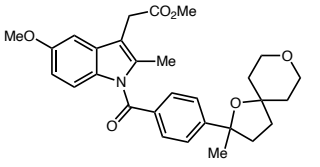


**50**

The title compound was prepared according to general procedure **E** from phthalimide ester **S–46** (65.8 mg, 0.15 mmol, 1.5 equiv.), vinyl loratidine[10] (**S–16**, 37.4 mg, 0.1 mmol, 1.0 equiv.), Ir(4-$CF_3$ppy)$_3$ (0.9 mg, 0.001 mmol, 1.0 mol%), and $(PhO)_2PO_2H$ (31.3 mg, 0.125 mmol, 1.25 equiv.) in acetone (250 µL, 0.4 M). Purification was carried out by preparative thin layer chromatography on silica (35% acetone / hexanes), and the product tetrahydrofuran **50** was isolated as a colorless oil (45% yield, average of two runs; Run 1: 27.4 mg, 0.044 mmol, 44% yield; Run 2: 28.6 mg, 0.046 mmol, 46% yield). Product appears as a rotameric mixture in NMR analysis.

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 8.38 (1H, d, $^3J_{HH}$ = 4.3 Hz), 7.42 (1H, d, $^3J_{HH}$ = 7.4 Hz), 7.33–7.36 (4H, m), 7.28–7.32 (1H, m), 7.11–7.17 (3H, m), 7.07 (1H, dd, $^3J_{HH}$ = 7.9, 4.7 Hz), 5.13 (2H, s), 4.88–4.92 (1H, m), 4.13 (2H, q, $^3J_{HH}$ = 7.0 Hz), 3.67–3.90 (4H, br m), 3.32–3.51 (4H, m), 3.07–3.15 (2H, m), 2.80–2.88 (2H, m), 2.44–2.50 (1H, m), 2.27–2.39 (3H, m), 1.98–2.09 (1H, m), 1.55–1.97 (6H, m), 1.42 (1H, s),1.24 (3H, t, $^3J_{HH}$ = 7.0 Hz).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 157.8, 157.7, 155.6, 155.4, 146.6, 143.0, 142.2, 138.4, 138.3, 137.8, 137.6, 137.5, 137.1, 136.8, 135.2, 133.8, 129.6, 129.5, 129.4, 129.3, 128.6, 128.1, 128.0, 127.9, 126.7, 126.5, 123.8, 122.2, 102.5, 102.5, 80.6, 80.5, 80.2, 75.6, 72.5, 67.1, 67.1, 61.4, 45.0, 45.0, 41.6, 41.5, 40.6, 37.5, 37.5, 37.2, 34.7, 32.3, 32.2, 32.1, 32.0, 32.0, 31.9, 31.8, 31.8, 31.8, 30.8, 30.7, 30.3, 29.8, 29.4, 29.4, 29.3, 27.8, 14.8.
**HRMS (ESI-TOF):** Calc. for $C_{38}H_{44}N_3O_5^+$ ([M+H]$^+$): 622.32755, found: 622.32807, Δ 0.41 ppm.
**FTIR (ATR, cm$^{-1}$):** 2928w, 1699s, 1436m, 1277w, 1231m, 1114w.

### Methyl 2-(5-methoxy-2-methyl-1-(4-(2-methyl-1,8-dioxaspiro[4.5]decan-2-yl)benzoyl)-1*H*-indol-3-yl)acetate (51)

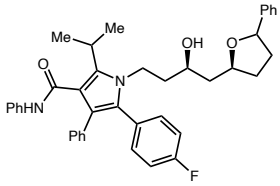


**51**

The title compound was prepared according to general procedure **E** from phthalimide ester **S–47** (46.0 mg, 0.15 mmol, 1.5 equiv.), isopropenyl indomethacin methyl ester (**S–29**, 37.7 mg, 0.1 mmol, 1.0 equiv.), Ir(4-$CF_3$ppy)$_3$ (0.9 mg, 0.001 mmol, 1.0 mol%), and $(PhO)_2PO_2H$ (6.3 mg, 0.025 mmol, 25 mol%) in acetone (250 µL, 0.4 M). Purification was carried out by preparative thin layer chromatography on silica (35% acetone / hexanes), and the product tetrahydrofuran **51** was isolated as a colorless oil (60% yield, average of two runs; Run 1: 31.0 mg, 0.063 mmol, 63% yield; Run 2: 27.5 mg, 0.056 mmol, 56% yield).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.67 (2H, d, $^3J_{HH}$ = 8.2 Hz), 7.56 (2H, d, $^3J_{HH}$ = 8.2 Hz), 6.96 (1H, d, $^4J_{HH}$ = 2.1 Hz), 6.91 (1H, d, $^3J_{HH}$ = 9.0 Hz), 6.65 (1H, dd, $^3J_{HH}$ = 9.0 Hz, $^4J_{HH}$ = 2.1 Hz), 3.88–3.96 (2H, m), 3.84 (3H, s), 3.70 (3H, s), 3.61–3.68 (4H, m), 2.36 (3H, s), 2.22–2.33 (2H, m), 1.93–1.98 (1H, m), 1.73–1.82 (3H, m), 1.67–1.70 (1H, m), 1.57–1.62 (1H, m), 1.55 (3H, s).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 171.6, 169.5, 156.0, 155.0, 136.1, 133.7, 131.1, 130.6, 129.8, 125.2, 115.1, 112.1, 111.6, 101.2, 84.5, 80.9, 65.7, 65.6, 55.8, 52.3, 39.3, 38.9, 38.4, 36.5, 31.6, 30.3, 13.4.
**HRMS (ESI-TOF):** Calc. for $C_{29}H_{34}NO_6^+$ ([M+H]$^+$): 492.23806, found: 492.23862, Δ 0.73 ppm.
**FTIR (ATR, cm$^{-1}$):** 2950m, 2859w, 1736m, 1679m, 1606w, 1477m, 1456m, 1355m, 1311s, 1263m, 1224s, 1166m, 1069s, 1016m, 895m, 733s.

**5-(4-Fluorophenyl)-1-((3*R*)-3-hydroxy-4-((2*S*)-5-phenyltetrahydrofuran-2-yl)butyl)-2-isopropyl-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide (57)**




**57**

The title compound was prepared according to general procedure **E** from *N*-hydroxyphthalimide ester **54** (74.4 mg, 0.1 mmol, 1.0 equiv.), styrene (25.0 µL, 0.2 mmol, 2.0 equiv.), Ir(4-$CF_3$ppy)$_3$ (0.9 mg, 0.001 mmol, 1.0 mol%), and $(PhO)_2PO_2H$ (50.0 mg, 0.2 mmol, 2.0 equiv.) in acetone (200 µL, 0.5 M). Purification was carried out by preparative thin layer chromatography on silica (35% EtOAc / Hexanes), and the product tetrahydrofurans **57** were isolated as a colorless oil as an inseparable 1:1 mixture of diastereoisomers (68% yield, d.r. 1:1, average of two runs; Run 1: 42.6 mg, 0.069 mmol, 69% yield, d.r. 1:1; Run 2: 41.7 mg, 0.067 mmol, 67% yield, d.r. 1:1).

**Mixture of diastereoisomers :**

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.28–7.37 (5H, m), 7.16–7.25 (9H, m), 7.07–7.09 (2H, m), 6.97–7.05 (3H, m), 6.90 (1H, br s), 5.06 (0.5 H, diastereoisomer 1, dd, $^3J_{HH}$ = 8.7, 8.2 Hz), 4.91 (0.5 H, diastereoisomer 2, app t, $^3J_{HH}$ = 7.4 Hz), 4.28–4.37 (0.5 H, m), 4.06–4.23 (1.5 H, m), 3.93–4.03 (1.5 H), 3.74–3.85 (1H,m), 3.58–3.69 (1.5 H, m), 2.26–2.42 (1H, m), 2.06–2.24 (1H, m), 1.65–1.90 (4H, m), 1.60 (3H, s), 1.59 (6H, d, $^3J_{HH}$ = 7.1 Hz), 1.51–1.55 (1H, m).

**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 165.0, 163.3, 161.4, 142.9, 142.4, 141.7, 138.5, 134.8, 133.4, 133.4, 133.3, 133.3, 130.6, 128.9, 128.9, 128.8, 128.5, 128.5, 128.4, 127.6, 127.4, 126.6, 125.9, 125.5, 123.6, 121.9, 121.9, 119.7, 115.6, 115.4, 115.4, 81.9, 80.8, 80.7, 80.5, 69.9, 69.9, 42.5, 42.4, 41.6, 41.6, 39.2, 39.2, 34.7, 33.7, 33.4, 32.2, 26.3, 26.2, 21.9, 21.9, 21.8.

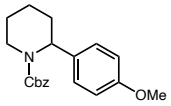
**$^{19}$F-NMR (δ, 376 MHz, $CDCl_3$):** -113.6 (diastereoisomer 1), -113.7 (diastereoisomer 2).

**HRMS (ESI-TOF):** Calc. for $C_{40}H_{42}FN_2O_3^+$ ([M+H]$^+$): 617.3174, found: 617.31619, Δ 1.06 ppm.

**FTIR (ATR, cm$^{-1}$):** 3409w br, 3058w, 2930w, 1664m, 1594m, 1558s, 1525s, 1508s, 1435m, 1311s, 1221m, 1156m, 1078m, 842w, 753s, 735s.

### 7.2.3. Piperidine products

#### Benzyl 2-(4-methoxyphenyl)piperidine-1-carboxylate (35)

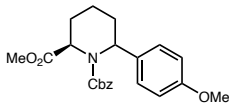


35

The title compound was prepared according to general procedure **E** from phthalimide ester **31** (191 mg, 0.50 mmol, 1.0 equiv.), 4-methoxystyrene (115 µL, 1.0 mmol, 2.0 equiv.), Ir(4-$CF_3$ppy)$_3$ (4.3 mg, 0.005 mmol, 1.0 mol%), and $(PhO)_2PO_2H$ (375 mg, 1.50 mmol, 3.0 equiv.) in acetone (5.0 mL, 0.1 M). Purification was carried out by flash column chromatography on silica (1–15% EtOAc / hexanes), and the product piperidine **35** was isolated as a colorless oil (76% yield, average of two runs; run 1: 119.8 mg, 0.37 mmol, 74% yield.; run 2: 126.7 mg, 0.39 mmol, 79% yield).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.31–7.37 (5H, m), 7.15 (2H, d, $^3J_{HH}$ = 8.5 Hz), 6.88 (2H, d, $^3J_{HH}$ = 8.5 Hz), 5.50 (1H, s), 5.21 (2H, s), 4.13 (1H, d, $^2J_{HH}$ = 13.4 Hz), 3.81 (3H, s), 2.84 (1H, td, $^2J_{HH}$ = 13.1 Hz, $^3J_{HH}$ = 3.8 Hz), 2.31 (1H, d, $^2J_{HH}$ = 14.1 Hz), 1.87–1.93 (1H, m), 1.48–1.64 (4H, m).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 158.3, 156.1, 137.0, 131.7, 128.6, 128.5, 127.9, 127.8, 127.8, 114.0, 67.2, 55.3, 53.0, 40.3, 28.1, 25.6, 19.3.
**HRMS (ESI-TOF):** Calc. for $C_{20}H_{23}NO_3Na^+$ ([M+Na]$^+$): 348.15701, found: 348.1571, Δ 0.24 ppm.
**FTIR (ATR, cm$^{-1}$):** 2936w, 2863w, 1690s, 1511m, 1454m, 1421m, 1245s, 1178m, 1161m, 1028s, 853m, 738m.
Characterization data is consistent with that reported by Pandey and co-workers.[31]

#### 1-Benzyl 2-methyl (2*R*)-6-(4-methoxyphenyl)piperidine-1,2-dicarboxylate (36)



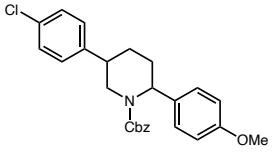
36

The title compound was prepared according to general procedure **E** from phthalimide ester **S–50** (220 mg, 0.50 mmol, 1.0 equiv.), 4-methoxystyrene (115 µL, 1.0 mmol, 2.0 equiv.), Ir(4-$CF_3$ppy)$_3$ (4.3 mg, 0.005 mmol, 1.0 mol%), and $(PhO)_2PO_2H$ (250 mg, 1.0 mmol, 2.0 equiv.) in acetone (5.0 mL, 0.1 M). Purification was carried out by flash column chromatography on silica (1–20% $Et_2O$ / hexanes), and the product piperidines **36** as a mixture of diastereoisomers were isolated as a colorless oil (76% yield, 1.2:1 d.r., average of two runs; run 1: 142 mg, 0.37 mmol, 74% yield, 1.2:1 d.r.; run 2: 149 mg, 0.39 mmol, 78% yield, 1.2:1 d.r.). An analytical sample was further separated into component diastereoisomers using preparative TLC on silica (20% $Et_2O$ / hexanes).

Diastereoisomer 1:
**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.29–7.35 (7H, m), 6.81 (2H, d, $^3J_{HH}$ = 8.7 Hz), 5.38 (1H, t, $^3J_{HH}$ = 4.5 Hz), 5.21 (2H, d, $J_{HH}$ = 3.0 Hz), 4.88 (1H, t, $^3J_{HH}$ = 4.8 Hz), 3.78 (3H, s), 3.28 (3H, s), 2.21–2.24 (1H, m), 2.12–2.16 (1H, m), 1.96–2.03 (1H, m), 1.87–1.93 (1H, m), 1.71–1.78 (1H, m), 1.62–1.68 (1H, m).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 172.5, 158.4, 156.7, 136.6, 133.1, 128.7, 128.6, 128.1, 128.0, 113.4, 67.8, 55.4, 52.9, 52.6, 51.7, 27.2, 25.2, 16.6.
**HRMS (ESI-TOF):** Calc. for $C_{22}H_{26}NO_5^+$ ([M+H]$^+$): 384.1805, found: 384.1803, Δ 0.67 ppm.
**FTIR (ATR, cm$^{-1}$):** 2951w, 1738m, 1696s, 1513m, 1411m, 1324m, 1282m, 1248m, 1181m, 1071m.

Diastereoisomer 2:
**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.23–7.27 (4H, m), 7.06–7.15 (3H, m), 6.84 (2H, d, $^3J_{HH}$ = 8.6 Hz), 5.18 (1H, t, $^3J_{HH}$ = 4.9 Hz), 5.12 (1H, d, $^2J_{HH}$ = 12.5 Hz), 5.00 (1H, d, $^2J_{HH}$ = 12.5 Hz), 4.61 (1H, t, $^3J_{HH}$ = 5.4 Hz), 3.80 (3H, s), 3.69 (3H, br s), 2.08–2.15 (1H, m), 1.93–2.06 (3H, m), 1.46–1.49 (2H, m).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 173.6, 158.3, 136.5, 135.5, 128.4, 128.0, 127.9, 126.8, 113.9, 67.4, 55.4, 55.4, 55.1, 52.4, 28.9, 25.0, 15.6.
**HRMS (ESI-TOF):** Calc. for $C_{22}H_{26}NO_5^+$ ([M+H]$^+$): 384.1805, found: 384.1803, Δ 0.64 ppm.
**FTIR (ATR, cm$^{-1}$):** 2951w, 1746m, 1699s, 1512s, 1455m, 1403m, 1247s, 1179m, 1032m.

Benzyl 5-(4-chlorophenyl)-2-(4-methoxyphenyl)piperidine-1-carboxylate (56)



56

The title compound was prepared according to general procedure **E** from phthalimide ester **53** (247 mg, 0.50 mmol, 1.0 equiv.), 4-methoxystyrene (115 µL, 1.0 mmol, 2.0 equiv.), $Ir(4\text{-}CF_3ppy)_3$ (4.3 mg, 0.005 mmol, 1.0 mol%), and $(PhO)_2PO_2H$ (250 mg, 1.0 mmol, 2.0 equiv.) in acetone (5.0 mL, 0.1 M). Purification was carried out by flash column chromatography on silica (10% EtOAc / hexanes), and the product piperidines **56** as a mixture of diastereoisomers were isolated as a colorless oil (77% yield, d.r. 1.5:1, average of two runs; run 1: 169 mg, 0.39 mmol, 78% yield, d.r. 1.5:1; run 2: 165 mg, 0.38 mmol, 76% yield, d.r. 1.5:1). An analytical sample was further separated into component diastereoisomers using preparative HPLC (AD-H (3 x 25 cm) 90 mL/min @ 35% MeOH (0.1% DEA); 220 nm detection).

Diastereoisomer 1:

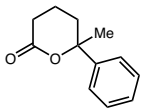
**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.34–7.39 (4H, m), 7.24–7.29 (5H, m), 7.20 (2H, d, $^3J_{HH}$ = 8.5 Hz), 6.93 (2H, d, $^3J_{HH}$ = 8.6 Hz), 5.39 (1H, br t, $^3J_{HH}$ = 4.8 Hz), 5.27 (1H, d, $^2J_{HH}$ = 12.0 Hz), 5.16 (1H, d, $^2J_{HH}$ = 12.0 Hz), 4.46 (1H, d, $^2J_{HH}$ = 14.3 Hz), 3.85 (3H, s), 3.46 (1H, dd, $^2J_{HH}$ = 14.0 Hz, $^3J_{HH}$ = 4.7 Hz), 3.00 (1H, br s), 2.01–2.07 (3H, m), 1.80–1.86 (1H, m).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 158.4, 156.3, 142.2, 136.7, 132.2, 131.8, 128.9, 128.5, 128.1, 128.0, 127.3, 114.2, 114.1, 67.3, 55.3, 55.3, 53.8, 43.3, 37.4, 25.9, 24.7.
**HRMS (ESI-TOF):** Calc. for $C_{26}H_{27}ClNO_3^+$ ([M+H]$^+$): 436.16740, found: 436.16730, Δ 0.07 ppm.
**FTIR (ATR, cm$^{-1}$):** 2951w, 1686m, 1512m, 1423m, 1245m, 1179m, 1093m, 1035m, 905s, 724s, 697m, 647m.

Diastereoisomer 2:

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.32–7.44 (5H, br m), 7.24 (2H, d, $^3J_{HH}$ = 8.3 Hz), 7.20 (2H, d, $^3J_{HH}$ = 6.4 Hz), 7.06 (2H, d, $^3J_{HH}$ = 6.4 Hz), 6.93 (2H, d, $^3J_{HH}$ = 8.3 Hz), 5.54–5.66 (1H, br m), 5.25 (2H, s), 4.12–4.34 (2H, br m), 3.85 (3H, s), 2.73–2.87 (2H, br m), 2.50 (1H, br d, $^2J_{HH}$ = 14.2 Hz), 2.07 (1H, br t, $^2J_{HH}$ = 13.6 Hz), 1.86 (1H, br d, $^2J_{HH}$ = 12.8 Hz), 1.67–1.77 (1H, br m).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 158.5, 156.1, 141.7, 136.9, 132.5, 131.0, 128.7, 128.6, 128.6, 128.5, 128.1, 127.9, 127.7, 114.3, 67.5, 55.4, 52.4, 52.2, 46.2, 42.6, 42.2, 28.3, 27.6, 27.1, 26.6.
**HRMS (ESI-TOF):** Calc. for $C_{26}H_{27}ClNO_3^+$ ([M+H]$^+$): 436.16740, found: 436.16710, Δ 1.42 ppm.
**FTIR (ATR, cm$^{-1}$):** 2933w, 2868w, 1689s, 1511m, 1406m, 1247m, 1178m, 1101m, 1035m, 826m, 756m, 689m.

## 7.2.4. Other annulation products – Morpholines, δ-valerolactones, and dioxanone

### 6-Methyl-6-phenyltetrahydro-2*H*-pyran-2-one (37)

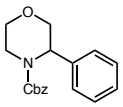



**37**

The title compound was prepared according to general procedure **E** from phthalimide ester **32** (160 mg, 0.50 mmol, 1.0 equiv.), styrene (115 µL, 1.0 mmol, 2.0 equiv.), Ir(4-$CF_3$ppy)$_3$ (4.3 mg, 0.005 mmol, 1.0 mol%), and $(PhO)_2PO_2H$ (125 mg, 0.50 mmol, 1.0 equiv.) in acetone (2.5 mL, 0.2 M). Purification was carried out by flash column chromatography on silica (30% $Et_2O$ / petroleum ether 40-60), and the product δ-valerolactone **37** was isolated as a colorless oil (77% yield, average of two runs; run 1: 73 mg, 0.38 mmol, 76% yield.; run 2: 74 mg, 0.39 mmol, 78% yield).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.32–7.39 (4H, m), 7.28 (1H, tt, $^3J_{HH}$ = 7.0 Hz, $^4J_{HH}$ = 1.5 Hz), 2.49 (1H, ddd, $^2J_{HH}$ = 18.3 Hz, $^3J_{HH}$ = 9.0, 7.6 Hz), 2.42 (1H, ddd, $^2J_{HH}$ = 18.3 Hz, $^3J_{HH}$ = 7.5, 4.8 Hz), 2.32 (1H, dt, $^2J_{HH}$ = 14.2 Hz, $^3J_{HH}$ = 4.6 Hz), 2.00 (1H, ddd, $^2J_{HH}$ = 14.2 Hz, $^3J_{HH}$ = 10.6, 4.2 Hz), 1.76–1.83 (1H, m), 1.68 (3H, s), 1.57–1.64 (1H, m).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 171.8, 144.7, 128.8, 127.5, 124.6, 85.5, 34.5, 31.5, 29.2, 16.7.
**FTIR (ATR, cm$^{-1}$):** 2978w, 1730s, 1257m, 1063m, 1055m, 765m, 702m.
Characterization data is consistent with that reported by Nishikawa, Hara, and coworkers.[32]

### Benzyl 3-phenylmorpholine-4-carboxylate (38)

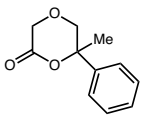



**38**

The title compound was prepared according to general procedure **E** from phthalimide ether **33** (340 mg, 1.0 mmol, 2.0 equiv.), styrene (62.5 µL, 0.1 mmol, 1.0 equiv.), Ir(4-$CF_3$ppy)$_3$ (4.3 mg, 0.005 mmol, 1.0 mol%), and $(PhO)_2PO_2H$ (250 mg, 1.0 mmol, 2.0 equiv.) in acetone (1.25 mL, 0.4 M). Purification was carried out by flash column chromatography on silica (10% EtOAc / hexanes), and the product morpholine **38** was isolated as a colorless oil (70% yield, average of two runs; Run 1: 102 mg, 0.34 mmol, 69% yield; Run 2: 106 mg, 0.36 mmol, 71% yield).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$, T = 323 K):** 7.27–7.40 (10H, m), 5.65–5.92 (1H, m), 5.21 (2H, s), 4.50–4.64 (2H, m), 4.28–4.44 (1H, m), 3.03–3.37 (1H, m), 1.74–1.99 (2H, m).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$, T = 323 K):** 154.9, 141.5, 136.7, 128.7, 128.6, 128.2, 128.1, 128.0, 126.0, 79.8, 76.9, 67.6, 43.5, 33.2.
**HRMS (ESI-TOF):** Calc. for $C_{18}H_{20}NO_3^+$ ([M+H]$^+$): 298.1438, found 298.1438, Δ 0.04 ppm.
**FTIR (ATR, cm$^{-1}$):** 3031w, 2919w, 2864w, 1700s, 1423m, 1262s, 1212m, 1192m, 1134m, 1051s, 1022s, 976m, 923m, 743m, 695s, 543w.

### 6-Methyl-6-phenyl-1,4-dioxan-2-one (39)

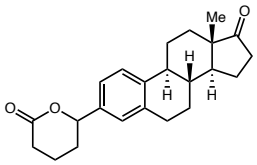



**39**

The title compound was prepared according to general procedure **E** from phthalimide ether **34** (139 mg, 0.50 mmol, 1.0 equiv.), styrene (115 µL, 1.0 mmol, 2.0 equiv.), Ir(4-$CF_3$ppy)$_3$ (4.3 mg, 0.005 mmol, 1.0 mol%), and $(PhO)_2PO_2H$ (250 mg, 1.0 mmol, 2.0 equiv.) in acetone (1.25 mL, 0.4 M). Purification was carried out by flash column chromatography on silica (10% EtOAc / petroleum ether 40-60), and the product dioxanone **39** was isolated as a colorless oil (75% yield, average of two runs; run 1: 71 mg, 0.37 mmol, 74% yield.; run 2: 74 mg, 0.38 mmol, 76% yield).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.32–7.43 (5H, m), 4.42 (1H, d, $^2J_{HH}$ = 17.6 Hz), 4.28 (1H, s, $^2J_{HH}$ = 17.6 Hz), 3.90 (2H, s), 1.77 (3H, s).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 167.4, 141.0, 128.9, 128.3, 124.7, 84.2, 71.6, 65.4, 25.9.
**HRMS (ESI-TOF):** Calc. for $C_{11}H_{13}O_3^+$ ([M+H]$^+$): 193.08592, found: 193.08610, Δ 0.93 ppm.
**FTIR (ATR, cm$^{-1}$):** 2939w, 2924w, 2855w, 1743s, 1294m, 1268s, 1186m, 1134s, 948m, 764m, 700m.

**6-((8*R*,9*S*,13*S*,14*S*)-13-Methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl)tetrahydro-2*H*-pyran-2-one (43)**

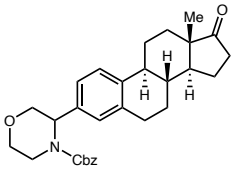



**43**

The title compound was prepared according to general procedure **E** from phthalimide ester **32** (31.9 mg, 0.1 mmol, 1.0 equiv.), vinyl estrone[9] (**40**, 28.0 mg, 0.1 mmol, 1.0 equiv.), Ir(4-$CF_3$ppy)$_3$ (0.9 mg, 0.001 mmol, 1.0 mol%), and $(PhO)_2PO_2H$ (25.0 mg, 0.1 mmol, 1.0 equiv.) in acetone (500 µL, 0.2 M). Purification was carried out by flash column chromatography on silica (30% EtOAc / hexanes), and the product δ-valerolactone **43** was isolated as a colorless oil (65% yield, d.r. 1:1, average of two runs; Run 1: 22.0 mg, 0.063 mmol, 63% yield, d.r. 1:1; Run 2: 24.0 mg, 0.068 mmol, 68% yield, d.r. 1:1).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.30 (1H, d, $^3J_{HH}$ = 8.6 Hz), 7.10–7.12 (2H, m), 5.31 (1H, dd, $^3J_{HH}$ = 10.6, 3.2 Hz), 2.92 (2H, dd, $^3J_{HH}$ = 9.7, 4.1 Hz), 2.70 (1H, dt, $^2J_{HH}$ = 17.7 Hz, $^3J_{HH}$ = 6.3 Hz), 2.56 (1H, dt, $^2J_{HH}$ = 25.4 Hz, $^3J_{HH}$ = 7.8 Hz), 2.51 (1H, dd, $^2J_{HH}$ = 18.4 Hz, $^3J_{HH}$ = 8.7 Hz), 2.41–2.44 (1H, m), 2.31 (1H, td, $^3J_{HH}$ = 10.8, 3.4 Hz), 2.11–2.19 (2H, m), 1.94–2.09 (5H, m), 1.83–1.91 (1H, m), 1.41–1.68 (8H, m), 0.91 (3H, s).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 221.0, 171.6, 171.6, 140.0, 140.0, 137.3, 137.3, 137.0, 137.0, 126.5, 126.5, 125.7, 123.3, 123.2, 81.7, 81.6, 50.6, 48.1, 44.5, 38.2, 38.2, 36.0, 31.7, 30.6, 30.5, 29.7, 29.6, 29.5, 26.6, 26.6, 25.8, 25.8, 21.7, 18.8, 13.98.
**HRMS (ESI-TOF):** Calc. for $C_{23}H_{29}O_3^+$ ([M+H]$^+$): 353.21112, found: 353.21109, Δ 0.85 ppm.
**FTIR (ATR, cm$^{-1}$):** 2929m, 1753s, 1457w, 1371w, 1240m, 1045m, 734m.

**Benzyl 3-((8*R*,9*S*,13*S*,14*S*)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl)morpholine-4-carboxylate (44)**

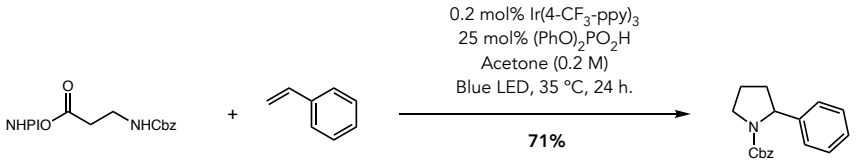



**44**

The title compound was prepared according to general procedure **E** from phthalimide ether **33** (68.0 mg, 0.20 mmol, 2.0 equiv.), vinyl estrone[9] (**40**, 28.0 mg, 0.1 mmol, 1.0 equiv.), Ir(4-$CF_3$ppy)$_3$ (0.9 mg, 0.001 mmol, 1.0 mol%), and $(PhO)_2PO_2H$ (50.0 mg, 0.2 mmol, 2.0 equiv.) in acetone (250 µL, 0.4 M). Purification was carried out by preparative thin layer chromatography on silica (35% acetone / hexanes), and the product morpholine **44** was isolated as a colorless oil (91% yield, d.r. 1:1, average of two runs; Run 1: 44.1 mg, 0.093 mmol, 93% yield, d.r. 1:1; Run 2: 42.6 mg, 0.090 mmol, 90% yield, d.r. 1:1).

**$^1$H-NMR (δ, 500 MHz, $CDCl_3$):** 7.31–7.40 (8H, m), 7.28 (1H, d, $^3J_{HH}$ = 8.1 Hz), 7.08–7.13 (2H, m), 5.71–5.83 (1H, m), 5.07–5.25 (4H, m), 4.47–4.57 (2H, m), 4.31–4.42 (1H, m), 3.12–3.30 (1H, m), 2.92 (2H, dd, $^3J_{HH}$ = 9.7, 3.8 Hz), 2.51 (1H, dd, $^2J_{HH}$ = 18.9 Hz, $^3J_{HH}$ = 8.8 Hz), 2.40–2.45 (1H, m), 2.30 (1H, td, $^2J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 4.2 Hz), 2.15 (1H, dt, $^2J_{HH}$ = 18.9 Hz, $^3J_{HH}$ = 8.9 Hz), 2.00–2.09 (2H, m), 1.95–1.98 (1H, m), 1.77–1.80 (1H, m), 1.57–1.66 (2H, m), 1.49–1.55 (3H, m), 1.41–1.46 (1H, m), 0.91 (3H, s).
**$^{13}$C-NMR (δ, 126 MHz, $CDCl_3$):** 221.0, 154.8, 154.2, 139.6, 138.8, 136.8, 136.8, 136.5, 135.9, 128.6, 128.6, 128.4, 128.2, 128.2, 128.1, 126.6, 125.6, 123.5, 79.6, 68.0, 67.5, 50.6, 48.1, 44.4, 43.3, 43.3, 38.2, 38.2, 35.9, 33.2, 32.8, 31.7, 29.5, 29.5, 26.6, 25.8, 21.7, 13.9.
**HRMS (ESI-TOF):** Calc. for $C_{30}H_{36}NO_4^+$ ([M+H]$^+$): 474.26389, found: 474.26426, Δ 0.49 ppm.
**FTIR (ATR, cm$^{-1}$):** 2927w, 2864w, 1703s, 1423m, 1263m, 1196m, 1050m, 1026m, 888m, 731s, 697s.

## 7.3. Procedures for gram-scale annulation reactions of NHPI ester reagents 1 and S–42, with styrene

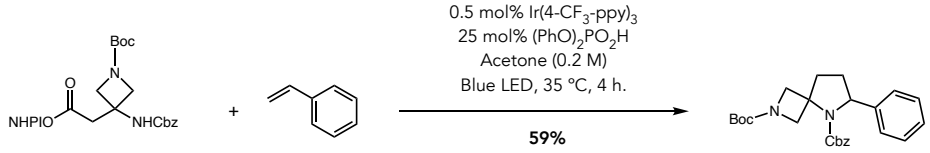



**1**
1.0 equiv.
6.0 mmol

2.0 equiv.

**2**

An oven-dried 40 mL scintillation vial (Wheaton E-C sample vial) was charged with Teflon-coated magnetic stir bar, Ir(4-$CF_3$ppy)$_3$ photocatalyst (10.3 mg, 0.012 mmol, 0.2 mol%), diphenyl phosphoric acid co-catalyst (375 mg, 1.5 mmol, 25 mol%) and *N*-Cbz β-alanine NHPI ester (**1**, 2.21 g, 6.0 mmol, 1.0 equiv.). The vial was brought into a nitrogen-filled glovebox. Acetone (Acros, 99.8%, Extra-Dry, AcroSeal, 30 mL) was added to the open vial whilst stirring, and the reaction vial sealed with a septum and cap, then electrical tape around the neck of the vial. The reaction vial was taken out of the glovebox, and a nitrogen-flushed inlet needle was inserted through the septum seal. Styrene (1.38 mL, 12.0 mmol, 2.0 equiv.) was added through the septum seal *via* syringe in one portion. The nitrogen inlet was removed, and the pierced septum sealed with electrical tape. The vial was placed on a stir plate between two blue LED light source (Kessil PRL160L 456 nm, 50 W max, set to 50% lamp intensity) with each side of the reaction vial placed a distance of 1 cm from each lamp face. The reaction vial was stirred and irradiated for 24 h. with cooling provided by overhead fans to maintain a reaction temperature of 35 ± 3 °C. The septum and cap were removed (Warning: vigorous effervescence of gas observed at this point), and the reaction mixture transferred to a 250 mL round bottomed flask. All volatiles were removed *in vacuo*. The residue was taken up in diethyl ether (250 mL) and washed with 1.0 M aq. NaOH solution (2 x 30 mL) and brine (30 mL) and dried over magnesium sulfate. Filtration of drying agents and evaporation of solvents gave a yellow oil, which was purified by flash column chromatography on silica (5-25% EtOAc / hexanes) to afford pure pyrrolidine **2** as a colorless oil (1.20 g, 4.25 mmol, 71%). Analytical data was in agreement with that obtained for reaction run on 0.5 mmol scale (*vide supra*).




**S–42**
1.0 equiv.
6.0 mmol

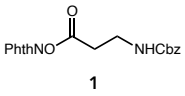
2.0 equiv.

**23**

An oven-dried 40 mL scintillation vial (Wheaton E-C sample vial) was charged with Teflon-coated magnetic stir bar, Ir(4-$CF_3$ppy)$_3$ photocatalyst (25.8 mg, 0.03 mmol, 0.5 mol%), diphenyl phosphoric acid co-catalyst (375 mg, 1.5 mmol, 25 mol%) and β-Spiro *N*-Cbz pyrrolidine / *N*-Boc azetidine NHPI reagent (**S–42**, 3.06 g, 6.0 mmol, 1.0 equiv.). The vial was brought into a nitrogen-filled glovebox. Acetone (Acros, 99.8%, Extra-Dry, AcroSeal, 30 mL) was added to the open vial whilst stirring, and the reaction vial sealed with a septum and cap, then electrical tape around the neck of the vial. The reaction vial was taken out of the glovebox, and a nitrogen-flushed inlet needle was inserted through the septum seal. Styrene (1.38 mL, 12.0 mmol, 2.0 equiv.) was added through the septum seal *via* syringe in one portion. The nitrogen inlet was removed, and the pierced septum sealed with electrical tape. The vial was placed on a stir plate between two blue LED light source (Kessil PRL160L 456 nm, 50 W max, set to 50% lamp intensity) with each side of the reaction vial placed a distance of 1 cm from each lamp face. The reaction vial was stirred and irradiated for 24 h. with cooling provided by overhead fans to maintain a reaction temperature of 35 ± 3 °C. The septum and cap were removed (Warning: vigorous effervescence of gas observed at this point), and the reaction mixture transferred to a 250 mL round bottomed flask. All volatiles were removed *in vacuo*. The residue was taken up in diethyl ether (250 mL) and washed with 1.0 M aq. NaOH solution (2 x 30 mL) and brine (30 mL) and dried over magnesium sulfate. Filtration of drying agents and evaporation of solvents gave a yellow oil, which was purified by flash column chromatography on silica (5-25% EtOAc / hexanes) to afford pure pyrrolidine **23** as a colorless oil (1.50 g, 3.55 mmol, 59%). Analytical data was in agreement with that obtained for reaction run on 0.5 mmol scale (*vide supra*).

## 8. Stern Volmer emission quenching experiments

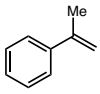
Steady-state Stern-Volmer emission quenching experiments were performed in anhydrous, degassed acetonitrile under an atmosphere of nitrogen. Constant concentration of Ir(4-$CF_3$-ppy)$_3$ = 2.0 μM. For sample NHPI ester + diphenyl phosphoric acid, concentration of NHPI ester was varied whilst that of diphenyl phosphoric acid was held constant at 0.15 M. Sample excitation was at 440 nm, and emission was measured at 508 nm.



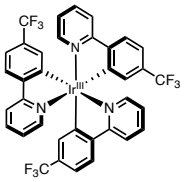

**1**

NHPI ester **1**

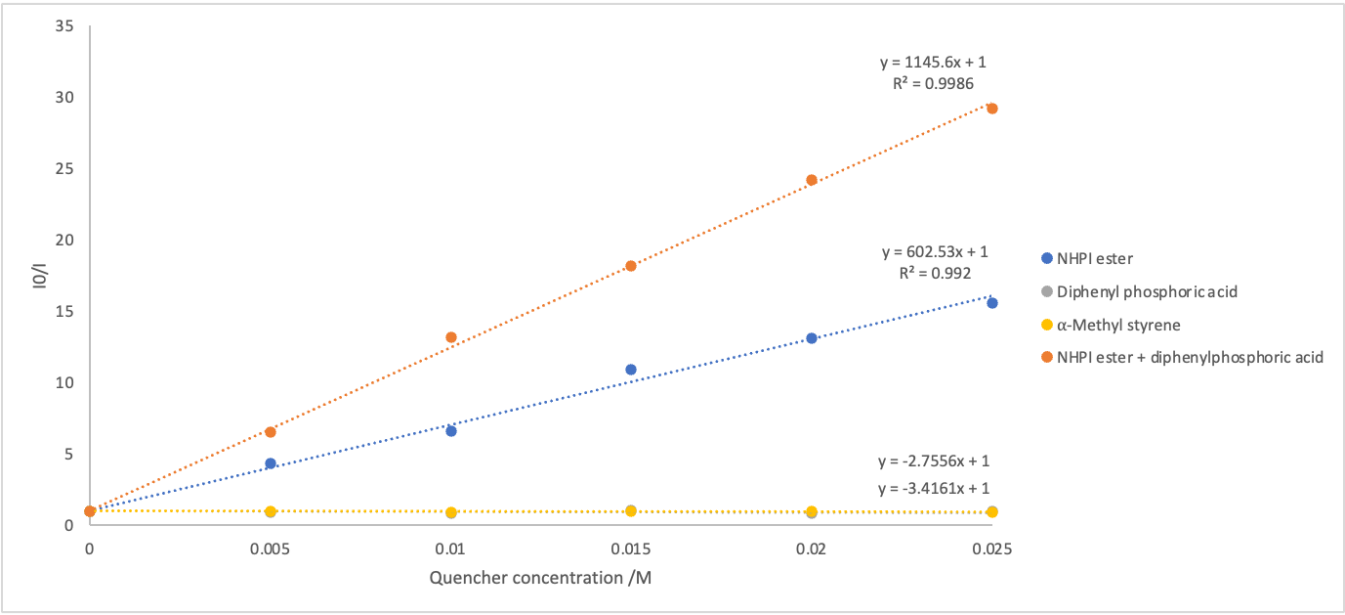

Diphenyl phosphoric acid




α-Methyl styrene

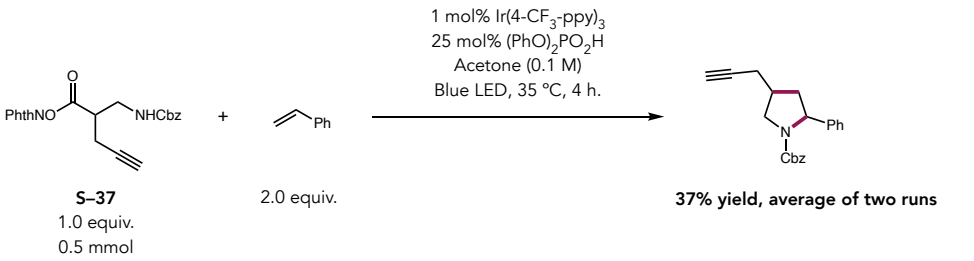



Ir(4-$CF_3$-ppy)$_3$



## 9. Poorly efficient or ineffective substrates / pairings in two-component annulation protocol

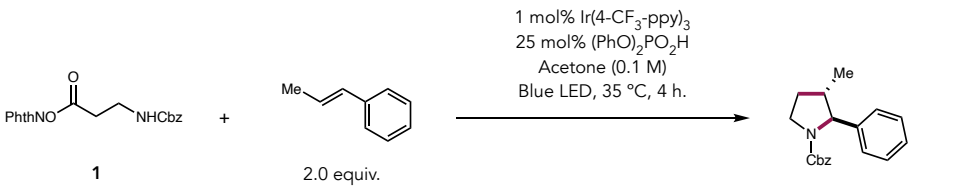
– Successful annulation but in low yields:




**S–37**
1.0 equiv.
0.5 mmol

2.0 equiv.

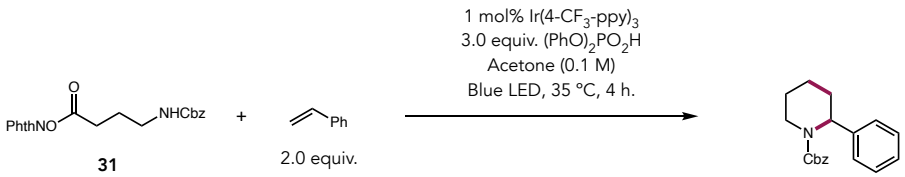
**37% yield, average of two runs**




**1**
1.0 equiv.
0.5 mmol

2.0 equiv.

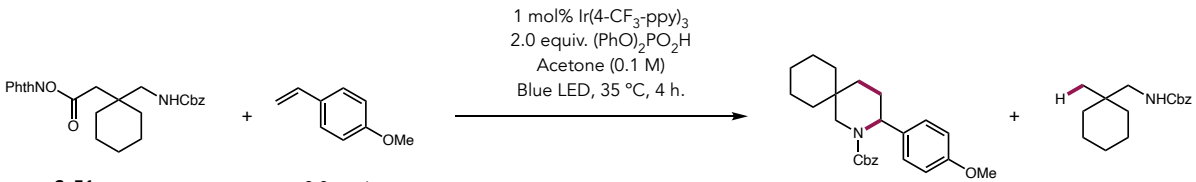
**28% yield, average of two runs**




**31**
1.0 equiv.
0.5 mmol

2.0 equiv.

**S–53**
**39%, average of two runs**



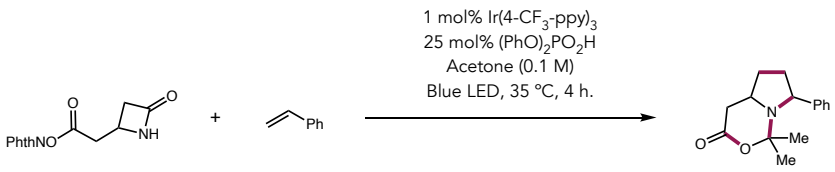

**S–51**
1.0 equiv.
0.5 mmol

2.0 equiv.

**42%** **29%**

**Average of two runs**

– Successful annulation but observed ring opening of a **β**-lactam-containing product:

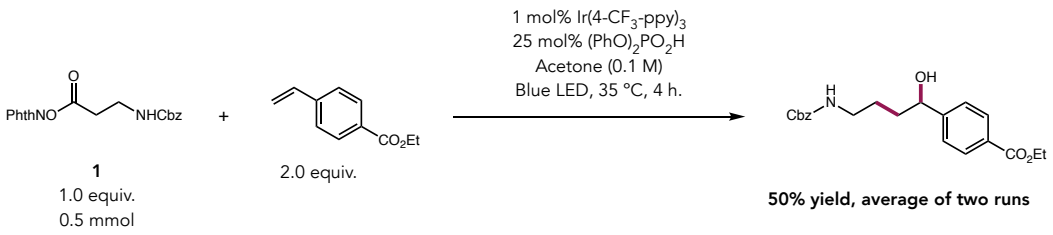



1.0 equiv.
0.5 mmol

2.0 equiv.

**37% yield, average of two runs**

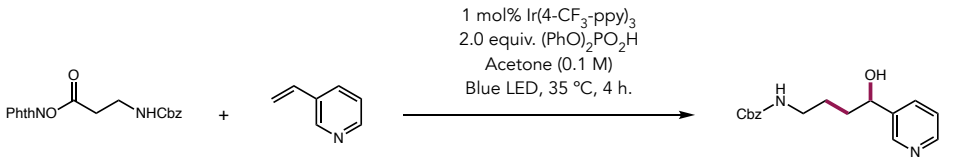
– Examples of electron-deficient styrene derivatives gave hydration, linear termination, or carbocation desaturation products, as opposed to desired annulation:




**1**
1.0 equiv.
0.5 mmol

2.0 equiv.

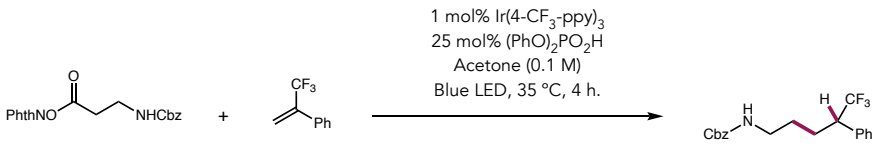
**50% yield, average of two runs**




**1**
1.0 equiv.
0.5 mmol

2.0 equiv.

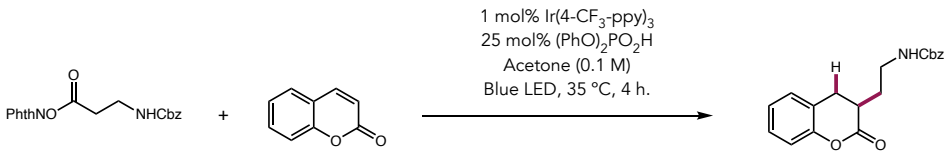
**79% yield, average of two runs**




**1**
1.0 equiv.
0.1 mmol

2.0 equiv.

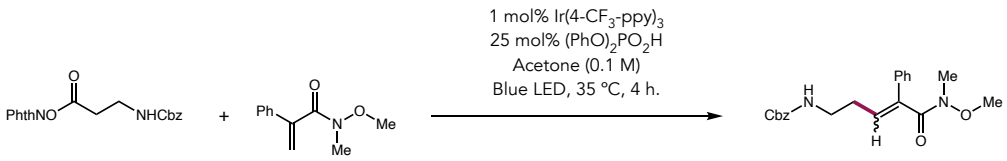
**Exclusive product**




**1**
1.0 equiv.
0.1 mmol

2.0 equiv.

**Exclusive product**

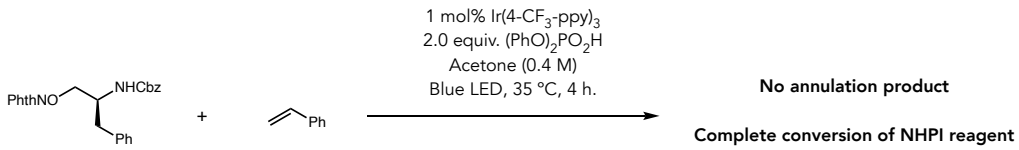



**1**
1.0 equiv.
0.5 mmol

2.0 equiv.

**Exclusive product**
**47%, average of two runs**

– A substituted morpholine reagent gave no annulation product, due to hypothesized dominating β-scission reactivity of the intermediate alkoxy radical:



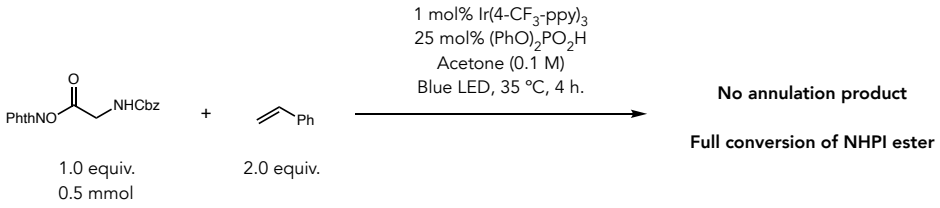

2.0 equiv.
1.0 mmol

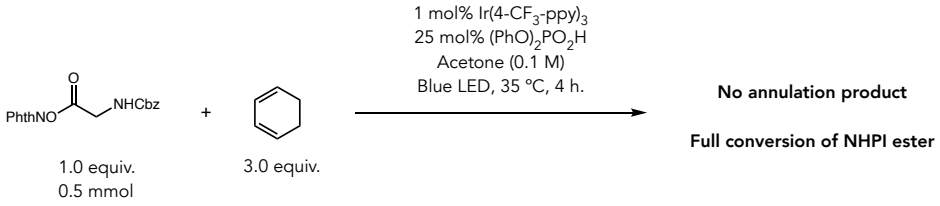
1.0 equiv.

**No annulation product**

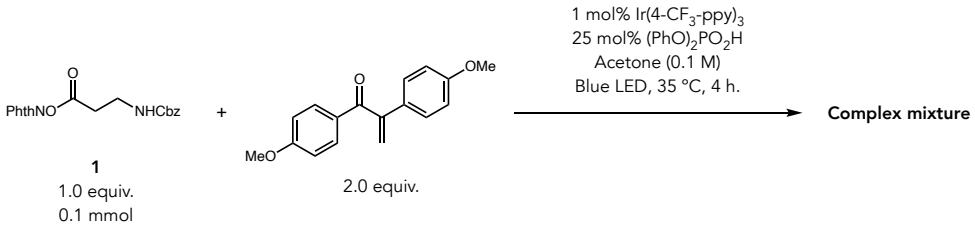
**Complete conversion of NHPI reagent**

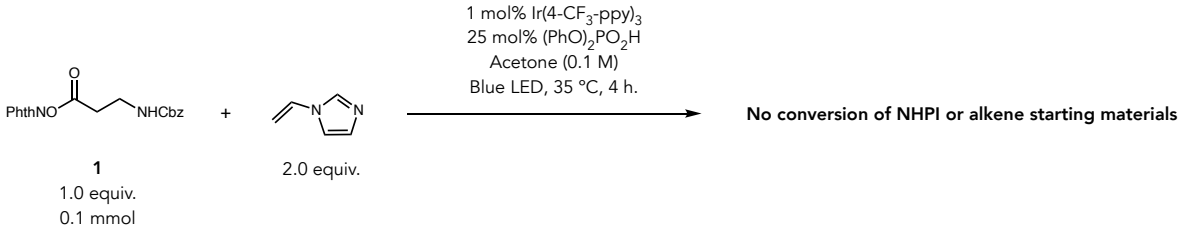
– *N*–Cbz-Glycine NHPI ester was unsuccessful in this annulation protocol:



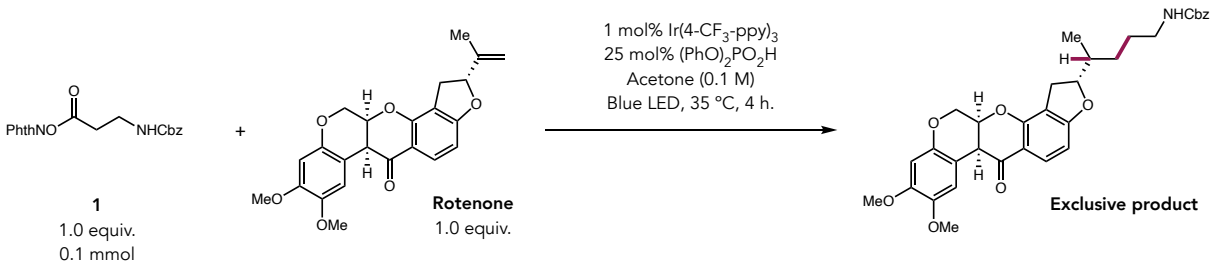



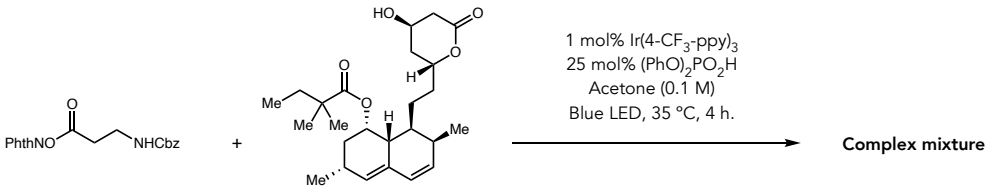

– Unsuccessful alkene types:



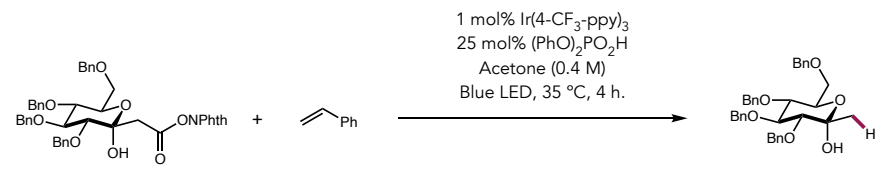

– Additional attempts with complex coupling partners:






**1**
1.0 equiv.
0.1 mmol

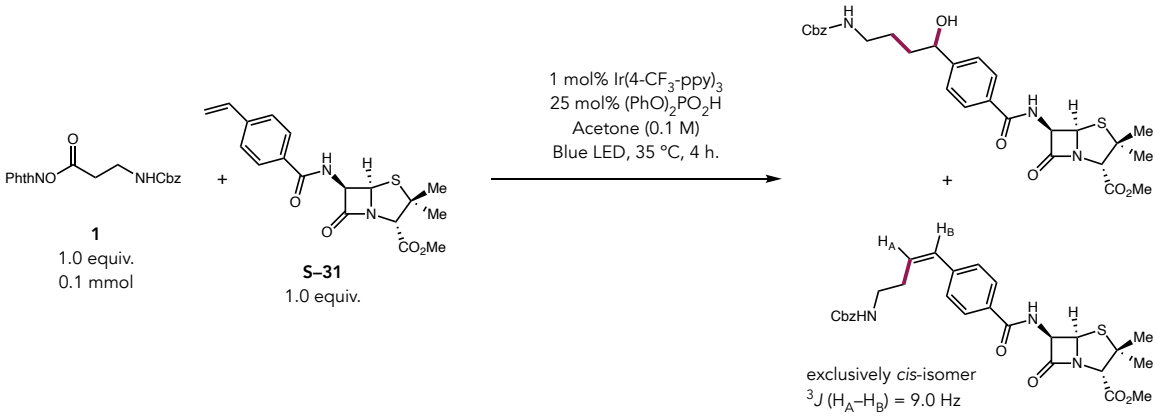
**Simvastatin**
1.0 equiv.




**Glucopyranose derivative**
1.0 equiv.
0.1 mmol

2.0 equiv.

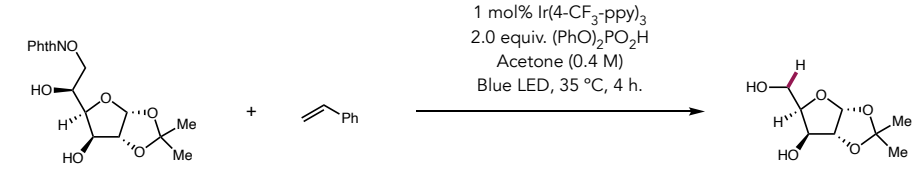
**Exclusive product**
**71%, 2:1 d.r., average of two runs**




**1**
1.0 equiv.
0.1 mmol

**S–31**
1.0 equiv.

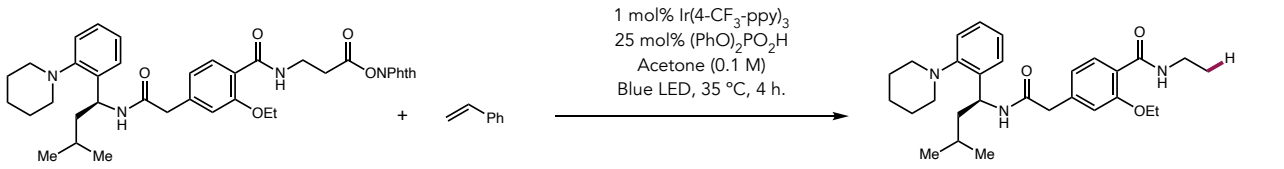
**60% combined yield**
**1.0:0.7 mixture of hydration product and carbocation deprotonation product**




**Glucofuranose derivative**
1.0 equiv.
0.1 mmol

2.0 equiv.

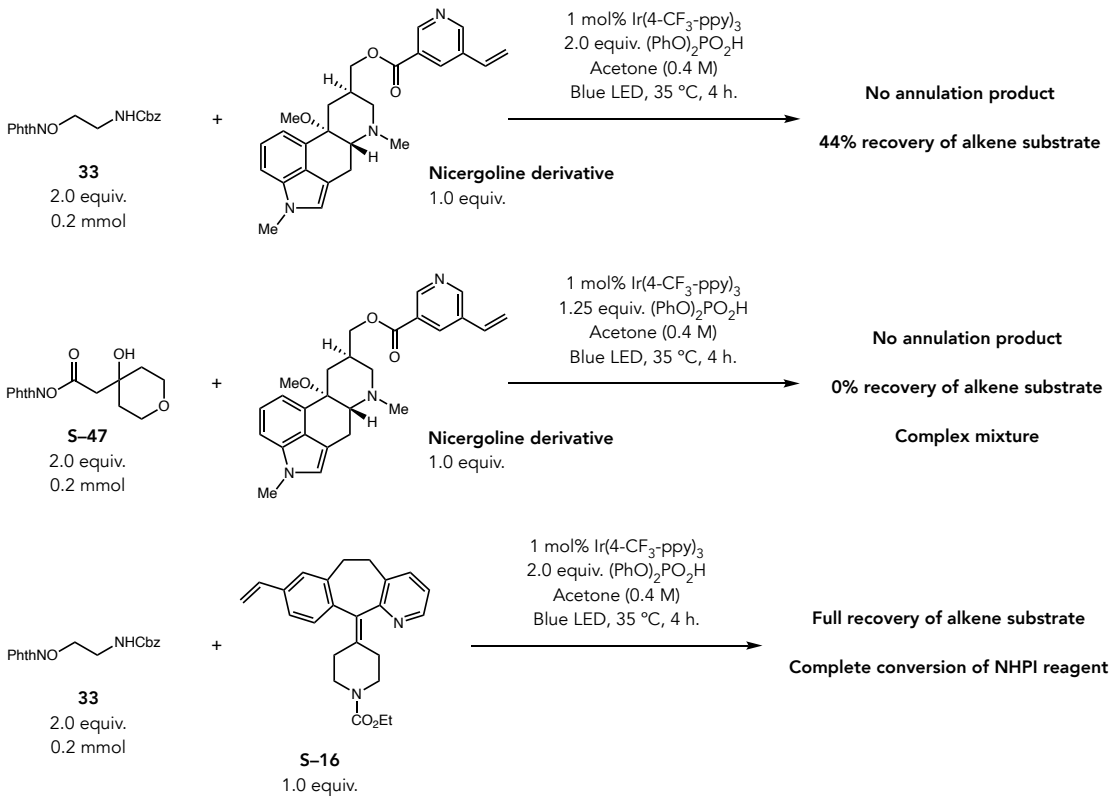
**Exclusive product**




**Repaglinide derivative**
1.0 equiv.
0.1 mmol

2.0 equiv.

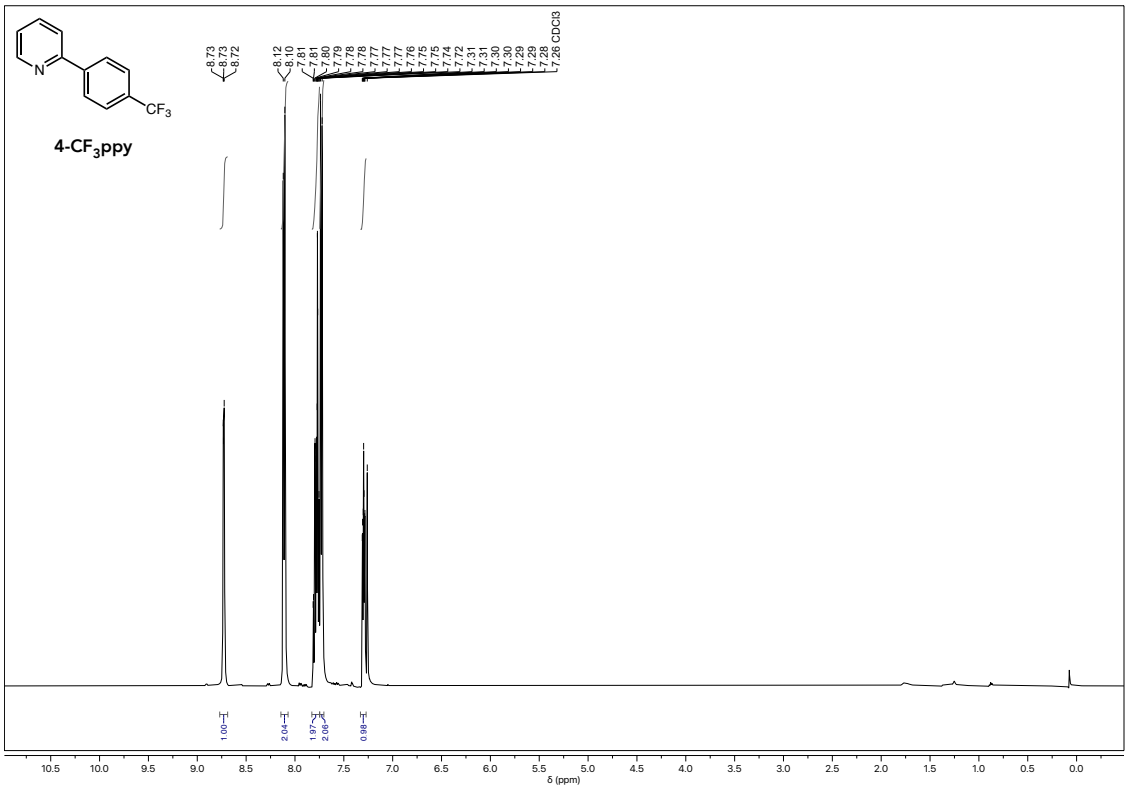
***ca.* 10%**
**+ complex mixture of multiple other products**

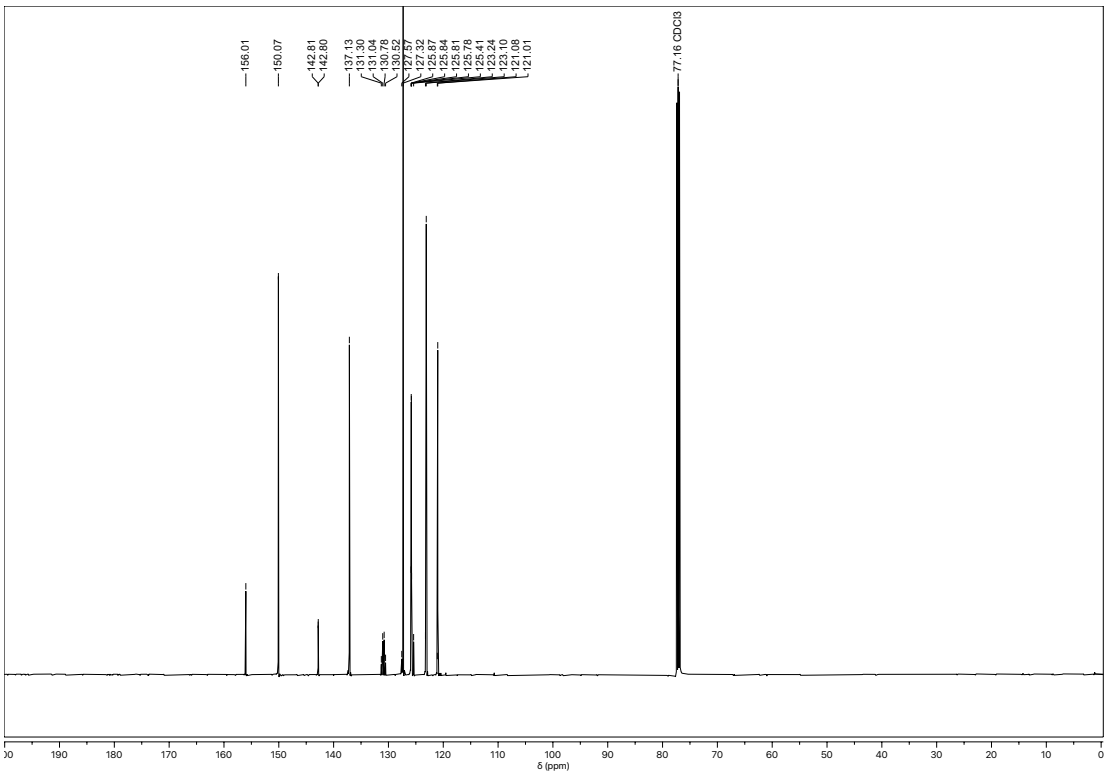

1 mol% Ir(4-CF3-ppy)3
2.0 equiv. (PhO)2PO2H
Acetone (0.4 M)
Blue LED, 35 °C, 4 h.
No annulation product
44% recovery of alkene substrate
33
2.0 equiv.
0.2 mmol
Nicergoline derivative
1.0 equiv.
1 mol% Ir(4-CF3-ppy)3
1.25 equiv. (PhO)2PO2H
Acetone (0.4 M)
Blue LED, 35 °C, 4 h.
No annulation product
0% recovery of alkene substrate
Complex mixture
S–47
2.0 equiv.
0.2 mmol
Nicergoline derivative
1.0 equiv.
1 mol% Ir(4-CF3-ppy)3
2.0 equiv. (PhO)2PO2H
Acetone (0.4 M)
Blue LED, 35 °C, 4 h.
Full recovery of alkene substrate
Complete conversion of NHPI reagent
33
2.0 equiv.
0.2 mmol
S–16
1.0 equiv.

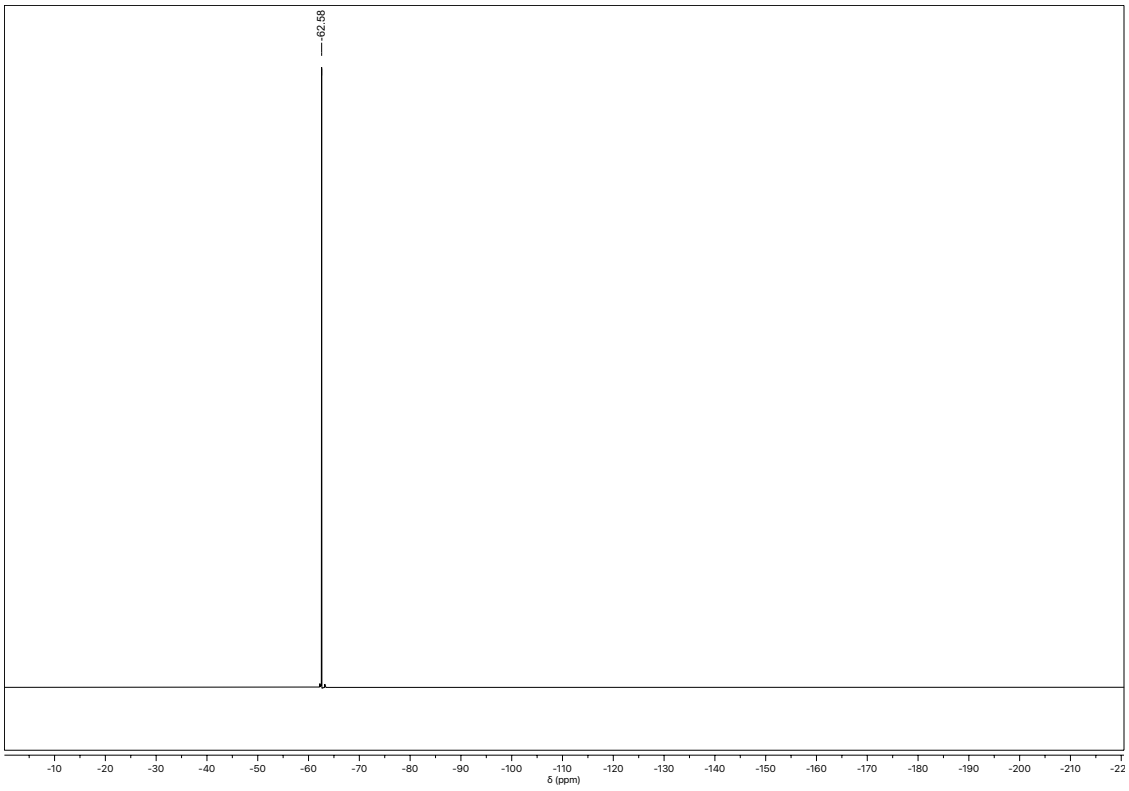
## 10. NMR Spectra

### 10.1. Photocatalyst materials

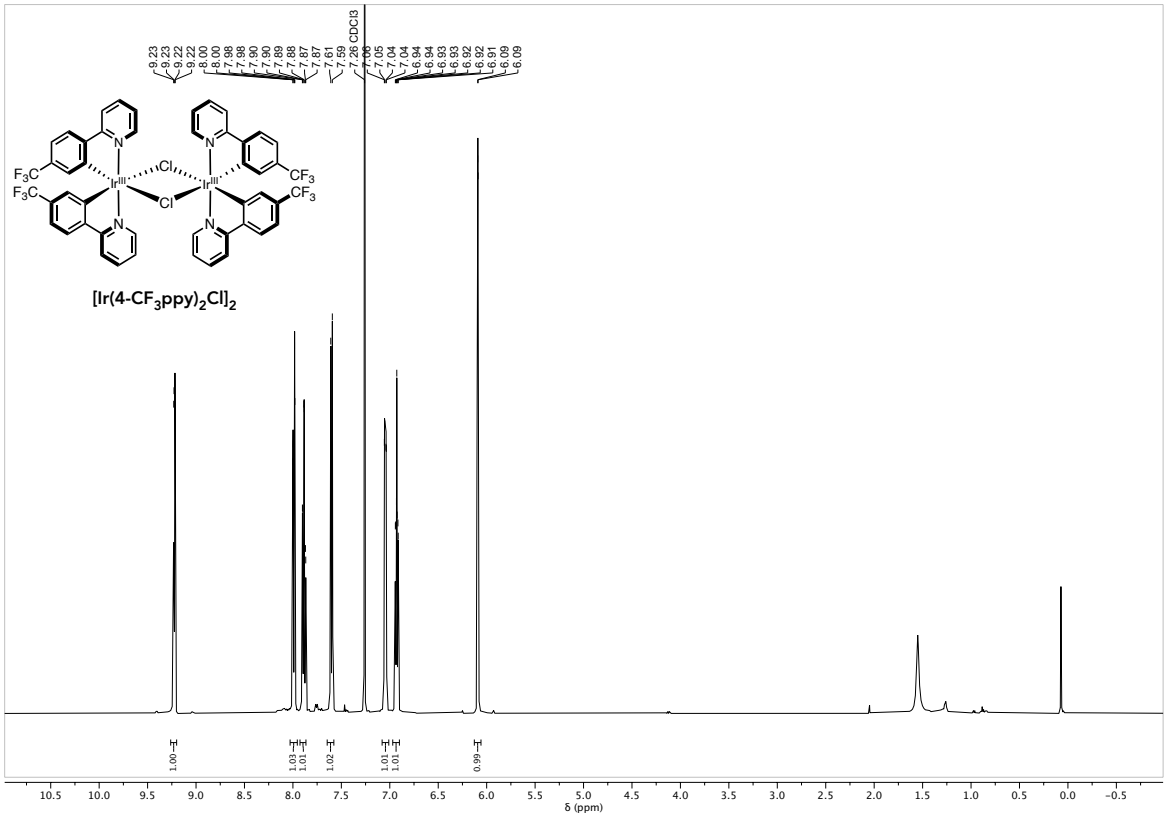
2-(4-Trifluoromethylphenyl)pyridine (4-$CF_3$-ppy)

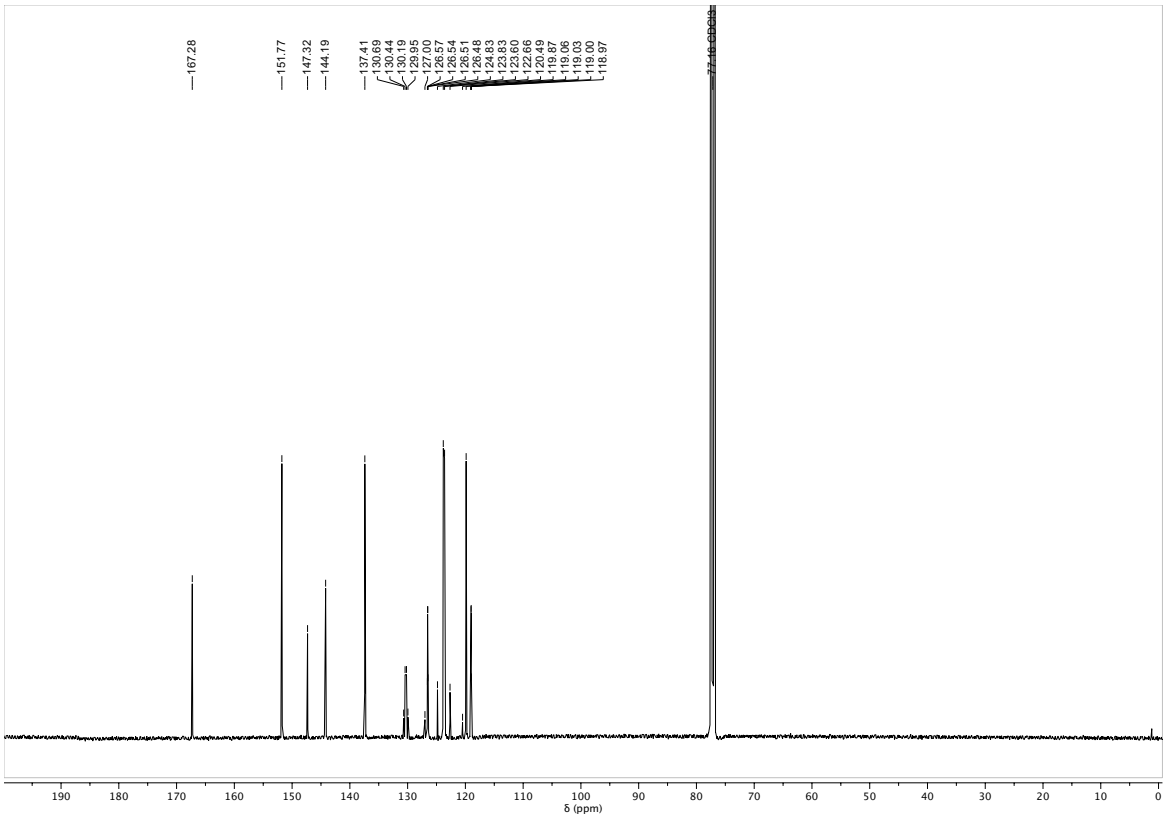


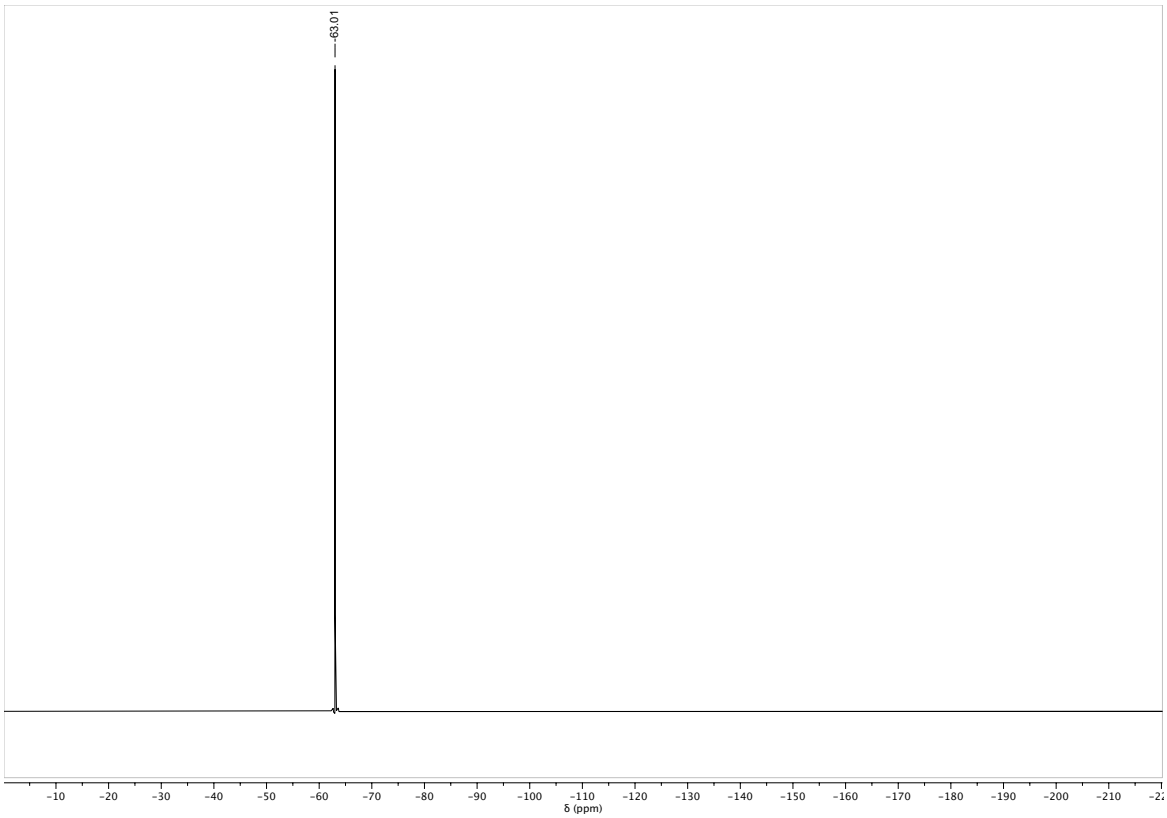




-62.68
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
δ (ppm)

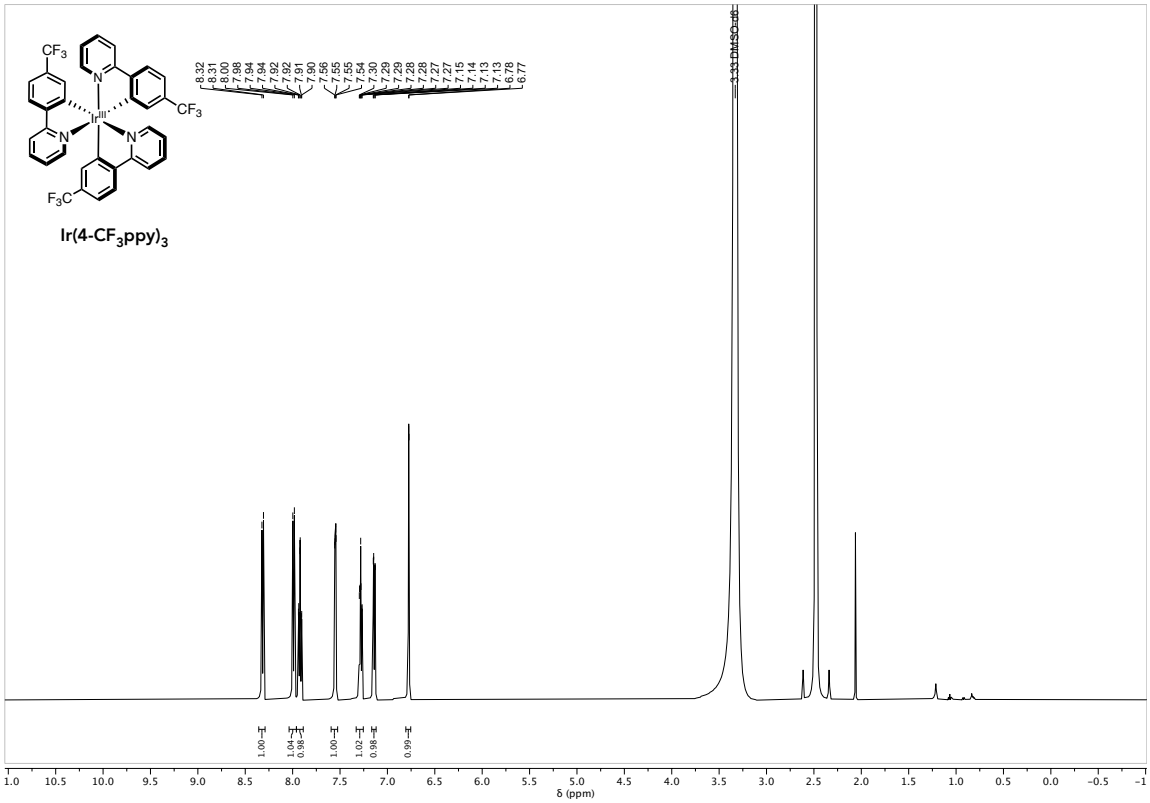
[(4-$CF_3$ppy)$_2$Ir(μ-Cl)]$_2$

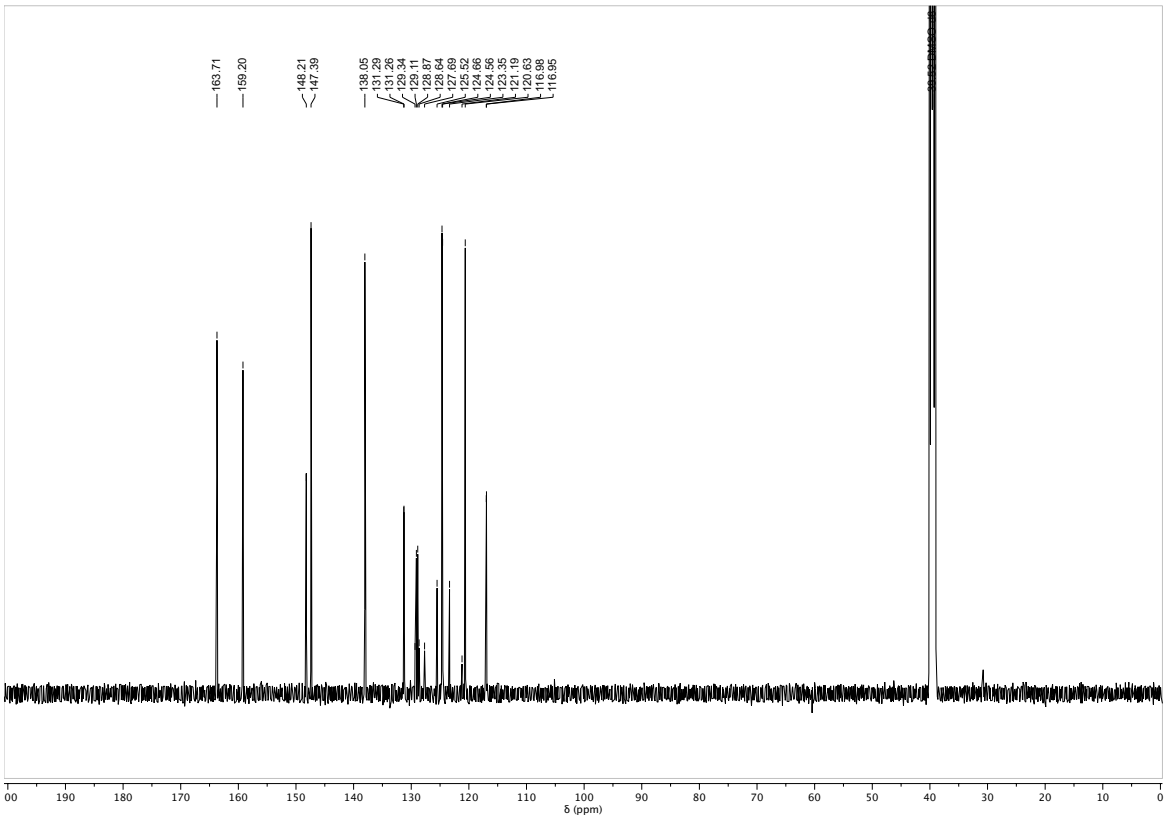


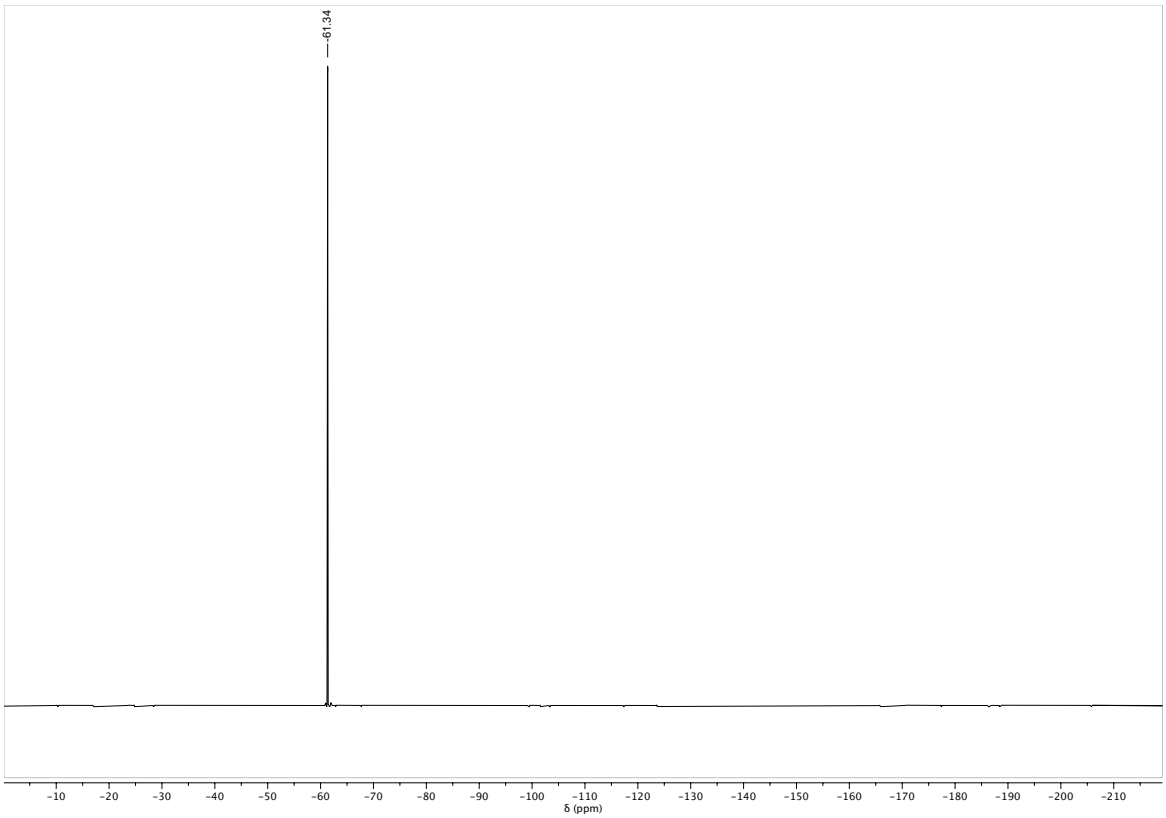




-63.01
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
δ (ppm)

## Ir(4-$CF_3$ppy)$_3$

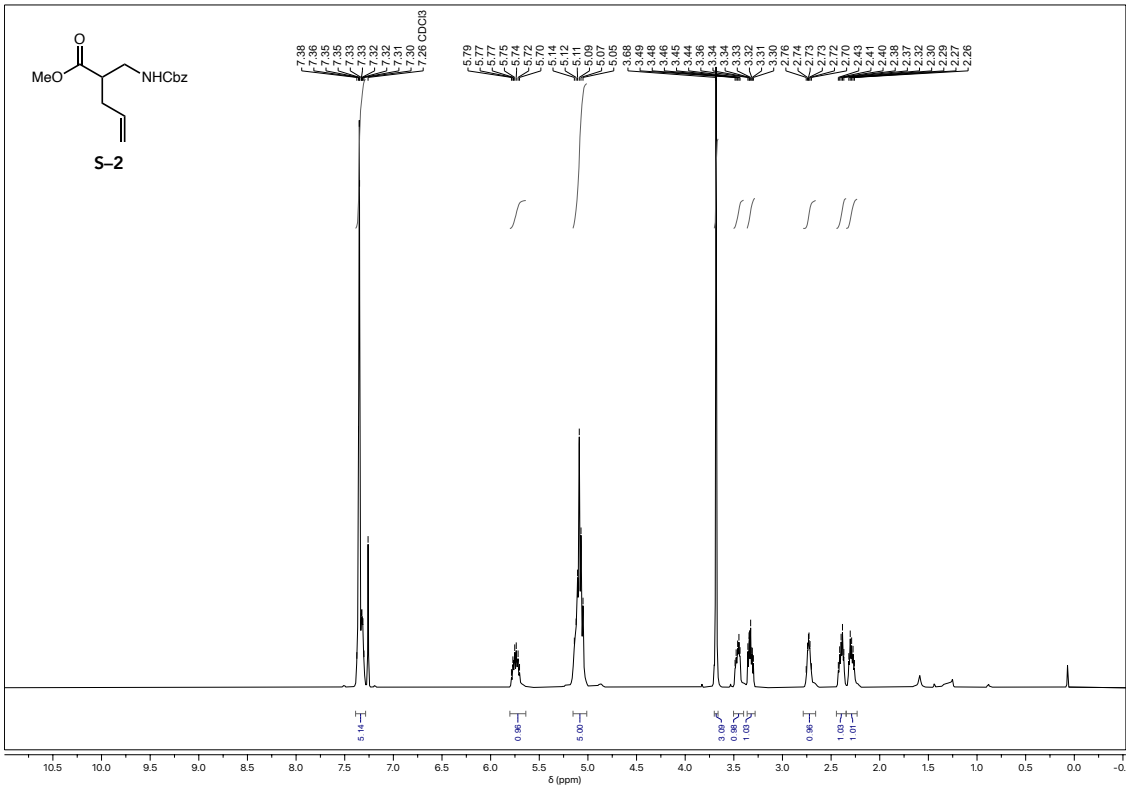


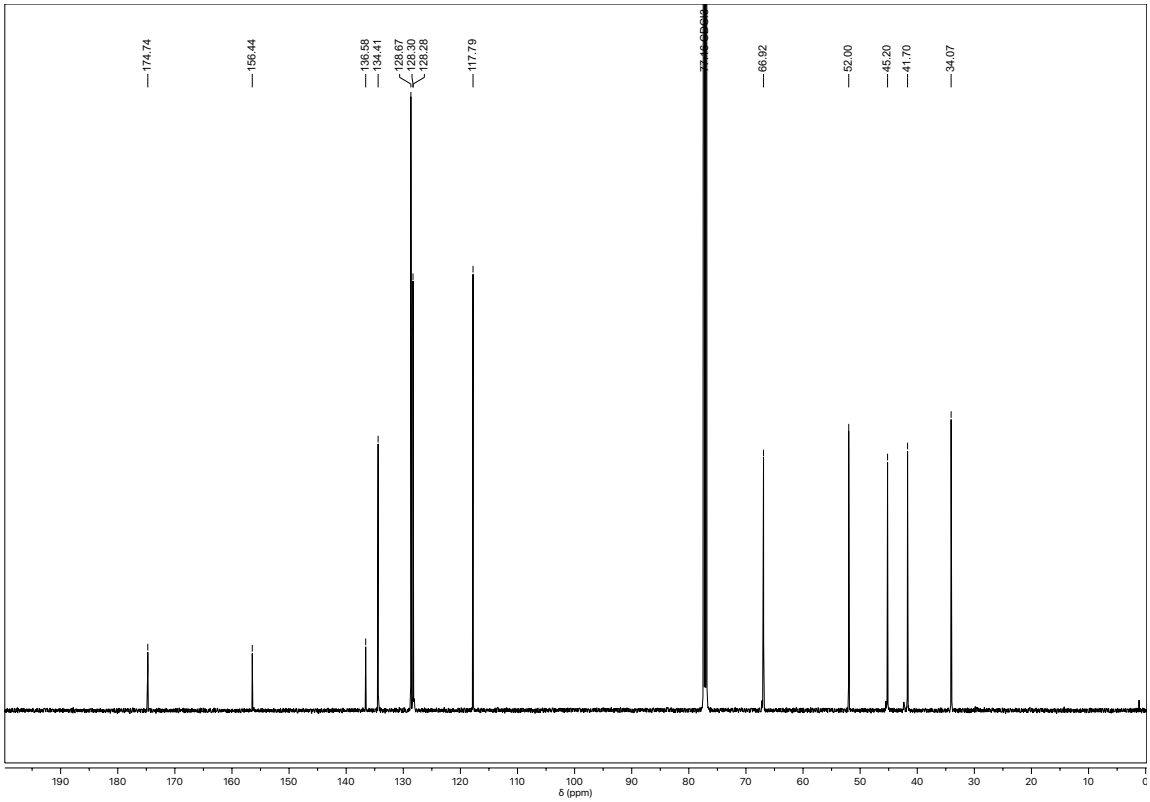




-61.34
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
δ (ppm)

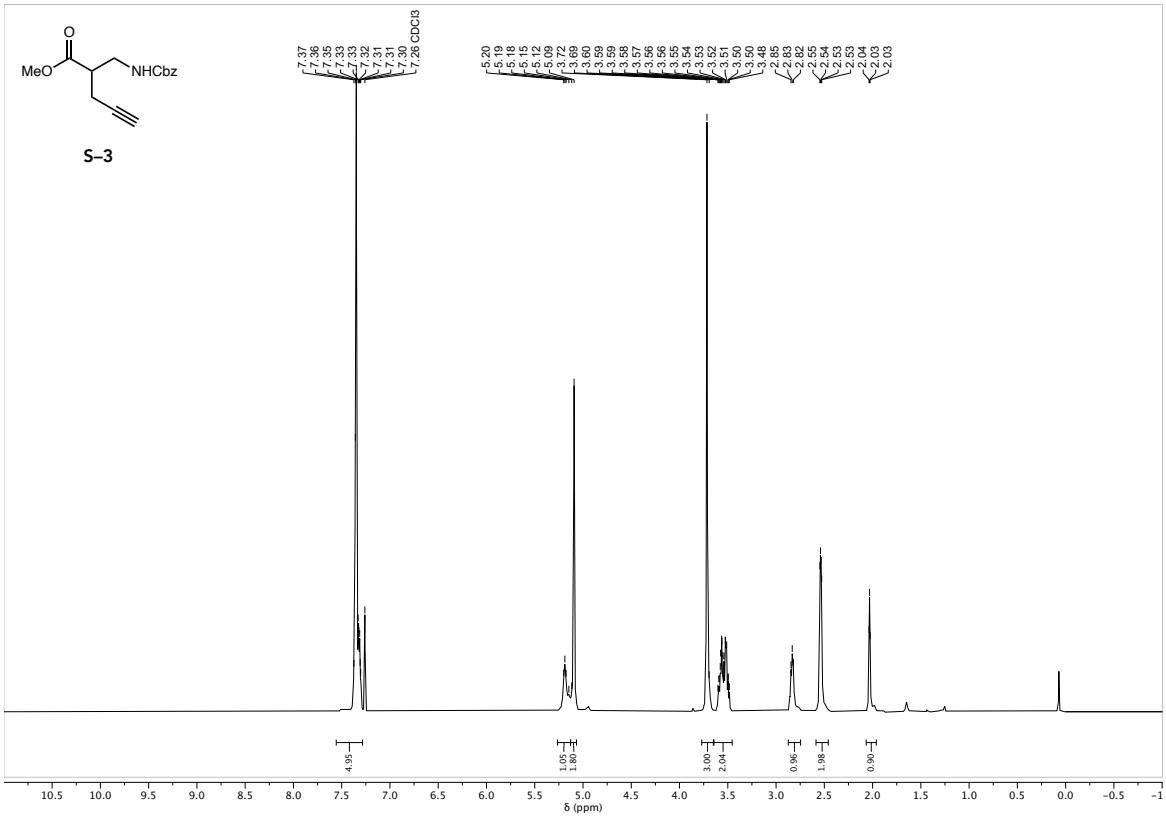
## 10.2 Precursors to NHPI reagents

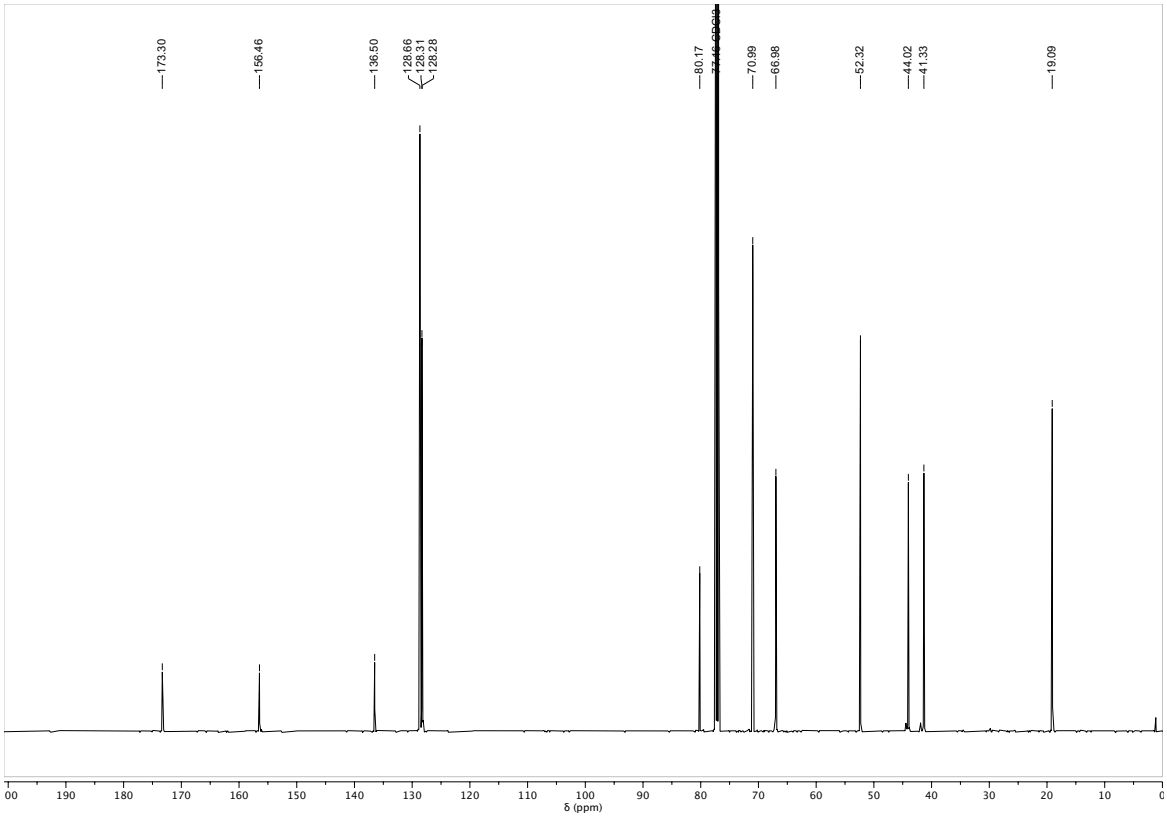
Methyl 2-((((benzyloxy)carbonyl)amino)methyl)pent-4-enoate (S–2)



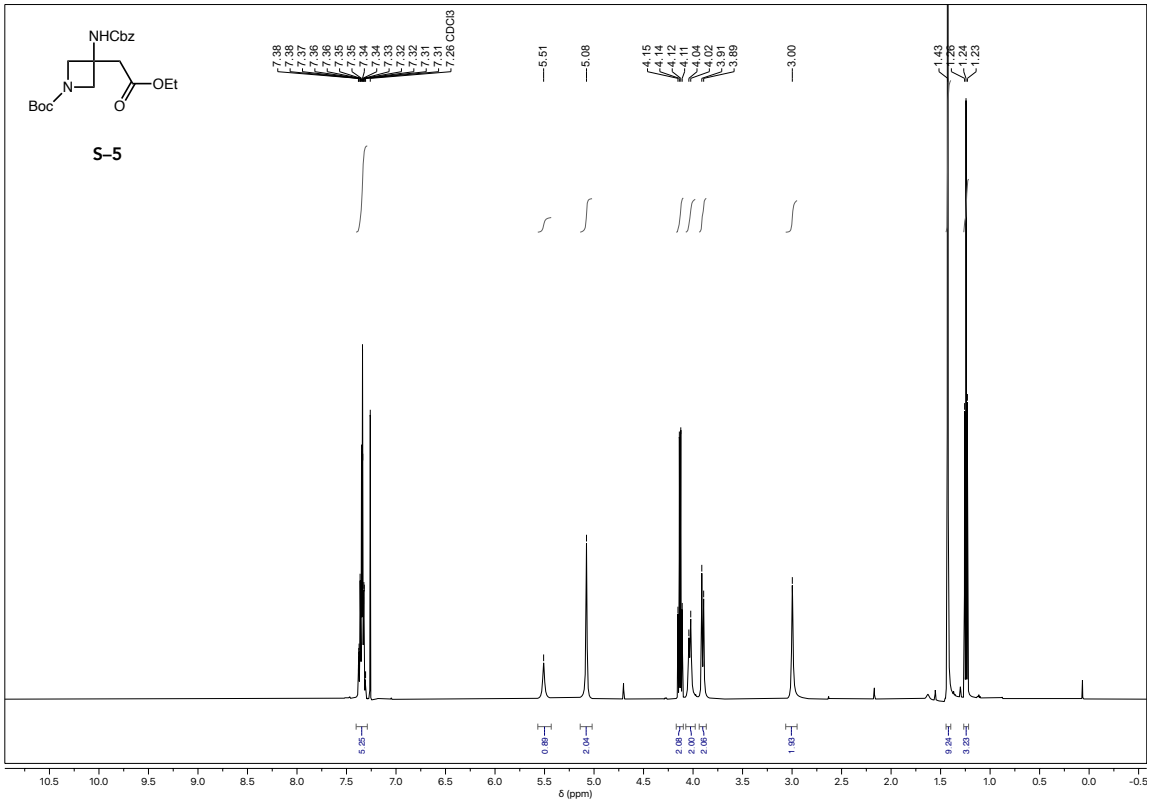



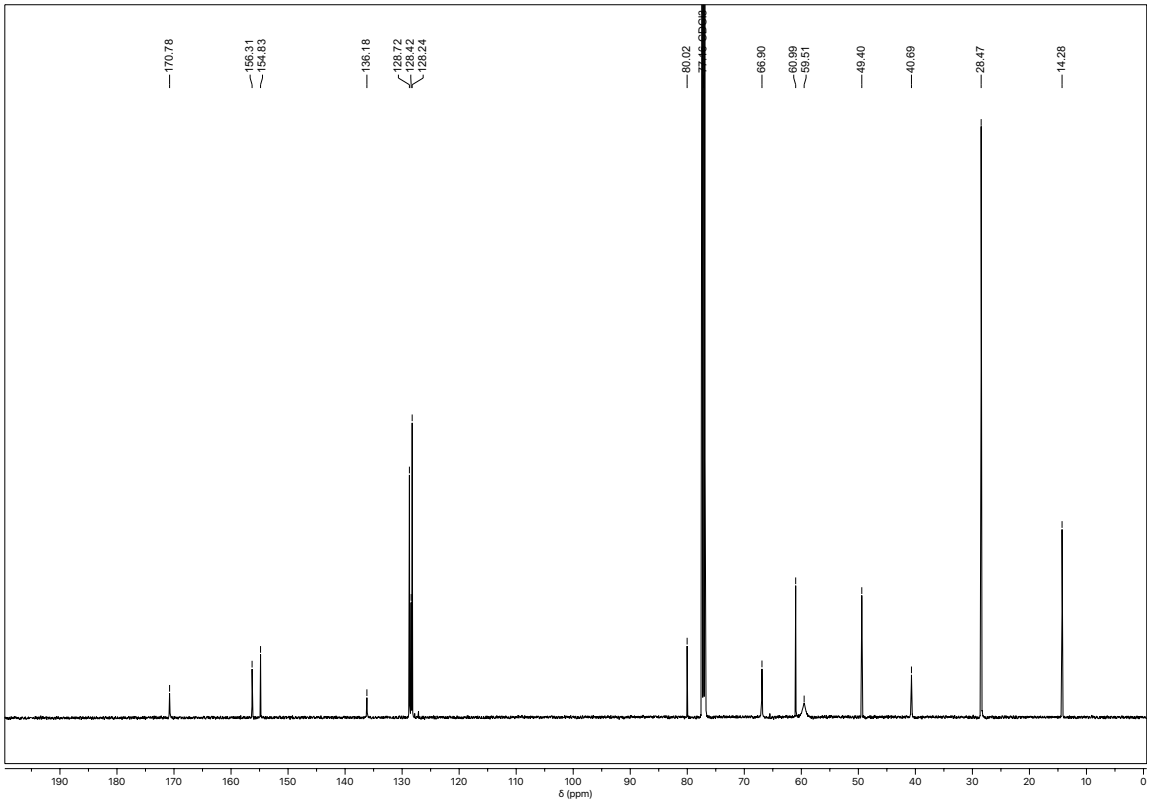
Methyl 2-((((benzyloxy)carbonyl)amino)methyl)pent-4-ynoate (S–3)



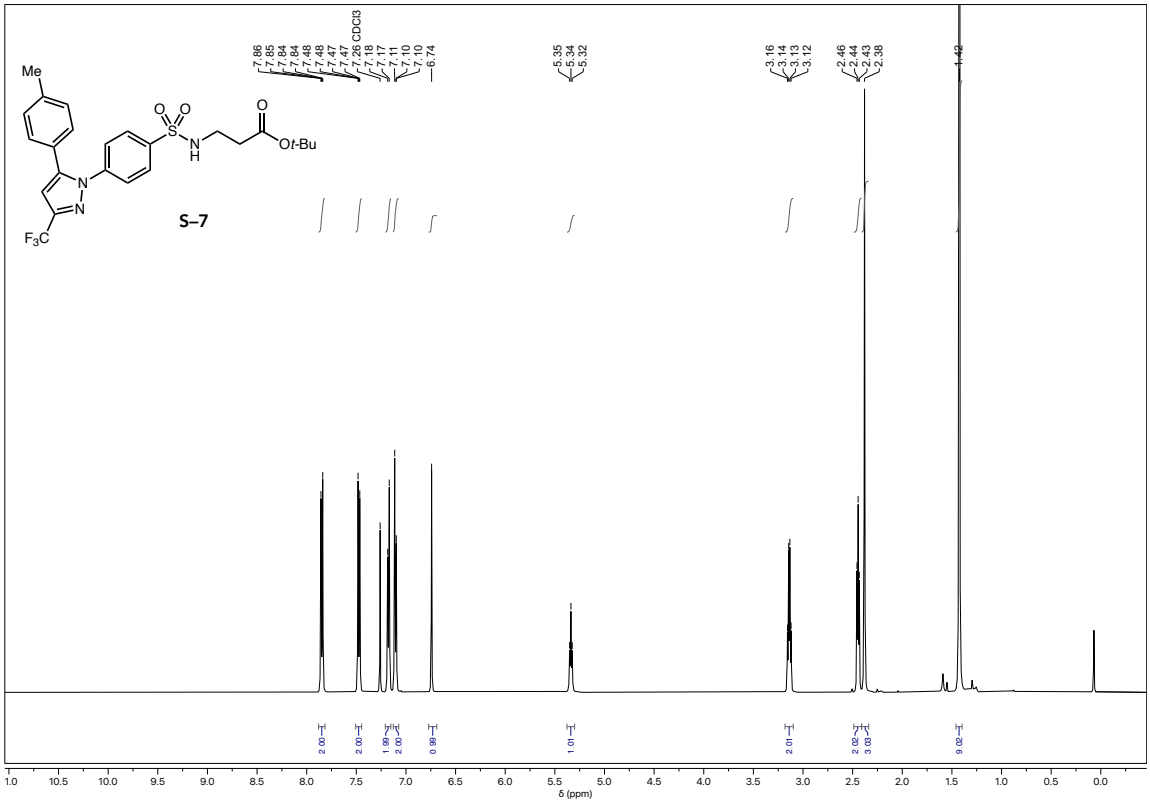



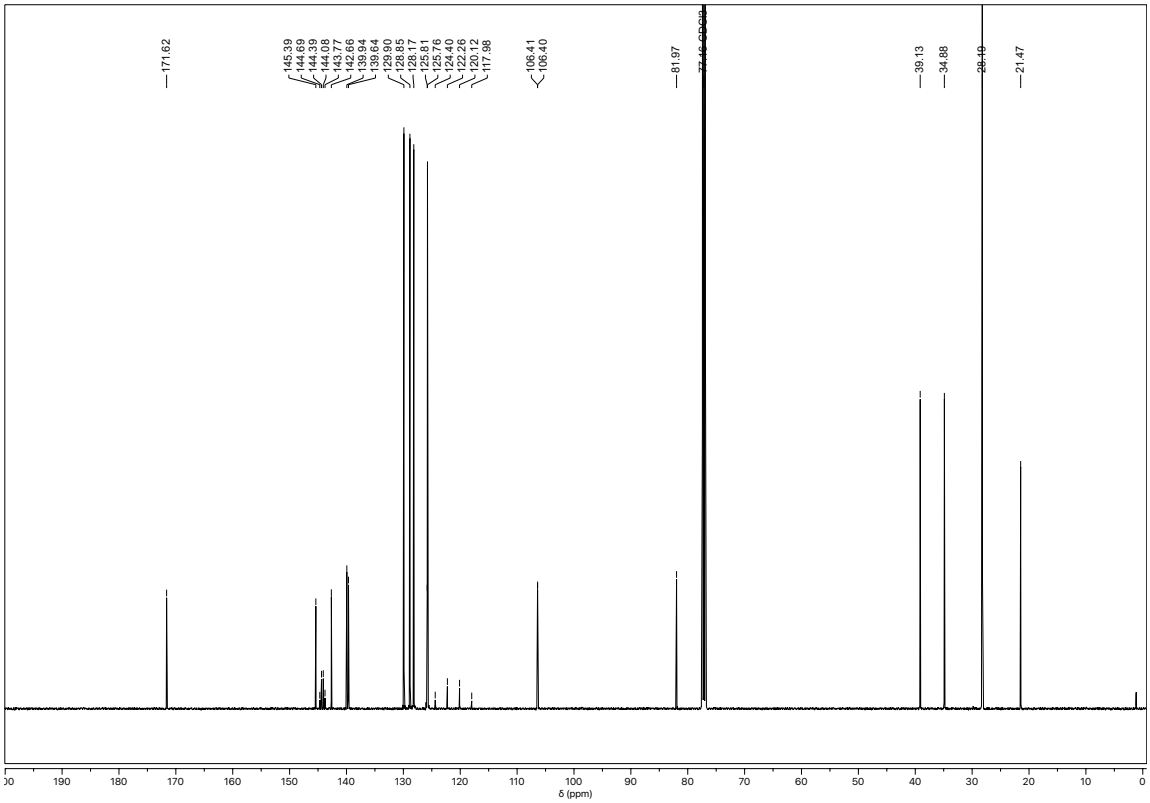
*Tert*-butyl 3-(((benzyloxy)carbonyl)amino)-3-(2-ethoxy-2-oxoethyl)azetidine-1-carboxylate (S–5)

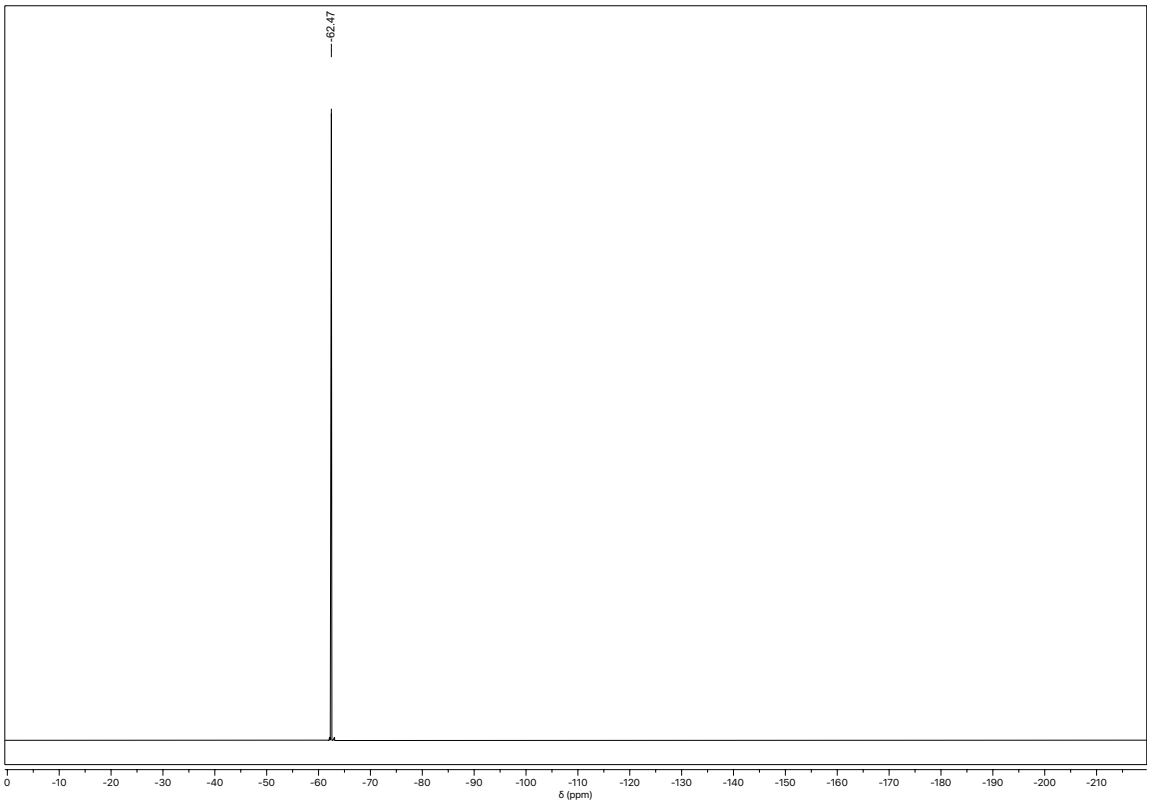


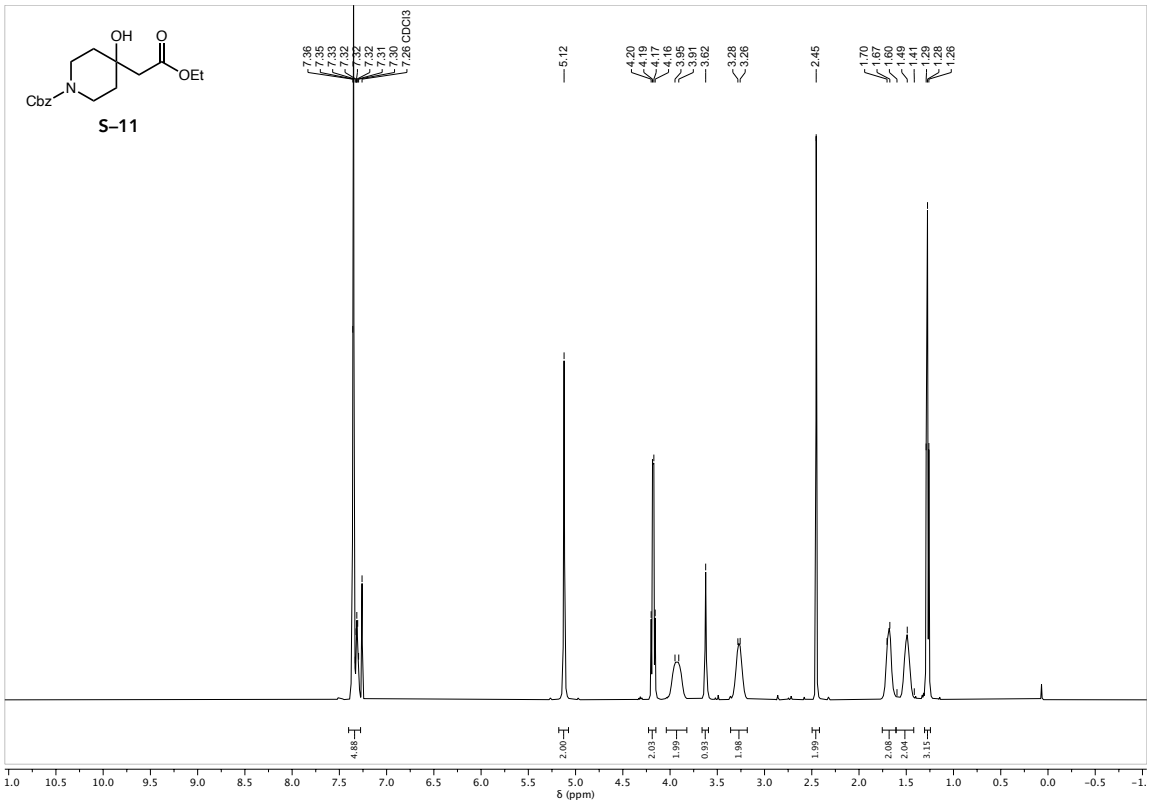
*Tert*-butyl 3-((4-(5-(*p*-tolyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)sulfonamido)propanoate (*S*–7)

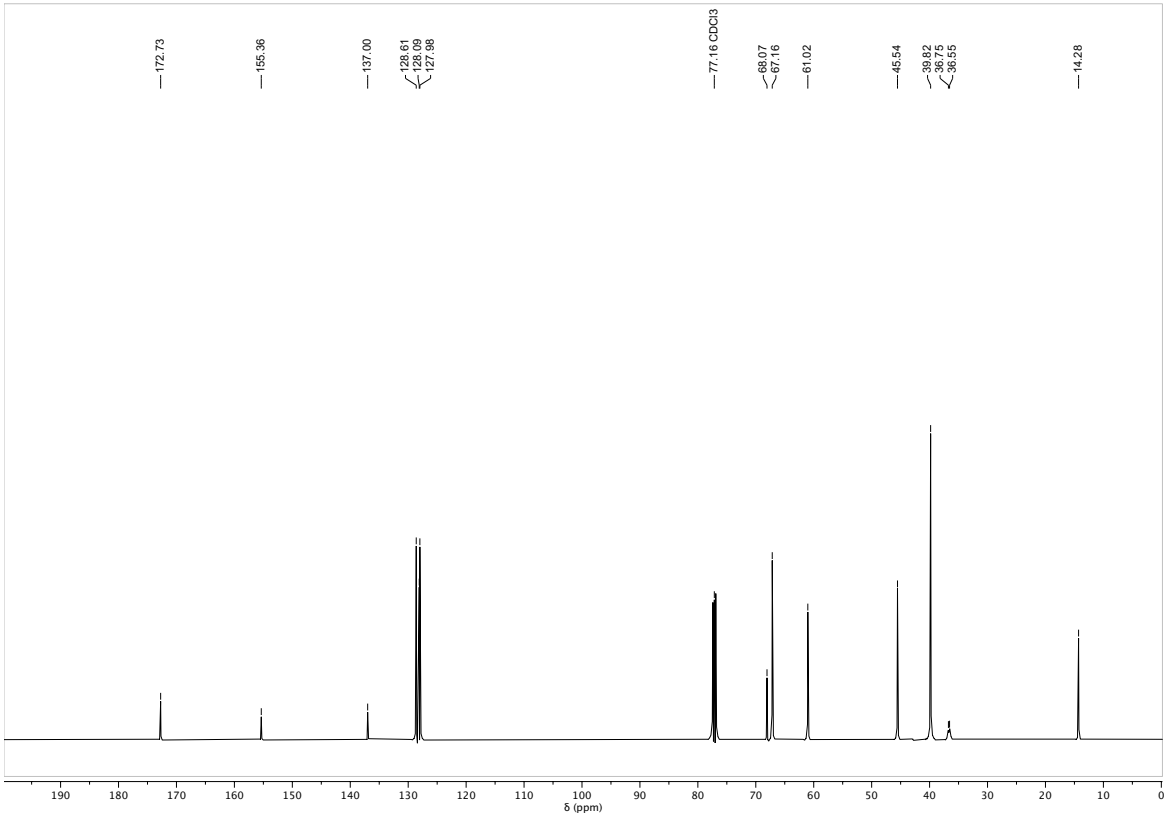


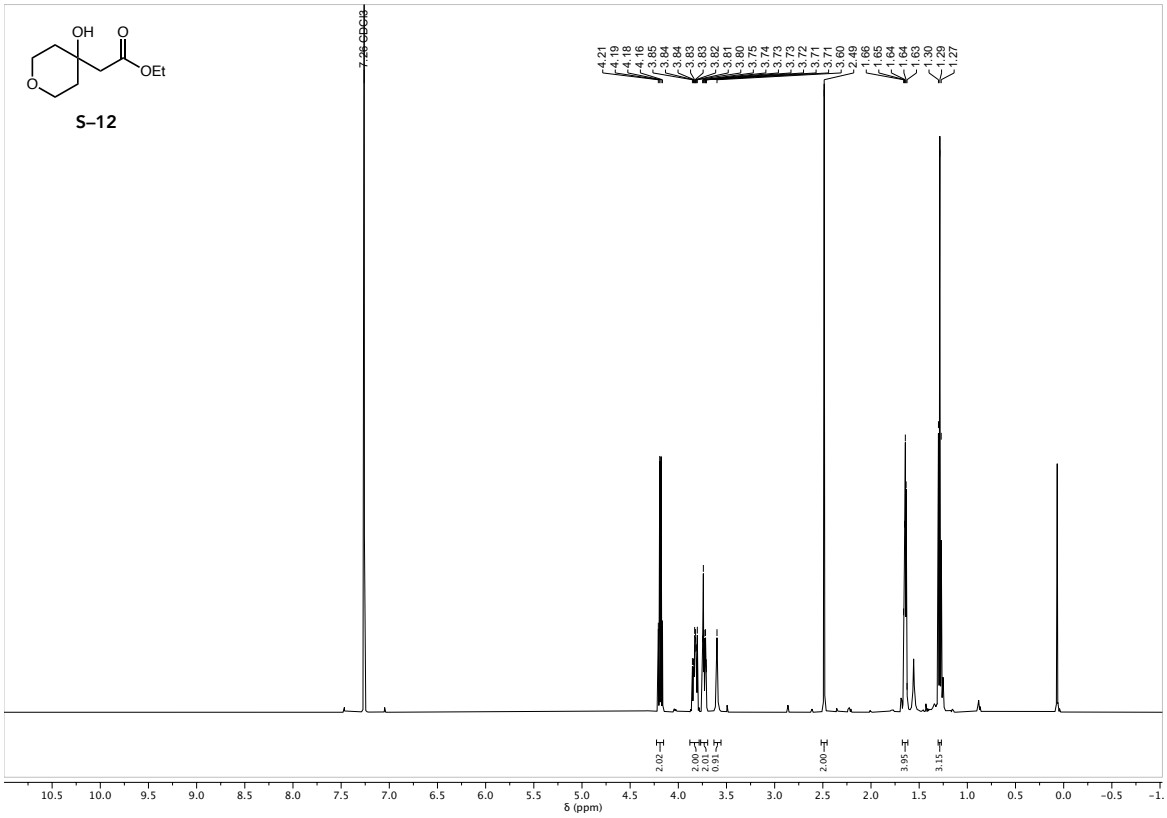

-62.47
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
δ (ppm)

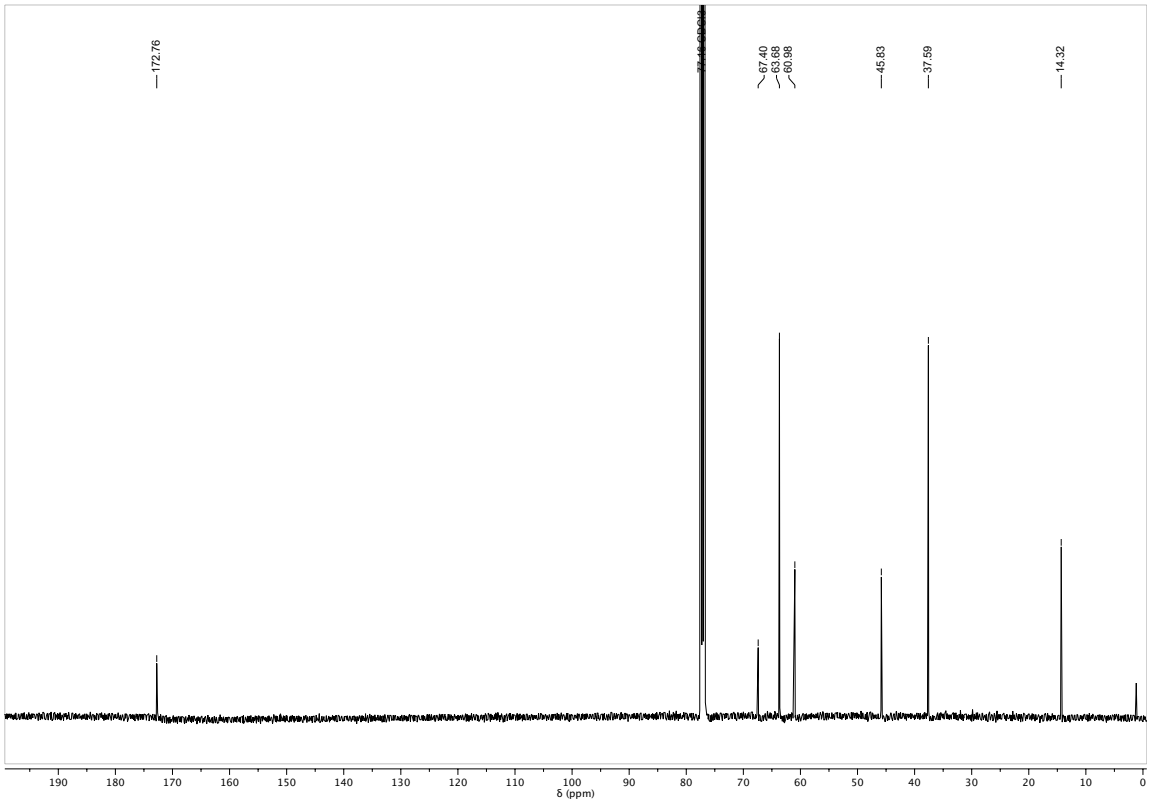
Benzyl 4-(2-ethoxy-2-oxoethyl)-4-hydroxypiperidine-1-carboxylate (S–11)



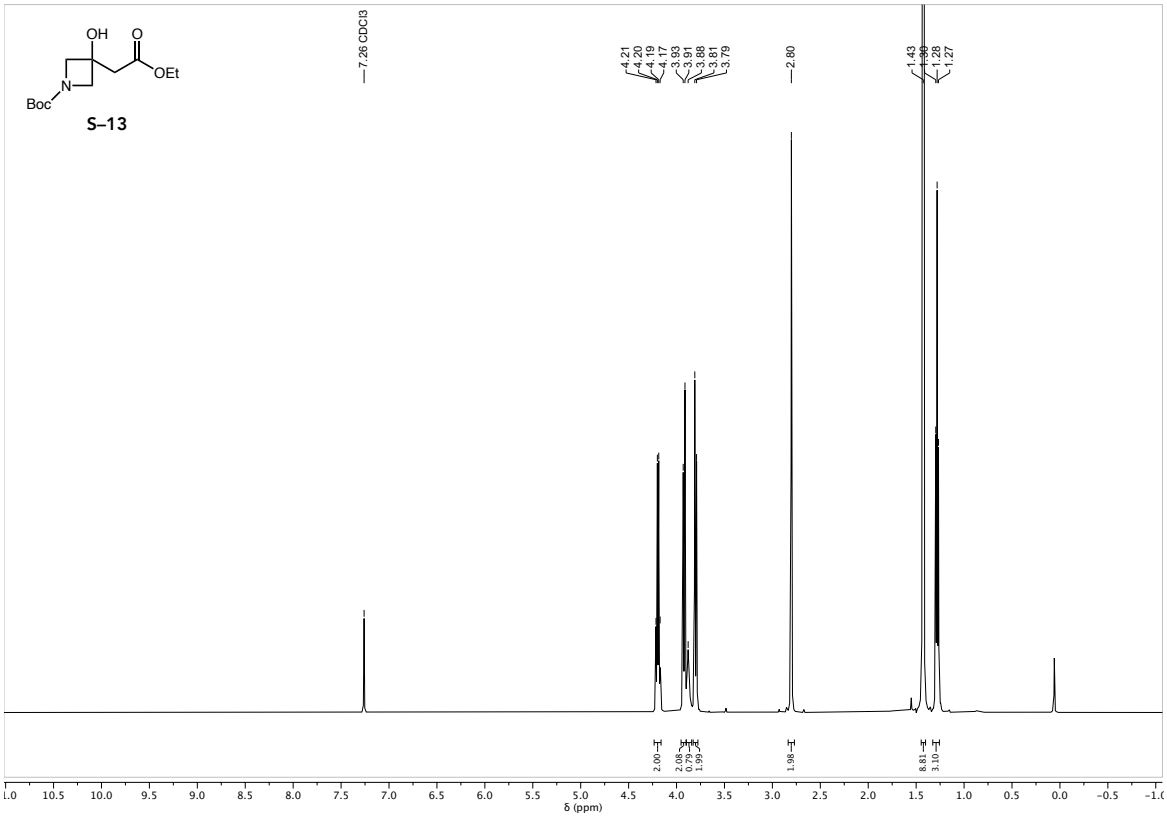



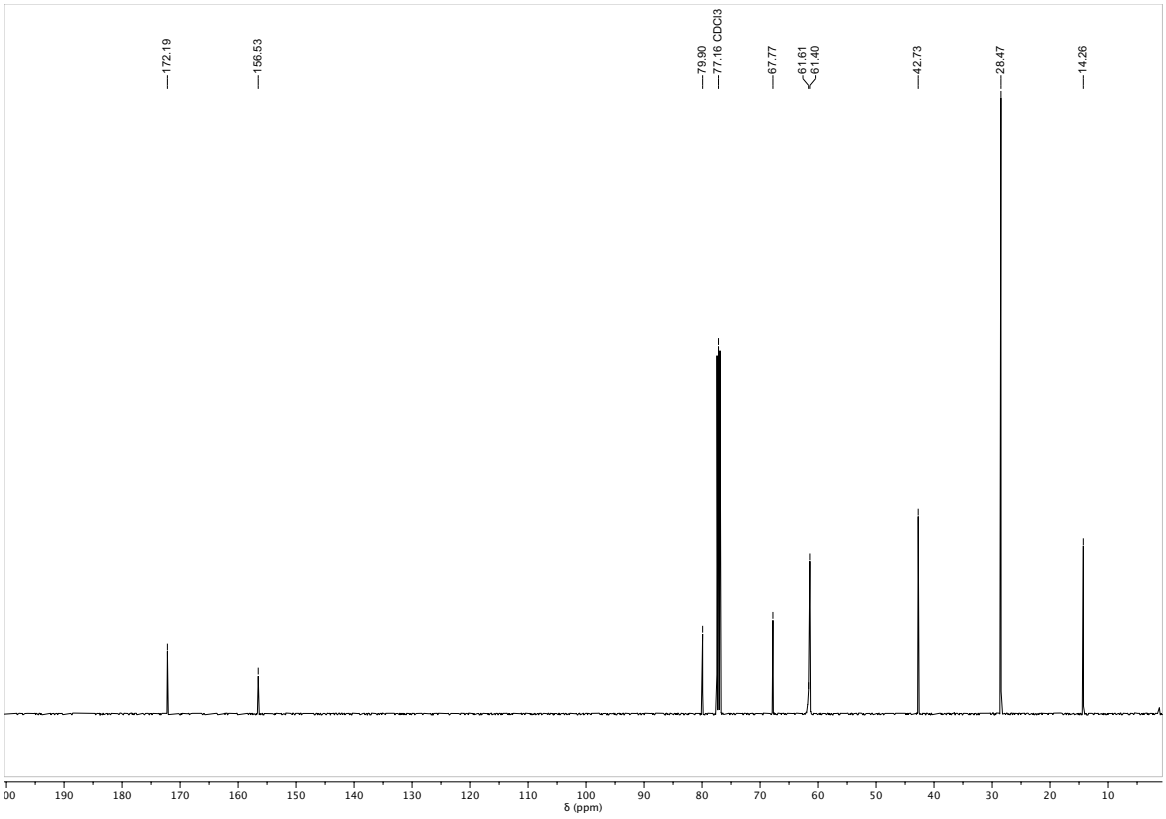
Ethyl 2-(4-hydroxytetrahydro-2H-pyran-4-yl)acetate (S–12)



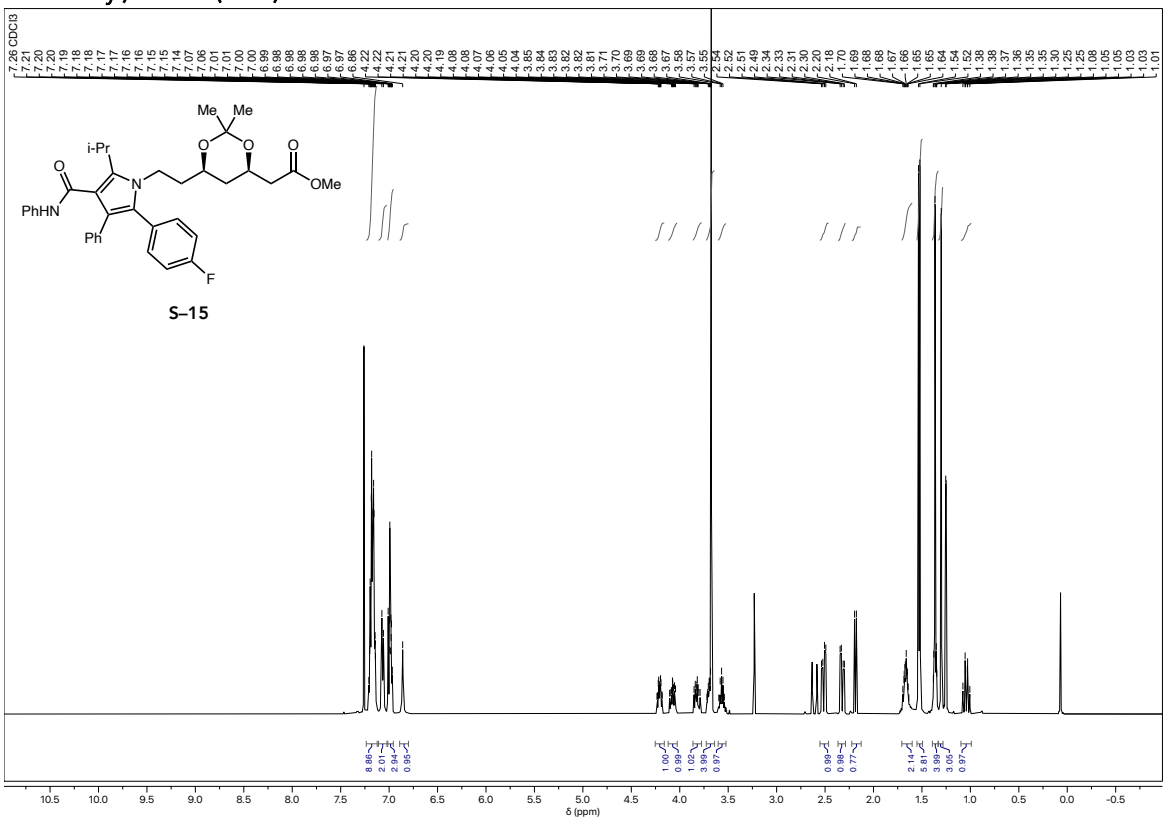



*Tert*-butyl 3-(2-ethoxy-2-oxoethyl)-3-hydroxyazetidine-1-carboxylate (S–13)

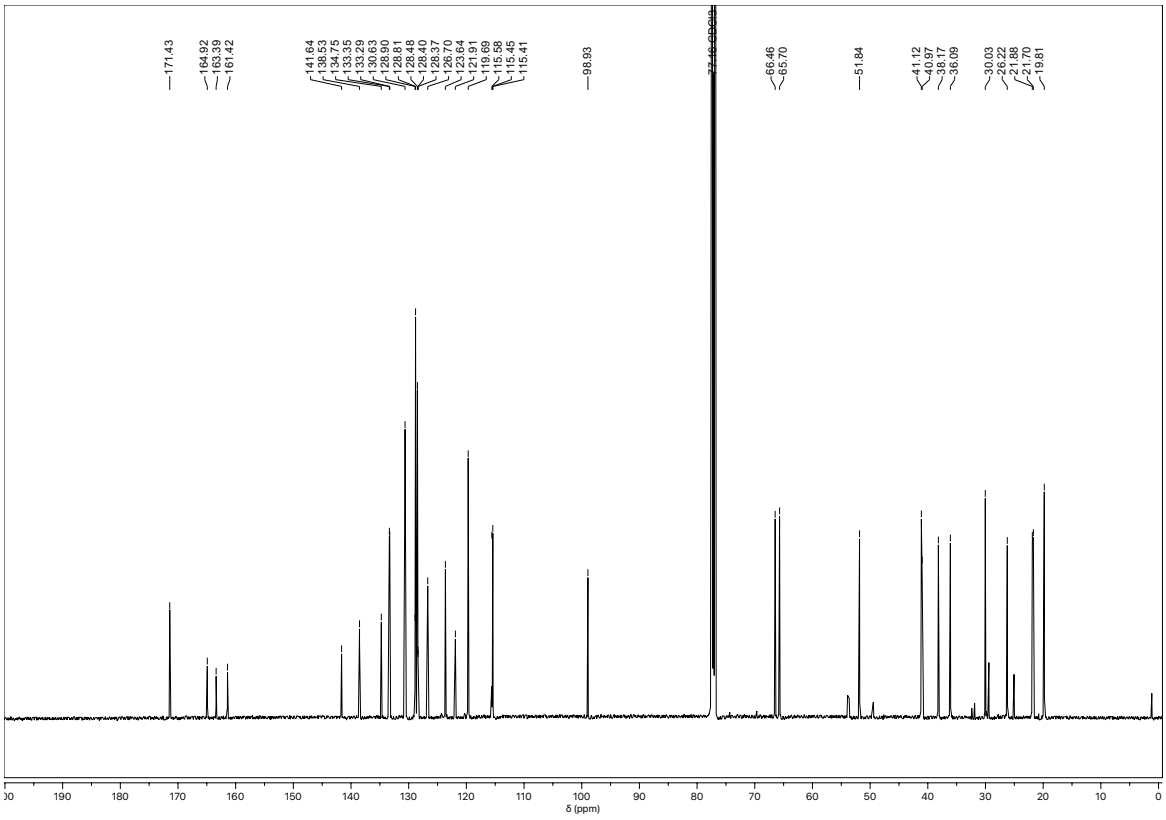


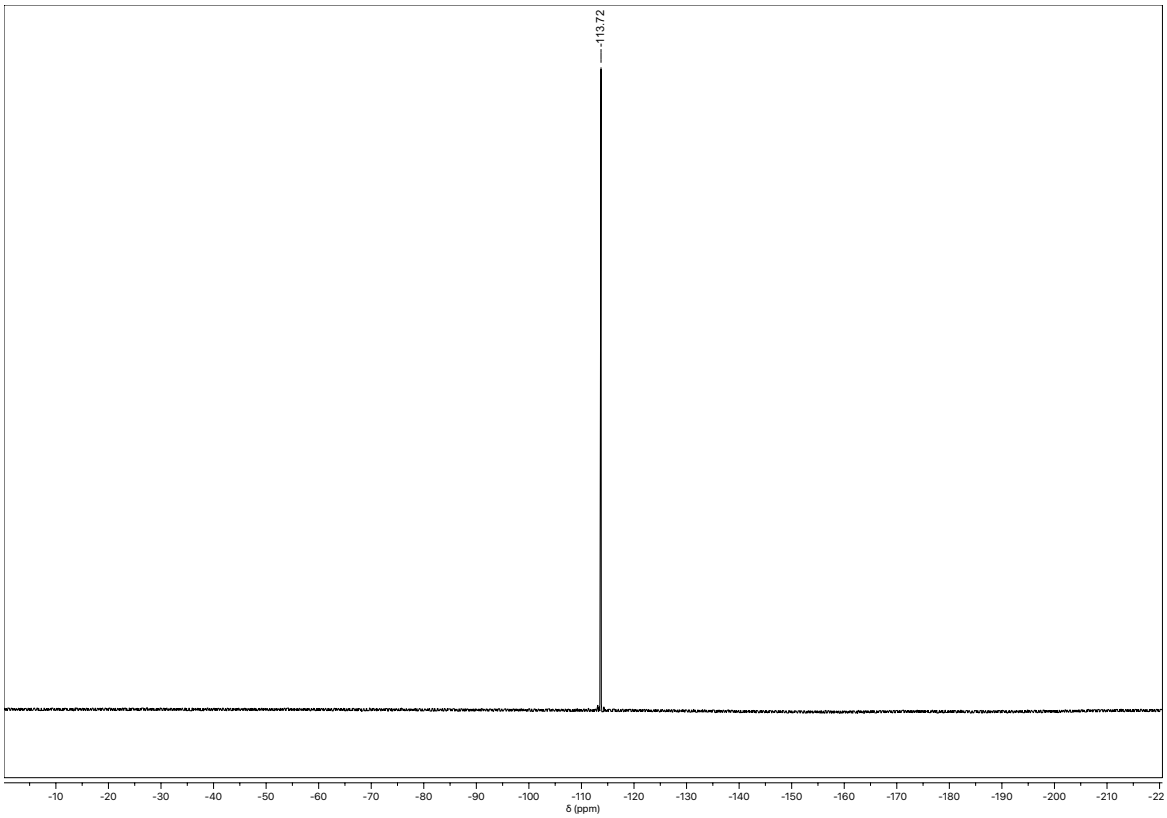



Methyl 2-((4*R*,6*R*)-6-(2-(2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1*H*-pyrrol-1-yl)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (S–15)



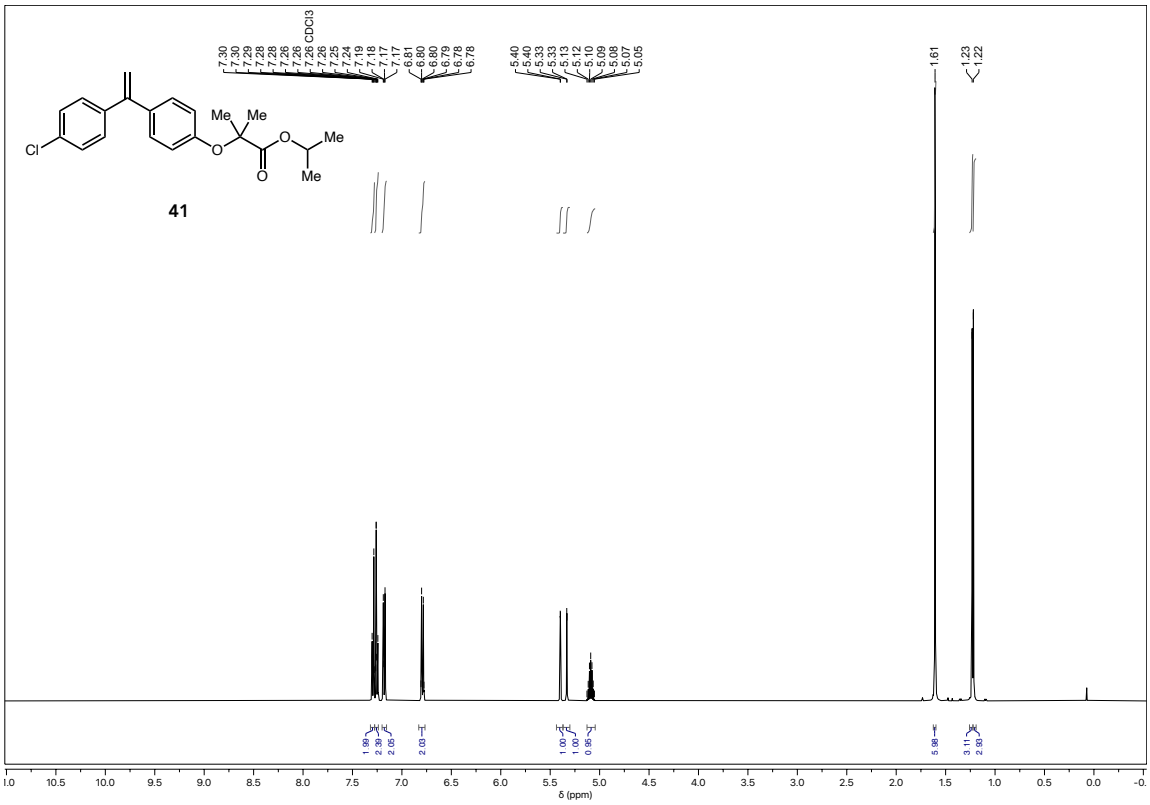

**S–15**

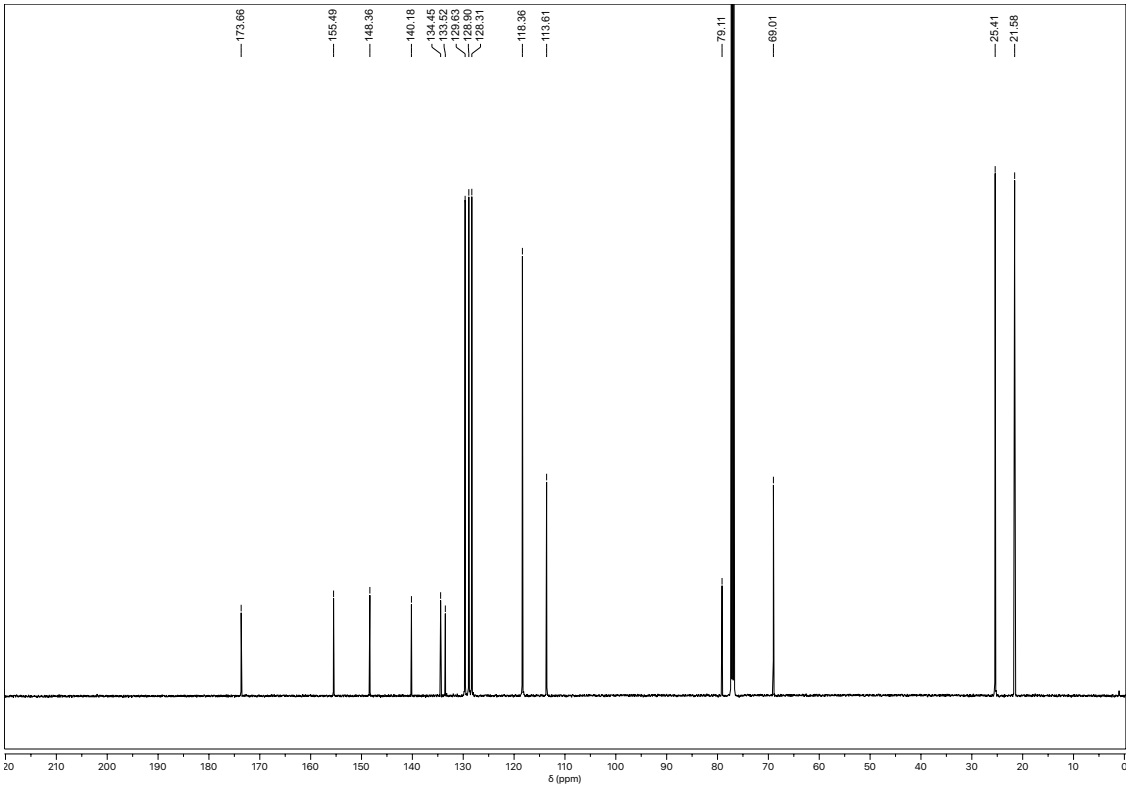



-113.72
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-22
δ (ppm)

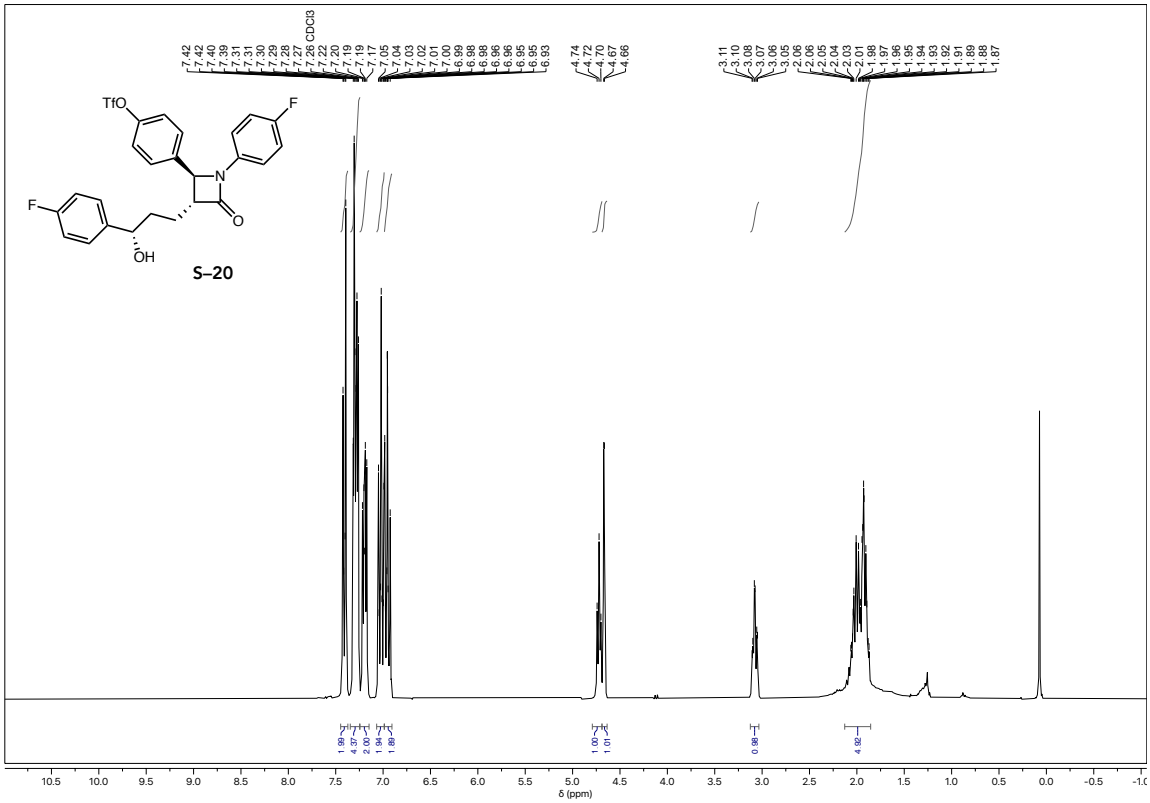
## 10.3. Alkene substrates

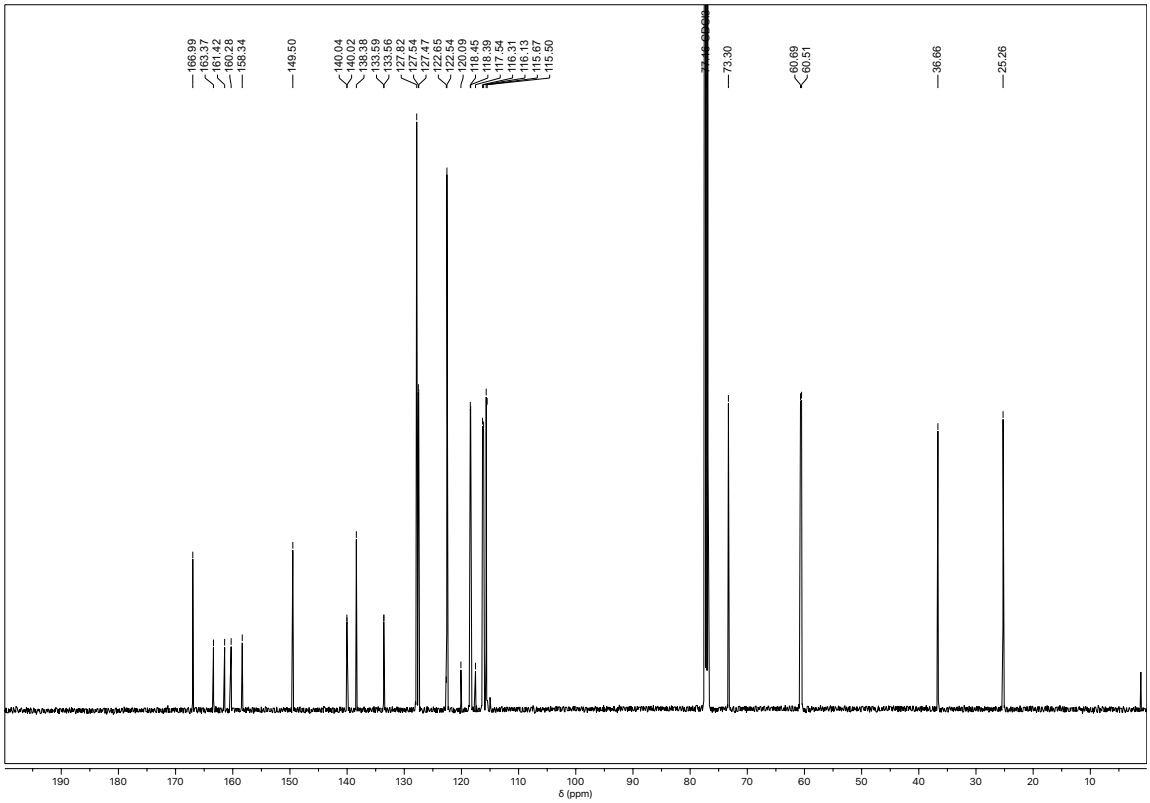
Fenofibrate 1,1-diaryl ethylene (41)

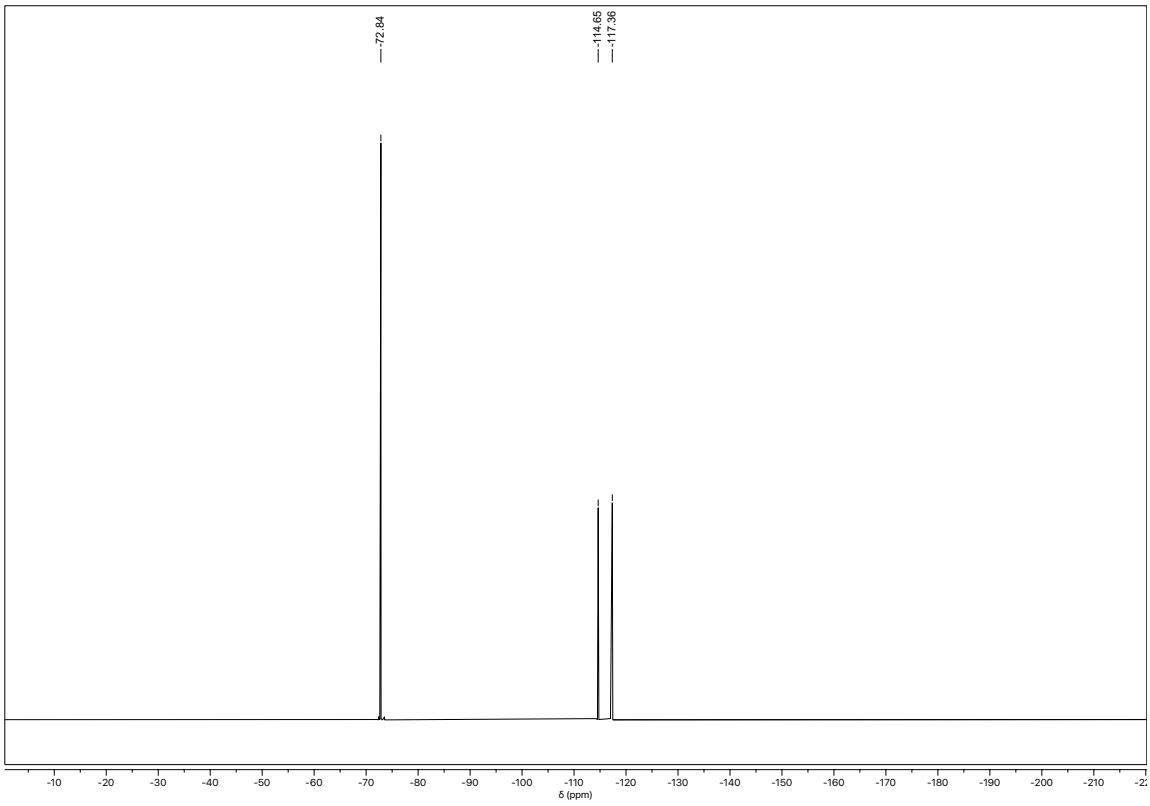


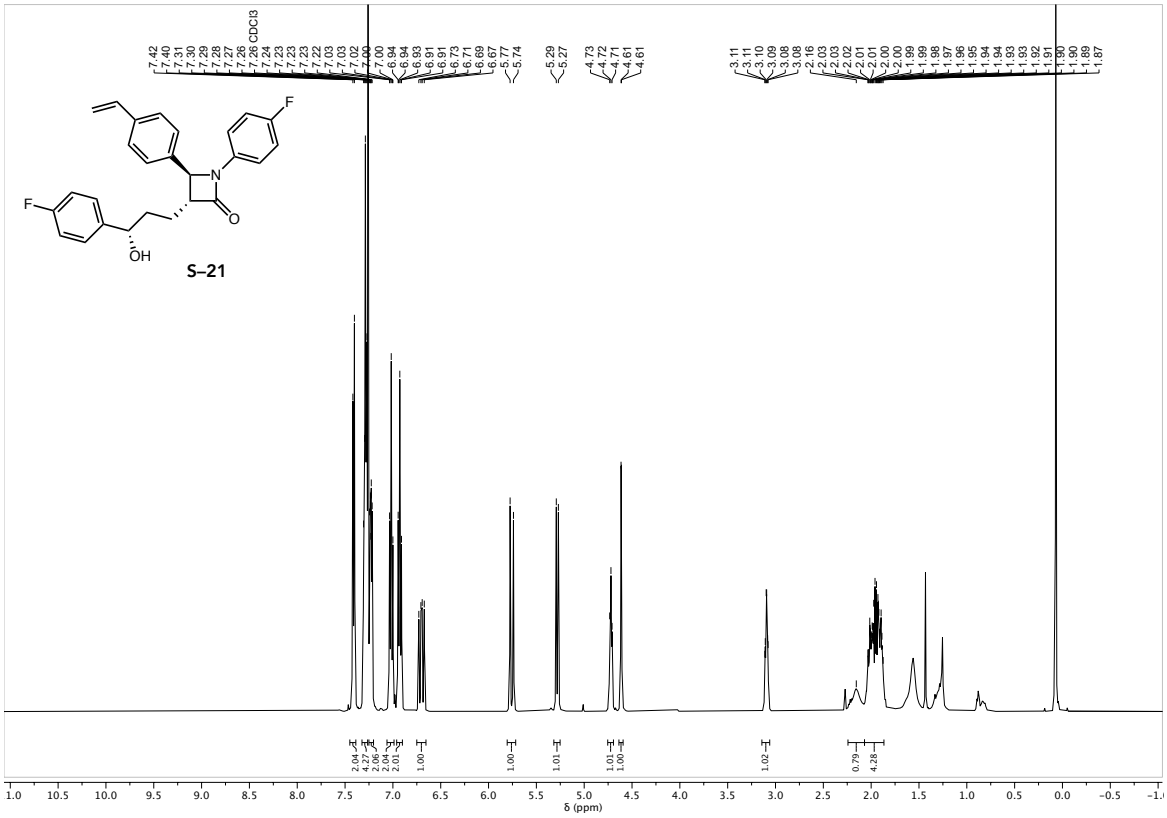
Ezetimibe triflate (S–20)

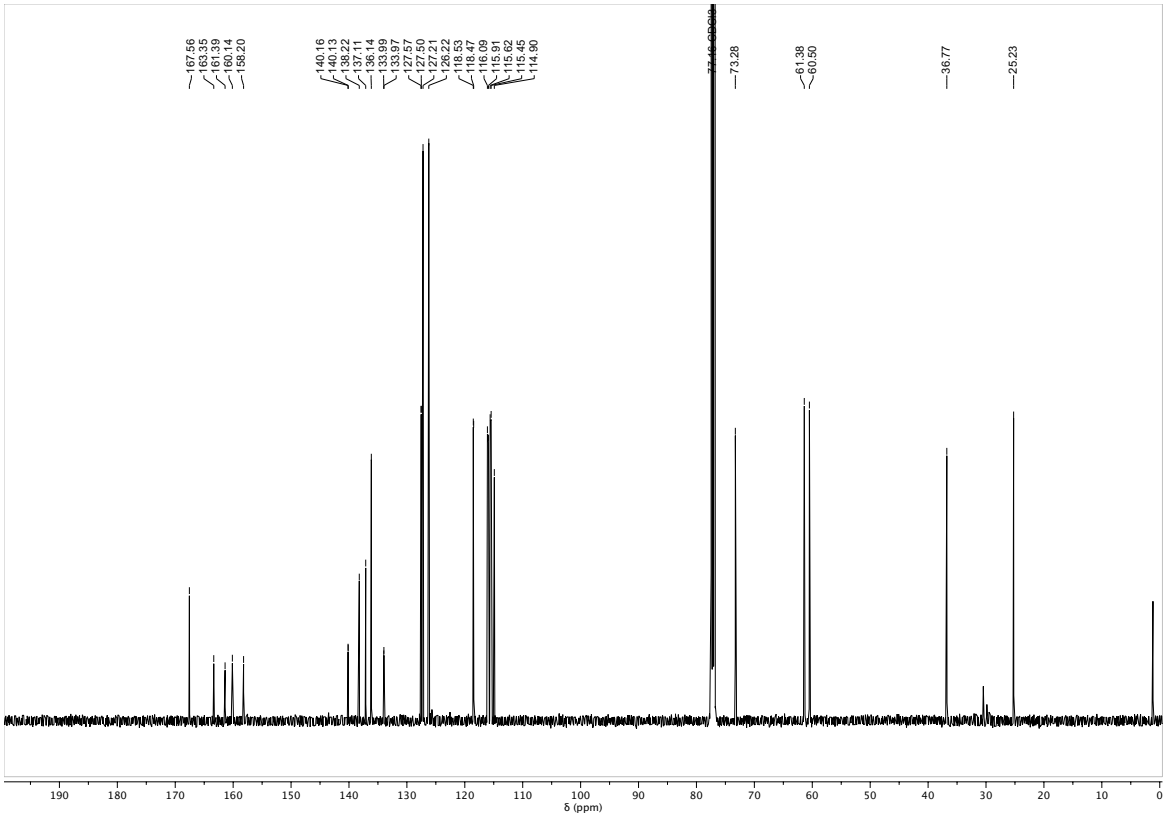


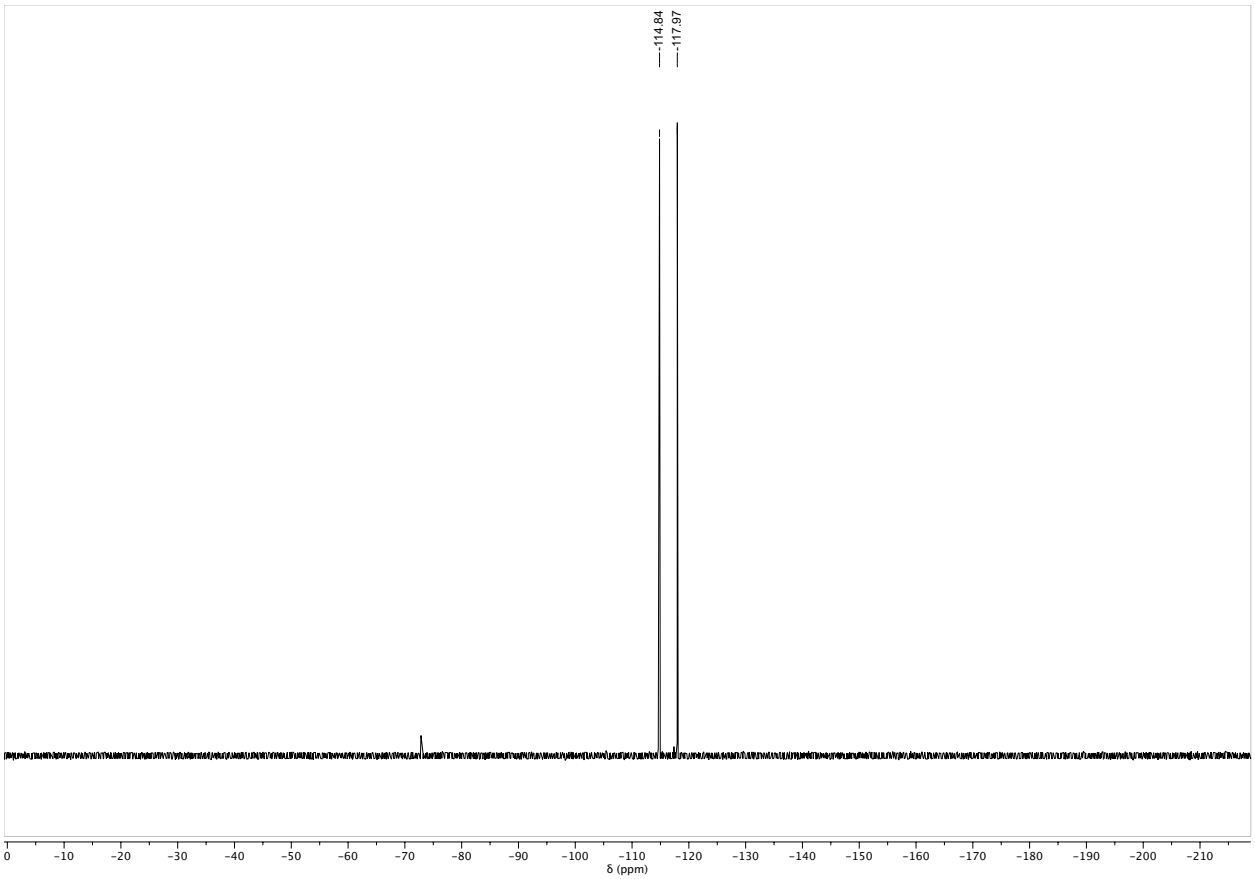




-72.84
-114.65
-117.36
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
δ (ppm)

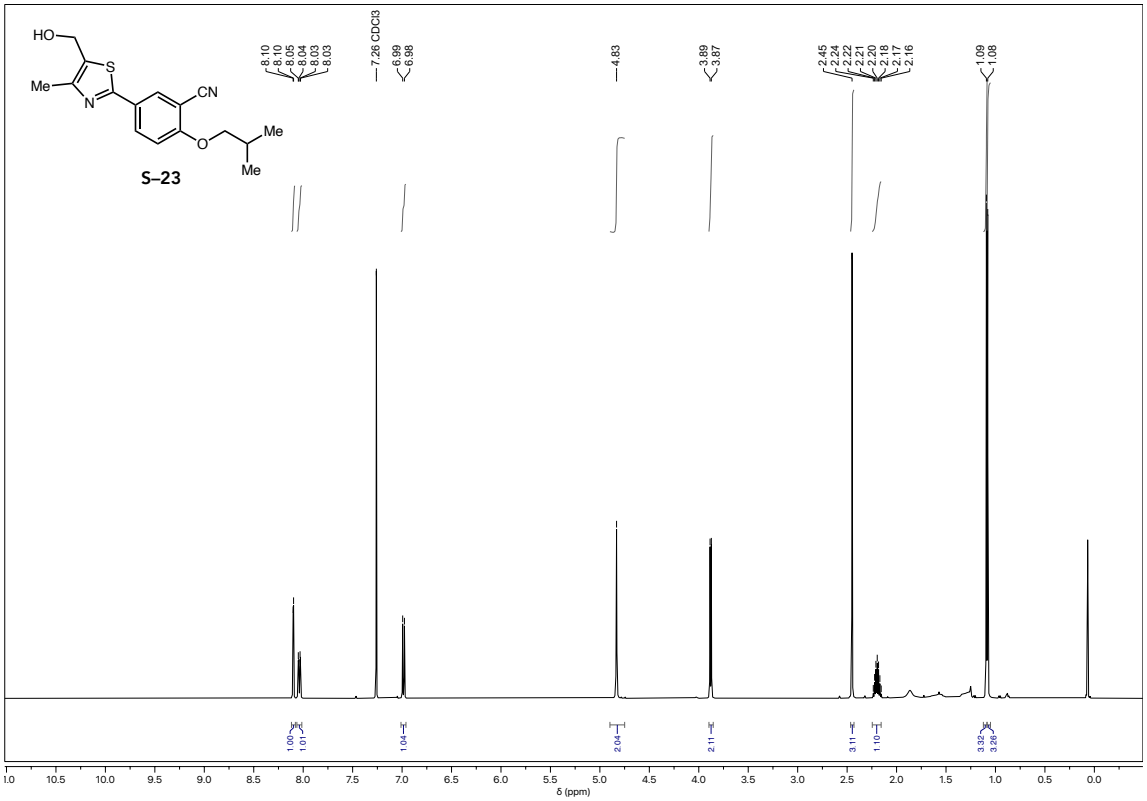
## Vinyl ezetimibe (S–21)

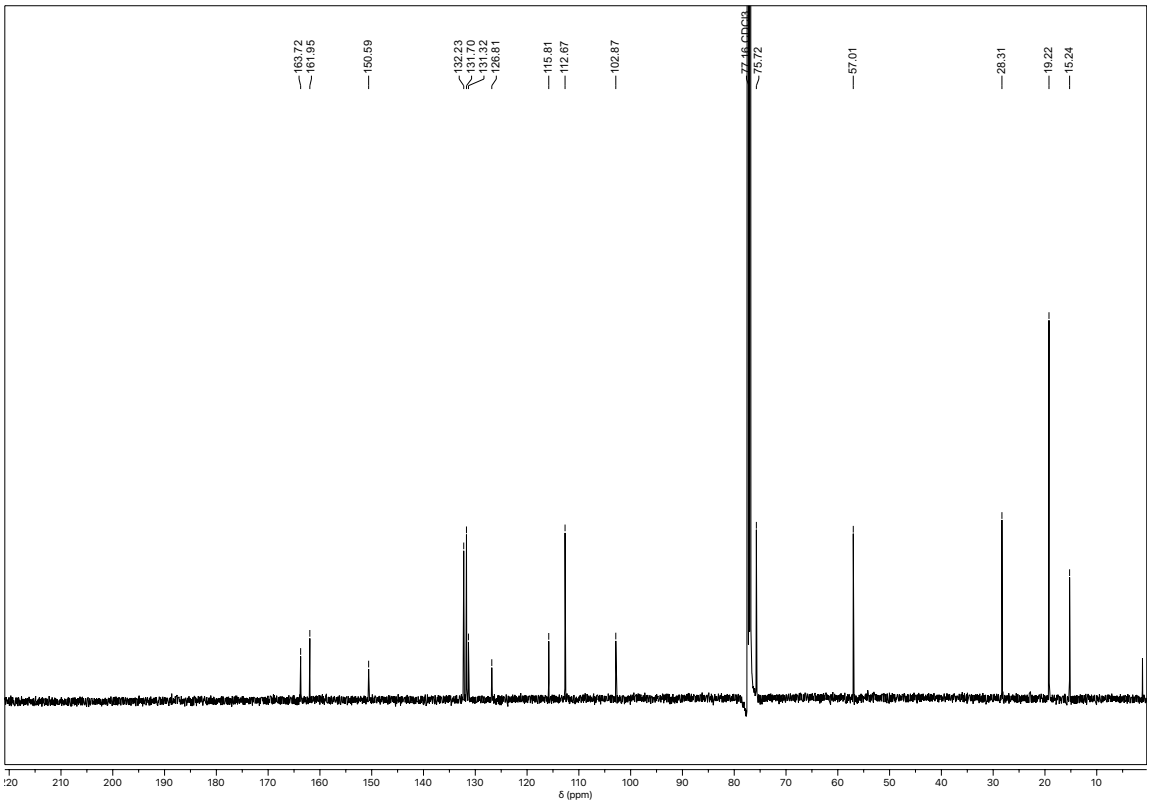


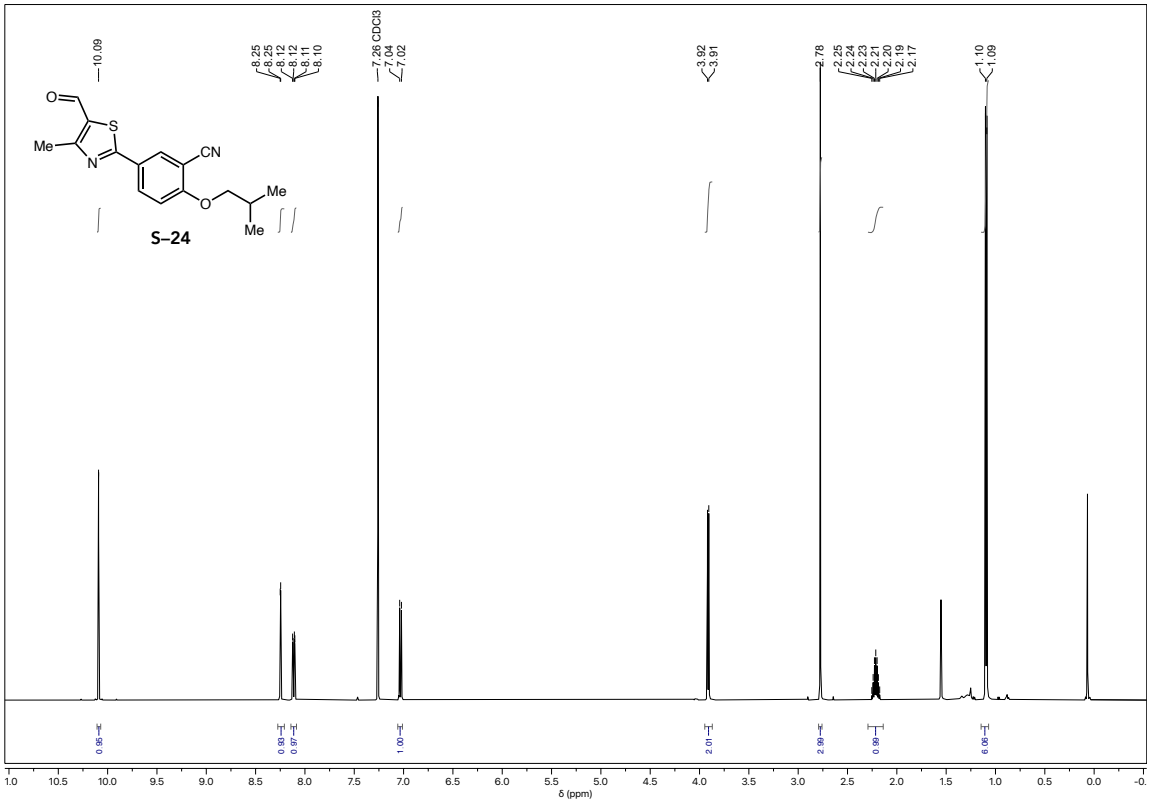

-114.84
-117.97
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
δ (ppm)

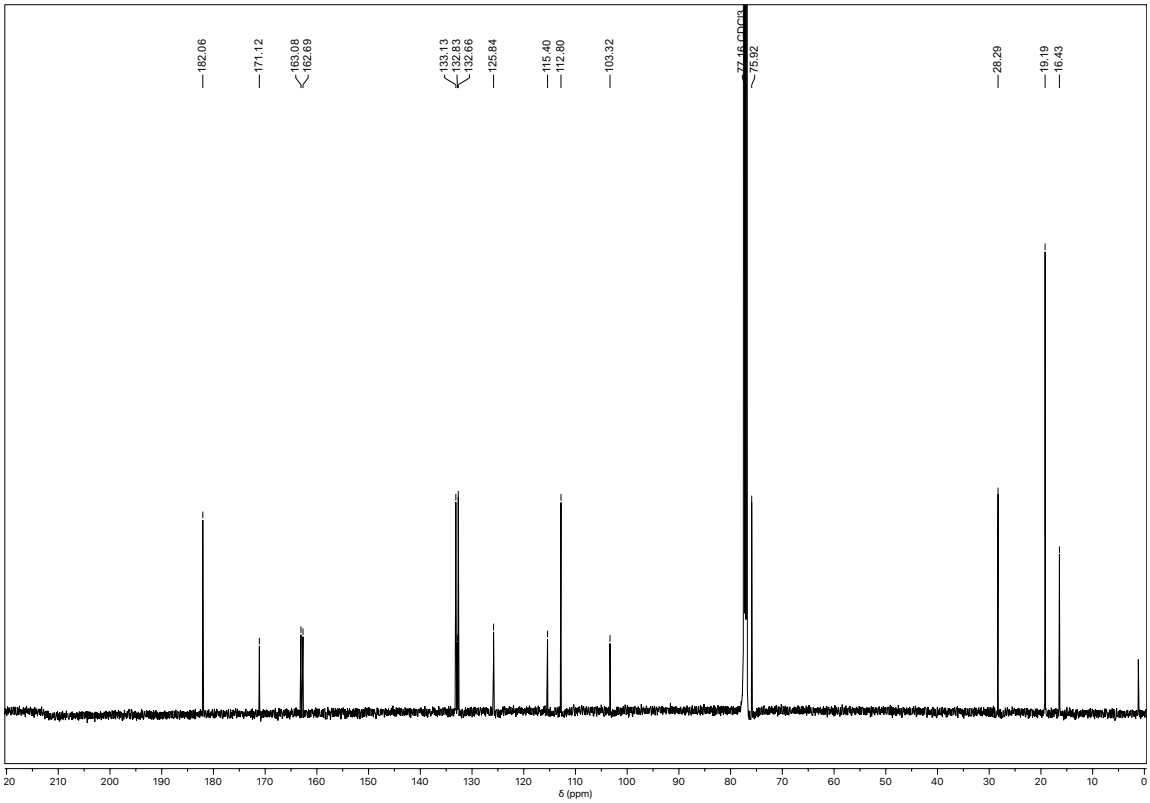
## Febuxostat alcohol (S–23)



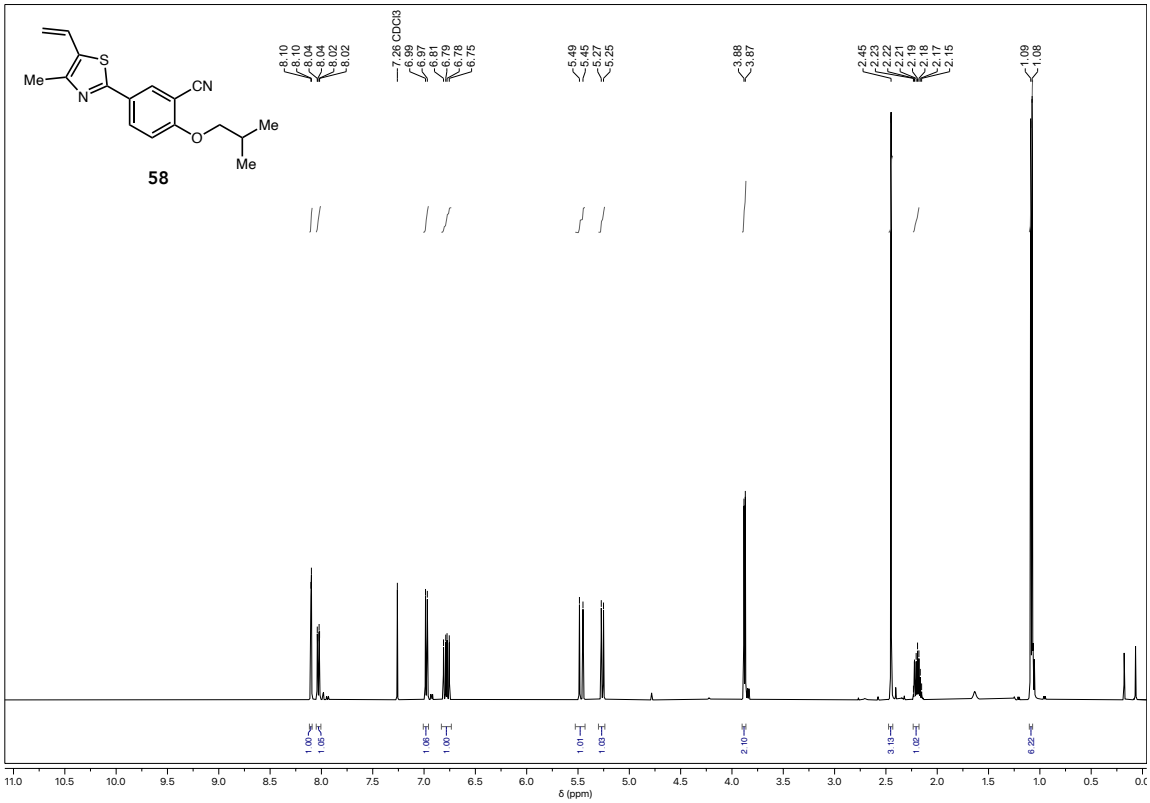



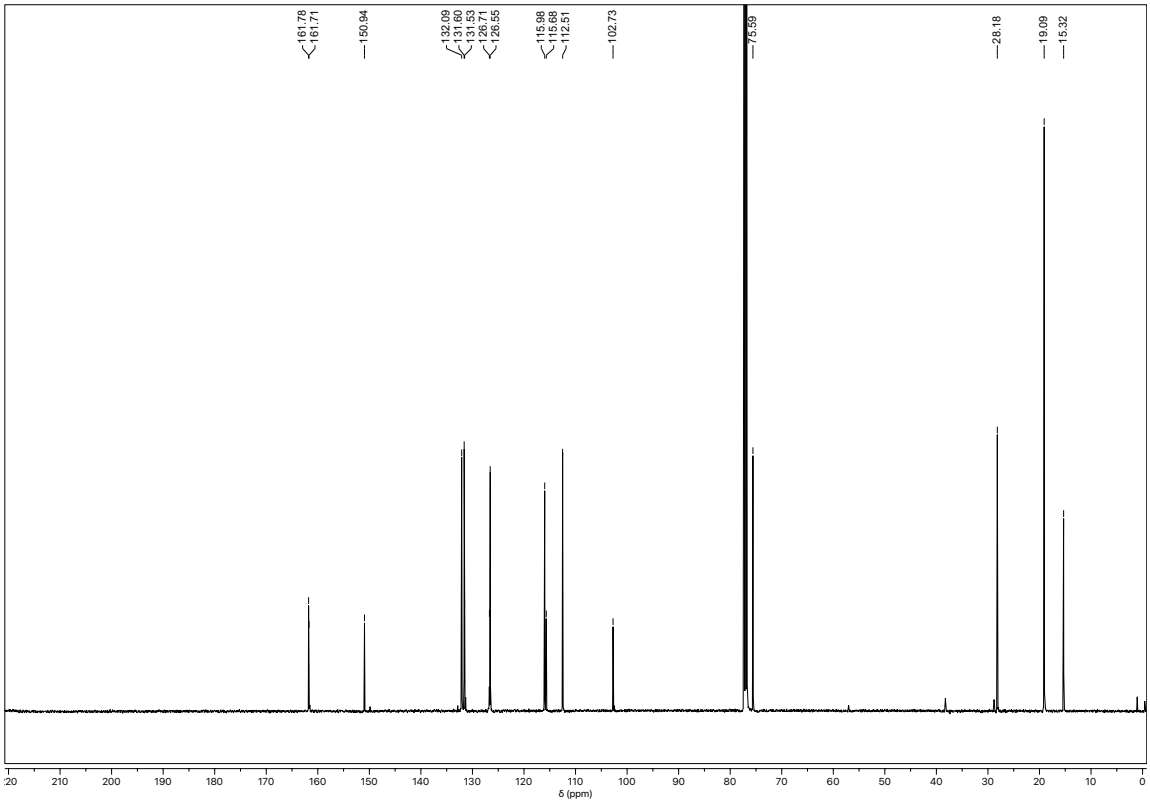
## Febuxostat aldehyde (S–24)



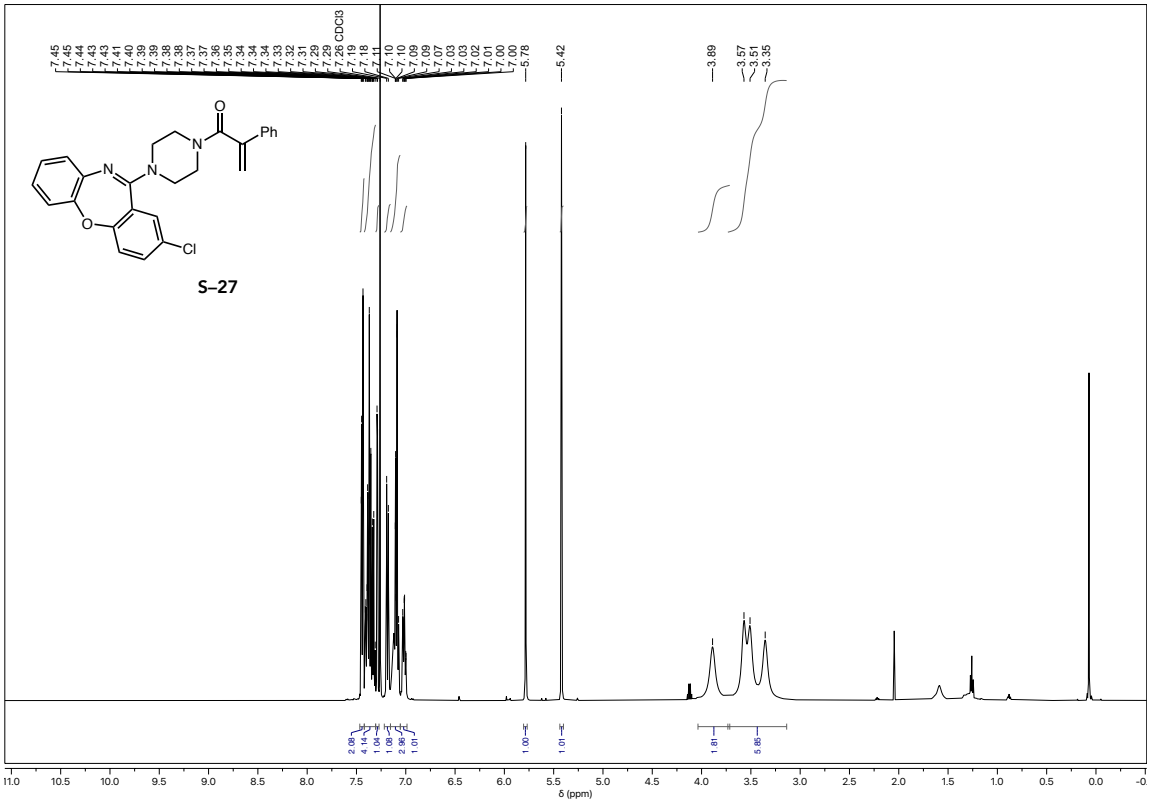



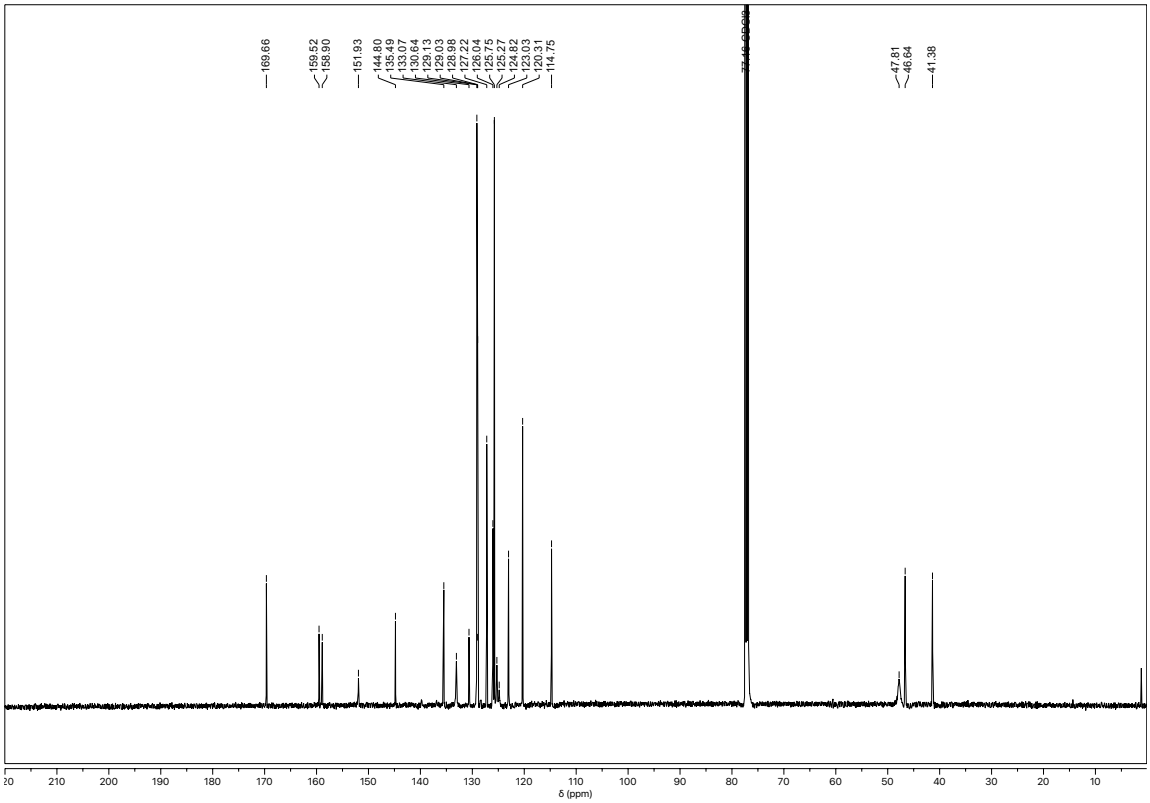
## Vinyl febuxostat (58)



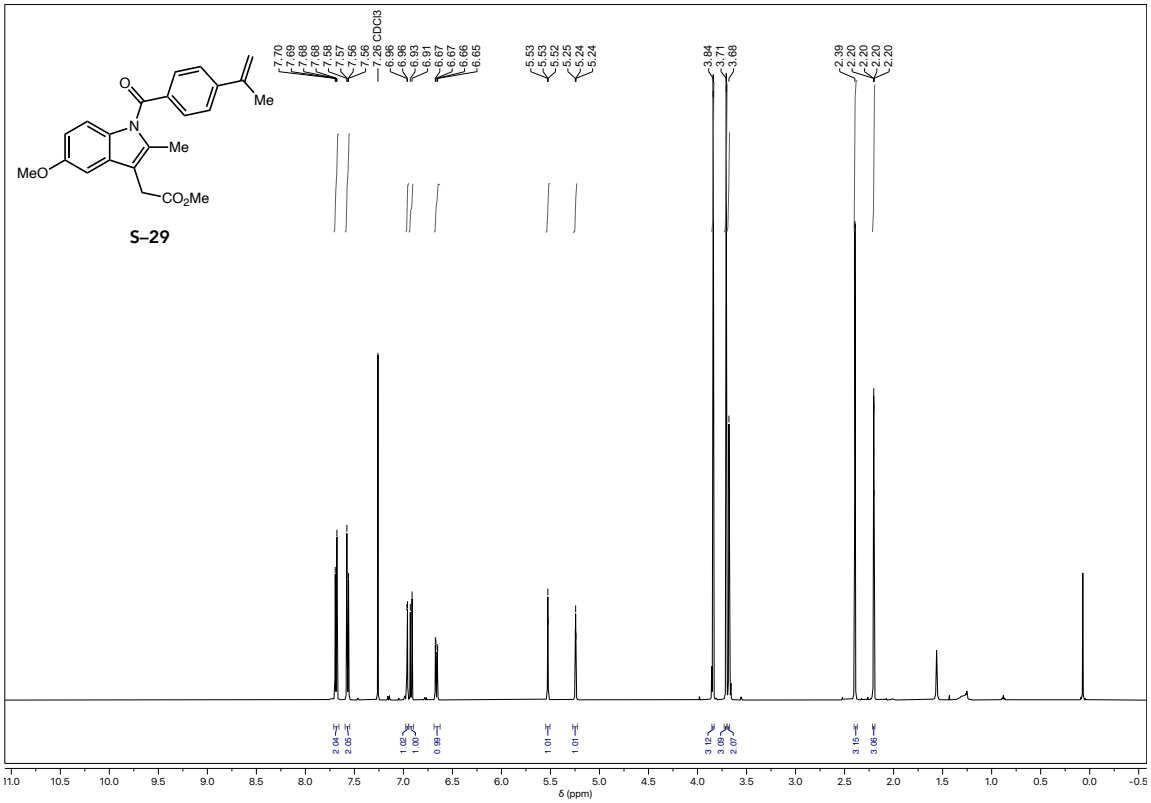



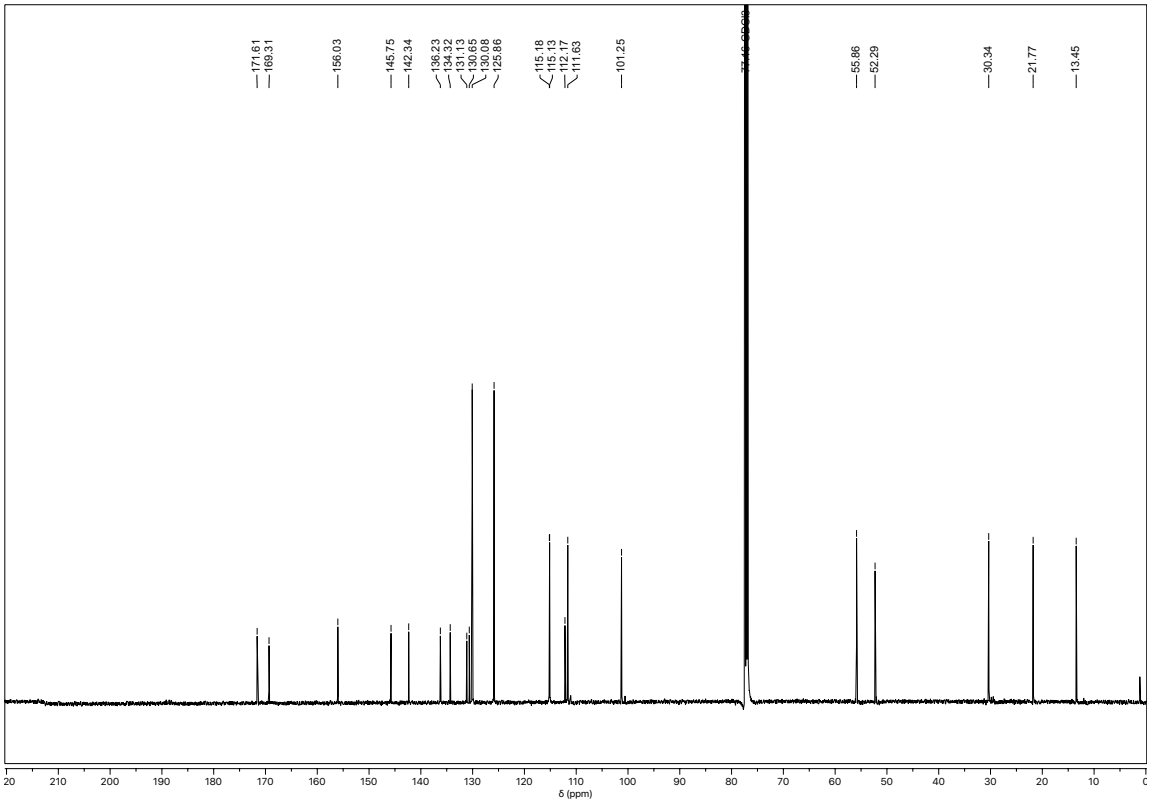
## Amoxapine α-phenyl acrylamide (S–27)



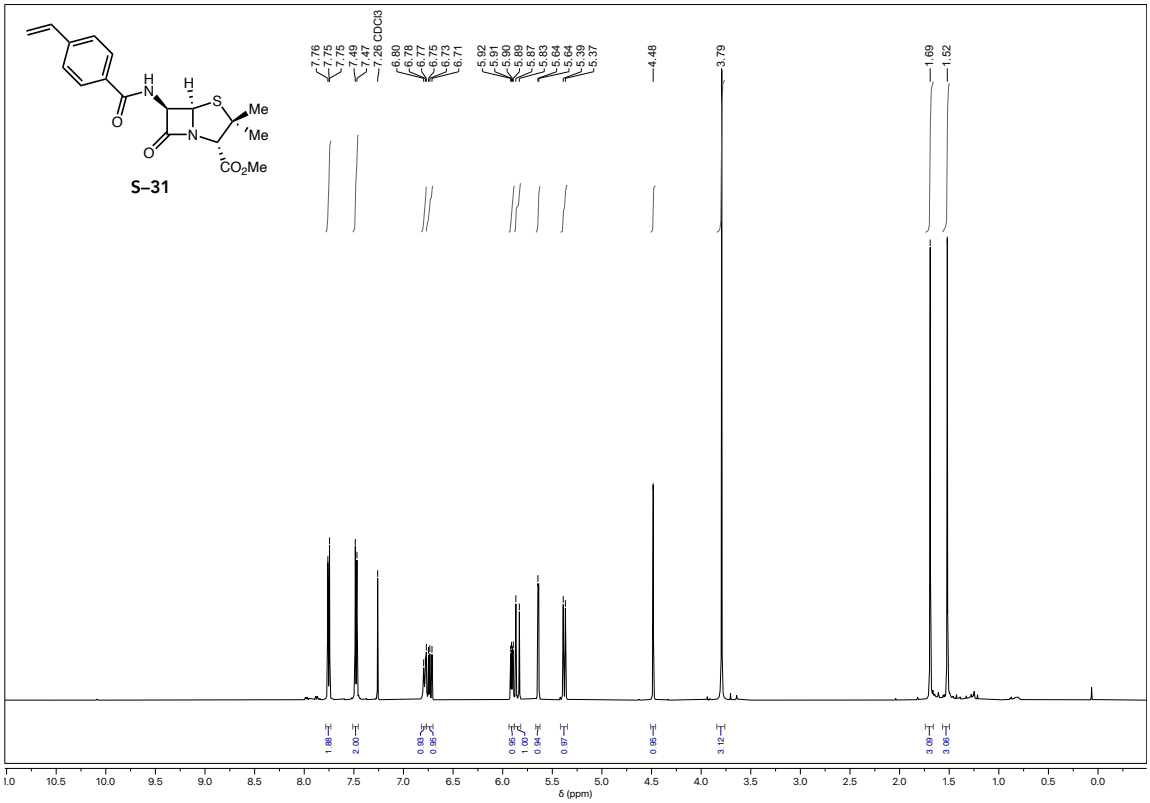



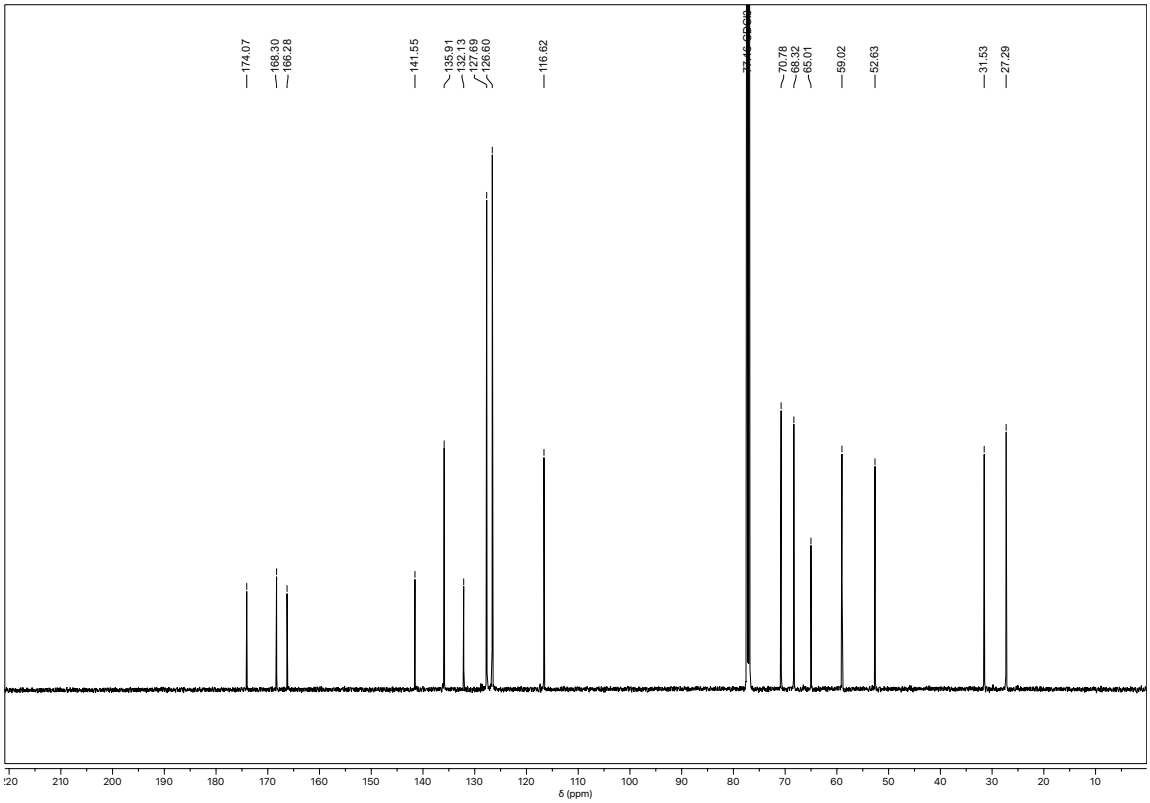
## Isopropenyl indomethacin methyl ester (S–29)



*N*-(4-Vinylbenzamido)Penicillin methyl ester (S–31)

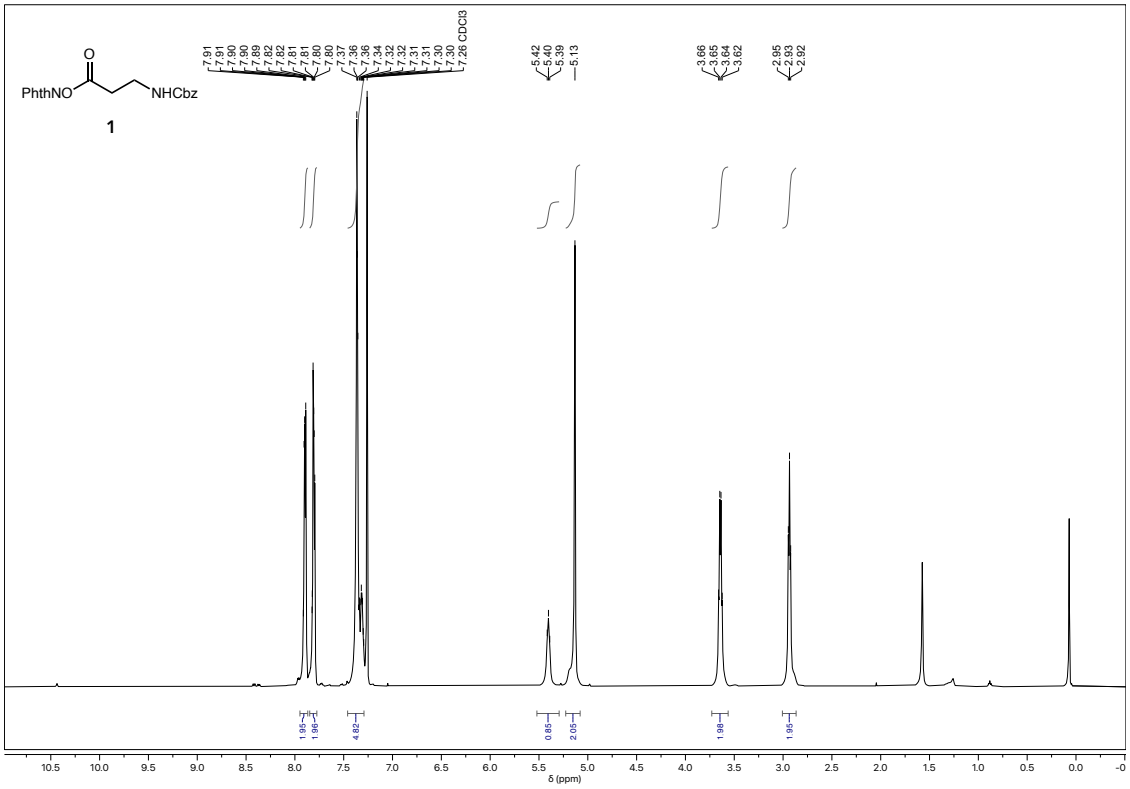


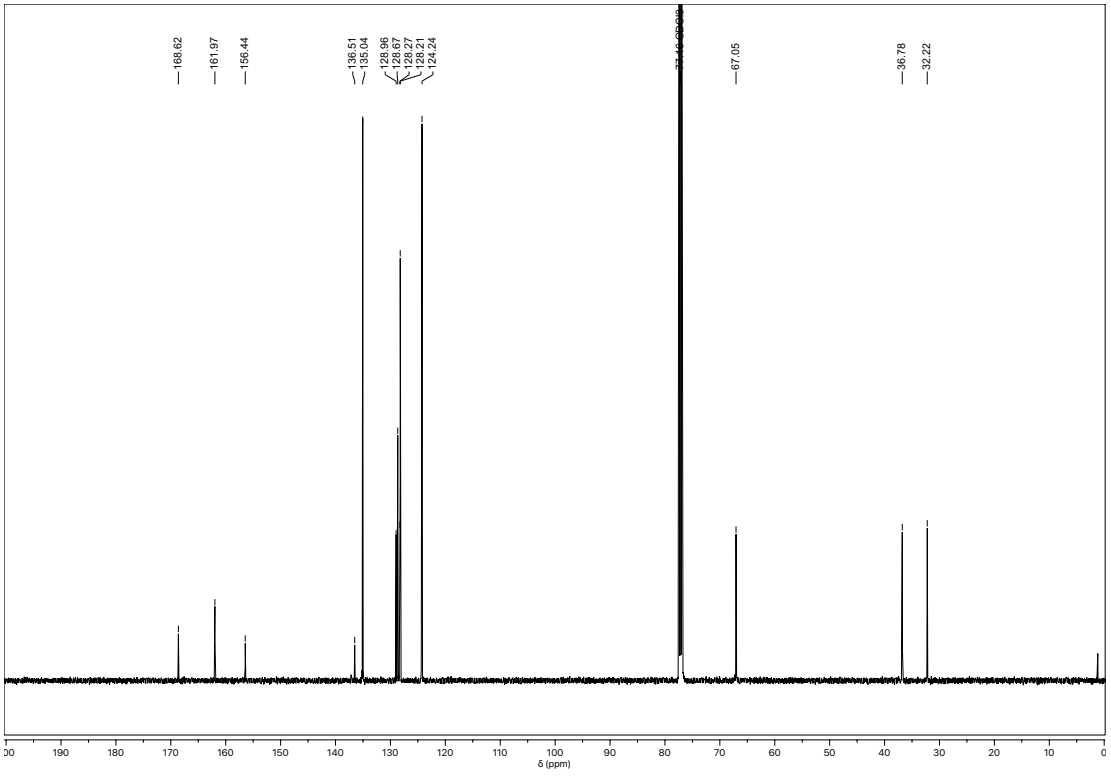



## 10.4. NHPI reagents

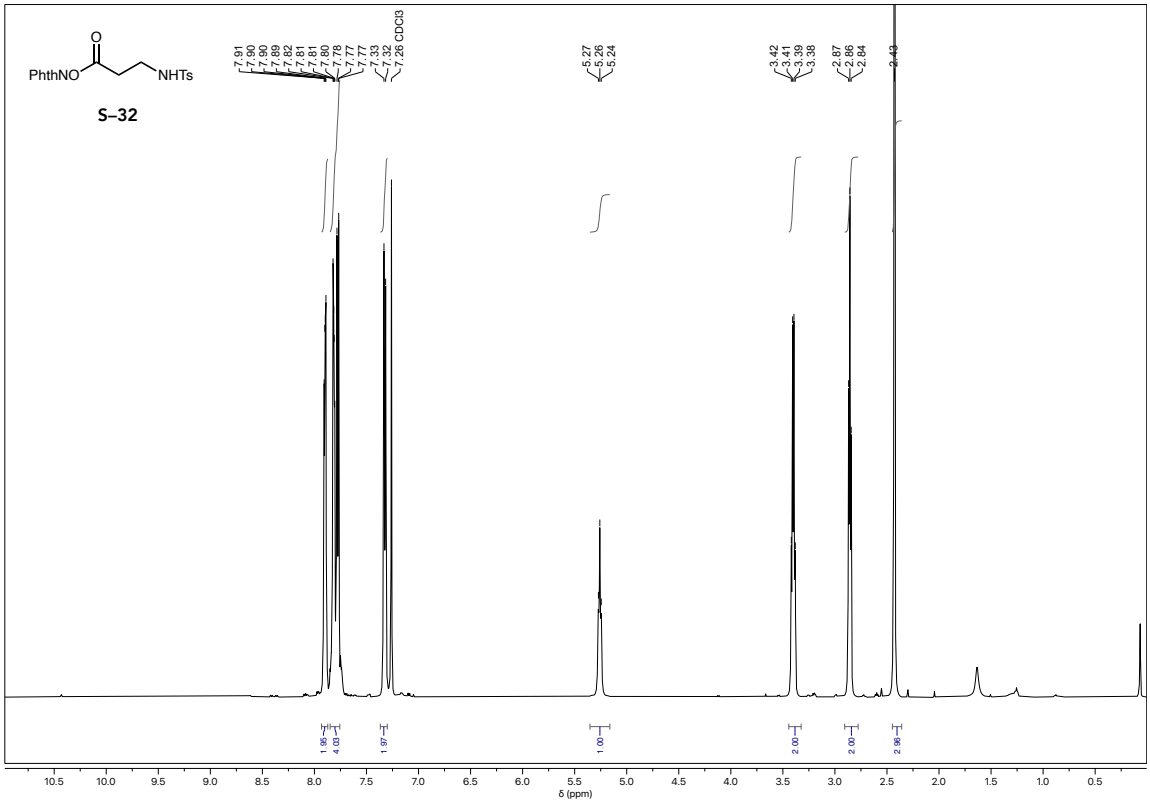
### 10.4.1. Pyrrolidine NHPI reagents

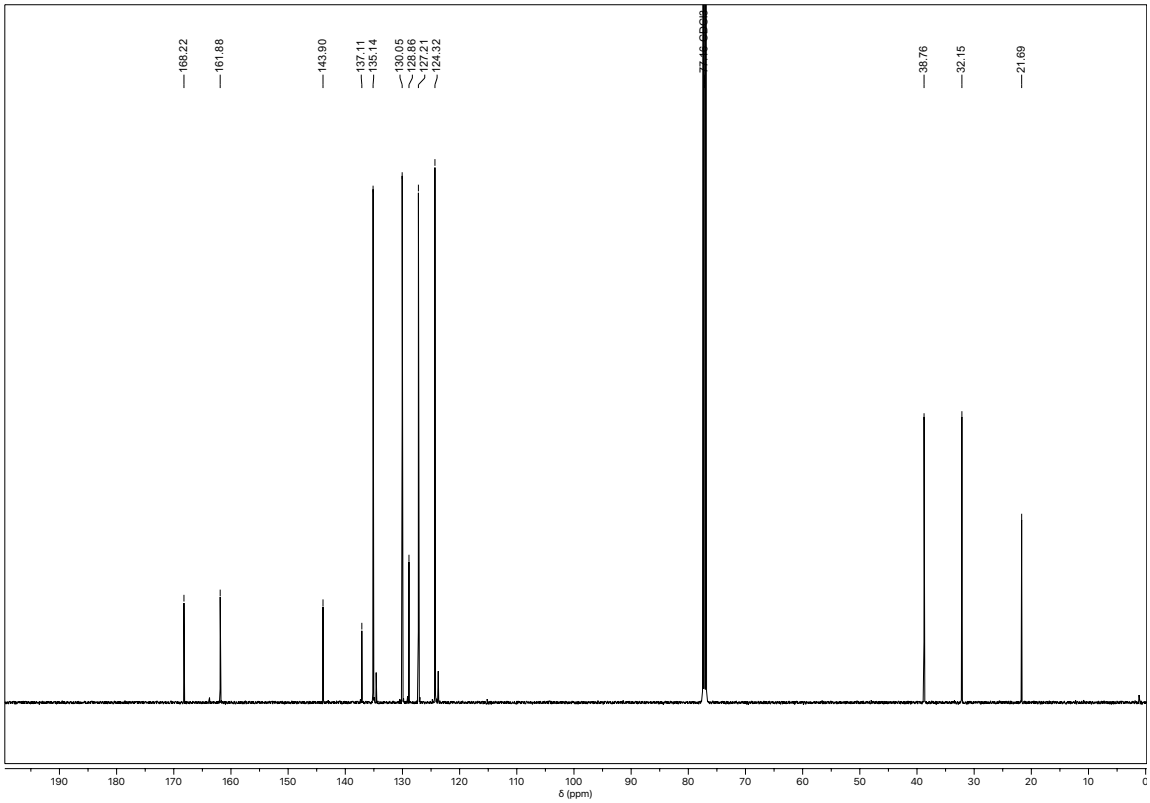
Parent *N*-Cbz pyrrolidine [3+2] reagent (1)



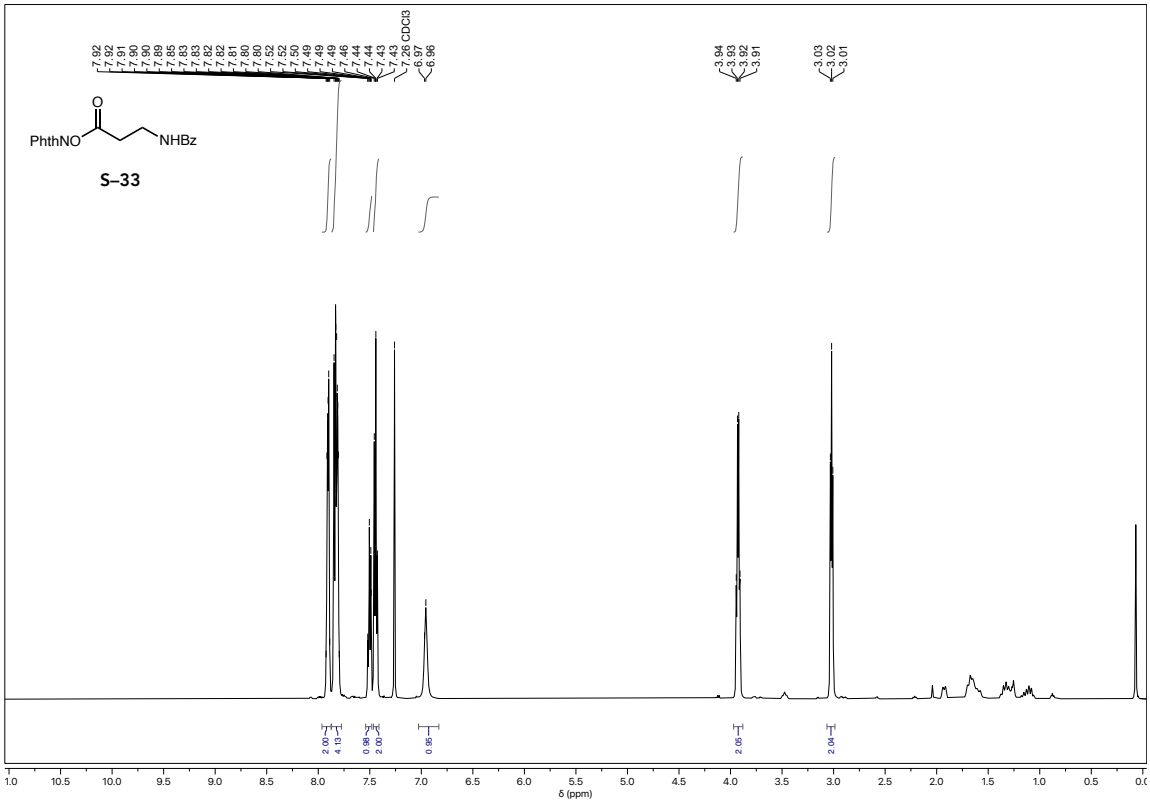



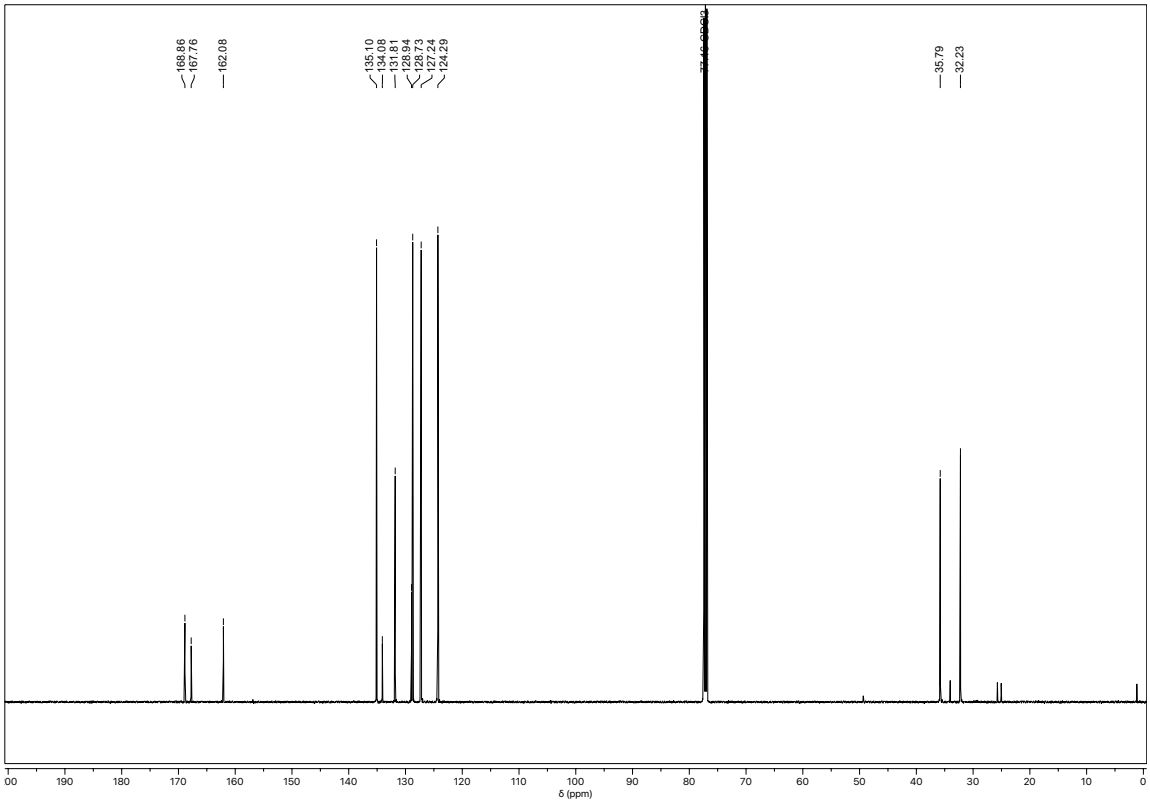
Parent *N*-Ts pyrrolidine [3+2] reagent (*S*–32)



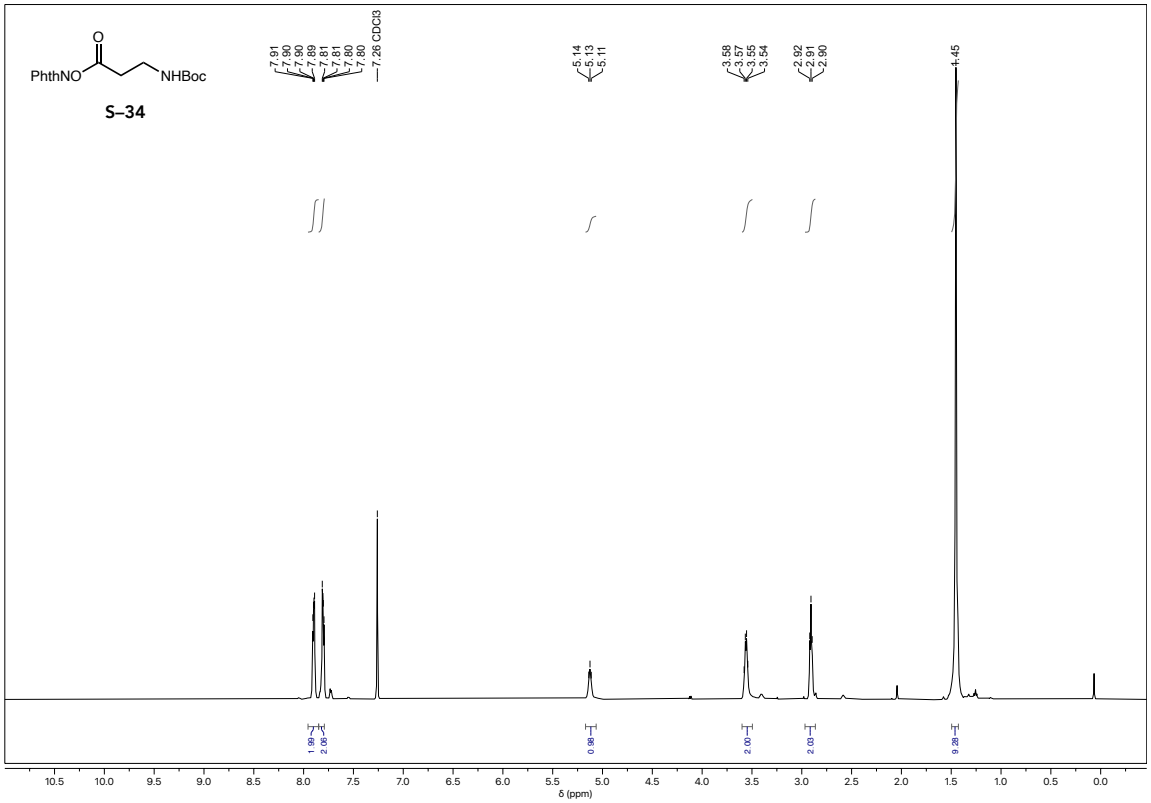



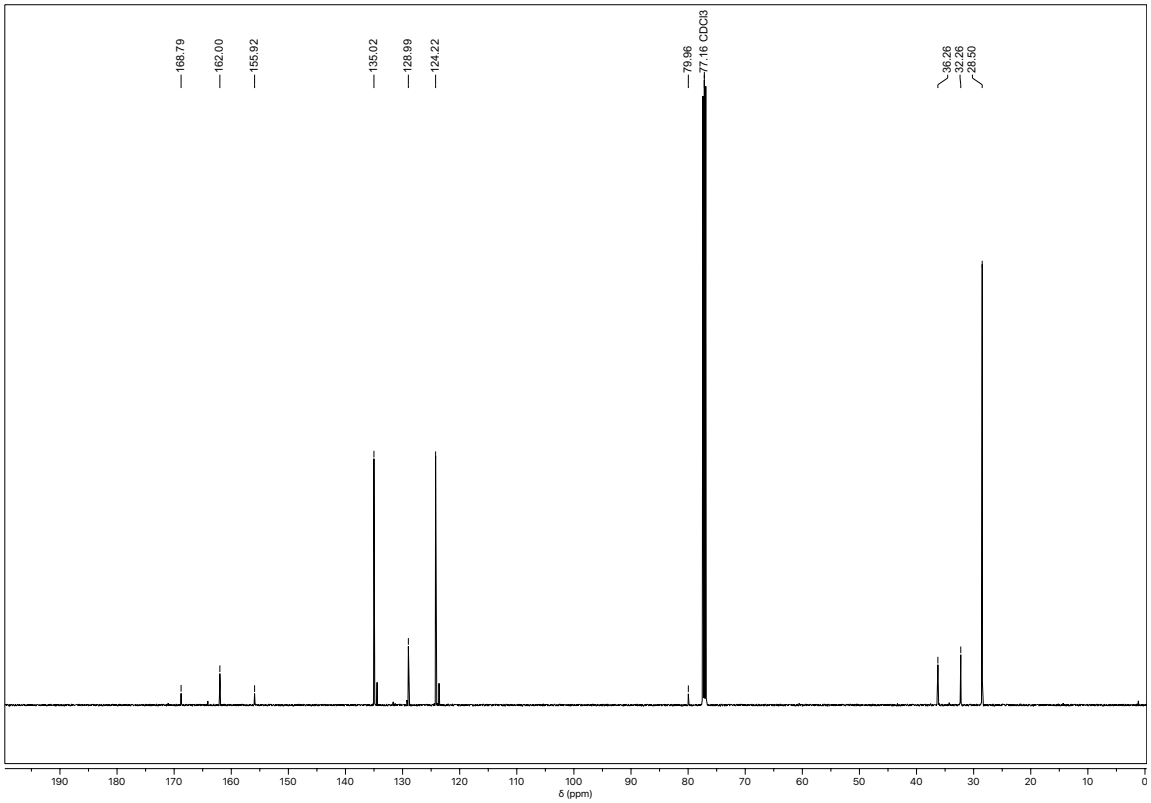
Parent *N*-Bz pyrrolidine [3+2] reagent (S–33)



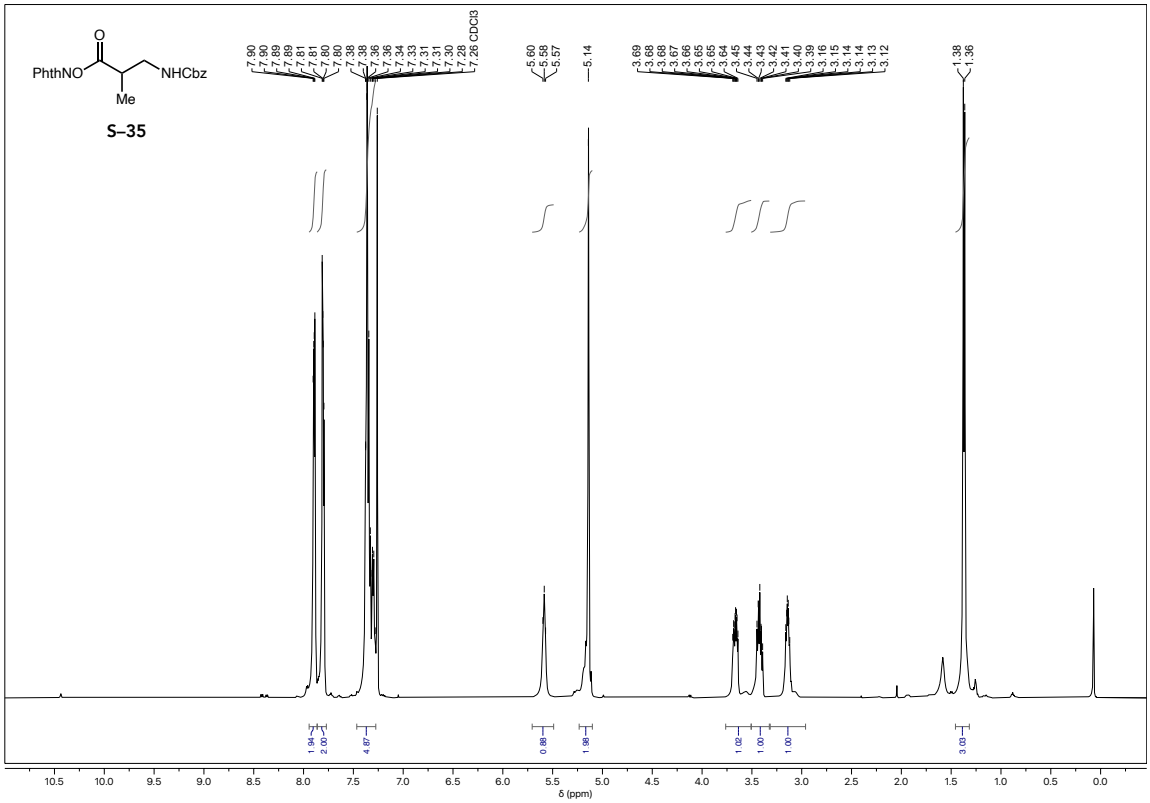



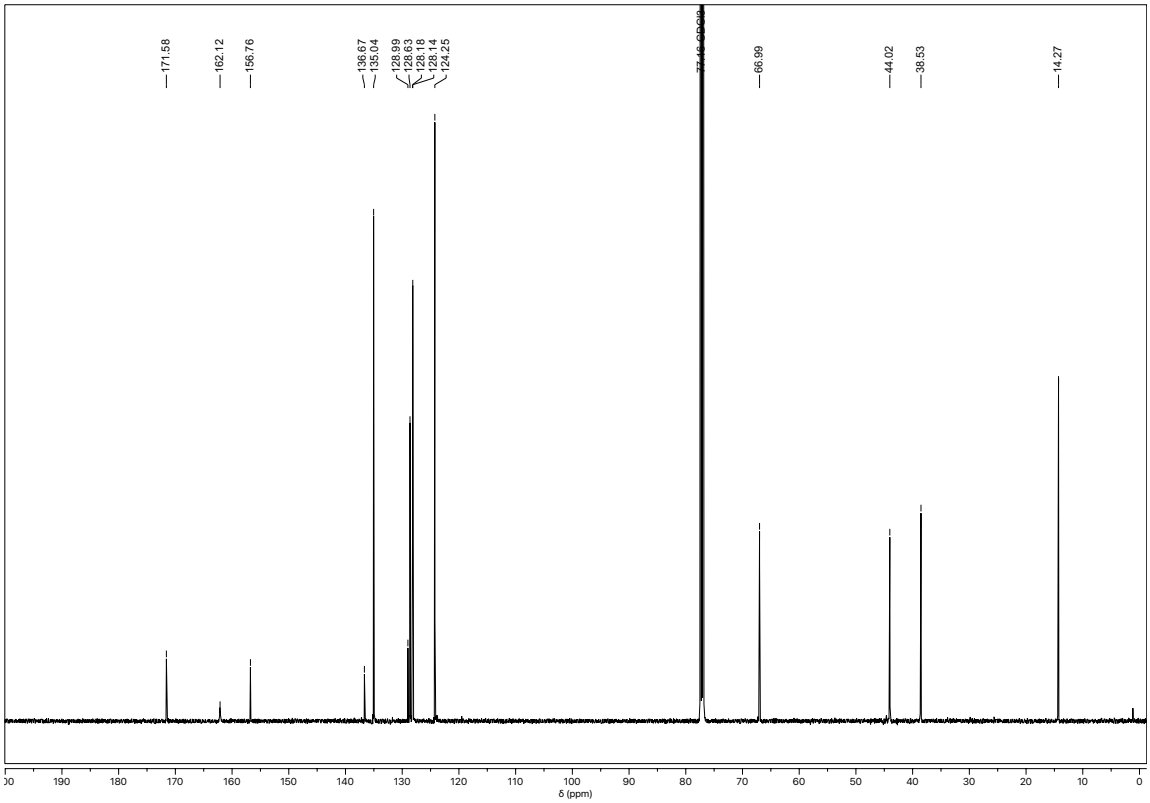
Parent *N*-Boc pyrrolidine [3+2] reagent (*S*–34)



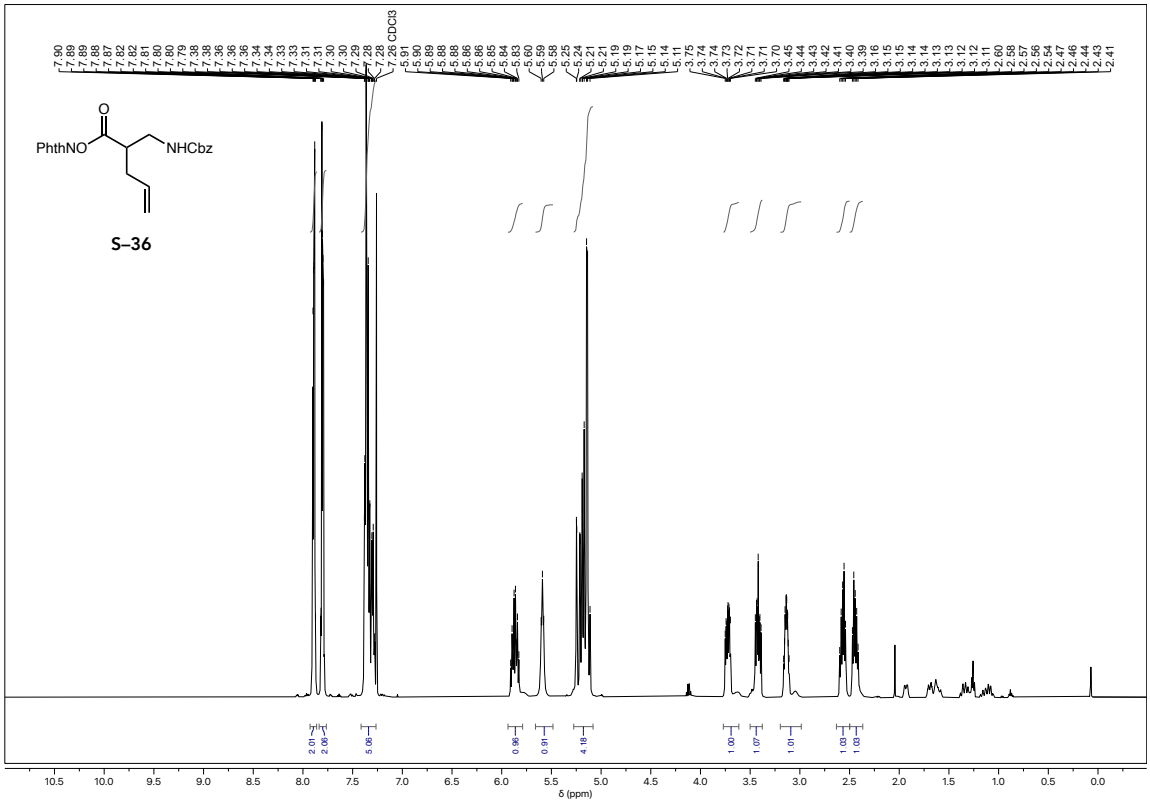



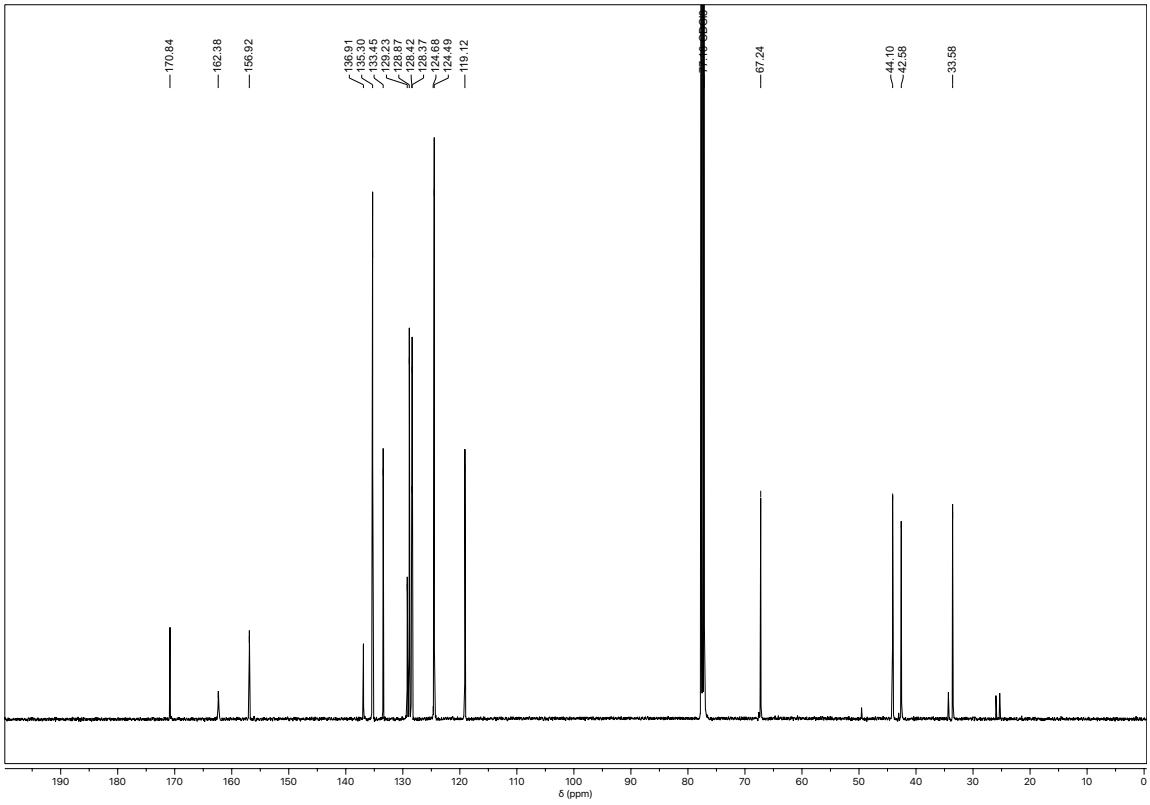
## α-Methyl pyrrolidine [3+2] reagent (S–35)



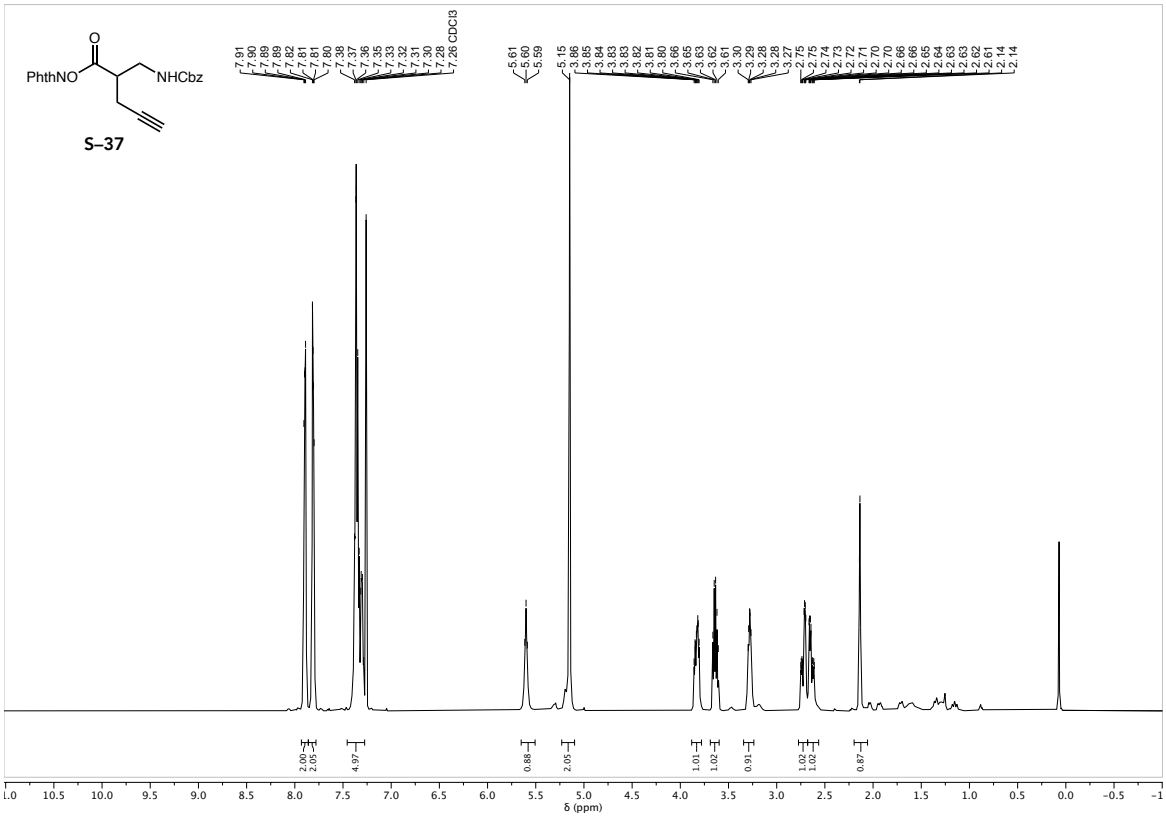



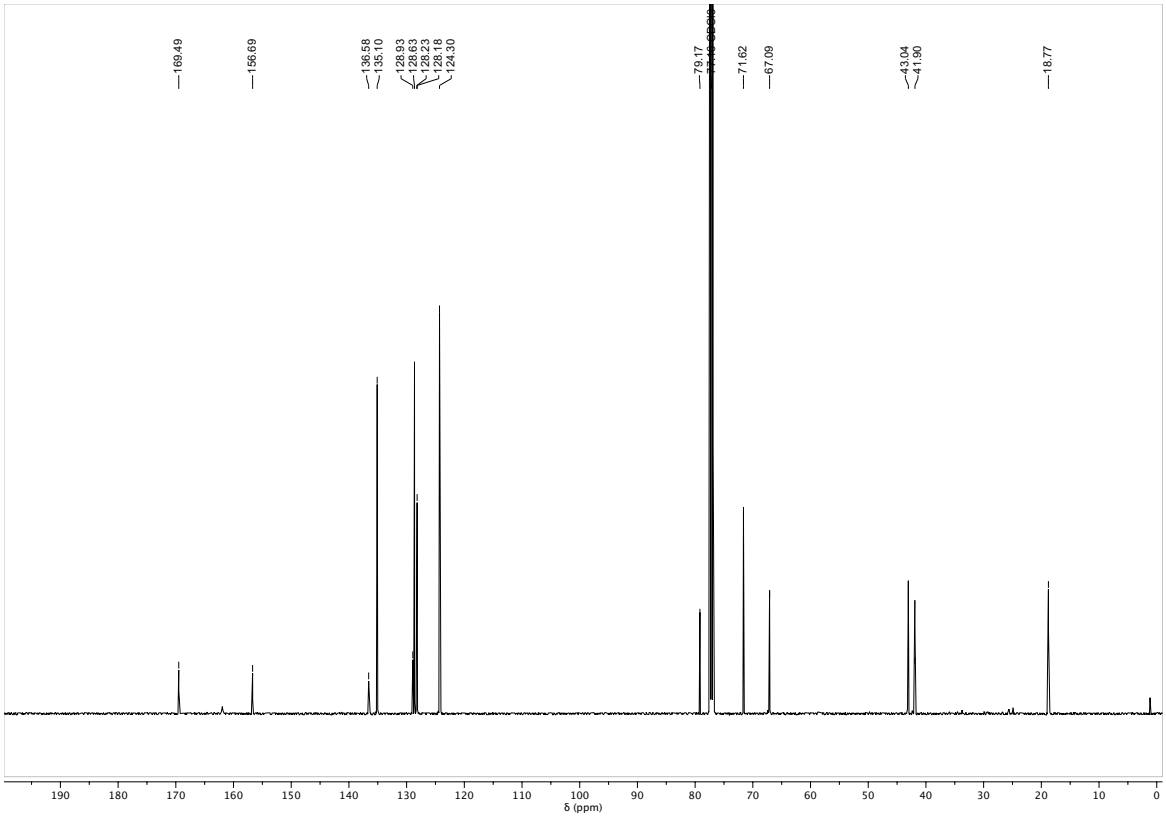
α-Allyl *N*-Cbz [3+2] pyrrolidine reagent (S–36)



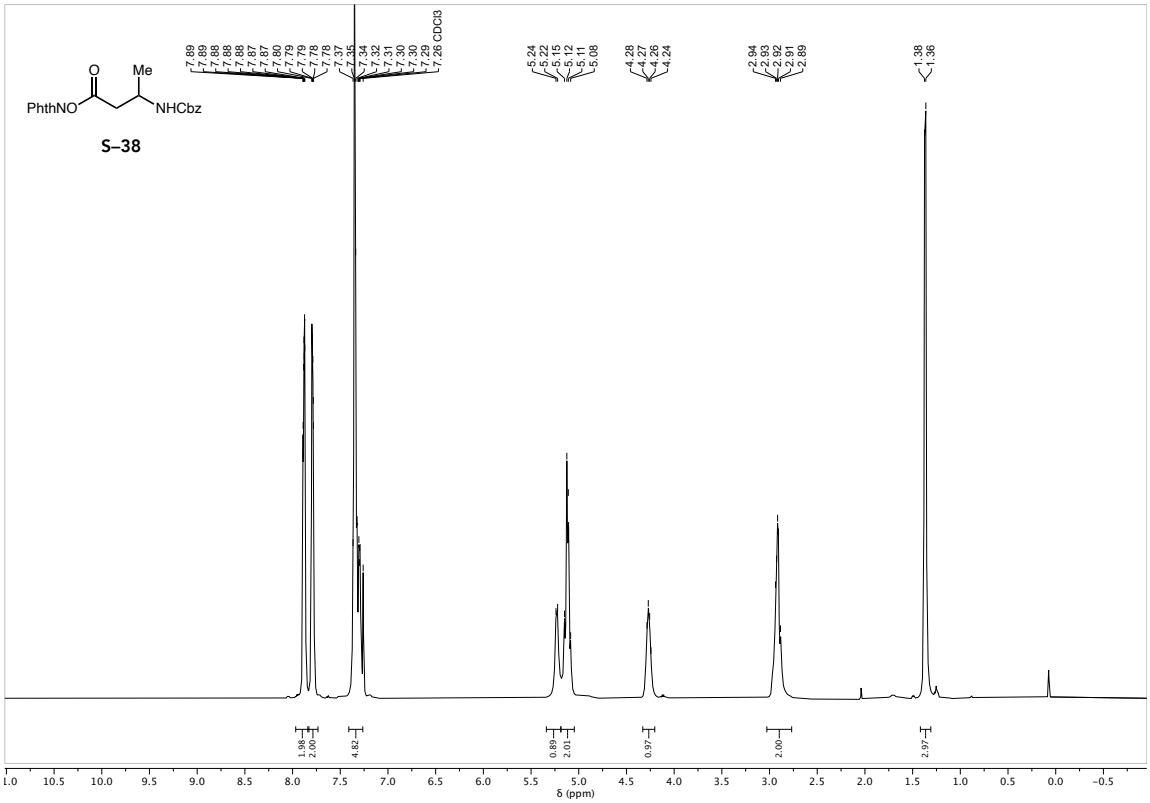



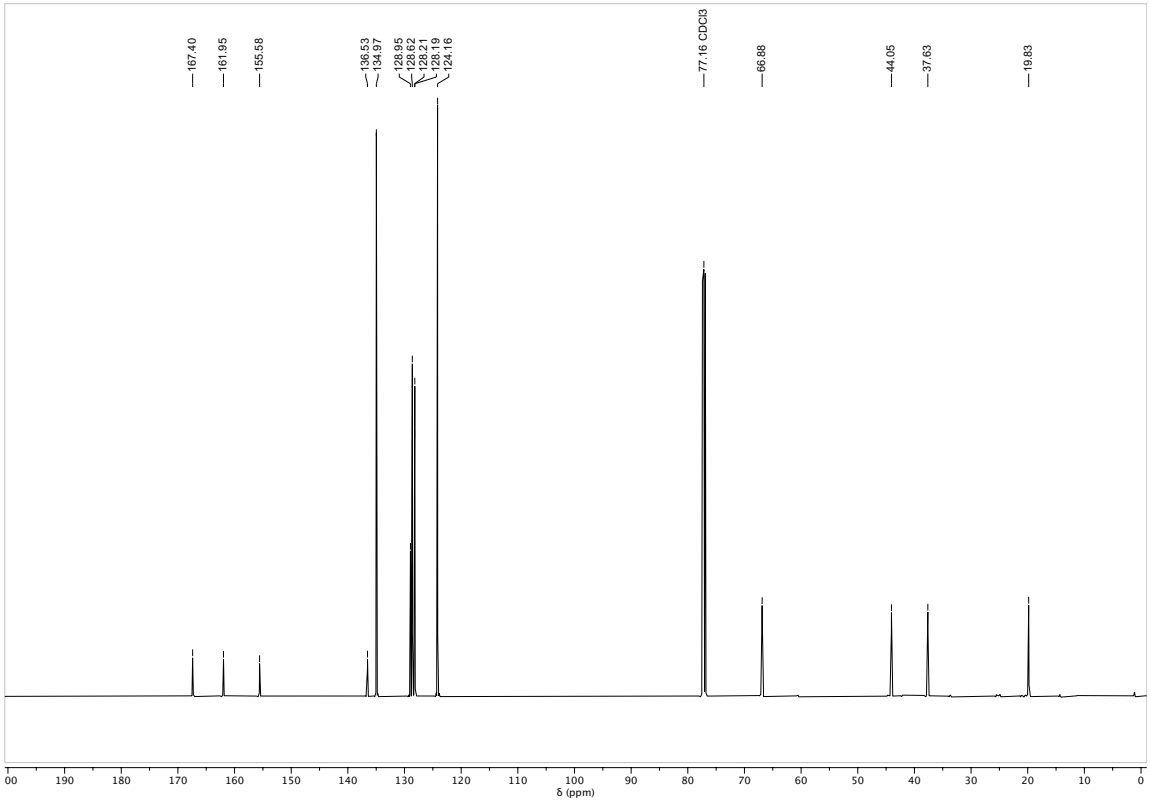
## α-Propargyl *N*-Cbz pyrrolidine [3+2] reagent (S–37)



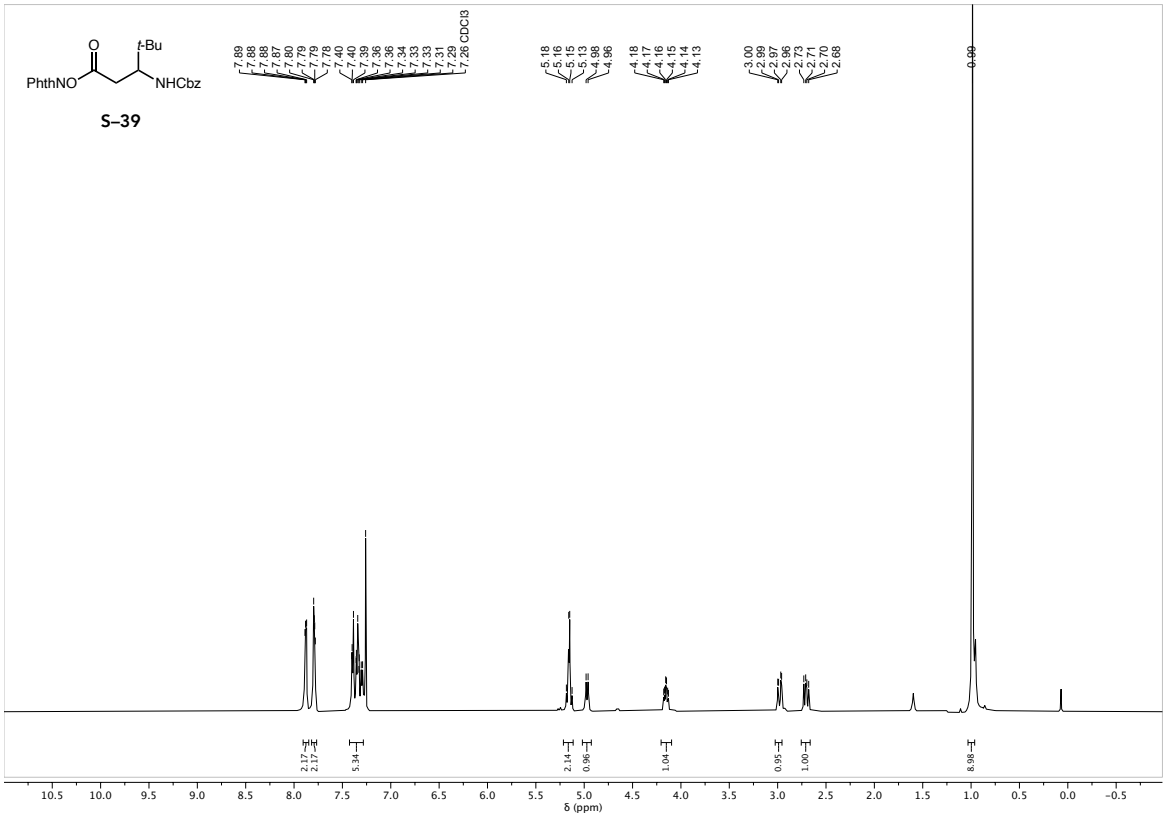



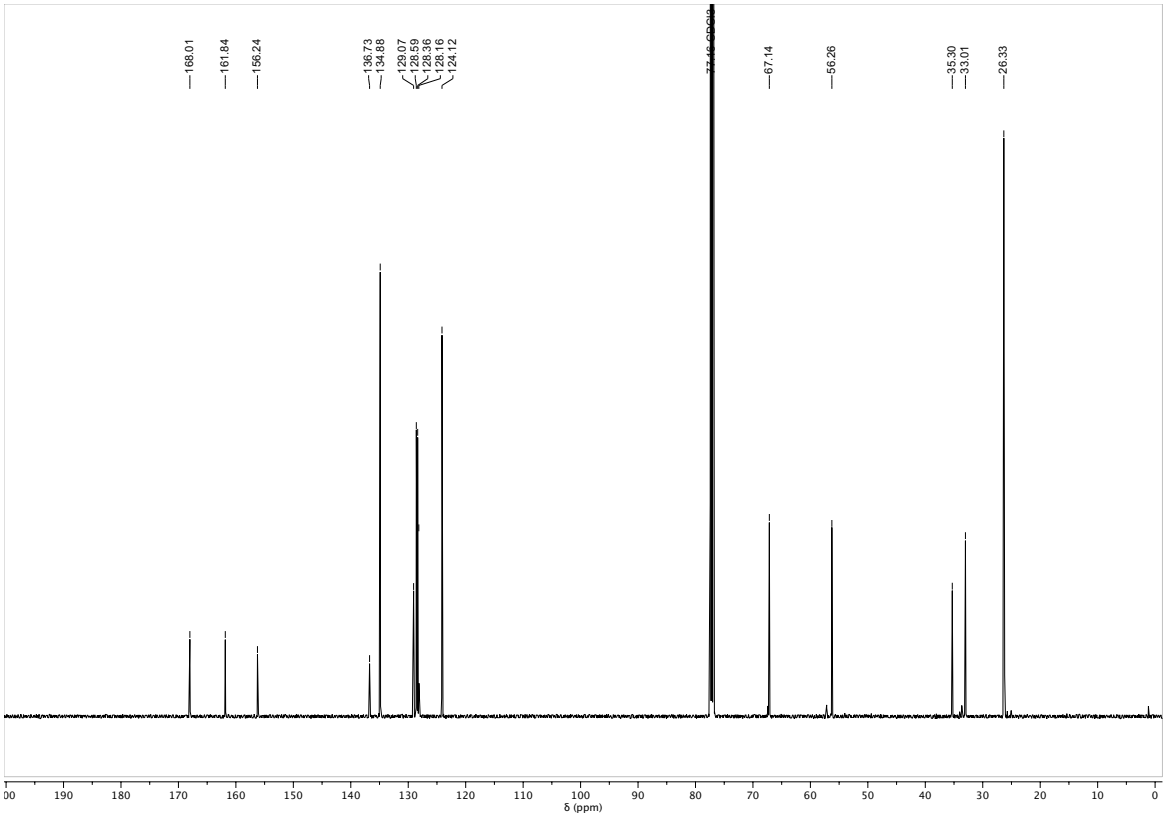
## β-Me *N*-Cbz pyrrolidine [3+2] reagent (*S*–38)



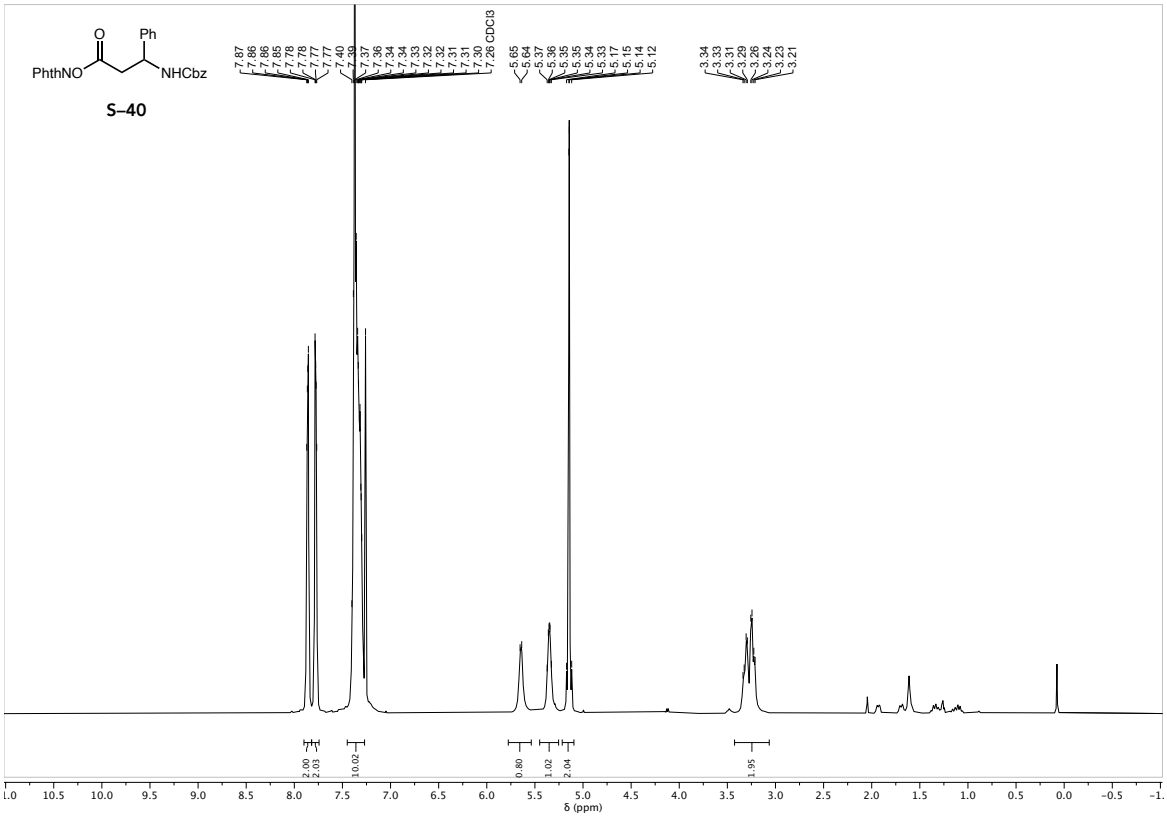



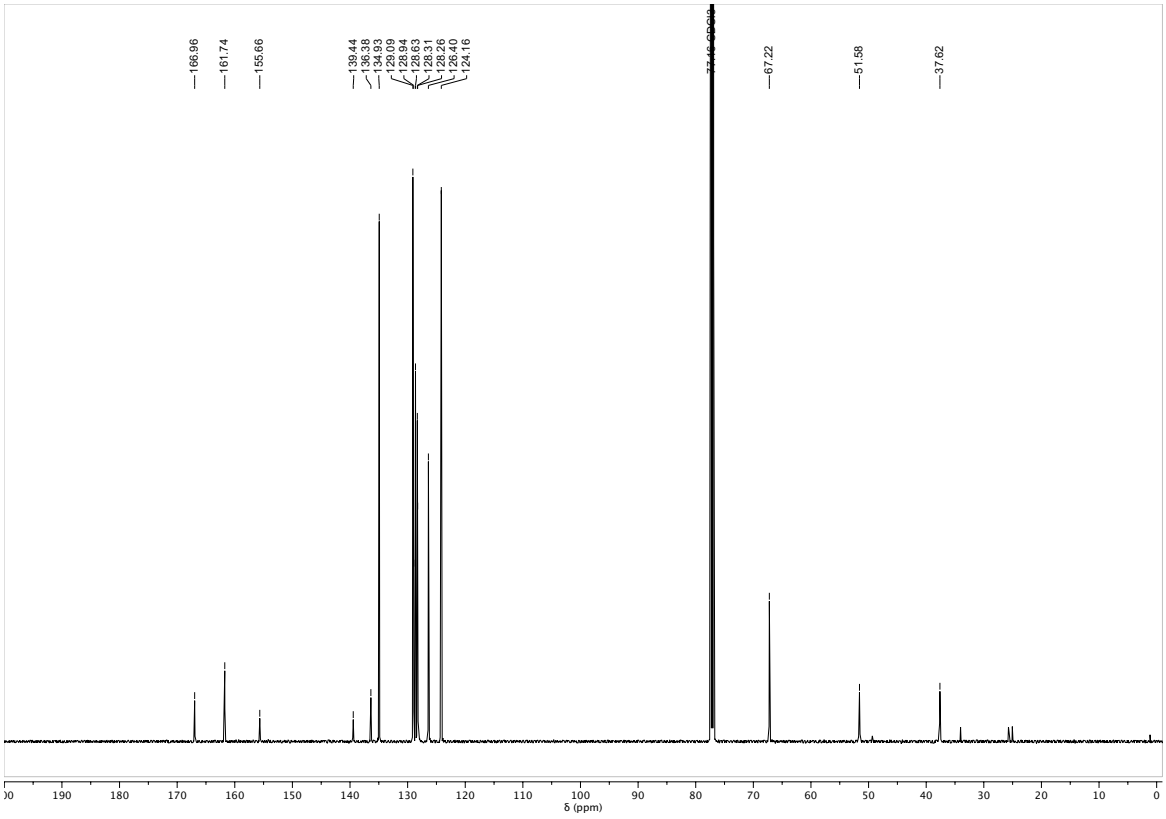
## β-$^t$Bu *N*-Cbz pyrrolidine [3+2] reagent (S–39)



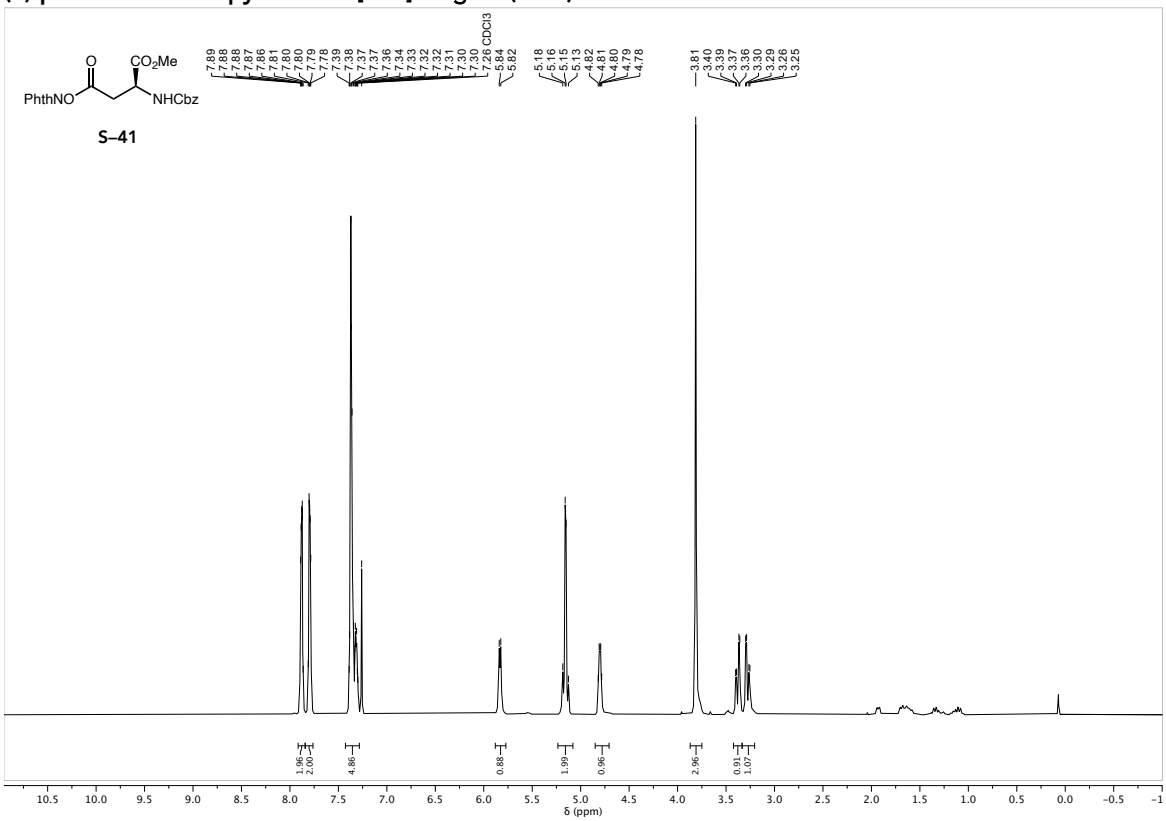



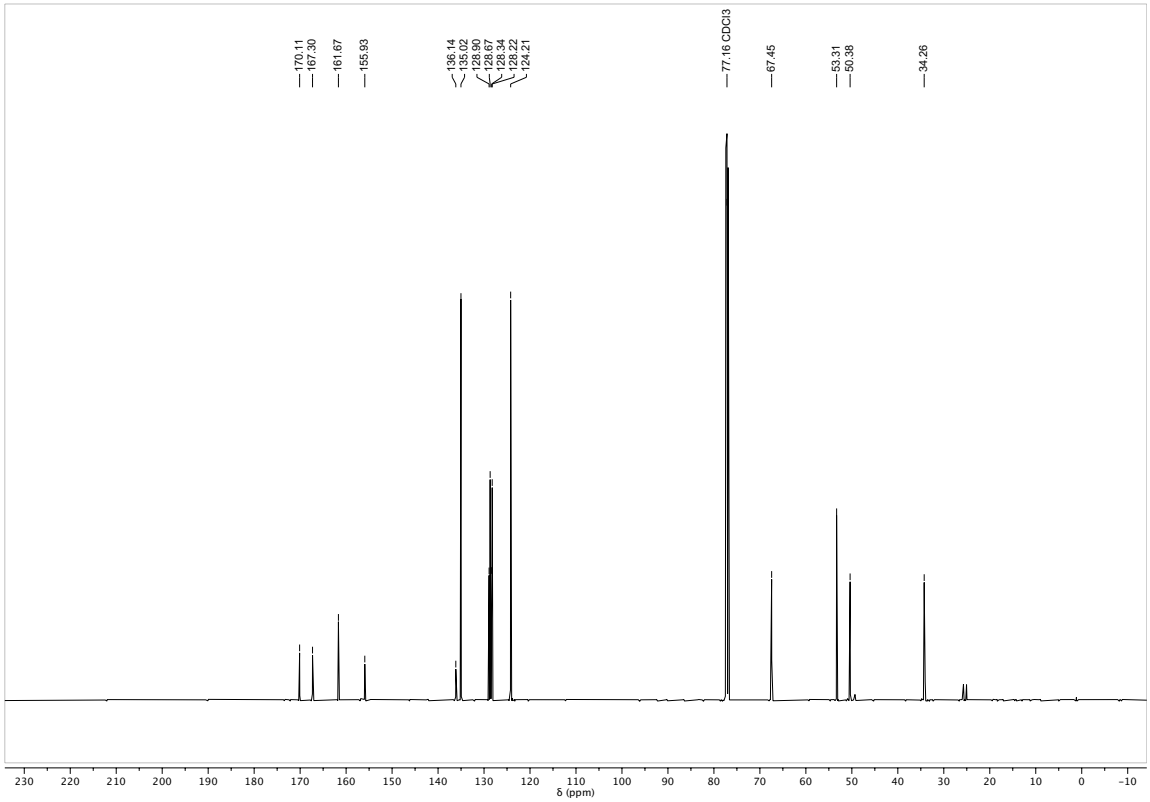
## β-Ph *N*-Cbz pyrrolidine [3+2] reagent (S–40)



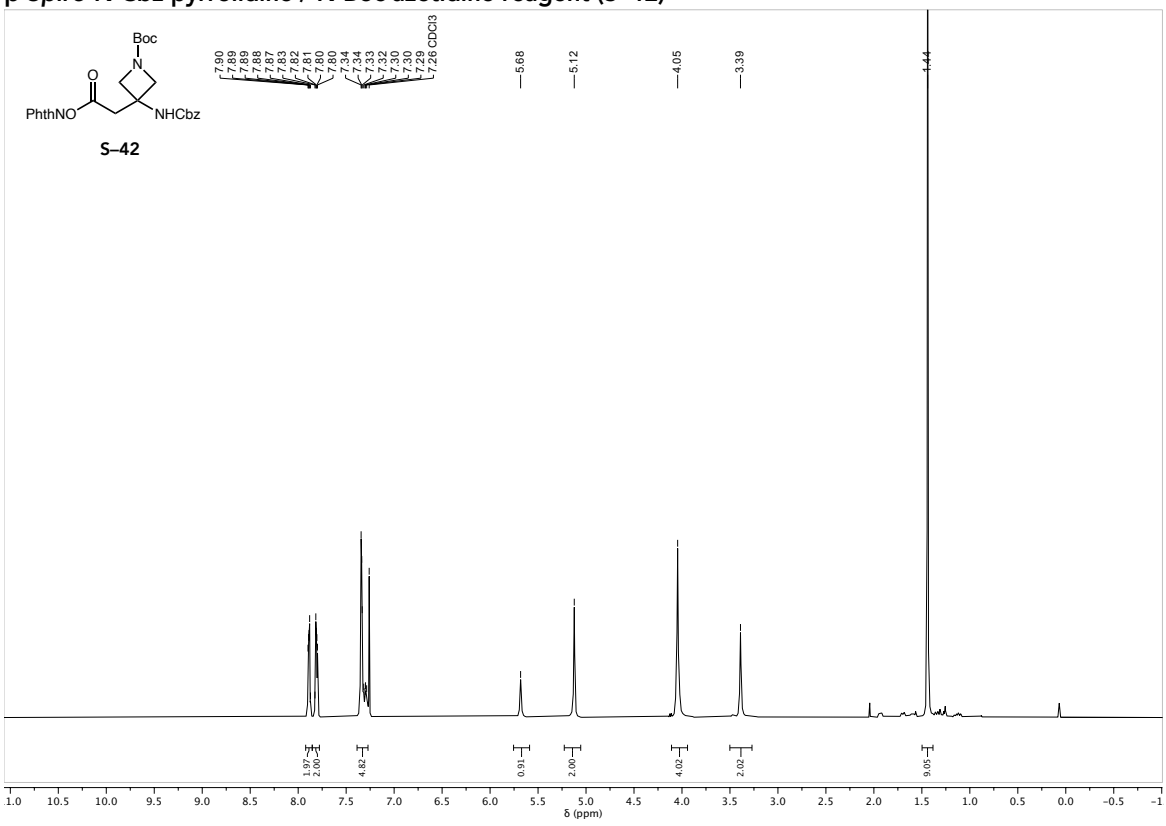



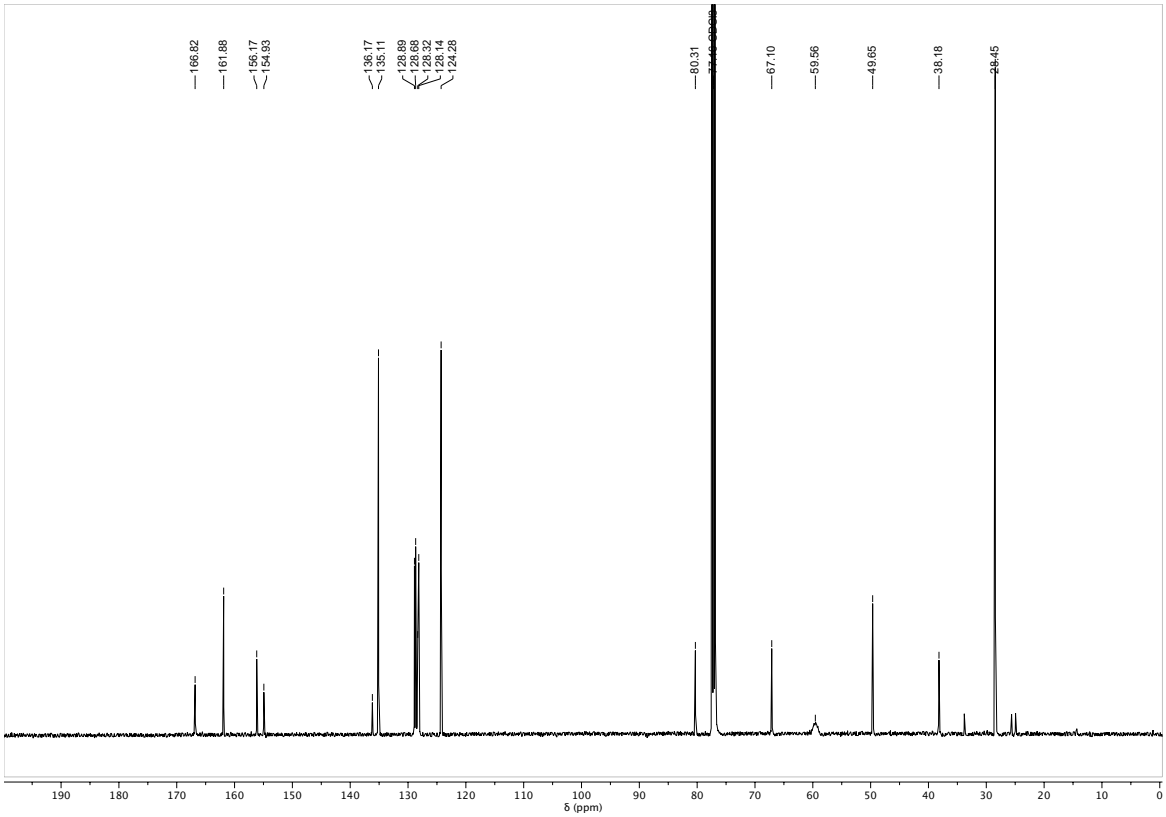
## (S)-β-$CO_2Me$ *N*-Cbz pyrrolidine [3+2] reagent (S–41)



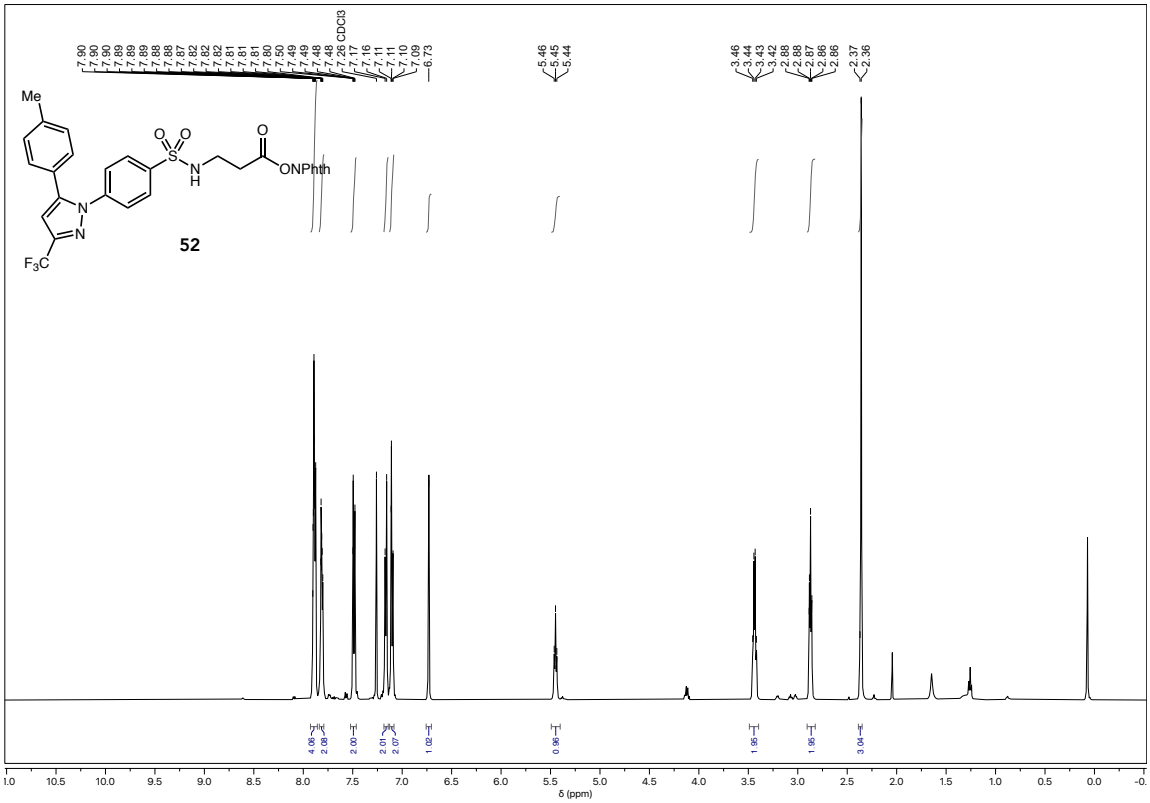



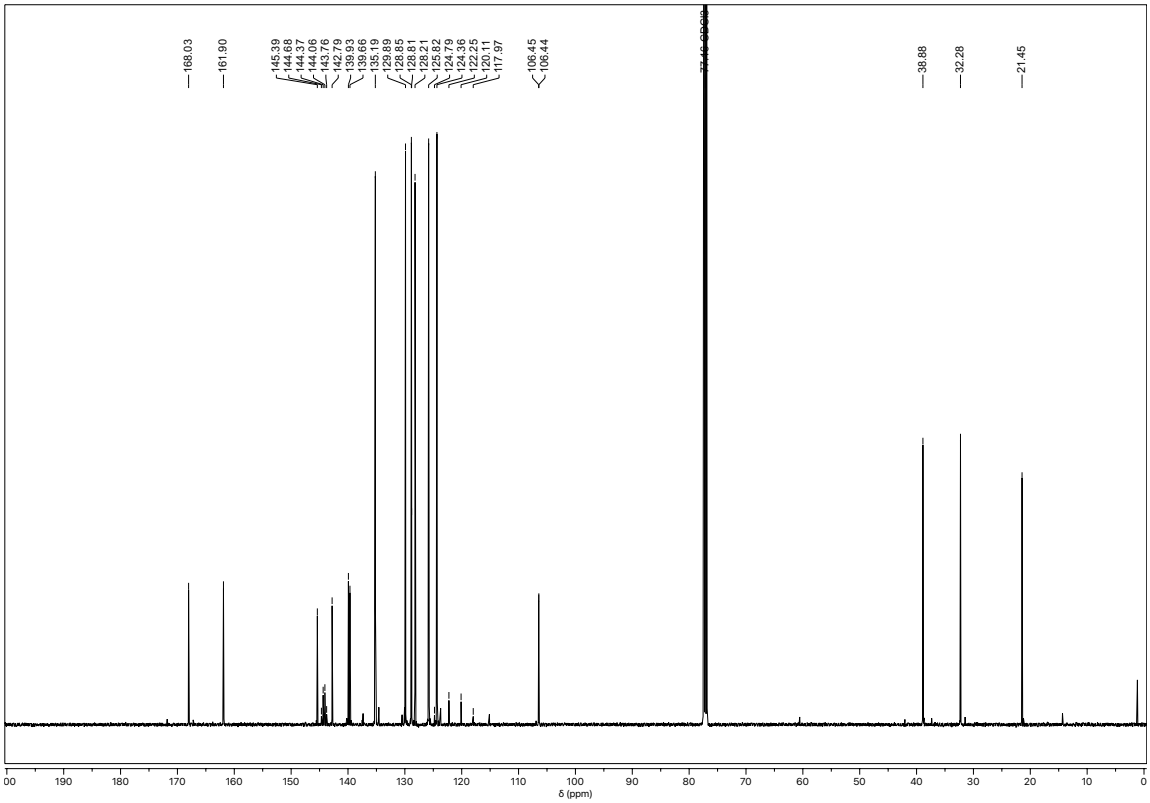
## β-*Spiro*-*N*-Cbz pyrrolidine / *N*-Boc azetidine reagent (S–42)

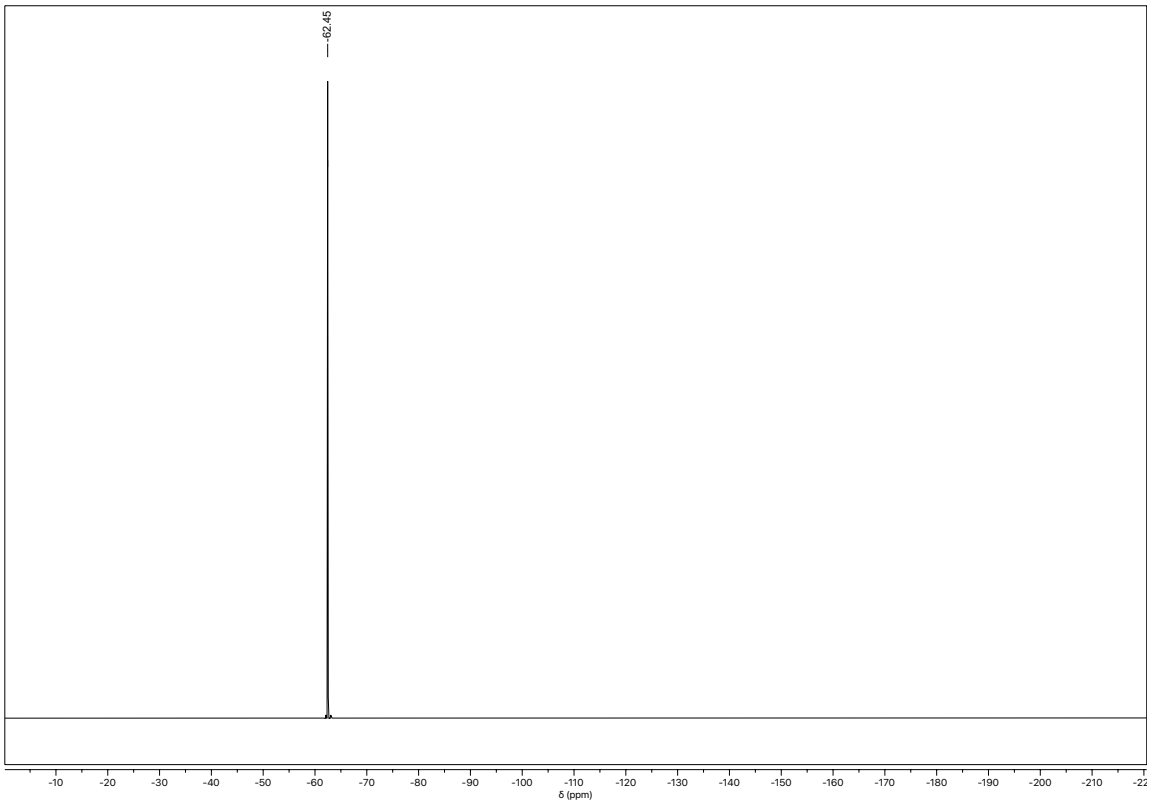


## Celecoxib β-alanine NHPI reagent (52)

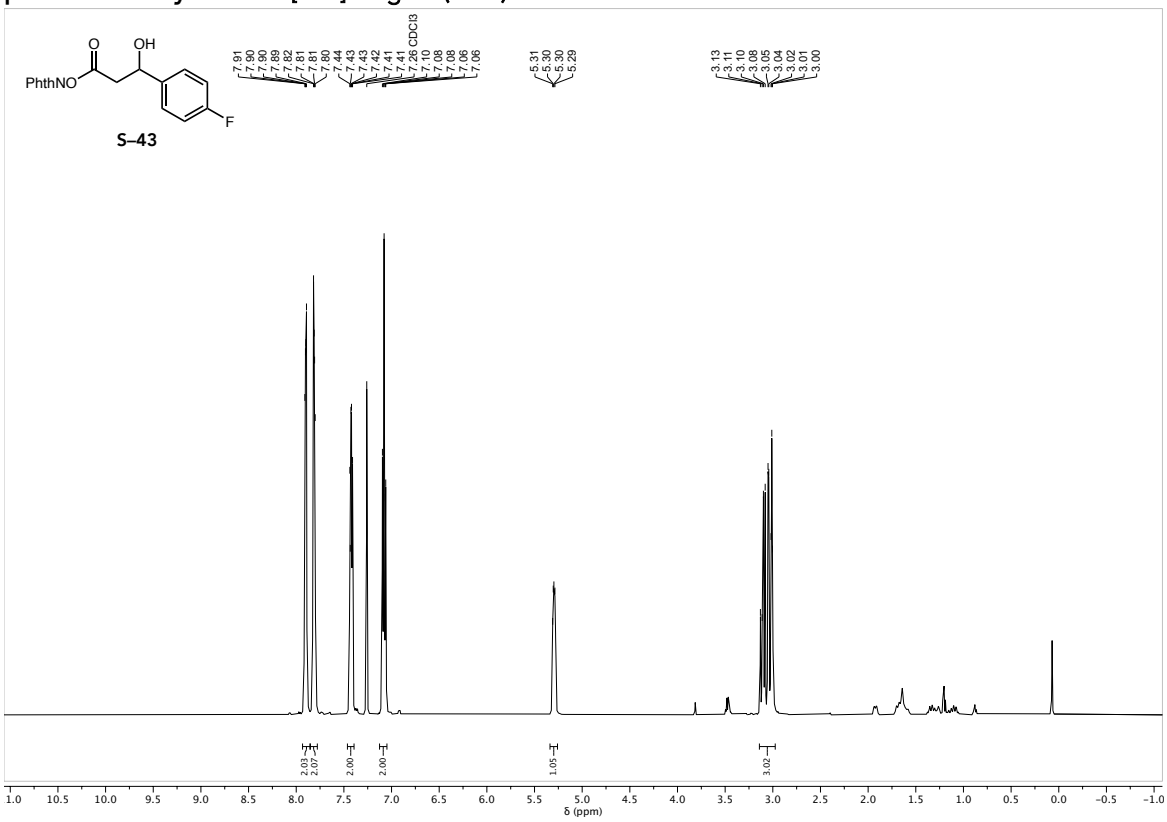


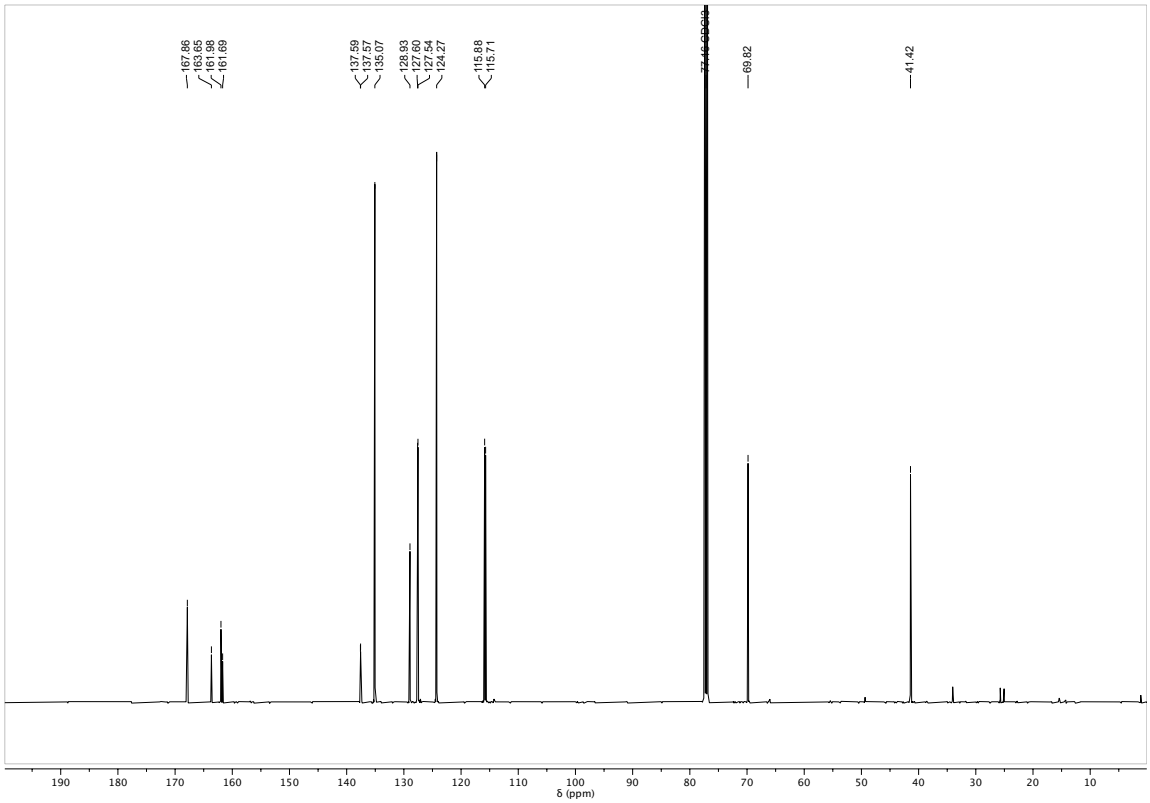



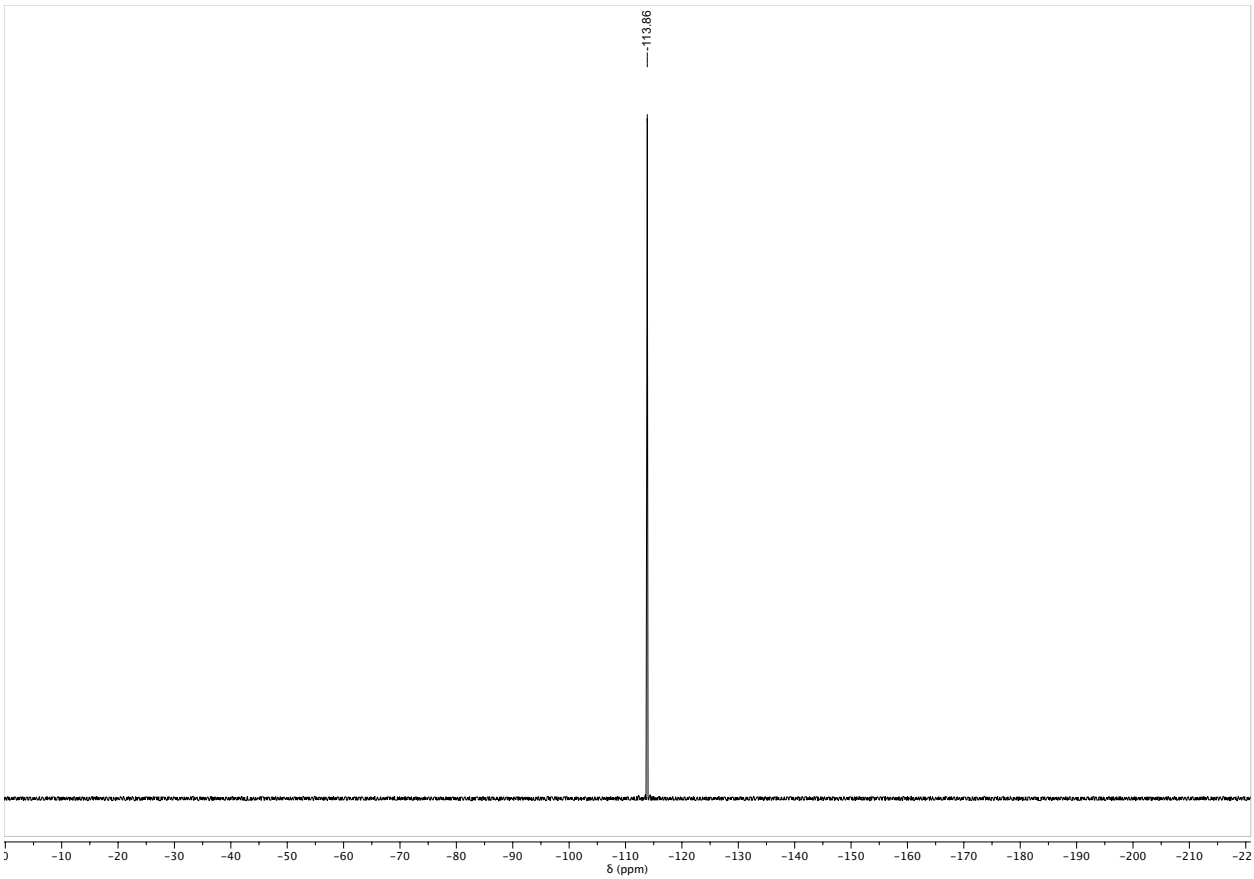

-62.45
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
δ (ppm)

## 10.4.2. Tetrahydrofuran NHPI reagents

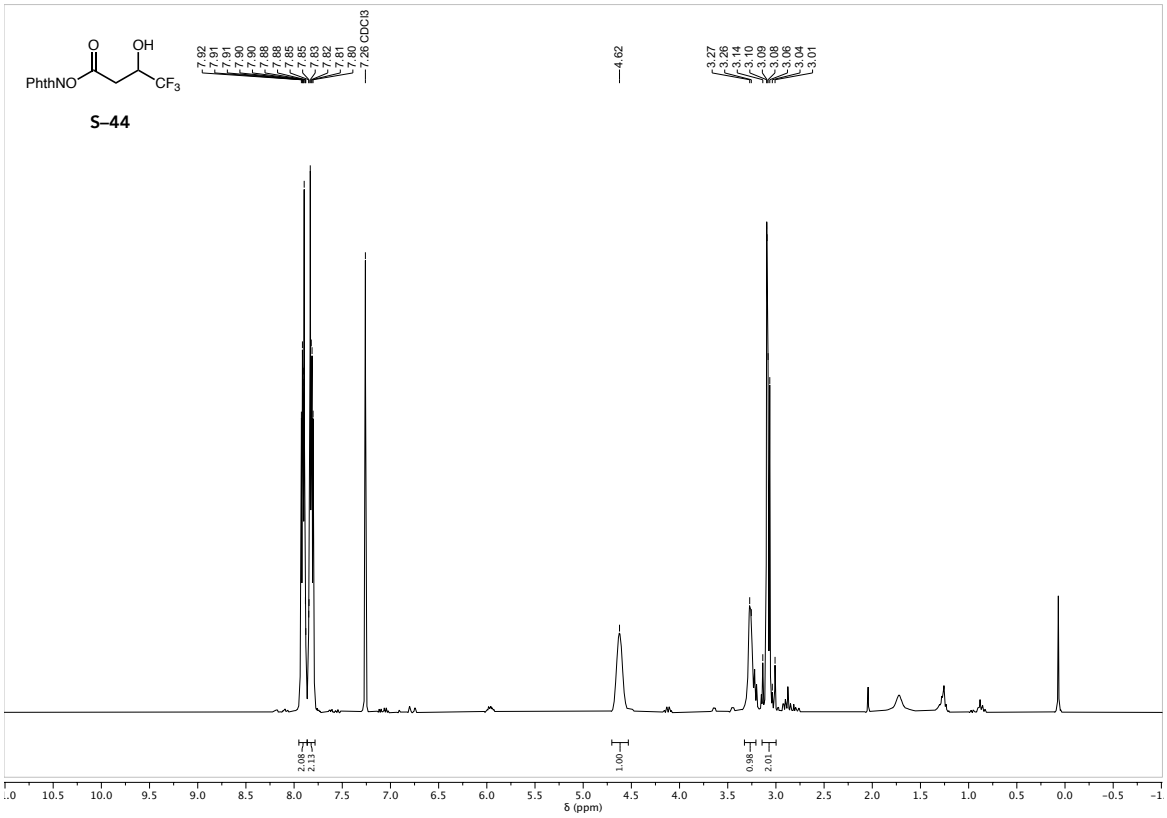
### β-4-F-Ph tetrahydrofuran [3+2] reagent (S–43)

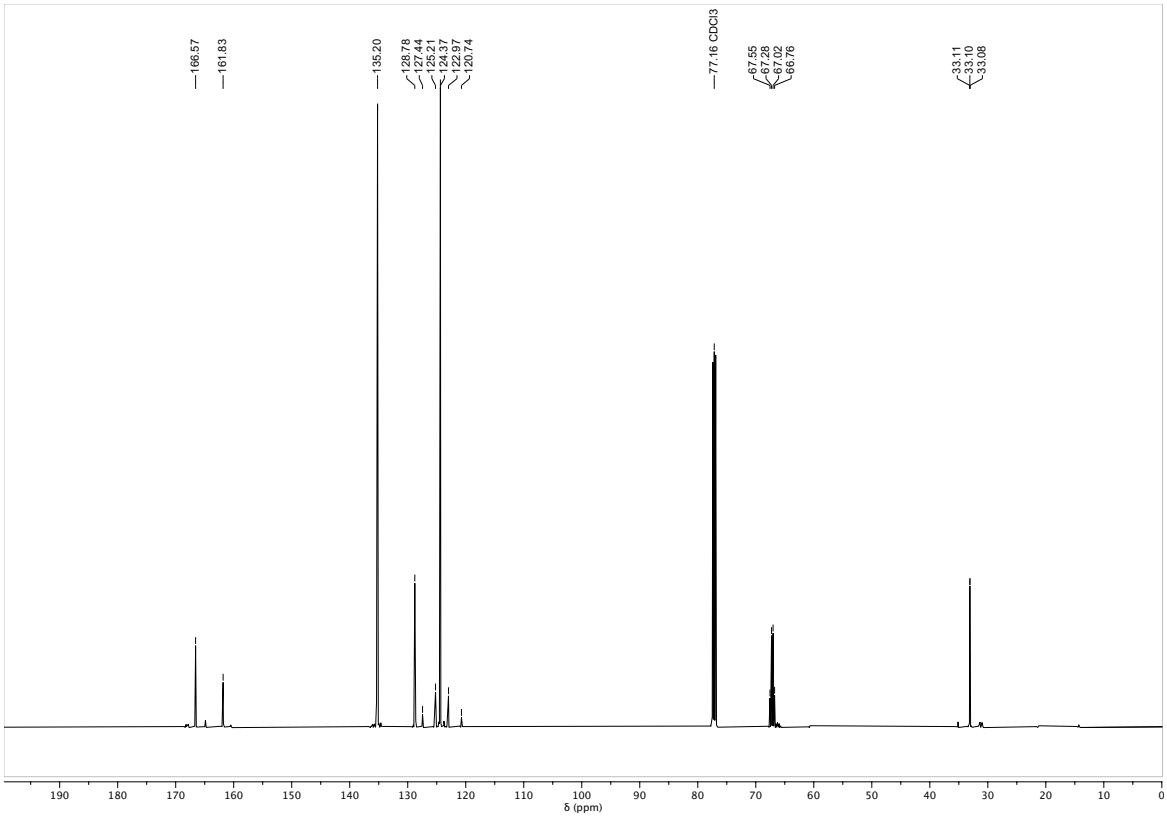


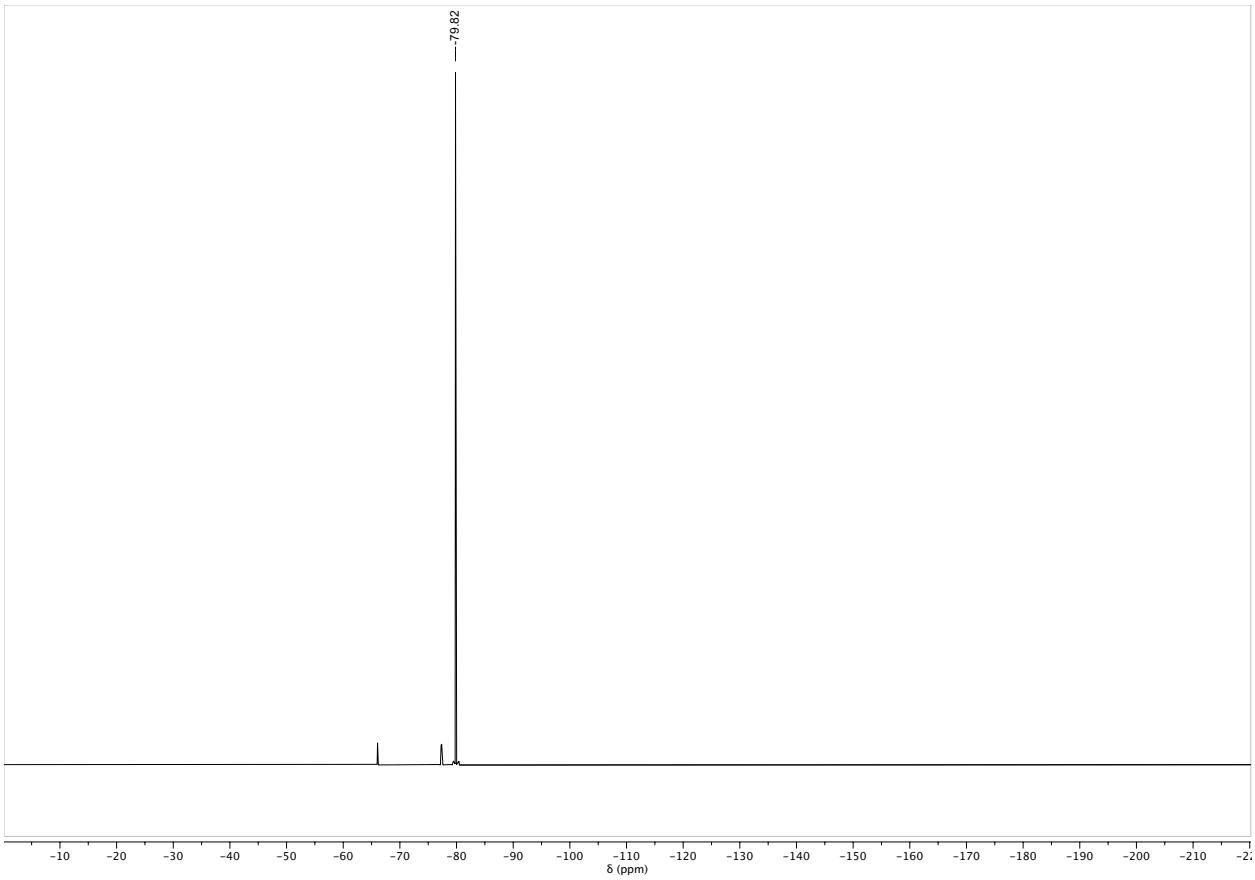




-113.86
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-22
δ (ppm)

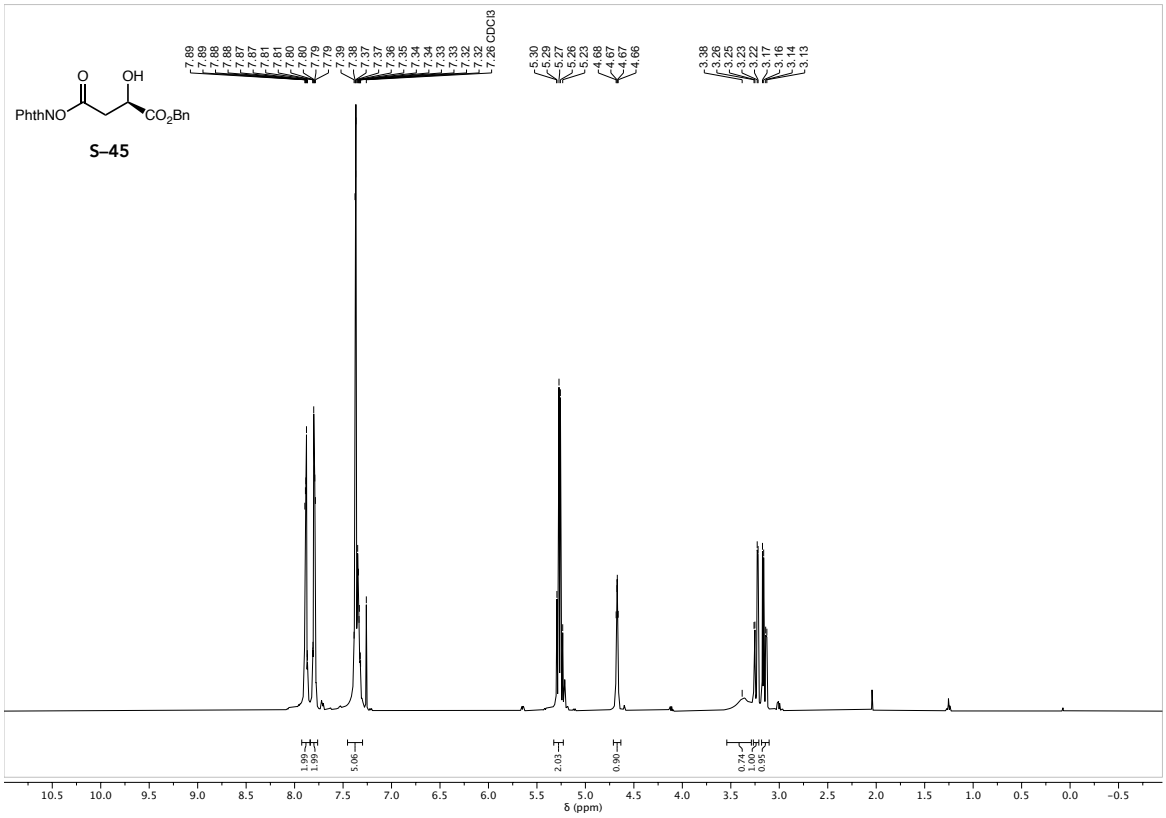
## β-$CF_3$ tetrahydrofuran [3+2] reagent (S–44)

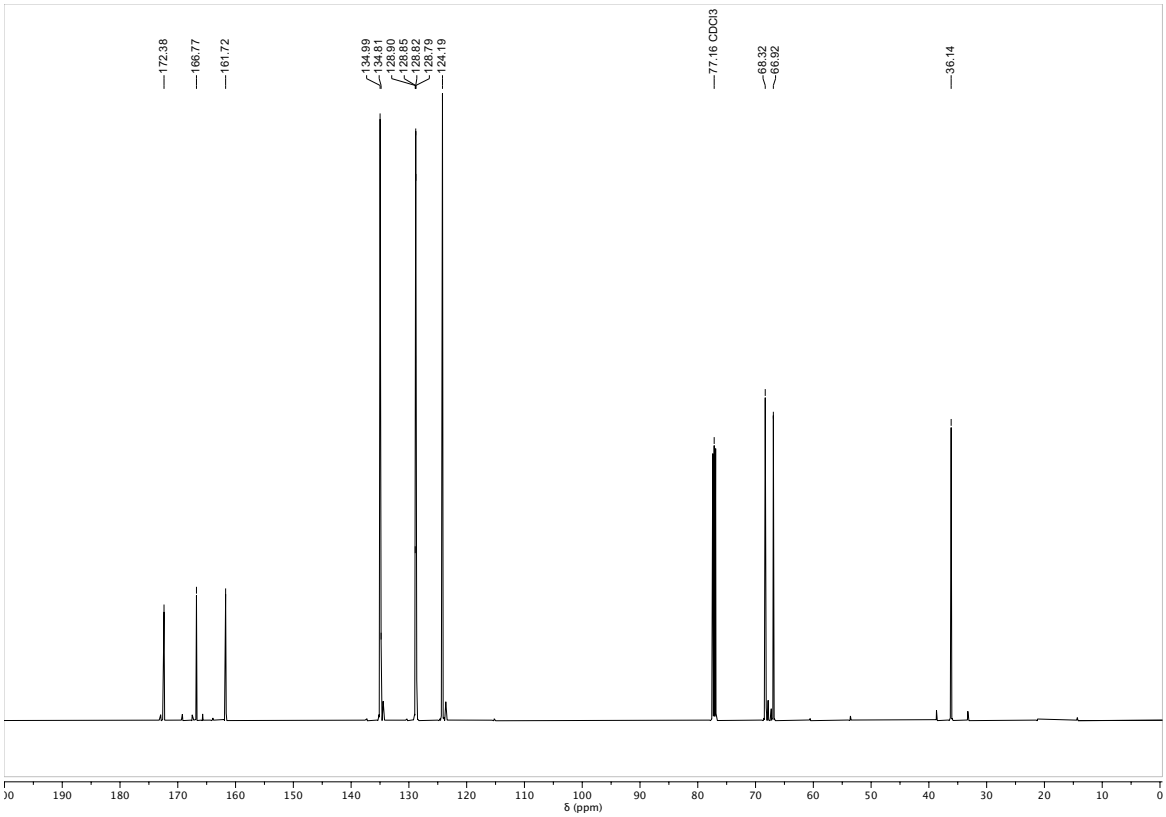


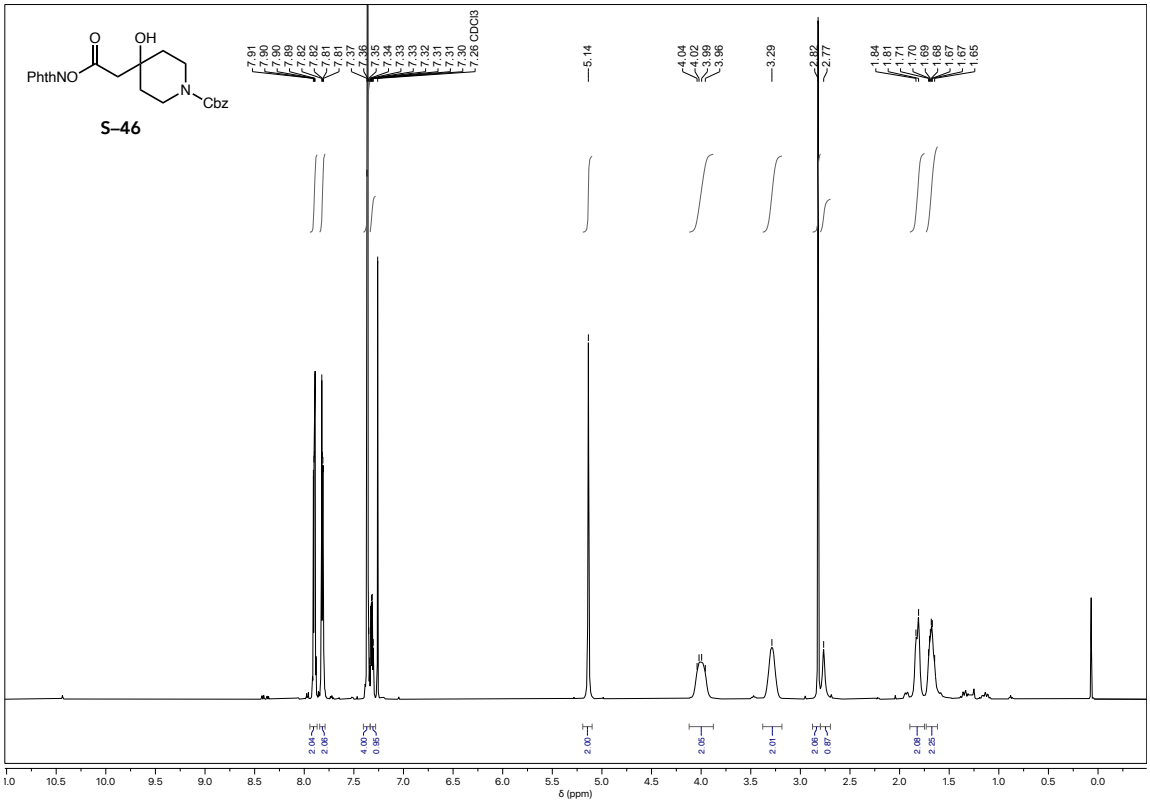

-79.82
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
δ (ppm)

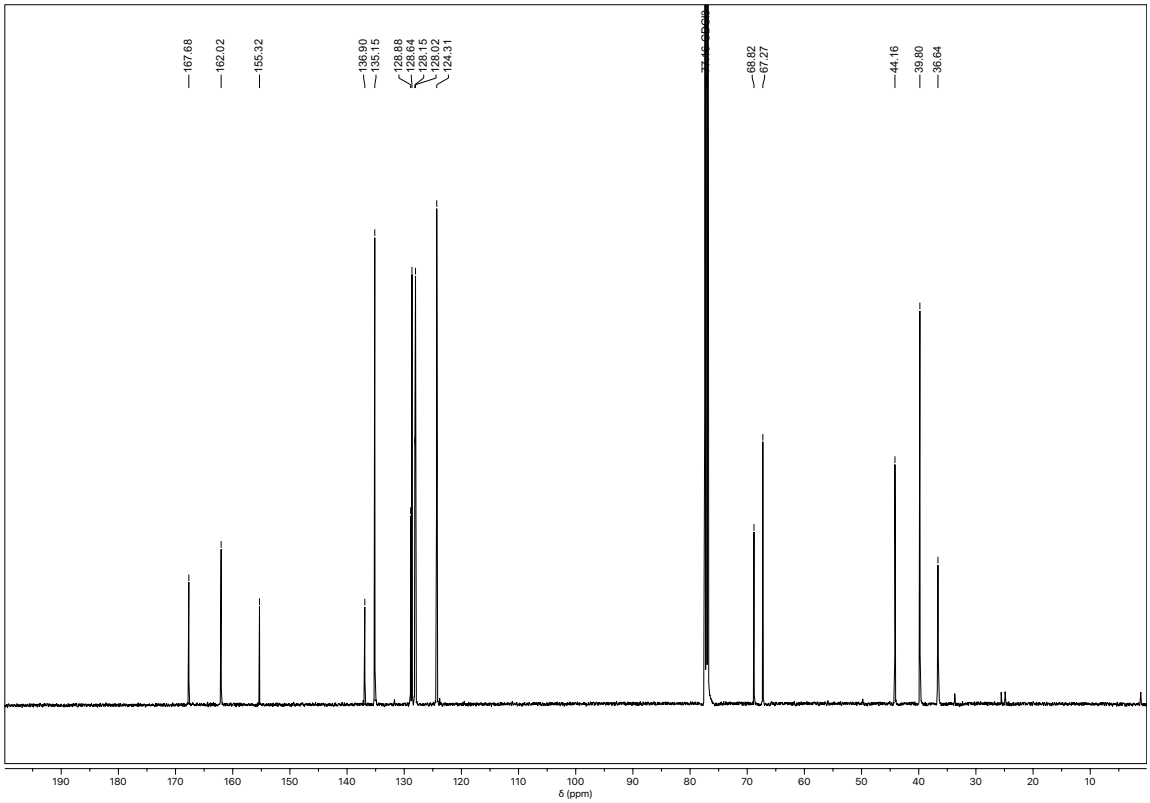
**(*R*)-β-$CO_2$Bn tetrahydrofuran [3+2] reagent (*S*–45)**



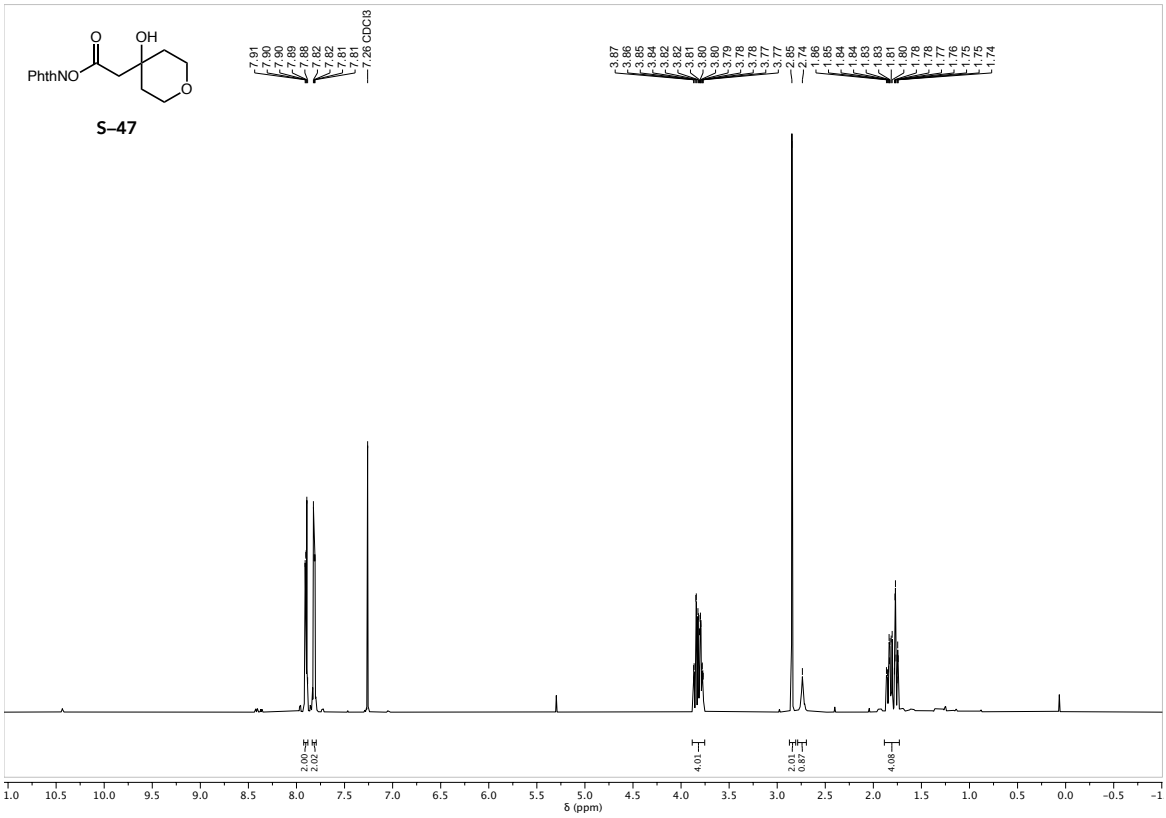



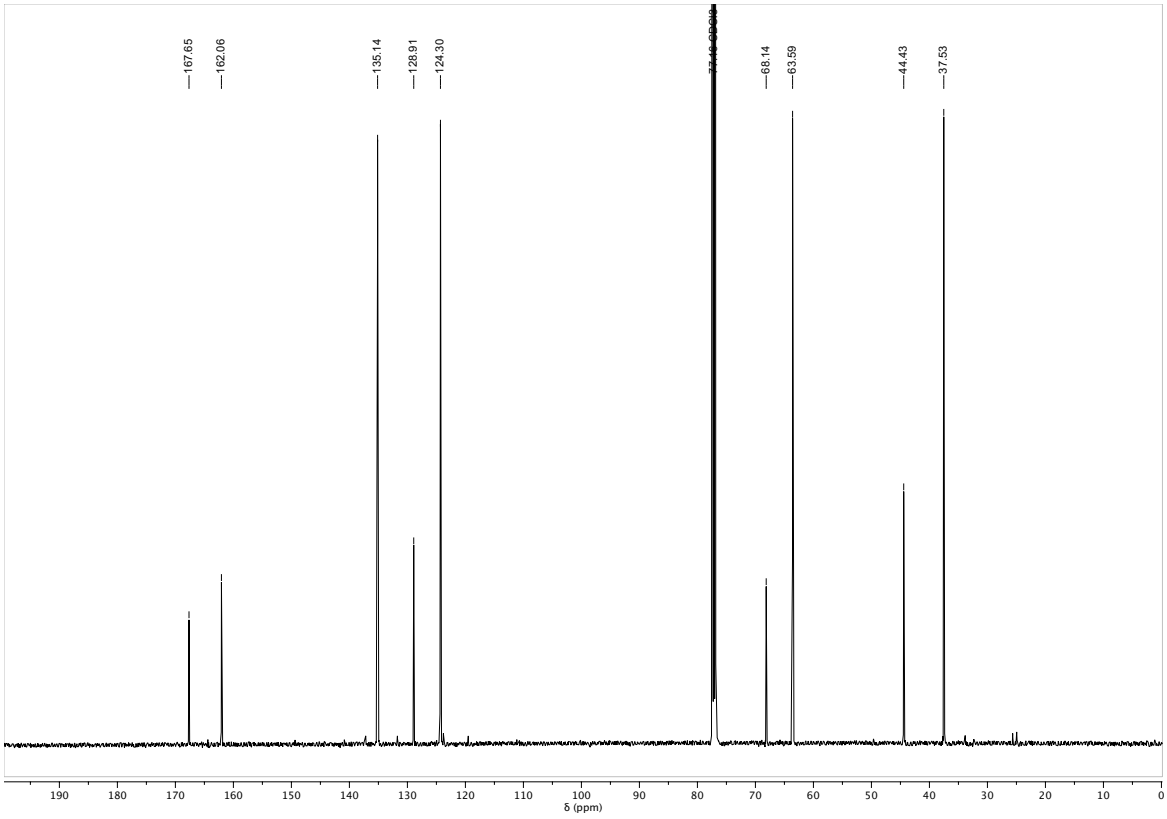
## *Spiro-N*-Cbz piperidine / tetrahydrofuran [3+2] reagent (S–46)



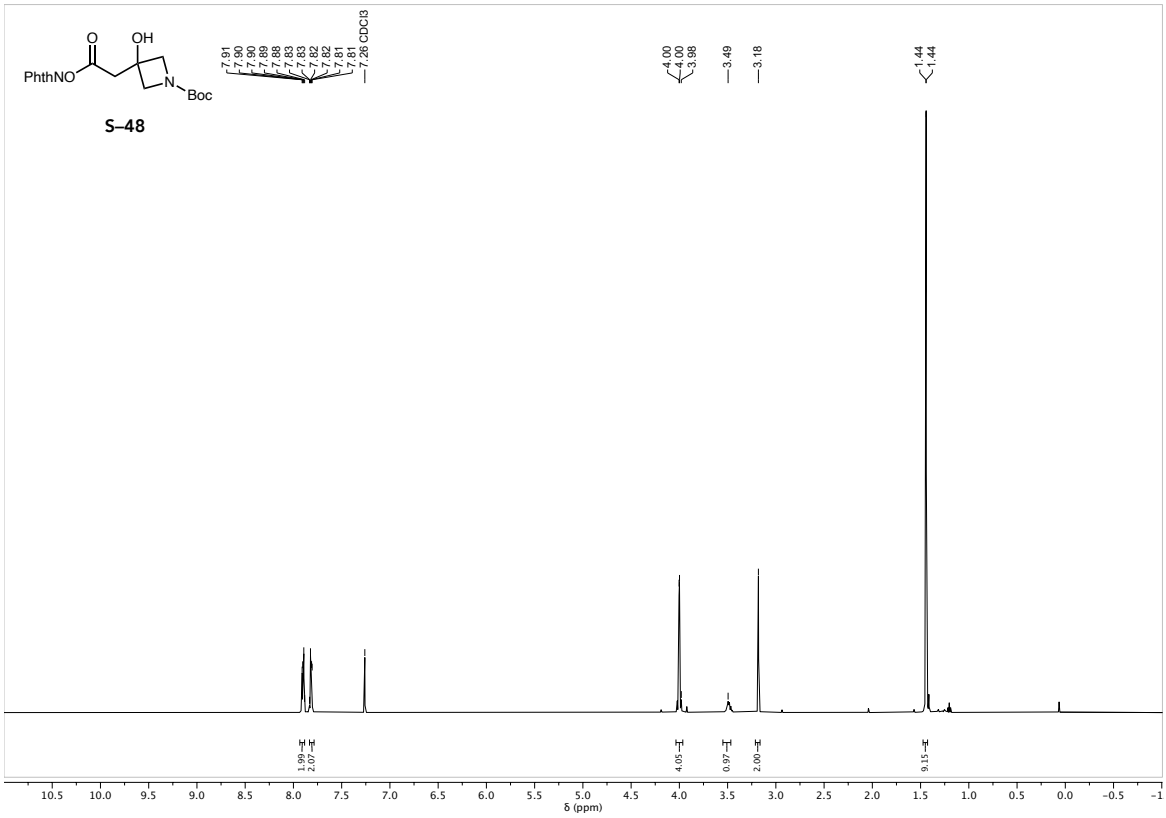



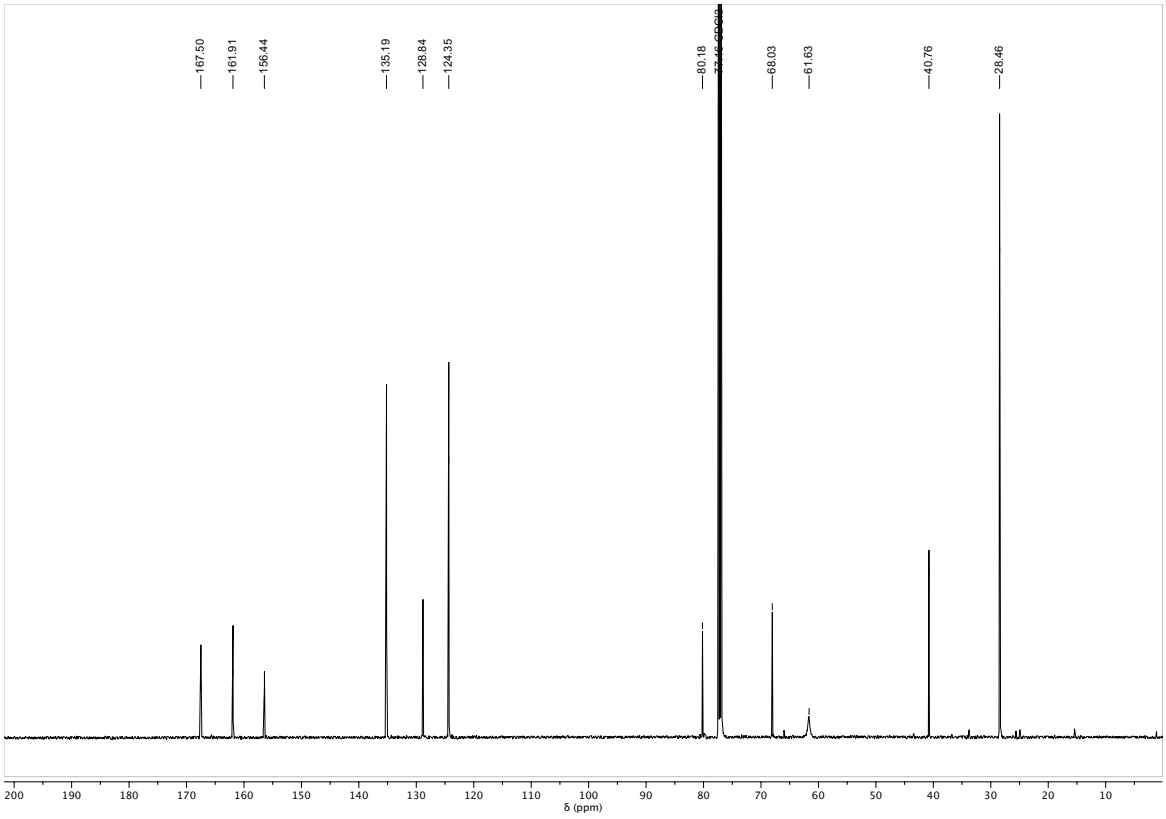
## *Spiro*-tetrahydropyran / tetrahydrofuran [3+2] reagent (S–47)



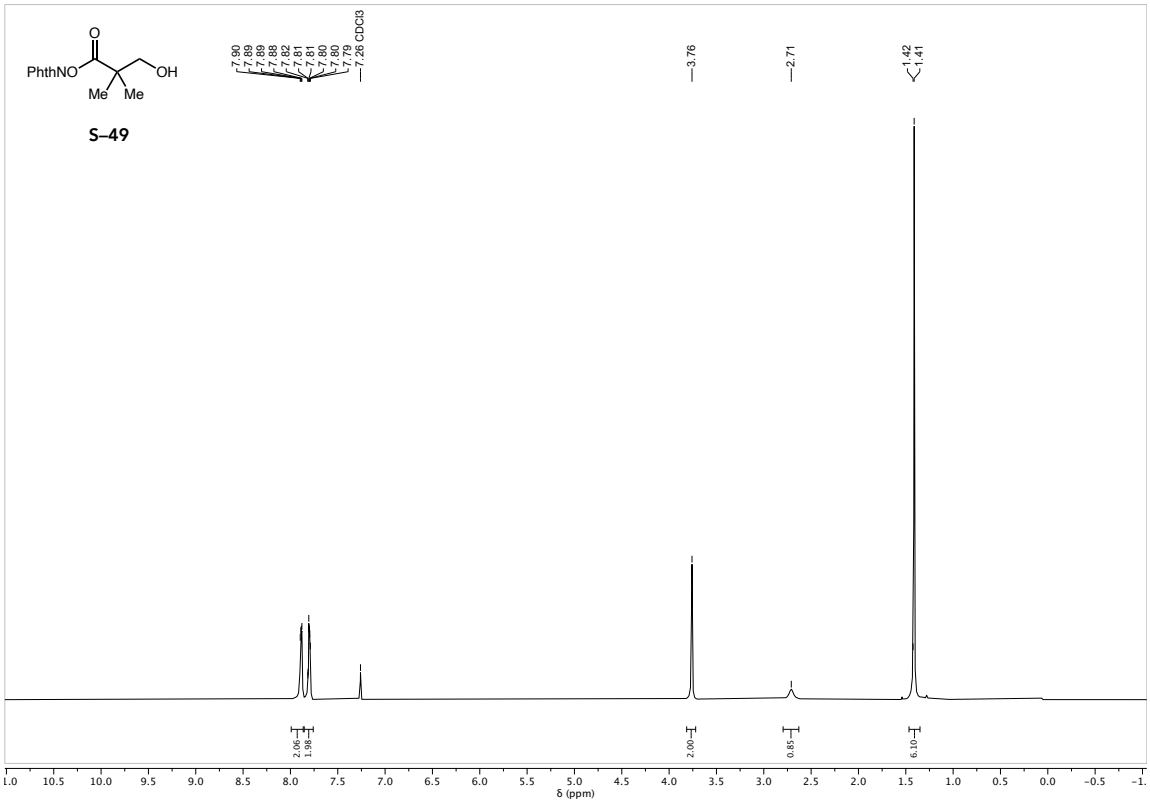



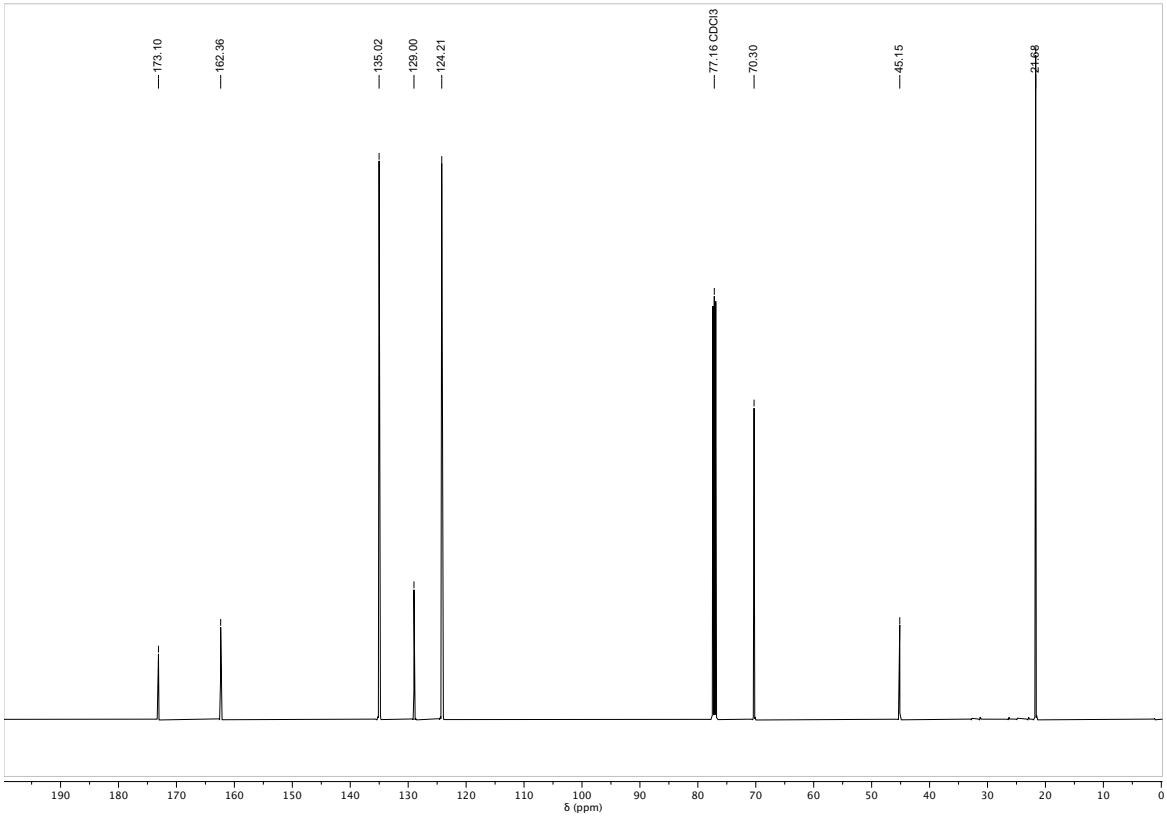
*Spiro*-*N*-Boc azetidine / tetrahydrofuran [3+2] reagent (S–48)



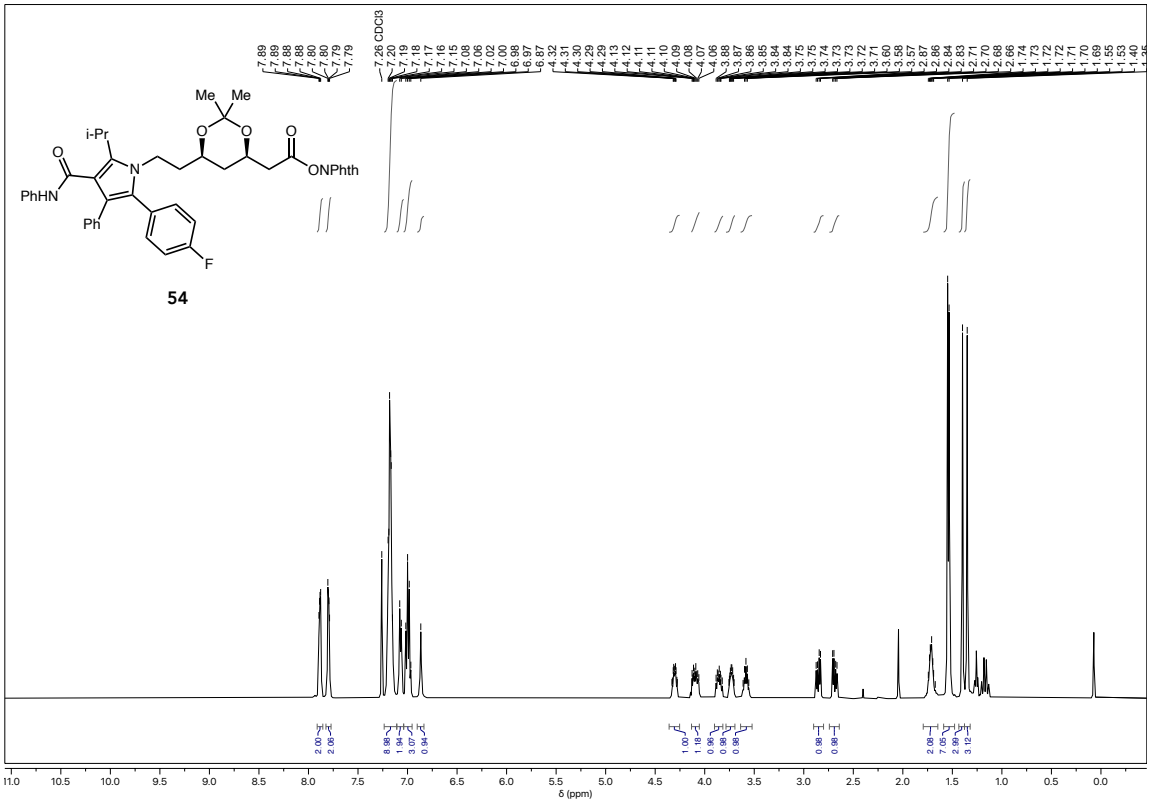



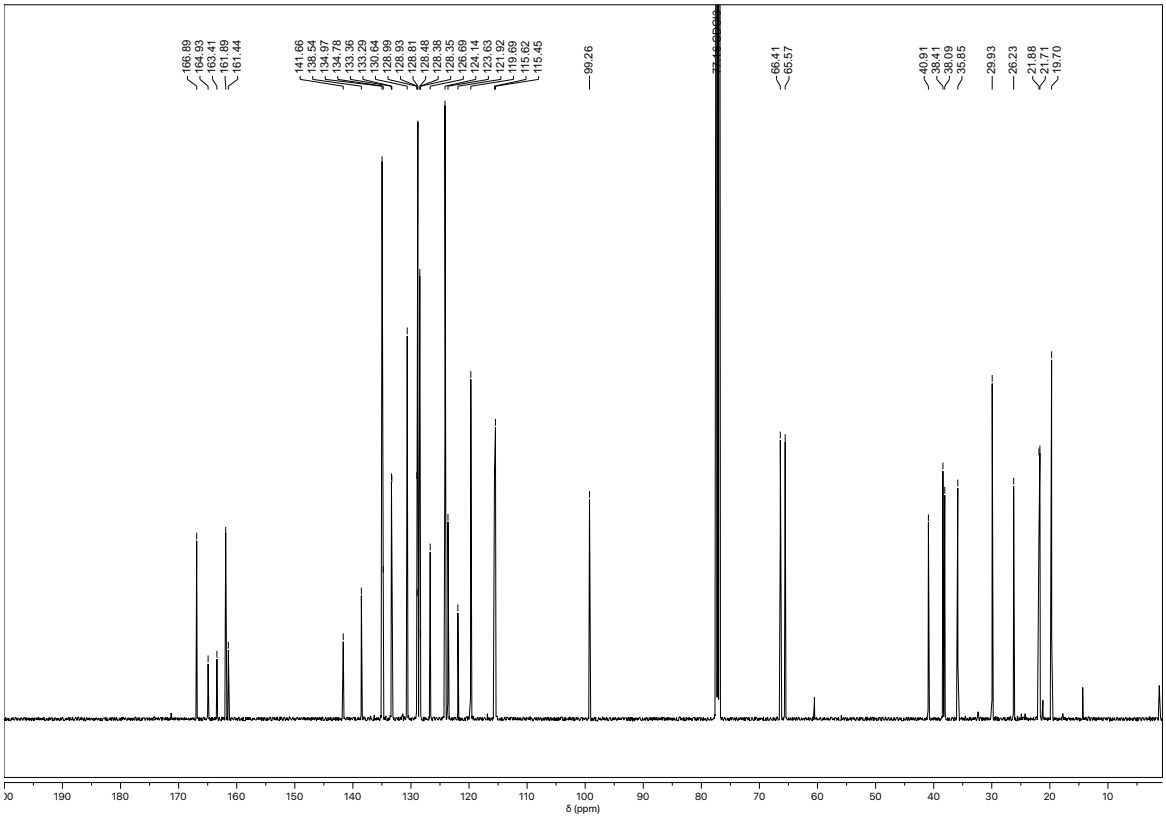
α,α-Dimethyl tetrahydrofuran [3+2] reagent (S–49)

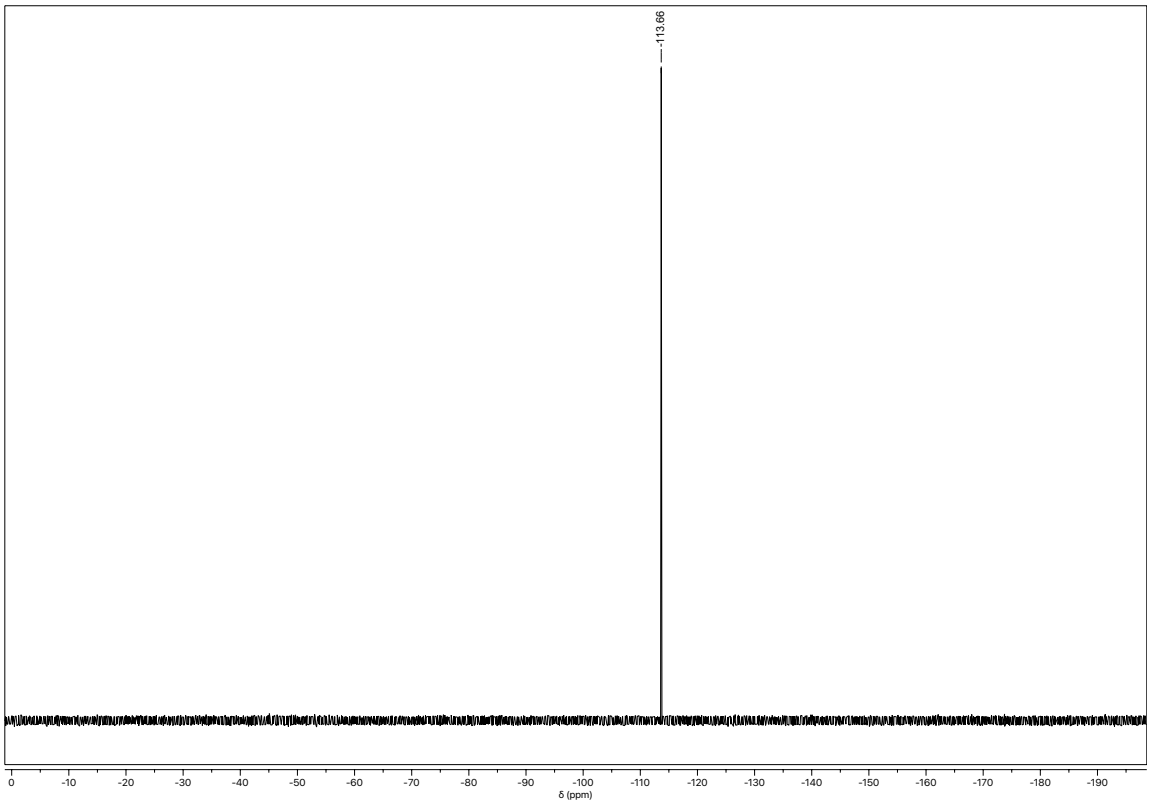


## Atorvastatin acetonide NHPI ester reagent (54)

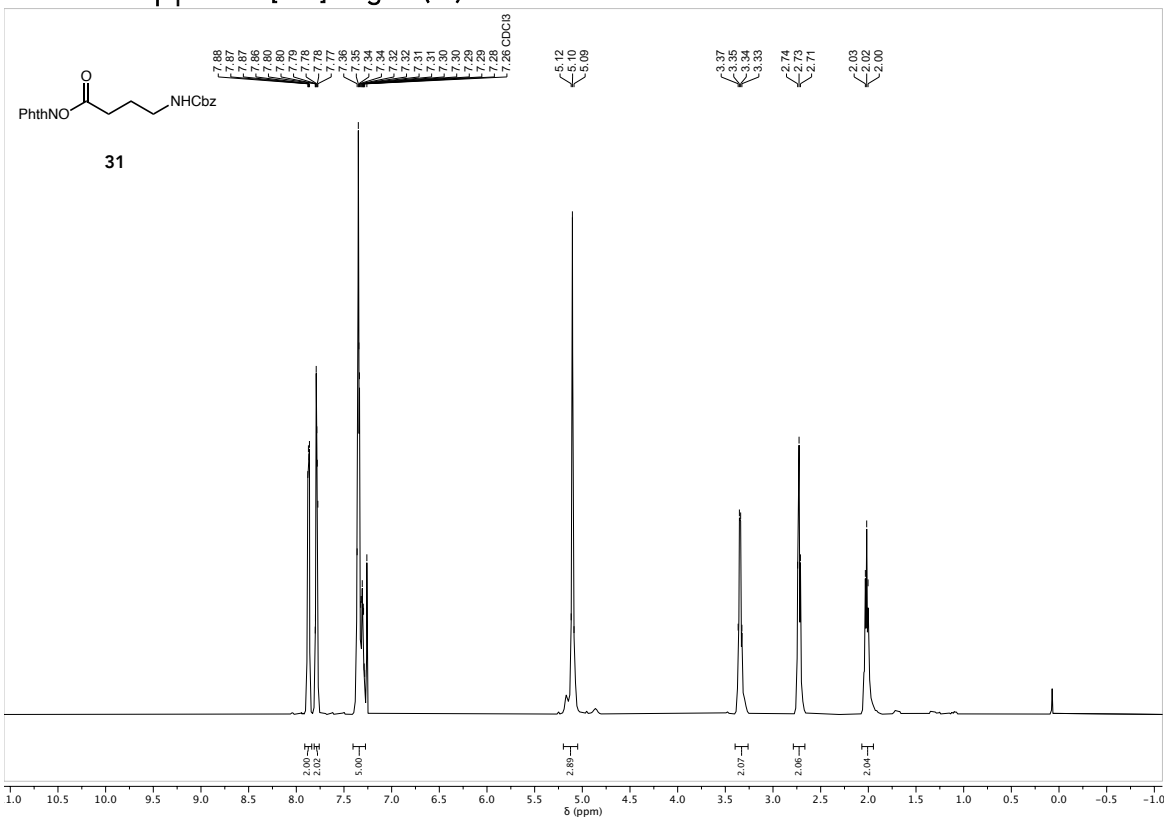


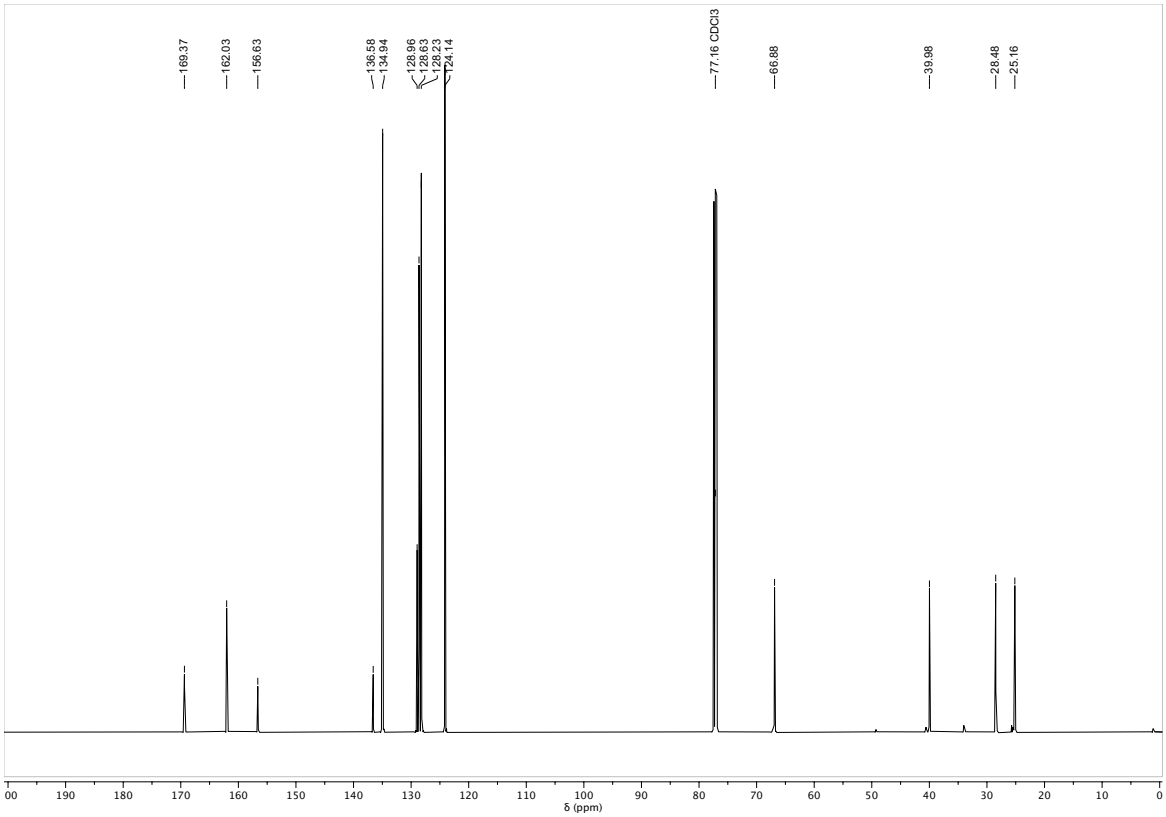




-113.66
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
δ (ppm)

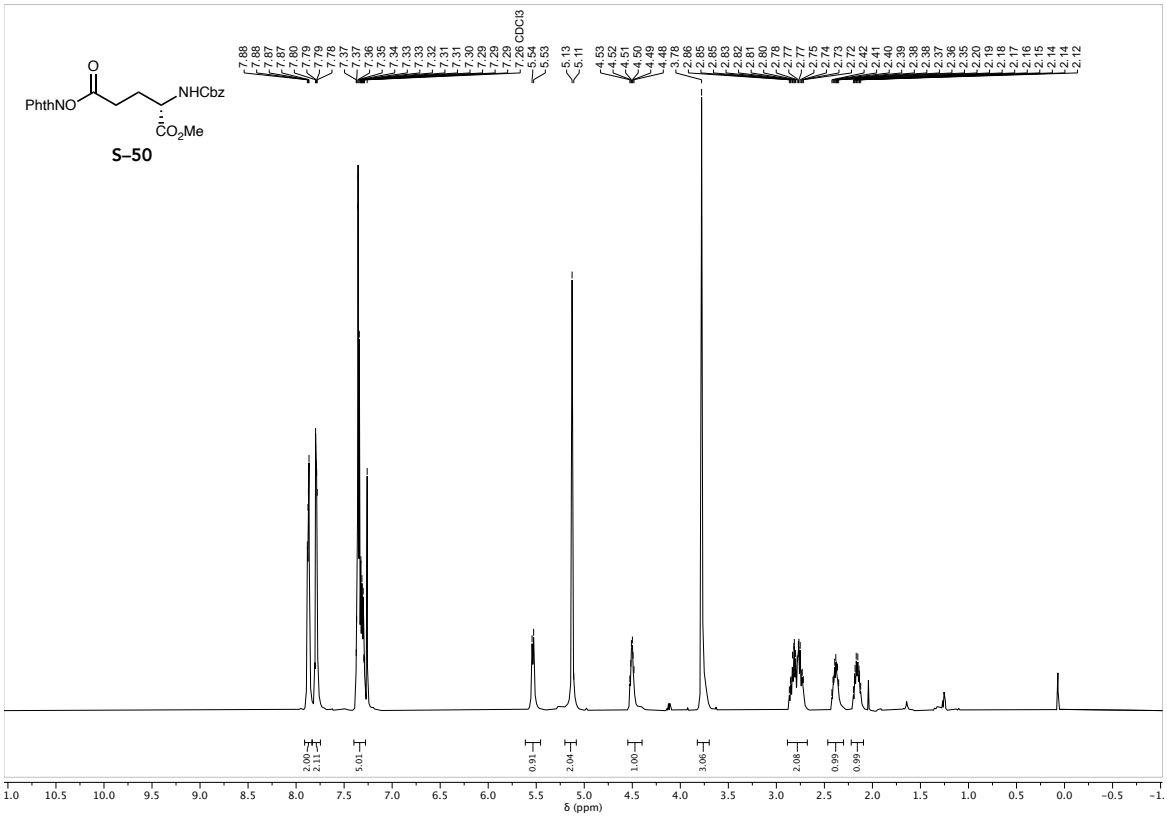
## 10.4.3. Piperidine NHPI reagents

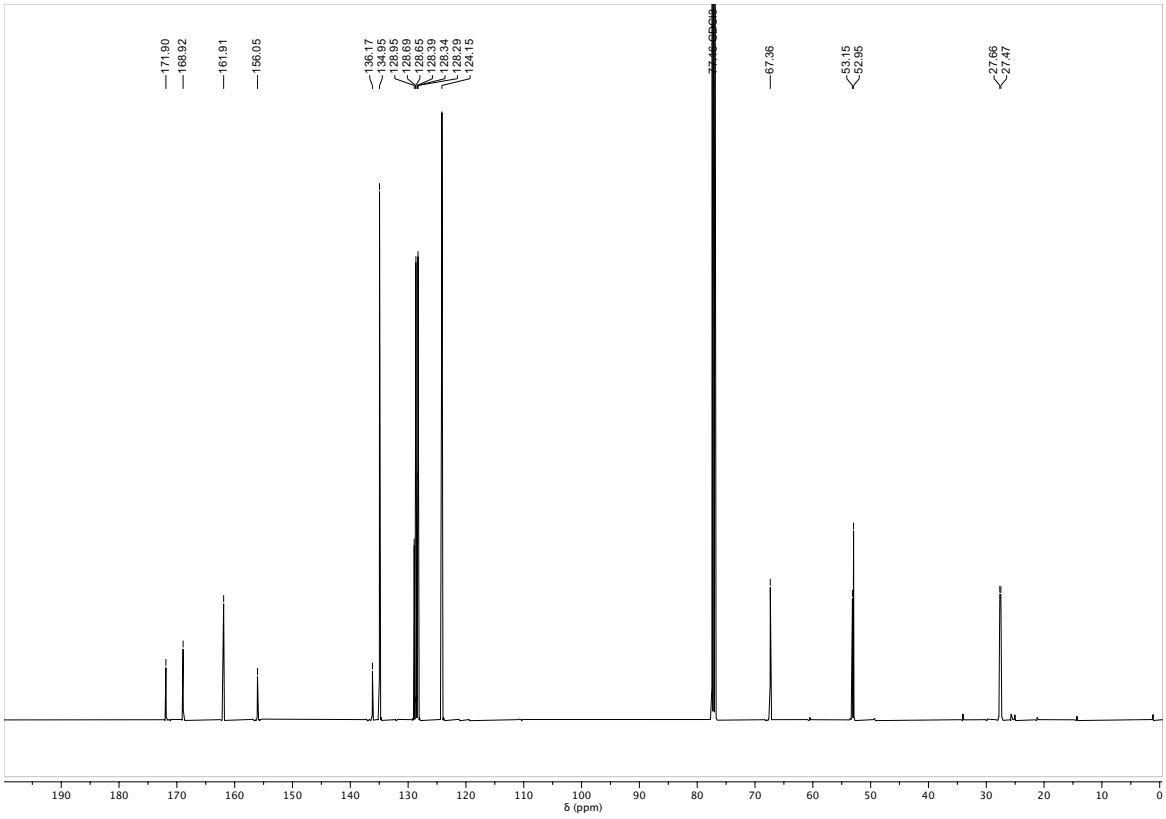
### Parent *N*-Cbz piperidine [4+2] reagent (31)



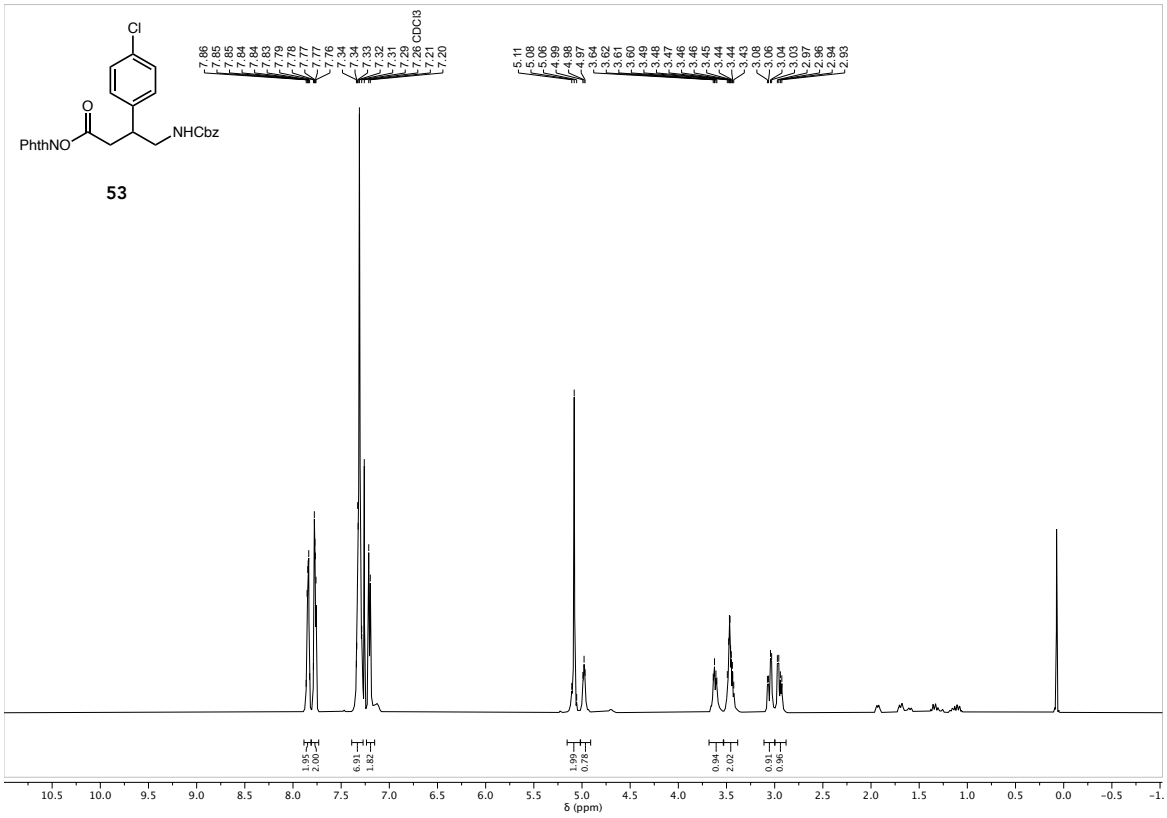



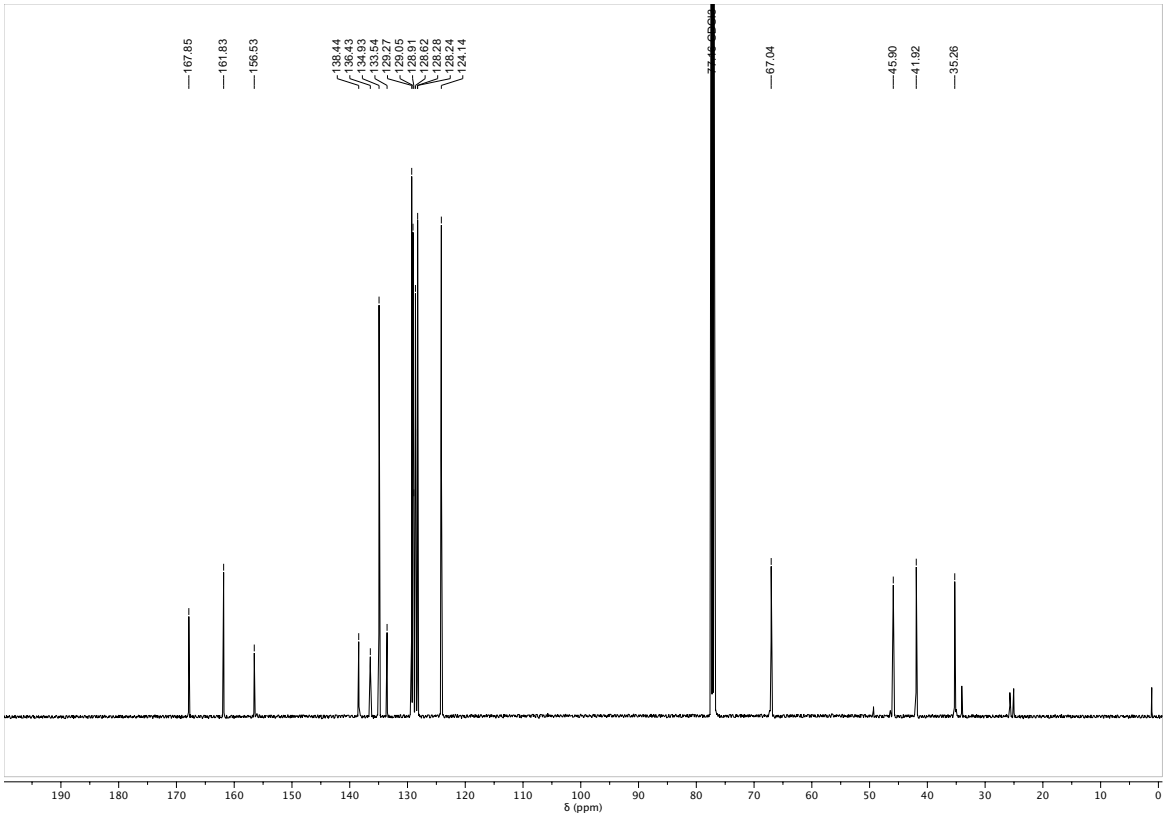
(*S*)-γ-$CO_2Me$ piperidine [4+2] reagent (*S*–50)



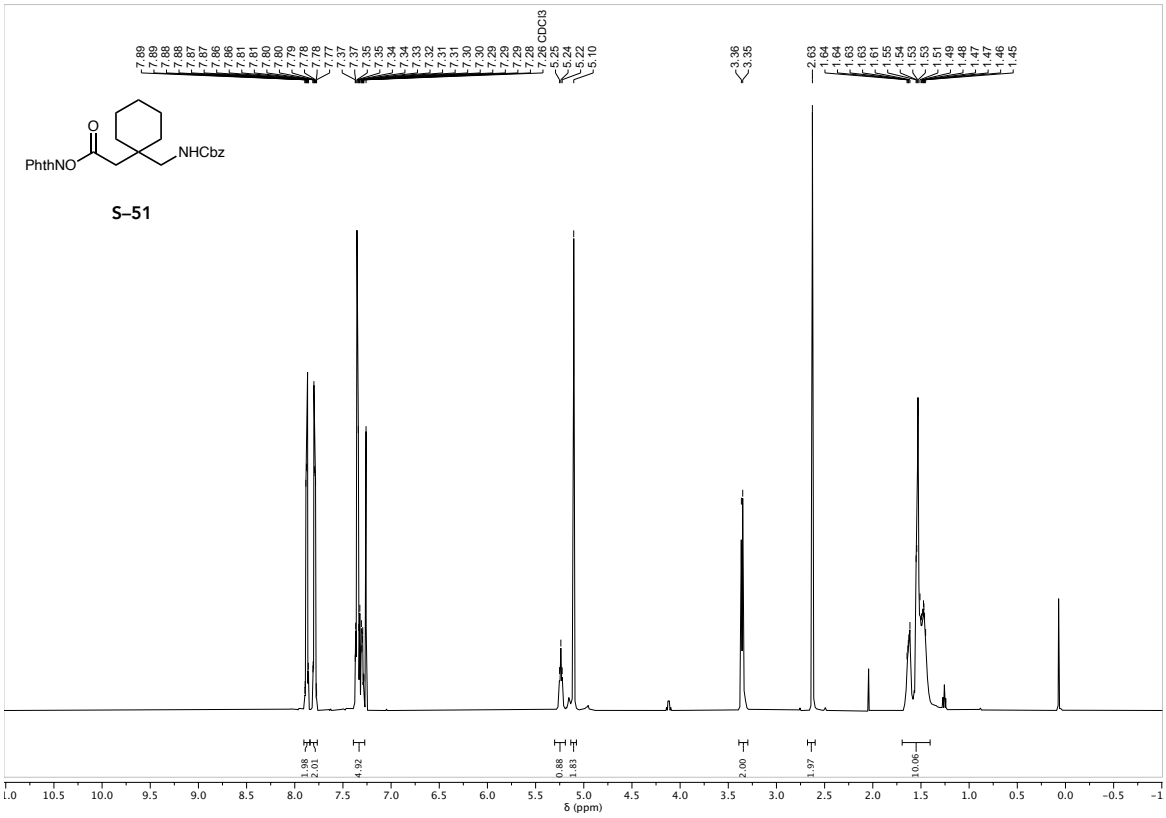



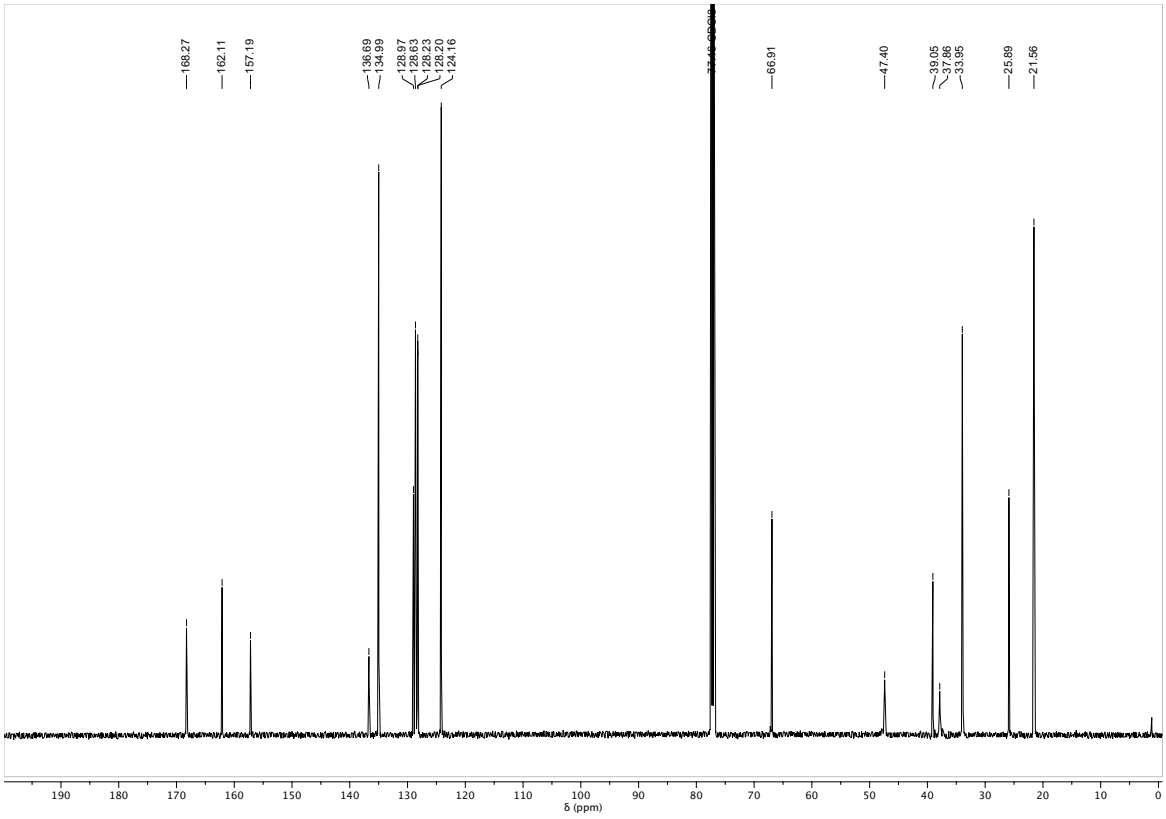
## Baclofen piperidine [4+2] reagent (53)



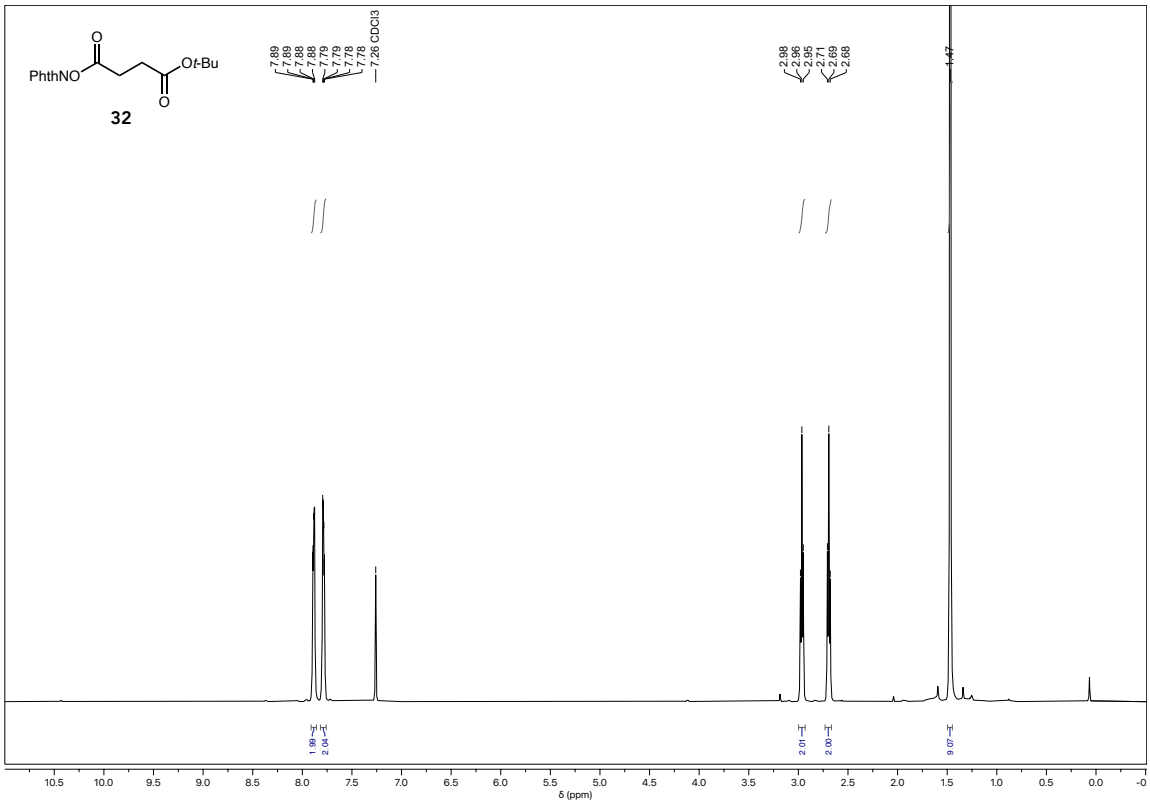
## Gabapentin-derived piperidine [4+2] reagent (S–51)

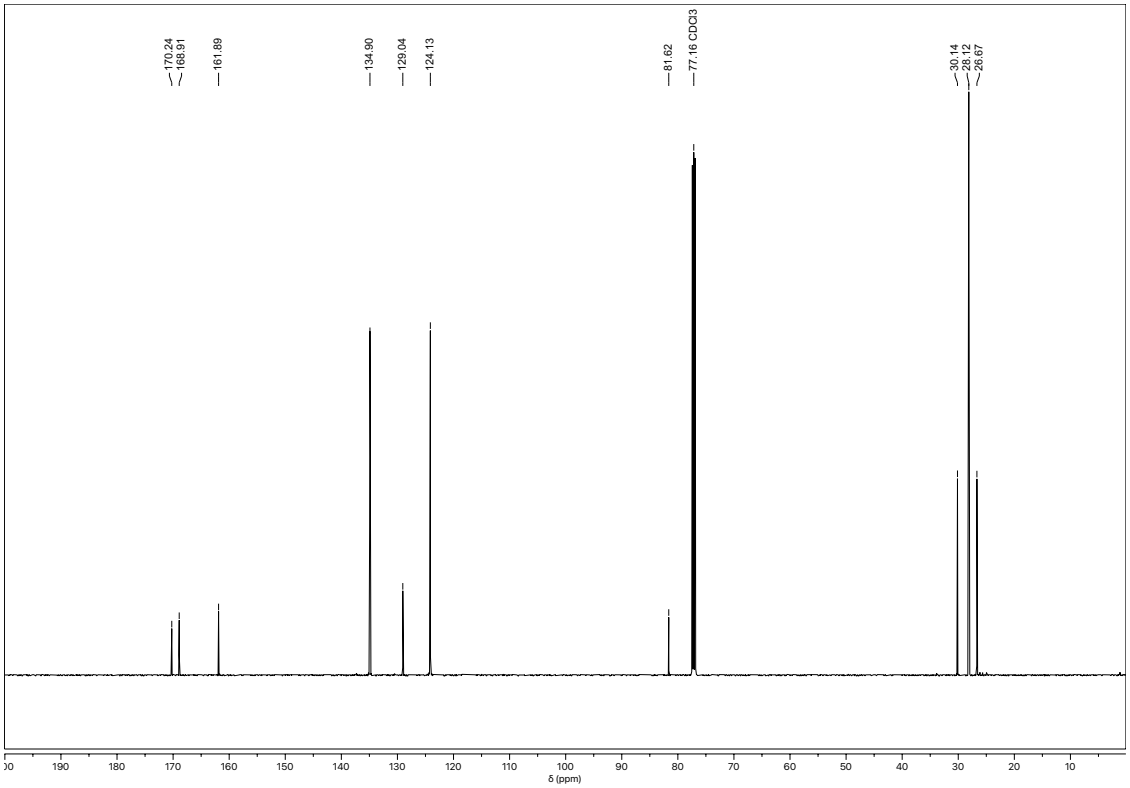


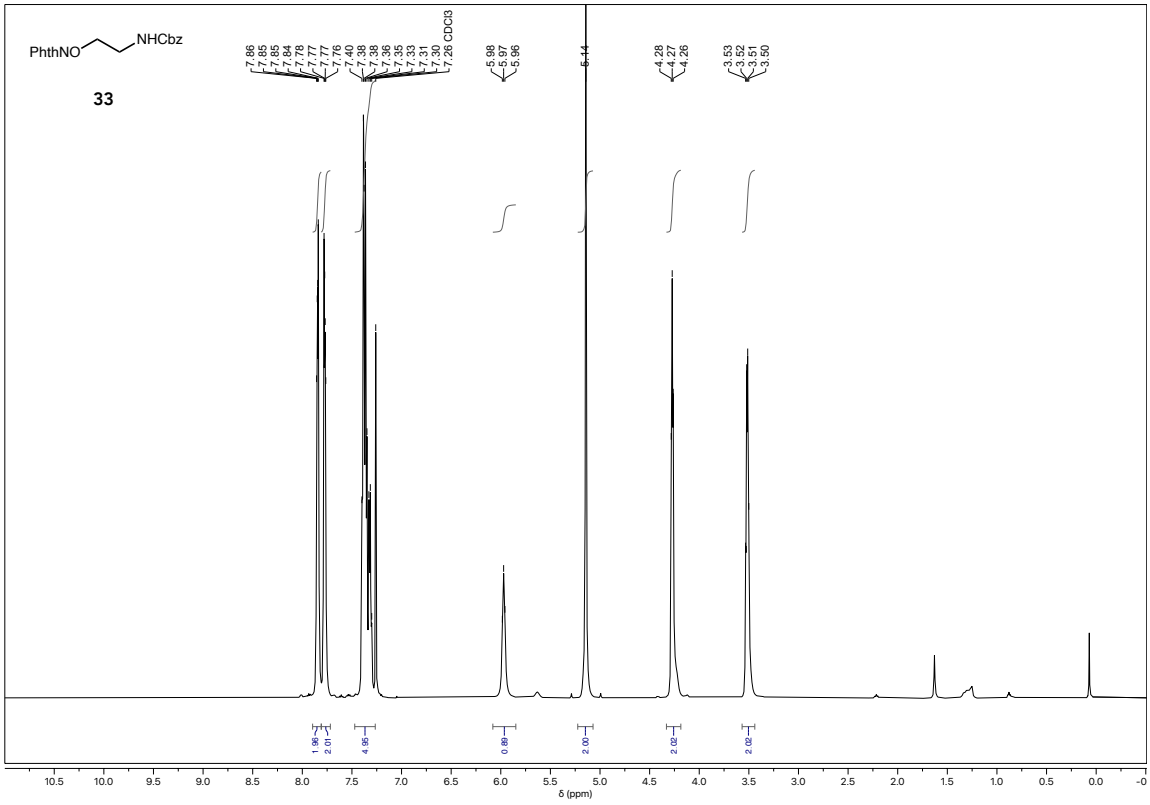
## 10.4.4. Other NHPI reagents

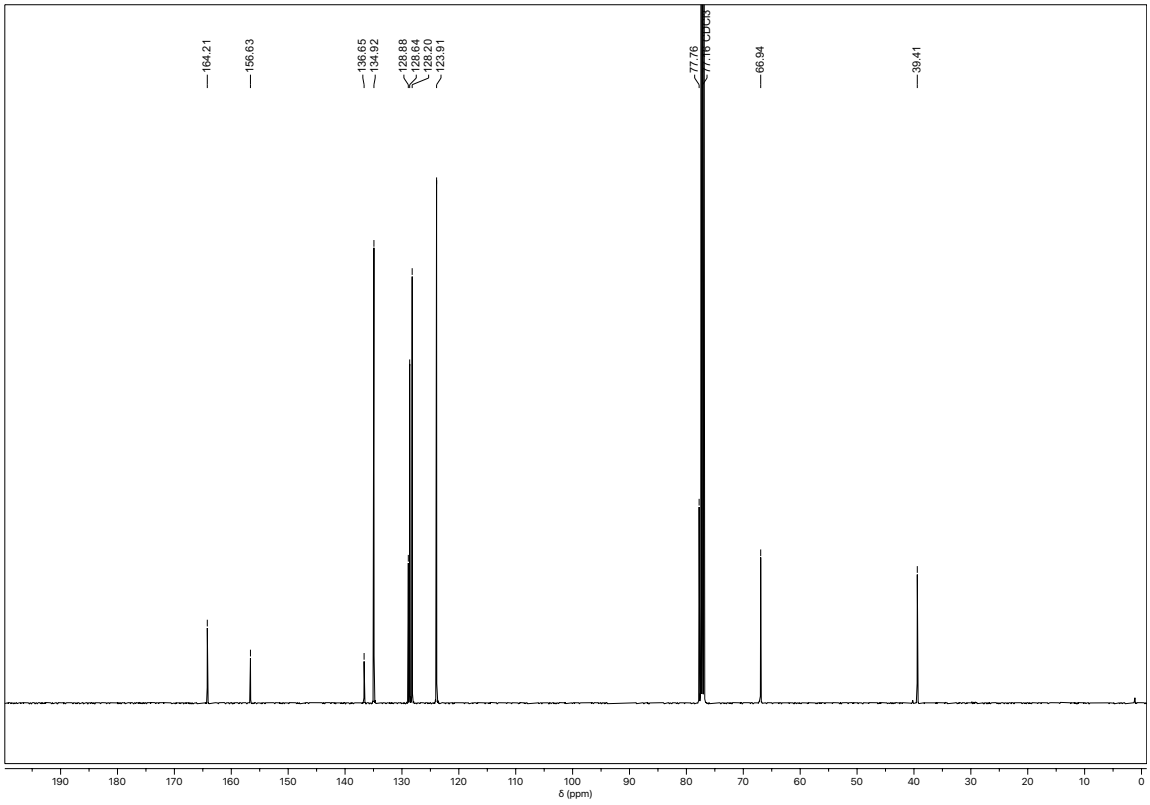
Parent δ-valerolactone [4+2] reagent (32)



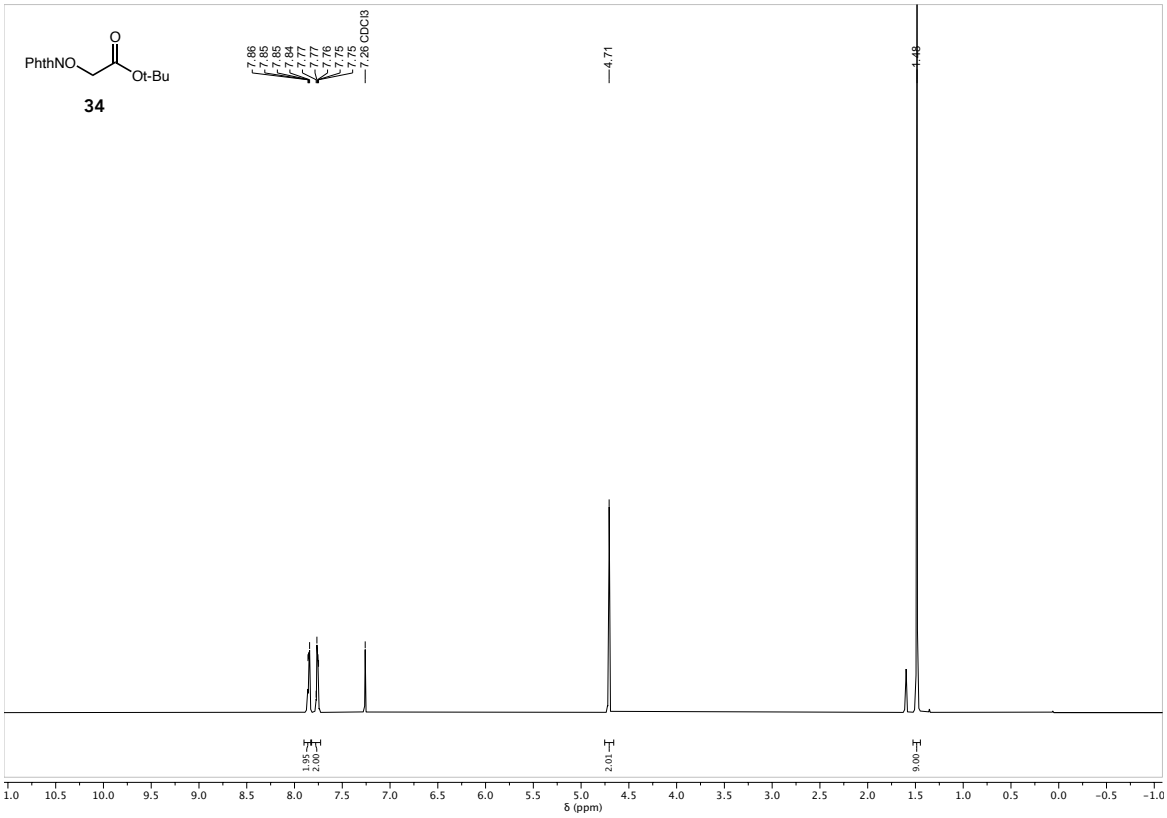



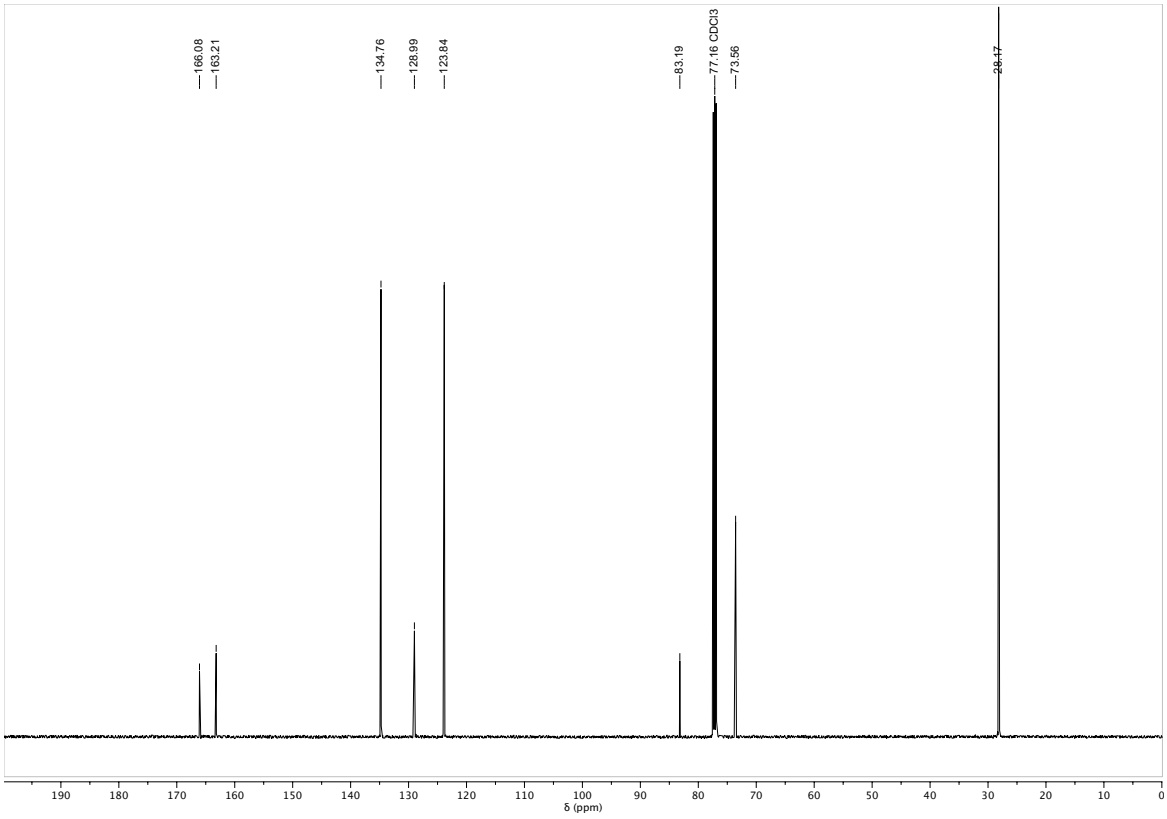
Parent N-Cbz morpholine [4+2] NHPI reagent (33)



## Parent dioxanone [4+2] reagent (34)

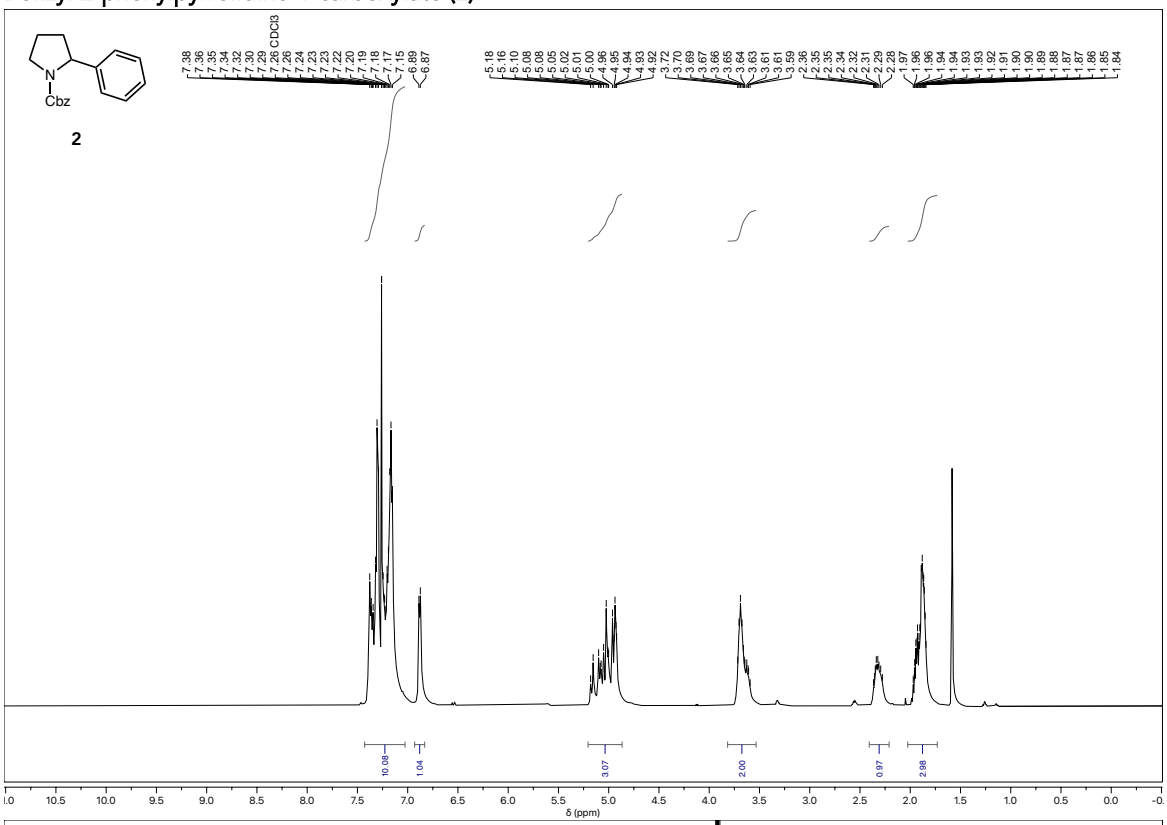


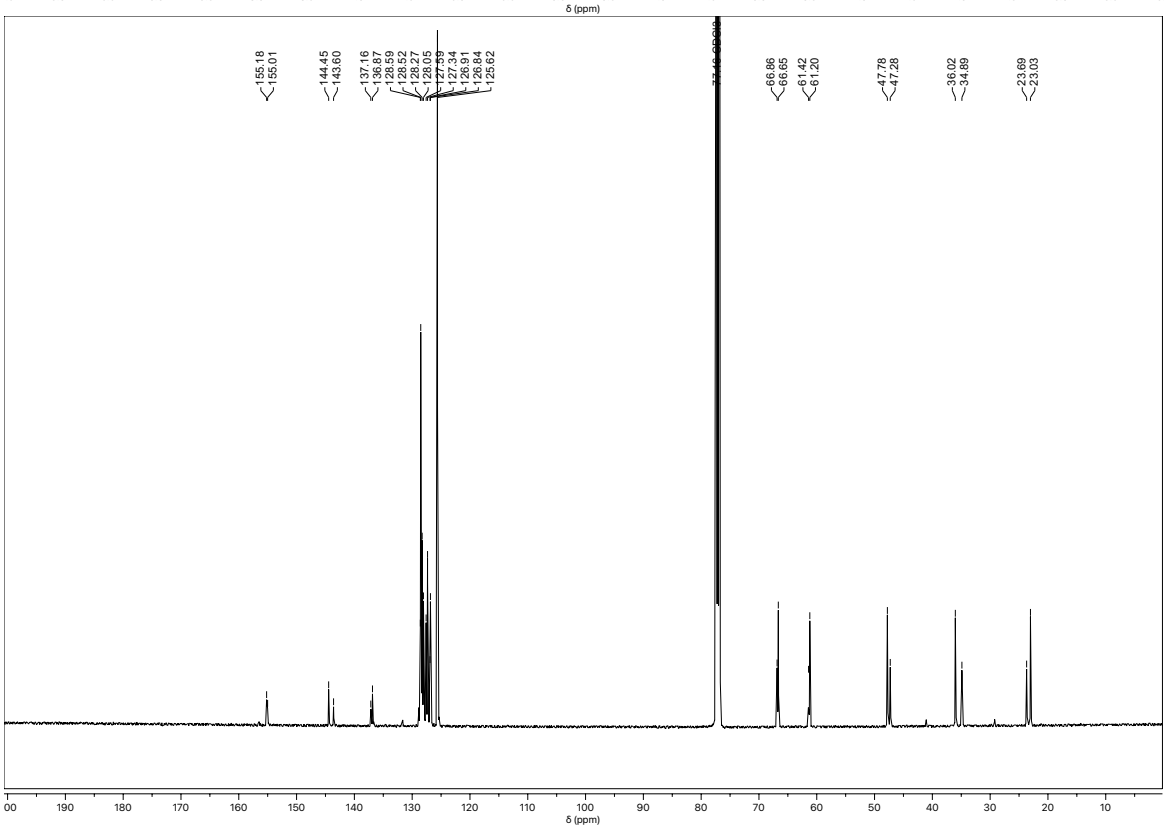



## 10.5. Annulation products

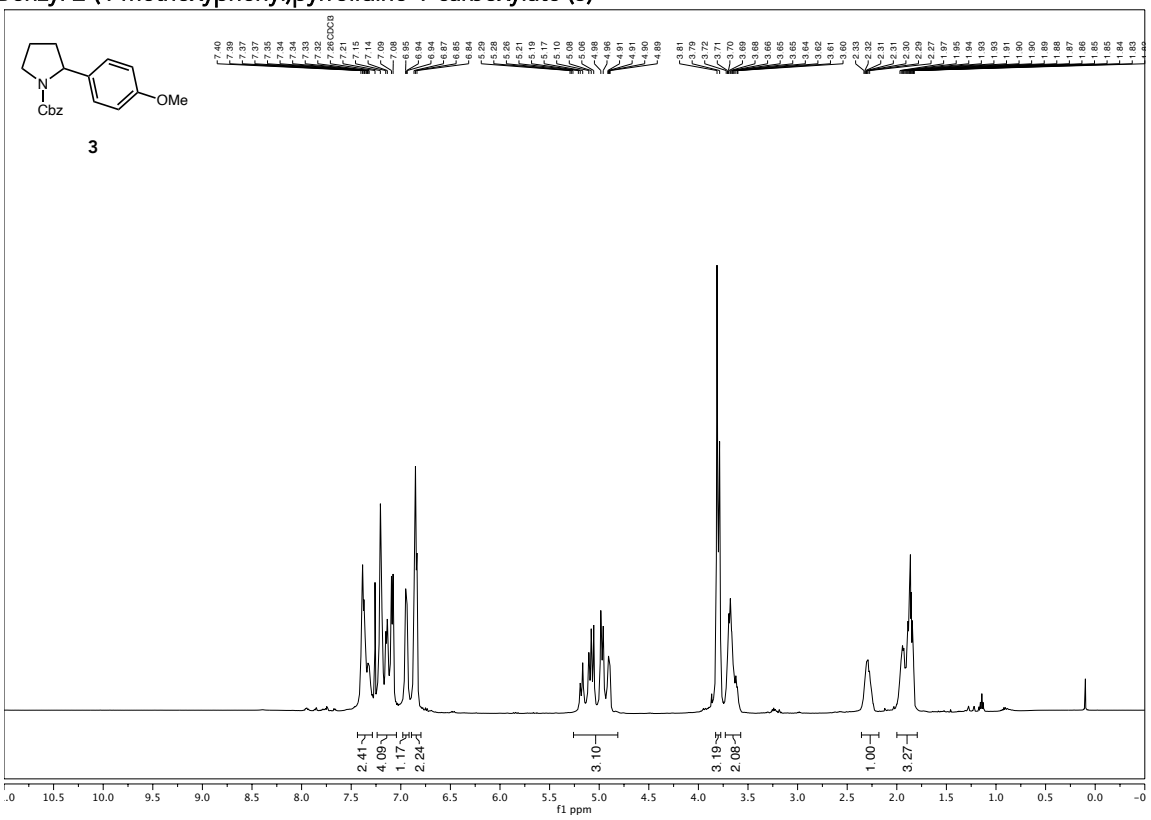
### 10.5.1. Pyrrolidine products

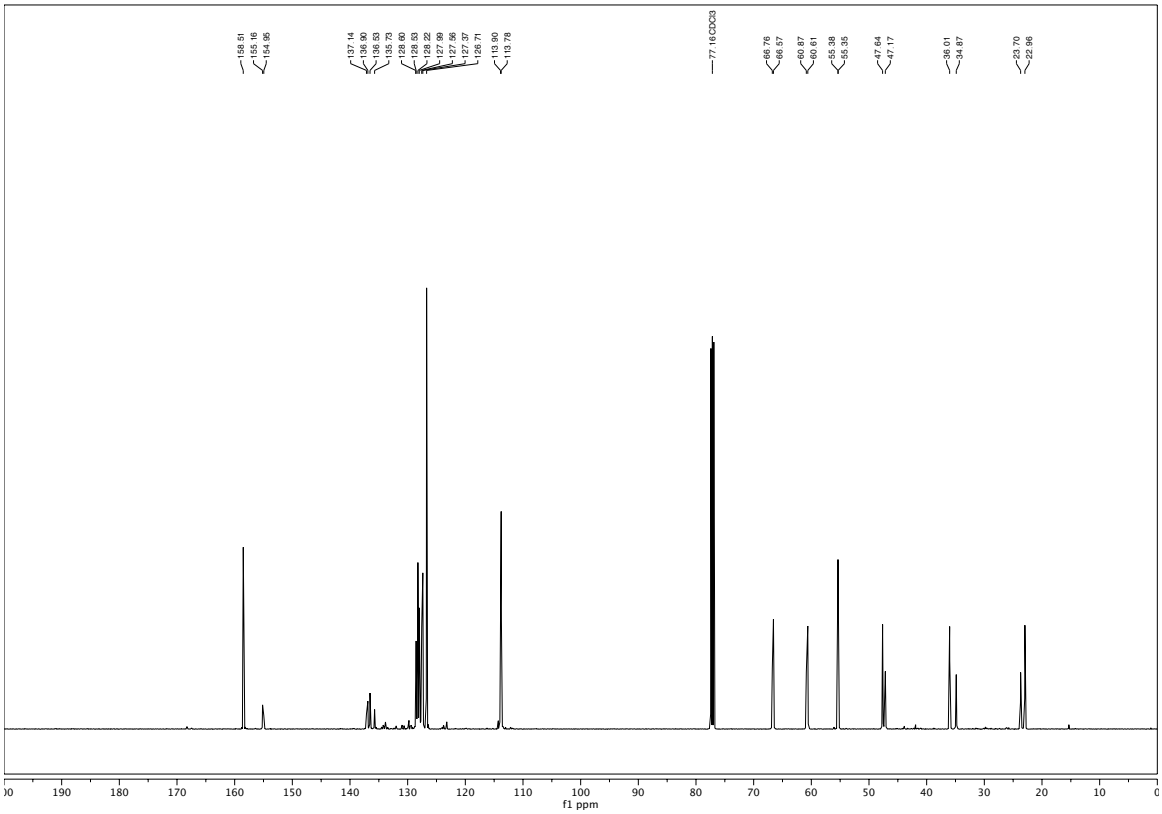
Benzyl 2-phenylpyrrolidine-1-carboxylate (2)



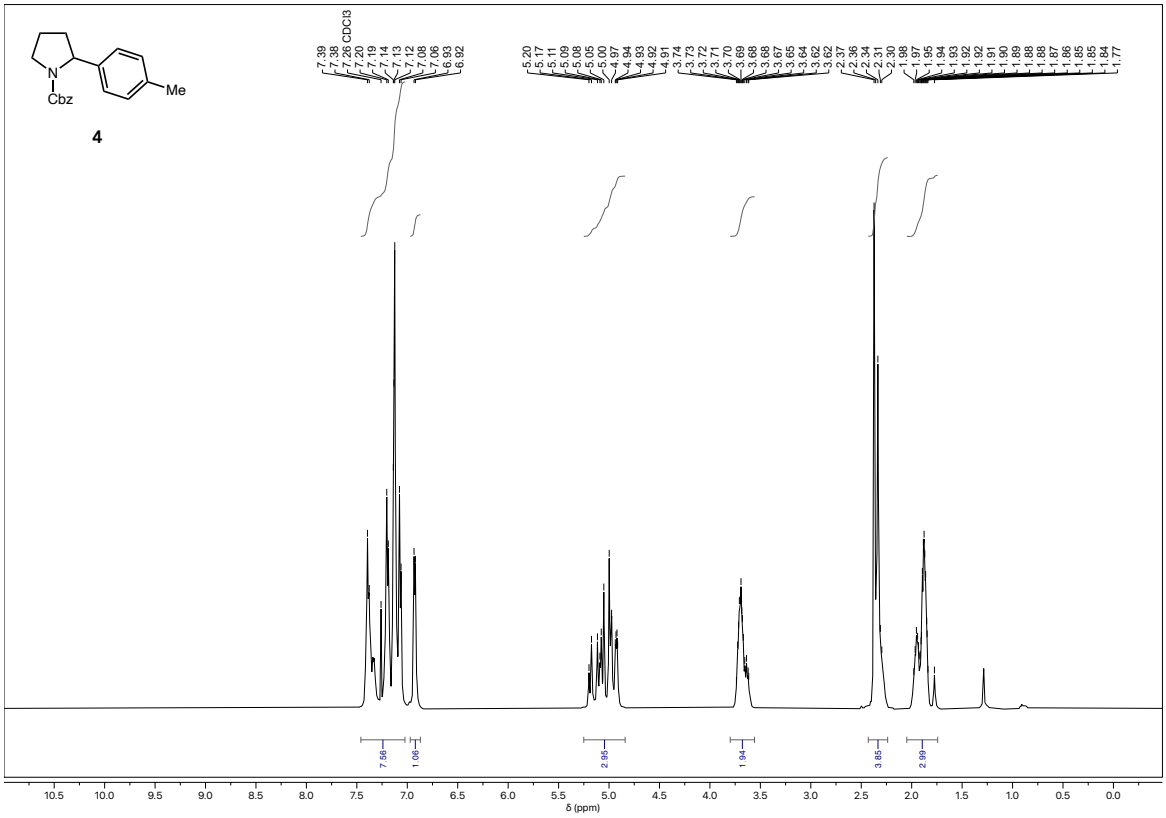



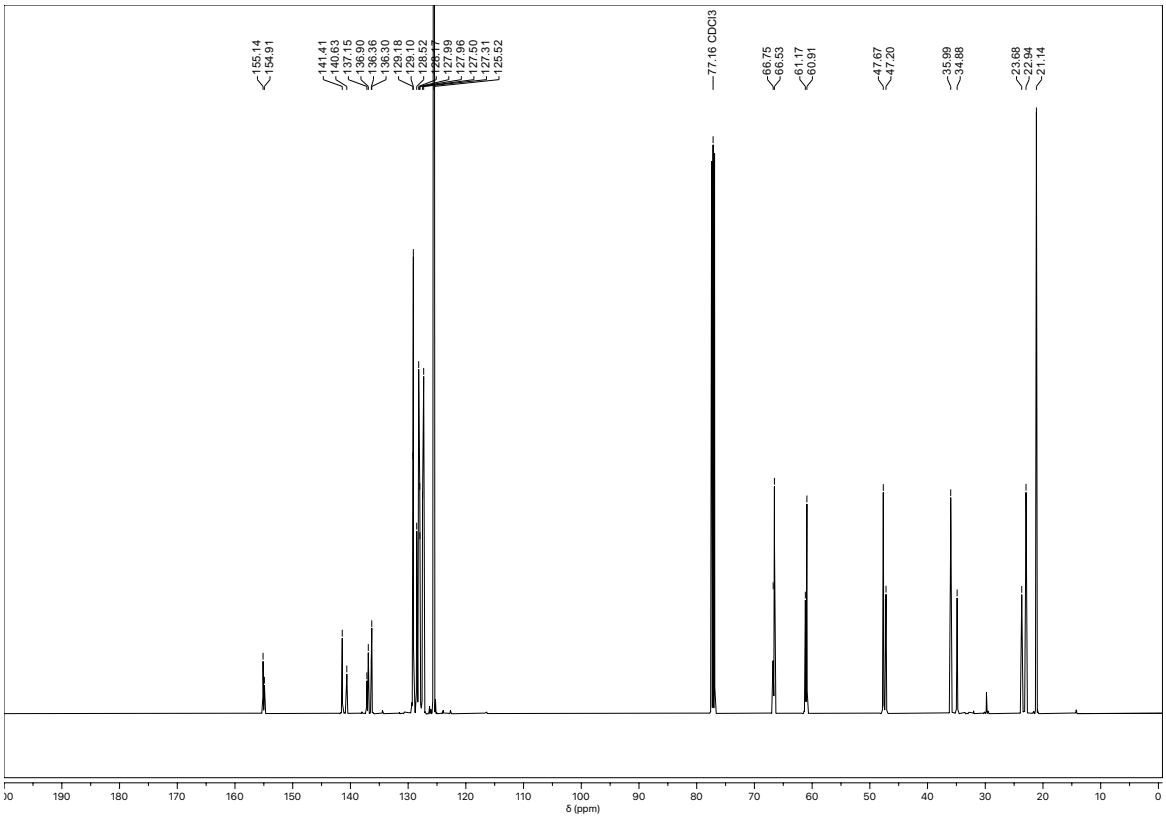
## Benzyl 2-(4-methoxyphenyl)pyrrolidine-1-carboxylate (3)



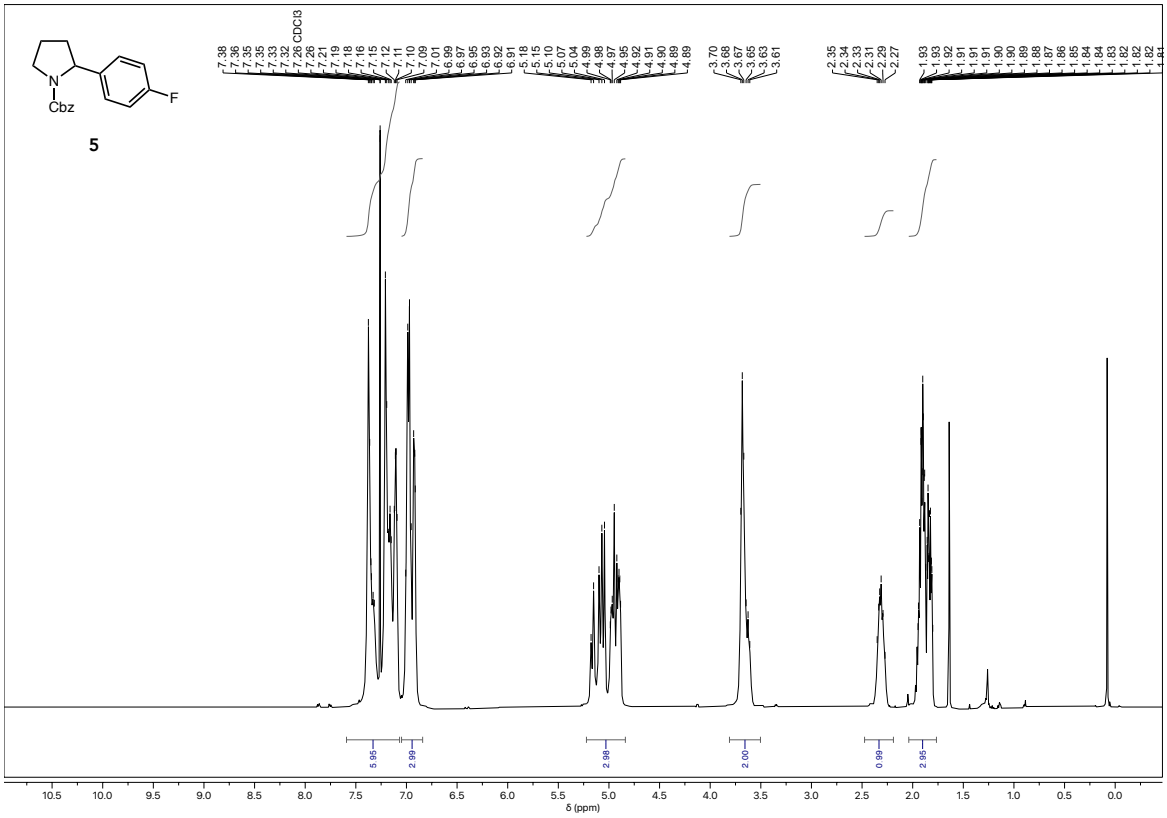



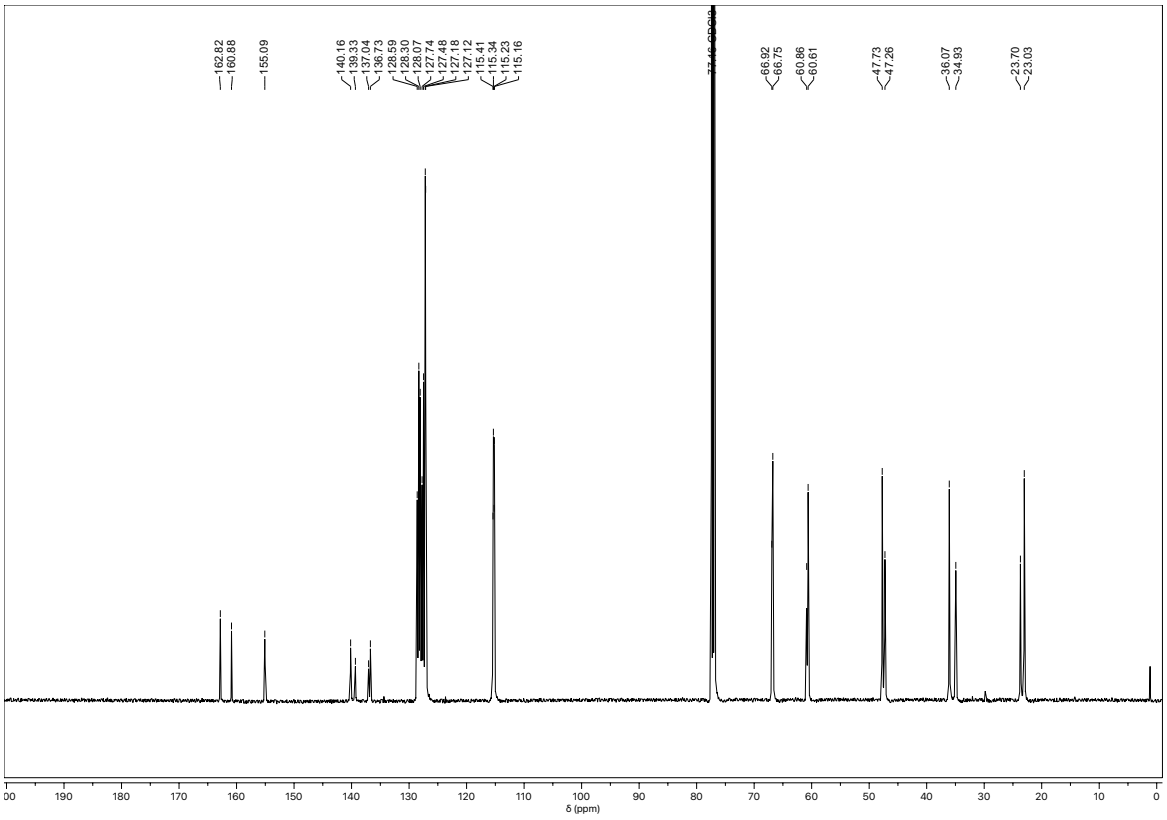
## Benzyl 2-(p-tolyl)pyrrolidine-1-carboxylate (4)

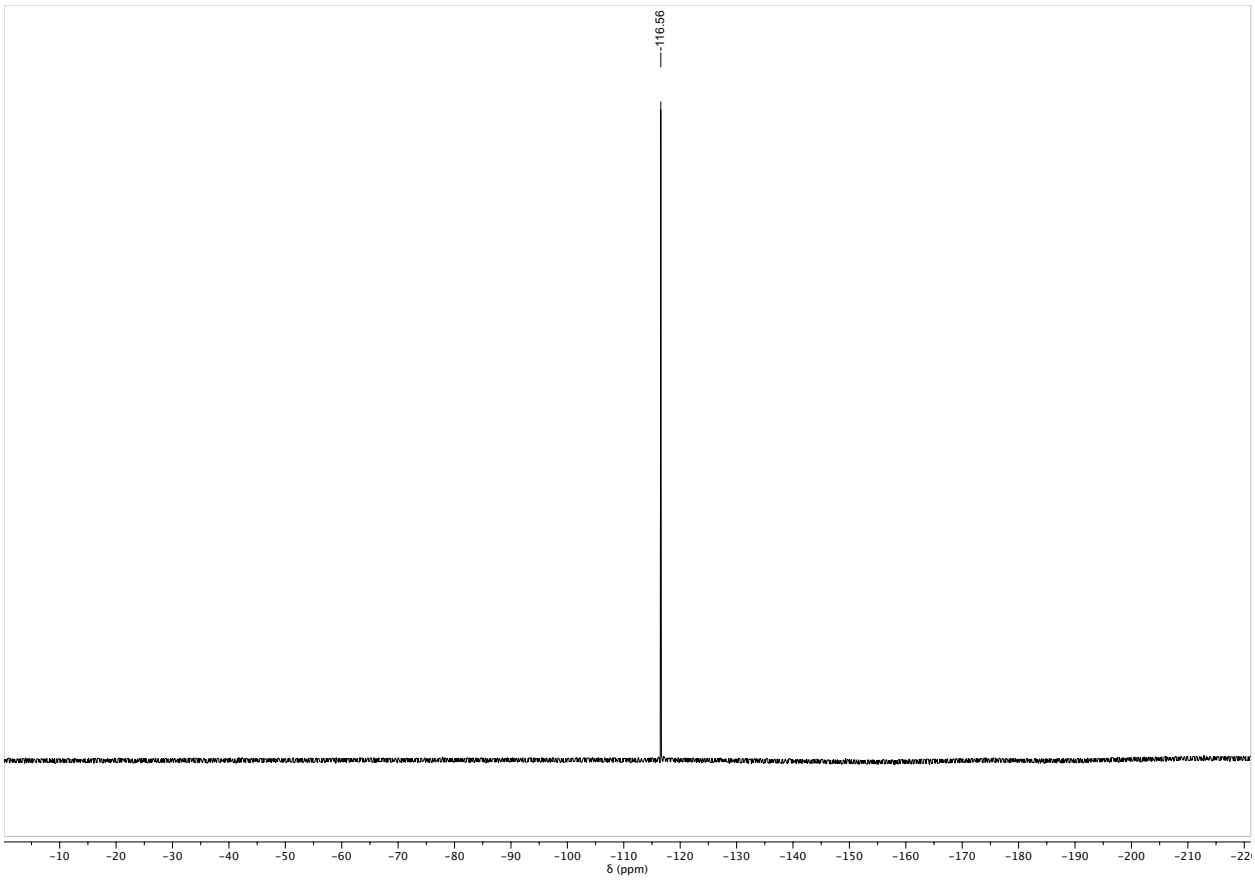


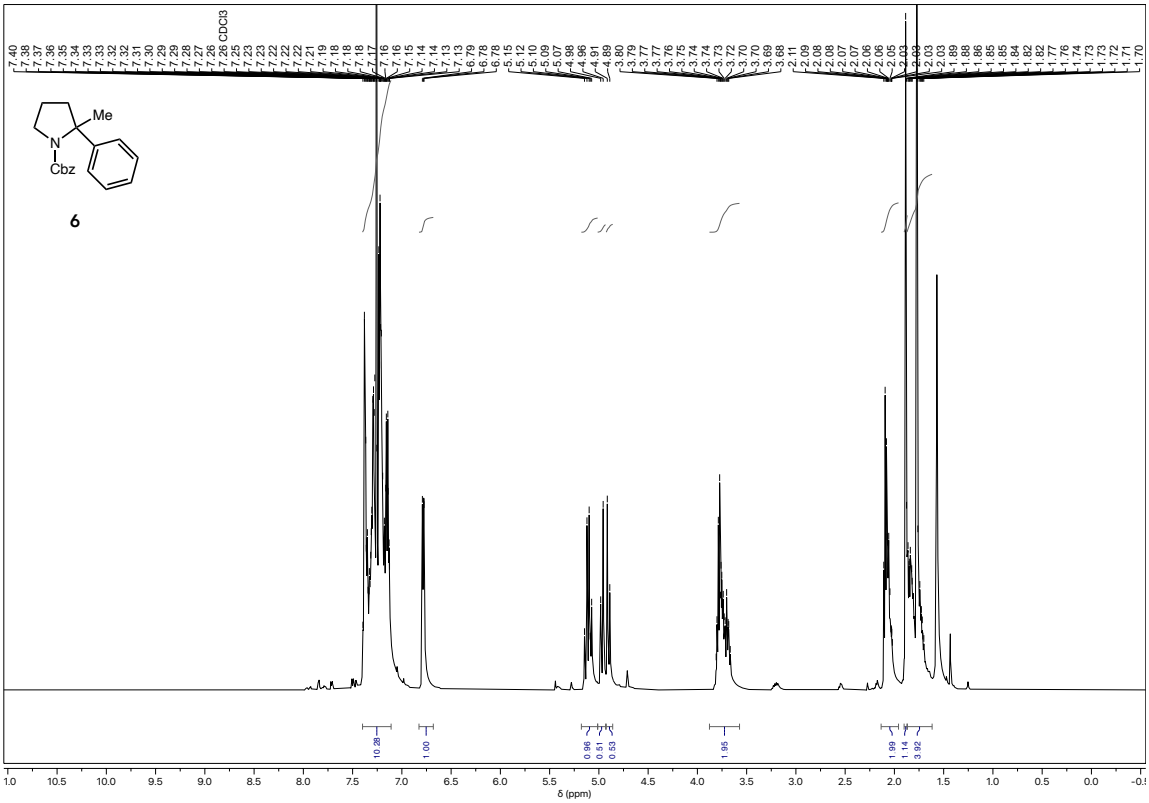
## Benzyl 2-(4-fluorophenyl)pyrrolidine-1-carboxylate (5)

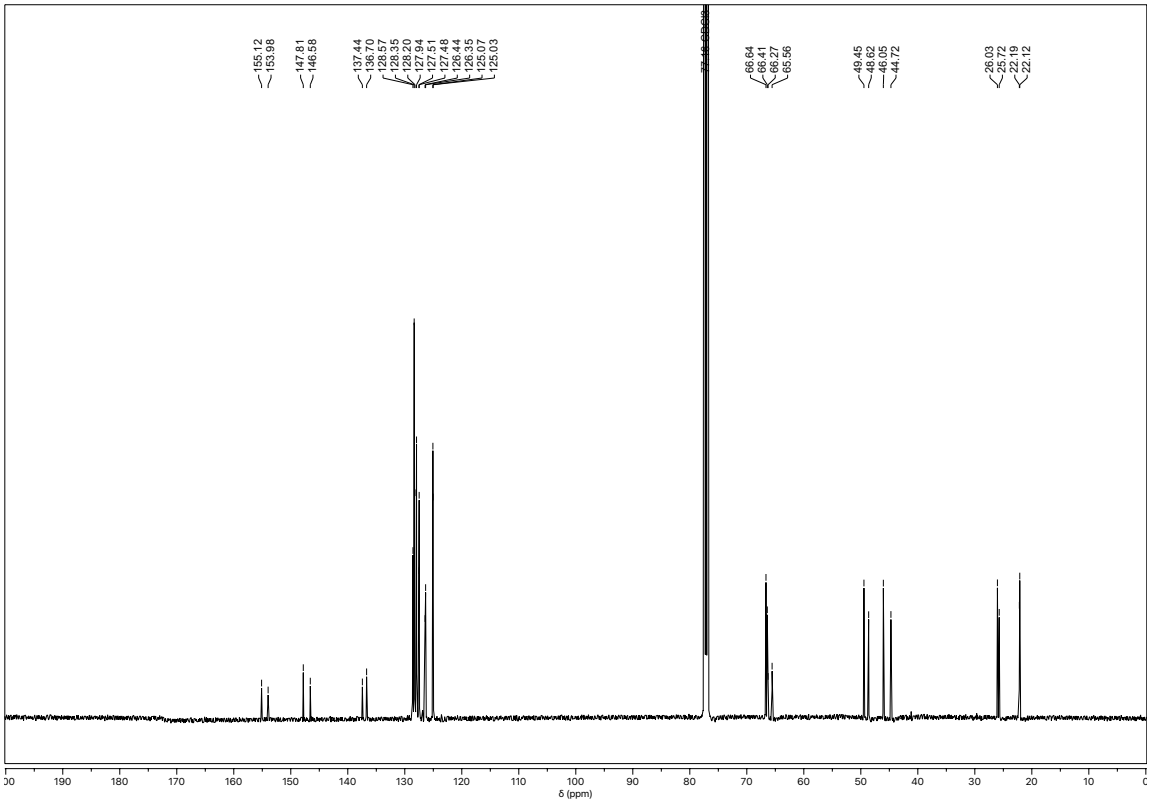


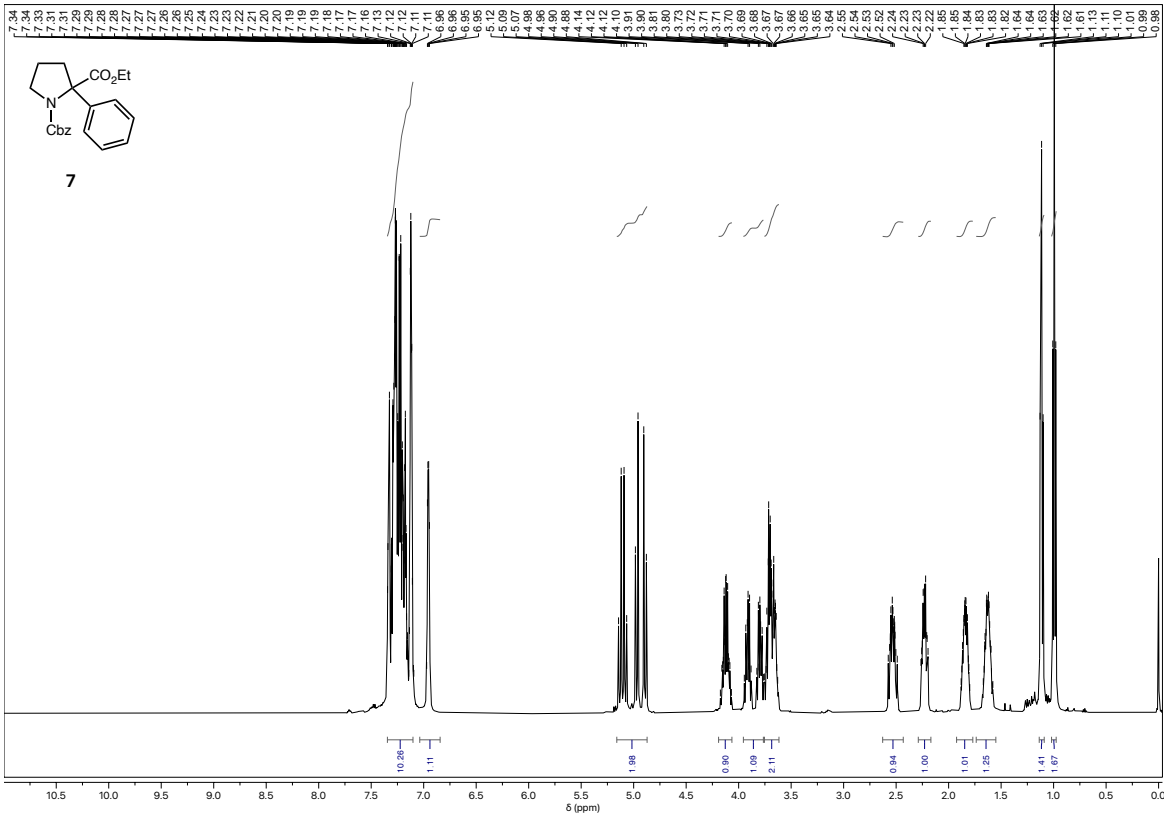

-116.56
−10
−20
−30
−40
−50
−60
−70
−80
−90
−100
−110
−120
−130
−140
−150
−160
−170
−180
−190
−200
−210
δ (ppm)

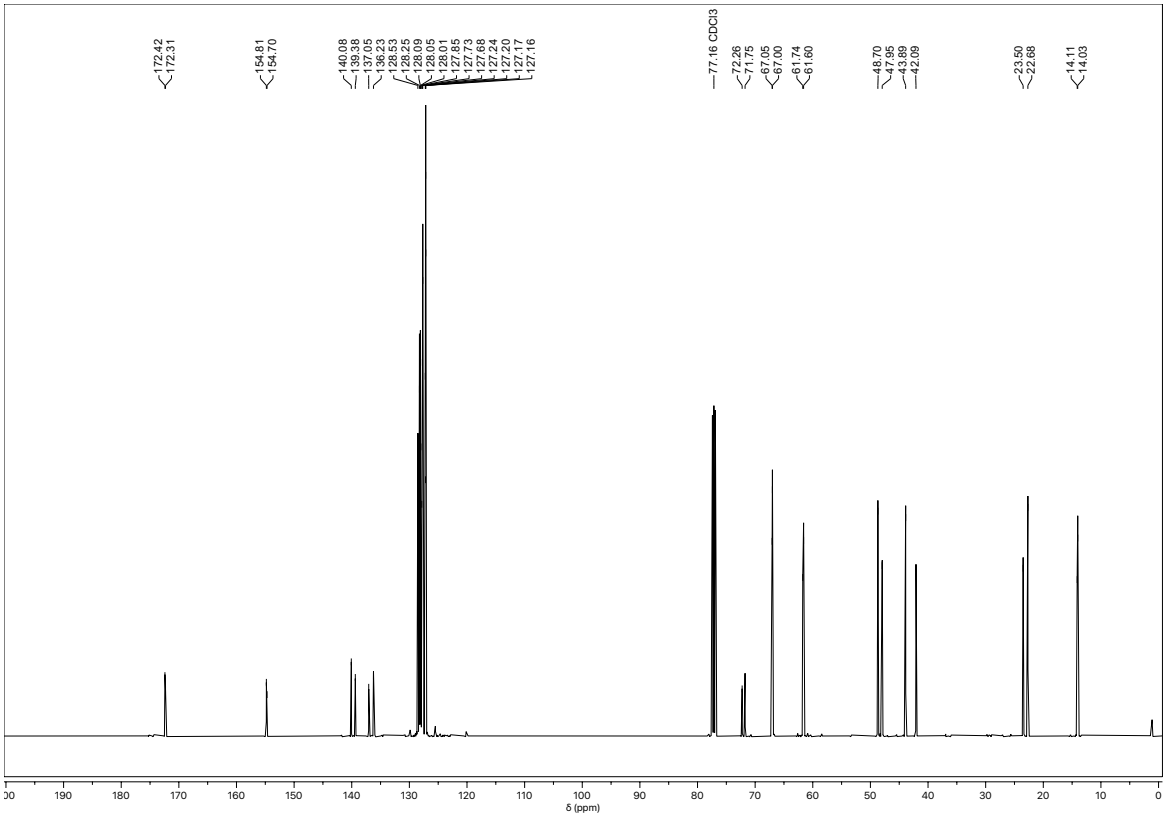
## Benzyl 2-methyl-2-phenylpyrrolidine-1-carboxylate (6)



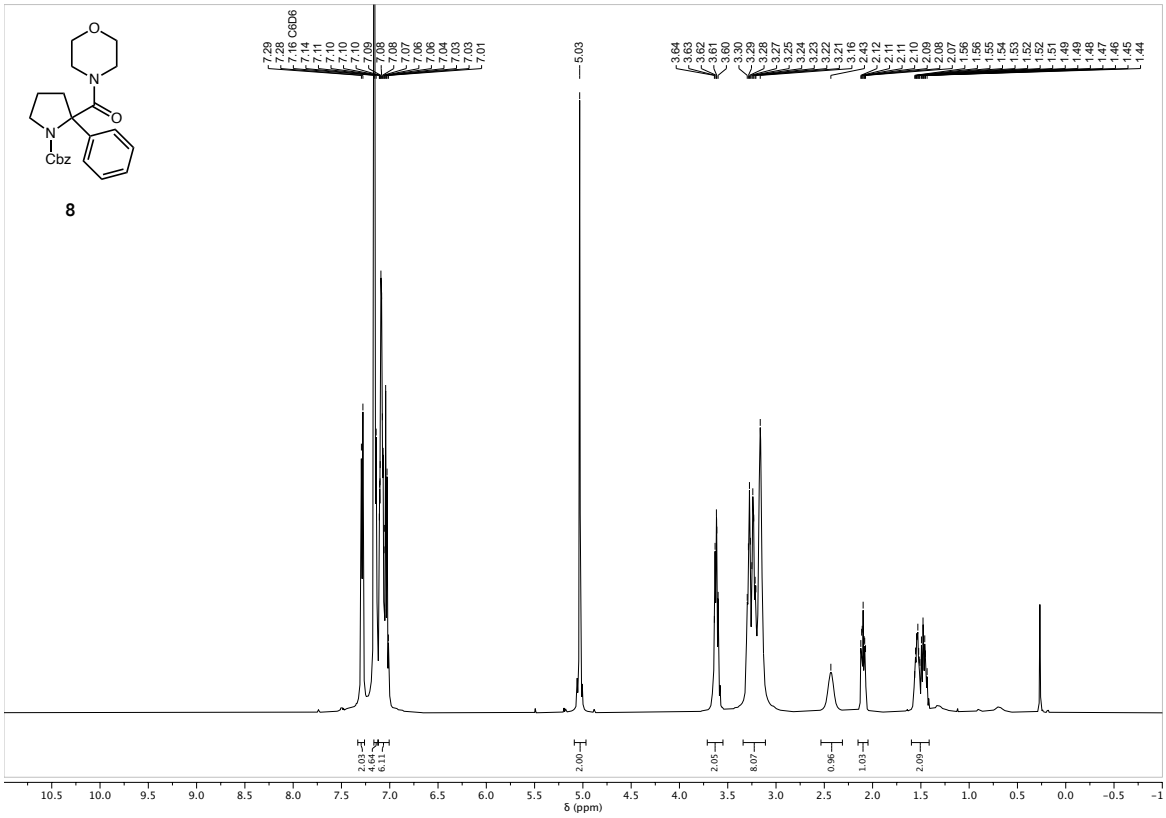



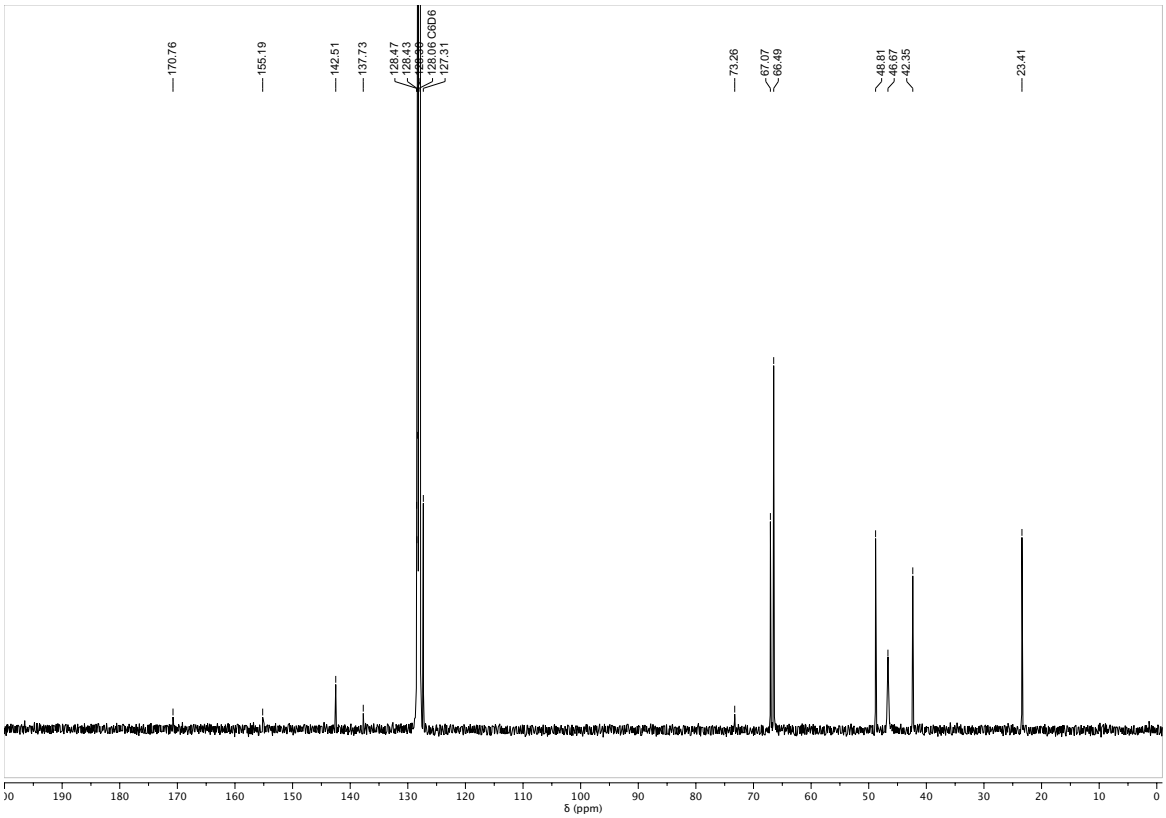
## 1-Benzyl 2-ethyl 2-phenylpyrrolidine-1,2-dicarboxylate (7)



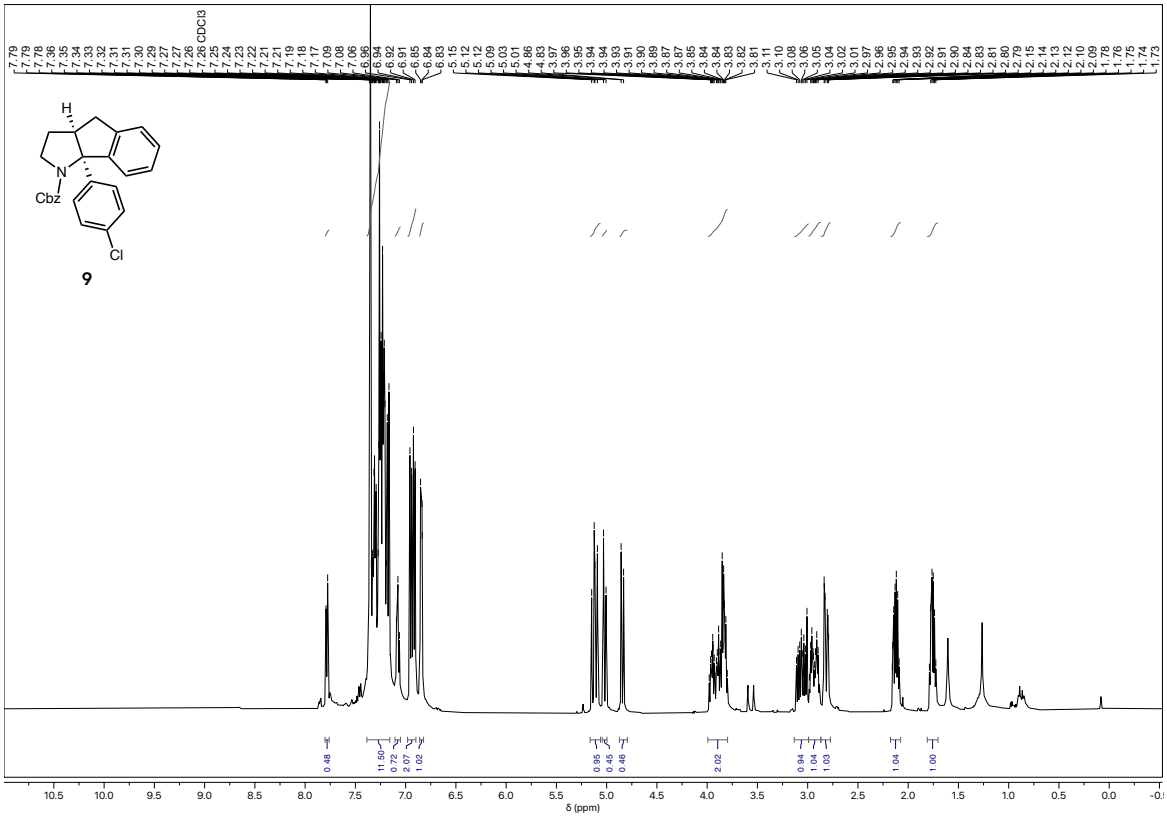



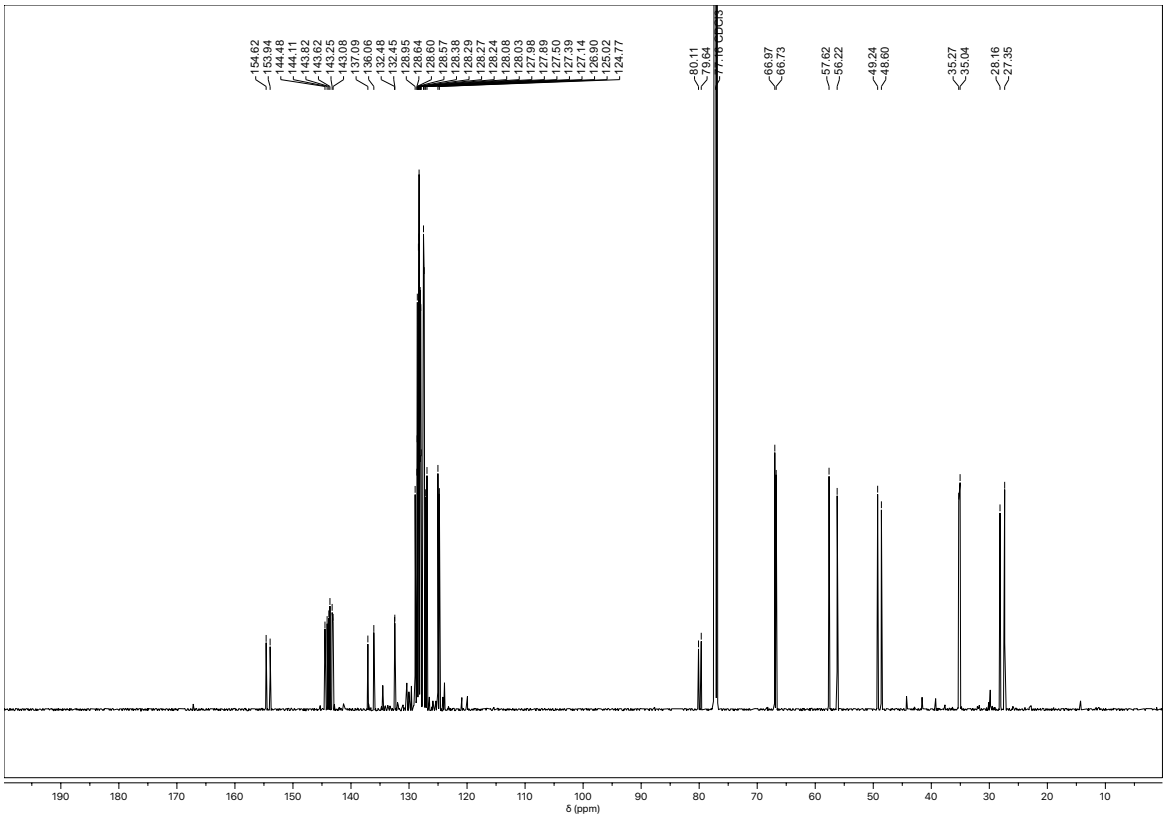
## Benzyl 2-(morpholine-4-carbonyl)-2-phenylpyrrolidine-1-carboxylate (8)



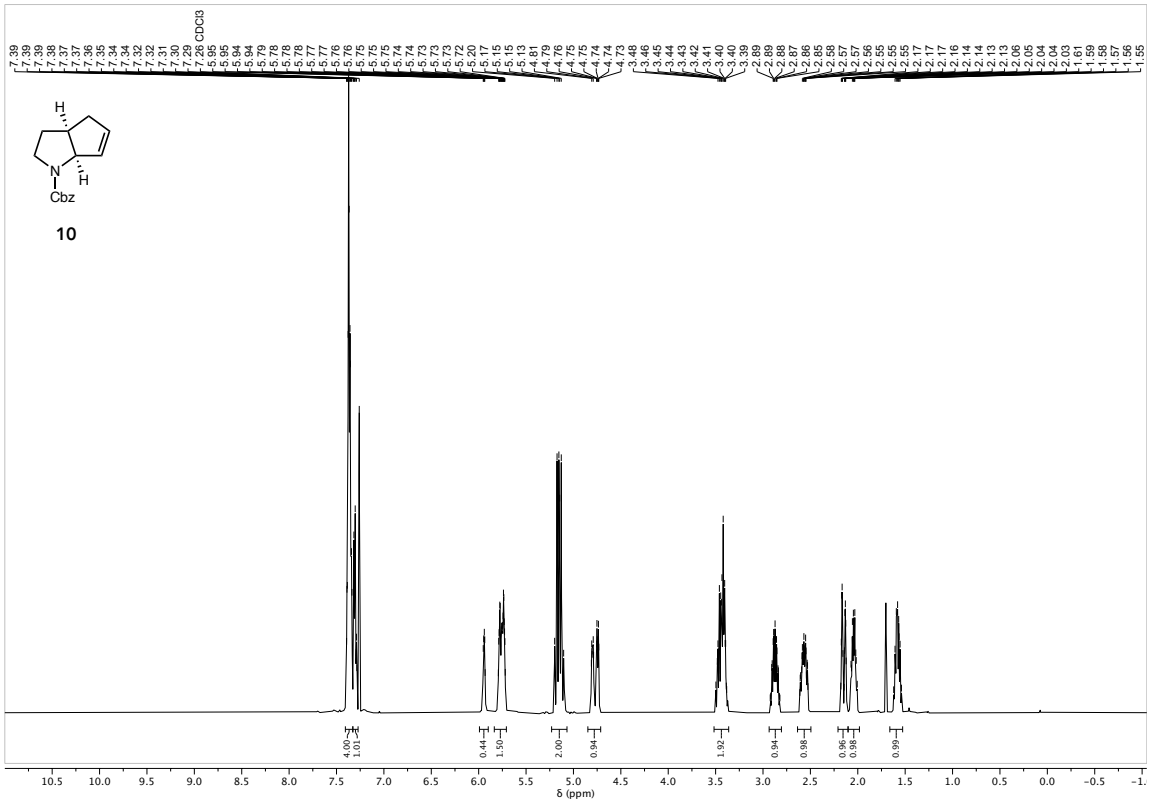



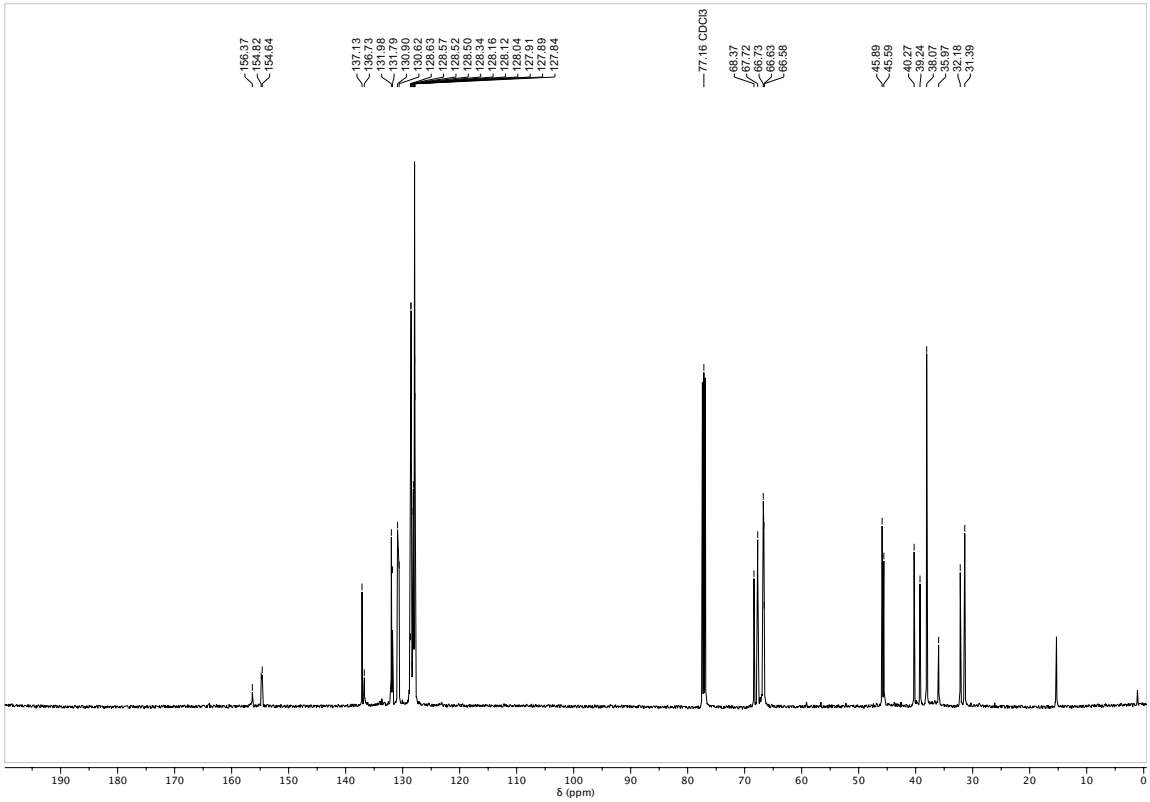
Benzyl (3a*R*,8b*R*)-8b-(4-chlorophenyl)-3,3a,4,8b-tetrahydroindeno[1,2-*b*]pyrrole-1(2*H*)-carboxylate (9)



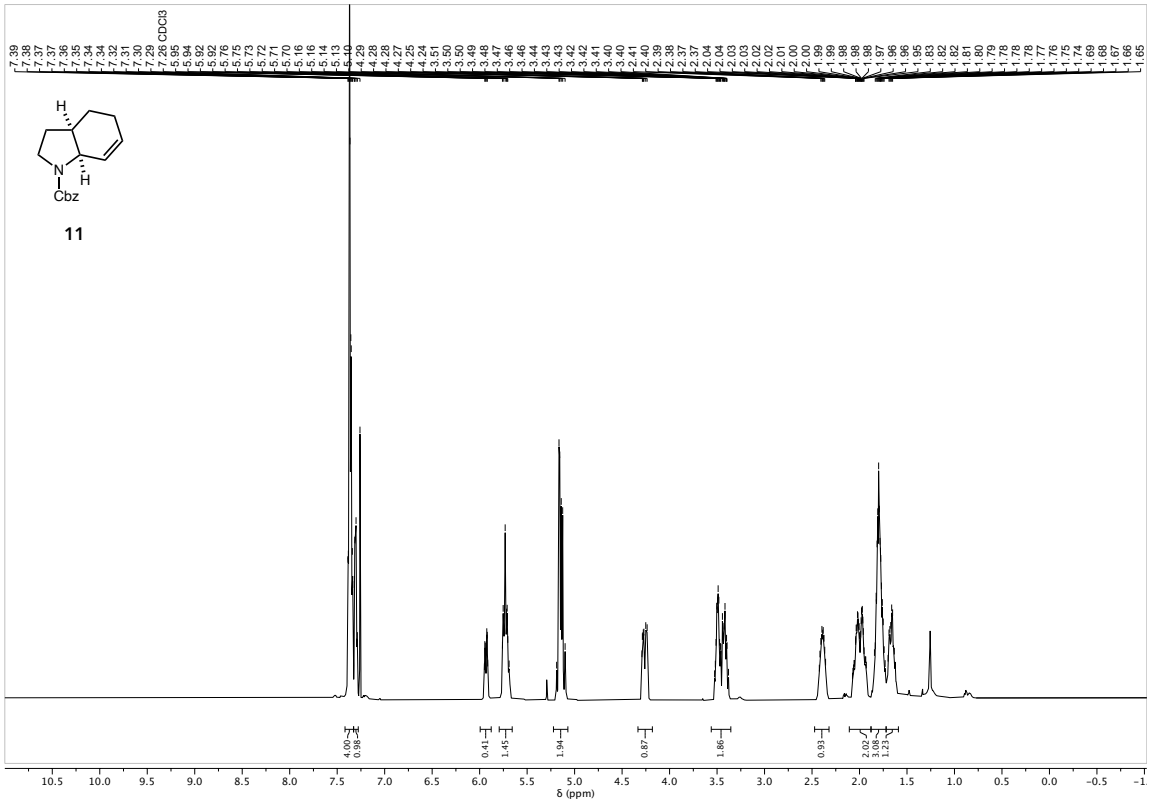



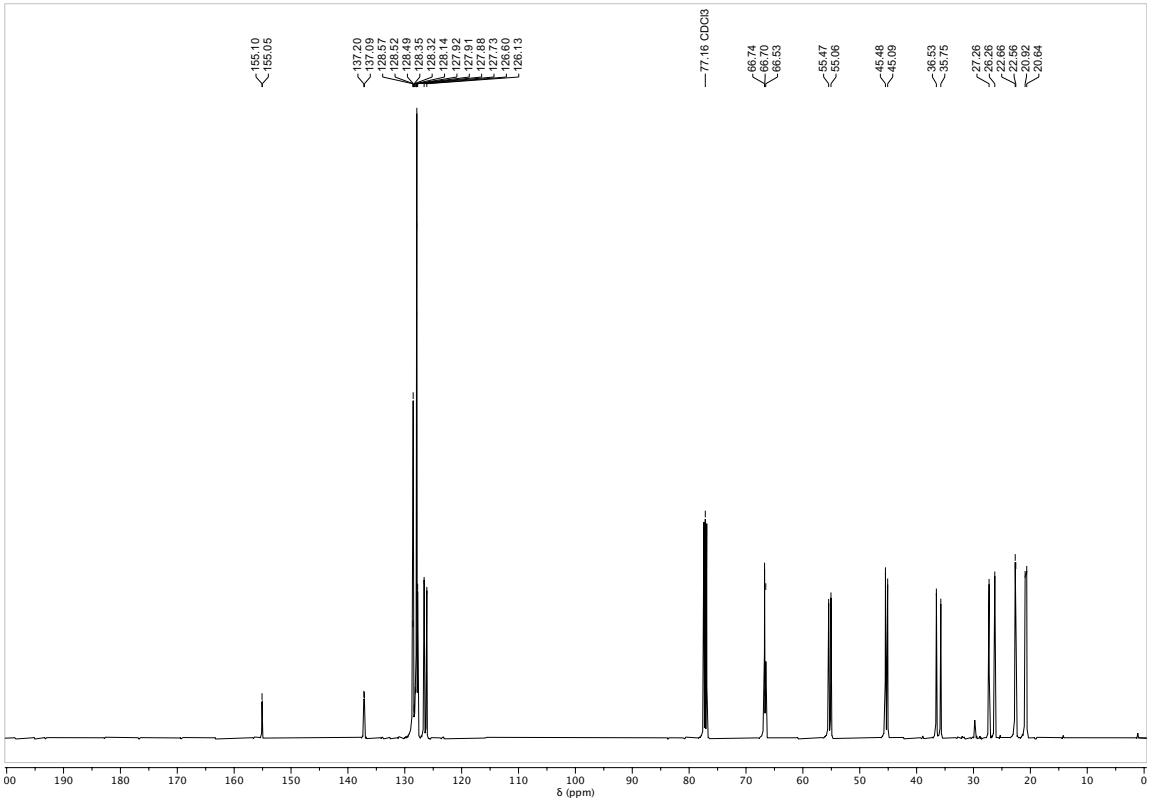
Benzyl (3aR,6aS)-3,3a,4,6a-tetrahydrocyclopenta[*b*]pyrrole-1(2*H*)-carboxylate (10)



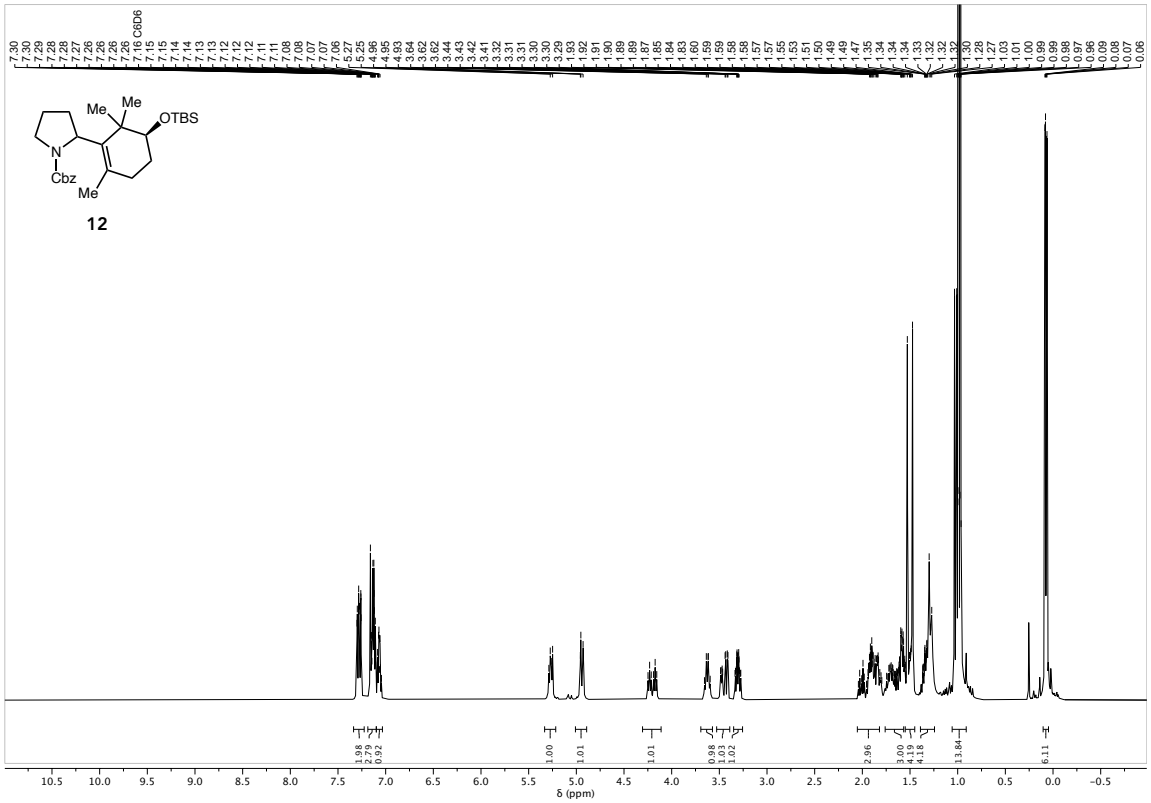



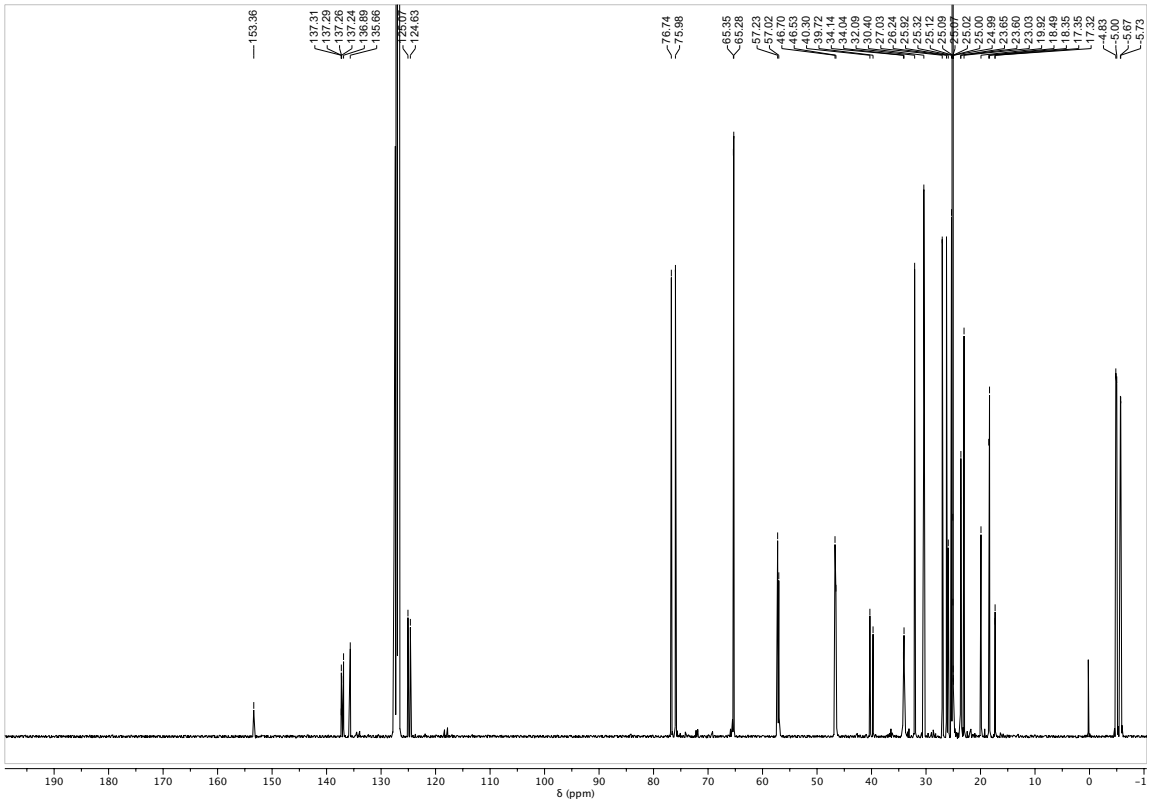
Benzyl (3a*R*,7a*S*)-2,3,3a,4,5,7a-hexahydro-1*H*-indole-1-carboxylate (11)



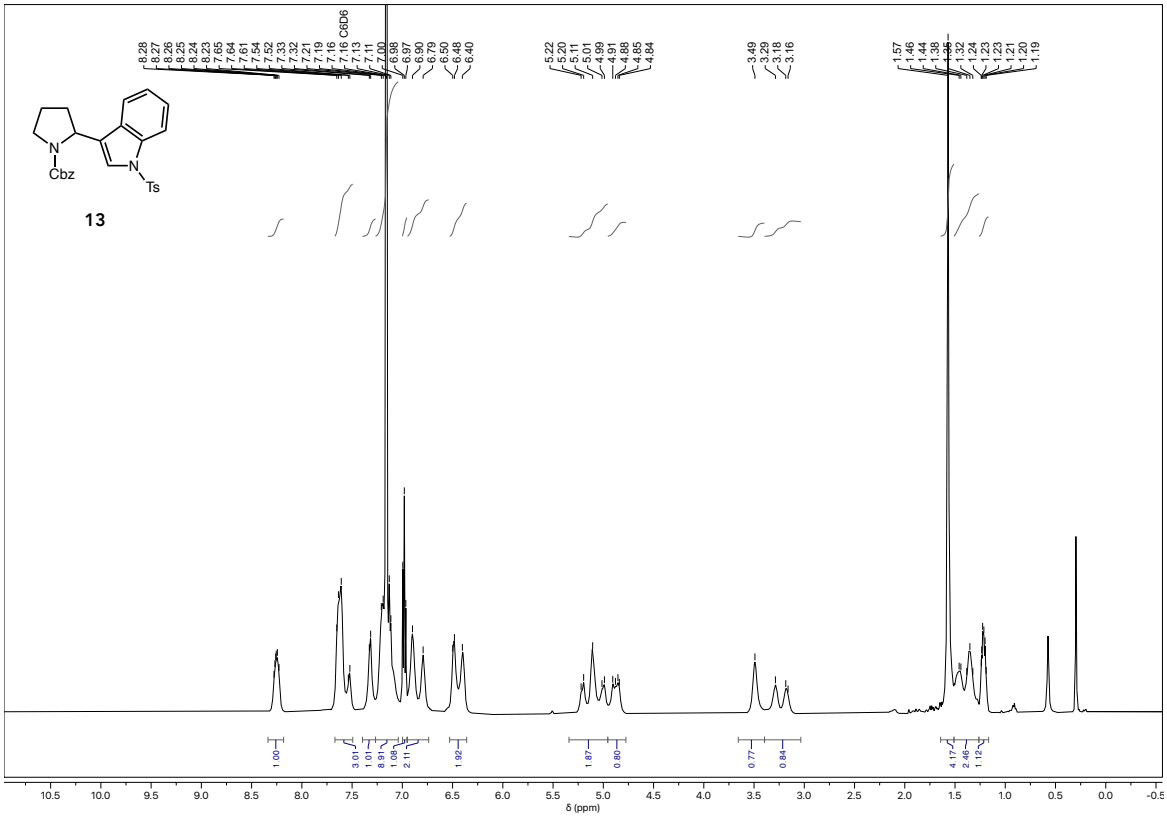



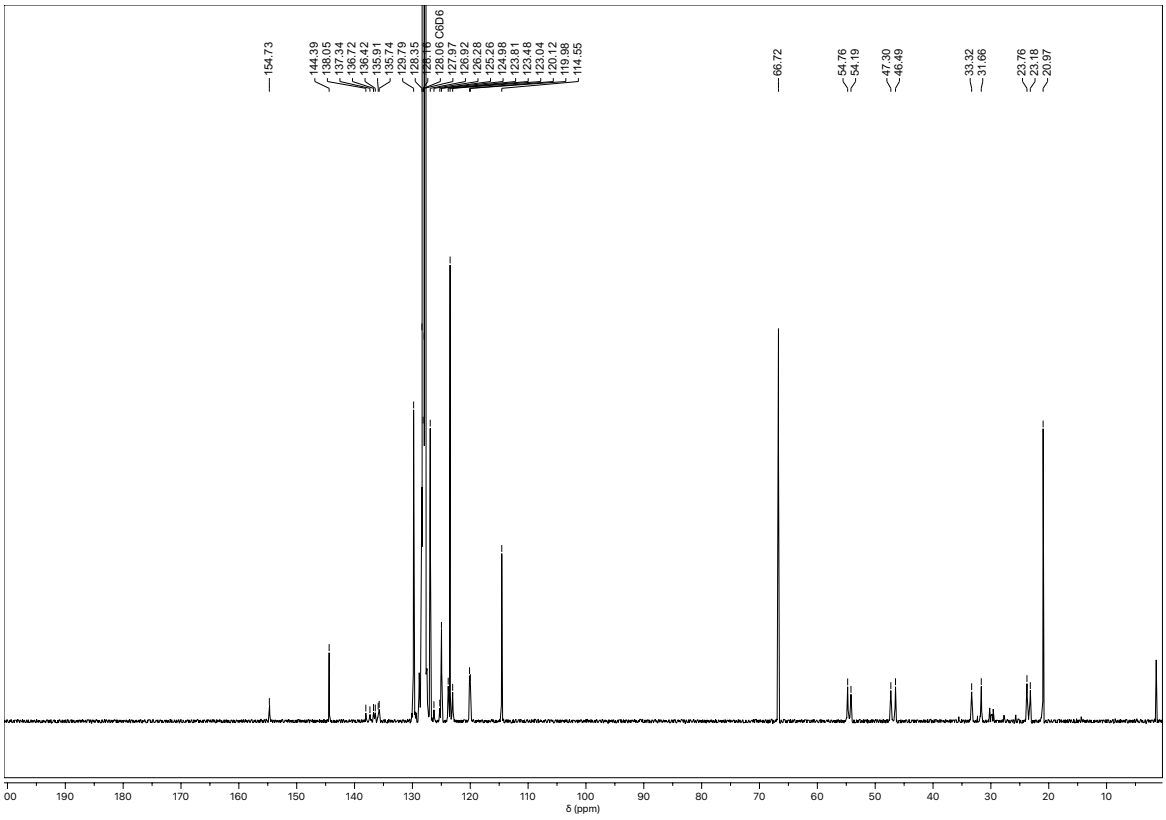
Benzyl 2-((*S*)-5-((*tert*-butyldimethylsilyl)oxy)-2,6,6-trimethylcyclohex-1-en-1-yl)pyrrolidine-1-carboxylate (12)



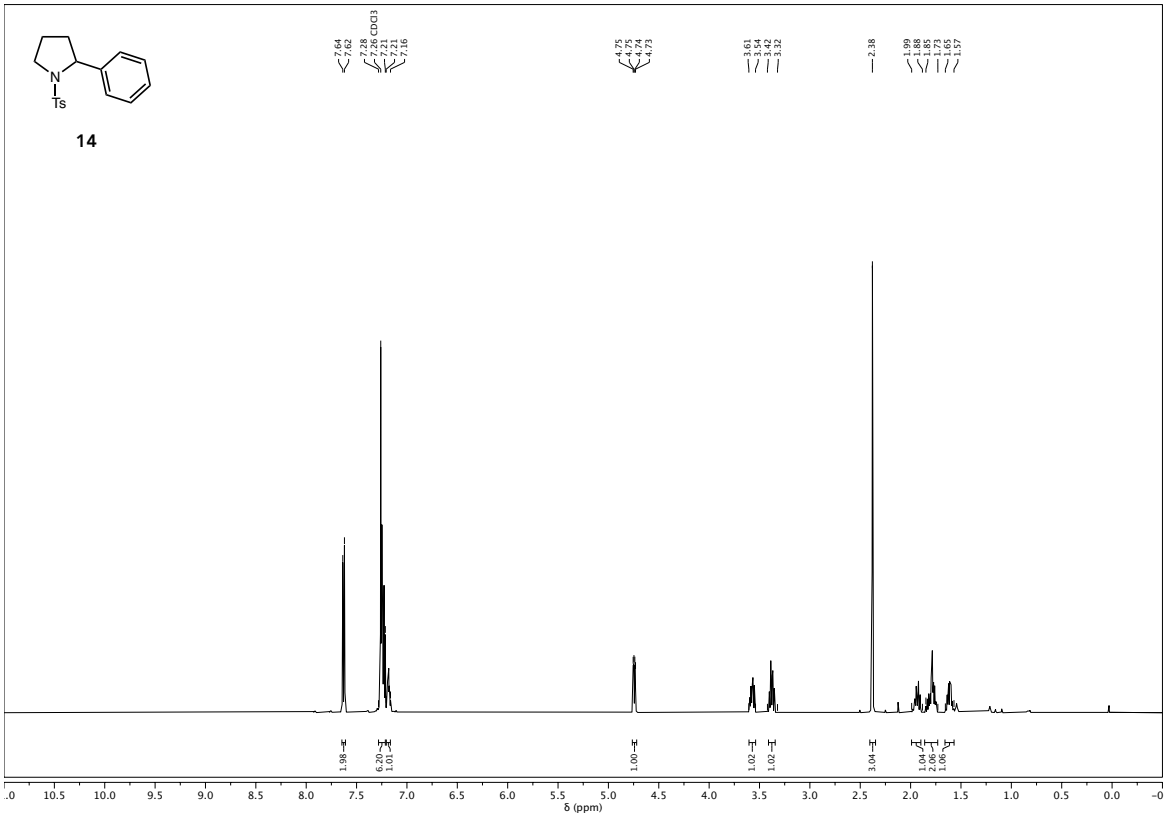



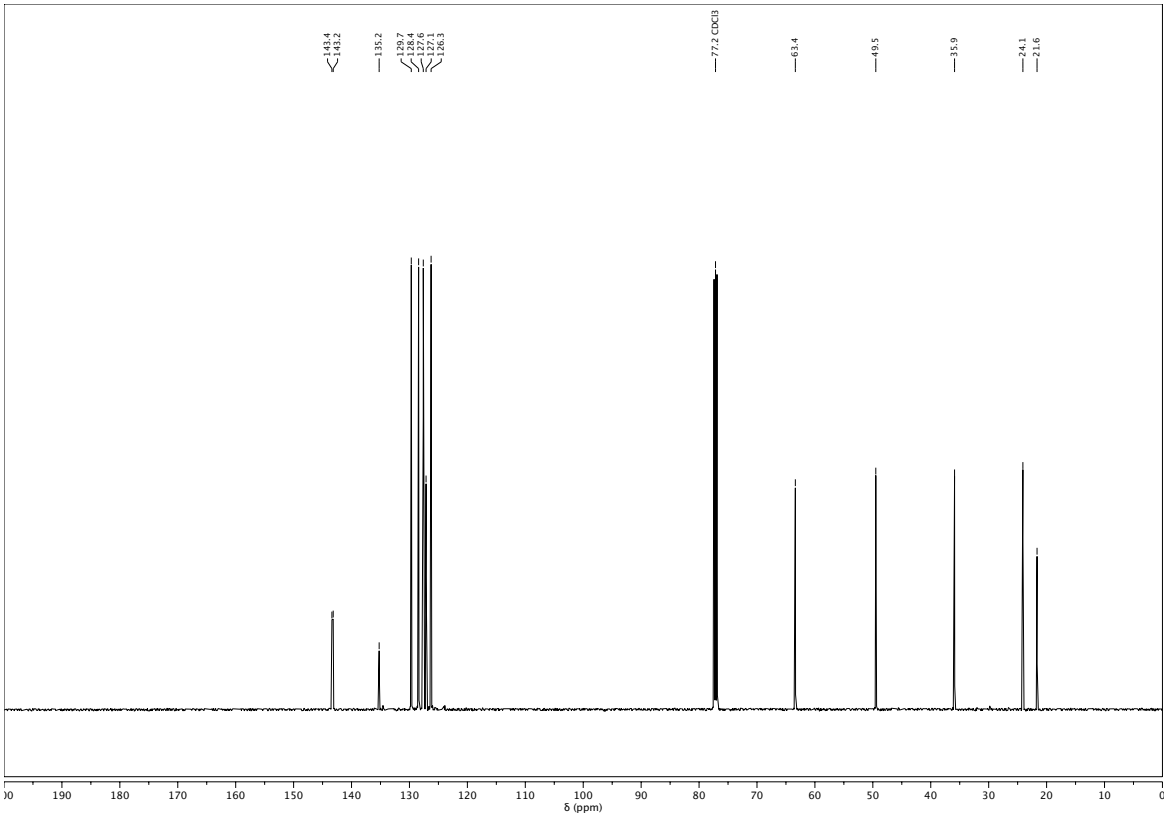
Benzyl 2-(1-tosyl-1*H*-indol-3-yl)pyrrolidine-1-carboxylate (13)



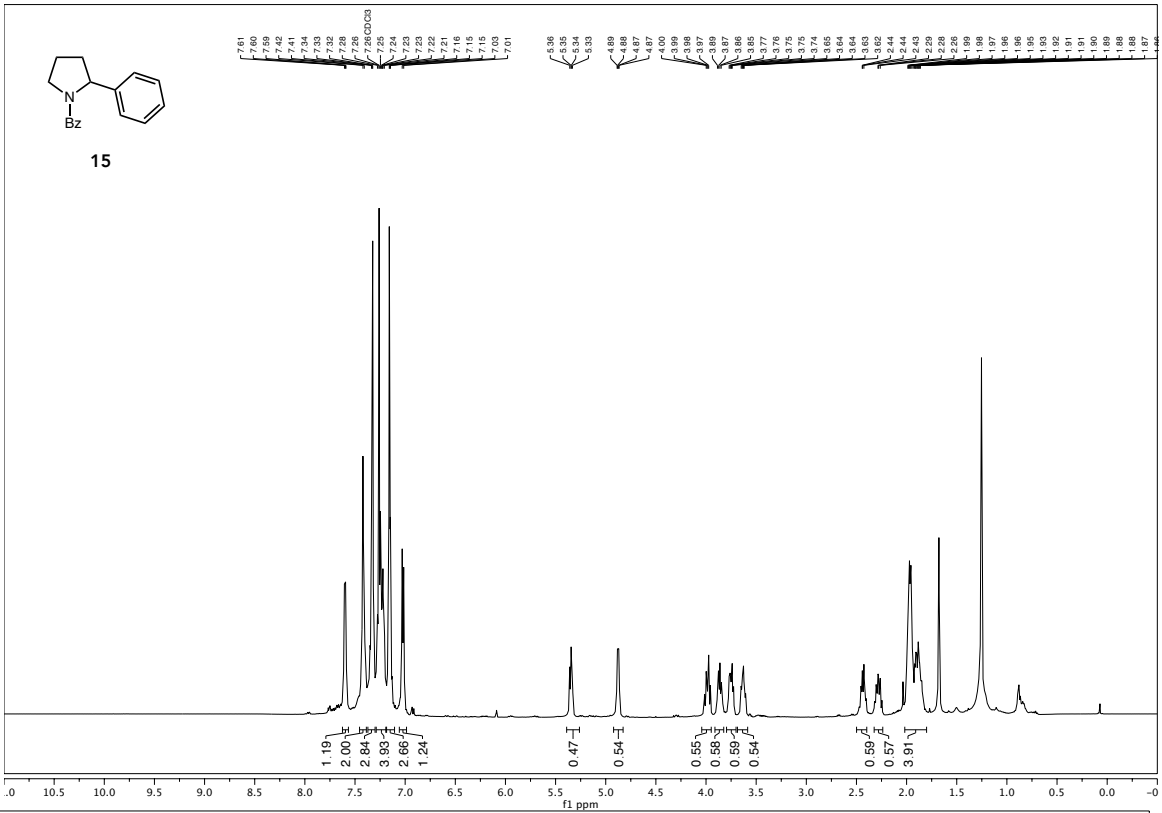



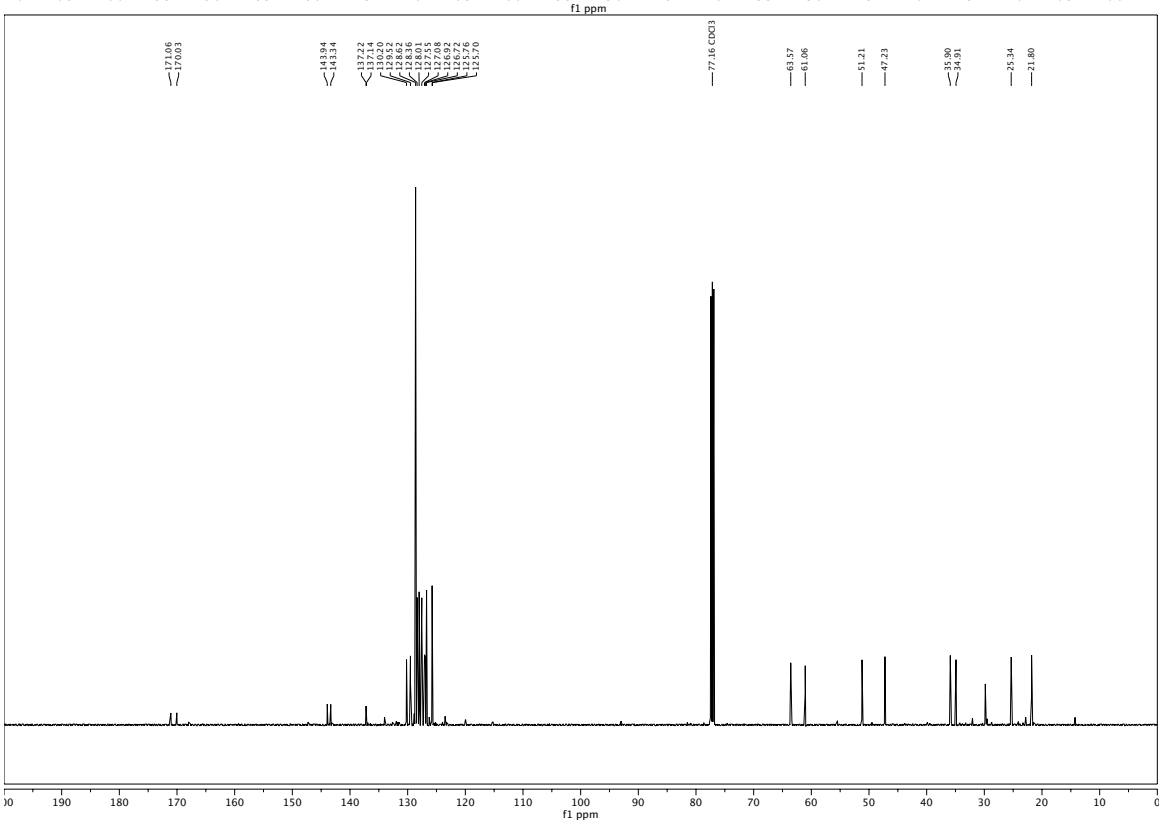
## 2-Phenyl-1-tosylpyrrolidine (14)



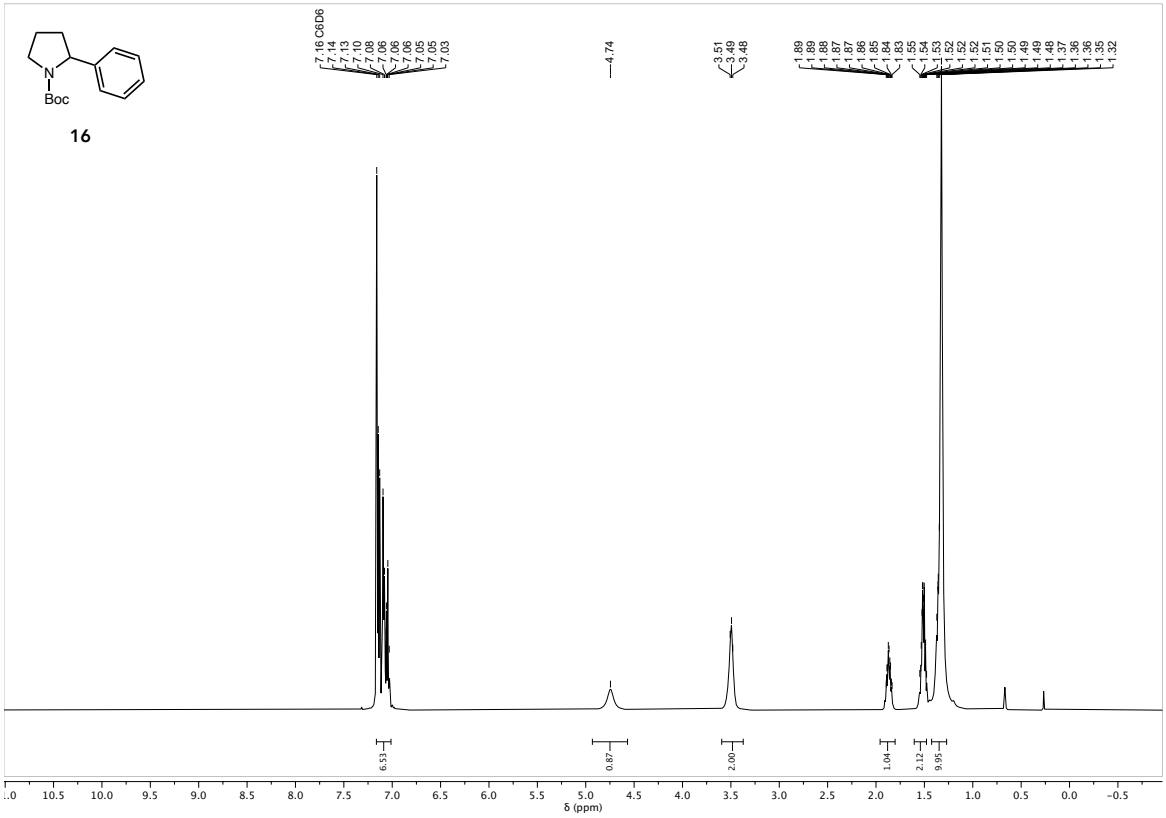



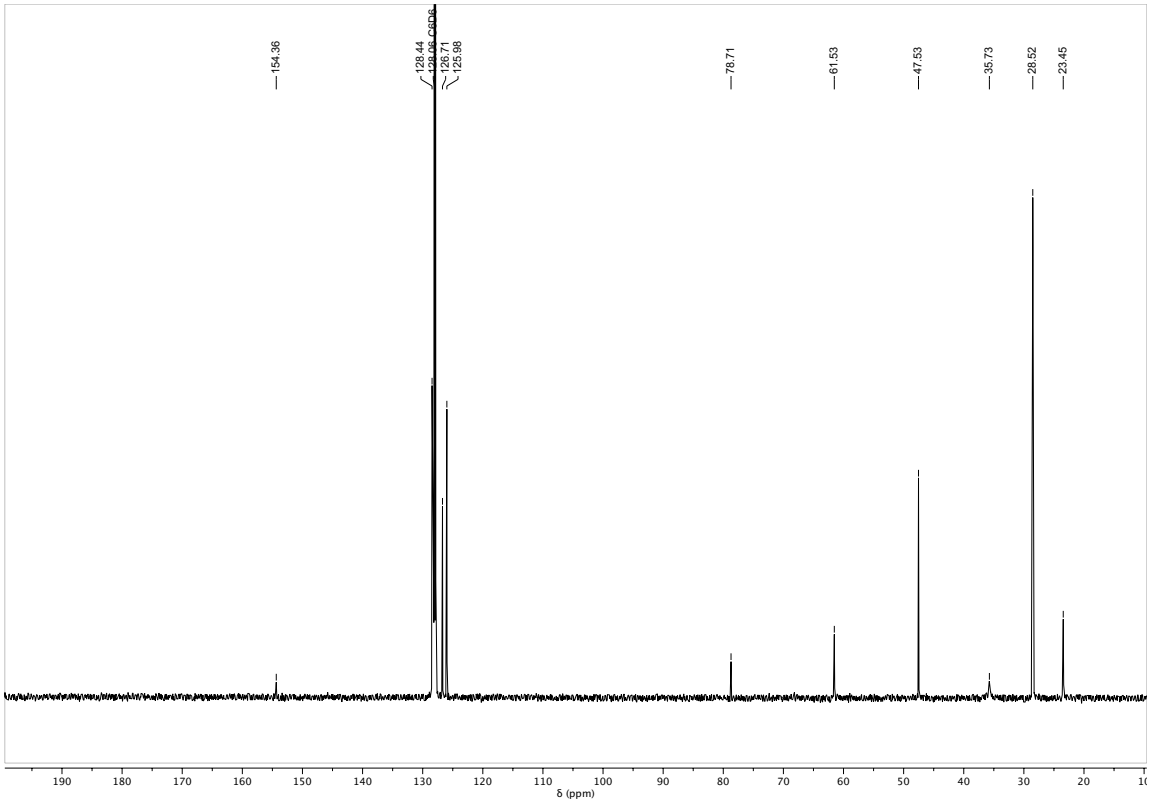
Phenyl(2-phenylpyrrolidin-1-yl)methanone (15)



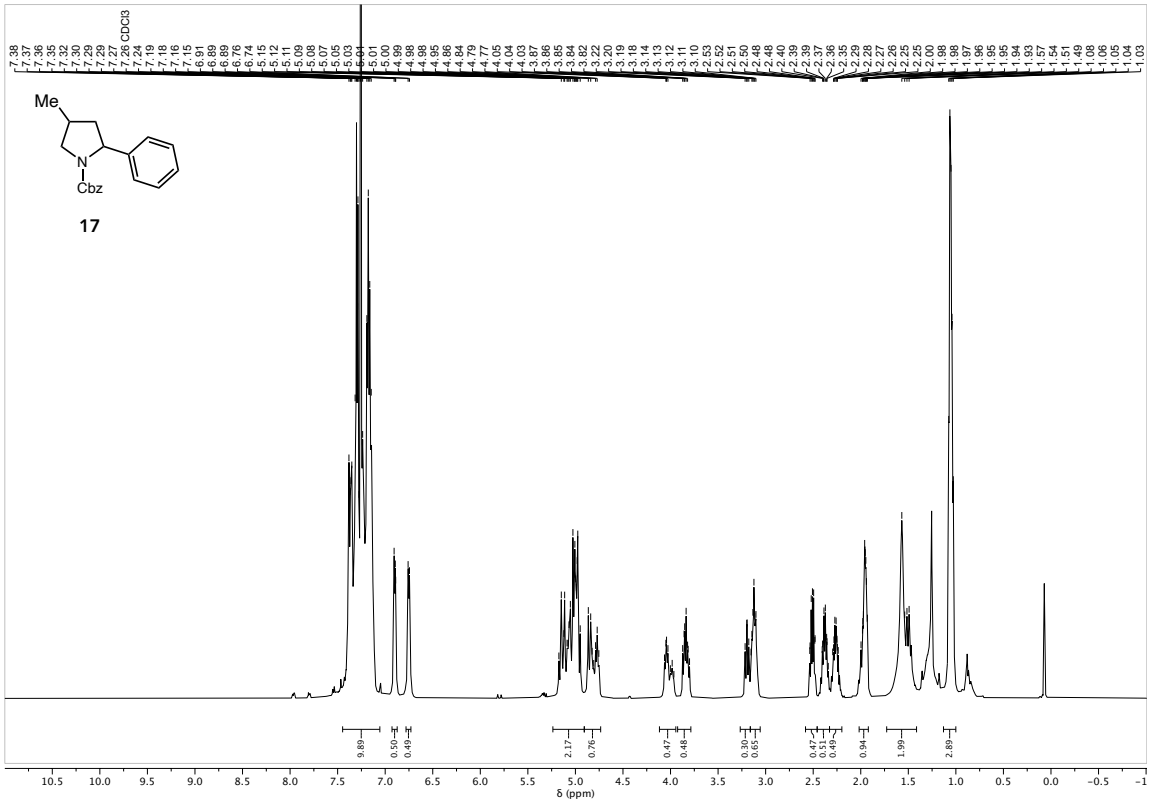

*Tert*-butyl 2-phenylpyrrolidine-1-carboxylate (16)

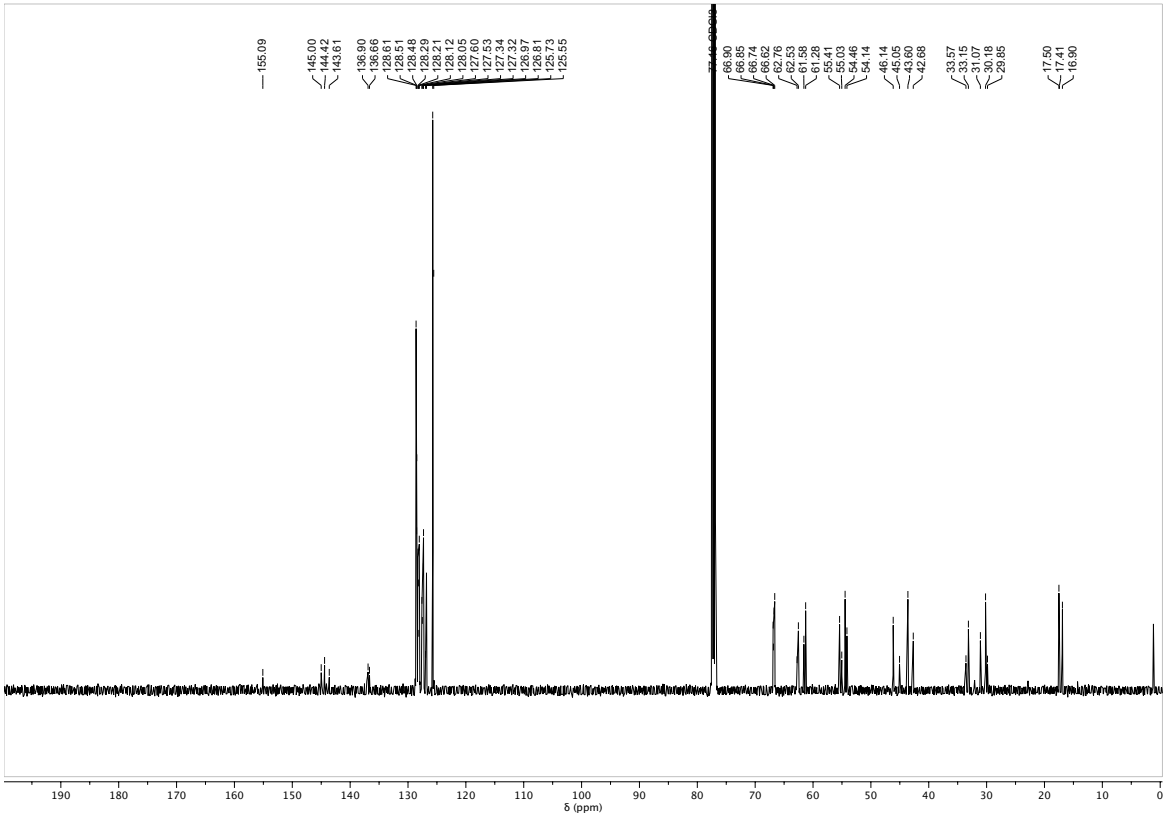



Benzyl 4-methyl-2-phenylpyrrolidine-1-carboxylate (17)

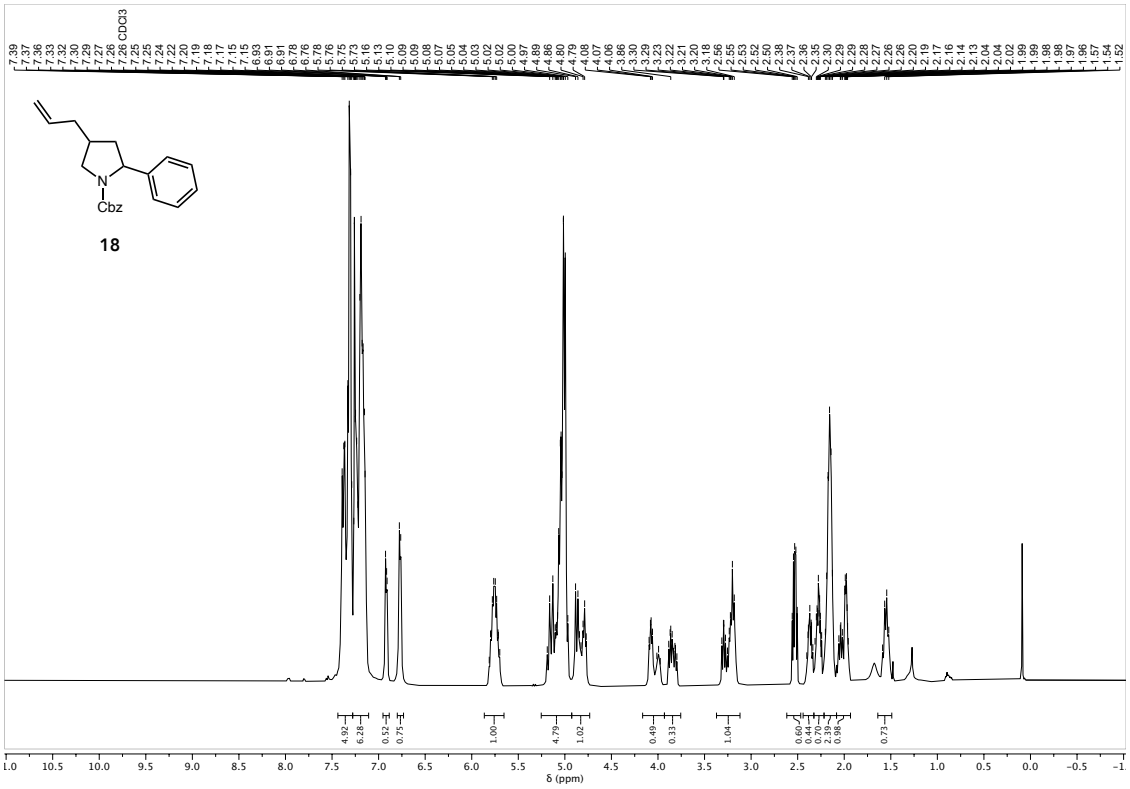
Mixture of diastereoisomers

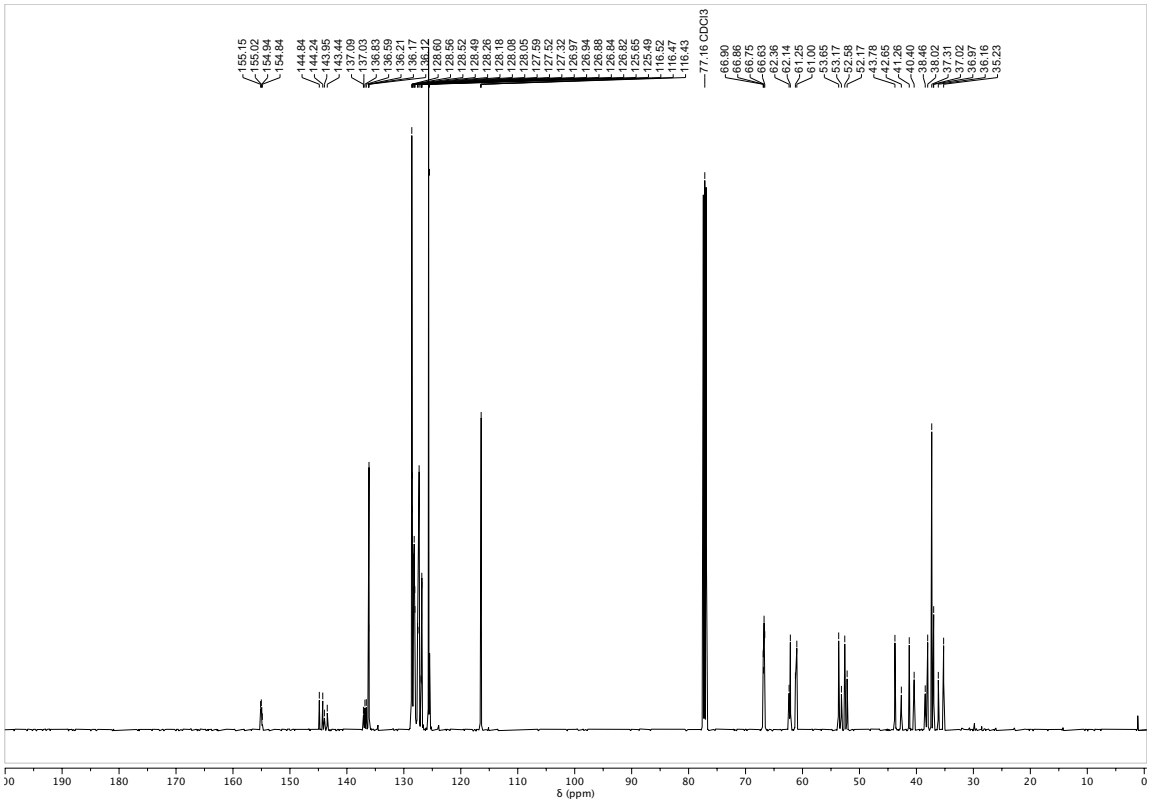



Benzyl 4-allyl-2-phenylpyrrolidine-1-carboxylate (18)

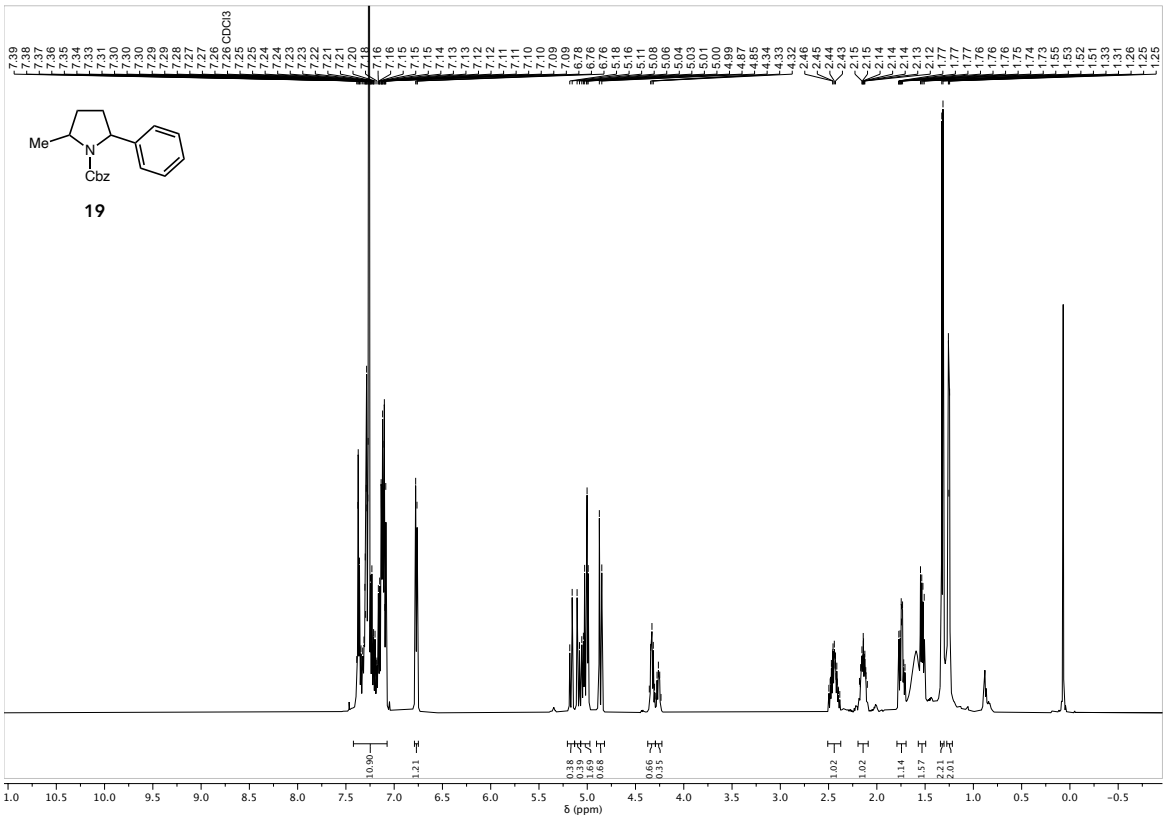
Mixture of diastereoisomers

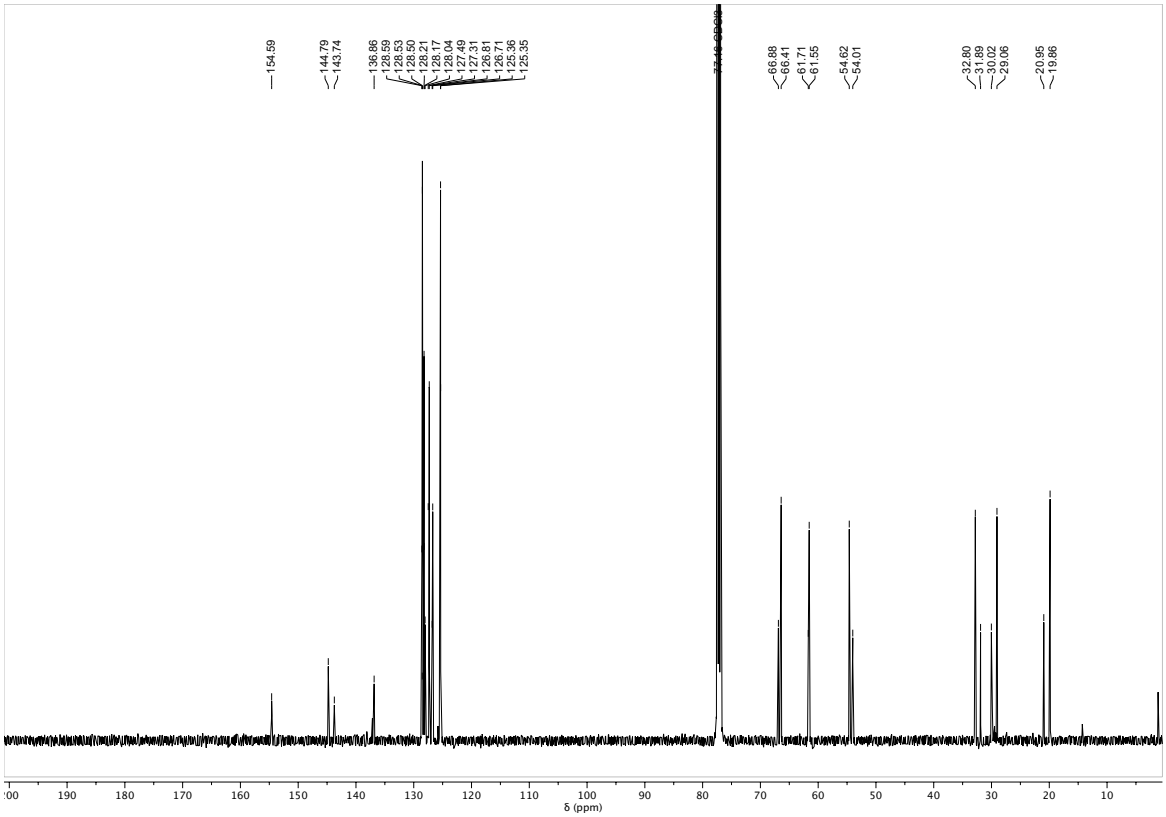



Benzyl 2-methyl-5-phenylpyrrolidine-1-carboxylate (19)

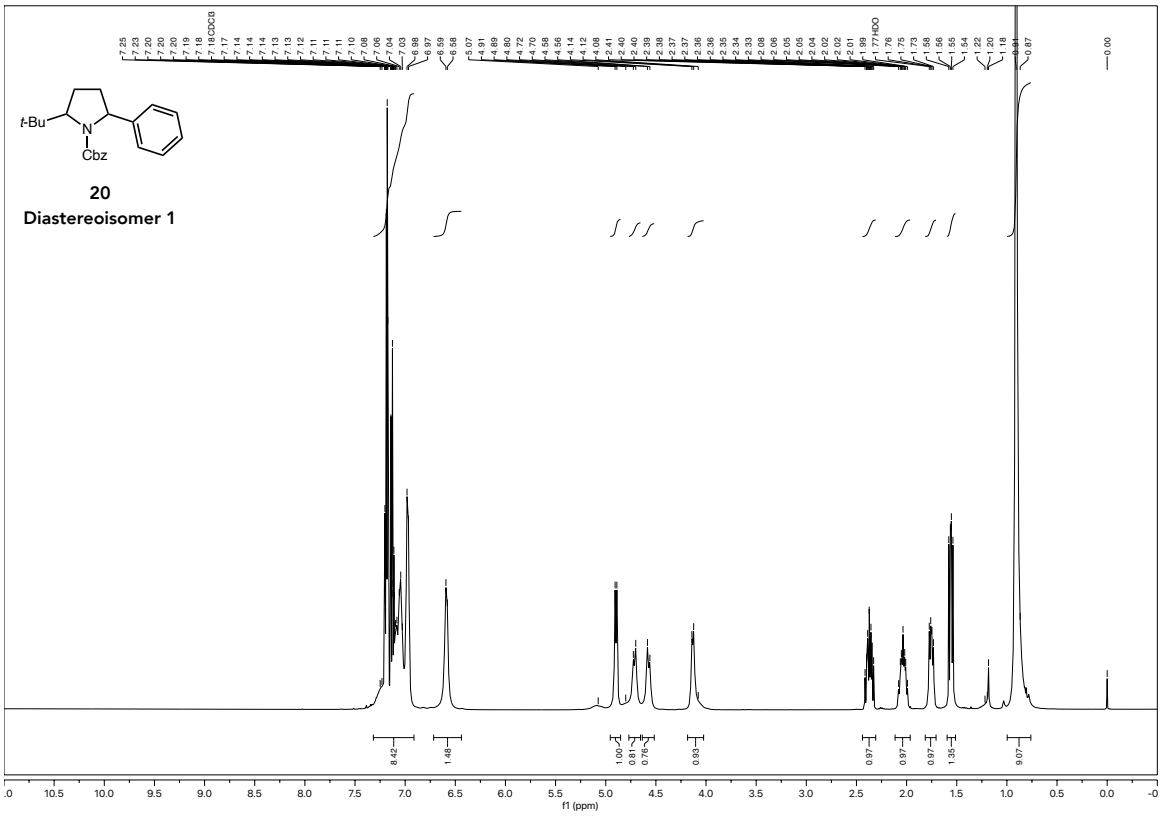
Mixture of diasteroisomers

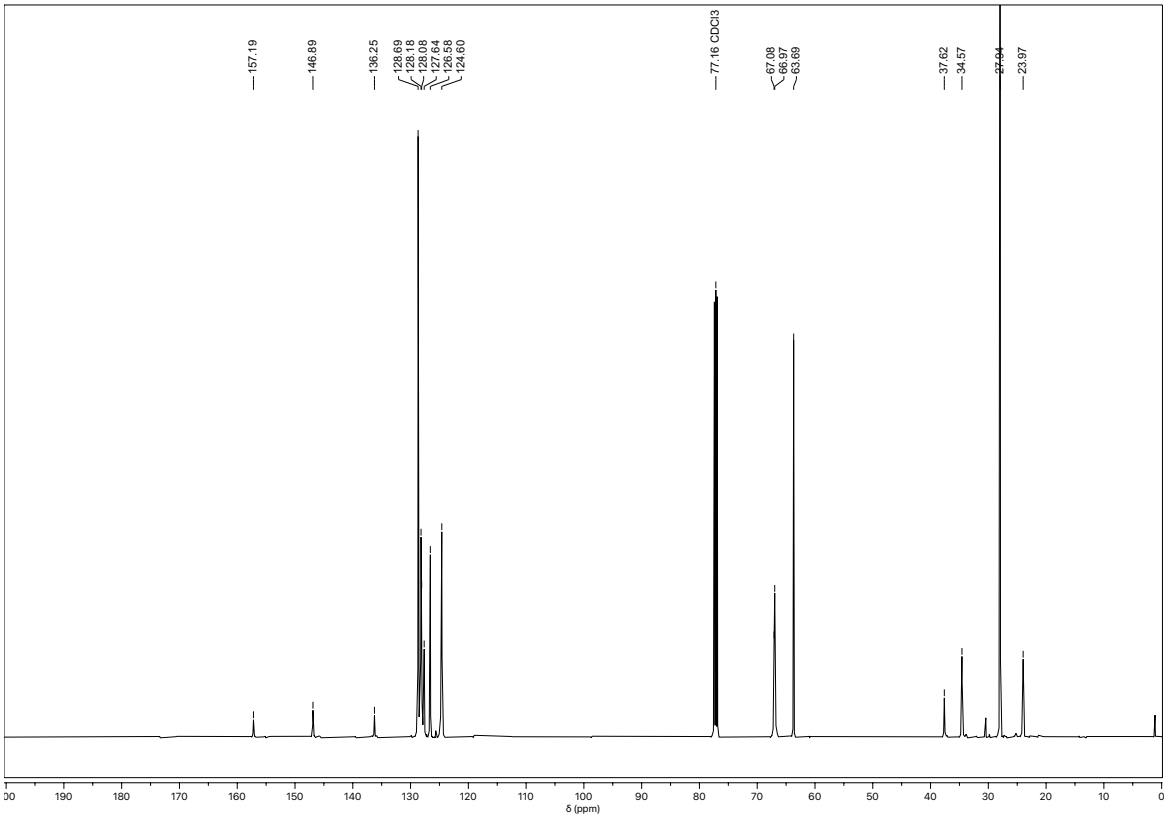



Benzyl 2-(*tert*-butyl)-5-phenylpyrrolidine-1-carboxylate (20)

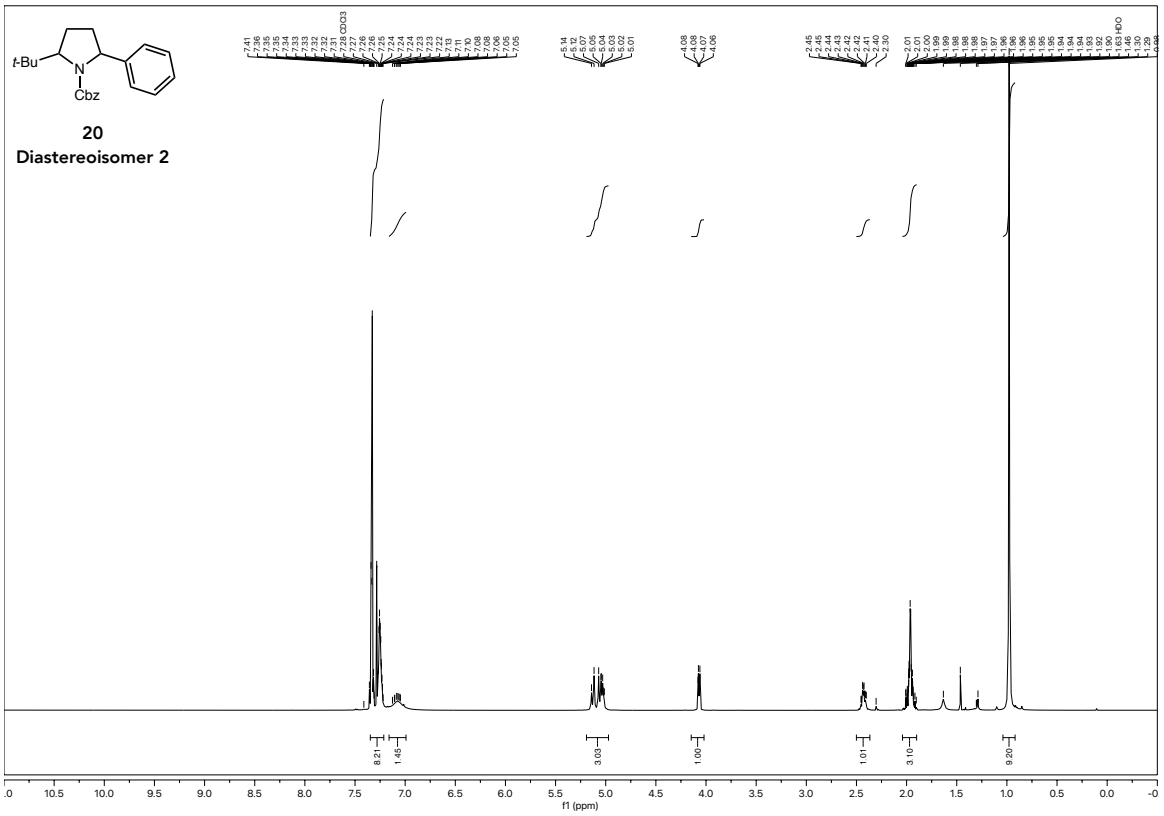
Diastereoisomer 1

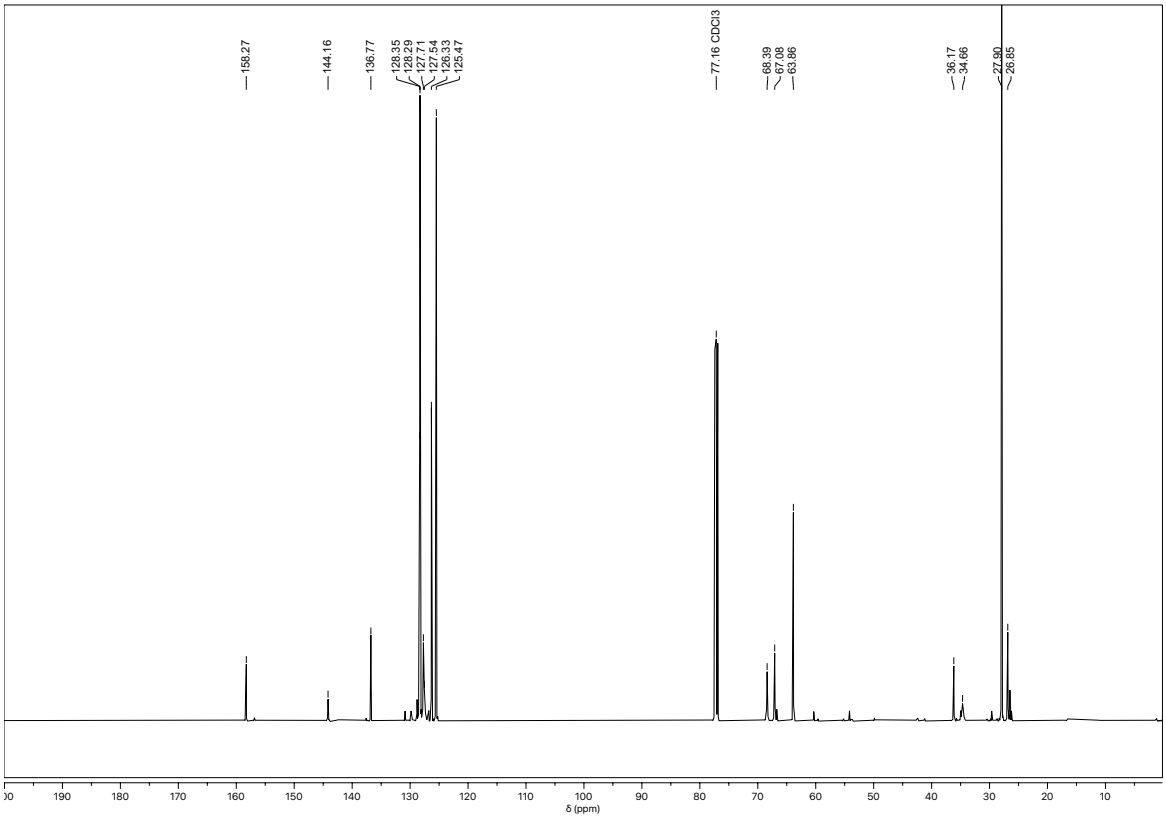



Benzyl 2-(*tert*-butyl)-5-phenylpyrrolidine-1-carboxylate (20)

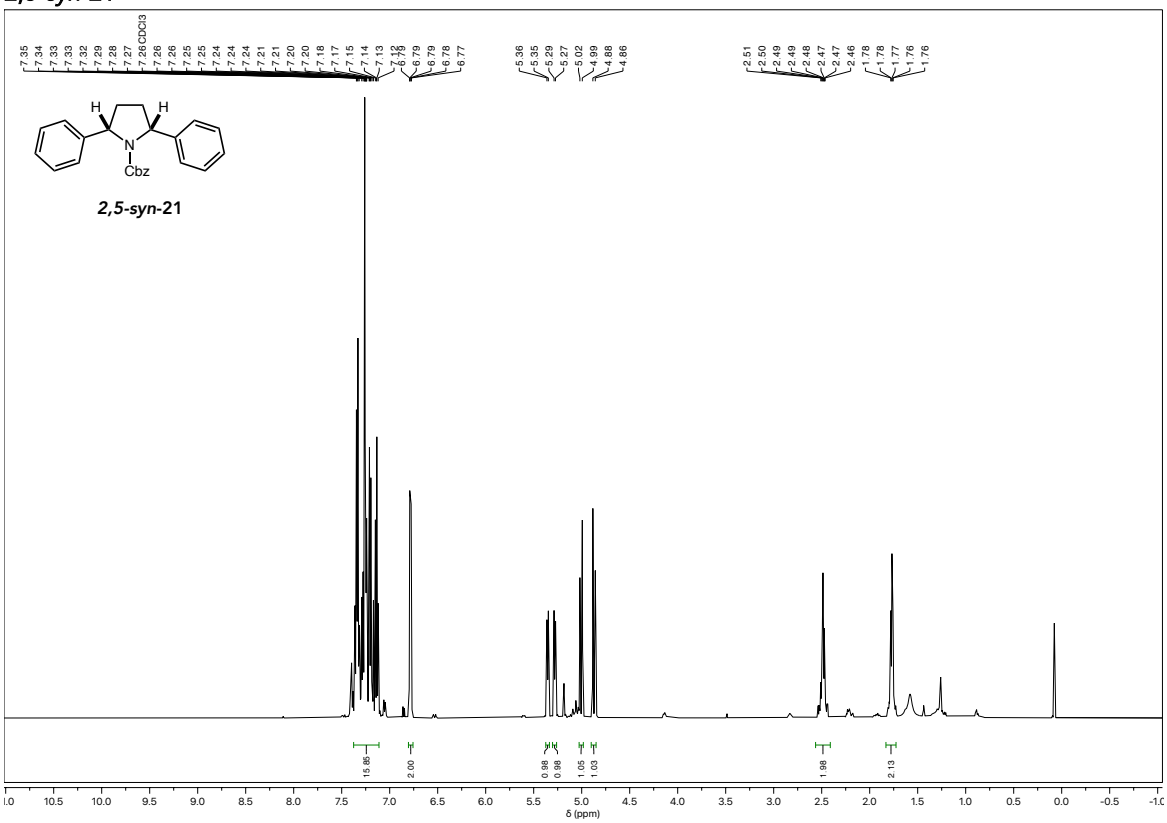
Diastereoisomer 2

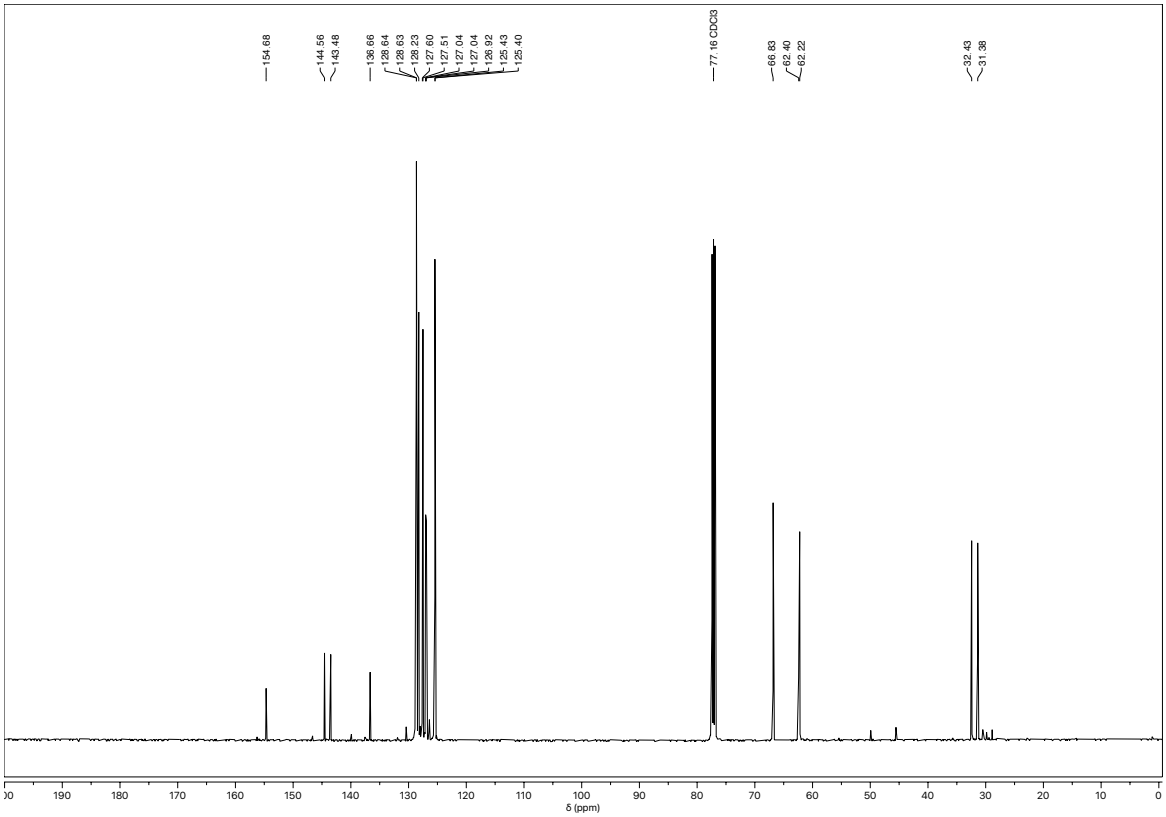



Benzyl 2,5-diphenylpyrrolidine-1-carboxylate (21)

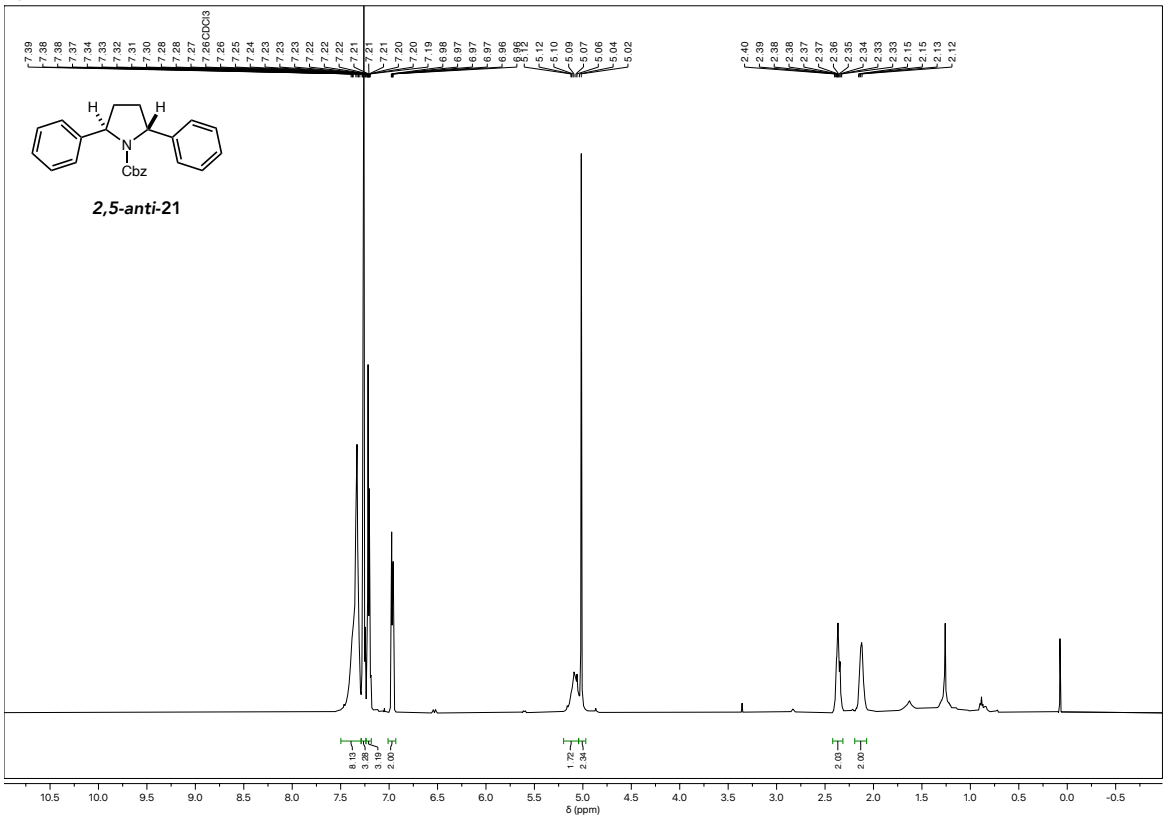
2,5-*syn*-21

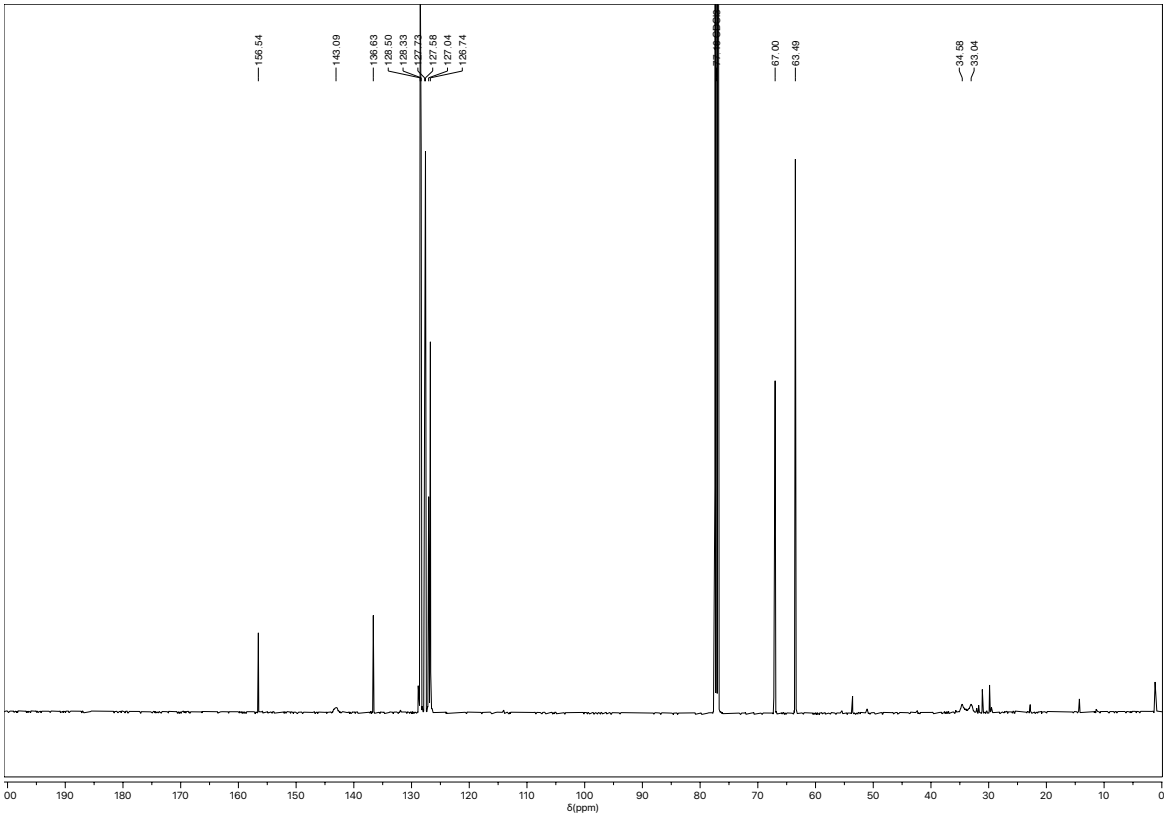



Benzyl 2,5-diphenylpyrrolidine-1-carboxylate (21)

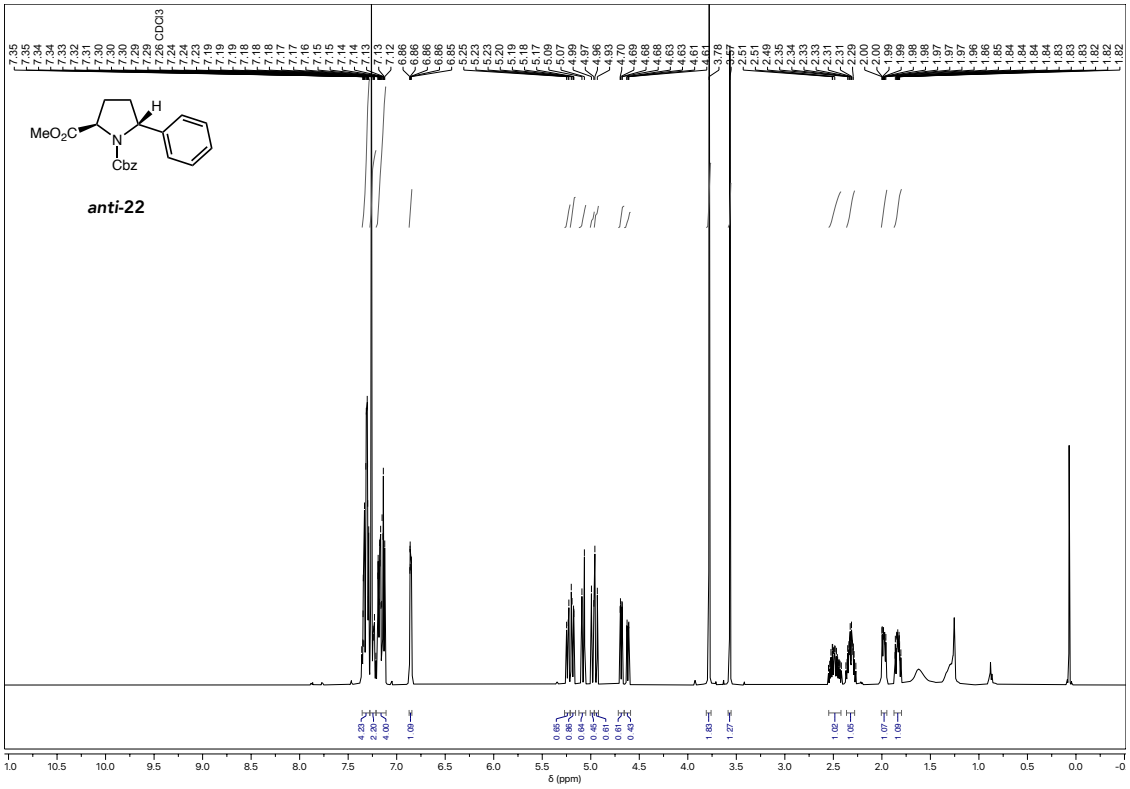
2,5-*anti*-21

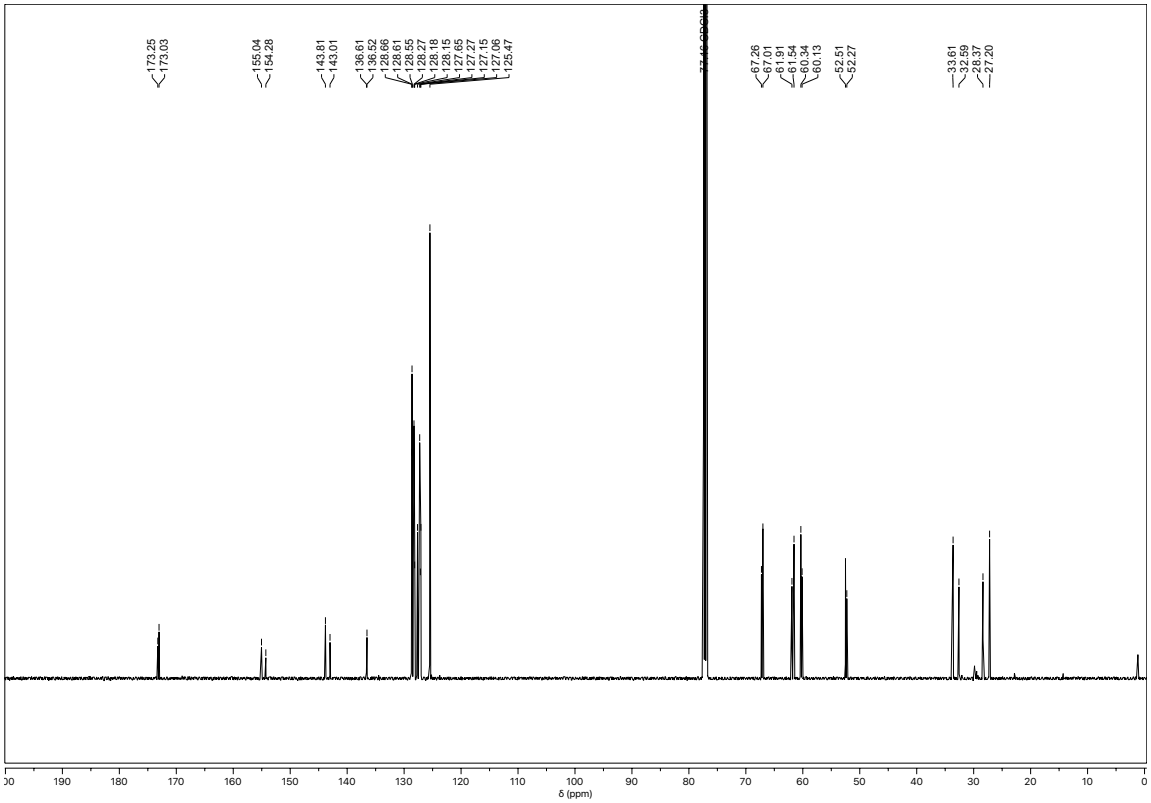



1-Benzyl 2-methyl (2*R*)-5-phenylpyrrolidine-1,2-dicarboxylate (22)

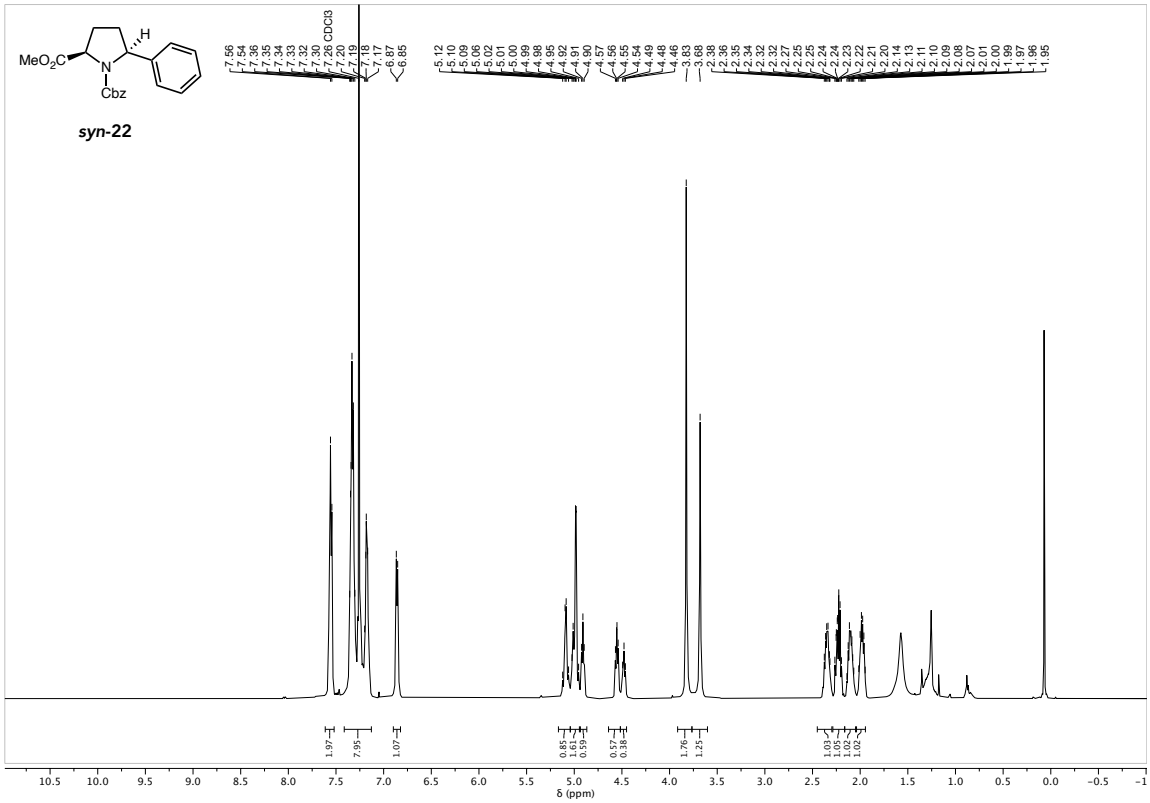
2,5-*Anti*-diasteroisomer (*anti*-22):

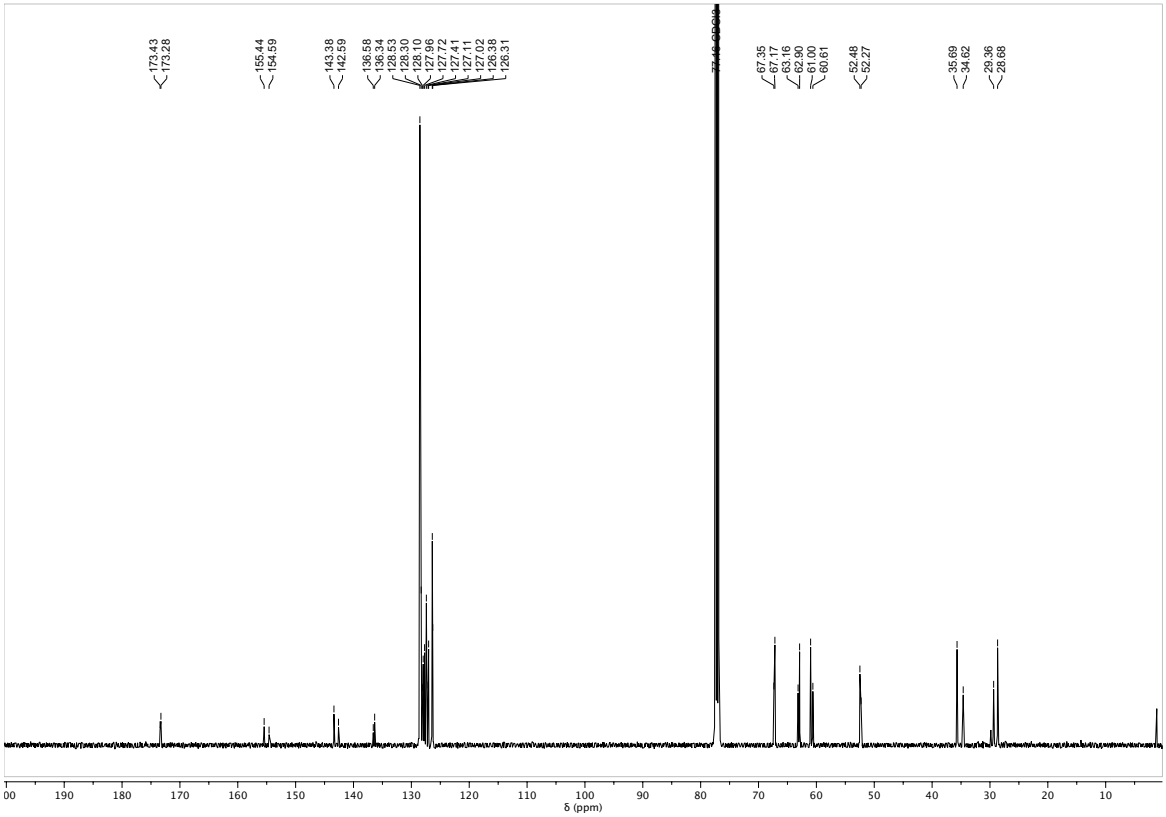


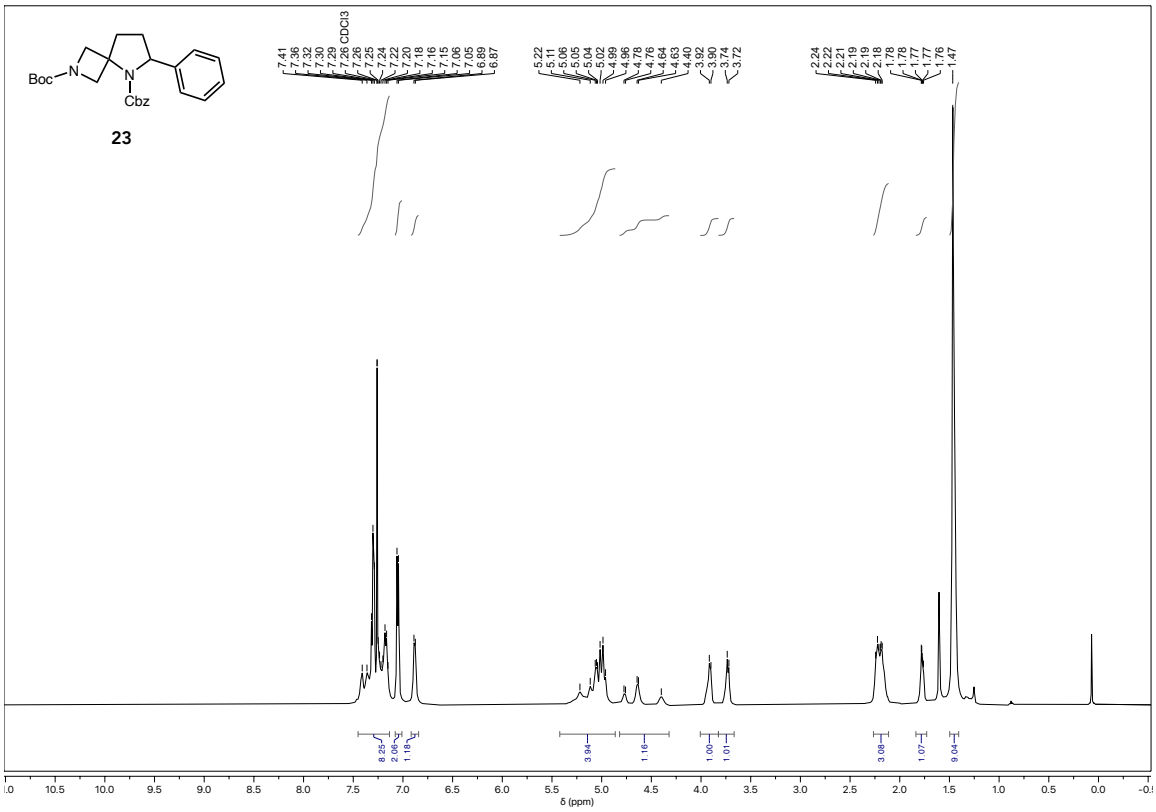

1-Benzyl 2-methyl (2*R*)-5-phenylpyrrolidine-1,2-dicarboxylate (22)

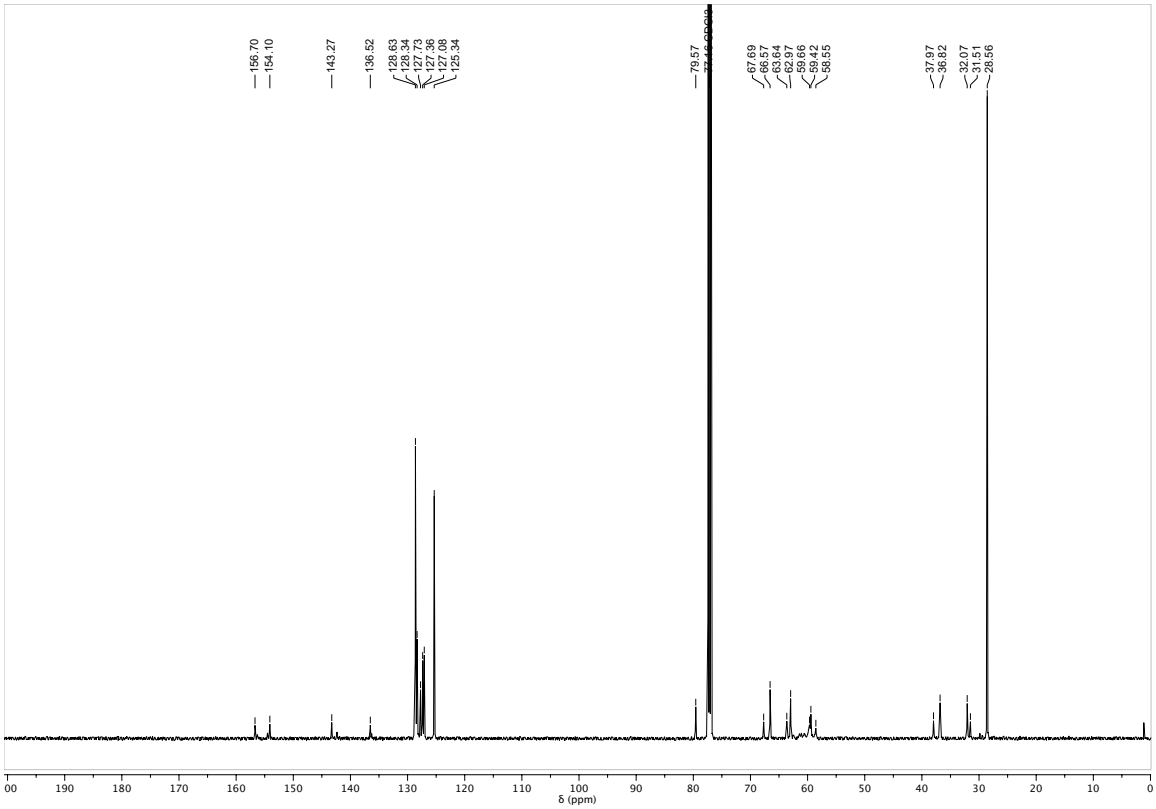
2,5-Syn diastereoisomer (*syn*-22):



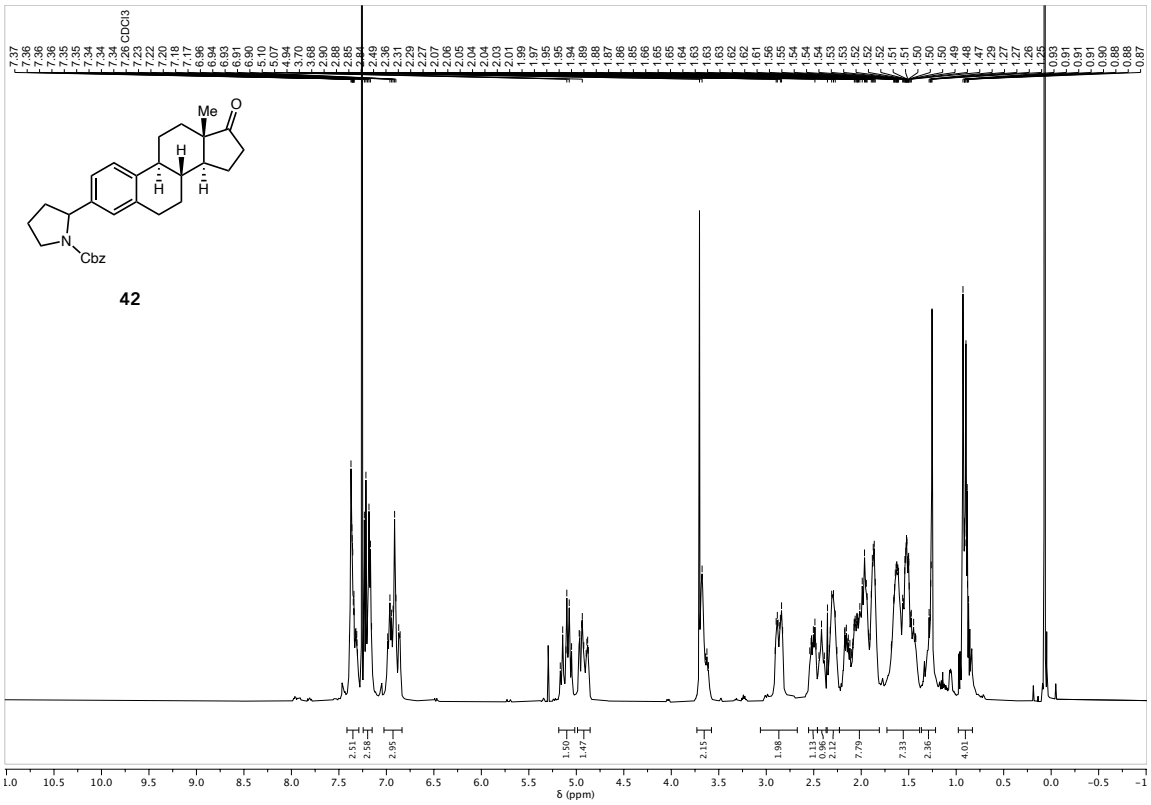



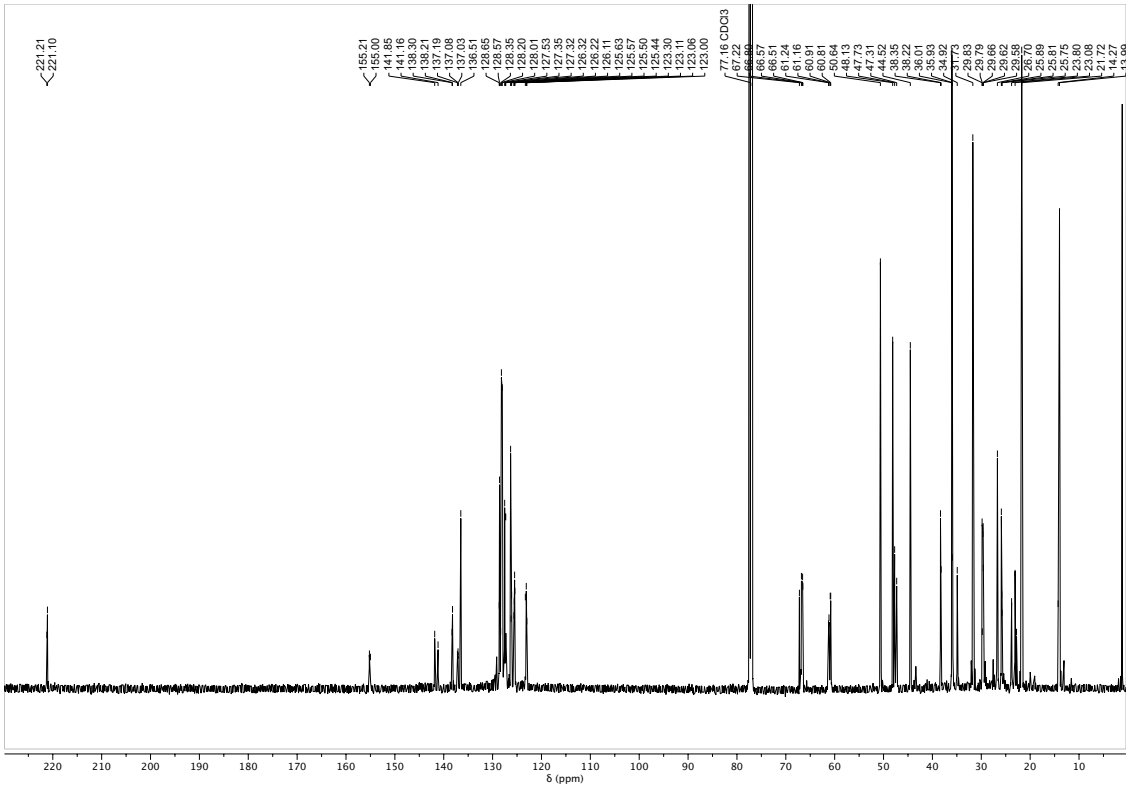

5-Benzyl 2-(*tert*-butyl) 6-phenyl-2,5-diazaspiro[3.4]octane-2,5-dicarboxylate (23)


Boc
N
N
Cbz
23
δ (ppm)

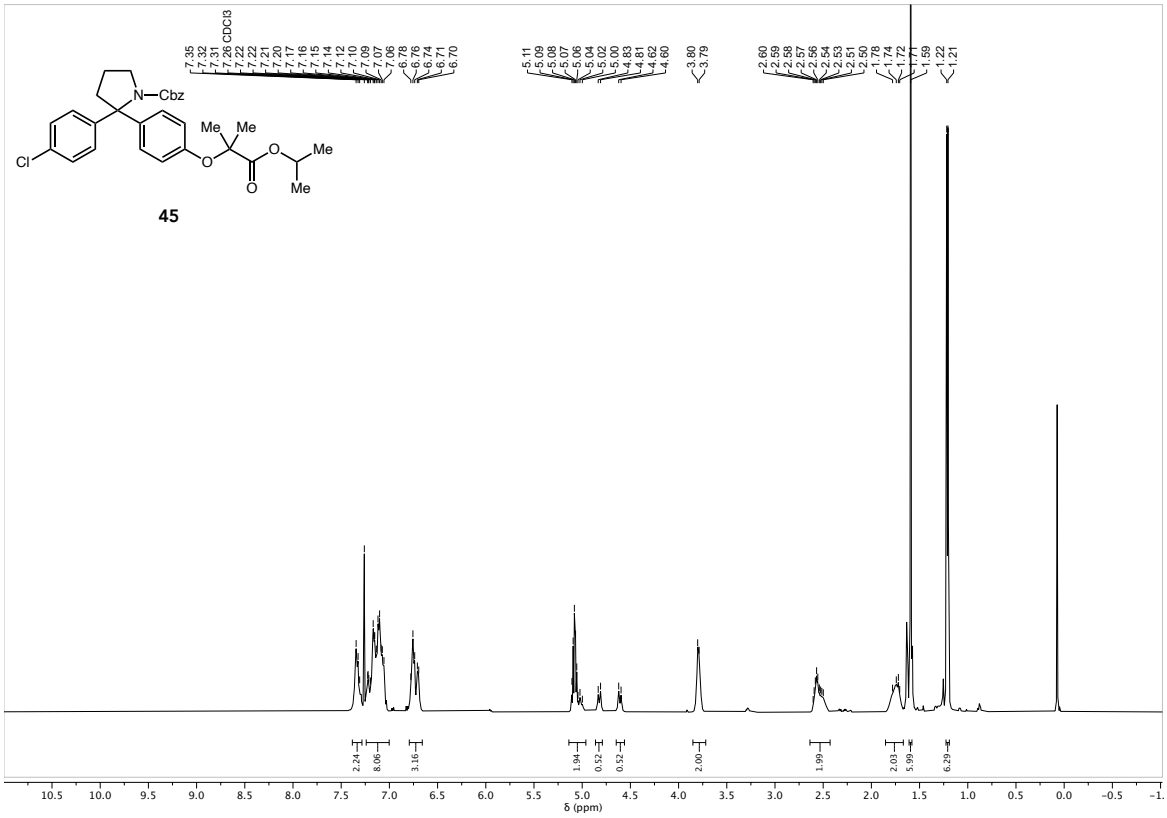

δ (ppm)

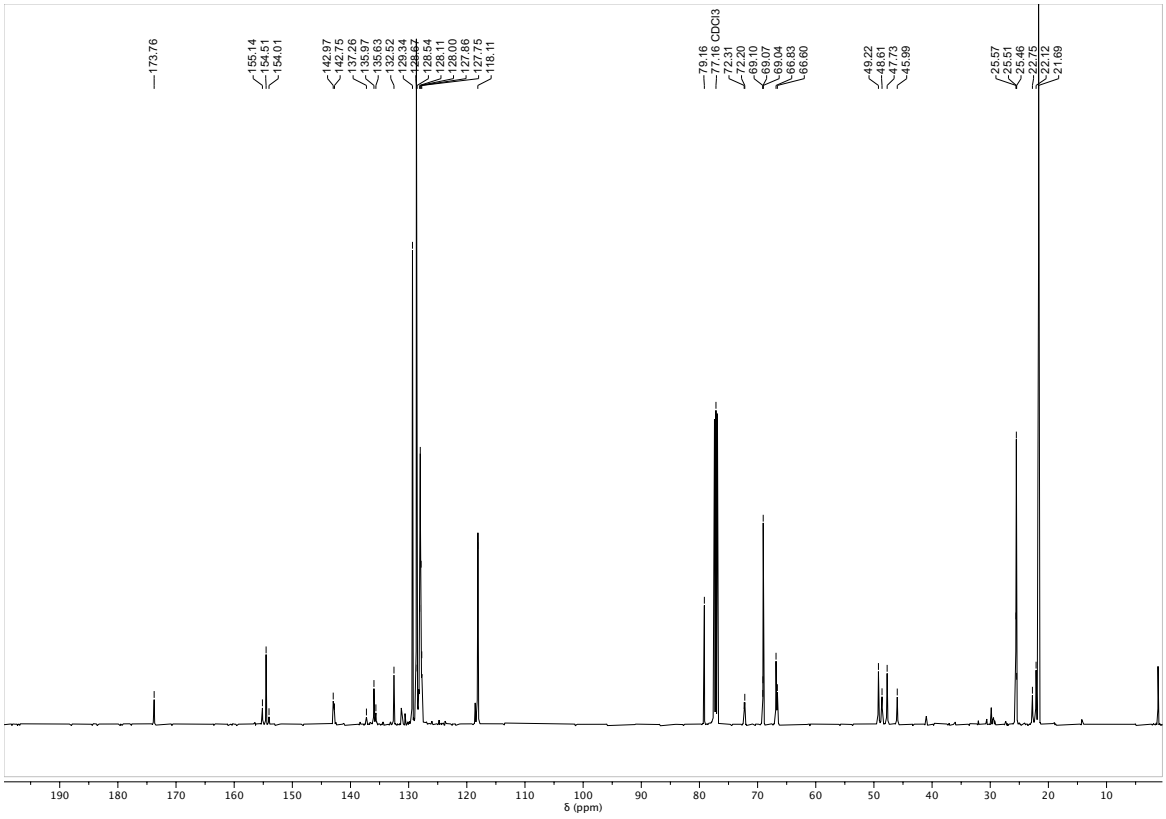
Benzyl 2-((8*R*,9*S*,13*S*,14*S*)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl)pyrrolidine-1-carboxylate (42)



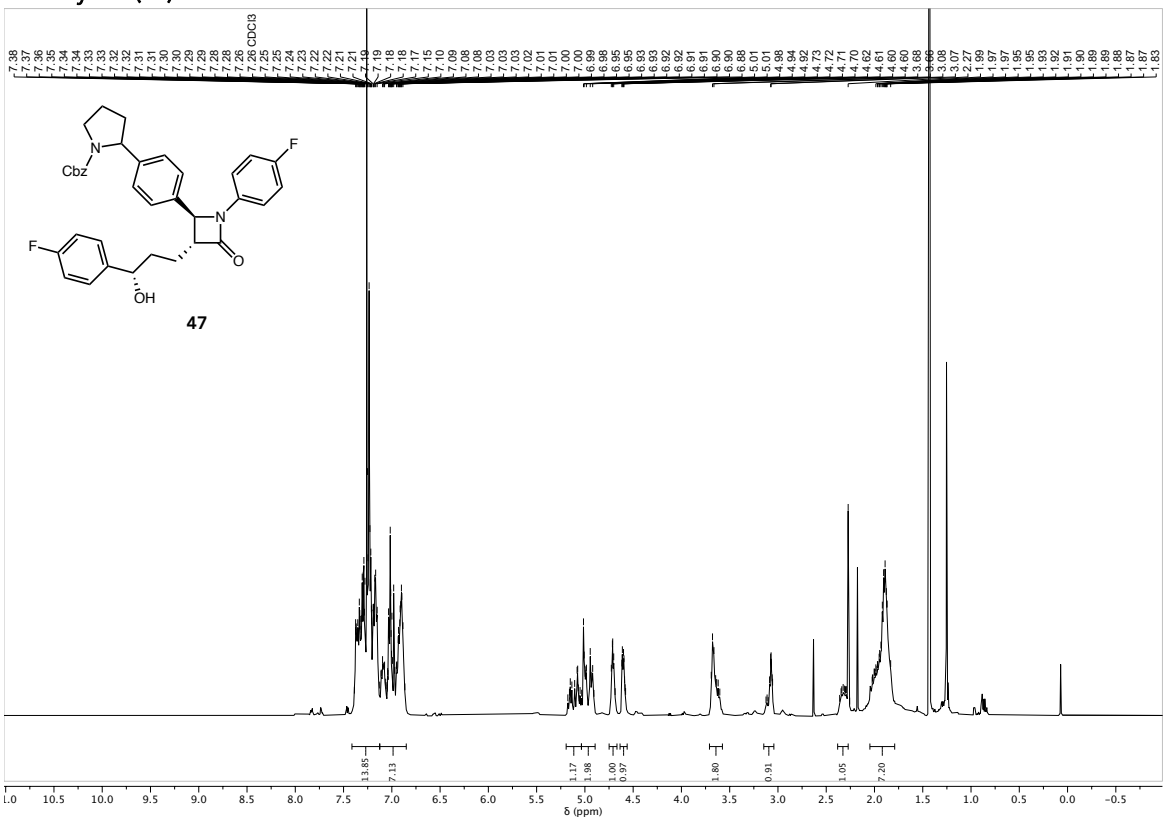



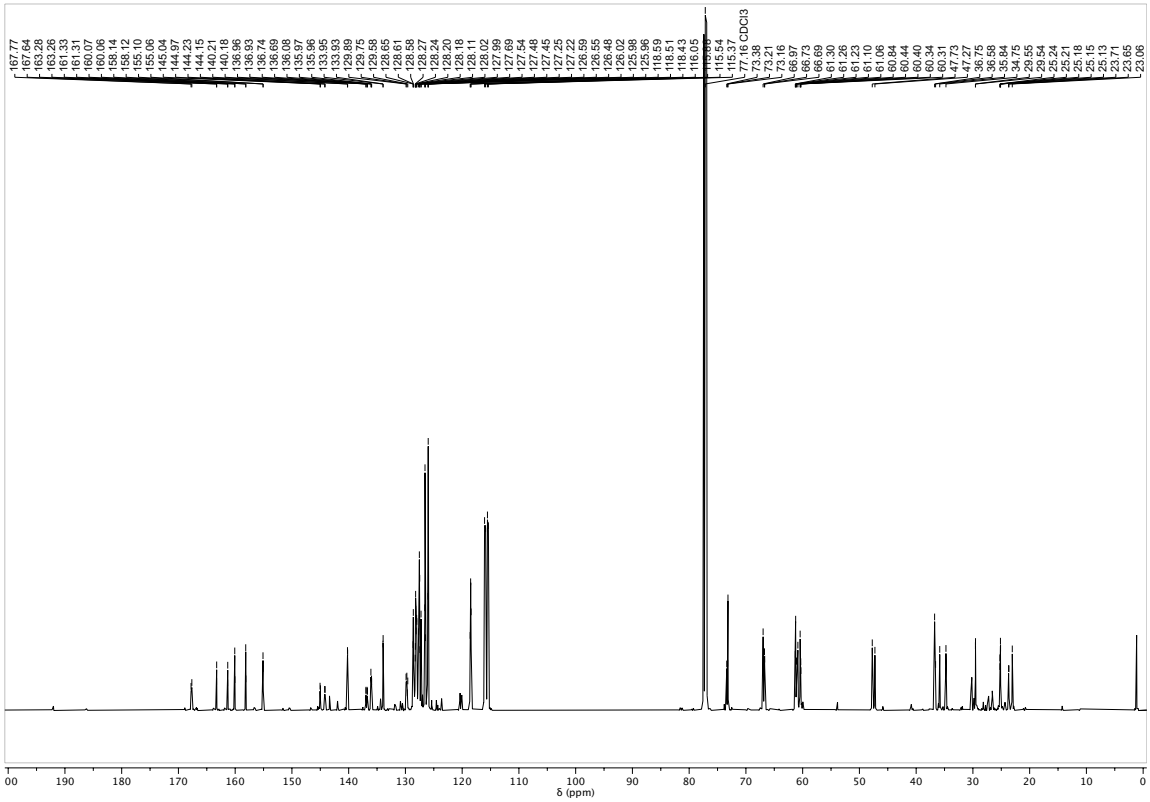
Benzyl 2-(4-chlorophenyl)-2-(4-((1-isopropoxy-2-methyl-1-oxopropan-2-yl)oxy)phenyl)pyrrolidine-1-carboxylate (45)

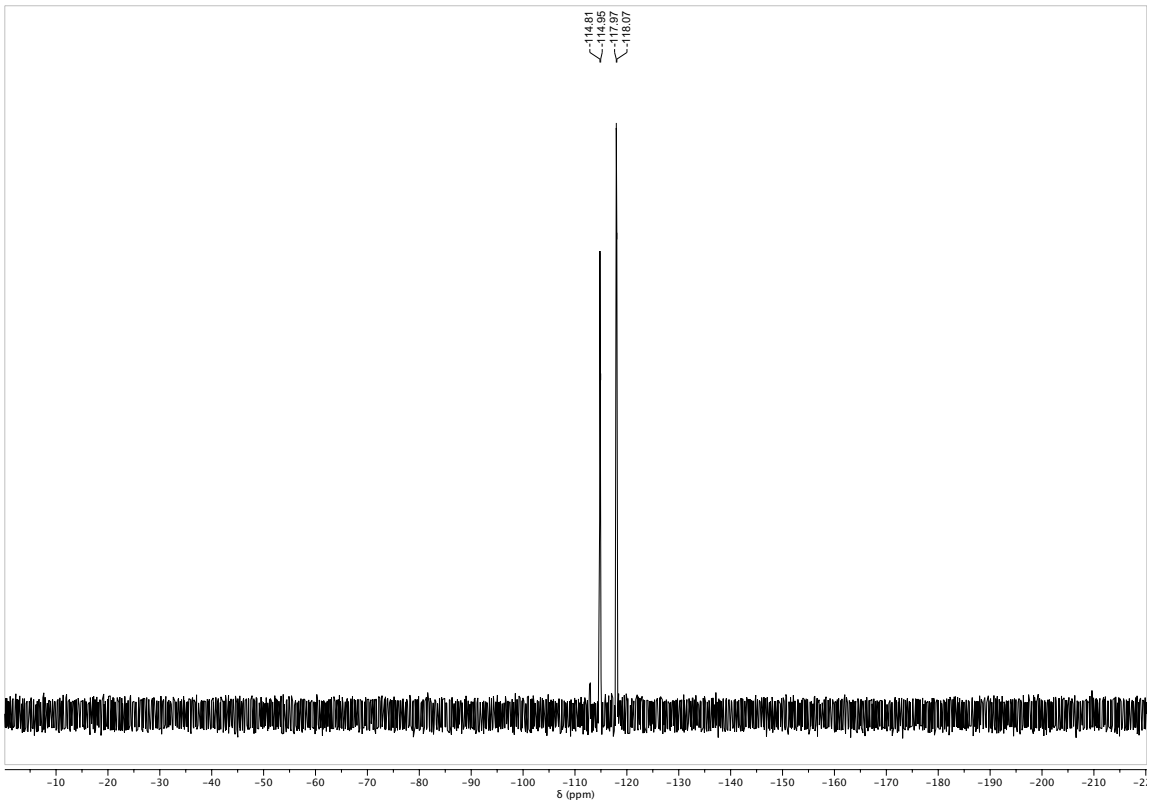


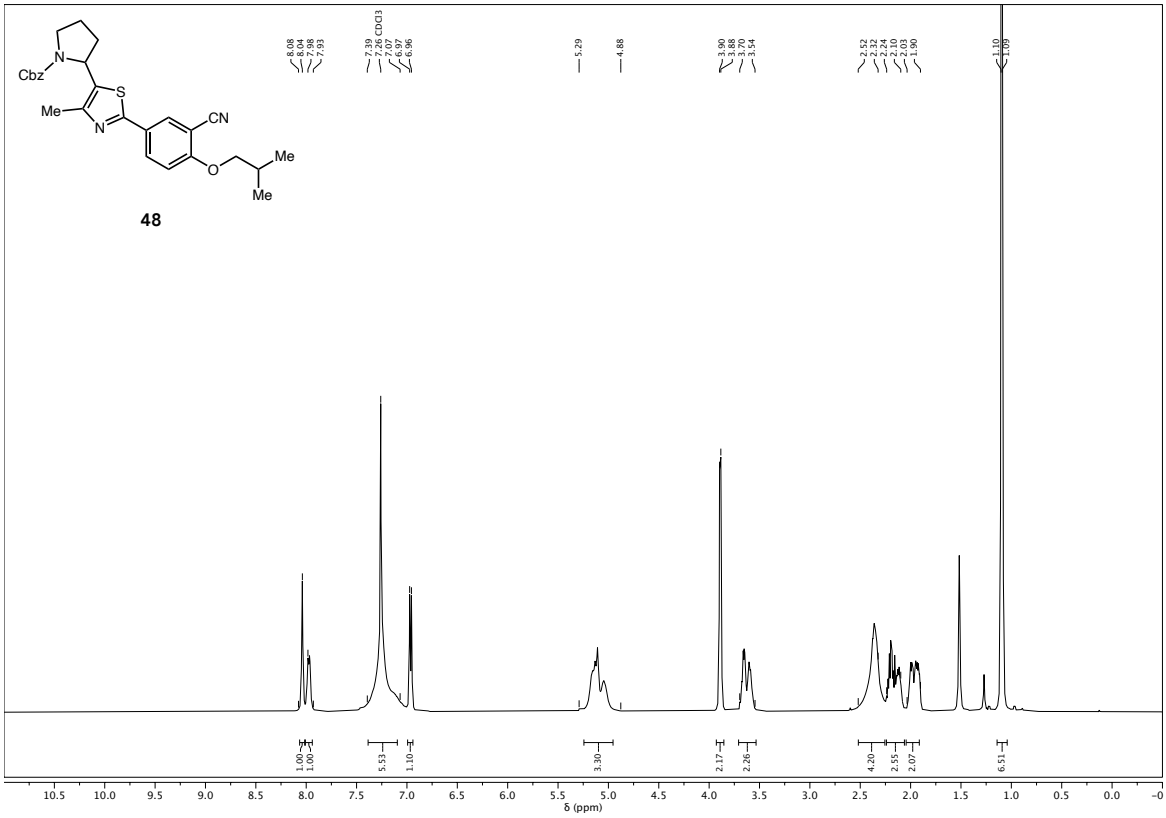
Benzyl 2-(4-((2*S*,3*R*)-1-(4-fluorophenyl)-3-((*S*)-3-(4-fluorophenyl)-3-hydroxypropyl)-4-oxoazetidin-2-yl)phenyl)pyrrolidine-1-carboxylate (47)

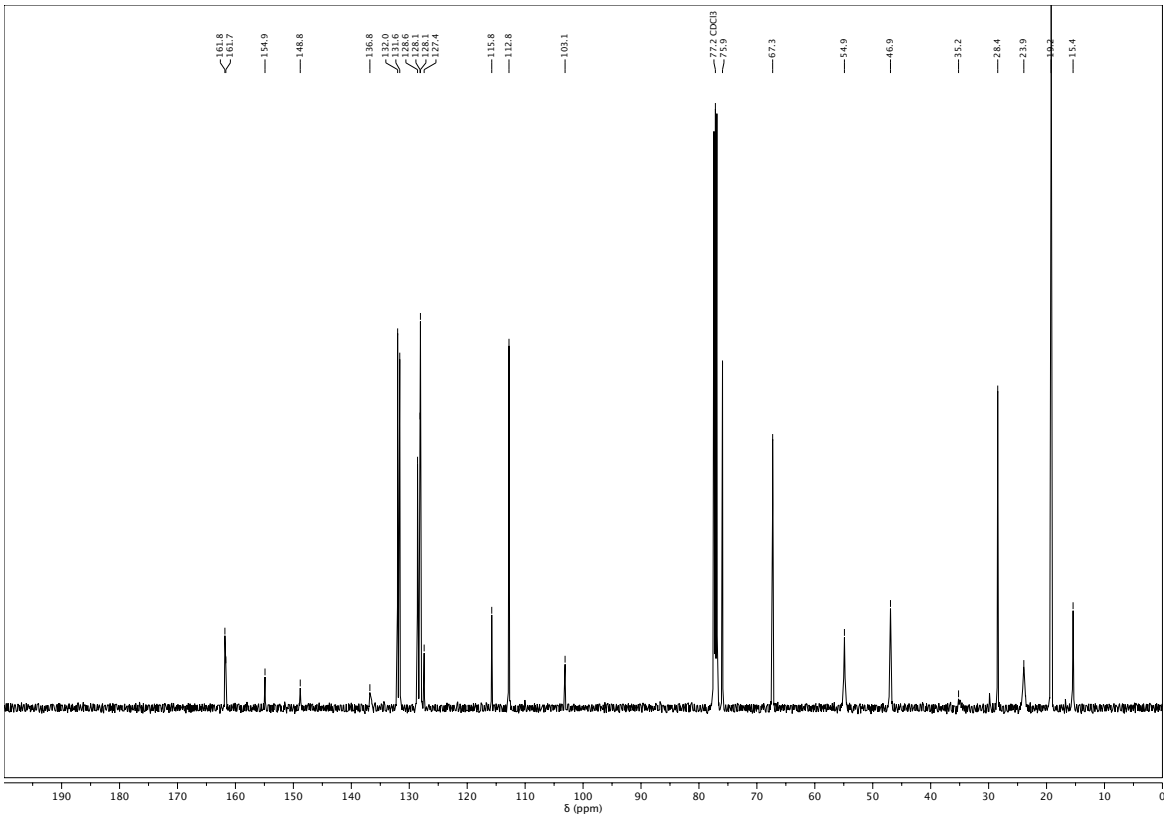


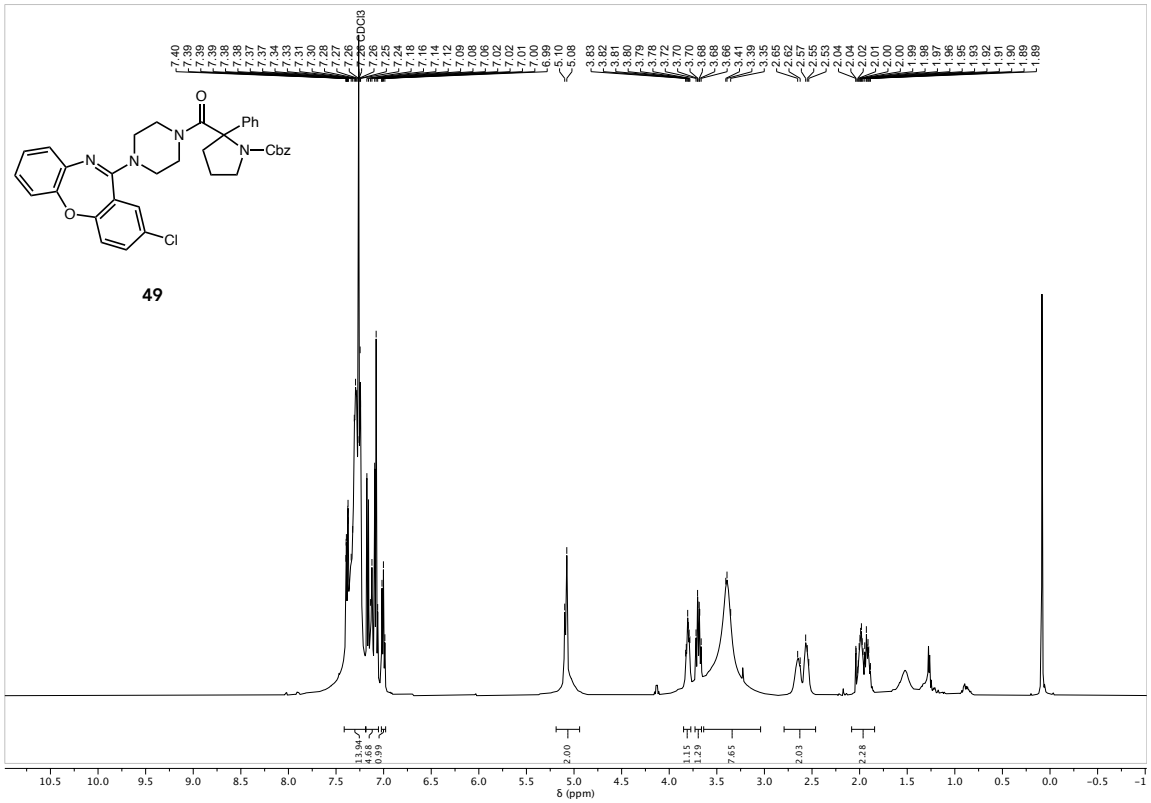

-114.81
-114.95
-117.97
-118.07
−10
−20
−30
−40
−50
−60
−70
−80
−90
−100
−110
−120
−130
−140
−150
−160
−170
−180
−190
−200
−210
δ (ppm)

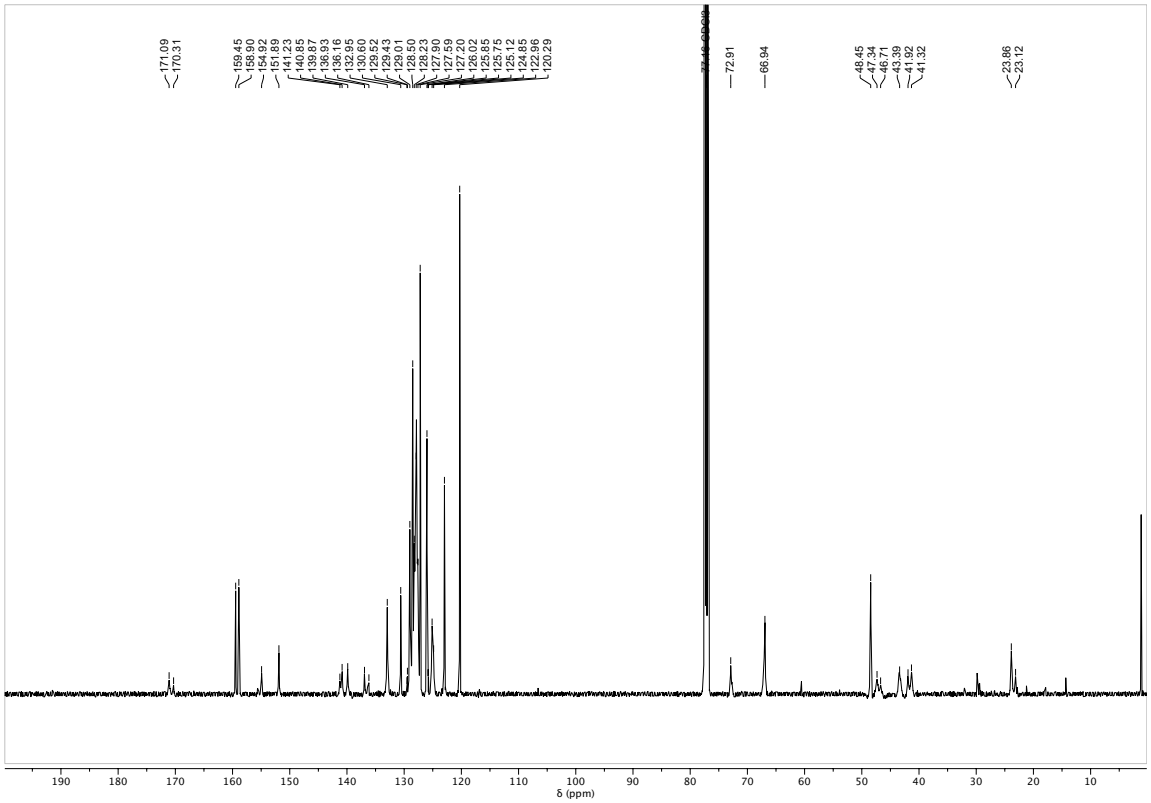
Benzyl 2-(2-(3-cyano-4-isobutoxyphenyl)-4-methylthiazol-5-yl)pyrrolidine-1-carboxylate (48)



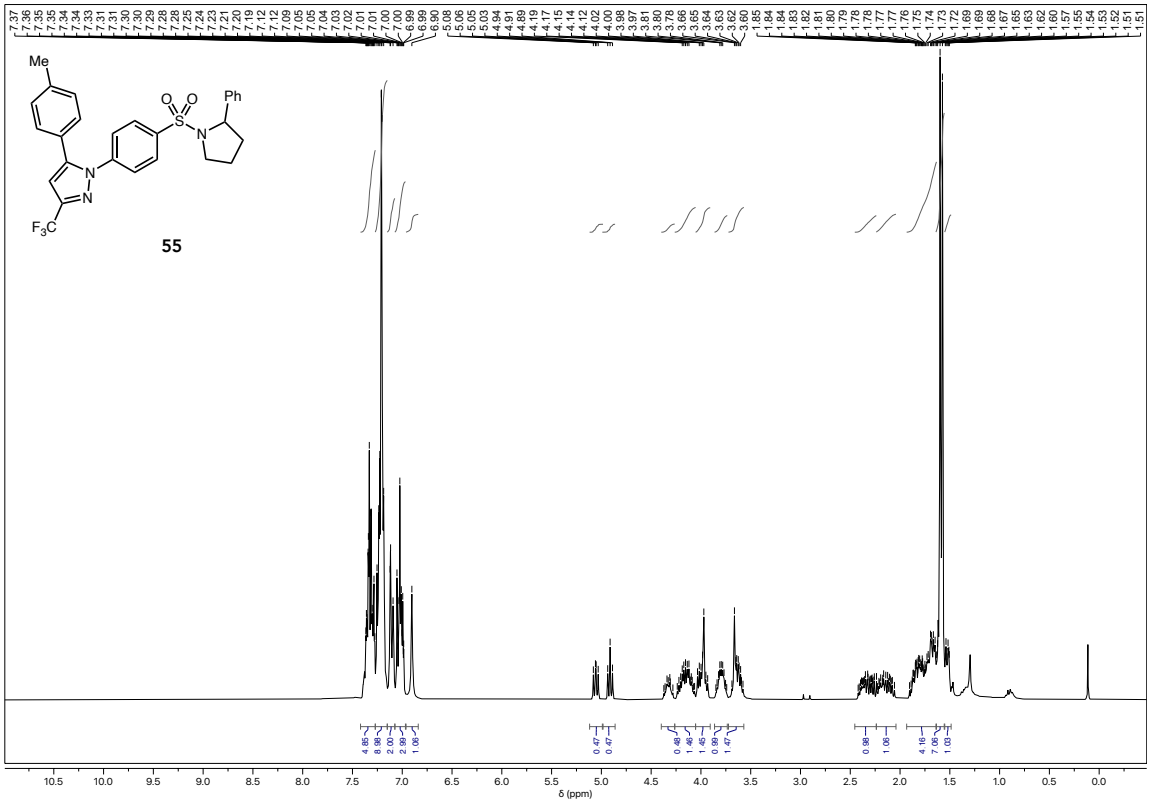



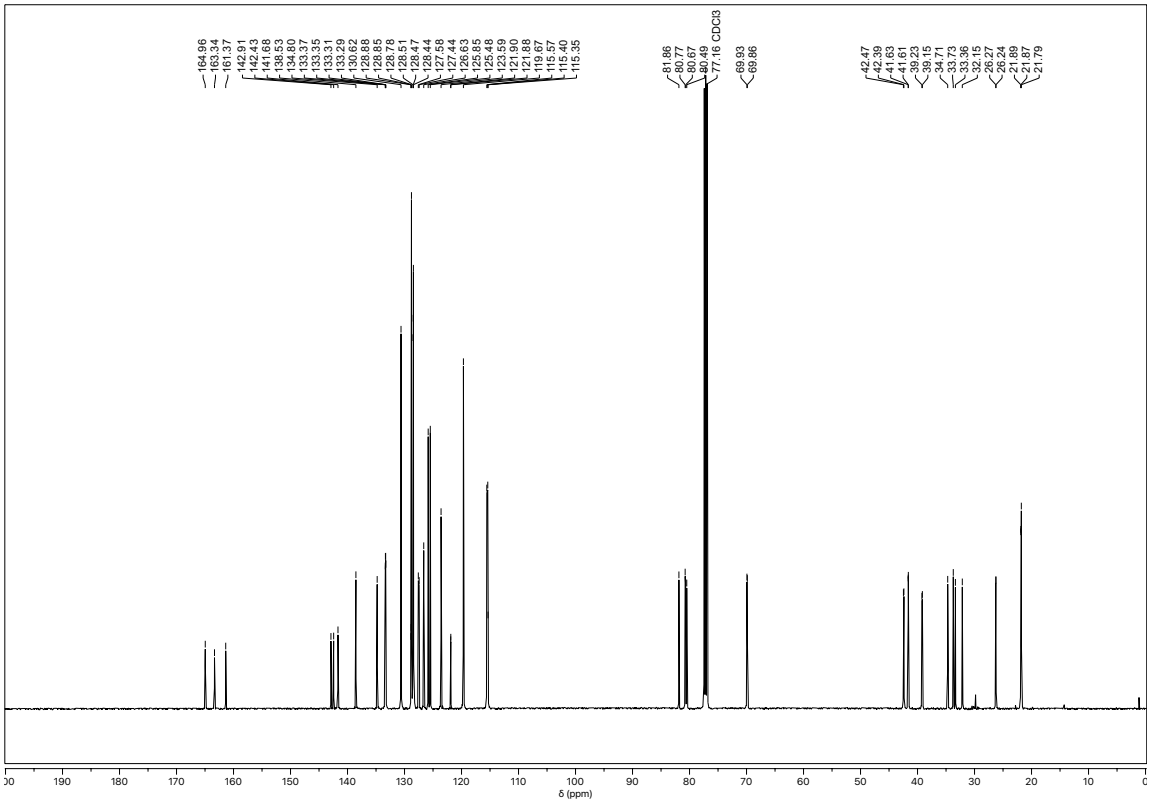
Benzyl 2-(4-(2-chlorodibenzo[*b*,*f*][1,4]oxazepin-11-yl)piperazine-1-carbonyl)-2-phenylpyrrolidine-1-carboxylate (49)

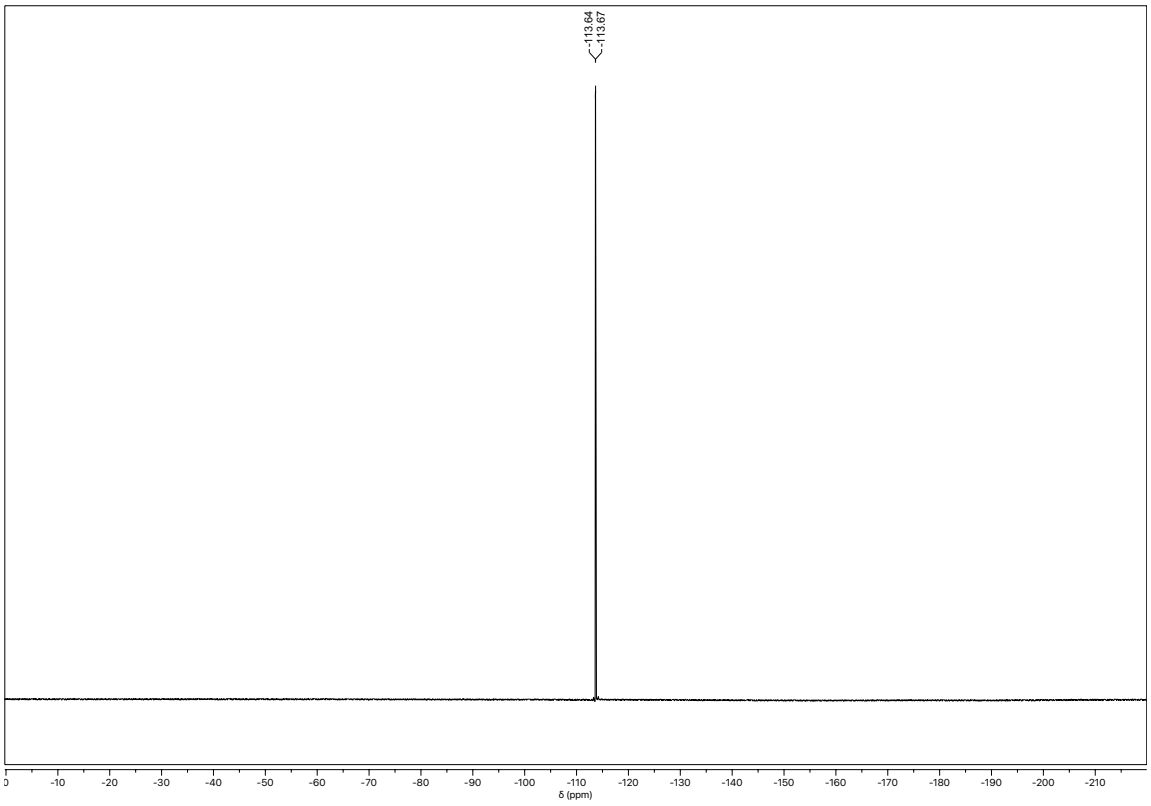


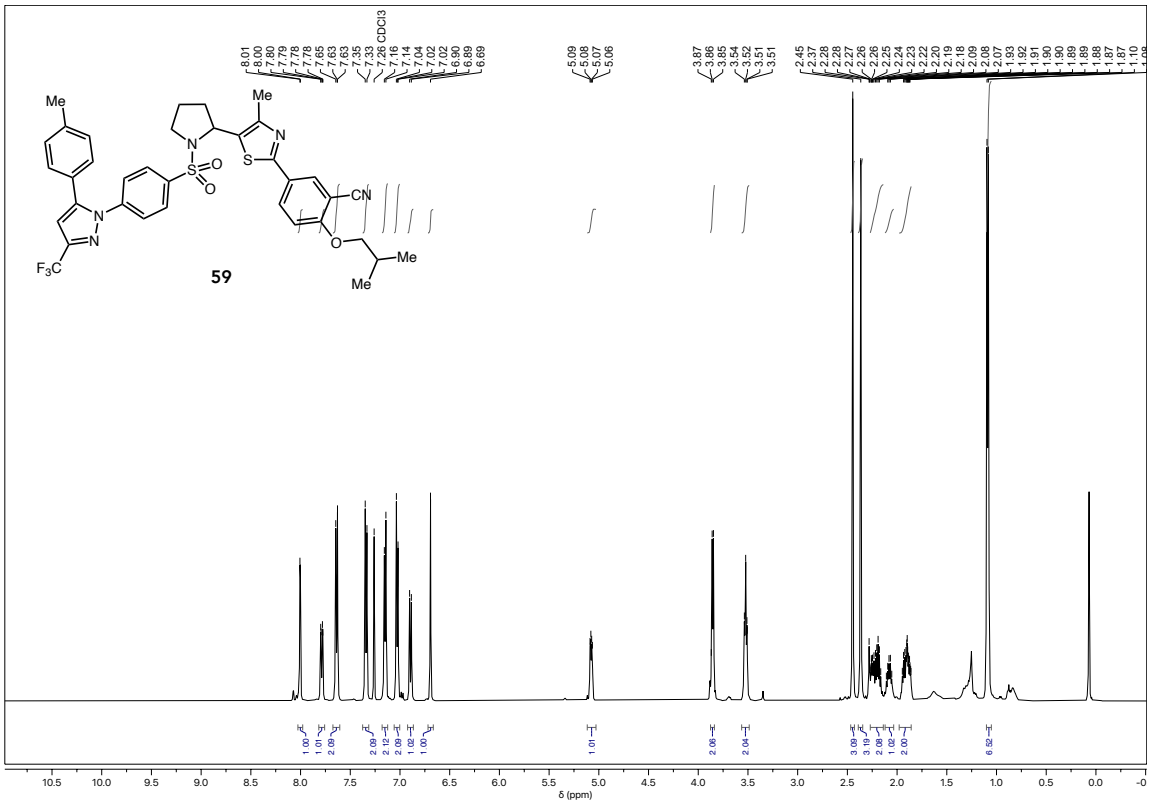
1-(4-((2-Phenylpyrrolidin-1-yl)sulfonyl)phenyl)-5-(*p*-tolyl)-3-(trifluoromethyl)-1*H*-pyrazole (55)

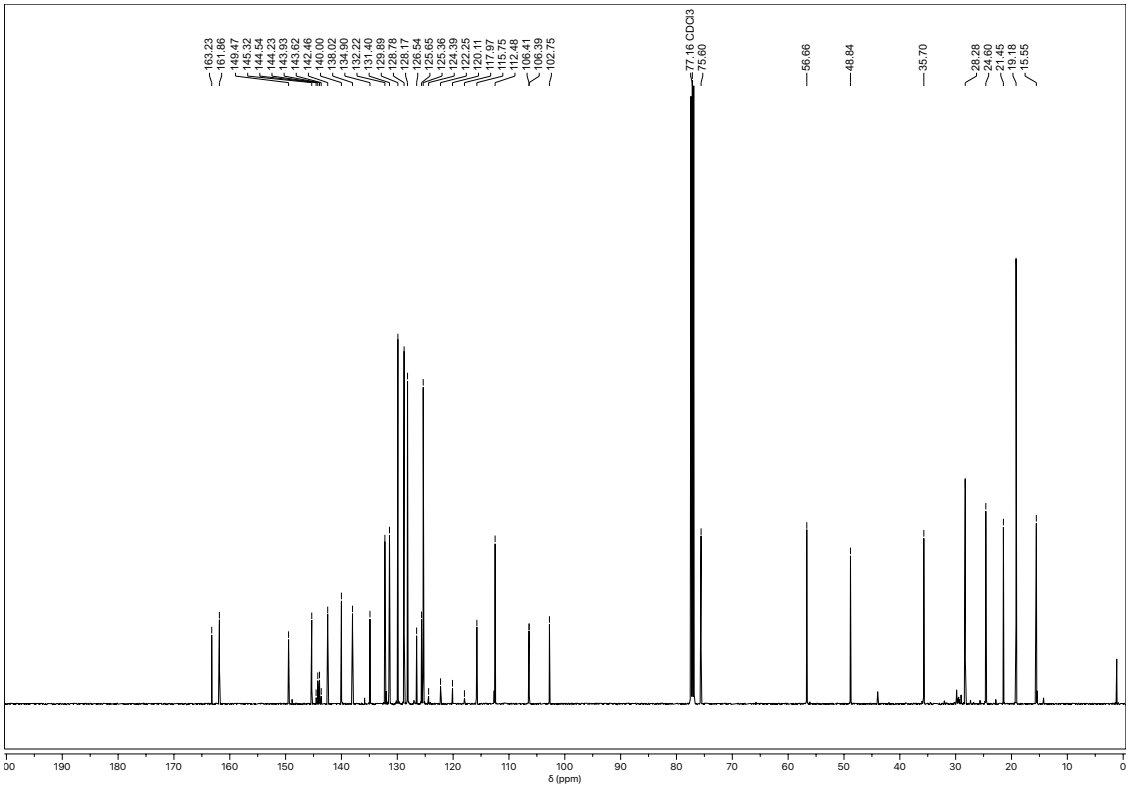


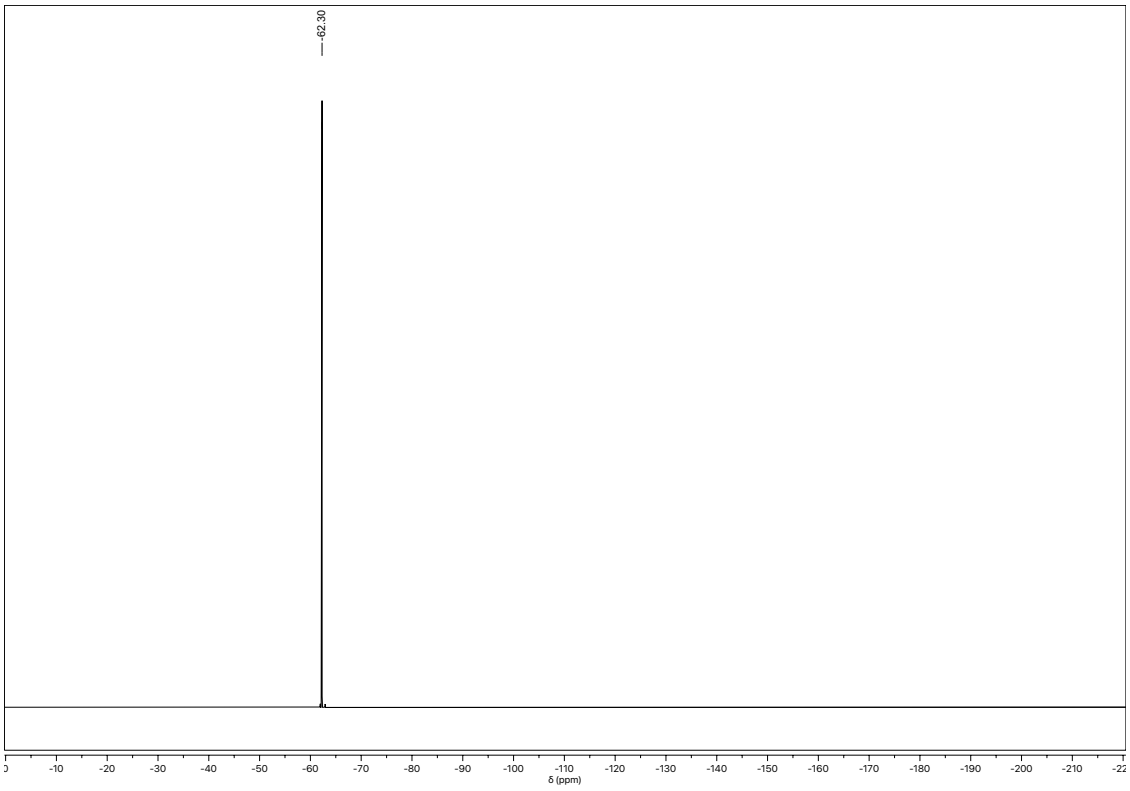




-113.64
-113.67
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
δ (ppm)

2-Isobutoxy-5-(4-methyl-5-(1-((4-(5-(*p*-tolyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)sulfonyl)pyrrolidin-2-yl)thiazol-2-yl)benzonitrile (59)



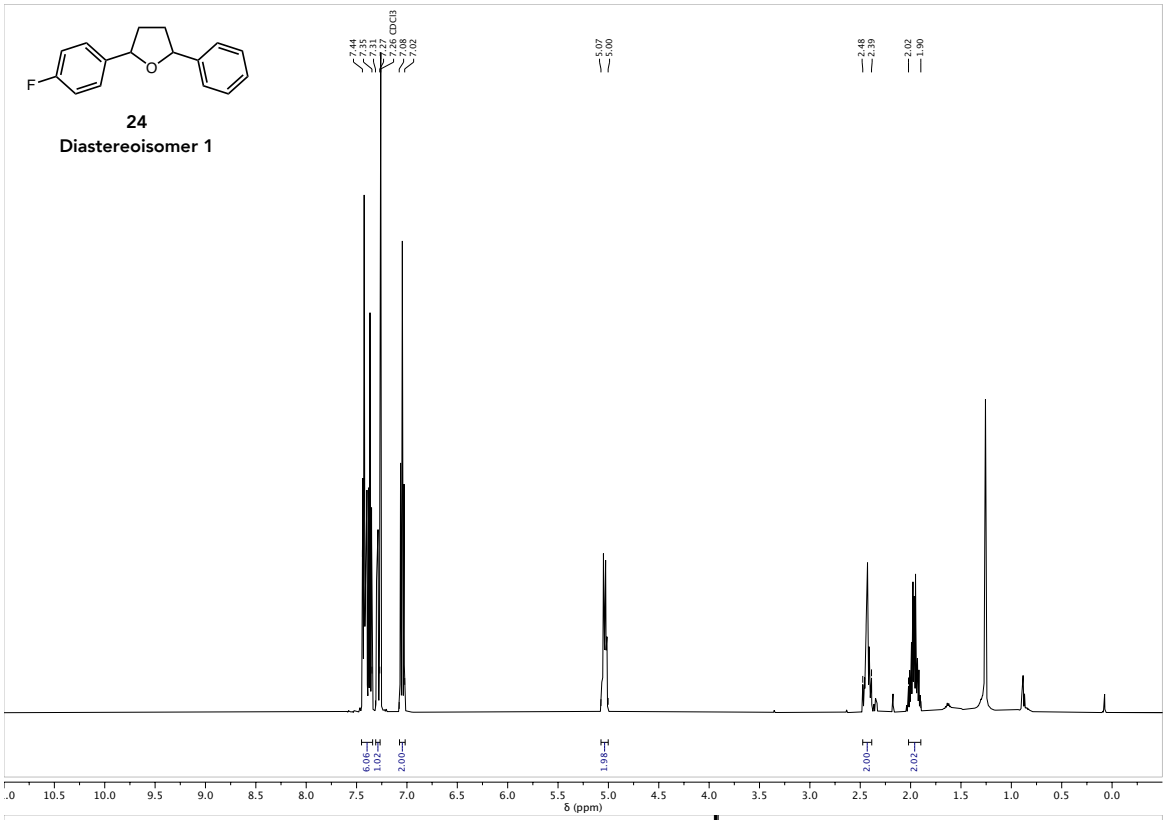



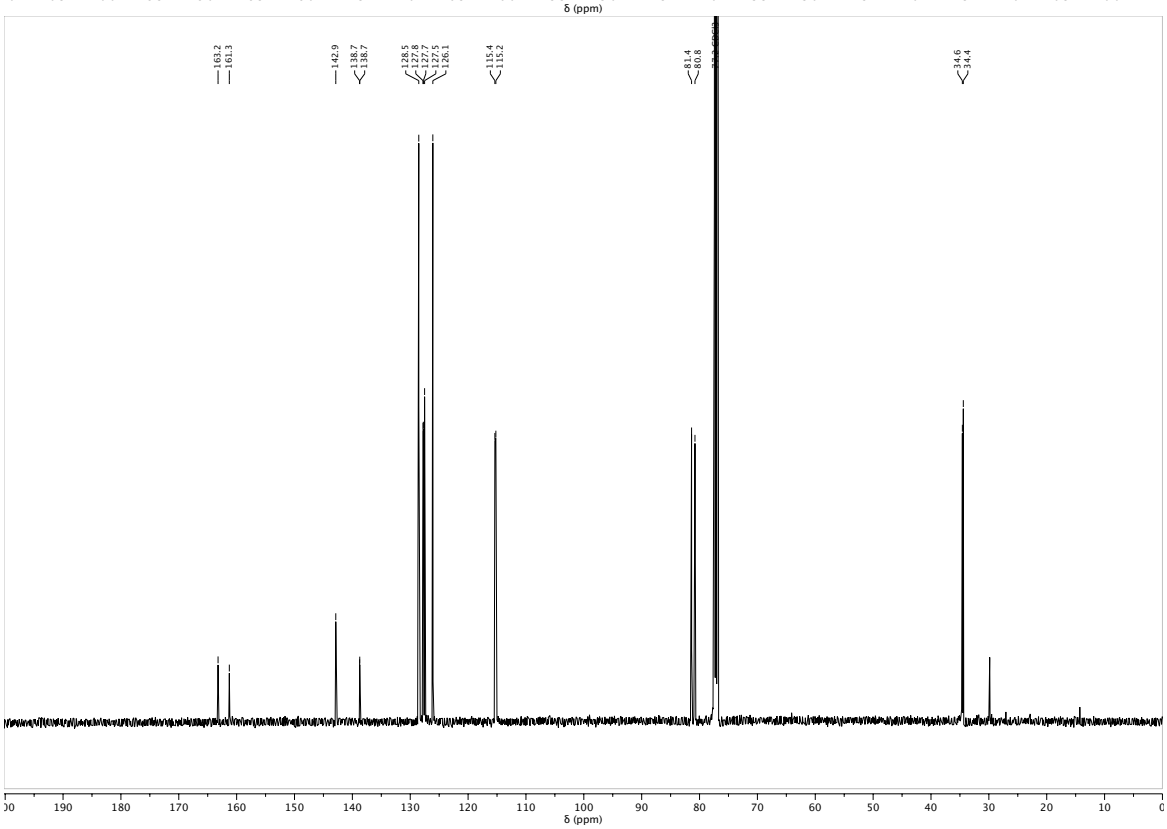

-62.30
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
δ (ppm)

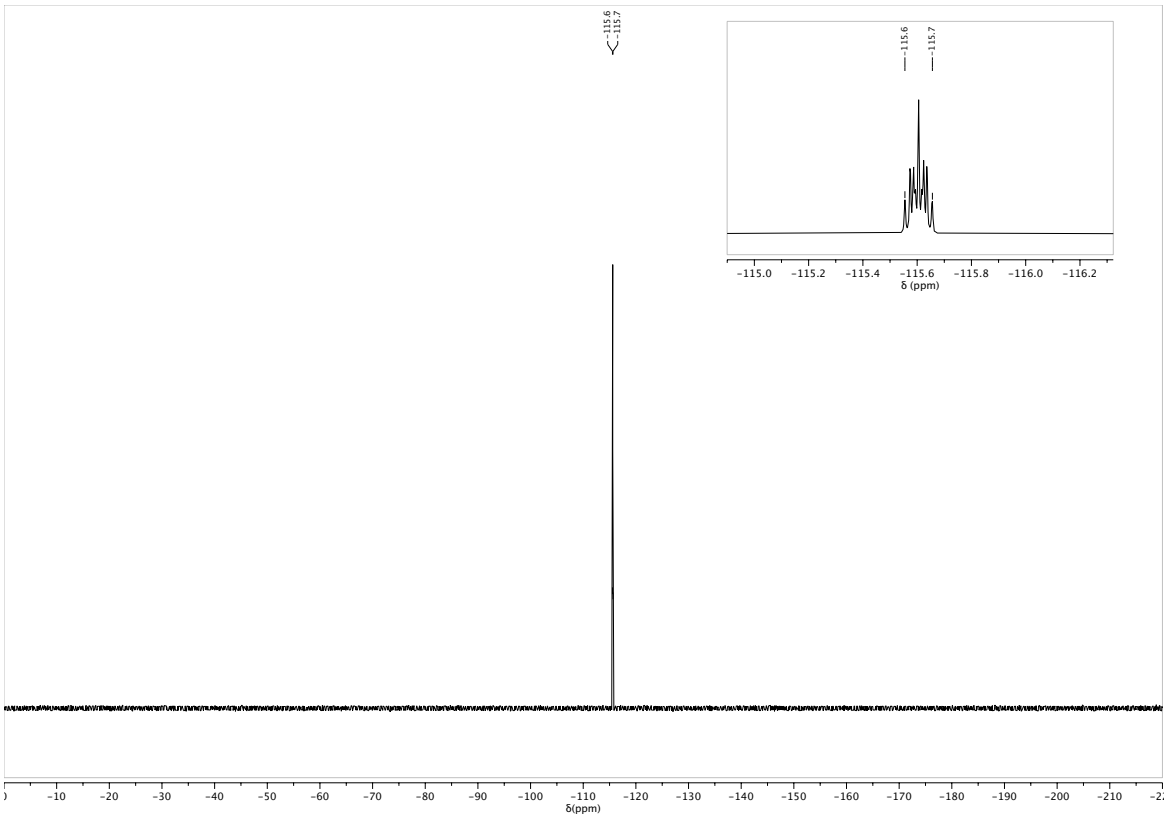
## 10.5.2. Tetrahydrofuran products

### 2-(4-Fluorophenyl)-5-phenyltetrahydrofuran (24)

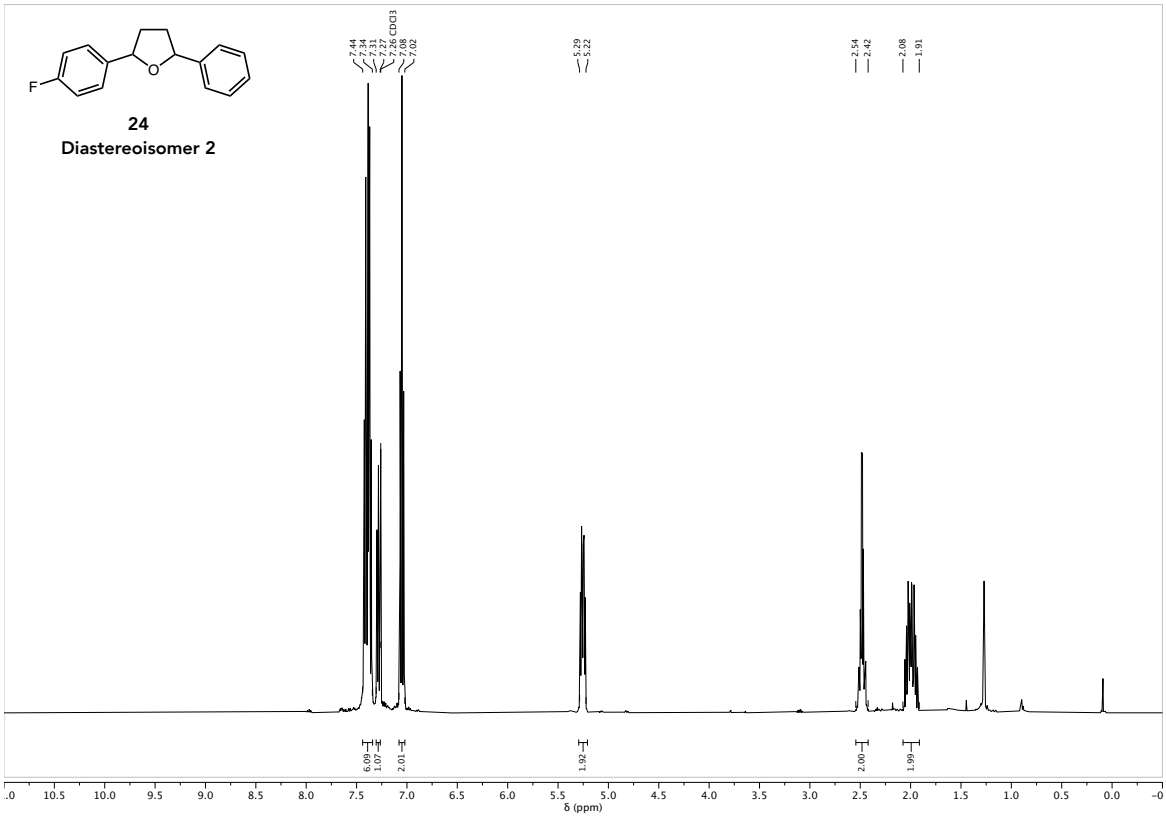
### Diastereoisomer 1

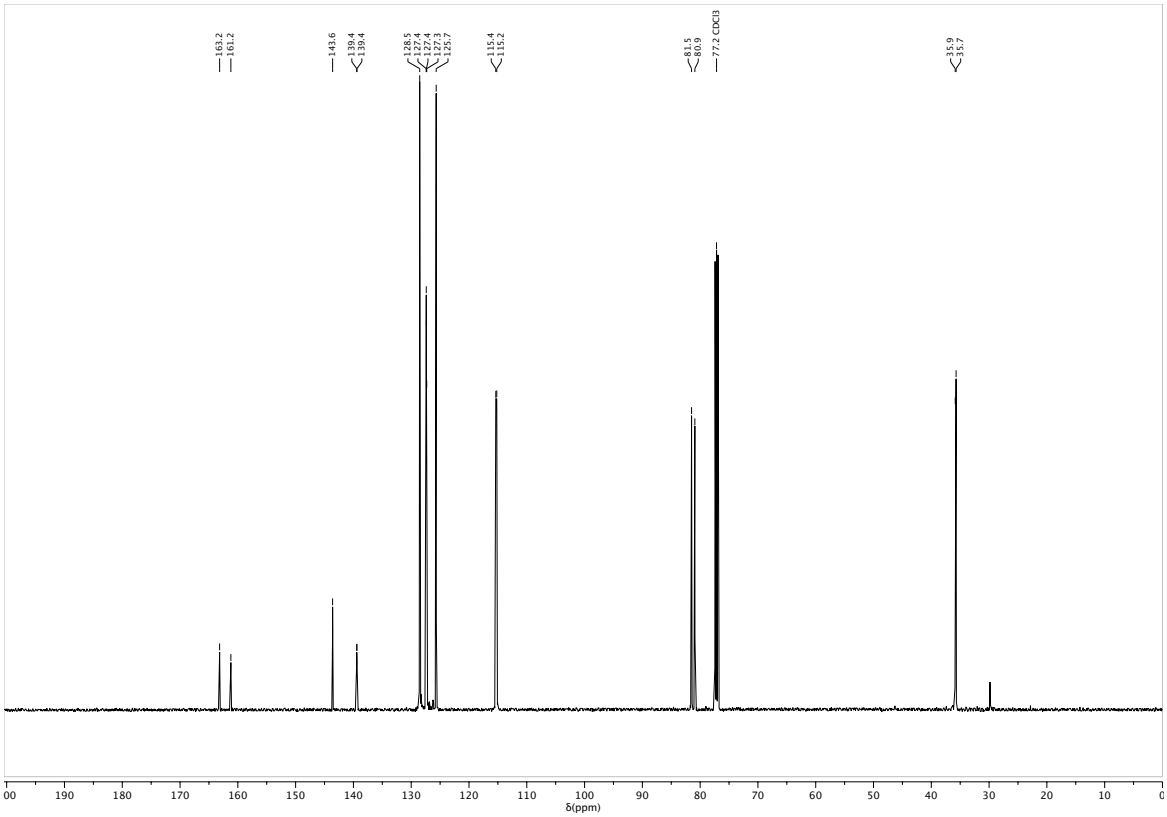


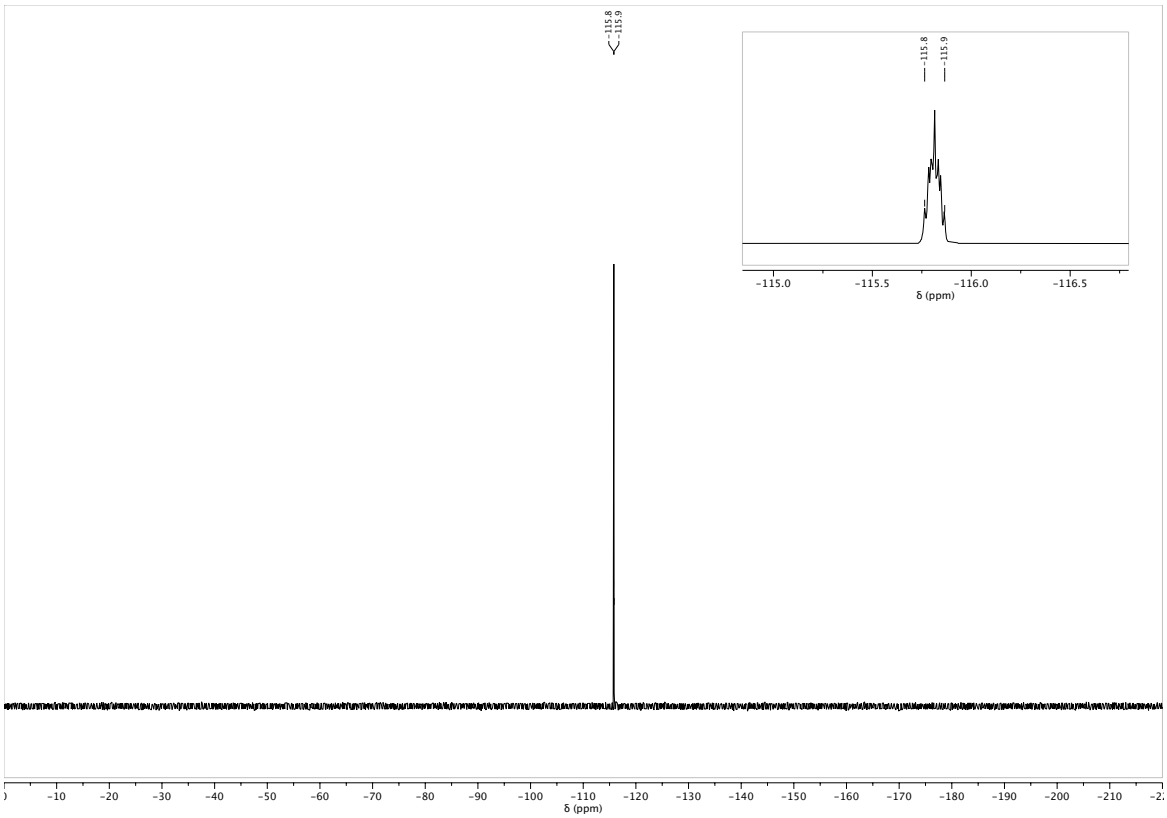




-115.6
-115.7
-115.6
-115.7
-115.0
-115.2
-115.4
-115.6
-115.8
-116.0
-116.2
δ (ppm)
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
δ(ppm)

## 2-(4-Fluorophenyl)-5-phenyltetrahydrofuran (24)
## Diastereoisomer 2

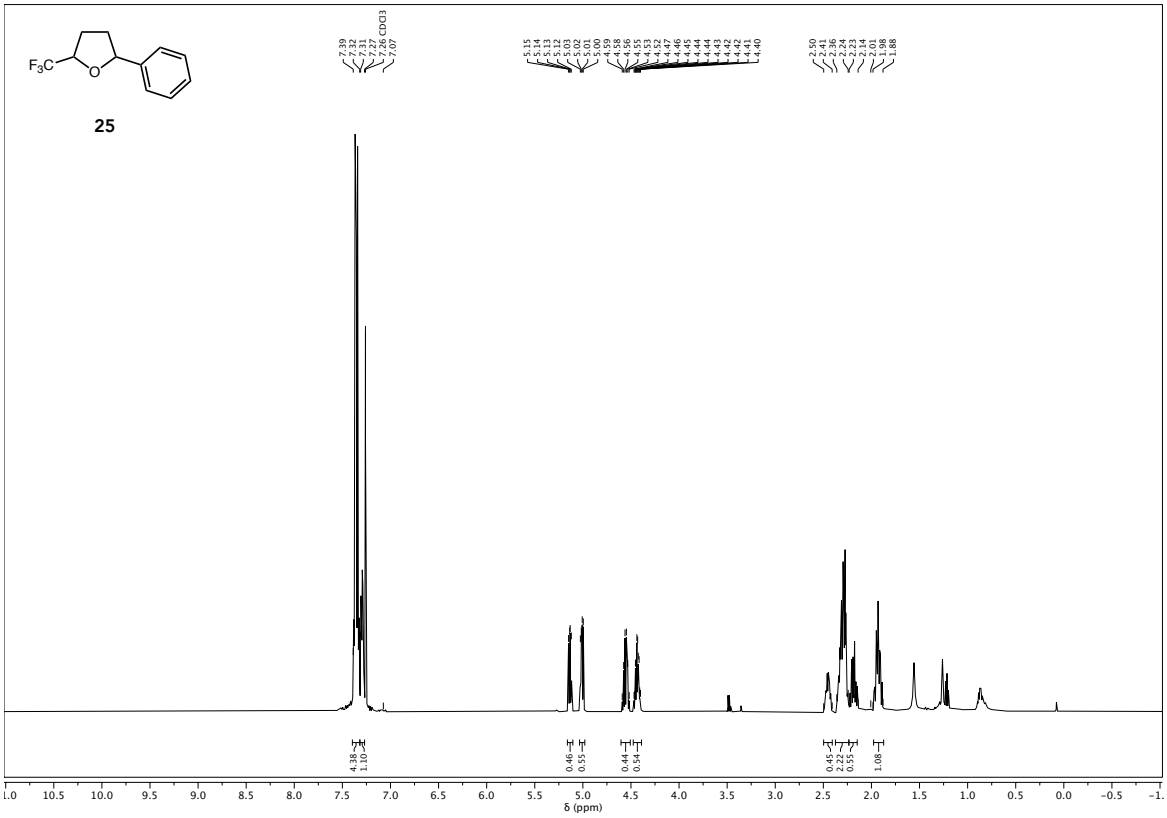


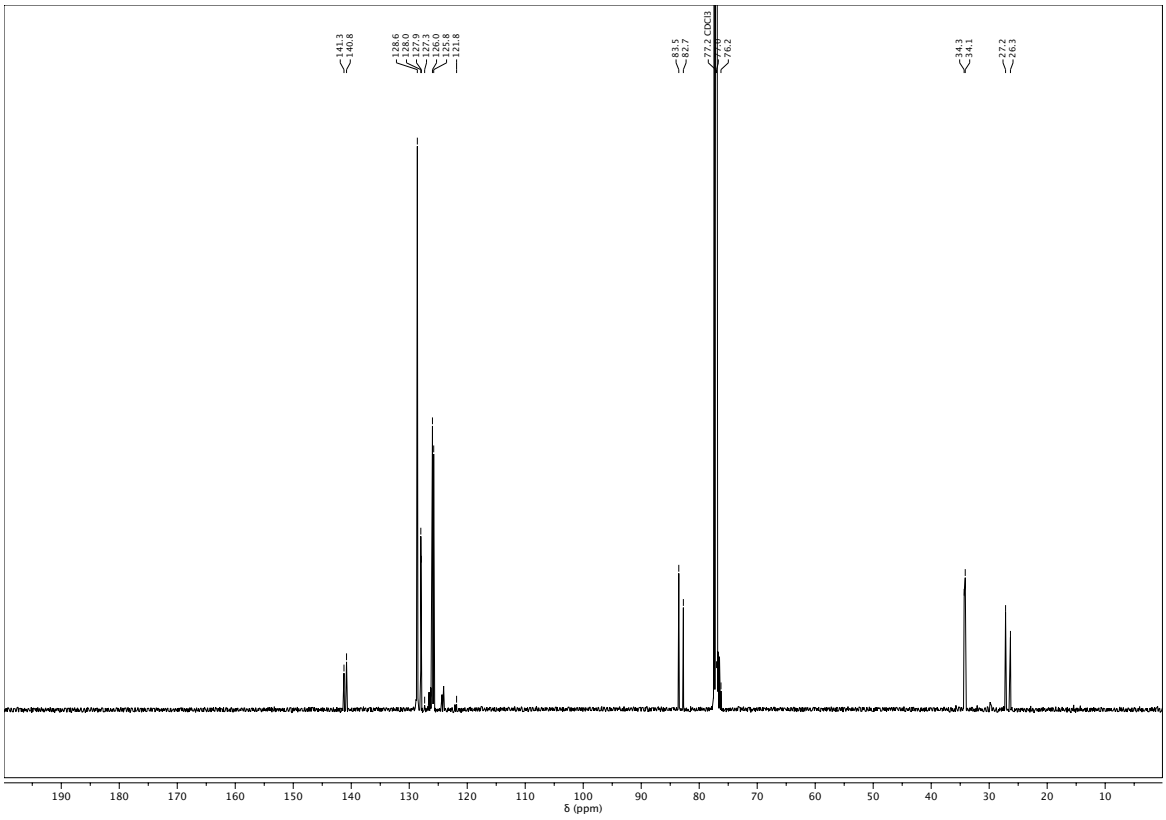



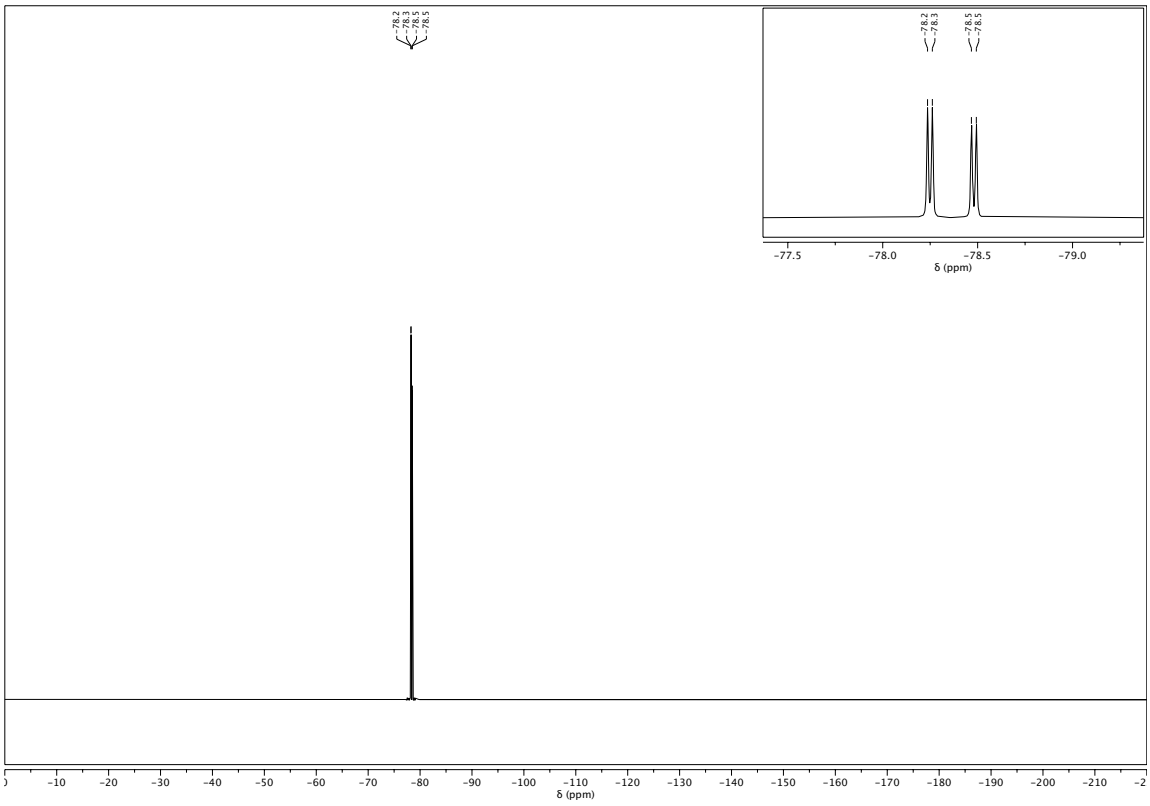

−115.8
−115.9
−115.8
−115.9
−115.0
−115.5
−116.0
−116.5
δ (ppm)
−10
−20
−30
−40
−50
−60
−70
−80
−90
−100
−110
−120
−130
−140
−150
−160
−170
−180
−190
−200
−210
δ (ppm)

2-Phenyl-5-(trifluoromethyl)tetrahydrofuran (25)

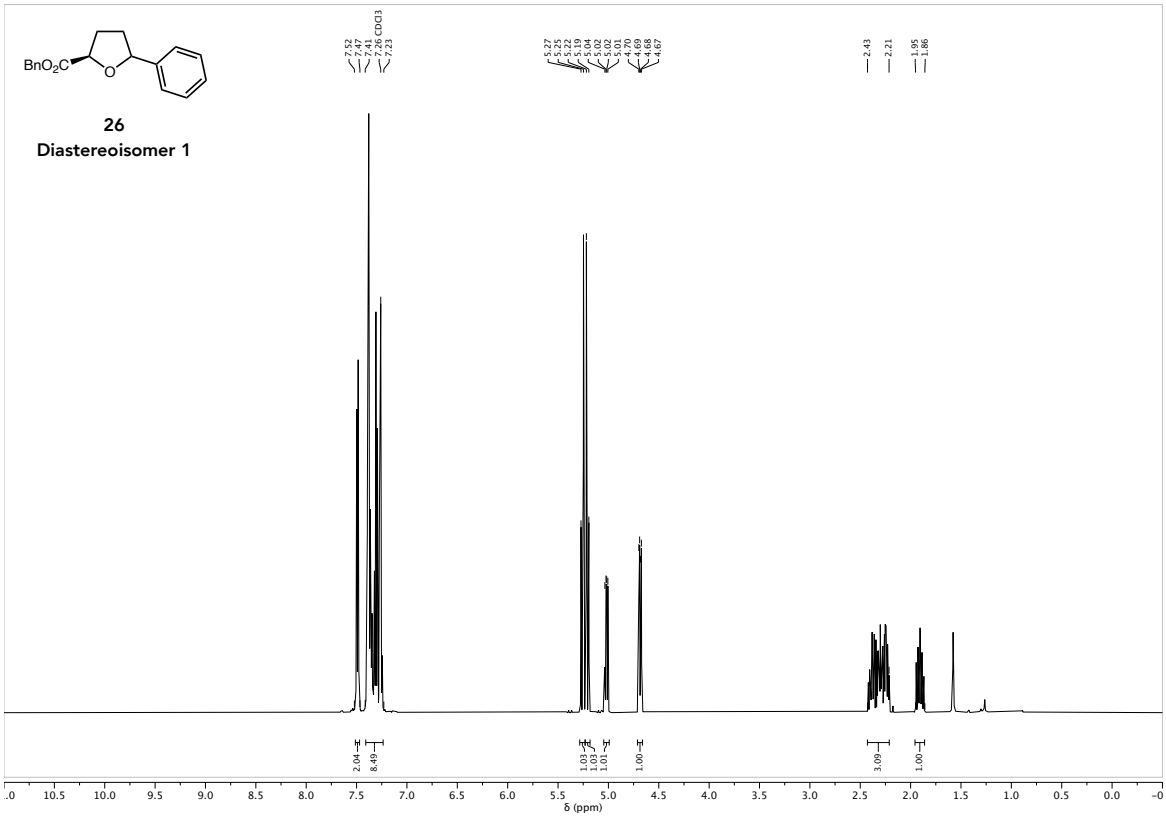
Mixture of diastereoisomers

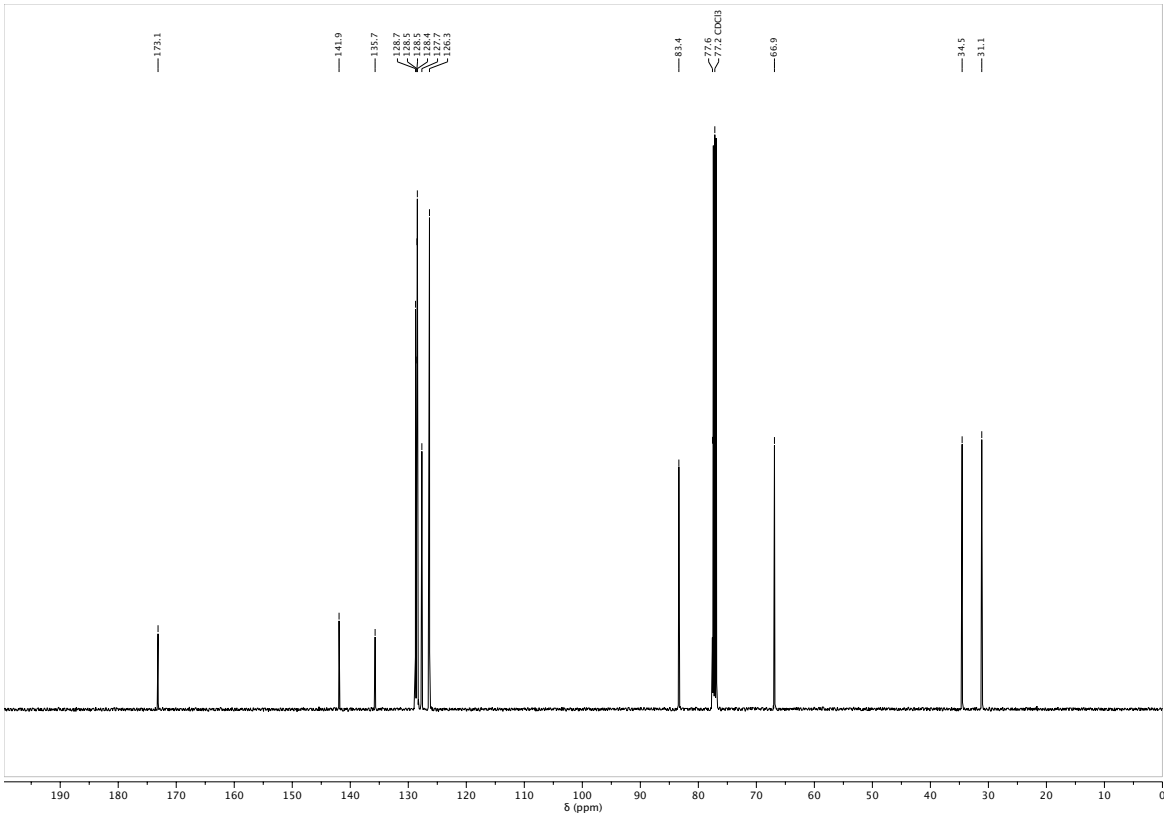


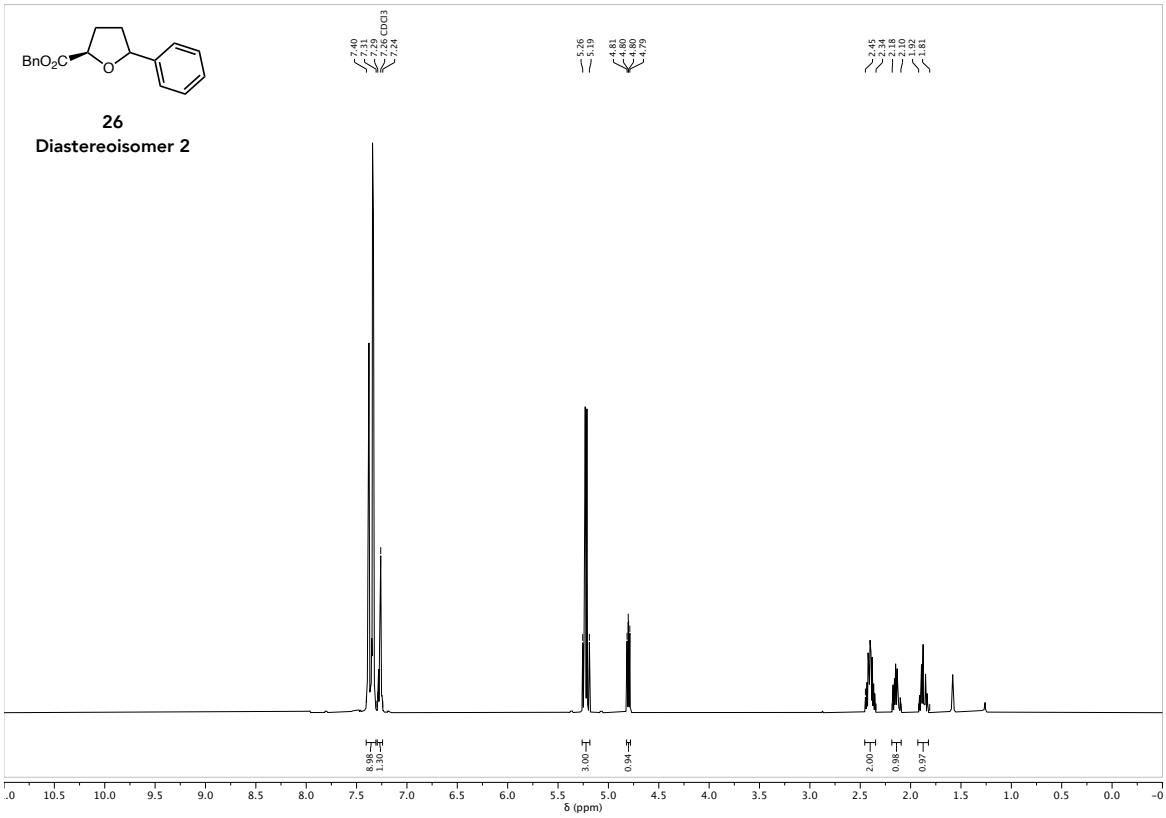

-78.2
-78.3
-78.5
-78.5
-78.2
-78.3
-78.5
-78.5
-77.5
-78.0
-78.5
-79.0
δ (ppm)
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
δ (ppm)

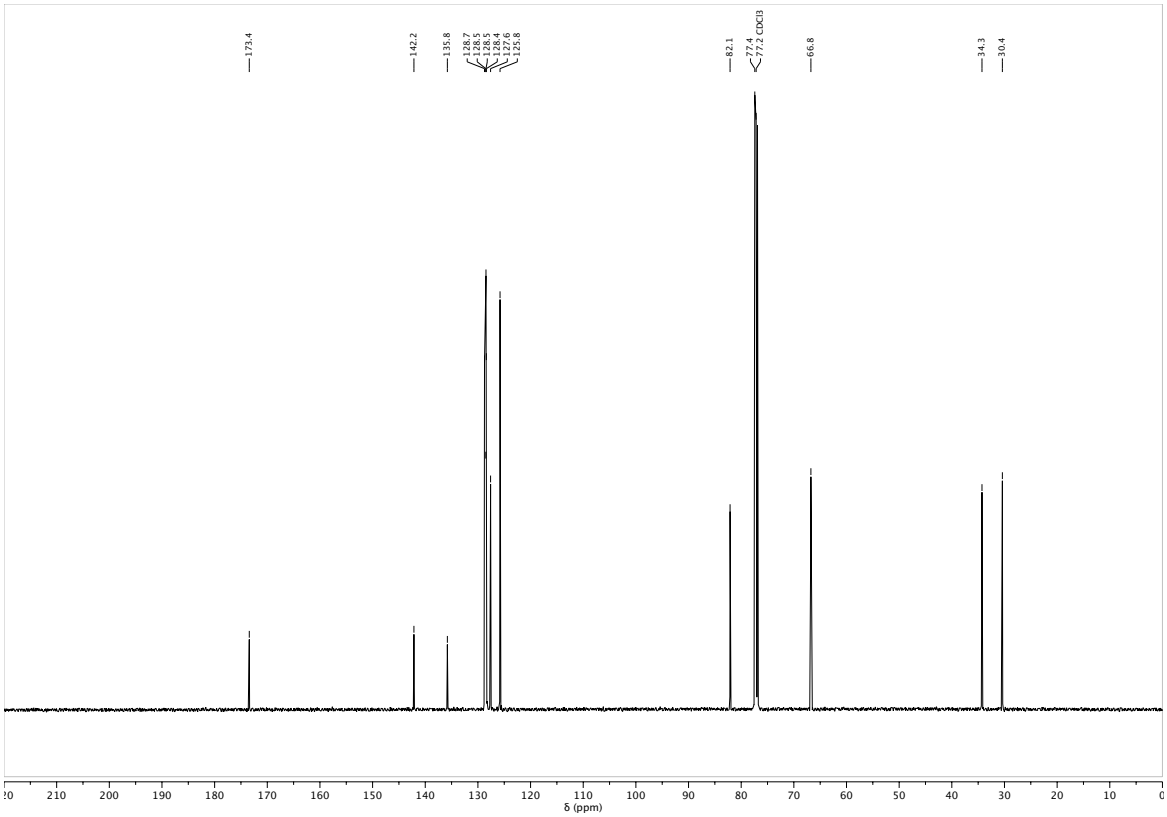
Benzyl (2*R*)-5-phenyltetrahydrofuran-2-carboxylate (26)
Diastereoisomer 1



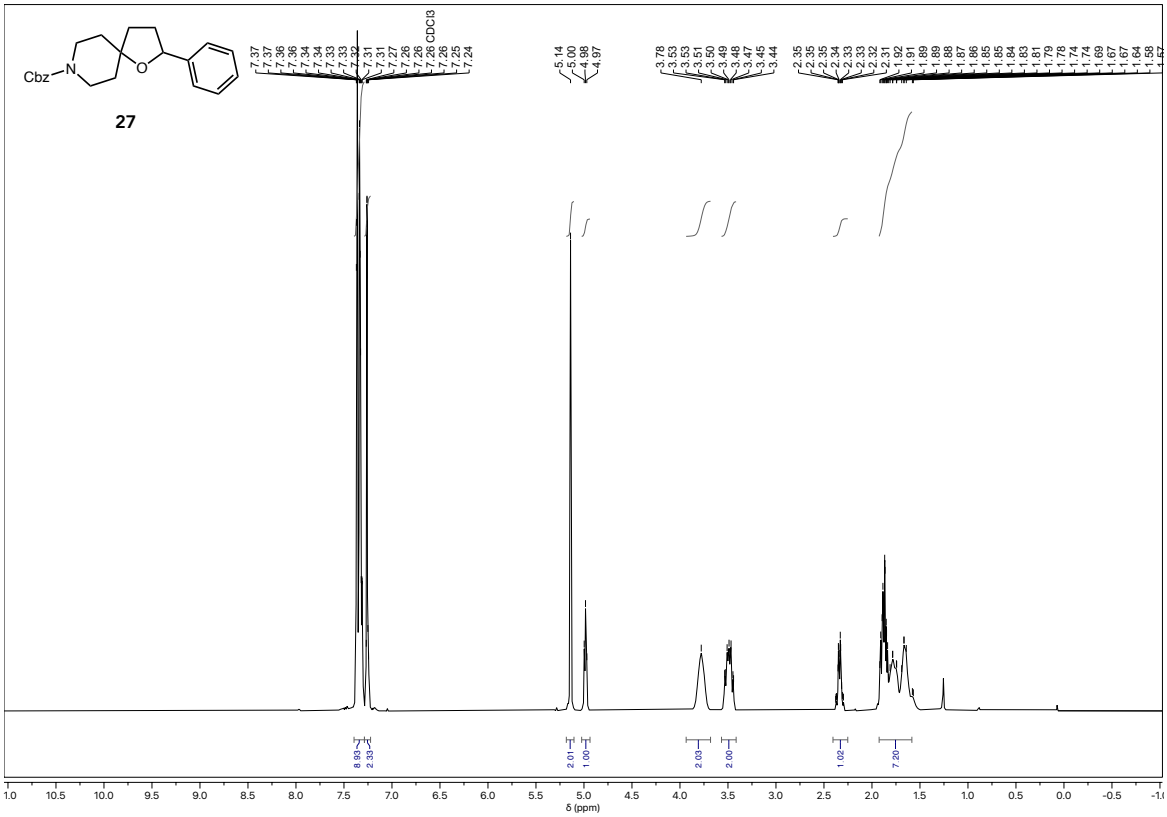



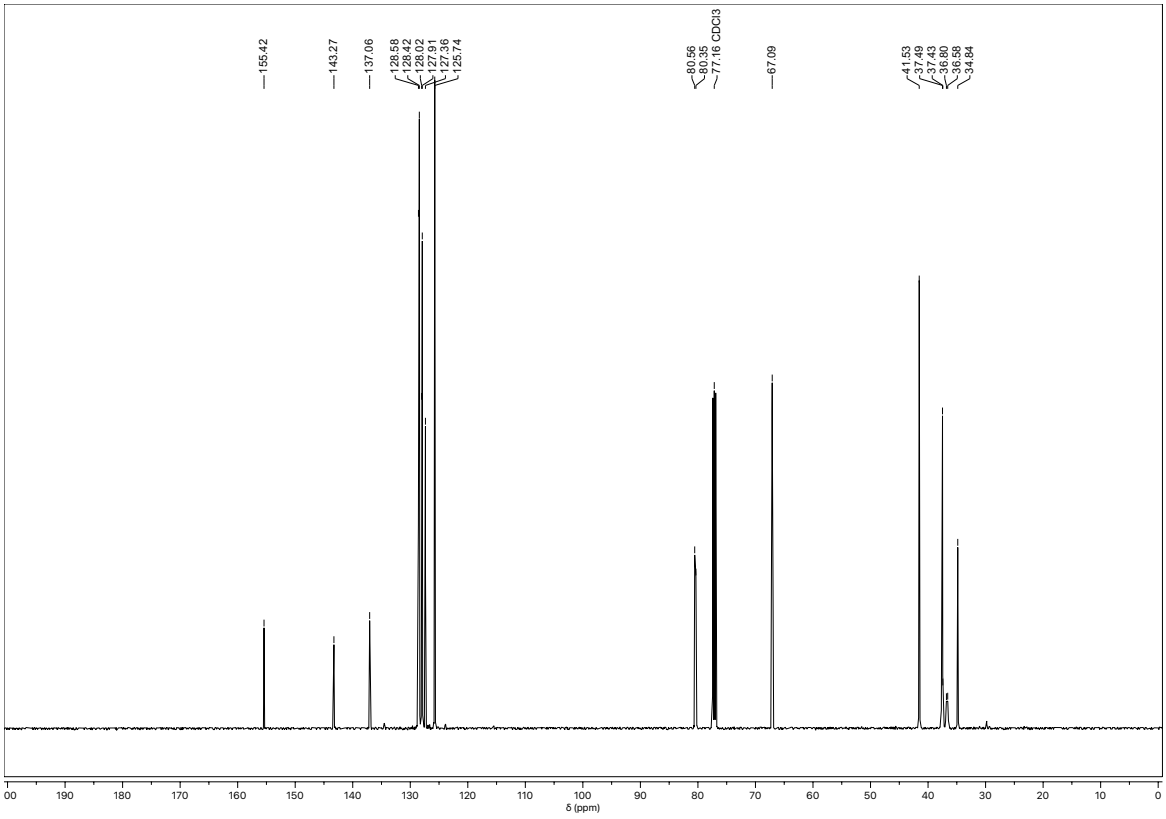
Benzyl (2*R*)-5-phenyltetrahydrofuran-2-carboxylate (26)
Diastereoisomer 2



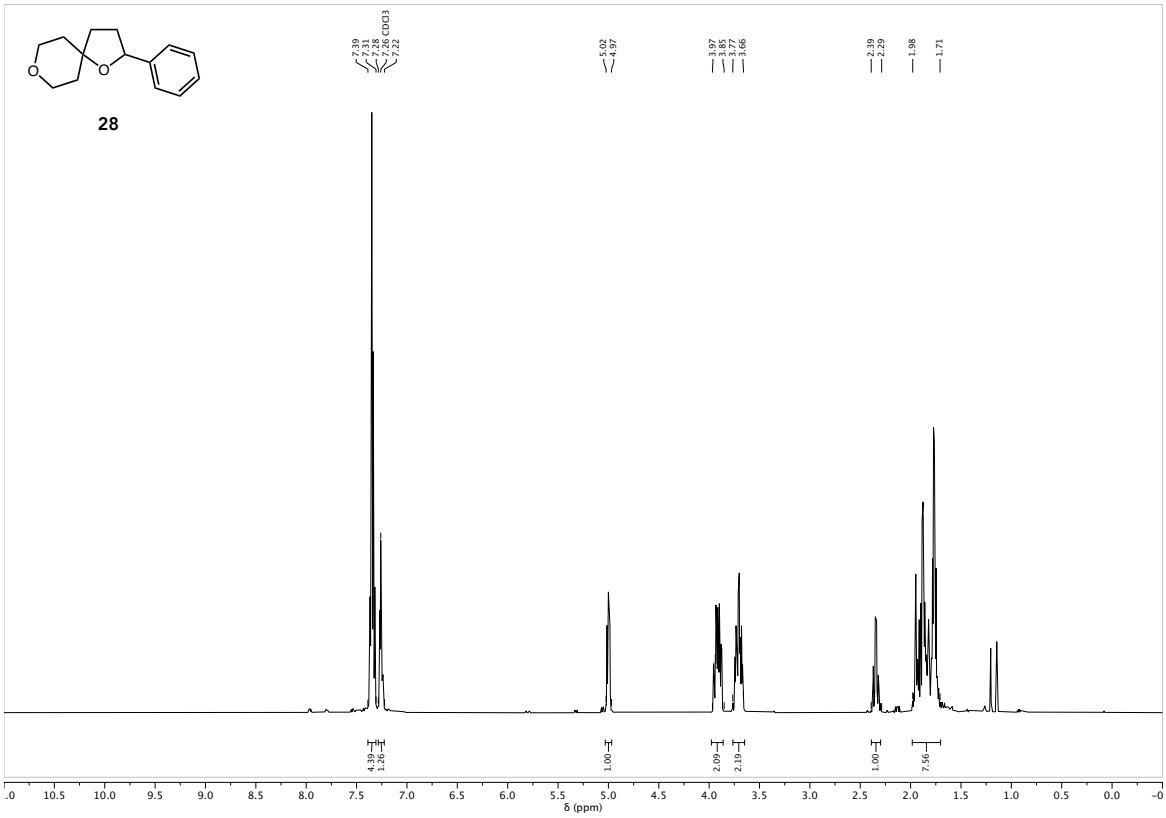



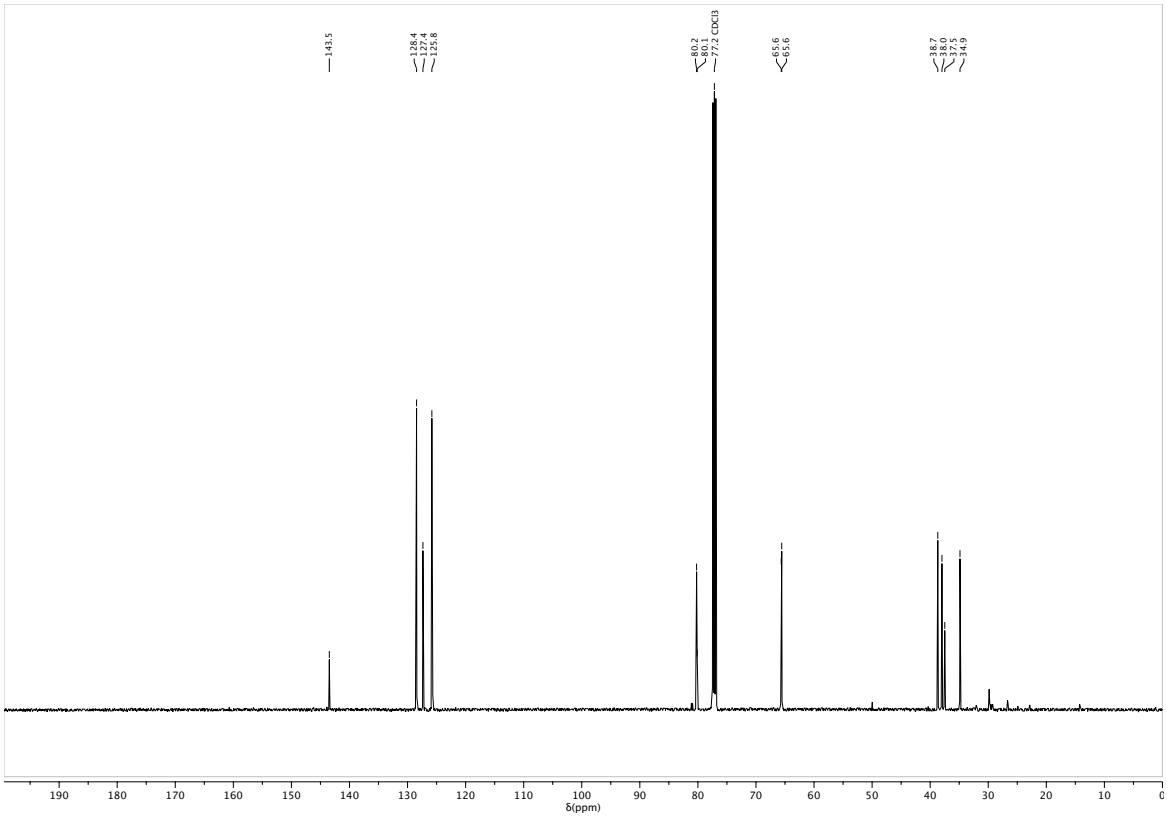
Benzyl 2-phenyl-1-oxa-8-azaspiro[4.5]decane-8-carboxylate (27)



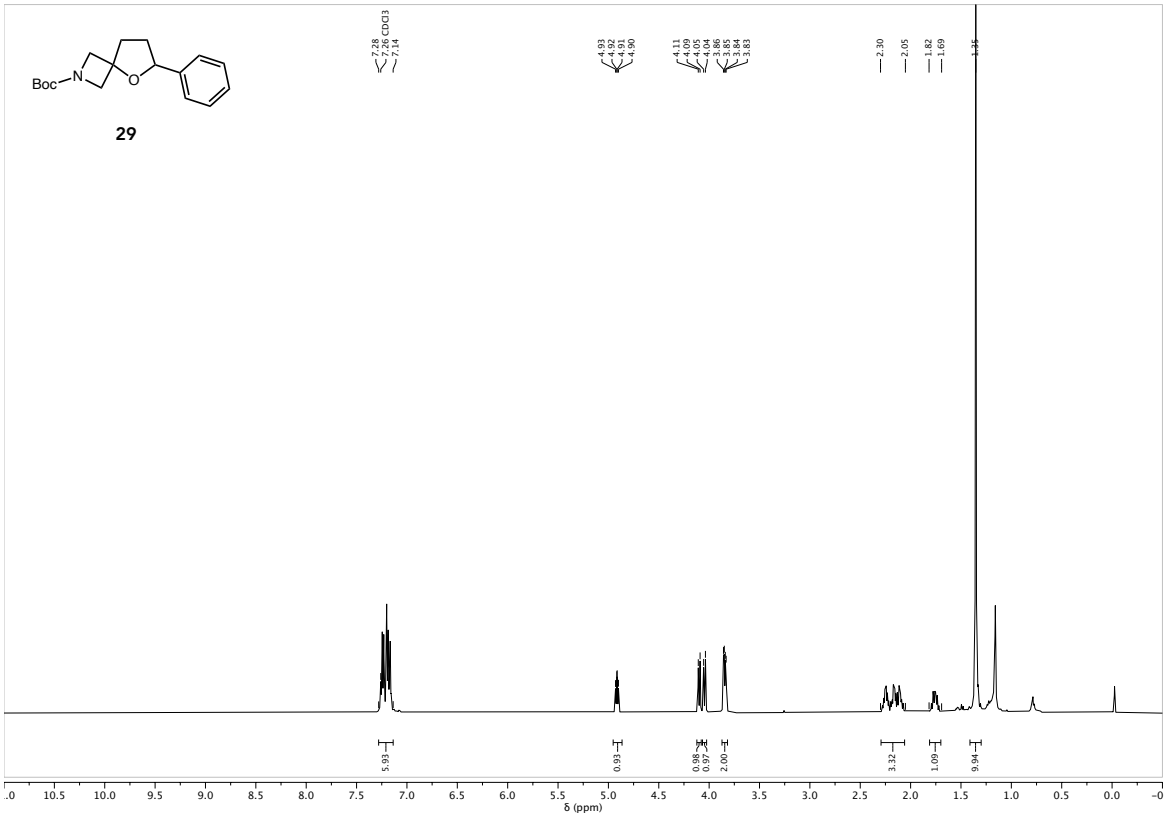



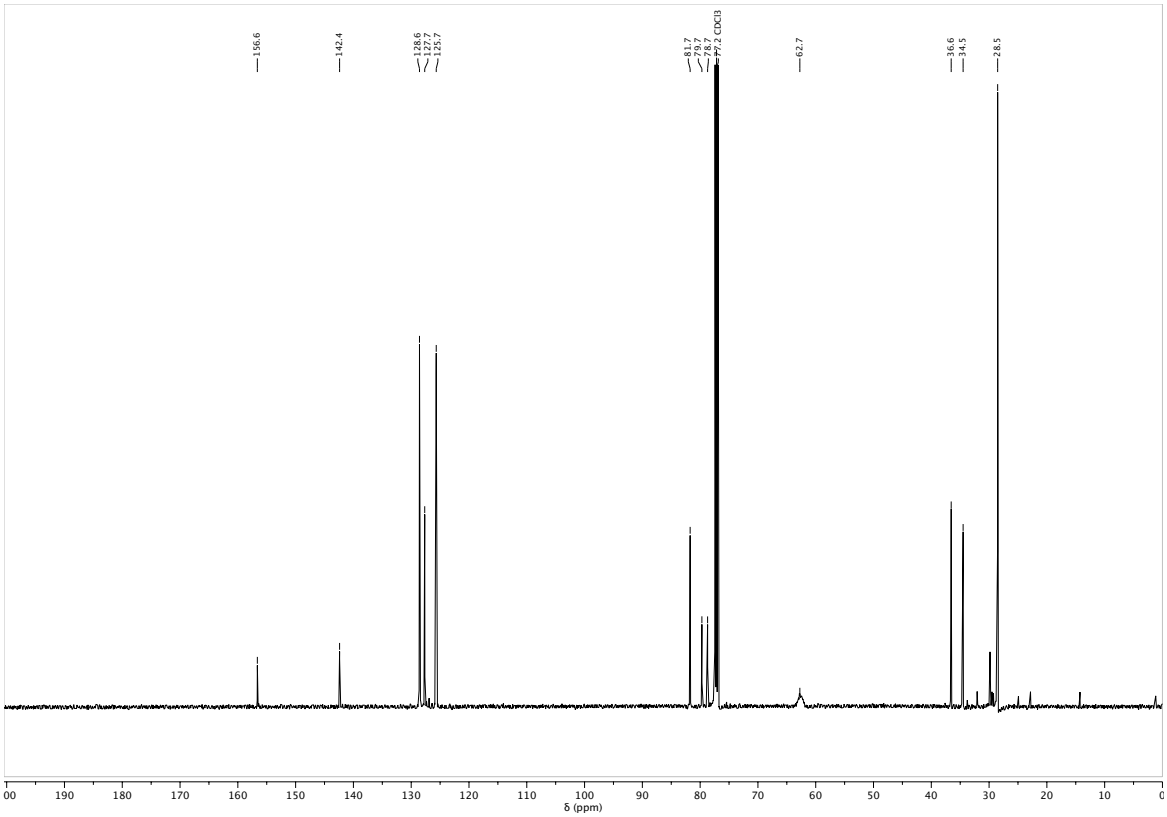
## 2-Phenyl-1,8-dioxaspiro[4.5]decane (28)



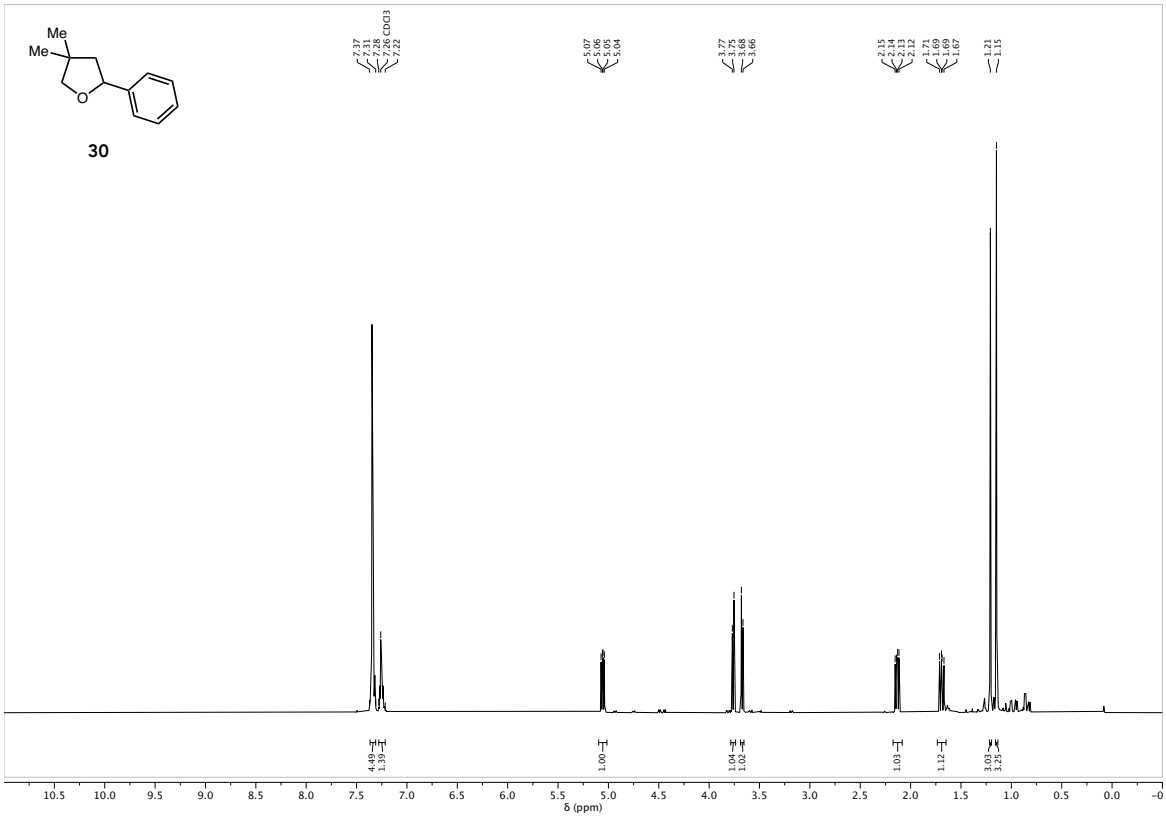



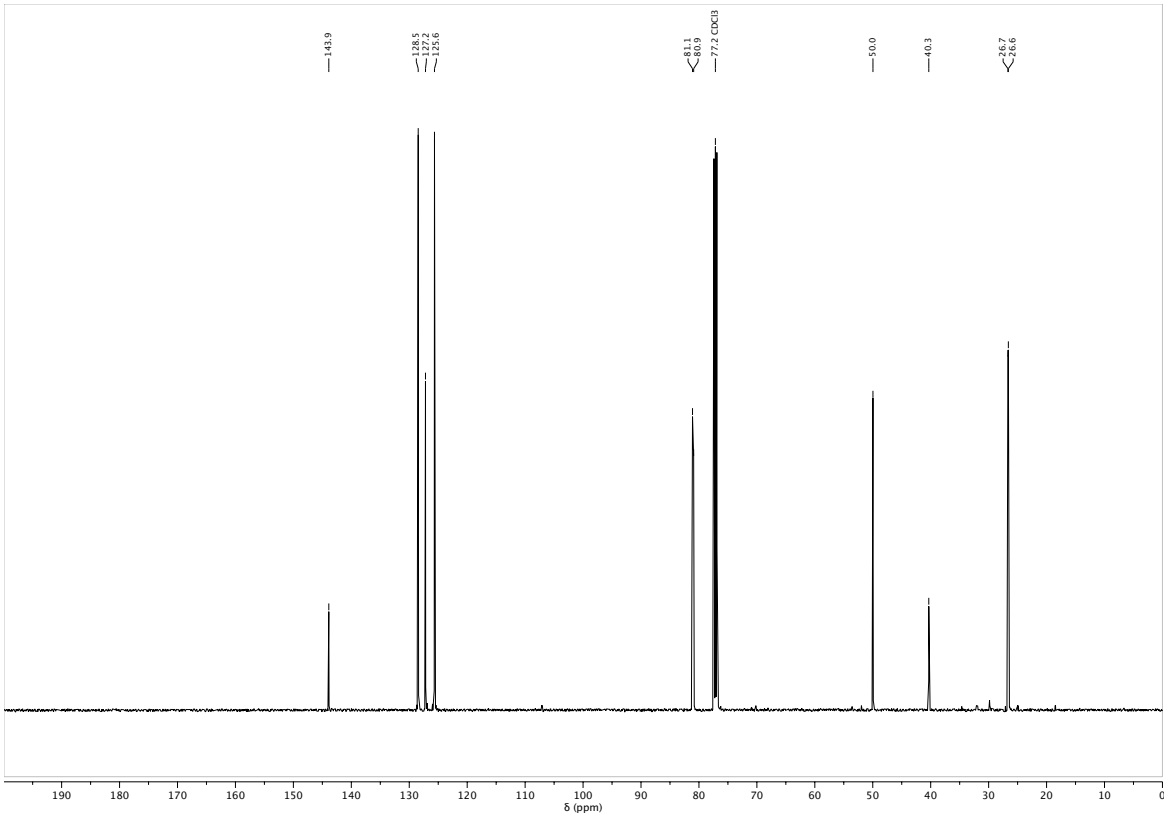
*Tert*-butyl 6-phenyl-5-oxa-2-azaspiro[3.4]octane-2-carboxylate (29)



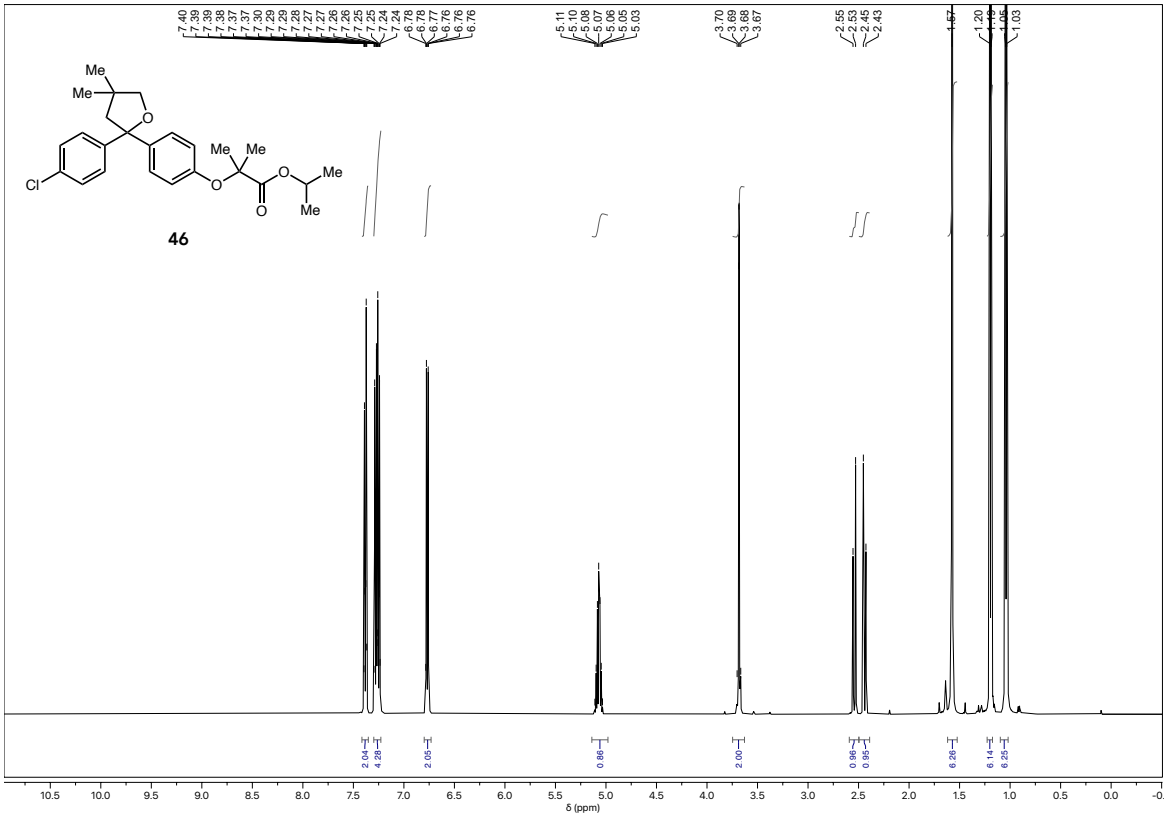



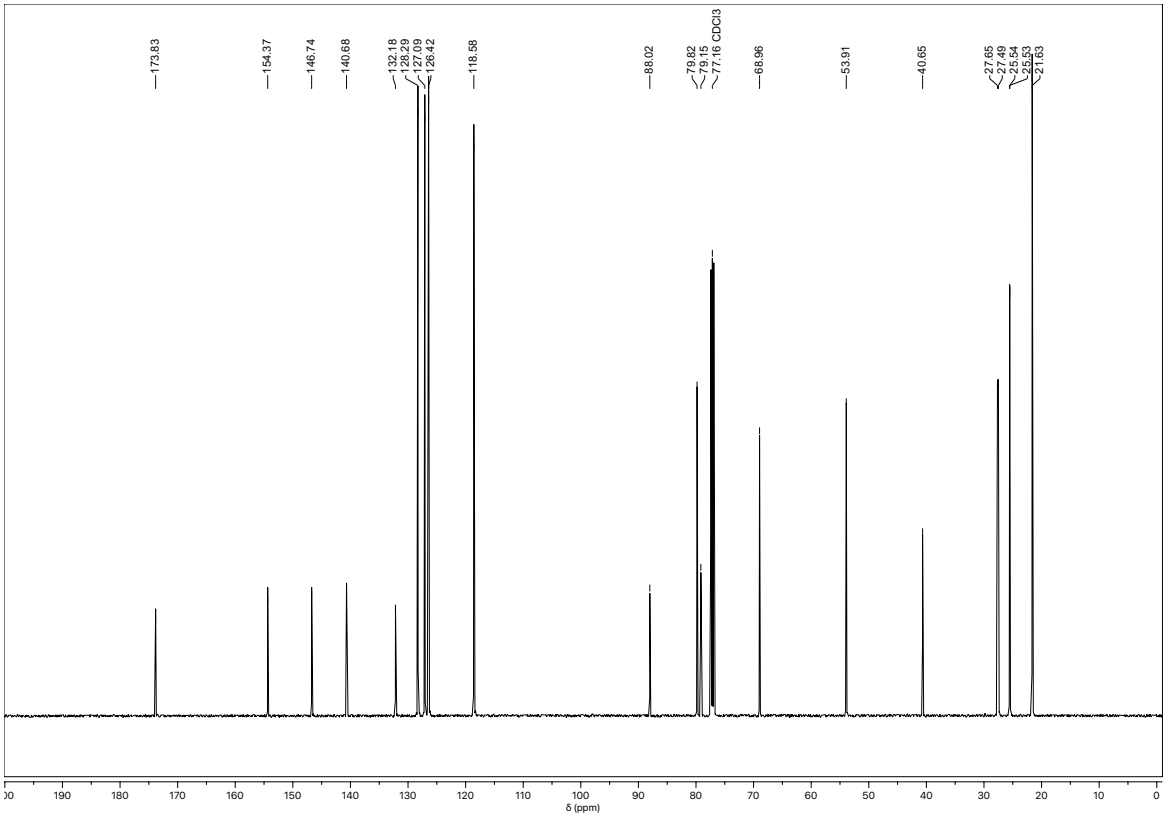
## 4,4-Dimethyl-2-phenyltetrahydrofuran (30)



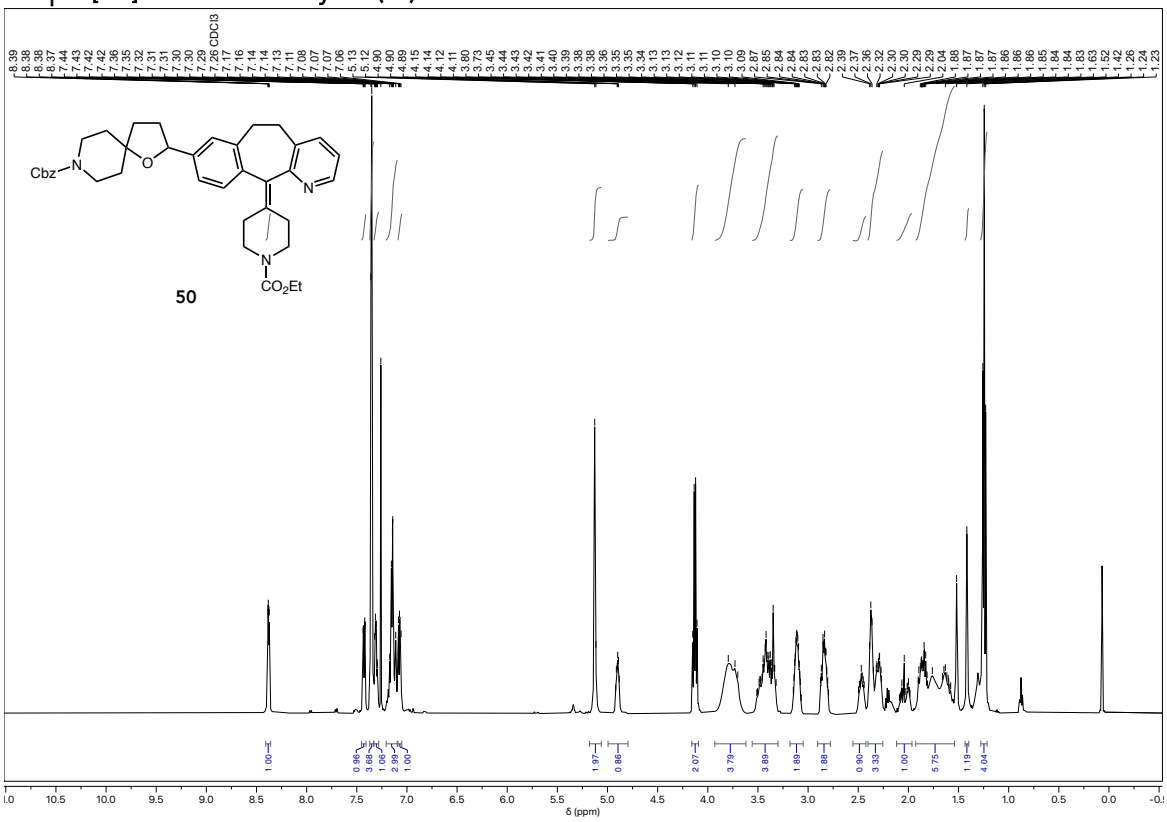



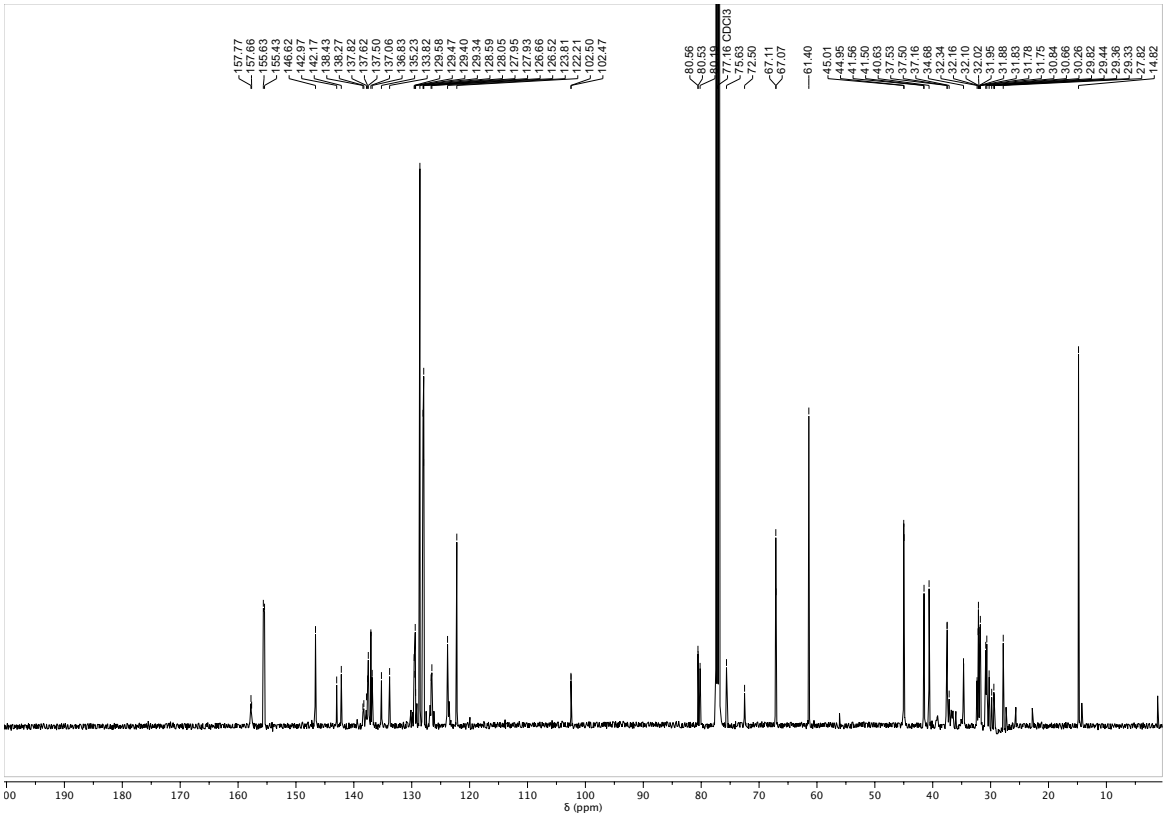
Isopropyl 2-(4-(2-(4-chlorophenyl)tetrahydrofuran-2-yl)phenoxy)-2-methylpropanoate (46)



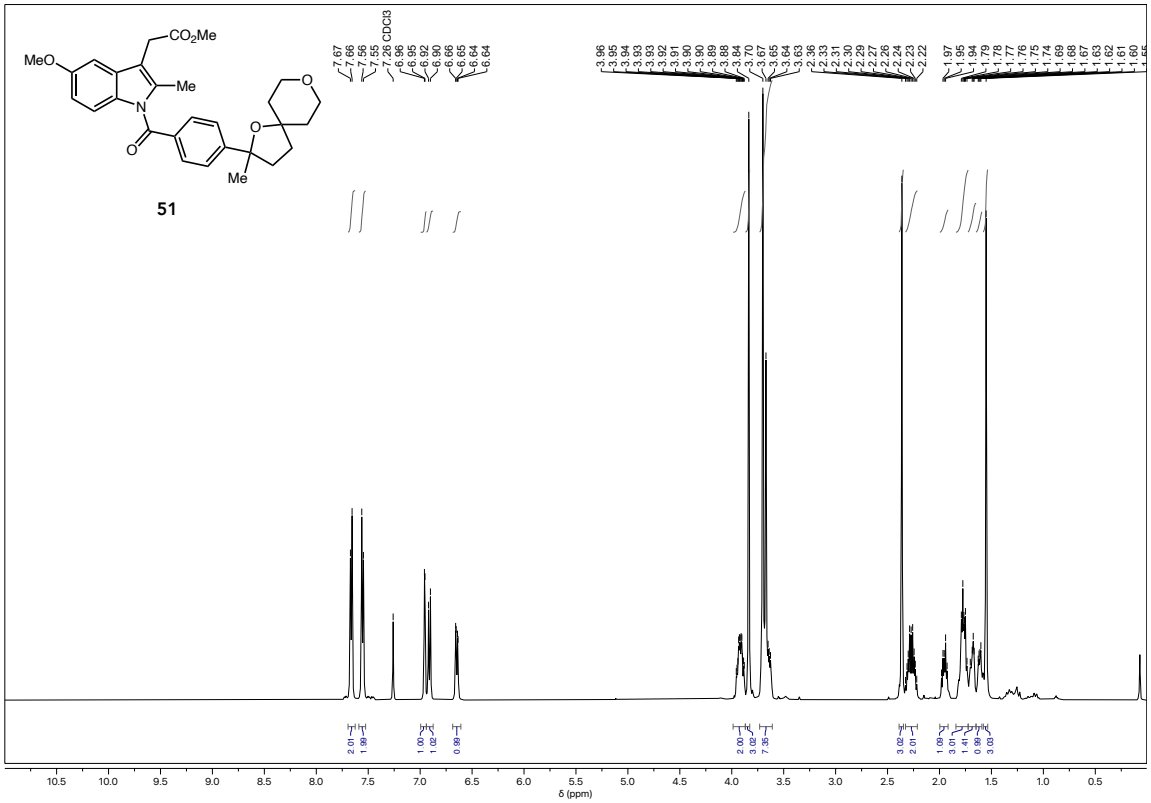



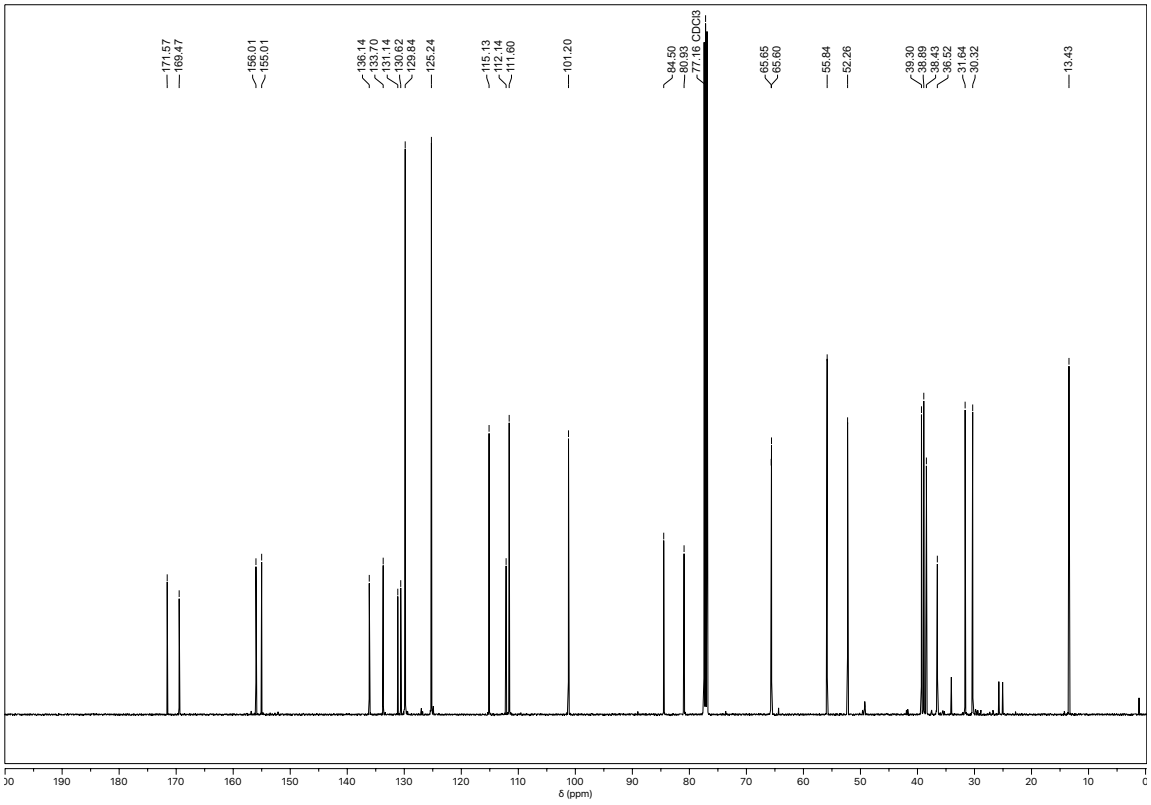
Benzyl 2-(11-(1-(ethoxycarbonyl)piperidin-4-ylidene)-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-8-yl)-1-oxa-8-azaspiro[4.5]decane-8-carboxylate (50)



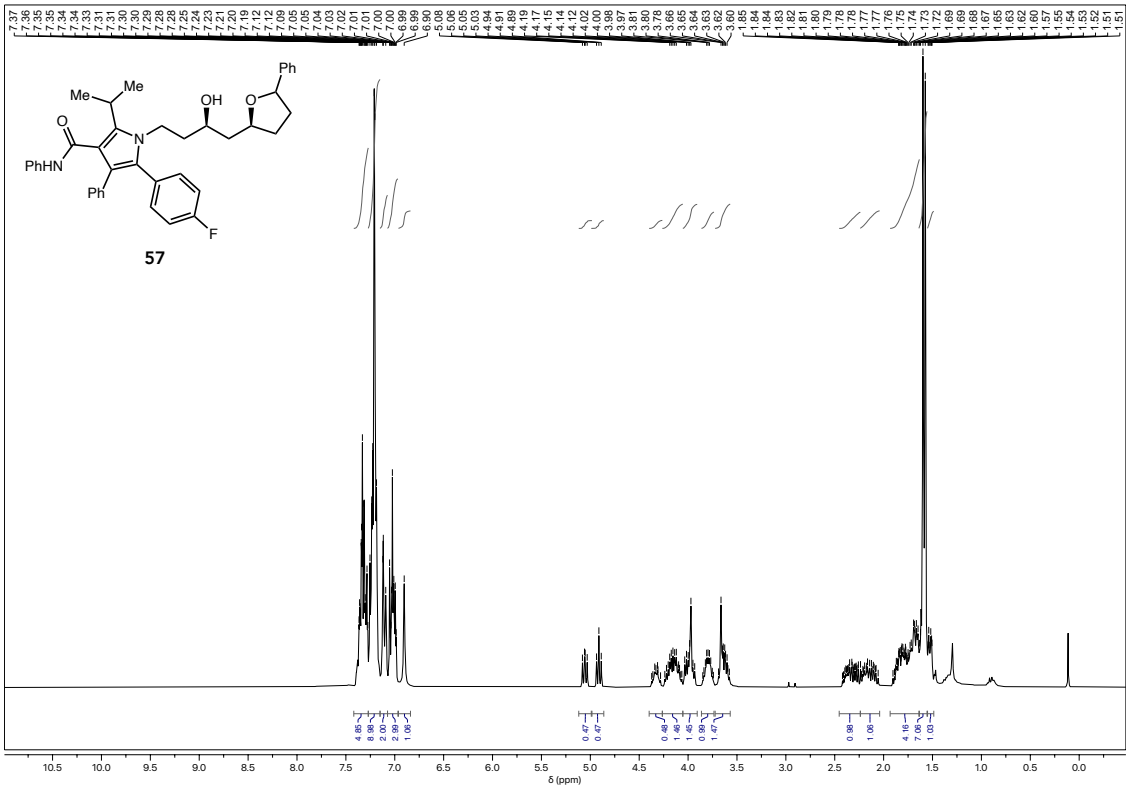



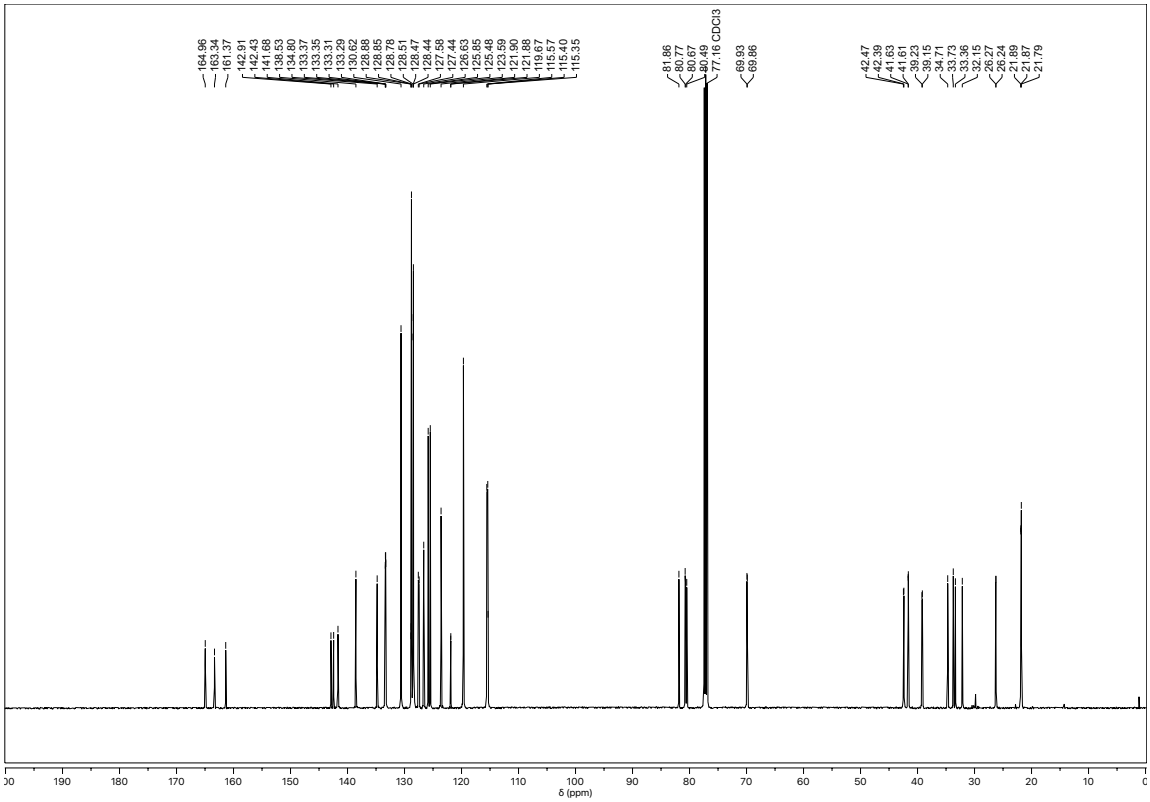
Methyl 2-(5-methoxy-2-methyl-1-(4-(2-methyl-1,8-dioxaspiro[4.5]decan-2-yl)benzoyl)-1*H*-indol-3-yl)acetate (51)

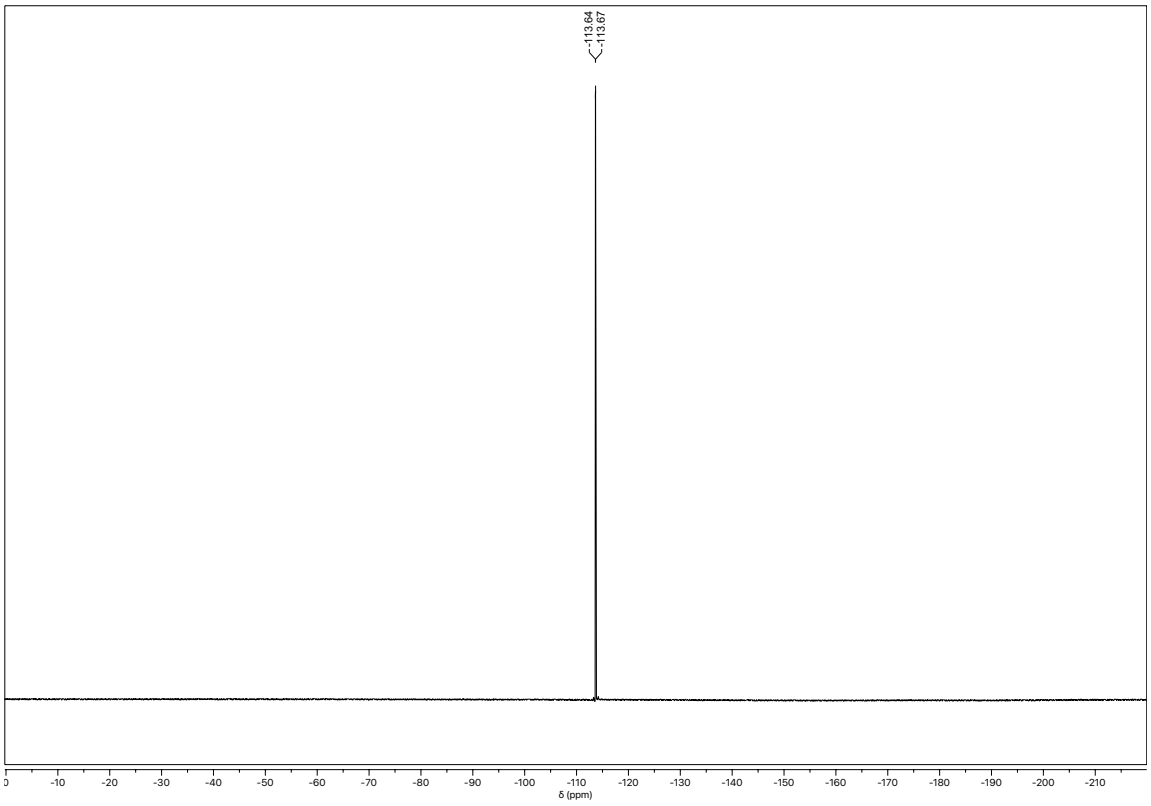


5-(4-Fluorophenyl)-1-((3*R*)-3-hydroxy-4-((2*S*)-5-phenyltetrahydrofuran-2-yl)butyl)-2-isopropyl-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide (57)

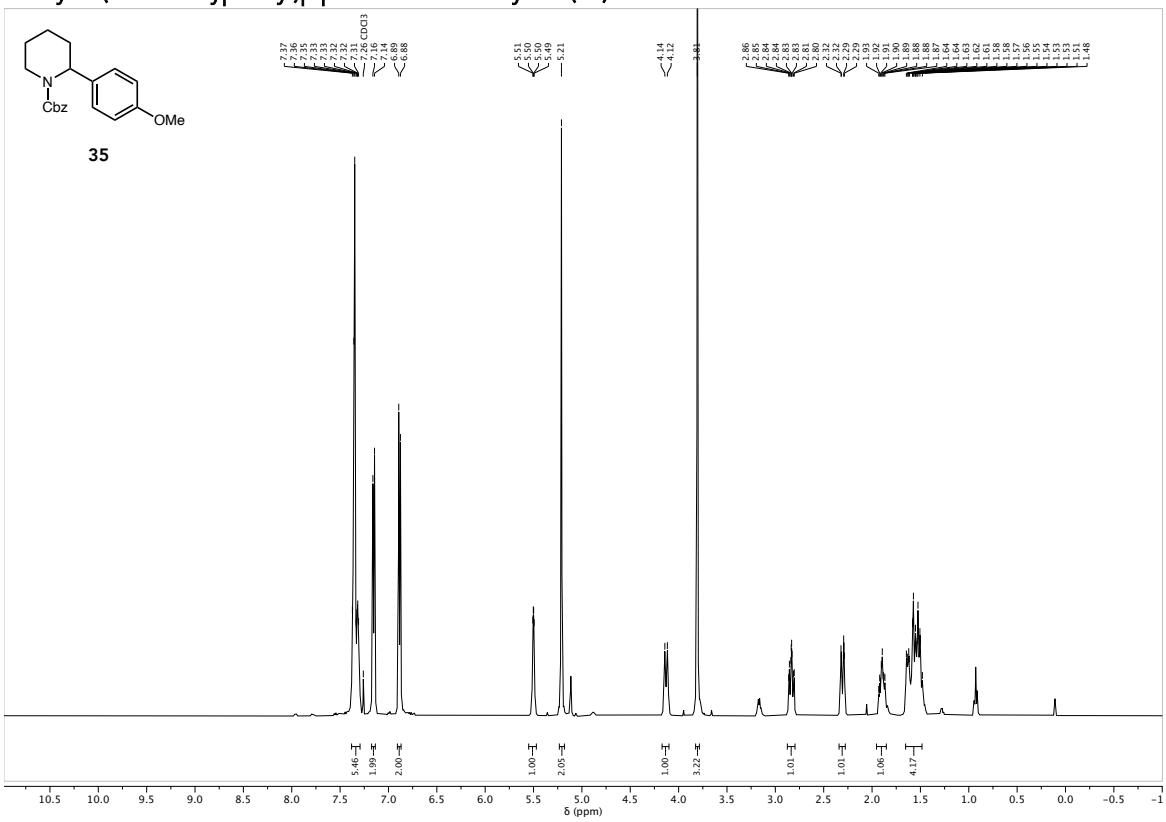


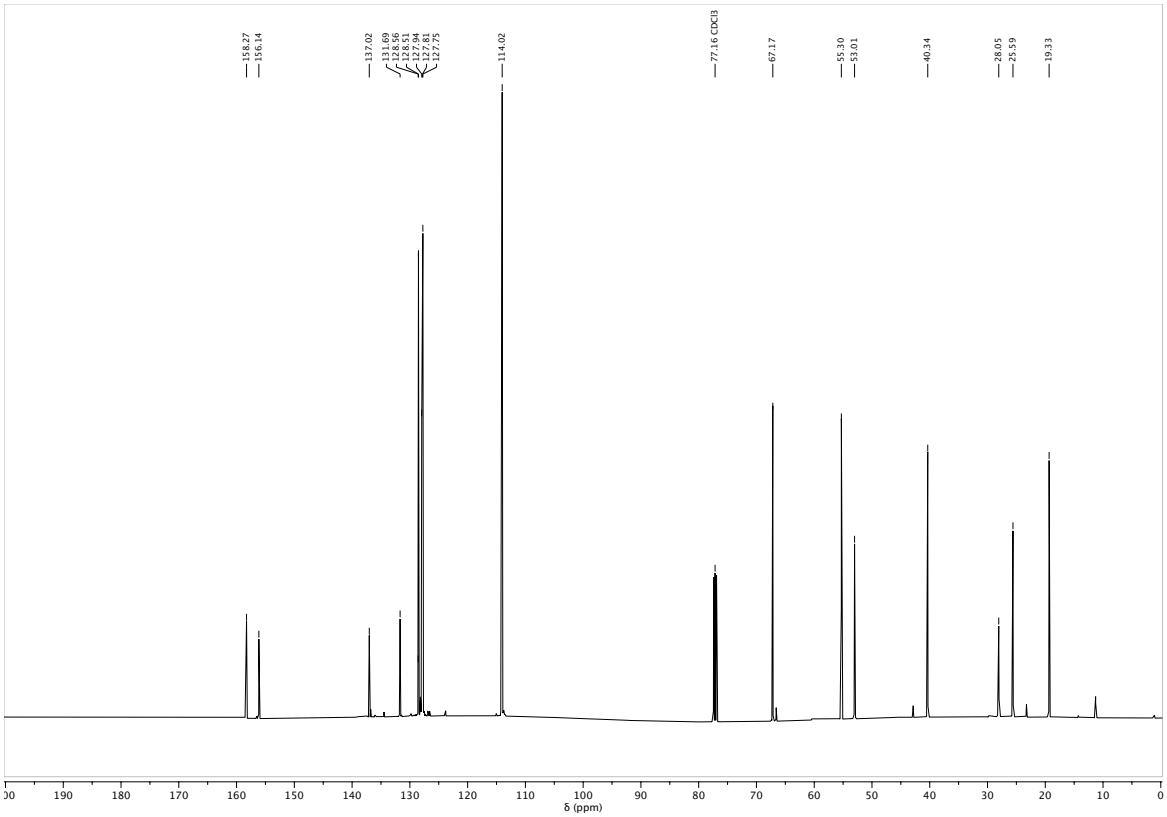




-113.64
-113.67
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
δ (ppm)

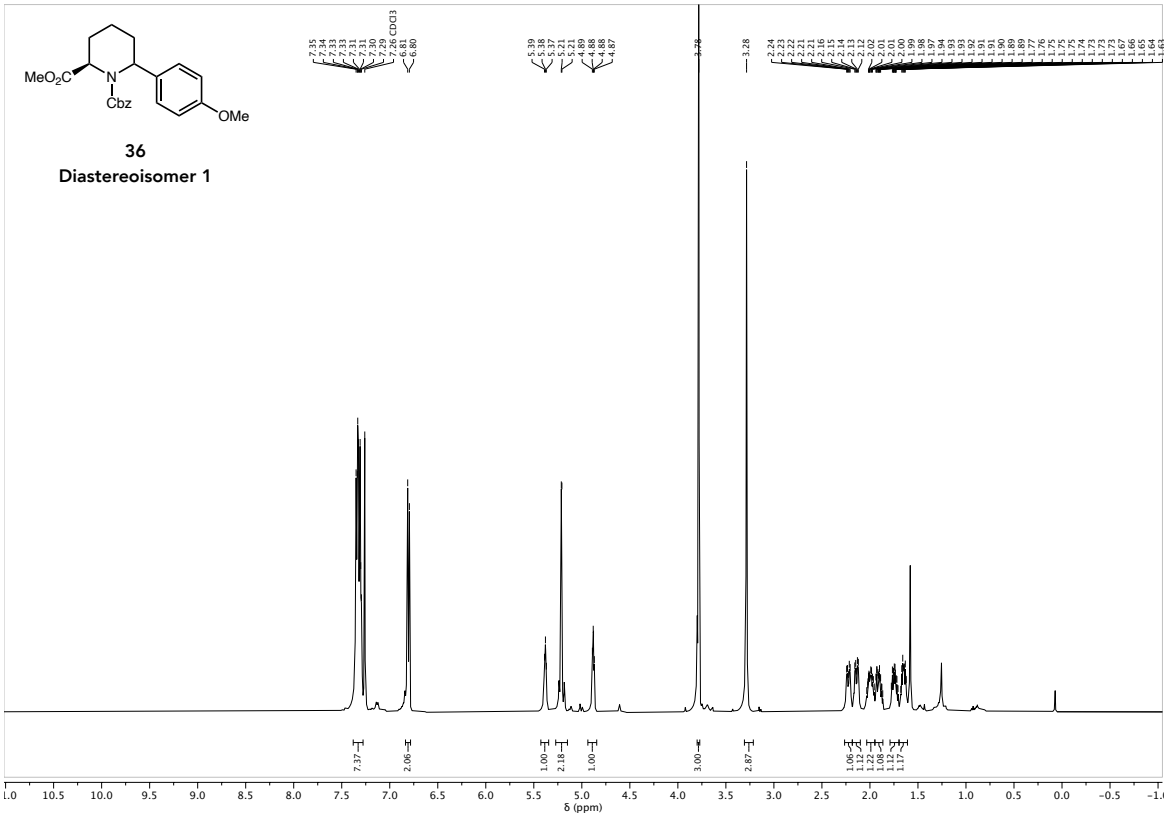
## 10.5.3. Piperidine Products

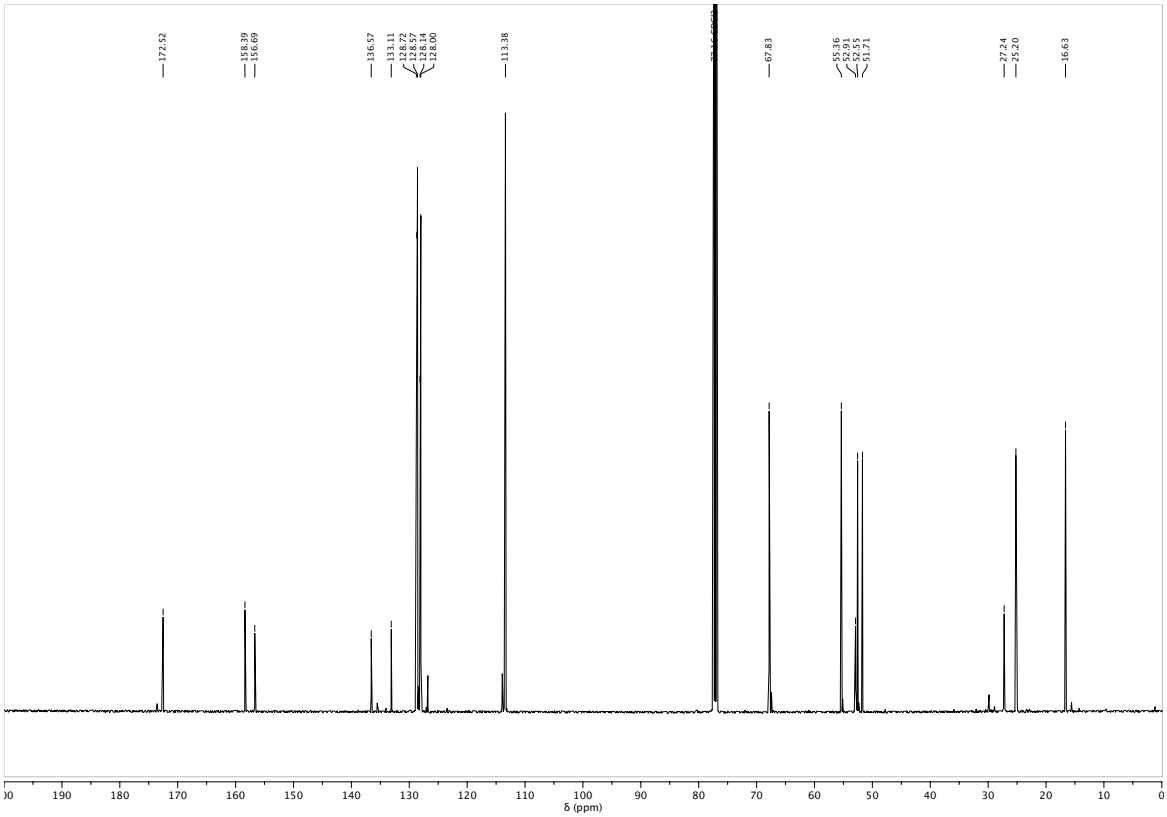
### Benzyl 2-(4-methoxyphenyl)piperidine-1-carboxylate (35)



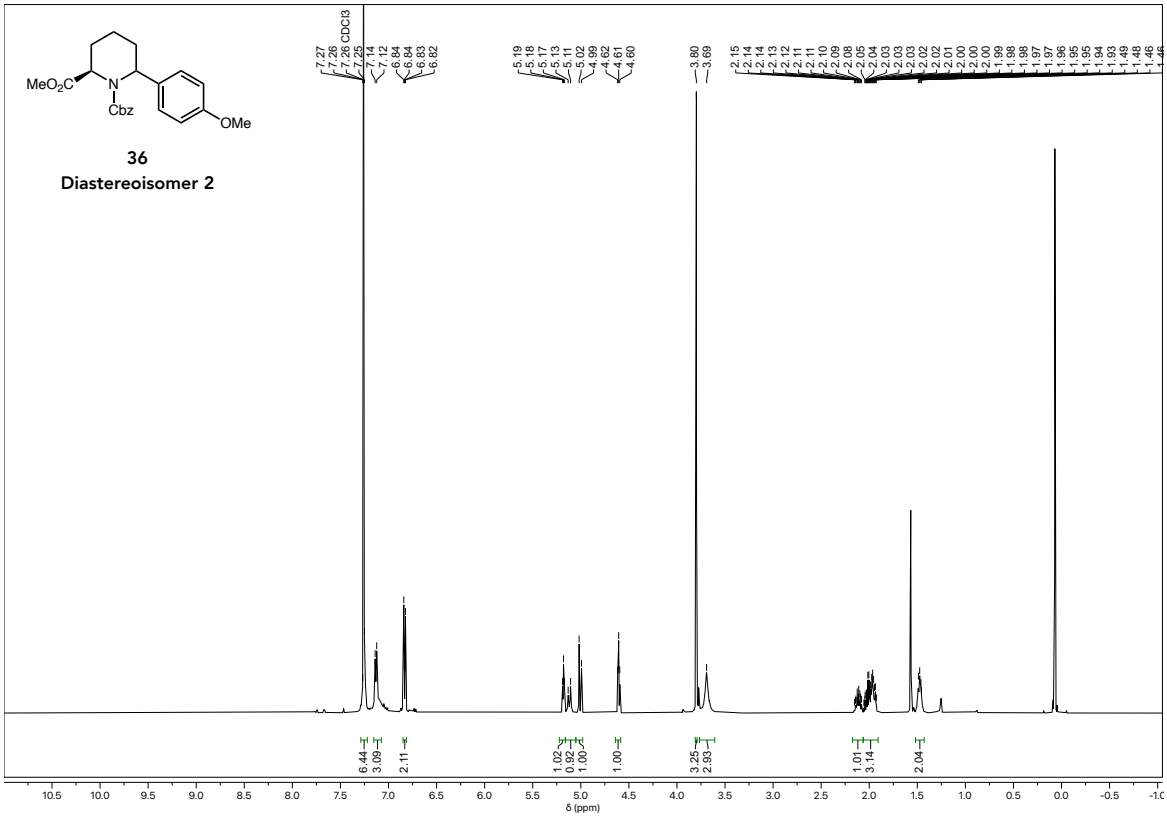



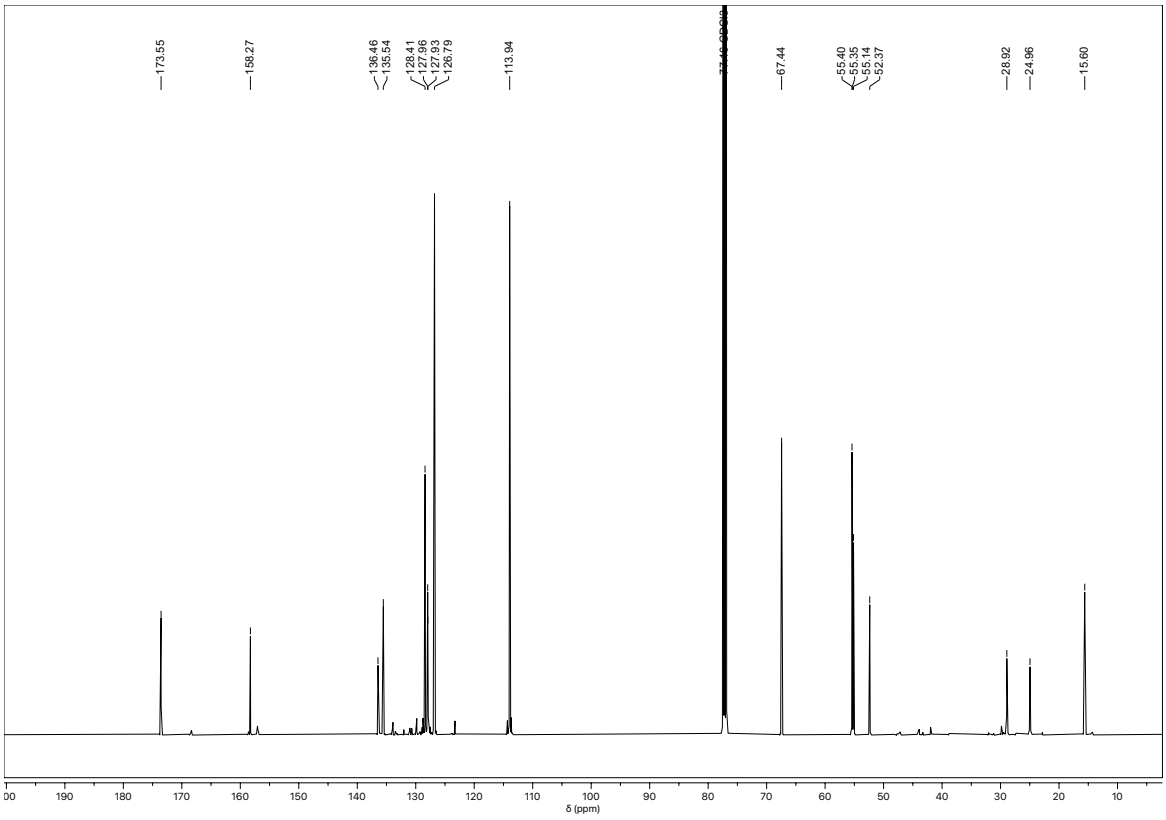
1-Benzyl 2-methyl (2*R*)-6-(4-methoxyphenyl)piperidine-1,2-dicarboxylate (36)
Diastereoisomer 1



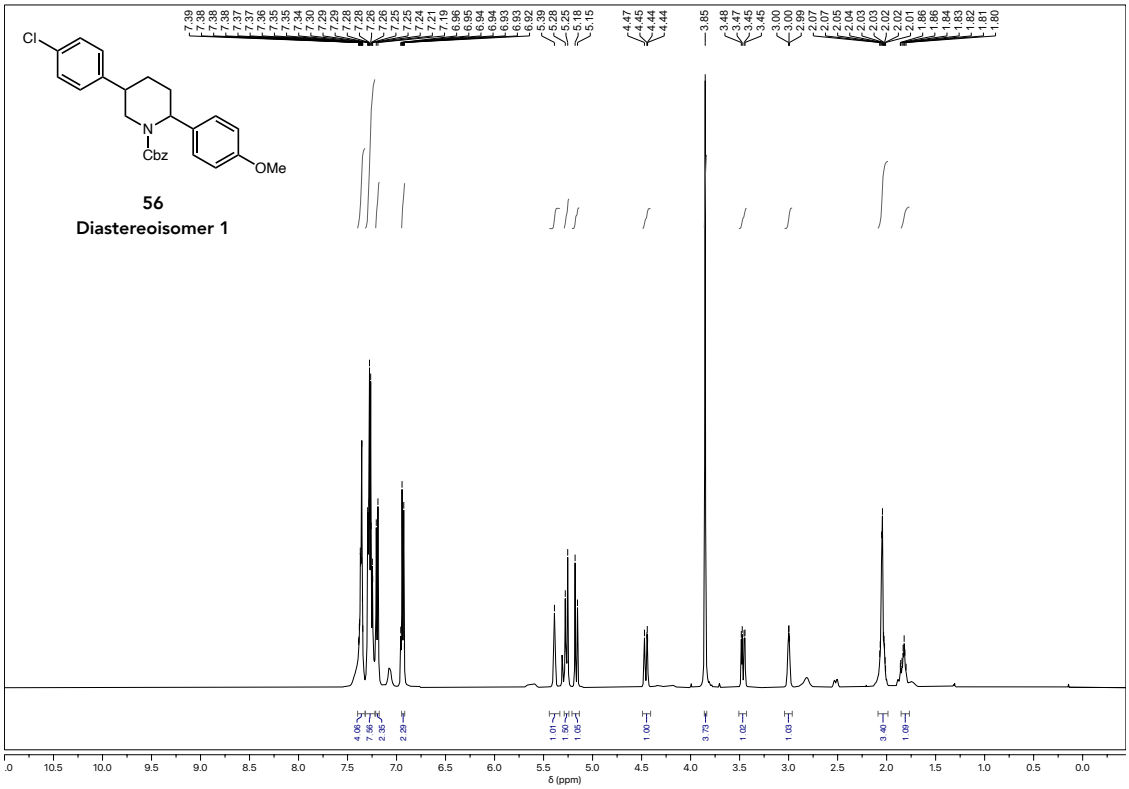



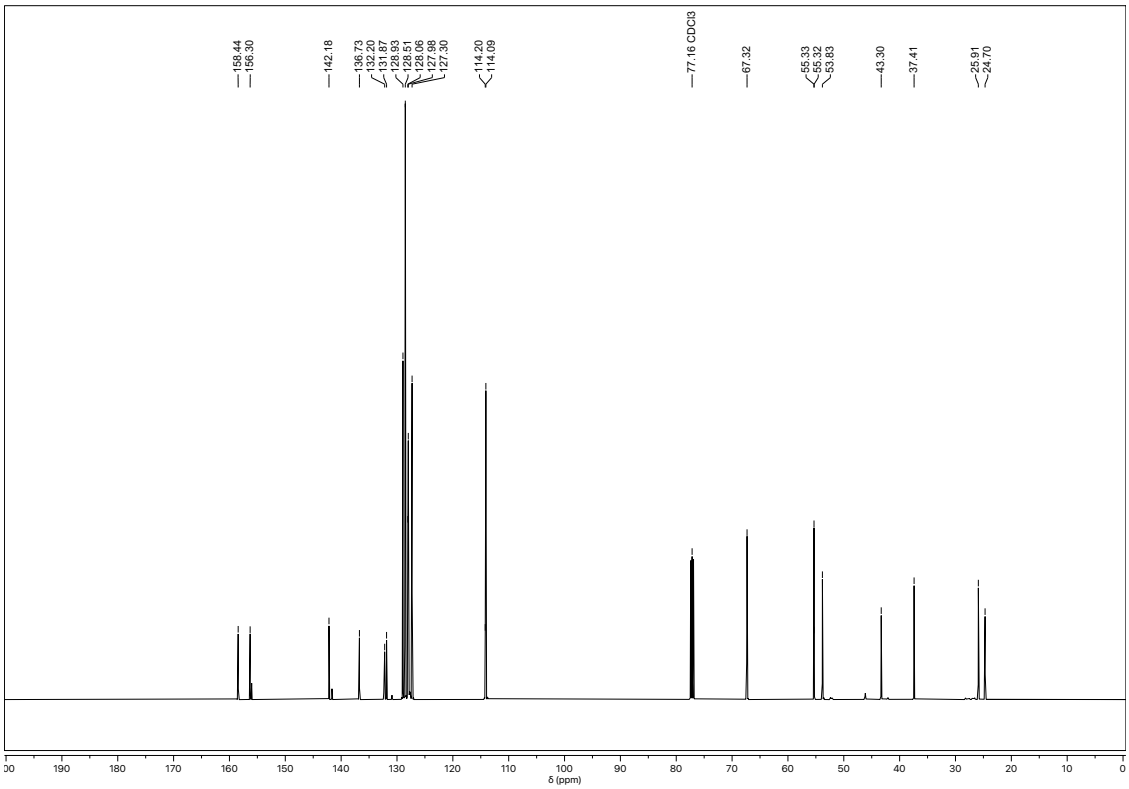
1-Benzyl 2-methyl (2*R*)-6-(4-methoxyphenyl)piperidine-1,2-dicarboxylate (36)
Diastereoisomer 2



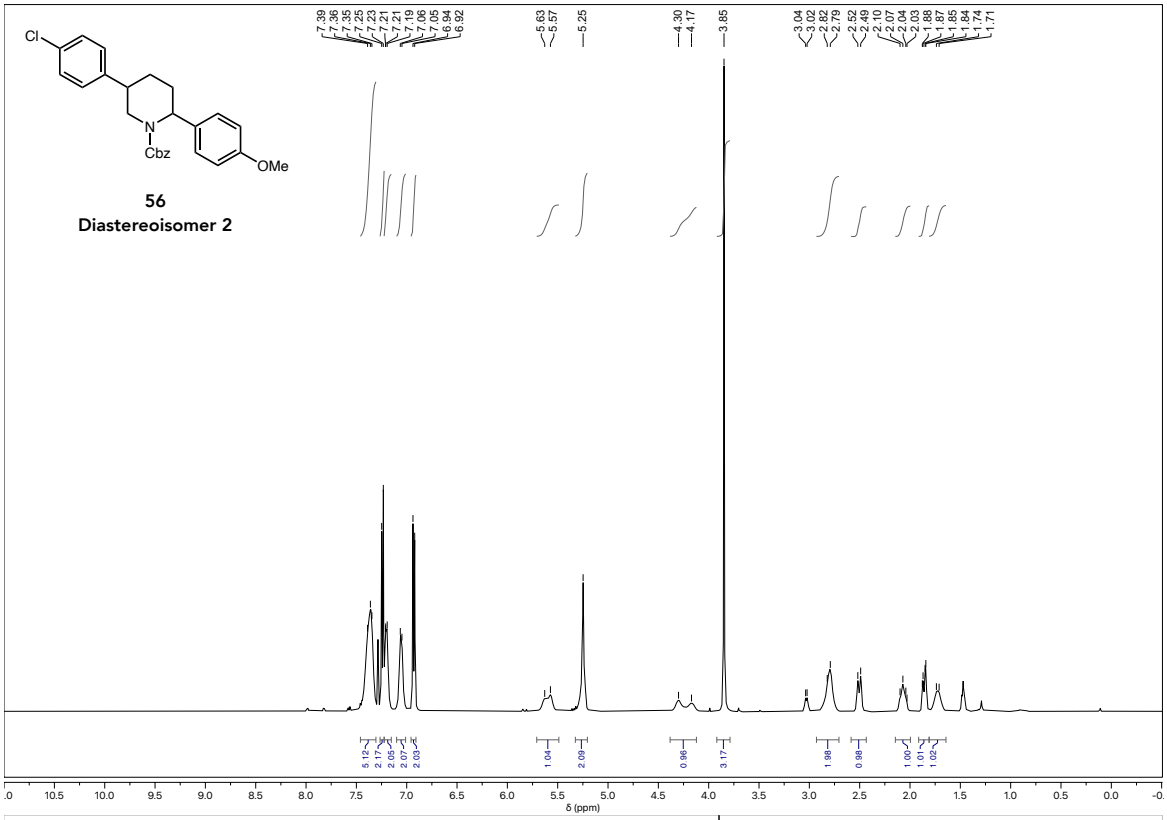



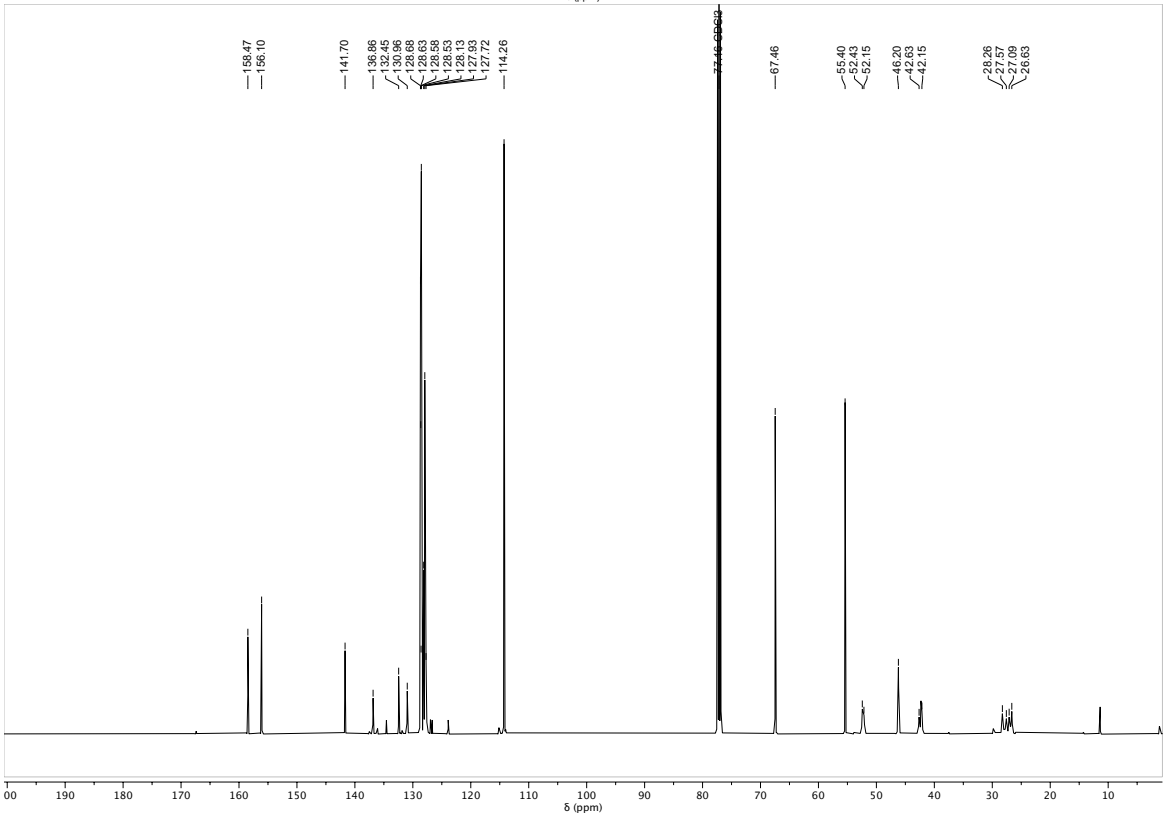
Benzyl 5-(4-chlorophenyl)-2-(4-methoxyphenyl)piperidine-1-carboxylate (56)
Diastereoisomer 1



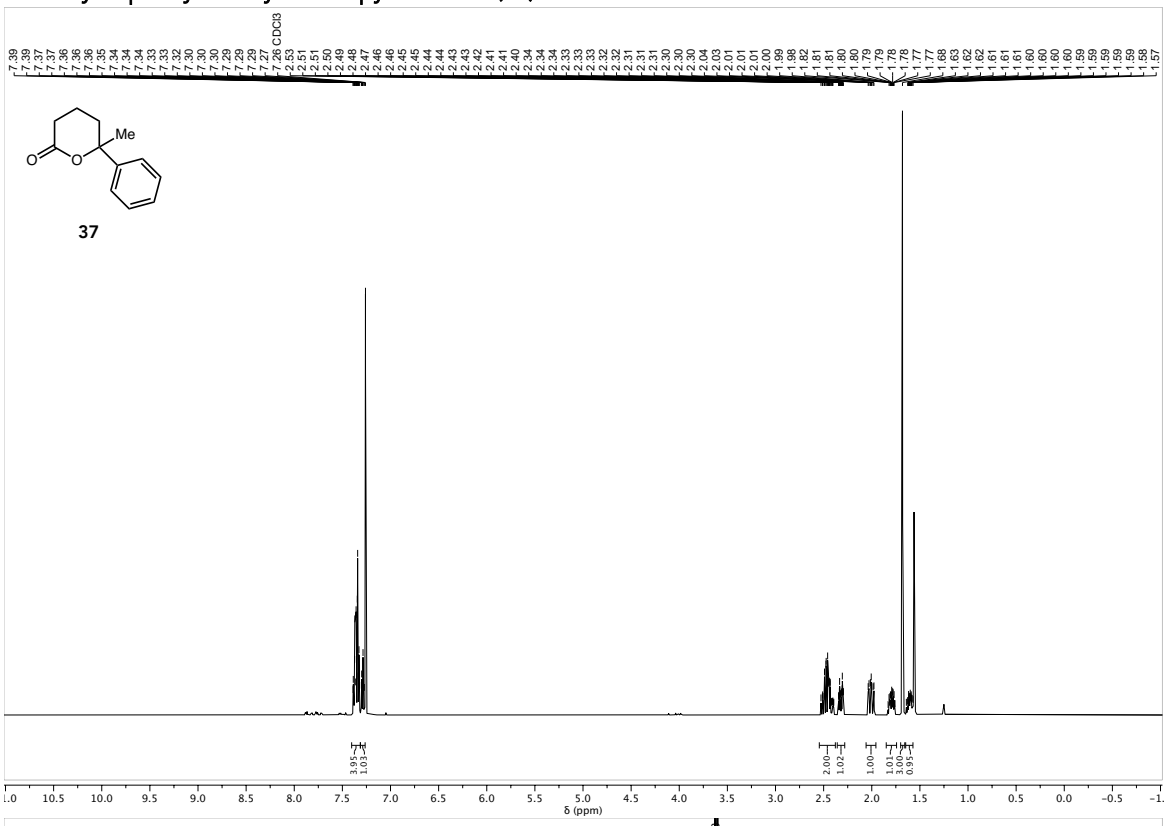
Benzyl 5-(4-chlorophenyl)-2-(4-methoxyphenyl)piperidine-1-carboxylate (56)
Diastereoisomer 2

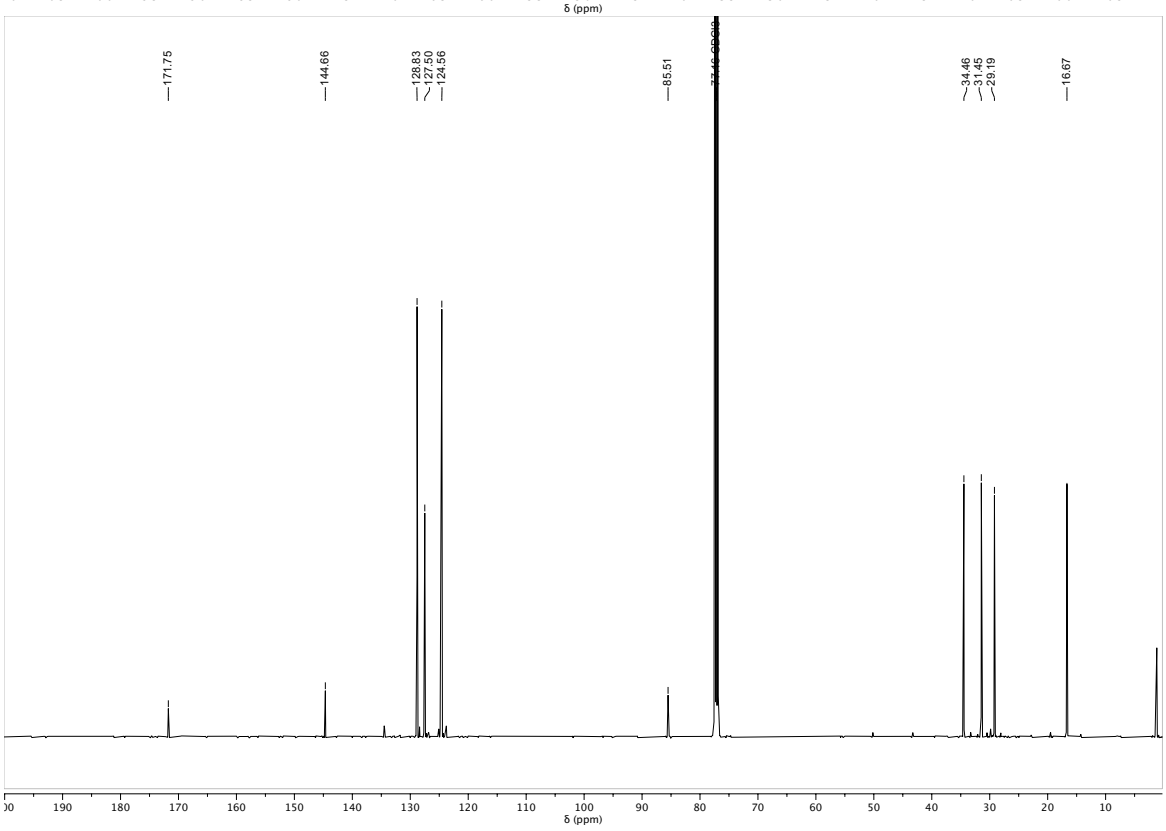


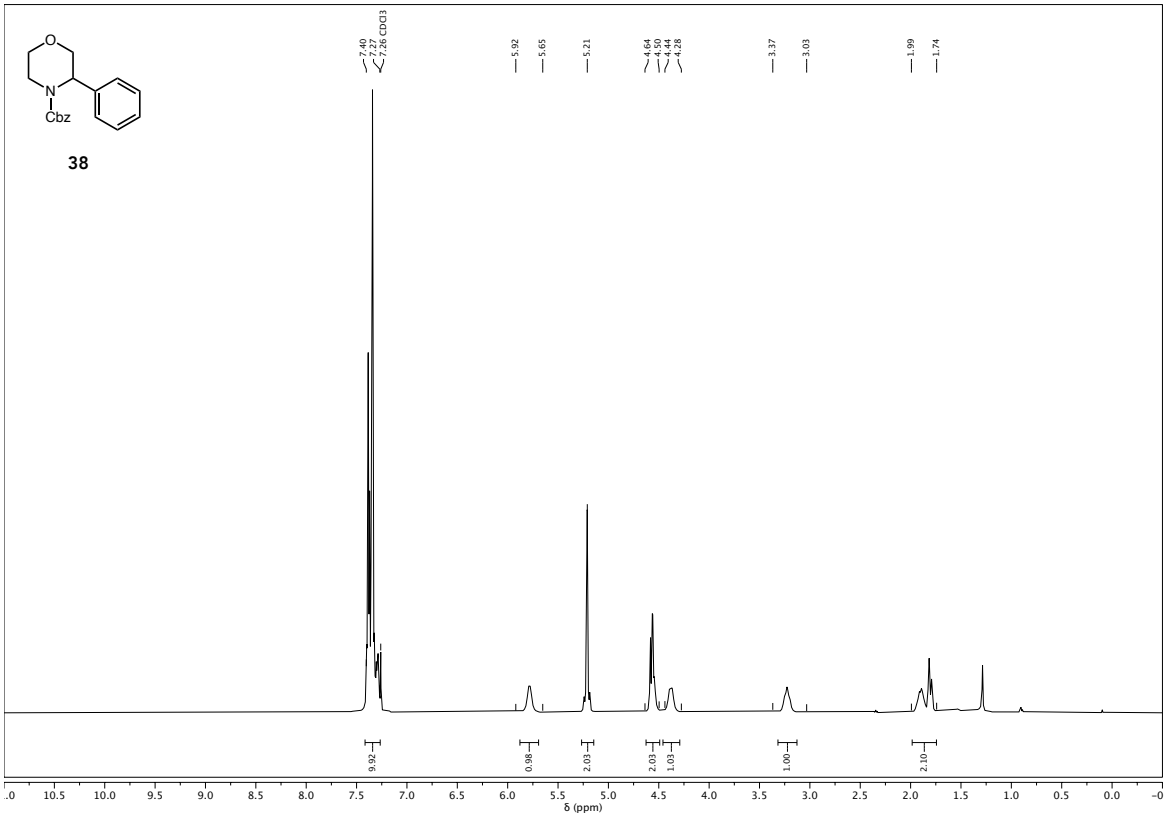
## 10.5.4. Other annulation products – Morpholines, δ-valerolactones, and dioxanone.

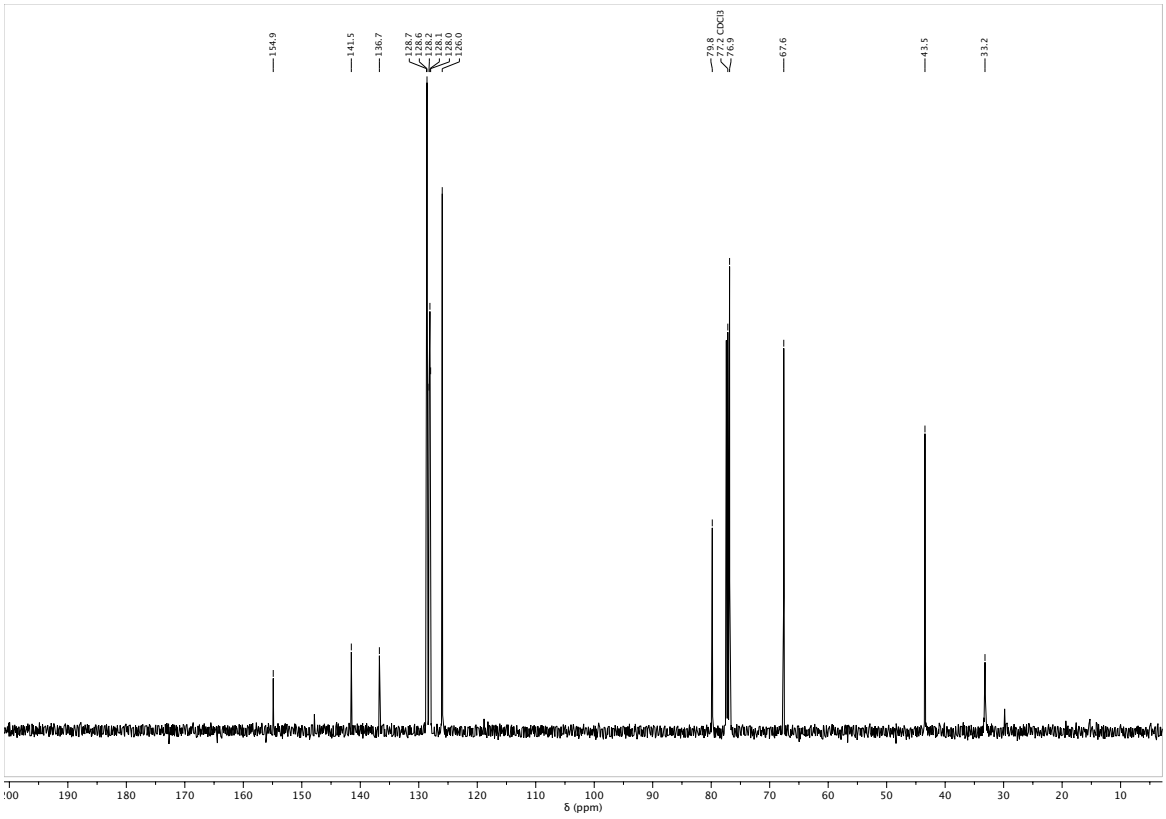
### 6-Methyl-6-phenyltetrahydro-2*H*-pyran-2-one (37)



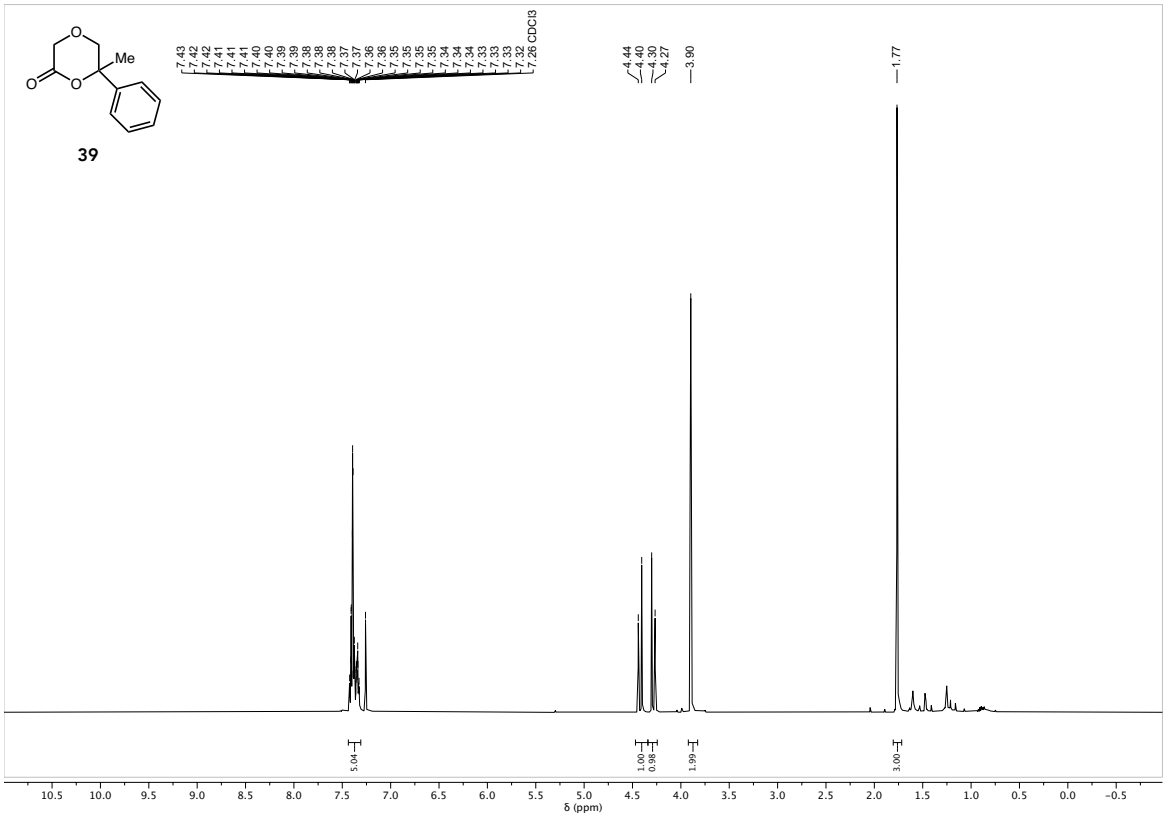



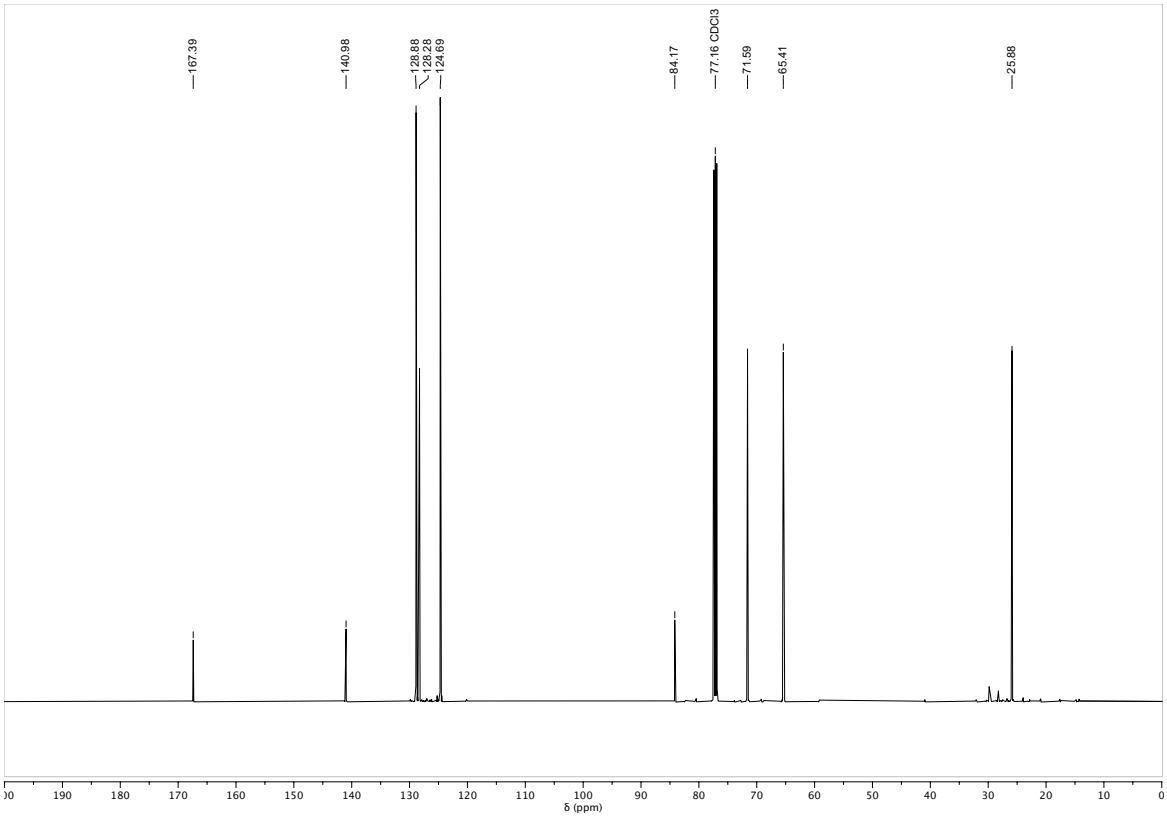
## Benzyl 3-phenylmorpholine-4-carboxylate (38)



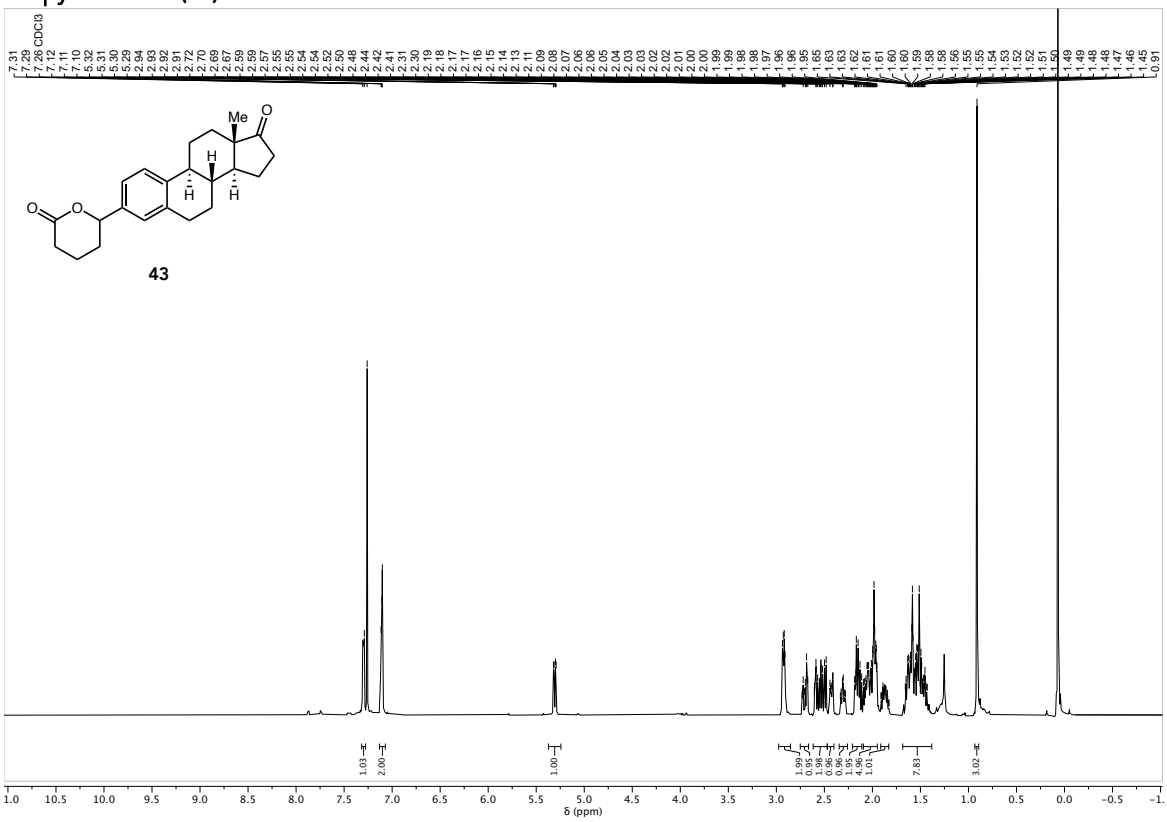



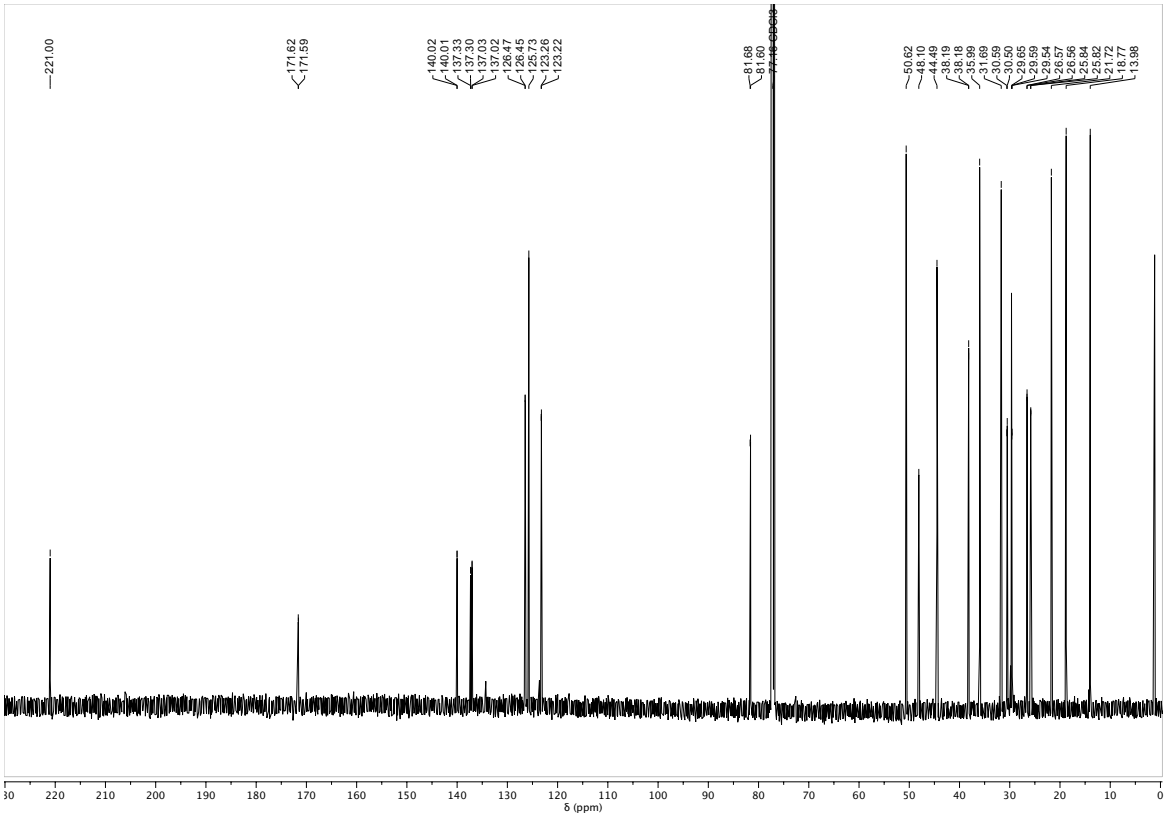
## 6-Methyl-6-phenyl-1,4-dioxan-2-one (39)



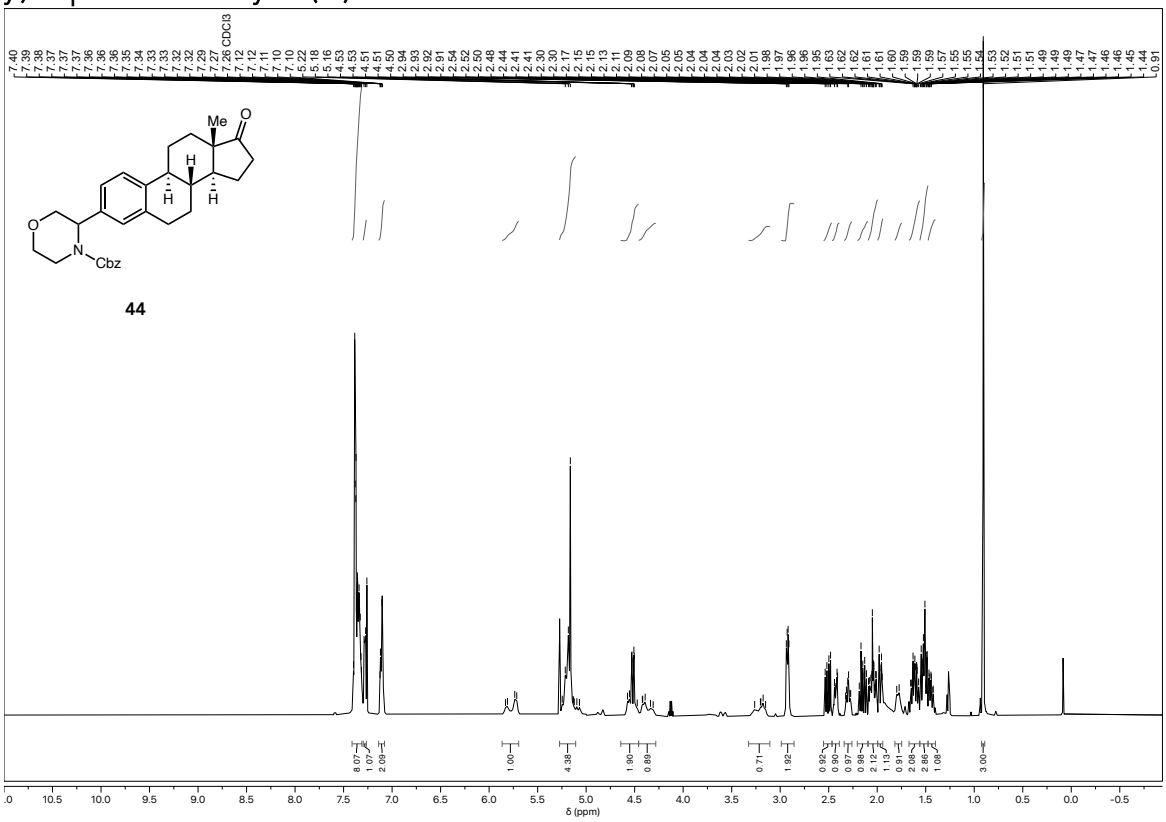



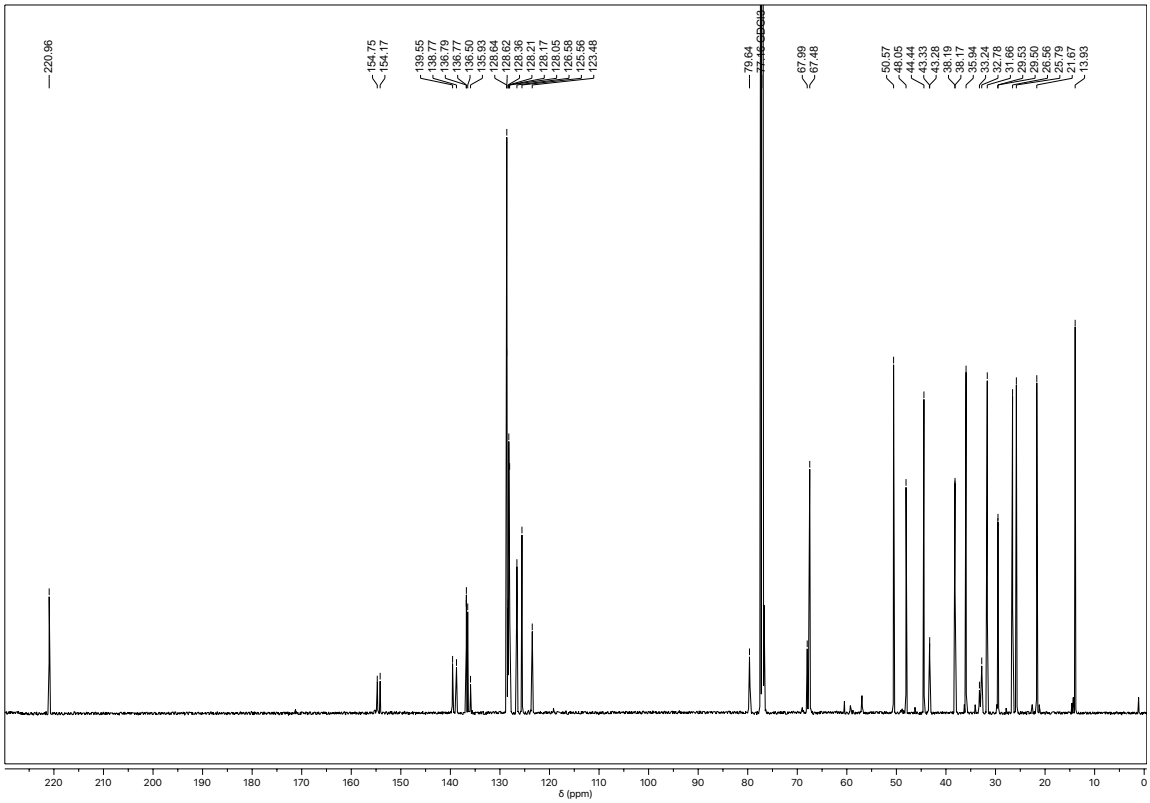
6-((8*R*,9*S*,13*S*,14*S*)-13-Methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[a]phenanthren-3-yl)tetrahydro-2*H*-pyran-2-one (43)



Benzyl 3-((8*R*,9*S*,13*S*,14*S*)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl)morpholine-4-carboxylate (44)



## 11. Supporting information bibliography


(1) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. Safe and Convenient Procedure for Solvent Purification. *Organometallics* **1996**, *15*, 1518–1520.

(2) Still, W. C.; Kahn, M.; Mitra, A. Rapid Chromatographic Technique for Preparative Separations with Moderate Resolution. *Journal of Organic Chemistry*. 1978, pp 2923–2925.

(3) Lu, G. Z.; Jing, Y. M.; Han, H. B.; Fang, Y. L.; Zheng, Y. X. Efficient Electroluminescence of Two Heteroleptic Platinum Complexes with a 2-(5-Phenyl-1,3,4-Oxadiazol-2-Yl)Phenol Ancillary Ligand. *Organometallics* **2017**, *36*, 448–454.

(4) Shavaleev, N. M.; Monti, F.; Scopelliti, R.; Armaroli, N.; Grätzel, M.; Nazeeruddin, M. K. Blue Phosphorescence of Trifluoromethyl- and Trifluoromethoxy-Substituted Cationic Iridium(III) Isocyanide Complexes. *Organometallics* **2012**, *31*, 6288–6296.

(5) Andreini, M.; Felten, A. S.; Thien, H. T. T.; Taillefumier, C.; Pellegrini-Moïse, N.; Chapleur, Y. Synthesis of New C-Glycosyl Aza-**B**3-Amino Acids Building Blocks. *Tetrahedron Lett.* **2012**, *53*, 2702–2705.

(6) Fier, P. S.; Maloney, K. M. NHC-Catalyzed Deamination of Primary Sulfonamides: A Platform for Late-Stage Functionalization. *J. Am. Chem. Soc.* **2019**, *141*, 1441–1445.

(7) Hannick, S. M.; Kishi, Y. Improved Procedure for the Blaise Reaction: A Short, Practical Route to the Key Intermediates of the Saxitoxin Synthesis. *J. Org. Chem.* **1983**, *48*, 3833–3835.

(8) Mizoi, K.; Takahashi, M.; Haba, M.; Hosokawa, M. Synthesis and Evaluation of Atorvastatin Esters as Prodrugs Metabolically Activated by Human Carboxylesterases. *Bioorganic Med. Chem. Lett.* **2016**, *26*, 921–923.

(9) Mato, M.; Herlé, B.; Echavarren, A. M. Cyclopropanation by Gold- or Zinc-Catalyzed Retro-Buchner Reaction at Room Temperature. *Org. Lett.* **2018**, *20*, 4341–4345.

(10) Niu, D.; Buchwald, S. L. Design of Modified Amine Transfer Reagents Allows the Synthesis of **α**-Chiral Secondary Amines via CuH-Catalyzed Hydroamination. *J. Am. Chem. Soc.* **2015**, *137*, 9716–9721.

(11) Mori, K.; Watanabe, H. Synthesis of Both the Enantiomers of Polygodial, an Insect Antifeedant Sesouiterpene. *Tetrahedron* **1986**, *42*, 273–281.

(12) Zalán, Z.; Martinek, T. A.; Lázár, L.; Fülöp, F. Synthesis and Conformational Analysis of 1,3,2-Diazaphosphorino[6,1-a]Isoquinolines, a New Ring System. *Tetrahedron* **2003**, *59*, 9117–9125.

(13) Evans, P. A.; Holmes, A. B.; McGeary, R. P.; Nadin, A.; Russell, K.; O'Hanlon, P. J.; Pearson, N. D. New Methodology for the Synthesis of Unsaturated 8-, 9- and 10-Membered Lactams. *J. Chem. Soc. - Perkin Trans. 1* **1996**, No. 2, 123–138.

(14) ter Wiel, M. K. J.; Arnold, M.; Peter, S.; Troltsch, I.; Merget, S.; Glaser, F.; Schwarm, M.; Bhatti, H. S.; Kuriakose, B.; Pol, S. S.; et al. Enantiopure **B**3-Neopentylglycine: Synthesis and Resolution. *Tetrahedron Asymmetry* **2009**, *20*, 478–482.

(15) Balázs, Á.; der Eycken, E. Van; Fülöp, F. A Novel, Microwave-Assisted Method for the Synthesis of Alicyclic-Condensed 5H-1,4,6,7-Tetrahydro-1,4-Diazepin-5-Ones. *Tetrahedron Lett.* **2008**, *49*, 4333–4335.

(16) Downey, C. W.; Johnson, M. W.; Lawrence, D. H.; Fleisher, A. S.; Tracy, K. J. Acetic Acid Aldol Reactions in the Presence of Trimethylsilyl Trifluoromethanesulfonate. *J. Org. Chem.* **2010**, *75*, 5351–5354.

(17) Rueping, M.; Albert, M.; Seebach, D. On the Structure of PHB (=Poly[(R)-3-Hydroxybutanoic Acid]) in Phospholipid Bilayers: Preparation of Trifluoromethyl-Labeled Oligo[(R)-3-Hydroxybutanoic Acid] Derivatives. *Helv. Chim. Acta* **2004**, *87*, 2473–2486.

(18) Schobert, R.; Jagusch, C. An Efficient Synthesis of Carlosic Acid and Other 5-Carboxymethyltetronates from Malates. *Synthesis (Stuttg).* **2005**, *2*, 2421–2425.

(19) Shu, C.; Noble, A.; Aggarwal, V. K. Photoredox-Catalyzed Cyclobutane Synthesis by a Deboronative Radical Addition–Polar Cyclization Cascade. *Angew. Chemie - Int. Ed.* **2019**, *58*, 3870–3874.

(20) Cardenal, C.; Vollrath, S. B. L.; Schepers, U.; Brase, S. Synthesis of Functionalized Glutamine- and Asparagine-Type Peptoids – Scope and Limitations. *Helv. Chim. Acta* **2012**, *95*, 2237–2248.

(21) Lu, T.; Markotan, T.; Ballentine, S. K.; Giardino, E. C.; Spurlino, J.; Brown, K.; Maryanoff, B. E.; Tomczuk, B. E.; Damiano, B. P.; Shukla, U.; et al. Discovery and Clinical Evaluation of 1-{N-[2-(Amidinoaminooxy)Ethyl]Amino} Carbonylmethyl-6-Methyl-3-[2,2-Difluoro-2-Phenylethylamino]Pyrazinone (RWJ-671818), a Thrombin Inhibitor with an Oxyguanidine P1 Motif. *J. Med. Chem.* **2010**, *53*, 1843–1856.

(22) Si, X.; Zhang, L.; Hashmi, A. S. K. Benzaldehyde- And Nickel-Catalyzed Photoredox C(Sp3)-H Alkylation/Arylation with Amides and Thioethers. *Org. Lett.* **2019**, *21*, 6329–6332.

(23) Um, C.; Chemler, S. R. Synthesis of 2-Aryl- and 2-Vinylpyrrolidines via Copper-Catalyzed Coupling of Styrenes and Dienes with

Potassium β-Aminoethyl Trifluoroborates. *Org. Lett.* **2016**, *18*, 2515–2518.

(24) Sandoval, B. A.; Clayman, P. D.; Oblinsky, D. G.; Oh, S.; Nakano, Y.; Bird, M.; Scholes, G. D.; Hyster, T. K. Photoenzymatic Reductions Enabled by Direct Excitation of Flavin-Dependent "Ene"-Reductases. *J. Am. Chem. Soc.* **2021**, *143*, 1735–1739.

(25) Yu, S.; Noble, A.; Bedford, R. B.; Aggarwal, V. K. Methylenespiro[2.3]Hexanes via Nickel-Catalyzed Cyclopropanations with [1.1.1]Propellane. *J. Am. Chem. Soc.* **2019**, *141*, 20325–20334.

(26) Gui, J.; Cai, X.; Chen, L.; Zhou, Y.; Zhu, W.; Jiang, Y.; Hu, M.; Chen, X.; Hu, Y.; Zhang, S. Facile and Practical Hydrodehalogenations of Organic Halides Enabled by Calcium Hydride and Palladium Chloride. *Org. Chem. Front.* **2021**, *8*, 4685–4692.

(27) Herold, S.; Bafaluy, D.; Muñiz, K. Anodic Benzylic C(Sp3)–H Amination: Unified Access to Pyrrolidines and Piperidines. *Green Chem.* **2018**, *20*, 3191–3196.

(28) Lazib, Y.; Retailleau, P.; Saget, T.; Darses, B.; Dauban, P. Asymmetric Synthesis of Enantiopure Pyrrolidines by C(Sp3)−H Amination of Hydrocarbons. *Angew. Chemie - Int. Ed.* **2021**, *60*, 21708–21712.

(29) Haddad, M.; Imogaï, H.; Larchevêque, M. The First Enantioselective Synthesis of the CIS-2-Carboxy-5- Phenylpyrrolidine. *J. Org. Chem.* **1998**, *63*, 5680–5683.

(30) Im, H.; Kang, D.; Choi, S.; Shin, S.; Hong, S. Visible-Light-Induced C-O Bond Formation for the Construction of Five- and Six-Membered Cyclic Ethers and Lactones. *Org. Lett.* **2018**, *20*, 7437–7441.

(31) Pandey, G.; Laha, R.; Mondal, P. K. Heterocyclization Involving Benzylic C(Sp3)-H Functionalization Enabled by Visible Light Photoredox Catalysis. *Chem. Commun.* **2019**, *55*, 9689–9692.

(32) Nishikawa, Y.; Hamamoto, Y.; Satoh, R.; Akada, N.; Kajita, S.; Nomoto, M.; Miyata, M.; Nakamura, M.; Matsubara, C.; Hara, O. Enantioselective Bromolactonization of Trisubstituted Olefinic Acids Catalyzed by Chiral Pyridyl Phosphoramides. *Chem. - A Eur. J.* **2018**, *24*, 18880–18885.