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Submitted date: 07/01/2021 • Posted date: 08/01/2021

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Citation information: Liu, Zhonglin; Oxtoby, Lucas; Liu, Mingyu; Li, Zi-Qi; Tran, Van; Gao, Yang; et al. (2021): A Transient Directing Group Strategy Enables Enantioselective Multicomponent Organofluorine Synthesis. ChemRxiv. Preprint. <https://doi.org/10.26434/chemrxiv.13537283.v1>

The vicinal fluorofunctionalization of alkenes represents an expedient strategy for converting feedstock olefins into valuable fluorinated molecules and as such has garnered significant attention from the synthetic community; however, current methods remain limited in terms of scope and selectivity. Here we report the site-selective palladium-catalyzed three-component coupling of alkenylbenzaldehydes, arylboronic acids, and N-fluoro-2,4,6-trimethylpyridinium hexafluorophosphate facilitated by a transient directing group. The synthetically enabling methodology constructs vicinal stereocenters with excellent regio-, diastereo-, and enantioselectivities, forging products that map onto bioactive compounds.

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A Transient Directing Group Strategy Enables Enantioselective Multicomponent Organofluorine Synthesis

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Abstract: The vicinal fluorofunctionalization of alkenes represents an expedient strategy for converting feedstock olefins into valuable fluorinated molecules and as such has garnered significant attention from the synthetic community; however, current methods remain limited in terms of scope and selectivity. Here we report the site-selective palladium-catalyzed three-component coupling of alkenylbenzaldehydes, arylboronic acids, and *N*-fluoro-2,4,6-trimethylpyridinium hexafluorophosphate facilitated by a transient directing group. The synthetically enabling methodology constructs vicinal stereocenters with excellent regio-, diastereo-, and enantioselectivities, forging products that map onto bioactive compounds.

Main Text: The incorporation of carbon–fluorine (C–F) bonds into drug molecules can often improve their pharmacokinetic properties, including increasing oral bioavailability, protein binding affinities, and metabolic stability, especially in the case of replacement of benzylic C–H bonds prone to metabolic oxidation^{1,2}. As such, the development of strategies that enable the enantioselective formation of C–F bonds has become a major research area of both industrial and academic importance in recent years^{3–5}. In particular, intermolecular 1,2-carbofluorination of alkenes is an attractive transformation as it allows for the conversion of alkene feedstocks into fluorinated molecules with potential applications in the pharmaceutical, agrochemical, and material sectors⁶; however, this type of transformation remains challenging to execute due to issues with regio-, stereo-, and chemoselectivity. In early work, the groups of Ma⁷, Gagné⁸, Alexakis⁹, and Gouverneur¹⁰ reported pioneering examples of asymmetric fluorocyclizations of prochiral alkenes, in which a functional group tethered to the alkene reacts in the cyclization process.

More recently, Toste and coworkers have reported an elegant series of intermolecular (three-component) asymmetric arylfluorination reactions to construct chiral benzyl fluorides using palladium/*N,N*-ligand systems. This strategy has been used for both 1,1-arylfluorination (where regioselectivity is governed by substrate electronics)^{11,12} and 1,2-arylfluorination (where selectivity is governed by substrate directivity)¹³. While the aforementioned work represents a great deal of progress, significant limitations remain. Palladium-catalyzed arylfluorination reactions are sensitive to alkene substitution patterns; for instance, disubstituted alkenes require double activation to enhance reactivity¹⁴, and no existing methods are able to construct fully substituted C(*sp*³)–F or C(*sp*³)–Ar stereocenters. Additionally, achieving high levels of pathway selectivity for a given substrate class (favoring 1,2-arylfluorination over 1,1-arylfluorination, β -hydride elimination, or other side reactions) often requires extensive ligand optimization and the use of potentially synthetically restrictive directing groups¹⁵.

With the previous efforts in mind, we wondered if we could address these issues by implementing a chiral transient directing group (TDG) strategy. The viability of catalytic TDGs has previously been established in several mechanistically distinct transition-metal catalyzed reactions, including notably in the field of C–H activation¹⁶; however, the scope of transiently directed asymmetric alkene functionalizations remains quite limited, and 1,2-difunctionalization reactions using a TDG approach remain unknown. Herein, we report a highly enantioselective 1,2-arylfuorination of alkenyl benzaldehydes that is able to form two vicinal chiral centers, including fully substituted C(*sp*³)–F and C(*sp*³)–Ar stereocenters, in synthetically useful yields with broad functional group tolerance.

To reduce this idea to practice, we based our initial reaction design on our recently reported enantioselective reductive Heck hydroarylation of alkenyl benzaldehydes using an amino acid TDG¹⁷. In our previous work, a stabilized alkylpalladium(II) intermediate is intercepted with formate, which decarboxylates to generate an alkylpalladium(II)–hydride species that subsequently undergoes reductive elimination. In the case of the envisioned transiently directed arylfluorination, the stabilized alkylpalladium(II) intermediate would react with a fluorinating oxidant (an [F⁺] reagent) to generate a palladium(IV) species that could undergo C–F reductive elimination¹⁸. This seemingly simple extension is fraught with challenges, including undesired oxidation of the native aldehyde functional handle by [F⁺], competitive homocoupling of arylboronic acids in the presence of palladium(II) and oxidant, and deleterious interactions between the TDG and [F⁺].

In a series of pilot experiments, we found that *L*-*tert*-leucine (the optimal TDG in our previous system) did not lead to product formation, suggesting that a different TDG design was needed to support palladium(IV) formation. In their study on enantioselective C–H fluorination of electron-deficient benzaldehydes, Yu and coworkers found that switching from an LX-type amino acid to an L₂-type α -amino amide TDG promoted C–F reductive elimination through formation of a pentacoordinate cationic Pd(IV) complex¹⁹. We reasoned our system would benefit from the same effect and carried out a new screen using a library of TDGs that offered the potential of L₂-type binding after aldehyde condensation. An initial hit was observed reacting alkene starting material **1** with *N*-fluoro-2,4,6-trimethylpyridinium salt ([F⁺]) and phenylboronic acid in the presence of a palladium(II) catalyst, previously unreported **TDG-A**, silver fluoride additive, and water in a 2:1 mixture of DCM/MeCN. A variety of unproductive side reactions were observed, including formation of palladium black and decomposition of the [F⁺] reagent and benzaldehyde SM (see SI for details). Because it was expected that most of the components would have strong interactions with each other that would impact the final yield of the reaction, our system appeared better suited for optimization via Design of Experiments (DoE) as opposed to typical “One Variable At a Time” (OVAT) screening. Despite its advantages over OVAT and its widespread adoption in industry, DoE remains underutilized in academic research^{20,21}.

We elected to use a modified Definitive Screening Design (DSD) (Table 1), which allowed us to develop a linear regression model that describes the sensitivity of a response (in this case reaction yield) to a variety of input parameters with continuous levels (reagent loadings)²². The high- and low-end values for each reagent loading in the subsequent experiments were set based on what we expected to be the most extreme values the reaction would tolerate. We then ran just 18 experiments using values within those ranges to train a model, which subsequently predicted conditions that more than doubled our initial yield. While the arylboronic acid loading of 4.67 equivalents is relatively high, we deemed this acceptable in our system, as the arylboronic acid

was not among the most valuable components of the reaction. It should be noted that while this technique can be used for rapid optimization and identification of major interactions, it does not suggest an explanation for why a given response is dependent on a particular input parameter; moreover, the DSD model does not necessarily accurately predict reaction performance in totally different chemical space. Multiple powerful techniques have emerged for the statistical prediction of out-of-sample reactions, including multivariate regression of physical organic descriptors (23) and machine-learning based chemical featurization approaches^{24,25}, but these methods rely on much larger data sets with more input parameters. Our model translated well to other disubstituted and trisubstituted alkenes, but we did find that it was necessary to change TDGs for terminal alkene substrates (see SI for details).

Having optimized the conditions, we began investigating the scope of alkene substitution. The reaction with 1,2,2-trisubstituted alkenes to form quaternary carbon–aryl bonds proceeded in moderate to good yields with excellent enantioselectivity and broad functional group tolerance. A number of approaches for the enantioselective formation of fully substituted C(*sp*³)–F stereocenters have been developed²⁶, including enolate-type reactions of carbonyl derivatives with electrophilic fluorinating reagents^{27–34}, enolate-type reactions of α -fluorinated carbonyl derivatives with arylating/alkylating reagents^{35–39}, the reaction of alkenes with electrophilic fluorinating reagents to form allylic fluoride products^{40–45}, iridium-catalyzed allylic substitution reactions of alkenyl fluorides^{46–48}, and the redox-relay palladium-catalyzed enantioselective Heck reaction of acyclic alkenyl fluorides with arylboronic acids⁴⁹. Successful reaction of 1,1,2-trisubstituted alkene substrates with our conditions would form tertiary C(*sp*³)–F stereocenters, which would be a valuable addition to previously reported methods; however, this requires an unprecedented asymmetric formation of a fully substituted C(*sp*³)–F stereocenter through C–F reductive elimination. Gratifyingly, the reaction with 1,1,2-trisubstituted alkenes was able to form tertiary C(*sp*³)–F stereocenters, with somewhat lower, but still high enantioselectivity ranging from 90–96% *ee*. Next, we explored the effects of other alkene and benzaldehyde substitutions on the reaction. Both electron-rich and electron-poor benzaldehydes gave good yields with excellent enantioselectivity, with performance being similar between *E*- and *Z*-isomers of the alkene starting material (**2y** to **3y** and **2z** to **3z**, respectively). Unfortunately, the method is ineffective for alkenes that are tetrasubstituted or whose functionalization results in dearomatization (see SI for all examples tested).

We explored the scope of arylboronic acids with **1a** as the model alkene substrate. Both electron-rich and electron-poor *para*-substituted boronic acids afforded the desired products in good yields with excellent enantioselectivity. Arylboronic acids with electron-withdrawing *meta*-substituents (**4f**) performed markedly worse than those with electron-donating substituents (**4g**), requiring either prolonged reaction time or higher temperatures. The reaction did proceed with benzofuran (**3h**) and benzodioxole (**4i**) boronic acids, but did not tolerate other heterocycles, including substituted pyridines and pyrazoles. Additional limitations include both alkenyl and alkyl boronic acids. In order to demonstrate the potential synthetic utility of the reaction, multiple diversifications were performed. Both oxidation (**5a**) and reduction (**5c**) of the aldehyde proceeded in high yields while maintaining the high *ee* of **4a**. Olefination (**5b**) and decarbonylation (**5d**) gave the desired products in moderate yields with little to no erosion in *ee*. To further demonstrate the synthetically enabling nature of this method, we targeted the synthesis of the bioactive compound MCJ001F^{50,51}. The reported patent route to the (*R,R*)-stereoisomer involves a chiral resolution of a racemic intermediate and late-stage separation of diastereomers in a 10-step sequence. In contrast, our procedure is both enantio- and diastereoselective, affording MCJ001F-RR in fewer

steps from commercially available materials and in overall higher yield. By starting from the opposite alkene isomer (*Z*-configured), we were also able to prepare the (*R,S*)-stereoisomer in higher overall yield than the reported patent route (see SI for a full comparison to previous syntheses).

In an attempt to gain insight into the reaction mechanism, we performed several control reactions and kinetic experiments. First, we confirmed that the TDG was essential by excluding it from a standard reaction with **7f** as well as subjecting ester **7e**, which cannot condense with the TDG, to standard conditions. In both cases, only recovered starting material was observed. Next, we confirmed the reaction does not occur through C–H activation by subjecting substrate **7g** to our standard conditions and observing that it was unreactive. The role of AgF was also briefly considered. While the reaction of model substrate **1a** does proceed without silver fluoride, the reaction only reaches roughly 40% yield by ¹H NMR, with the remaining mass balance of **1a** being decomposed material. We observe the formation of palladium black when stirring a mixture of **1a**, various loadings of **TDG-A**, and Pd(MeCN)₄(BF₄)₂ (10 mol%) in the standard solvent conditions, raising the possibility of catalyst deactivation in the reaction system. Palladium black was qualitatively observed forming over the course of roughly 6 hours at 35 °C for loadings of TDG higher than 75 mol%. Competitive homocoupling of the boronic acid (confirmed by GC-MS) helps explain the high amount of boronic acid required and the potential beneficial effect of Ag(I) for reoxidation of inactive Pd(0).

Experiments aimed at establishing the robustness of the palladium catalyst and the concentration dependencies of the reaction components were carried out according to the “same-excess” and “different-excess” protocols of Reaction Progress Kinetic Analysis (RPKA), respectively⁵². RPKA allows for visual analysis of the kinetic data over the entire time course of the reaction at synthetically relevant conditions. To identify if there is significant catalyst deactivation or product inhibition in our system, we compared temporal concentration profiles ([**1a**] vs. time) of reactions carried out under same-excess conditions (Figure 2). This comparison is facilitated by shifting the profile of a reaction started at lower concentration to the right on the timescale until the first point overlays with the second profile (the standard conditions)⁵³. For any point on the time-adjusted profile, both reactions will have the same concentration of starting materials, but different concentration of product and a different number of turnovers completed by the catalyst. The lack of overlay between these profiles indicates that product inhibition or catalyst deactivation is occurring. These possibilities can be discerned by running a third experiment with the amount of product generated by the reaction until this reaction point added. This reaction is identical by composition, but the catalyst has completed fewer turnovers; therefore, the lack of overlay in this case is indicative of mild catalyst deactivation.

Having confirmed the presence of catalyst deactivation, initial rates from reaction progress profiles were employed to probe concentration dependencies of the reaction components. A series of “different-excess” experiments, in which the order in a given substrate is determined by comparison of reactions with different concentrations of that specific substrate but identical concentrations of other reaction components showed the reaction to have a positive dependence on [Pd] and a negative rate dependence on [TDG]. Studies established the absence of a nonlinear effect of TDG *ee*, showing that product *ee* varies linearly with TDG *ee*. This, coupled with an observed first-order dependence on palladium, confirms the absence of Pd dimers or other higher order Pd species either on or off the cycle, but does not preclude the possibility of monomeric off-cycle species⁵⁴. The reaction was shown to be zero-order in water, silver fluoride, and alkene. The

initial rates for reactions with lower [PhB(OH)₂] or lower [F⁺] were reduced compared to the reaction run under standard conditions, suggesting a positive rate dependence; however, when comparing increased concentrations of these reagent during the “different excess” experiments, the resulting rates showed an apparent zero-order dependence in [F⁺] and boronic acid, pointing to saturation kinetics in both of these components.

Taken together, the kinetics data are consistent with the mechanism proposed in Figure 2 where transmetalation is turnover-limiting at low concentrations of boronic acid and oxidative addition is turnover-limiting at low concentrations of [F⁺]. A zero-order dependence in all components under standard conditions is consistent with the C–F reductive elimination step being turnover-limiting. Negative-order rate dependence on the concentration of TDG is consistent with the TDG mediating decomposition of [F⁺] or potentially forming an off-cycle TDG•Pd^{II} complex (the nonlinear experiments suggest this off-cycle intermediate would be monometallic)⁵⁴. Analogous to our previous studies, we hypothesize that the chiral TDG mediates enantiodetermining migratory insertion by attenuating geometric distortion in the favored metallatricyclic transition state¹⁷. The kinetics data as a whole underscore the mechanistic complexity of this TDG-mediated arylfluorination reaction and highlights the value of DoE for optimization of complicated dual catalytic systems of this type in the absence of a detailed *a priori* mechanistic picture. Not only does the highly enantioselective 1,2-arylfluorination of alkenyl benzaldehydes presented here allow expedient access to organofluorine compounds that are otherwise difficult to prepare; its successful development sets the stage for expansion of chiral TDG strategies across increasingly diverse alkene difunctionalization reactions.

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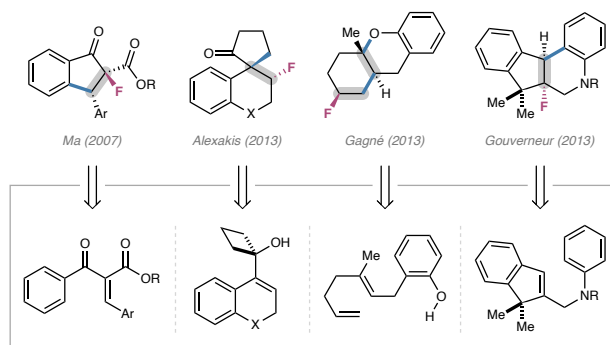
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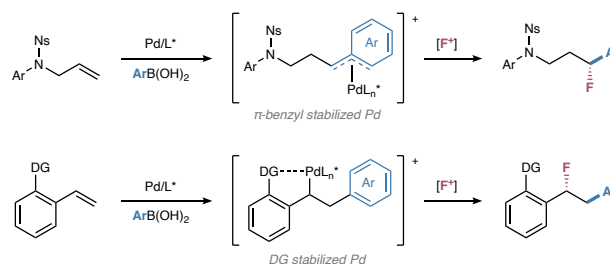
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Acknowledgments: We thank Dr. Dee-Hua Huang and Dr. Laura Pasternack for assistance with NMR spectroscopy. We also thank Dr. Gary J. Balaich (UCSD) for X-ray crystallographic analysis. Dr. Jason Chen, Brittany Sanchez, and Emily Sturgell (Scripps Research Automated Synthesis Facility) are acknowledged for HPLC, SFC, and HRMS analysis. We also thank Dr. Joseph Derosa and Dr. Donna Blackmond for helpful discussion. **Funding:** Financial support for this work was provided by the National Institutes of Health (R35GM125052) and the Cottrell Scholars program. Additional support was provided through an SIOC Fellowship (Z.L.) and a National Science Foundation Graduate Research Fellowship (NSF/DGE-184247, L.J.O.). **Author contributions:** Z.L., L.J.O., and K.M.E. conceived the concept. Z.L., L.J.O., M.L., Z.-Q.L., V.T.T., and Y.G. carried out the experiments. All of the authors analyzed the data. L.J.O. and K.M.E. wrote the manuscript with input from all authors. **Competing interests:** The authors declare no competing interests. **Data and materials availability:** All data is available in the main text or the supplementary materials.

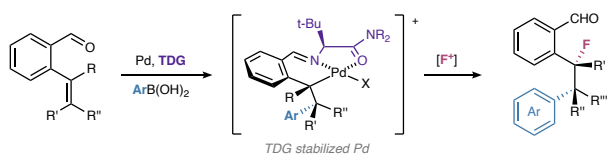
a pioneering work in asymmetric fluorocyclizations of alkenes



b previous approaches to Pd-catalyzed alkene arylation



c Pd-catalyzed alkene arylation using TDG (this work)



d optimization using a definitive screening design

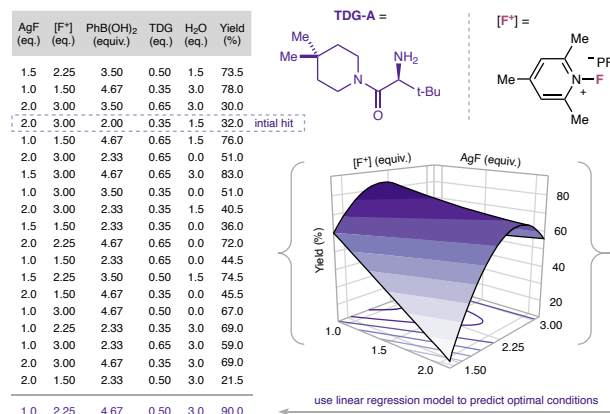
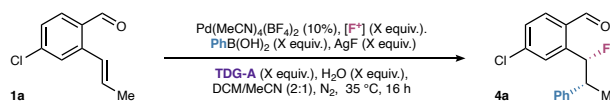
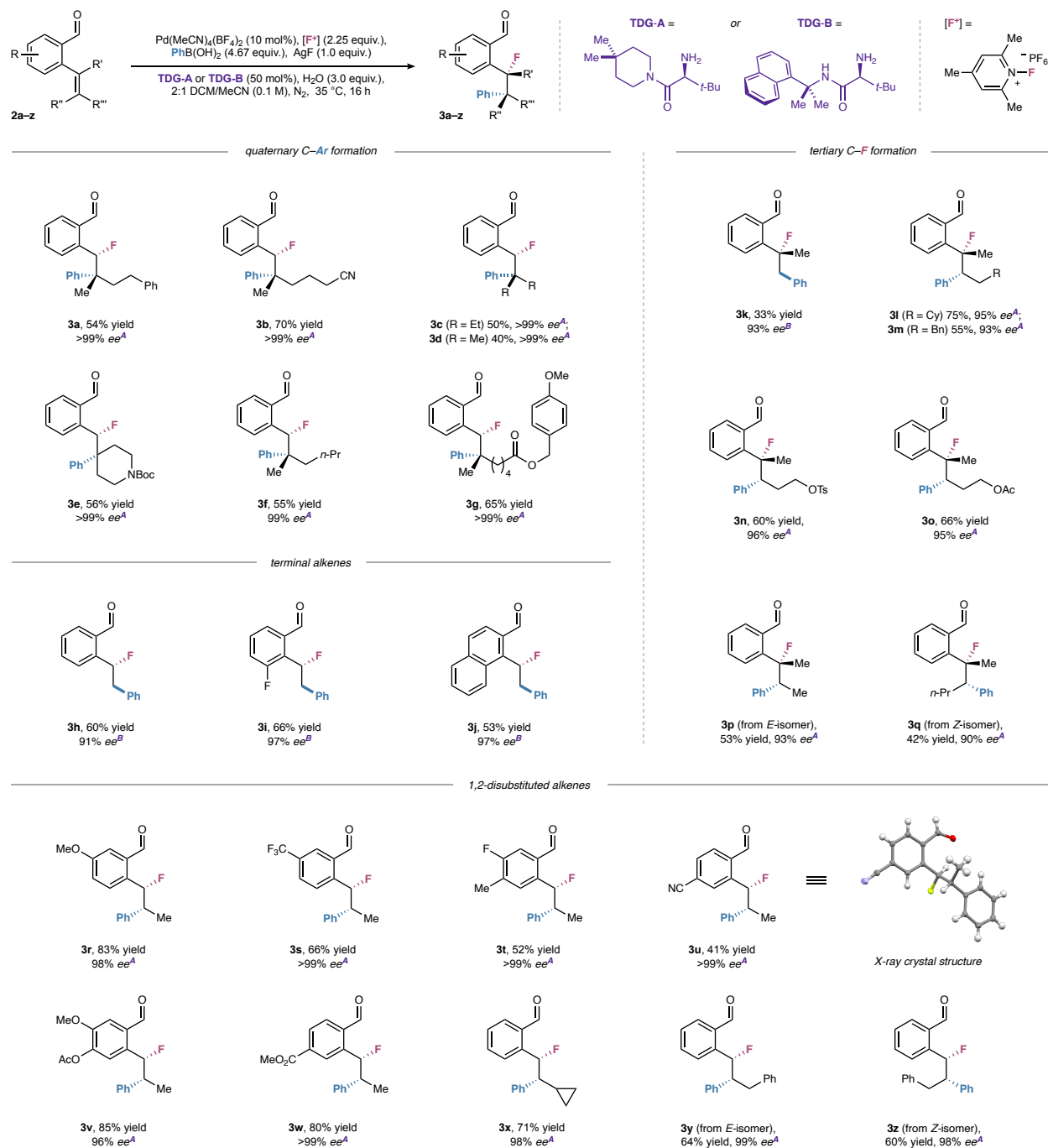


Figure 1 | Approaches to alkene fluorofunctionalization. **a**, Pioneering examples of asymmetric fluorocyclizations of alkenes. **b**, State of the art in palladium-catalyzed alkene arylation. **c**, General depiction of an arylation facilitated by an in situ formed imine using a chiral TDG strategy. **d**, Optimization of reaction conditions.



5

Table 1 | Alkenylbenzaldehyde scope of the arylfluorination reaction. Reactions were carried out on 0.1 mmol scale. All reported yields are isolated yields. The use of TDG-A or TDG-B is designated by a superscript A or B, respectively.

10

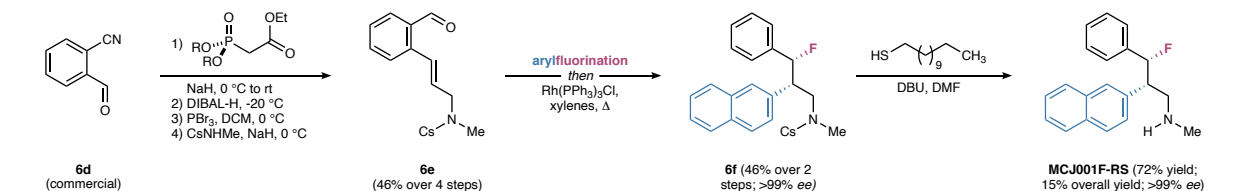
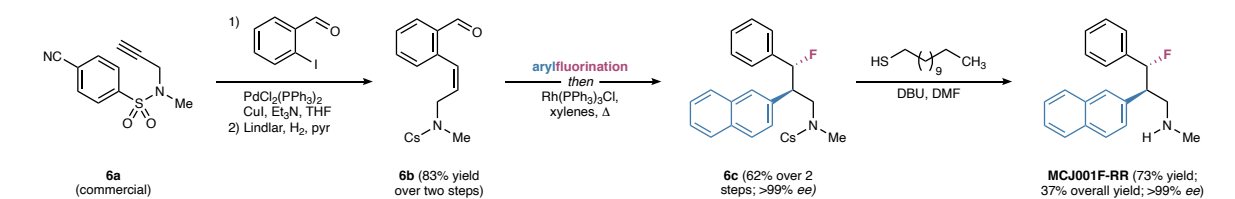
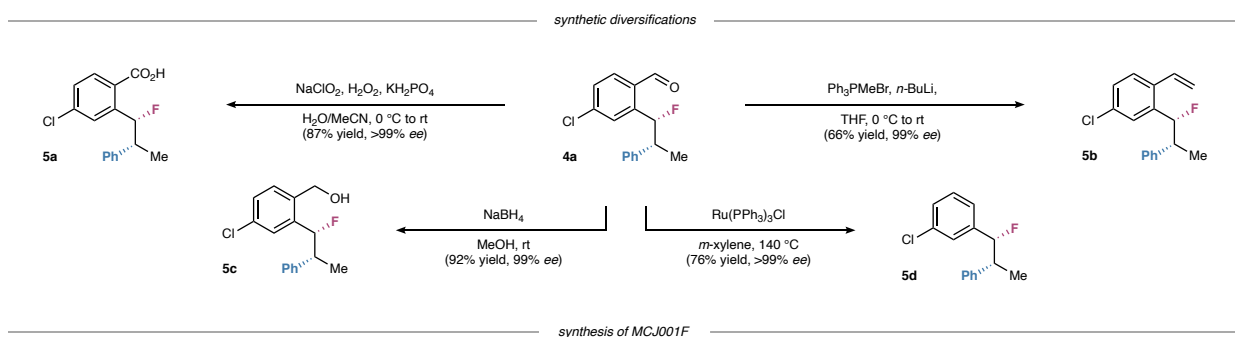
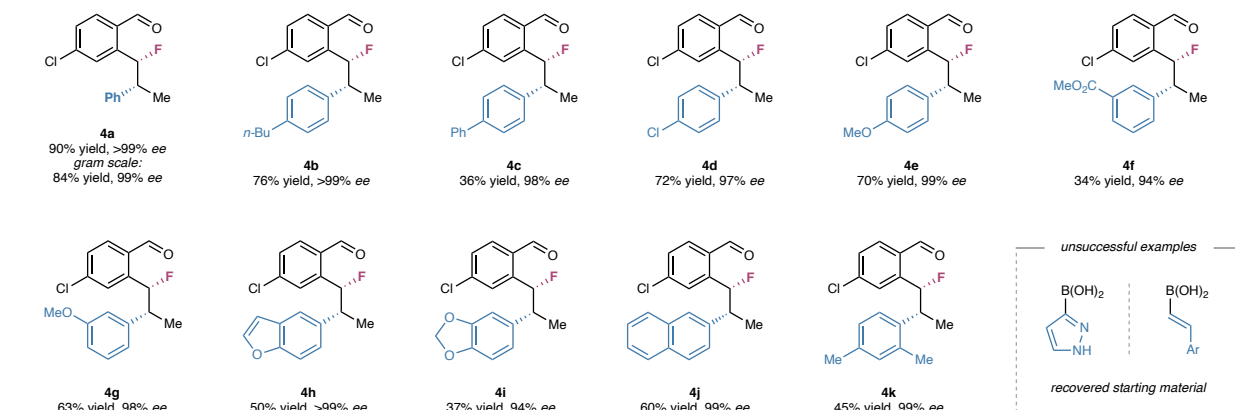
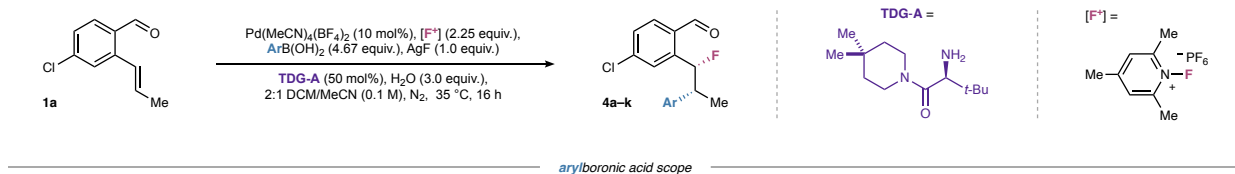


Table 2 | Arylboronic acid scope of the arylfluorination reaction and synthetic diversifications. Reactions for the arylboronic acid scope and synthetic diversifications were run on 0.1 mmol scale unless otherwise noted. See SI for details regarding scale and specific conditions for the synthesis of MCJ001F.

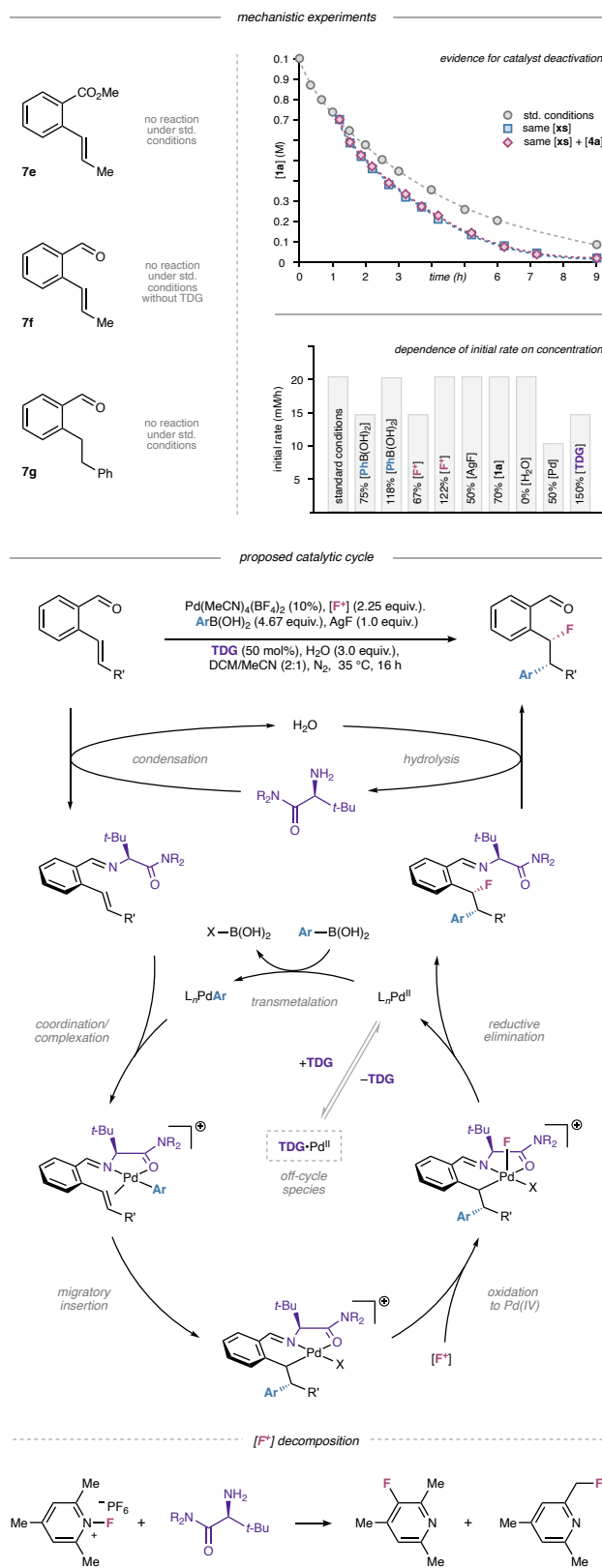


Figure 2 | Mechanistic investigation. Summary of control experiments and kinetics investigation (see SI for experimental details and all data) and proposed catalytic cycle.

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Supplementary Materials for

A Transient-Directing-Group Strategy Enables an Enantioselective Multicomponent Arylfluorination of Alkenes

Zhonglin Liu, Lucas J. Oxtoby, Mingyu Liu, Zi-Qi Li, Van T. Tran, Yang Gao, Keary M. Engle

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Screening and Optimization Data

Initial Screening

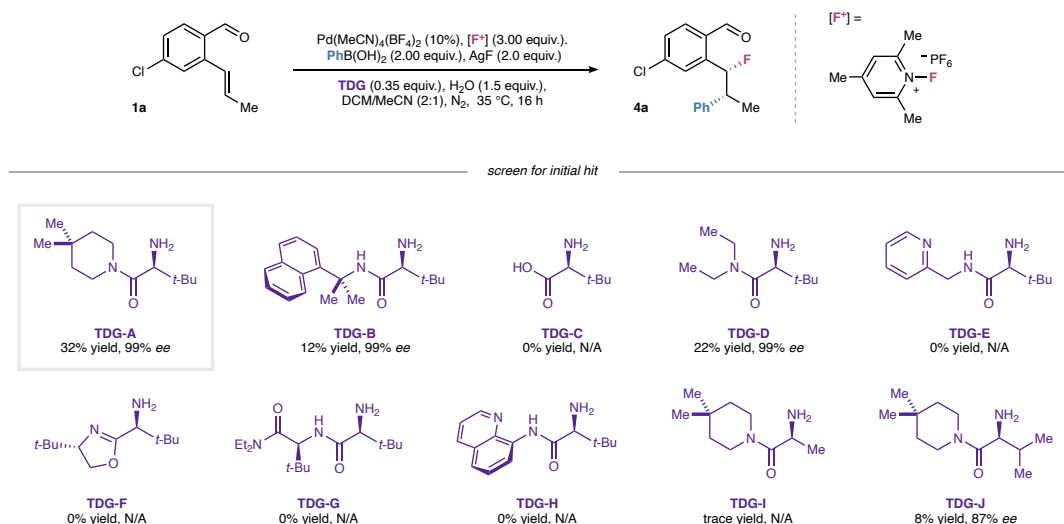


Figure S1. Initial screen of conditions on model substrate **1a**.

Optimization Using a Definitive Screening Design

In order to optimize the reaction conditions, we used the software JMP to generate a Definitive Screening Design (22). Reaction yields were entered into JMP and the results were analyzed using JMP's "Fit Definitive Screening platform" to develop a predictive linear regression model. This model was used as a guide to inform which conditions were selected as "optimal." We ultimately used the model's predicted values except for TDG loading, where we opted for 50 mol % because the model suggested TDG loading would have a minor impact on yield within the range screened. Parameter estimates and the actual-yield-by-predicted-yield plot are depicted in **Table S1**.

Term	Estimate	Std Error	PValue
[PhB(OH) ₂]	12.0714	0.5406	<.0001
[F ⁺]*[F ⁺]	-19.9263	1.2774	<.0001
[AgF]	-8.2143	0.5406	<.0001
[F ⁺]	6.3571	0.5406	<.0001
[AgF]*[F ⁺]	9.3000	0.8255	<.0001
[F ⁺]*[TDG]	4.6478	0.5943	<.0001
[H ₂ O]	3.0357	0.5406	0.0005
[TDG]	1.8929	0.5406	0.0080
[TDG]*[H ₂ O]	2.1631	0.8752	0.0386

Table S1. Parameter estimates and actual by predicted plot from DSD analysis.

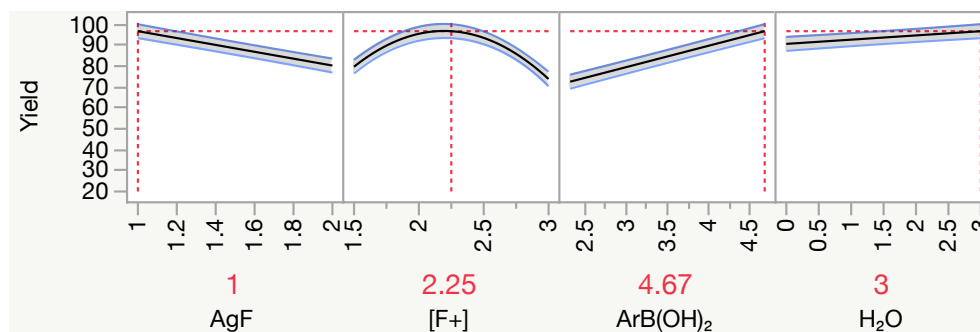


Figure S2. JMP prediction profiler graph output for model.

Re-Optimization for Terminal Alkene Substrates

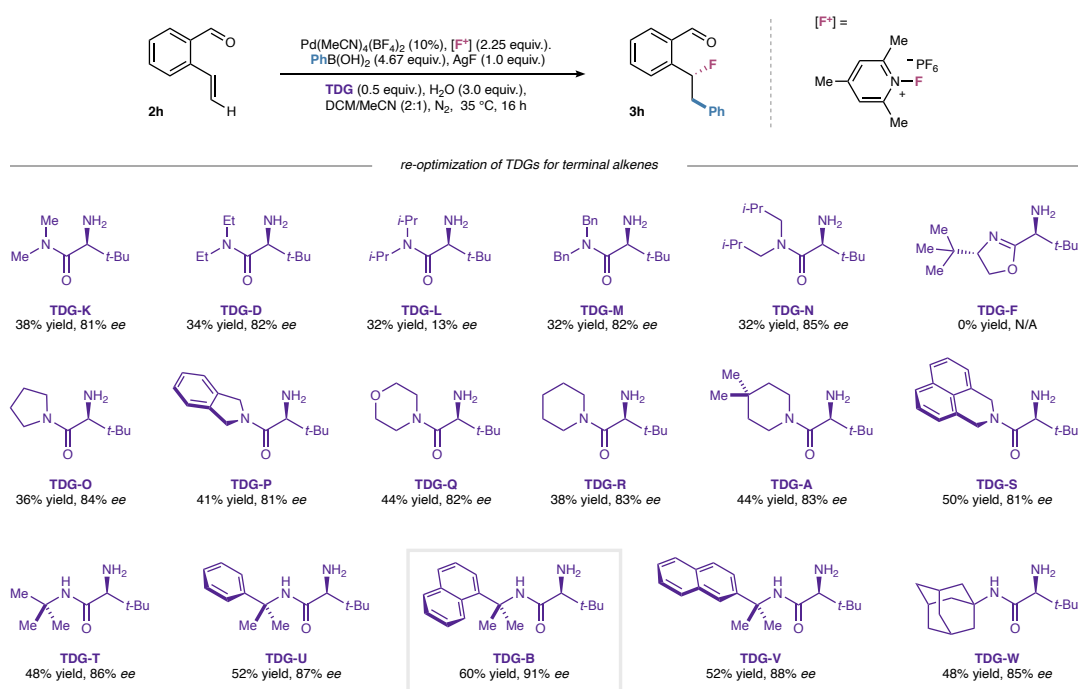


Figure S3. Screening of TDGs for re-optimization of terminal alkene substrates.

General Information

All materials were used as received from commercial sources without further purification. All commercial reagents were purchased from Aldrich, Oakwood, and Combi-Blocks. Unless otherwise stated, all reagents were handled open to air and not stored under inert atmosphere. NMR spectra were recorded on Bruker AV-600 or AV-400 instruments and internally referenced to SiMe_4 or solvent signals. The following abbreviations (or combinations thereof) were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet. High-resolution mass spectra (HRMS) for new compounds were recorded on a Waters LC-TOF mass spectrometer. Enantiomeric excess (ee) was determined on a Waters UPC² system using commercially available chiral columns.

Experimental Section

Substrate Preparation

All alkenes in **Figure S4** were prepared following literature procedures (17, 55–57).

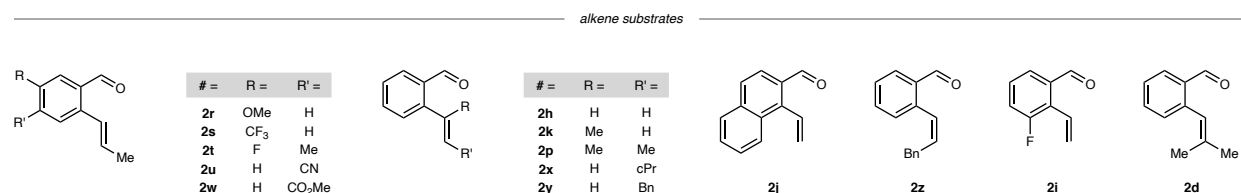
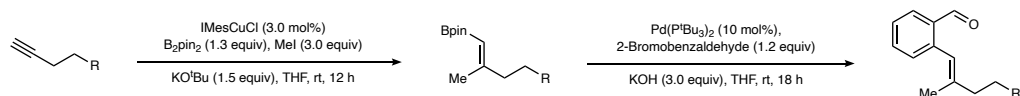


Figure S4. Previously prepared alkene substrates.

General Procedure for Synthesis of 1,2,2-Trisubstituted Alkenes

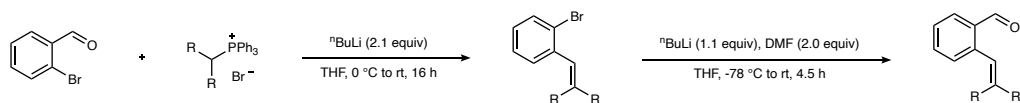
General Procedure A:



To an oven-dried round-bottom flask, IMeCuCl (61 mg, 0.015 mmol%), B₂pin₂ (1.65 g, 6.5 mmol), and anhydrous THF (20 mL) were added under inert atmosphere, and the resulting solution was cooled to 0 °C. The mixture was allowed to stir at 0 °C for 10 minutes, at which point alkyne (5.0 mmol) dissolved in THF (5 mL) and iodomethane (0.95 mL, 15 mmol) were added to the solution. The reaction mixture was stirred at room temperature for 12 hours before being quenched with saturated NH₄Cl solution and extracted with EtOAc. The combined organic phases were concentrated *in vacuo* and purified by silica gel column chromatography to give the corresponding alkenyl pinacol boronate (58).

To an oven-dried round-bottom flask containing a solution of Pd(P^tBu₃)₂ (102.2 mg, 0.2 mmol) and alkenyl pinacol boronate (2.0 mmol) dissolved in THF (20 mL) were added 2-bromobenzaldehyde (0.28 mL, 2.4 mmol) and aqueous KOH solution (2 mL, 3M). The reaction mixture was then stirred at room temperature for 18 hours. The resulting mixture was quenched by saturated NH₄Cl solution and extracted with EtOAc. The combined organic phases were concentrated *in vacuo* and purified by silica gel column chromatography (59).

General Procedure B:

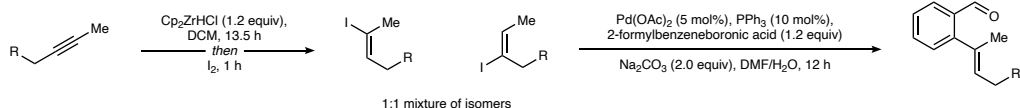


To an oven-dried round-bottom flask, pentan-3-yltriphenylphosphonium bromide (4.13 g, 10 mmol) and THF (100 mL) were added under inert atmosphere. ⁿBuLi was added at 0 °C, followed by 2-bromobenzaldehyde (0.58 mL, 5 mmol). The reaction was allowed to warm to room temperature and left to stir overnight. The resulting mixture was quenched with saturated NH₄Cl solution and extracted with EtOAc. The combined organic phases were concentrated *in vacuo* and purified by silica gel column chromatography.

An oven-dried round-bottom flask was charged with arylbromide (1 equiv) dissolved in THF (0.1 M) under inert atmosphere, and the resulting solution was cooled to -78 °C. Then, ⁿBuLi (1.1 equiv) was added dropwise and the mixture stirred for 2 hours at -78 °C before adding anhydrous DMF (2 equiv) in one portion. After stirring at -78 °C for 30 minutes, the reaction was allowed to warm to room temperature and left to stir overnight. The resulting mixture was quenched with saturated NH₄Cl solution and extracted with EtOAc. The combined organic phases were concentrated *in vacuo* and purified by silica gel column chromatography (60).

General Procedure for Synthesis of 1,1,2-Trisubstituted Alkenes

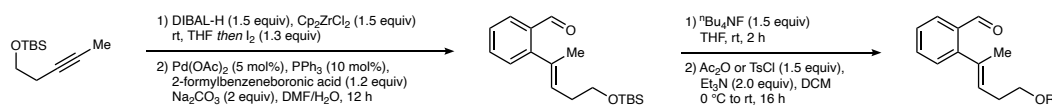
General Procedure C:



To a suspension of Cp₂ZrHCl (3.2 g, 12 mmol) in DCM (50 mL) was added alkyne (10 mmol) dropwise over 5 minutes at room temperature. The reaction was allowed to stir for 13.5 hours, at which point the now homogenous, pale-yellow solution was cooled to 0 °C and treated with I₂ (2.8 g, 11 mmol) added in one portion. Upon complete dissolution, the reaction was allowed to warm to room temperature and left to stir for 1 hour. The mixture was then poured into 1 M HCl (40 mL) containing ~50 g ice. After stirring vigorously for 0.5 hours, the resulting mixture was extracted with DCM. The combined organic phases were concentrated *in vacuo* and purified by silica gel column chromatography to give the isomeric mixture (61).

To an oven dried round flask, 2-formylbenzeneboronic acid (1.2 equiv), Na₂CO₃ (2 equiv), Pd(OAc)₂ (5 mol%), PPh₃ (10 mol%), and the isomeric mixture of alkenyl iodides (1 equiv) were added under inert atmosphere followed by addition of DMF/H₂O (0.2 M, 4:1). After stirring for 12 hours, the resulting mixture was extracted with EtOAc. The combined organic phases were concentrated *in vacuo* and purified by silica gel column chromatography and Prep-HPLC in sequence (62).

General Procedure D:



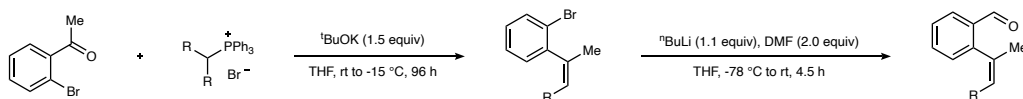
To a solution of Cp_2ZrCl_2 (4.38 g, 15 mmol) in THF (35 mL) was slowly added a solution of DIBAL-H (15 mmol, 1 M in THF) under inert atmosphere at 0 °C. The resultant suspension was stirred for 30 minutes at 0 °C, followed by addition of a solution of *tert*-butyldimethyl(pent-3-yn-1-yloxy)silane (10 mmol, 1.98 g) in THF (5 mL). The mixture was warmed to room temperature and stirred until a homogeneous solution formed, at which point the mixture was cooled to -78 °C and I_2 (3.3 g, 13 mmol) in THF (15 mL) was added. After stirring an additional 30 minutes at -78 °C, the reaction was quenched with 1N HCl and extracted with EtOAc. The combined organic phases were successively washed with saturated $\text{Na}_2\text{S}_2\text{O}_3$, NaHCO_3 , and brine, then concentrated *in vacuo* and purified by silica gel column chromatography (63).

To an oven-dried round-bottom flask, 2-formylbenzeneboronic acid (1.2 equiv), Na_2CO_3 (2 equiv), $\text{Pd}(\text{OAc})_2$ (5 mol%), PPh_3 (10 mol%), and the alkenyl iodide (1 equiv) were added under inert atmosphere followed by addition of DMF/ H_2O (0.2 M, 4:1). After stirring for 12 hours, the resulting mixture was extracted with EtOAc. The combined organic phases were concentrated *in vacuo* and purified by silica gel column chromatography (62).

To a solution of (*E*)-2-(5-((*tert*-butyldimethylsilyl)oxy)pent-2-en-2-yl)benzaldehyde (1.0 equiv) in THF (0.1 M) was added TBAF (1.5 equiv, 1.0 M in THF) under inert atmosphere. After stirring at room temperature for 3 hours, the mixture was extracted with EtOAc and the combined organic phases were concentrated *in vacuo* and purified by silica gel column chromatography.

To (*E*)-2-(5-hydroxypent-2-en-2-yl)benzaldehyde (1.0 equiv) in DCM (0.2 M) were added Et_3N (2 equiv) and Ac_2O or TsCl (1.5 equiv) at 0 °C and allowed to warm to room temperature. After stirring at room temperature overnight, the mixture was extracted with EtOAc and the combined organic phases were concentrated *in vacuo* and purified by silica gel column chromatography.

General Procedure E:



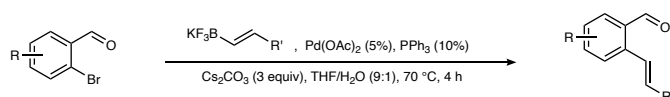
To an oven-dried round-bottom flask, butyltriphenylphosphonium bromide (1 equiv), THF (100 mL), and $t\text{BuOK}$ (15 mmol, 1.68 g) in THF (10 mL) were added in sequence. The mixture was stirred at room temperature for 30 minutes then cooled to -15 °C before adding 1-(2-Bromophenyl)ethan-1-one (10 mmol, 1.3 mL) in THF (10 mL). After stirring at -15 °C for 96 hours, the reaction was quenched with saturated NH_4Cl solution and extracted with EtOAc. The combined organic phases were concentrated *in vacuo* and purified by silica gel column chromatography (64).

An oven-dried round-bottom flask was charged with arylbromide (1 equiv) dissolved in THF (0.1M) under inert atmosphere and cooled to -78 °C. Then, $n\text{BuLi}$ (1.1 equiv) was added dropwise, and the mixture was stirred for 2 hours at -78 °C before anhydrous DMF (2 equiv) was added in

one portion. After stirring at -78 °C for 30 minutes, the reaction was allowed to warm to room temperature and left to stir overnight. The resulting mixture was quenched with saturated NH₄Cl solution and extracted with EtOAc. The combined organic phases were concentrated *in vacuo* and purified by silica gel column chromatography (60).

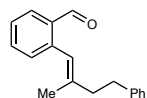
General Procedure for Synthesis of 1,2-Disubstituted Alkenes

General Procedure F:

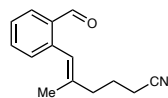


To a solution of the corresponding substituted *o*-bromobenzaldehyde (10 mmol, 1.0 equiv.) in THF/H₂O (9:1, 0.1M), were added Pd(OAc)₂ (112 mg, 0.5 mmol, 0.05 equiv.), PPh₃ (262 mg, 1 mmol, 0.1 equiv.), the corresponding potassium alkenyltrifluoroborate (12 mmol, 1.2 equiv.), and Cs₂CO₃ (9.1 g, 30 mmol, 3.0 equiv.), and the resulting solution was stirred at 70 °C for 4 h. The mixture was then cooled to room temperature, diluted with H₂O, and extracted with EtOAc (×3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (17).

Full Characterization of Reaction Products



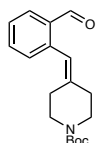
(*E*)-2-(2-Methyl-4-phenylbut-1-en-1-yl)benzaldehyde (**2a**). This compound was prepared according to General Procedure A in 51% yield over two steps. ¹H NMR (600 MHz, CDCl₃) δ 9.95 (d, *J* = 0.8 Hz, 1H), 7.87 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.52 (td, *J* = 7.5, 1.5 Hz, 1H), 7.38–7.29 (m, 3H), 7.25–7.20 (m, 3H), 7.17 (ddt, *J* = 7.7, 1.3, 0.7 Hz, 1H), 6.51 (s, 1H), 2.89 (dd, *J* = 8.7, 6.8 Hz, 2H), 2.68–2.33 (m, 2H), 1.68 (d, *J* = 1.4 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) δ 192.69, 142.05, 141.77, 141.50, 133.73, 133.51, 130.62, 128.42, 128.41, 127.79, 126.88, 126.02, 121.80, 41.44, 34.25, 17.69. HRMS (ESI-TOF) calculated for C₁₈H₁₉O⁺ [M+H]⁺ 251.1436, found 251.1439.



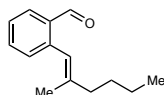
(*E*)-6-(2-Formylphenyl)-5-methylhex-5-enenitrile (**2b**). This compound was prepared according to General Procedure A in 42% yield over two steps. ¹H NMR (600 MHz, CDCl₃) δ 10.18 (s, 1H), 7.88 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.56 (td, *J* = 7.5, 1.4 Hz, 1H), 7.40 (td, *J* = 7.6, 1.2 Hz, 1H), 7.25 (d, *J* = 7.7 Hz, 1H), 6.69 (s, 1H), 2.46 (t, *J* = 7.1 Hz, 2H), 2.41 (td, *J* = 7.4, 1.2 Hz, 2H), 1.94 (p, *J* = 7.2 Hz, 3H), 1.67 (d, *J* = 1.4 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) δ 192.38, 140.96, 139.52, 133.68, 133.57, 130.71, 129.39, 127.17, 123.30, 119.51, 38.29, 23.45, 17.42, 16.60. HRMS (ESI-TOF) calculated for C₁₄H₁₆NO⁺ [M+H]⁺ 214.1232, found 214.1233.



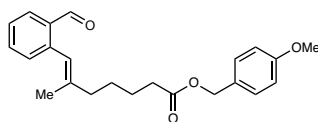
2-(2-Ethylbut-1-en-1-yl)benzaldehyde (**2c**). This compound was prepared according to General Procedure B in 67% yield over two steps. $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 10.26 (d, $J = 0.7$ Hz, 1H), 7.89 (dd, $J = 7.8, 1.5$ Hz, 1H), 7.54 (td, $J = 7.5, 1.4$ Hz, 1H), 7.39–7.33 (m, 1H), 7.23–7.19 (m, 1H), 6.52 (s, 1H), 2.27 (qd, $J = 7.5, 1.4$ Hz, 2H), 2.04 (qd, $J = 7.5, 0.7$ Hz, 2H), 1.16 (t, $J = 7.5$ Hz, 3H), 0.94 (t, $J = 7.5$ Hz, 3H). $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 192.76, 149.78, 142.63, 133.79, 133.64, 130.66, 127.72, 126.82, 119.06, 28.59, 24.02, 12.68, 12.60. **HRMS** (ESI-TOF) calculated for $\text{C}_{13}\text{H}_{17}\text{O}^+$ $[\text{M}+\text{H}]^+$ 189.1279, found 189.1279.



tert-Butyl 4-(2-formylbenzylidene)piperidine-1-carboxylate (**2e**). This compound was prepared according to General Procedure B in 26% yield over two steps from *N*-*tert*-butyloxycarbonylpiperidin-4-one. $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 10.24 (s, 1H), 7.89 (dd, $J = 7.8, 1.5$ Hz, 1H), 7.55 (td, $J = 7.5, 1.5$ Hz, 1H), 7.44–7.35 (m, 1H), 7.21 (d, $J = 7.6$ Hz, 1H), 6.69 (s, 1H), 3.54 (t, $J = 5.8$ Hz, 2H), 3.36 (d, $J = 6.0$ Hz, 2H), 2.41 (t, $J = 5.9$ Hz, 2H), 2.20 (s, 3H), 1.47 (s, 10H). $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 192.23, 154.60, 141.91, 140.45, 133.83, 133.57, 130.77, 128.74 (d, $J = 18.6$ Hz), 127.20, 120.65, 79.64, 35.95, 29.41, 28.35. **HRMS** (ESI-TOF) calculated for $\text{C}_{18}\text{H}_{23}\text{NNaO}_3^+$ $[\text{M}+\text{Na}]^+$ 324.1576, found 324.1575.

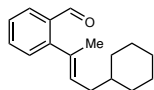


(*E*)-2-(2-Methylhex-1-en-1-yl)benzaldehyde (**2f**). This compound was prepared according to General Procedure B in 56% yield over two steps. $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 10.22 (d, $J = 0.8$ Hz, 1H), 7.89 (dd, $J = 7.7, 1.5$ Hz, 1H), 7.54 (td, $J = 7.5, 1.5$ Hz, 1H), 7.38–7.33 (m, 1H), 7.23 (ddt, $J = 7.7, 1.3, 0.7$ Hz, 1H), 6.58 (d, $J = 2.1$ Hz, 1H), 2.27–2.22 (m, 2H), 1.64 (d, $J = 1.4$ Hz, 3H), 1.57–1.49 (m, 2H), 1.39 (dq, $J = 14.7, 7.4$ Hz, 2H), 0.96 (t, $J = 7.3$ Hz, 3H). $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 192.75, 143.28, 142.43, 133.73, 133.53, 130.75, 127.84, 126.76, 120.65, 39.51, 30.07, 22.41, 17.64, 14.00. **HRMS** (ESI-TOF) calculated for $\text{C}_{14}\text{H}_{19}\text{O}^+$ $[\text{M}+\text{H}]^+$ 203.1436, found 203.1437.

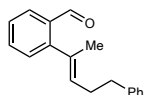


4-Methoxybenzyl (*E*)-7-(2-formylphenyl)-6-methylhept-6-enoate (**2g**). This compound was prepared according to General Procedure B in 43% yield over two steps. $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 10.19 (d, $J = 0.7$ Hz, 1H), 7.88 (dd, $J = 7.8, 1.5$ Hz, 1H), 7.53 (td, $J = 7.5, 1.5$ Hz, 1H), 7.36 (dddd, $J = 7.8, 7.2, 1.3, 0.7$ Hz, 1H), 7.32–7.28 (m, 2H), 7.21 (ddt, $J = 7.7, 1.3, 0.6$ Hz, 1H), 6.91–6.85 (m, 3H), 6.56 (s, 1H), 5.07 (s, 2H), 3.79 (s, 3H), 2.40 (t, $J = 7.4$ Hz, 2H), 2.24 (td, $J = 7.5, 1.2$ Hz, 2H), 1.77–1.66 (m, 2H), 1.61 (d, $J = 1.4$ Hz, 3H), 1.60–1.53 (m, 2H). $^{13}\text{C NMR}$ (150

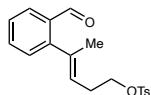
MHz, CDCl₃) δ 192.61, 173.47, 159.58, 142.43, 142.10, 133.70, 133.53, 130.73, 130.08, 128.16, 128.02, 126.84, 121.13, 113.90, 65.97, 55.24, 39.34, 34.14, 27.24, 24.56, 17.57. **HRMS** (ESI-TOF) calculated for C₂₃H₂₇O₄⁺ [M+H]⁺ 367.1909, found 367.1912.



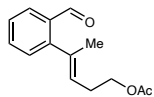
(*E*)-2-(4-Cyclohexylbut-2-en-2-yl)benzaldehyde (**2l**). This compound was prepared according to General Procedure C in 28% yield over two steps. **¹H NMR** (600 MHz, CDCl₃) δ 10.13 (s, 1H), 7.90 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.52 (td, *J* = 7.5, 1.5 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.31 (dd, *J* = 7.7, 1.2 Hz, 1H), 5.36 (tt, *J* = 7.6, 1.5 Hz, 1H), 2.13 (t, *J* = 7.1 Hz, 2H), 2.05 (d, *J* = 1.5 Hz, 3H), 1.78–1.68 (m, 4H), 1.68–1.61 (m, 1H), 1.43–1.35 (m, 1H), 1.34–1.12 (m, 3H), 0.98 (qd, *J* = 12.0, 3.0 Hz, 2H). **¹³C NMR** (150 MHz, CDCl₃) δ 192.61, 149.96, 133.97, 133.66, 133.34, 132.49, 128.89, 127.56, 126.78, 38.31, 36.69, 33.32, 26.49, 26.33, 19.00. **HRMS** (ESI-TOF) calculated for C₁₇H₂₃O⁺ [M+H]⁺ 243.1749, found 243.1754.



(*E*)-2-(5-Phenylpent-2-en-2-yl)benzaldehyde (**2m**). This compound was prepared according to General Procedure C in 32% yield over two steps. **¹H NMR** (600 MHz, CDCl₃) δ 9.99 (d, *J* = 0.8 Hz, 1H), 7.88 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.51 (td, *J* = 7.5, 1.5 Hz, 1H), 7.37–7.33 (m, 1H), 7.33–7.29 (m, 2H), 7.26 (d, *J* = 7.0 Hz, 1H), 7.23–7.19 (m, 3H), 5.37 (ddt, *J* = 7.3, 6.0, 1.5 Hz, 1H), 2.78 (t, *J* = 7.6 Hz, 2H), 2.67–2.48 (m, 2H), 1.97 (q, *J* = 1.0 Hz, 3H). **¹³C NMR** (150 MHz, CDCl₃) δ 192.49, 149.52, 141.52, 133.59, 133.58, 133.35, 132.94, 128.82, 128.46, 128.39, 127.58, 126.90, 126.01, 35.50, 30.65, 18.88. **HRMS** (ESI-TOF) calculated for C₁₈H₁₉O⁺ [M+H]⁺ 251.1436, found 251.1443.

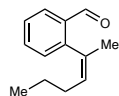


(*E*)-4-(2-Formylphenyl)pent-3-en-1-yl 4-methylbenzenesulfonate (**2n**). This compound was prepared according to General Procedure D in 25% yield over four steps. **¹H NMR** (600 MHz, CDCl₃) δ 10.03 (d, *J* = 0.8 Hz, 1H), 7.88 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.81–7.75 (m, 2H), 7.53 (td, *J* = 7.5, 1.5 Hz, 1H), 7.38 (tt, *J* = 7.4, 1.0 Hz, 1H), 7.34–7.30 (m, 2H), 7.24 (dd, *J* = 7.8, 1.2 Hz, 1H), 5.25–5.08 (m, 1H), 4.12 (t, *J* = 6.6 Hz, 2H), 2.72–2.53 (m, 2H), 2.43 (s, 3H), 2.03 (q, *J* = 1.0 Hz, 3H). **¹³C NMR** (150 MHz, CDCl₃) δ 191.96, 148.55, 144.85, 136.37, 133.47, 133.44, 132.98, 129.87, 128.83, 127.95, 127.86, 127.30, 127.28, 69.13, 28.52, 21.62, 19.22. **HRMS** (ESI-TOF) calculated for C₁₉H₂₀NaO₄S⁺ [M+Na]⁺ 367.0980, found 367.0986.

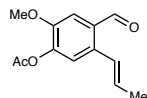


(*E*)-4-(2-Formylphenyl)pent-3-en-1-yl acetate (**2o**). This compound was prepared according to General Procedure D in 23% yield over four steps. **¹H NMR** (600 MHz, CDCl₃) δ 10.12 (d, *J* = 0.8 Hz, 1H), 7.90 (ddd, *J* = 7.8, 1.5, 0.6 Hz, 1H), 7.54 (td, *J* = 7.5, 1.5 Hz, 1H), 7.38 (ddt, *J* = 7.6,

6.3, 1.1 Hz, 1H), 7.30 (ddd, $J = 7.7, 1.2, 0.6$ Hz, 1H), 5.35 (tq, $J = 7.1, 1.5$ Hz, 1H), 4.18 (t, $J = 6.7$ Hz, 2H), 2.59 (tdd, $J = 7.7, 6.3, 0.9$ Hz, 2H), 2.09 (dt, $J = 1.6, 0.9$ Hz, 3H), 2.07 (s, 3H). **^{13}C NMR** (150 MHz, CDCl_3) δ 192.18, 171.05, 148.94, 135.09, 133.58, 133.42, 129.22, 128.76, 127.80, 127.14, 63.39, 28.17, 20.89, 19.04. **HRMS** (ESI-TOF) calculated for $\text{C}_{14}\text{H}_{16}\text{NaO}_3^+$ $[\text{M}+\text{Na}]^+$ 255.0997, found 255.1000.



(*Z*)-2-(Hex-2-en-2-yl)benzaldehyde (**2q**). This compound was prepared according to General Procedure D in 66% yield over two steps. **^1H NMR** (600 MHz, CDCl_3) δ 10.11 (d, $J = 0.8$ Hz, 1H), 7.94 (ddd, $J = 7.9, 1.5, 0.6$ Hz, 1H), 7.57 (td, $J = 7.5, 1.4$ Hz, 1H), 7.39 (ddt, $J = 8.5, 7.5, 1.1$ Hz, 1H), 7.18 (dd, $J = 7.5, 1.2$ Hz, 1H), 5.77–5.60 (m, 1H), 2.06 (q, $J = 1.4$ Hz, 3H), 1.68 (q, $J = 7.4$ Hz, 2H), 1.29 (q, $J = 7.4$ Hz, 2H), 0.78 (t, $J = 7.4$ Hz, 3H). **^{13}C NMR** (150 MHz, CDCl_3) δ 192.56, 146.89, 134.11, 132.94, 132.59, 130.94, 129.46, 127.17, 127.11, 31.29, 26.92, 22.52, 13.72. **HRMS** (ESI-TOF) calculated for $\text{C}_{13}\text{H}_{17}\text{O}^+$ $[\text{M}+\text{H}]^+$ 189.1279, found 189.1278.



(*E*)-4-Formyl-2-methoxy-5-(prop-1-en-1-yl)phenyl acetate (**2v**). This compound was prepared according to General Procedure E in 52% yield. **^1H NMR** (600 MHz, CDCl_3) δ 10.30 (s, 1H), 7.42 (s, 1H), 7.17 (s, 1H), 7.10–6.96 (m, 1H), 6.07 (dq, $J = 15.5, 6.7$ Hz, 1H), 3.88 (s, 3H), 2.34 (s, 3H), 1.94 (dd, $J = 6.7, 1.8$ Hz, 3H). **^{13}C NMR** (150 MHz, CDCl_3) δ 190.49, 168.38, 150.38, 144.39, 135.52, 131.95, 130.84, 124.98, 122.00, 111.58, 56.11, 20.63, 18.84. **HRMS** (ESI-TOF) calculated for $\text{C}_{13}\text{H}_{15}\text{O}_4^+$ $[\text{M}+\text{H}]^+$ 235.0970, found 235.0974.

Preparation of TDGs

Transient directing groups **TDG-C**, **-E**, **-F**, **-K**, **-L**, **-M**, **-N**, **-O**, **-Q**, **-R**, **-T**, and **-W** were prepared following literature procedures (19, 65–70).

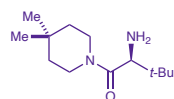
General Procedure



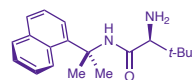
To a stirring solution of Boc-L-Tle-OH (1.16 g, 5.0 mmol), EDC·HCl (1.05 g, 5.5 mmol), HOAt (0.75 g, 5.5 mmol), and the corresponding amine (HNR¹R²) (5.5 mmol) in DCM (15 mL), was added DIPEA (1.2 mL, 7.5 mmol) dropwise at 0 °C. The reaction mixture was slowly warmed to room temperature and stirred for 24 hours. The reaction mixture was then diluted with DCM, washed with 10% KHSO₄ aqueous solution, saturated NaHCO₃ solution, and brine. The organic phase was then concentrated *in vacuo* and purified by silica gel column chromatography (19).

The protected amino amide was dissolved in DCM (5 mL), and TFA (2.5 mL) was added dropwise. After stirring at room temperature for 1 hour, the mixture was cooled to 0 °C, and saturated Na₂CO₃ solution was slowly added until the pH reached ~10. The mixture was then extracted with DCM, and the combined organic phases were concentrated *in vacuo* and purified by silica gel column chromatography.

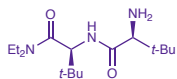
Full Characterization of Newly Prepared TDGs



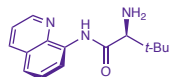
(*S*)-2-Amino-1-(4,4-dimethylpiperidin-1-yl)-3,3-dimethylbutan-1-one (**TDG-A**). This compound was prepared according to General Procedure F in 71% yield over two steps. ¹H NMR (600 MHz, CDCl₃) δ 3.69 (dddd, *J* = 13.6, 7.4, 4.1, 0.9 Hz, 1H), 3.57–3.48 (m, 3H), 3.44 (dt, *J* = 13.8, 5.9 Hz, 1H), 1.42–1.29 (m, 4H), 0.97 (d, *J* = 9.0 Hz, 6H), 0.97 (s, 9 H). ¹³C NMR (150 MHz, CDCl₃) δ 173.04, 57.32, 43.11, 39.03, 38.44, 38.22, 35.22, 29.09, 28.09, 27.39, 26.49. HRMS (ESI-TOF) calculated for C₁₃H₂₇N₂O⁺ [M+H]⁺ 227.2113, found 227.2117.



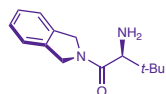
(*S*)-2-Amino-3,3-dimethyl-*N*-(2-(naphthalen-1-yl)propan-2-yl)butanamide (**TDG-B**). This compound was prepared according to General Procedure F in 63% yield over two steps. ¹H NMR (600 MHz, CDCl₃) δ 8.51–8.42 (m, 1H), 7.90–7.85 (m, 1H), 7.80–7.75 (m, 1H), 7.62 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.48–7.41 (m, 3H), 7.33 (s, 1H), 2.96 (s, 1H), 2.00 (d, *J* = 27.5 Hz, 6H), 0.99 (s, 9H). ¹³C NMR (150 MHz, CDCl₃) δ 172.27, 141.62, 135.03, 130.27, 129.71, 128.59, 125.86, 125.14, 125.01, 124.97, 123.67, 64.84, 56.57, 34.25, 28.58, 28.10, 26.88. HRMS (ESI-TOF) calculated for C₁₉H₂₇N₂O⁺ [M+H]⁺ 299.2123, found 299.2128.



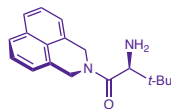
(*S*)-2-((*S*)-2-Amino-3,3-dimethylbutanamido)-*N,N*-diethyl-3,3-dimethylbutanamide (**TDG-G**). This compound was prepared according to General Procedure F in 53% yield over two steps. **¹H NMR** (600 MHz, CDCl₃) δ 7.51–7.35 (m, 1H), 4.81 (dd, *J* = 9.7, 6.9 Hz, 1H), 3.66 (ddt, *J* = 23.7, 14.4, 6.9 Hz, 2H), 3.27 (dt, *J* = 14.5, 7.2 Hz, 1H), 3.13–2.99 (m, 2H), 1.20 (q, *J* = 7.0 Hz, 3H), 1.10 (q, *J* = 7.0 Hz, 3H), 0.99 (dd, *J* = 7.5, 2.9 Hz, 18H). **¹³C NMR** (150 MHz, CDCl₃) δ 173.31, 170.53, 64.54, 64.53, 53.83, 53.82, 42.78, 40.30, 35.47, 34.28, 26.84, 26.66, 14.48, 12.89. **HRMS** (ESI-TOF) calculated for C₁₆H₃₄N₃O₂⁺ [M+H]⁺ 300.2651, found 300.2655.



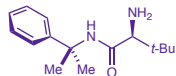
(*S*)-2-Amino-3,3-dimethyl-*N*-(quinolin-8-yl)butanamide (**TDG-H**). This compound was prepared according to General Procedure F in 49% yield over two steps. **¹H NMR** (600 MHz, CDCl₃) δ 10.84 (s, 1H), 8.86 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.82 (dd, *J* = 7.5, 1.5 Hz, 1H), 8.15 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.57–7.48 (m, 2H), 7.44 (dd, *J* = 8.2, 4.2 Hz, 1H), 3.40 (s, 1H), 1.12 (s, 9H). **¹³C NMR** (150 MHz, CDCl₃) δ 172.63, 148.47, 138.92, 136.21, 134.31, 128.03, 127.32, 121.49, 116.45, 65.85, 34.53, 26.80. **HRMS** (ESI-TOF) calculated for C₁₅H₂₀N₃O⁺ [M+H]⁺ 258.1606, found 258.1604.



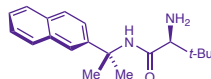
(*S*)-2-Amino-1-(isoindolin-2-yl)-3,3-dimethylbutan-1-one (**TDG-P**). This compound was prepared according to General Procedure F in 67% yield over two steps. **¹H NMR** (600 MHz, CDCl₃) δ 7.32–7.27 (m, 1H), 7.26–7.24 (m, 0H), 4.97 (dd, *J* = 13.1, 1.9 Hz, 0H), 4.93–4.87 (m, 1H), 4.77 (dd, *J* = 15.9, 2.1 Hz, 0H), 3.40 (s, 0H), 1.05 (d, *J* = 0.7 Hz, 3H). **¹³C NMR** (150 MHz, CDCl₃) δ 173.67, 136.34, 136.05, 127.85, 127.48, 123.01, 122.53, 60.40, 53.06, 52.12, 35.28, 26.28. **HRMS** (ESI-TOF) calculated for C₁₄H₂₁N₂O⁺ [M+H]⁺ 233.1654, found 233.1653.



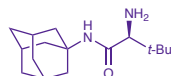
(*S*)-2-Amino-1-(1*H*-benzo[de]isoquinolin-2(3*H*)-yl)-3,3-dimethylbutan-1-one (**TDG-S**). This compound was prepared according to General Procedure F in 61% yield over two steps. **¹H NMR** (600 MHz, CDCl₃) δ 7.74 (dd, *J* = 11.7, 8.2 Hz, 2H), 7.44 (ddd, *J* = 11.4, 8.3, 7.0 Hz, 2H), 7.34 (dd, *J* = 6.9, 1.3 Hz, 1H), 7.25 (d, *J* = 6.6, 1.2 Hz, 1H), 5.21 (d, *J* = 16.1 Hz, 1H), 5.13–4.97 (m, 3H), 3.75 (s, 1H), 0.94 (s, 9H). **¹³C NMR** (150 MHz, CDCl₃) δ 173.47, 133.31, 131.60, 130.88, 127.97, 127.08, 126.50, 126.09, 125.62, 122.63, 121.60, 57.95, 49.73, 45.13, 35.36, 26.49. **HRMS** (ESI-TOF) calculated for C₁₈H₂₃N₂O⁺ [M+H]⁺ 283.1810, found 283.1806.



(*S*)-2-Amino-3,3-dimethyl-*N*-(2-phenylpropan-2-yl)butanamide (**TDG-U**). This compound was prepared according to General Procedure F in 66% yield over two steps. **¹H NMR** (600 MHz, CDCl₃) δ 7.43–7.39 (m, 2H), 7.35–7.30 (m, 2H), 7.24–7.20 (m, 1H), 7.05 (s, 1H), 3.00 (s, 1H), 1.72 (d, *J* = 13.9 Hz, 6H), 1.00 (s, 9H). **¹³C NMR** (150 MHz, CDCl₃) δ 172.48, 147.11, 128.32, 126.59, 124.80, 64.79, 55.37, 34.20, 28.96, 28.48, 26.82. **HRMS** (ESI-TOF) calculated for C₁₅H₂₅N₂O⁺ [M+H]⁺ 249.1967, found 249.1972.



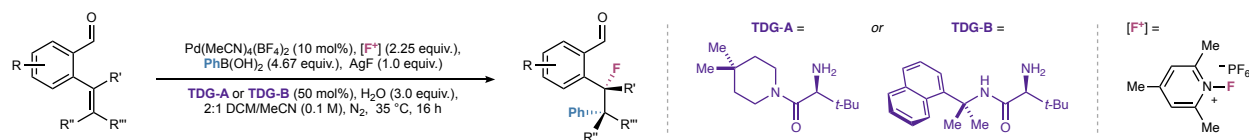
(*S*)-Amino-3,3-dimethyl-*N*-(2-(naphthalen-2-yl)propan-2-yl)butanamide (**TDG-V**). This compound was prepared according to General Procedure F in 65% yield over two steps. **¹H NMR** (600 MHz, CDCl₃) δ 7.88–7.73 (m, 4H), 7.55 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.50–7.40 (m, 2H), 7.18 (s, 1H), 3.02 (s, 1H), 1.81 (d, *J* = 10.9 Hz, 6H), 1.02 (s, 9H). **¹³C NMR** (150 MHz, CDCl₃) δ 172.55, 144.39, 133.21, 132.24, 128.15, 128.07, 127.36, 125.93, 125.62, 123.63, 123.23, 64.73, 55.40, 34.21, 28.88, 28.53, 26.82. **HRMS** (ESI-TOF) calculated for C₁₉H₂₇N₂O⁺ [M+H]⁺ 299.2123, found 299.2123.



(*S*)-*N*-((3*R*,5*R*,7*R*)-adamantan-1-yl)-2-amino-3,3-dimethylbutanamide (**TDG-W**). This compound was prepared according to General Procedure F in 62% yield over two steps. **¹H NMR** (600 MHz, CDCl₃) δ 6.28 (s, 1H), 2.93 (s, 1H), 2.07 (q, *J* = 3.1 Hz, 3H), 2.01 (d, *J* = 2.9 Hz, 7H), 1.72 – 1.65 (m, 7H), 0.99 (s, 9H). **¹³C NMR** (150 MHz, CDCl₃) δ 172.51, 64.96, 51.36, 41.63, 36.39, 33.97, 29.42, 26.75. **HRMS** (ESI-TOF) calculated for C₁₆H₂₉N₂O⁺ [M+H]⁺ 265.2280, found 265.2276.

Transiently Directed Arylfluorination

General Procedure



To a culture tube were added $\text{PhB}(\text{OH})_2$ (56.9 mg, 0.467 mmol), $[\text{F}^+]$ (64.2 mg, 0.225 mmol), TDG (0.05 mmol), $\text{Pd}(\text{MeCN})_4(\text{BF}_4)_2$ (4.4 mg, 0.01 mmol), and AgF (12.7 mg, 0.1 mmol) in a glovebox. The tube was then removed from the glovebox, and a solution of alkene (0.1 mmol) dissolved in DCM (0.67 mL), MeCN (0.33 mL), and H_2O (5.4 μL , 0.3 mmol) was added under inert atmosphere and stirred at 35 °C. After stirring at 35 °C for 16 hours, and the reaction was quenched with 1 N HCl aqueous solution (3 mL) and extracted with EtOAc (5 mL $\times$ 3). The combined organic phases were concentrated *in vacuo* and purified by preparatory TLC. Racemic samples were prepared according to the same procedure using the corresponding racemic TDG. The gram-scale reaction was set up in the glovebox.

Unsuccessful Coupling Partners

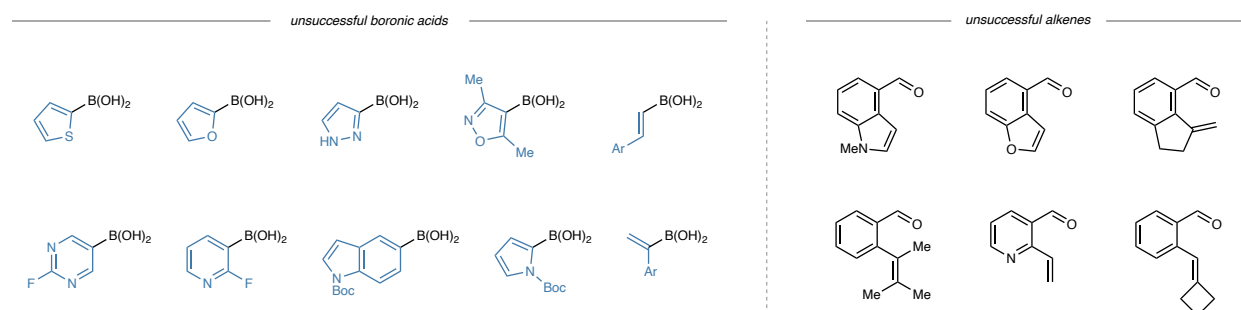


Figure S5. Examples of coupling partners that were unsuccessful (<5% yield by ^1H NMR).

Photographic Depiction of Procedure on Gram-Scale

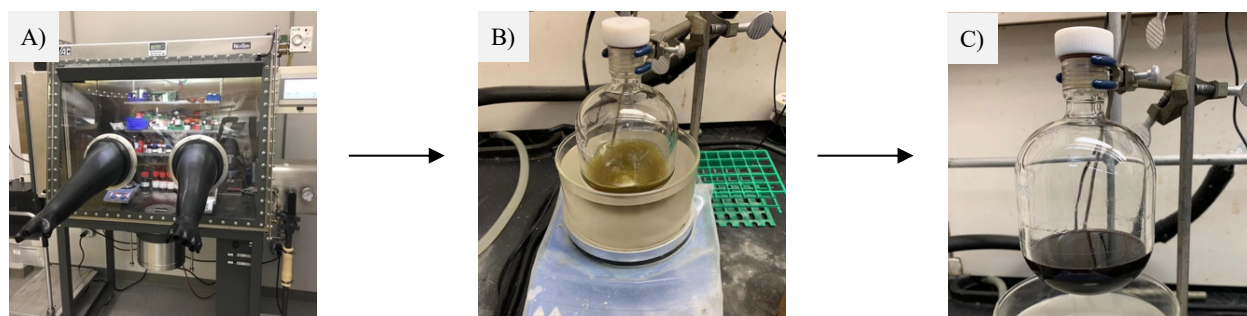
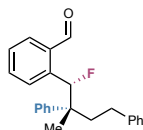


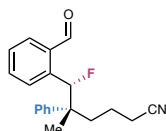
Figure S6. A) Glovebox used for reaction set-up under inert atmosphere. B) Reaction stirring at 35 °C. C) Reaction after stirring at 35 °C for 16 hours.

Full Characterization of Reaction Products

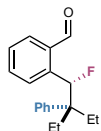
We do not observe any ^1H NMR signals in the crude reaction mixture that would be consistent with the alternative diastereomer; moreover, in the case of examples **3y** and **3z**, both diastereomers are characterized, allowing us to confirm that the alternative diastereomer is not formed in these cases. We conservatively report a *d.r.* >20:1.



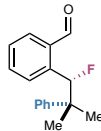
2-((1*R*,2*R*)-1-fluoro-2-methyl-2,4-diphenylbutyl)benzaldehyde (**3a**). This compound was prepared according to General Procedure (using **TDG-A**) as a yellow oil (18.7 mg, 54% yield, *d.r.* >20:1, >99% *ee*). ^1H NMR (600 MHz, CDCl_3) δ 9.77 (s, 1H), 7.74 (dt, $J = 7.6, 1.3$ Hz, 1H), 7.44 (td, $J = 7.5, 1.3$ Hz, 1H), 7.40 (td, $J = 7.6, 1.5$ Hz, 1H), 7.34–7.22 (m, 7H), 7.19–7.14 (m, 1H), 7.14–7.08 (m, 2H), 7.01 (dd, $J = 7.8, 1.3$ Hz, 1H), 6.60 (d, $J = 45.8$ Hz, 1H), 2.60 (td, $J = 13.1, 3.9$ Hz, 1H), 2.51 (td, $J = 13.1, 5.0$ Hz, 1H), 2.25 (td, $J = 13.0, 3.8$ Hz, 1H), 1.95 (td, $J = 12.9, 5.0$ Hz, 1H), 1.45 (d, $J = 1.7$ Hz, 3H). ^{13}C NMR (150 MHz, CDCl_3) δ 191.76, 142.52, 141.07, 138.50 (d, $J = 21.0$ Hz), 134.01 (d, $J = 3.8$ Hz), 132.65, 132.24, 128.92 (d, $J = 9.6$ Hz), 128.43, 128.35 (d, $J = 1.9$ Hz), 128.26, 128.03, 126.86, 125.74, 95.29 (d, $J = 179.6$ Hz), 47.19 (d, $J = 20.6$ Hz), 39.06 (d, $J = 3.7$ Hz), 30.27, 19.97 (d, $J = 5.5$ Hz). ^{19}F NMR (376 MHz, CDCl_3) δ -180.56 (d, $J = 45.9$ Hz, 1F). HRMS (ESI-TOF) calculated for $\text{C}_{24}\text{H}_{23}\text{O}^+$ $[\text{M}-\text{F}]^+$ 327.1749, found 327.1755; SFC (chiral column) The sample was analyzed on a Waters UPC² SFC with a Daicel IG column (3 μm , 4.6 $\times$ 250 mm) under isocratic conditions (4 mL/min, 20% MeOH / CO_2 , 1600 psi backpressure) at 30 $^\circ\text{C}$. The enantiomers were detected by UV light (245 nm).



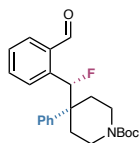
(5*R*,6*R*)-6-fluoro-6-(2-formylphenyl)-5-methyl-5-phenylhexanenitrile (**3b**). This compound was prepared according to General Procedure (using **TDG-A**) as a yellow oil (21.7 mg, 70% yield, *d.r.* >20:1, >99% *ee*). ^1H NMR (600 MHz, CDCl_3) δ 9.81 (s, 1H), 7.75 (dt, $J = 7.8, 1.2$ Hz, 1H), 7.48 (td, $J = 7.5, 1.3$ Hz, 1H), 7.41 (td, $J = 7.6, 1.5$ Hz, 1H), 7.33–7.23 (m, 3H), 7.20 (dd, $J = 7.6, 1.8$ Hz, 2H), 6.98 (dd, $J = 7.9, 1.2$ Hz, 1H), 6.63 (d, $J = 45.9$ Hz, 1H), 2.45 (td, $J = 13.0, 4.1$ Hz, 1H), 2.28 (td, $J = 7.1, 2.2$ Hz, 2H), 1.80–1.71 (m, 1H), 1.64–1.53 (m, 1H), 1.38–1.28 (m, 1H), 1.34 (s, 3H). ^{13}C NMR (150 MHz, CDCl_3) δ 192.11, 140.55, 138.11 (d, $J = 21.0$ Hz), 133.91 (d, $J = 4.1$ Hz), 133.00, 132.76, 128.88 (d, $J = 9.4$ Hz), 128.63, 128.13, 128.10, 128.09, 119.40, 94.74 (d, $J = 179.4$ Hz), 46.81 (d, $J = 20.8$ Hz), 36.29 (d, $J = 4.2$ Hz), 20.26, 19.59 (d, $J = 5.5$ Hz), 17.64. ^{19}F NMR (376 MHz, CDCl_3) δ -180.74 (d, $J = 45.8$ Hz, 1F). HRMS (ESI-TOF) calculated for $\text{C}_{20}\text{H}_{20}\text{NO}^+$ $[\text{M}-\text{F}]^+$ 290.1545, found 290.1552; SFC (chiral column) The sample was analyzed on a Waters UPC² SFC with a Daicel IBN column (3 μm , 4.6 $\times$ 250 mm) under isocratic conditions (4 mL/min, 15% MeOH / CO_2 , 1600 psi backpressure) at 30 $^\circ\text{C}$. The enantiomers were detected by UV light (215 nm).



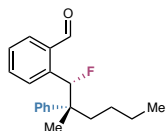
(*R*)-2-(2-Ethyl-1-fluoro-2-phenylbutyl)benzaldehyde (**3c**). This compound was prepared according to General Procedure (using **TDG-A**), but purified by prep-HPLC to give a yellow oil (14.2 mg, 50% yield, >99% *ee*). **¹H NMR** (600 MHz, CDCl₃) δ 9.54 (s, 1H), 7.74 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.40 (td, *J* = 7.5, 1.3 Hz, 1H), 7.35 (td, *J* = 7.2, 1.3 Hz, 1H), 7.24–7.18 (m, 3H), 7.02–6.99 (m, 2H), 6.81–6.78 (m, 1H), 6.42 (d, *J* = 45.9 Hz, 1H), 2.47 (dq, *J* = 14.5, 7.3 Hz, 1H), 1.90 (dq, *J* = 14.9, 7.4, 2.4 Hz, 2H), 1.57 (dq, *J* = 14.4, 7.2 Hz, 1H), 1.09 (t, *J* = 7.4 Hz, 3H), 0.81 (td, *J* = 7.4, 0.9 Hz, 3H). **¹³C NMR** (150 MHz, CDCl₃) δ 191.13 (d, *J* = 4.4 Hz), 139.69, 138.60 (d, *J* = 21.3 Hz), 134.61 (d, *J* = 2.6 Hz), 132.14, 130.35, 129.21 (d, *J* = 9.9 Hz), 129.03, 128.27, 127.65, 126.79, 94.26 (d, *J* = 180.2 Hz), 49.59 (d, *J* = 19.8 Hz), 24.02 (d, *J* = 4.7 Hz), 23.14 (d, *J* = 4.6 Hz), 8.11, 7.72 (d, *J* = 2.1 Hz). **¹⁹F NMR** (376 MHz, CDCl₃) δ -178.96 (d, *J* = 46.2 Hz, 1F). **HRMS** (ESI-TOF) calculated for C₁₉H₂₁O⁺ [M-F]⁺ 265.1592, found 265.1596; **SFC** (chiral column) The enantiomeric excess was determined by heart-cutting 2D LC-SFC (77). The LC dimension consisted of a Waters I-Class LC with a Waters BEH C18 column (1.7 μm, 2.1×100 mm) using a 0.1% aqueous formic acid:acetonitrile gradient (0.6 mL/min, 15–99% acetonitrile over 2.1 minutes) at 55 °C. The heart cut was performed at 1.52 minutes using a 6-port 2-position valve equipped with a 10 μL transfer loop. The SFC dimension consisted of a Waters UPC² SFC with a Daicel IC column (3 μm, 4.6×250 mm) using isocratic conditions (4 mL/min, 5% IPA / CO₂, 1600 psi backpressure) at 30 °C. The enantiomers were detected by UV light (245 nm).



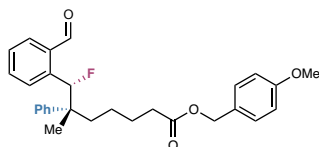
(*R*)-2-(1-Fluoro-2-methyl-2-phenylpropyl)benzaldehyde (**3d**). This compound was prepared according to General Procedure (using **TDG-A**), but purified by prep-HPLC to give a yellow oil (10.3 mg, 40% yield, >99% *ee*). **¹H NMR** (600 MHz, CDCl₃) δ 9.76 (s, 1H), 7.76 (ddd, *J* = 6.6, 2.3, 1.1 Hz, 1H), 7.47 (pd, *J* = 7.4, 1.7 Hz, 2H), 7.29–7.22 (m, 5H), 7.20 (dd, *J* = 7.3, 1.8 Hz, 1H), 6.50 (d, *J* = 45.8 Hz, 1H), 1.43 (d, *J* = 1.7 Hz, 3H), 1.42 (d, *J* = 1.1 Hz, 3H). **¹³C NMR** (150 MHz, CDCl₃) δ 191.36 (d, *J* = 2.0 Hz), 143.70 (d, *J* = 2.2 Hz), 138.84 (d, *J* = 21.1 Hz), 134.03 (d, *J* = 3.7 Hz), 132.62, 131.51, 128.63 (d, *J* = 10.5 Hz), 128.38, 127.92, 127.58, 126.77, 95.73 (d, *J* = 179.7 Hz), 43.51 (d, *J* = 21.6 Hz), 24.73 (d, *J* = 4.4 Hz), 23.70 (d, *J* = 5.4 Hz). **¹⁹F NMR** (376 MHz, CDCl₃) δ -180.69 (d, *J* = 45.9 Hz, 1F). **HRMS** (ESI-TOF) calculated for C₁₇H₁₇O⁺ [M-F]⁺ 237.1279, found 237.1284; **SFC** (chiral column) The enantiomeric excess was determined by heart-cutting 2D LC-SFC (77). The LC dimension consisted of a Waters I-Class LC with a Waters BEH C18 column (1.7 μm, 2.1×100 mm) using a 0.1% aqueous formic acid:acetonitrile gradient (0.6 mL/min, 15–99% acetonitrile over 2.1 minutes) at 55 °C. The heart cut was performed at 2.03 minutes using a 6-port 2-position valve equipped with a 10 μL transfer loop. The SFC dimension consisted of a Waters UPC² SFC with a Daicel IG column (3 μm, 4.6×250 mm) using isocratic conditions (4 mL/min, 25% MeOH / CO₂, 1600 psi backpressure) at 30 °C. The enantiomers were detected by UV light (245 nm).



tert-Butyl (*R*)-4-(fluoro(2-formylphenyl)methyl)-4-phenylpiperidine-1-carboxylate (**3e**). This compound was prepared according to General Procedure (using **TDG-A**) as a yellow oil (22.3 mg, 56% yield, >99% *ee*). **¹H NMR** (600 MHz, CDCl₃) δ 9.57 (s, 1H), 7.75–7.71 (m, 1H), 7.47–7.42 (m, 2H), 7.29–7.24 (m, 3H), 7.08–7.01 (m, 3H), 6.34 (d, *J* = 45.9 Hz, 1H), 3.97 (br, 2H), 2.69 (br, 2H), 2.56 (dd, *J* = 14.0, 2.9 Hz, 1H), 2.11–2.06 (m, 1H), 2.00 (ddd, *J* = 13.9, 12.6, 4.4 Hz, 1H), 1.88 (d, *J* = 14.0 Hz, 1H), 1.42 (s, 9H). **¹³C NMR** (150 MHz, CDCl₃) δ 191.06 (d, *J* = 2.5 Hz), 154.86, 137.50 (d, *J* = 21.3 Hz), 136.56 (d, *J* = 2.0 Hz), 134.16 (d, *J* = 3.2 Hz), 132.53, 131.46, 129.15, 128.80 (d, *J* = 10.4 Hz), 128.58, 128.44, 127.30, 95.93 (d, *J* = 174.0 Hz), 79.43, 46.92 (d, *J* = 21.2 Hz), 40.14 (d, *J* = 42.8 Hz), 39.12 (d, *J* = 47.2 Hz), 31.35 (d, *J* = 61.6 Hz), 29.91, 28.40. **¹⁹F NMR** (376 MHz, CDCl₃) δ -182.51 (br, 1F). **HRMS** (ESI-TOF) calculated for C₁₉H₂₁FNO⁺ [M-Boc+2H]⁺ 298.1607, found 298.1603; **SFC** (chiral column) The sample was analyzed on a Waters UPC² SFC with a Daicel IG column (3 μm, 4.6×250 mm) under isocratic conditions (4 mL/min, 25% MeOH / CO₂, 1600 psi backpressure) at 30 °C. The enantiomers were detected by UV light (250 nm).

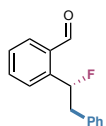


2-((1*R*,2*R*)-1-Fluoro-2-methyl-2-phenylhexyl)benzaldehyde (**3f**). This compound was prepared according to General Procedure (using **TDG-A**), as a yellow oil (16.7 mg, 55% yield, *d.r.* >20:1, 99% *ee*). **¹H NMR** (600 MHz, CDCl₃) δ 9.80 (s, 1H), 7.76 (dt, *J* = 7.6, 1.3 Hz, 1H), 7.44 (td, *J* = 7.4, 1.4 Hz, 1H), 7.40 (td, *J* = 7.5, 1.6 Hz, 1H), 7.29–7.23 (m, 3H), 7.20–7.17 (m, 2H), 7.00 (dd, *J* = 7.8, 1.4 Hz, 1H), 6.51 (d, *J* = 45.8 Hz, 1H), 2.26 (td, *J* = 12.9, 4.0 Hz, 1H), 1.61 (ddd, *J* = 13.5, 12.3, 4.8 Hz, 1H), 1.32 (d, *J* = 1.7 Hz, 3H), 1.29–1.24 (m, 2H), 1.22–1.16 (m, 1H), 0.97–0.90 (m, 1H), 0.83 (t, *J* = 7.3 Hz, 3H). **¹³C NMR** (150 MHz, CDCl₃) δ 191.63, 141.58, 138.77 (d, *J* = 21.4 Hz), 134.09 (d, *J* = 3.8 Hz), 132.54, 131.74, 128.95 (d, *J* = 9.5 Hz), 128.33, 128.29, 127.83, 126.61, 95.65 (d, *J* = 179.3 Hz), 46.93 (d, *J* = 20.5 Hz), 36.77 (d, *J* = 3.7 Hz), 25.88, 23.36, 19.91 (d, *J* = 5.5 Hz), 13.99. **¹⁹F NMR** (376 MHz, CDCl₃) δ -180.51 (d, *J* = 45.8 Hz, 1F). **HRMS** (ESI-TOF) calculated for C₂₀H₂₃O⁺ [M-F]⁺ 279.1749, found 279.1753; **SFC** (chiral column) The sample was analyzed on a Waters UPC² SFC with a Daicel IA column (3 μm, 4.6×250 mm) under isocratic conditions (4 mL/min, 5% MeOH / CO₂, 1600 psi backpressure) at 30 °C. The enantiomers were detected by UV light (245 nm).

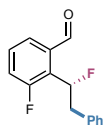


4-Methoxybenzyl (*6R*,*7R*)-7-fluoro-7-(2-formylphenyl)-6-methyl-6-phenylheptanoate (**3g**). This compound was prepared according to General Procedure (using **TDG-A**) as a yellow oil (30.1 mg, 65% yield, *d.r.* >20:1, >99% *ee*). **¹H NMR** (600 MHz, CDCl₃) δ 9.77 (s, 1H), 7.75 (d, *J* = 7.5 Hz,

1H), 7.46–7.43 (m, 1H), 7.40 (td, $J = 7.5, 1.6$ Hz, 1H), 7.24 (dd, $J = 8.2, 5.7$ Hz, 5H), 7.18–7.14 (m, 2H), 7.00 (d, $J = 7.7$ Hz, 1H), 6.89–6.85 (m, 2H), 6.51 (d, $J = 45.8$ Hz, 1H), 4.99 (d, $J = 2.9$ Hz, 2H), 3.80 (s, 3H), 2.26 (m, 3H), 1.65–1.54 (m, 3H), 1.29 (s, 3H), 1.24–1.18 (m, 1H), 0.95 (m, 1H). **¹³C NMR** (150 MHz, CDCl₃) δ 191.67, 173.45, 159.55, 141.31, 138.57 (d, $J = 21.0$ Hz), 134.03 (d, $J = 3.8$ Hz), 132.57, 132.01, 130.02, 128.90 (d, $J = 9.5$ Hz), 128.39, 128.19, 128.14, 127.90, 126.70, 113.90, 95.41 (d, $J = 179.4$ Hz), 65.89, 55.25, 46.91 (d, $J = 20.5$ Hz), 36.60 (d, $J = 3.7$ Hz), 34.18, 25.53, 23.31, 19.79 (d, $J = 5.4$ Hz). **¹⁹F NMR** (376 MHz, CDCl₃) δ -180.66 (d, $J = 45.9$ Hz, F). **HRMS** (ESI-TOF) calculated for C₂₉H₃₁O₄⁺ [M-F]⁺ 443.2222, found 443.2220; **SFC** (chiral column) The sample was analyzed on a Waters UPC² SFC with a Daicel IG column (3 μ m, 4.6×250 mm) under isocratic conditions (4 mL/min, 40% MeOH / CO₂, 1600 psi backpressure) at 30 °C. The enantiomers were detected by UV light (245 nm).

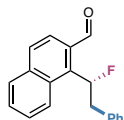


(*R*)-2-(1-Fluoro-2-phenylethyl)benzaldehyde (**3h**). This compound was prepared according to General Procedure (using **TDG-B**) as a yellow oil (13.7 mg, 60% yield, 91% *ee*). **¹H NMR** (600 MHz, CDCl₃) δ 10.10 (s, 1H), 7.85 (d, $J = 7.6$ Hz, 1H), 7.69–7.62 (m, 2H), 7.54 (td, $J = 7.3, 1.7$ Hz, 1H), 7.37–7.29 (m, 4H), 7.28–7.24 (m, 2H), 6.53 (ddd, $J = 48.8, 8.4, 3.0$ Hz, 1H), 3.21 (ddd, $J = 34.8, 14.5, 3.0$ Hz, 1H), 2.98 (ddd, $J = 21.2, 14.5, 8.4$ Hz, 1H). **¹³C NMR** (150 MHz, CDCl₃) δ 193.06, 142.54 (d, $J = 19.8$ Hz), 137.10, 134.70, 134.08, 131.88 (d, $J = 3.9$ Hz), 129.63, 128.31, 128.19, 126.70, 125.97 (d, $J = 13.4$ Hz), 91.85 (d, $J = 173.8$ Hz), 43.75 (d, $J = 23.2$ Hz). **¹⁹F NMR** (376 MHz, CDCl₃) δ -183.04 (ddd, $J = 48.6, 34.7, 21.3$ Hz, 1F). **HRMS** (ESI-TOF) calculated for C₁₅H₁₃O⁺ [M-F]⁺ 209.0966, found 209.0964; **SFC** (chiral column) The enantiomeric excess was determined by heart-cutting 2D LC-SFC (77). The LC dimension consisted of a Waters I-Class LC with a Waters BEH C18 column (1.7 μ m, 2.1×100 mm) using a 0.1% aqueous formic acid:acetonitrile gradient (0.6 mL/min, 15–99% acetonitrile over 2.1 minutes) at 55 °C. The heart cut was performed at 1.89 minutes using a 6-port 2-position valve equipped with a 10 μ L transfer loop. The SFC dimension consisted of a Waters UPC² SFC with a Daicel IG column (3 μ m, 4.6×250 mm) using isocratic conditions (4 mL/min, 30% MeOH / CO₂, 1600 psi backpressure) at 30 °C. The enantiomers were detected by UV light (245 nm).

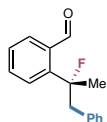


(*R*)-3-Fluoro-2-(1-fluoro-2-phenylethyl)benzaldehyde (**3i**). This compound was prepared according to General Procedure (using **TDG-B**) as a yellow oil (16.3 mg, 66% yield, 97% *ee*). **¹H NMR** (600 MHz, CDCl₃) δ 10.14 (q, $J = 0.8$ Hz, 1H), 7.70 (d, $J = 7.7$ Hz, 1H), 7.47 (td, $J = 8.0, 5.0$ Hz, 1H), 7.34–7.23 (m, 5H), 7.20–7.17 (m, 2H), 6.48 (ddd, $J = 46.8, 7.7, 4.9$ Hz, 1H), 3.39 (ddd, $J = 19.5, 14.3, 7.7$ Hz, 1H), 3.28 (ddd, $J = 26.4, 14.3, 4.9$ Hz, 1H). **¹³C NMR** (150 MHz, CDCl₃) δ 190.99 (dd, $J = 8.5, 3.0$ Hz), 160.06 (dd, $J = 250.6, 6.4$ Hz), 136.22 (d, $J = 2.4$ Hz), 135.52 (d, $J = 2.8$ Hz), 130.04 (d, $J = 8.9$ Hz), 129.67, 128.51, 128.02 (dd, $J = 20.9, 12.0$ Hz), 127.15, 126.30 (d, $J = 3.2$ Hz), 120.96 (d, $J = 23.1$ Hz), 89.18 (dd, $J = 175.6, 4.0$ Hz), 42.90 (d, $J = 23.0$ Hz). **¹⁹F NMR** (376 MHz, CDCl₃) δ -114.55 (td, $J = 10.9, 5.2$ Hz, 1F), -177.48 (dddd, $J =$

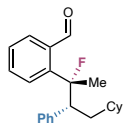
46.4, 26.3, 19.5, 11.1 Hz, 1F). **HRMS** (ESI-TOF) calculated for $C_{15}H_{12}FO^+$ $[M-F]^+$ 227.0872, found 227.0874; **SFC** (chiral column) The sample was analyzed on a Waters UPC² SFC with a Daicel IG column (3 μ m, 4.6×250 mm) under isocratic conditions (4 mL/min, 25% MeOH / CO₂, 1600 psi backpressure) at 30 °C. The enantiomers were detected by UV light (240 nm).



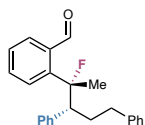
(*R*)-1-(1-Fluoro-2-phenylethyl)-2-naphthaldehyde (**3j**). This compound was prepared according to General Procedure (using **TDG-B**) as a yellow oil (14.8 mg, 53% yield, 97% *ee*). **¹H NMR** (600 MHz, CDCl₃) δ 10.40 (d, *J* = 1.6 Hz, 1H), 8.39 (d, *J* = 8.5 Hz, 1H), 7.96–7.89 (m, 3H), 7.68–7.59 (m, 2H), 7.33–7.24 (m, 5H), 6.98 (ddd, *J* = 47.1, 8.3, 4.6 Hz, 1H), 3.63 (ddd, *J* = 17.5, 14.4, 8.3 Hz, 1H), 3.43 (ddd, *J* = 27.7, 14.5, 4.7 Hz, 1H). **¹³C NMR** (150 MHz, CDCl₃) δ 192.27 (d, *J* = 8.5 Hz), 139.03 (d, *J* = 18.2 Hz), 136.20 (d, *J* = 2.7 Hz), 136.07, 131.78, 129.97 (d, *J* = 3.1 Hz), 129.59, 129.51, 129.11, 128.60, 128.47, 127.31, 127.17, 125.90 (d, *J* = 6.8 Hz), 124.94, 92.38 (d, *J* = 175.9 Hz), 43.66 (d, *J* = 22.6 Hz). **¹⁹F NMR** (376 MHz, CDCl₃) δ -173.07 (s, 1F). **HRMS** (ESI-TOF) calculated for $C_{19}H_{15}O^+$ $[M-F]^+$ 259.1123, found 259.1125; **SFC** (chiral column) The sample was analyzed on a Waters UPC² SFC with a Daicel IA column (3 μ m, 4.6×250 mm) under isocratic conditions (4 mL/min, 25% MeOH / CO₂, 1600 psi backpressure) at 30 °C. The enantiomers were detected by UV light (245 nm).



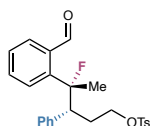
(*R*)-2-(2-Fluoro-1-phenylpropan-2-yl)benzaldehyde (**3k**). This compound was prepared according to General Procedure (using **TDG-A**) as a yellow oil (8.0 mg, 33% yield, 93% *ee*). **¹H NMR** (600 MHz, CDCl₃) δ 10.26 (dd, *J* = 3.0, 0.7 Hz, 1H), 7.86 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.51 (tt, *J* = 7.7, 1.5 Hz, 1H), 7.43–7.39 (m, 1H), 7.30 (dt, *J* = 7.9, 1.4 Hz, 1H), 7.22–7.18 (m, 3H), 7.03–6.98 (m, 2H), 3.39–3.32 (m, 2H), 1.82 (d, *J* = 23.6 Hz, 3H). **¹³C NMR** (150 MHz, CDCl₃) δ 193.29 (d, *J* = 15.4 Hz), 144.92 (d, *J* = 22.5 Hz), 135.31 (d, *J* = 2.2 Hz), 134.75, 132.83 (d, *J* = 1.9 Hz), 130.58, 130.24, 128.05, 127.99, 126.96, 126.01 (d, *J* = 11.6 Hz), 99.50 (d, *J* = 175.2 Hz), 48.92 (d, *J* = 23.2 Hz), 27.17 (d, *J* = 25.4 Hz). **¹⁹F NMR** (376 MHz, CDCl₃) δ -135.49 (h, *J* = 23.3 Hz, 1F). **HRMS** (ESI-TOF) calculated for $C_{16}H_{15}O^+$ $[M-F]^+$ 223.1123, found 223.1124; **SFC** (chiral column) The enantiomeric excess was determined by heart-cutting 2D LC-SFC (77). The LC dimension consisted of a Waters I-Class LC with a Waters BEH C18 column (1.7 μ m, 2.1×100 mm) using a 0.1% aqueous formic acid:acetonitrile gradient (0.6 mL/min, 15–99% acetonitrile over 2.1 minutes) at 55 °C. The heart cut was performed at 1.33 minutes using a 6-port 2-position valve equipped with a 10 μ L transfer loop. The SFC dimension consisted of a Waters UPC² SFC with a Daicel IG column (3 μ m, 4.6×250 mm) using isocratic conditions (4 mL/min, 20% MeOH / CO₂, 1600 psi backpressure) at 30 °C. The enantiomers were detected by UV light (245 nm).



2-((2*R*,3*R*)-4-Cyclohexyl-2-fluoro-3-phenylbutan-2-yl)benzaldehyde (**3l**). This compound was prepared according to General Procedure (using **TDG-A**) as a yellow oil (25.4 mg, 75% yield, *d.r.* >20:1, 95% *ee*). **¹H NMR** (600 MHz, CDCl₃) δ 10.32 (d, *J* = 2.0 Hz, 1H), 7.76 (d, *J* = 7.7 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 7.16–7.11 (m, 3H), 7.01–6.96 (m, 2H), 3.36 (ddd, *J* = 24.1, 12.0, 3.2 Hz, 1H), 1.94–1.80 (m, 4H), 1.71–1.47 (m, 6H), 1.13–1.01 (m, 2H), 1.00–0.86 (m, 3H), 0.72 (dq, *J* = 19.7, 9.3, 6.4 Hz, 1H). **¹³C NMR** (150 MHz, CDCl₃) δ 193.61 (d, *J* = 16.1 Hz), 145.59 (d, *J* = 22.6 Hz), 139.21, 134.52, 132.34 (d, *J* = 2.0 Hz), 129.85, 129.72, 127.76, 127.56, 126.75, 126.69 (d, *J* = 11.7 Hz), 102.06 (d, *J* = 179.0 Hz), 53.11 (d, *J* = 21.5 Hz), 36.52 (d, *J* = 3.9 Hz), 34.59 (d, *J* = 33.5 Hz), 31.63, 26.48, 26.13, 25.81, 25.56, 25.39. **¹⁹F NMR** (376 MHz, CDCl₃) δ -143.99 (s, 1F). **HRMS** (ESI-TOF) calculated for C₂₃H₂₇O⁺ [M-F]⁺ 319.2062, found 319.2063; **SFC** (chiral column) The sample was analyzed on a Waters UPC² SFC with a Daicel IC column (3 μm, 4.6×250 mm) under isocratic conditions (4 mL/min, 7% MeOH / CO₂, 1600 psi backpressure) at 30 °C. The enantiomers were detected by UV light (220 nm).

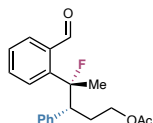


2-((2*R*,3*R*)-2-Fluoro-3,5-diphenylpentan-2-yl)benzaldehyde (**3m**). This compound was prepared according to General Procedure (using **TDG-A**) as a yellow oil (19.1 mg, 55% yield, *d.r.* >20:1, 93% *ee*). **¹H NMR** (600 MHz, CDCl₃) δ 10.24 (d, *J* = 2.2 Hz, 1H), 7.73 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.41 (tt, *J* = 7.6, 1.5 Hz, 1H), 7.32–7.28 (m, 1H), 7.26–7.22 (m, 2H), 7.21–7.13 (m, 5H), 7.03–7.00 (m, 4H), 3.24 (ddd, *J* = 23.9, 10.0, 4.6 Hz, 1H), 2.52–2.45 (m, 1H), 2.31–2.19 (m, 3H), 1.84 (d, *J* = 24.0 Hz, 3H). **¹³C NMR** (150 MHz, CDCl₃) δ 193.40 (d, *J* = 16.0 Hz), 145.26 (d, *J* = 22.6 Hz), 141.63, 138.64, 134.46, 132.37 (d, *J* = 2.0 Hz), 129.91, 129.80, 128.35, 128.29, 127.99, 127.61, 127.03, 126.63 (d, *J* = 11.9 Hz), 125.92, 101.74 (d, *J* = 179.1 Hz), 55.35 (d, *J* = 21.7 Hz), 33.58, 30.66 (d, *J* = 4.4 Hz), 25.61 (d, *J* = 25.7 Hz). **¹⁹F NMR** (376 MHz, CDCl₃) δ -143.87 (s, 1F). **HRMS** (ESI-TOF) calculated for C₂₄H₂₃O⁺ [M-F]⁺ 327.1749, found 327.1752; **SFC** (chiral column) The sample was analyzed on a Waters UPC² SFC with a Daicel IG column (3 μm, 4.6×250 mm) under isocratic conditions (4 mL/min, 15% MeOH / CO₂, 1600 psi backpressure) at 30 °C. The enantiomers were detected by UV light (212 nm).

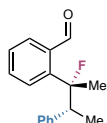


(3*R*,4*R*)-4-Fluoro-4-(2-formylphenyl)-3-phenylpentyl 4-methylbenzenesulfonate (**3n**). This compound was prepared according to General Procedure (using **TDG-A**) as a yellow oil (26.4 mg, 60% yield, *d.r.* >20:1, 96% *ee*). **¹H NMR** (600 MHz, CDCl₃) δ 10.11 (d, *J* = 2.4 Hz, 1H), 7.67–7.64 (m, 3H), 7.40 (tt, *J* = 7.6, 1.4 Hz, 1H), 7.29–7.25 (m, 3H), 7.17 (dt, *J* = 8.0, 1.2 Hz, 1H), 7.07–7.03 (m, 1H), 7.02–6.99 (m, 2H), 6.80–6.77 (m, 2H), 4.02 (ddd, *J* = 10.0, 6.4, 3.7 Hz, 1H), 3.64

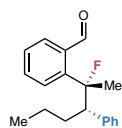
(td, $J = 9.9, 5.2$ Hz, 1H), 3.39 (ddd, $J = 27.9, 12.1, 3.3$ Hz, 1H), 2.49–2.43 (m, 1H), 2.43 (s, 3H), 2.20 (m, 1H), 1.87 (d, $J = 23.9$ Hz, 3H). **^{13}C NMR** (150 MHz, CDCl_3) δ 193.31 (d, $J = 15.9$ Hz), 144.67, 144.64 (d, $J = 22.0$ Hz), 137.26, 134.17, 132.79, 132.53, 130.41, 129.77, 129.30, 101.66 (d, $J = 180.4$ Hz), 68.50, 51.33 (d, $J = 21.8$ Hz), 28.71 (d, $J = 5.0$ Hz), 26.17 (d, $J = 26.0$ Hz), 21.59. **^{19}F NMR** (376 MHz, CDCl_3) δ -148.42 (q, $J = 25.4, 24.8$ Hz, 1F). **HRMS** (ESI-TOF) calculated for $\text{C}_{25}\text{H}_{25}\text{O}_4\text{S}^+ [\text{M-F}]^+$ 421.1474, found 421.1474; **SFC** (chiral column) The sample was analyzed on a Waters UPC² SFC with a Daicel IG column (3 μm , 4.6 $\times$ 250 mm) under isocratic conditions (4 mL/min, 35% MeOH / CO_2 , 1600 psi backpressure) at 30 $^\circ\text{C}$. The enantiomers were detected by UV light (225 nm).



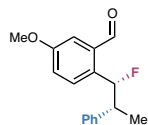
(3*R*,4*R*)-4-Fluoro-4-(2-formylphenyl)-3-phenylpentyl acetate (**3o**). This compound was prepared according to General Procedure (using **TDG-A**) as a yellow oil (21.7 mg, 66% yield, *d.r.* >20:1, 95% *ee*). **^1H NMR** (600 MHz, CDCl_3) δ 10.25 (d, $J = 2.0$ Hz, 1H), 7.73 (dd, $J = 7.8, 1.5$ Hz, 1H), 7.44–7.39 (m, 1H), 7.34–7.29 (m, 1H), 7.21 (dt, $J = 8.0, 1.2$ Hz, 1H), 7.15–7.07 (m, 3H), 6.97 (ddd, $J = 6.7, 3.1, 1.4$ Hz, 2H), 3.98 (ddd, $J = 11.0, 7.3, 4.6$ Hz, 1H), 3.75 (ddd, $J = 11.0, 8.4, 6.6$ Hz, 1H), 3.44 (ddd, $J = 26.0, 11.9, 3.4$ Hz, 1H), 2.32 (m, 1H), 2.22 (m, 1H), 1.98 (s, 3H), 1.90 (d, $J = 24.0$ Hz, 3H). **^{13}C NMR** (150 MHz, CDCl_3) δ 193.43 (d, $J = 14.6$ Hz), 170.88, 144.82 (d, $J = 22.3$ Hz), 138.01, 134.24, 132.56 (d, $J = 2.3$ Hz), 130.71, 129.44, 128.05, 127.68, 127.18, 126.56 (d, $J = 13.3$ Hz), 101.55 (d, $J = 180.0$ Hz), 62.66, 52.18 (d, $J = 22.0$ Hz), 28.23 (d, $J = 4.9$ Hz), 25.72 (d, $J = 25.8$ Hz), 20.83. **^{19}F NMR** (376 MHz, CDCl_3) δ -146.22 (s, 1F). **HRMS** (ESI-TOF) calculated for $\text{C}_{20}\text{H}_{21}\text{O}_3^+ [\text{M-F}]^+$ 309.1491, found 309.1490; **SFC** (chiral column) The sample was analyzed on a Waters UPC² SFC with a Daicel IG column (3 μm , 4.6 $\times$ 250 mm) under isocratic conditions (4 mL/min, 10% MeOH / CO_2 , 1600 psi backpressure) at 30 $^\circ\text{C}$. The enantiomers were detected by UV light (220 nm).



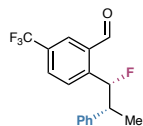
2-((2*R*,3*R*)-2-Fluoro-3-phenylbutan-2-yl)benzaldehyde (**3p**). This compound was prepared according to General Procedure (using **TDG-A**) as a yellow oil (13.6 mg, 53% yield, *d.r.* >20:1, 93% *ee*). **^1H NMR** (600 MHz, CDCl_3) δ 10.25 (d, $J = 2.6$ Hz, 1H), 7.76 (dd, $J = 7.7, 1.5$ Hz, 1H), 7.44 (tt, $J = 7.7, 1.5$ Hz, 1H), 7.33 (t, $J = 7.5$ Hz, 1H), 7.19 (dd, $J = 7.9, 1.6$ Hz, 1H), 7.14 (dd, $J = 5.1, 1.9$ Hz, 3H), 7.00 (dd, $J = 5.9, 2.6$ Hz, 2H), 3.43 (dq, $J = 24.0, 7.2$ Hz, 1H), 1.84 (d, $J = 24.0$ Hz, 3H), 1.44 (d, $J = 7.2$ Hz, 3H). **^{13}C NMR** (150 MHz, CDCl_3) δ 193.60 (d, $J = 17.0$ Hz), 145.18 (d, $J = 22.6$ Hz), 141.09, 134.80, 132.35 (d, $J = 2.0$ Hz), 129.69, 129.05, 127.79, 127.68, 126.86, 126.57 (d, $J = 11.4$ Hz), 101.87 (d, $J = 179.2$ Hz), 49.83 (d, $J = 22.1$ Hz), 25.24 (d, $J = 25.8$ Hz), 15.48 (d, $J = 5.2$ Hz). **^{19}F NMR** (376 MHz, CDCl_3) δ -143.34 (d, $J = 26.9$ Hz, 1F). **HRMS** (ESI-TOF) calculated for $\text{C}_{17}\text{H}_{17}\text{O}^+ [\text{M-F}]^+$ 237.1279, found 237.1282; **SFC** (chiral column) The sample was analyzed on a Waters UPC² SFC with a Daicel IG column (3 μm , 4.6 $\times$ 250 mm) under isocratic conditions (4 mL/min, 5% MeOH / CO_2 , 1600 psi backpressure) at 30 $^\circ\text{C}$. The enantiomers were detected by UV light (213 nm).



2-((2*R*,3*S*)-2-Fluoro-3-phenylhexan-2-yl)benzaldehyde (**3q**). This compound was prepared according to General Procedure (using **TDG-A**) as a yellow oil (11.9 mg, 42% yield, *d.r.* >20:1, 90% *ee*). ¹H NMR (600 MHz, CDCl₃) δ 10.38 (d, *J* = 3.3 Hz, 1H), 7.90 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.54–7.49 (m, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.31–7.23 (m, 4H), 7.18 (d, *J* = 7.3 Hz, 2H), 3.22 (ddd, *J* = 26.2, 12.0, 3.1 Hz, 1H), 1.85 (m, 1H), 1.59 (d, *J* = 24.2 Hz, 3H), 1.55–1.46 (m, 1H), 1.06 (m, 1H), 0.95 (m, 1H), 0.72 (t, *J* = 7.3 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) δ 193.68 (d, *J* = 16.2 Hz), 145.47 (d, *J* = 22.4 Hz), 139.35, 134.85, 132.63, 130.38, 129.78, 128.13, 127.72, 127.01, 126.27 (d, *J* = 12.7 Hz), 102.04 (d, *J* = 179.3 Hz), 55.77 (d, *J* = 21.3 Hz), 31.60 (d, *J* = 4.6 Hz), 26.71 (d, *J* = 25.8 Hz), 20.71, 13.79. ¹⁹F NMR (376 MHz, CDCl₃) δ -144.31 (br, 1F). HRMS (ESI-TOF) calculated for C₁₇H₁₇O⁺ [M-F]⁺ 237.1279, found 237.1282; SFC (chiral column) The sample was analyzed on a Waters UPC² SFC with a Daicel IG column (3 μm, 4.6×250 mm) under isocratic conditions (4 mL/min, 10% MeOH / CO₂, 1600 psi backpressure) at 30 °C. The enantiomers were detected by UV light (220 nm).

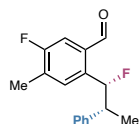


2-((1*R*,2*R*)-1-Fluoro-2-phenylpropyl)-5-methoxybenzaldehyde (**3r**). This compound was prepared according to General Procedure (using **TDG-A**) as a yellow oil (22.6 mg, 83% yield, *d.r.* >20:1, 98% *ee*). ¹H NMR (600 MHz, CDCl₃) δ 10.04 (s, 1H), 7.32 (dd, *J* = 2.8, 1.0 Hz, 1H), 7.25–7.18 (m, 3H), 7.13 (d, *J* = 8.6 Hz, 1H), 7.10–7.07 (m, 2H), 6.99 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.40 (dd, *J* = 46.9, 5.2 Hz, 1H), 3.85 (s, 3H), 3.20 (dq, *J* = 24.4, 7.2, 5.0 Hz, 1H), 1.38 (d, *J* = 7.3 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) δ 192.20, 159.33, 141.02, 133.79 (d, *J* = 3.4 Hz), 133.34 (d, *J* = 21.1 Hz), 128.76 (d, *J* = 11.1 Hz), 128.02, 126.75, 119.41, 117.26, 93.86 (d, *J* = 175.0 Hz), 55.50, 46.39 (d, *J* = 22.8 Hz), 17.51 (d, *J* = 4.8 Hz). ¹⁹F NMR (376 MHz, CDCl₃) δ -182.78 (dd, *J* = 47.0, 24.4 Hz, 1F). HRMS (ESI-TOF) calculated for C₁₇H₁₇O₂⁺ [M-F]⁺ 253.1229, found 253.1232; SFC (chiral column) The sample was analyzed on a Waters UPC² SFC with a Daicel IC column (3 μm, 4.6×250 mm) under isocratic conditions (4 mL/min, 7% MeOH / CO₂, 1600 psi backpressure) at 30 °C. The enantiomers were detected by UV light (220 nm).

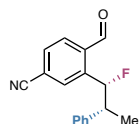


2-((1*R*,2*R*)-1-Fluoro-2-phenylpropyl)-5-(trifluoromethyl)benzaldehyde (**3s**). This compound was prepared according to General Procedure (using **TDG-A**) as a yellow oil (20.5 mg, 66% yield, *d.r.* >20:1, >99% *ee*). ¹H NMR (600 MHz, CDCl₃) δ 10.09 (s, 1H), 8.07 (s, 1H), 7.64 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.24 (d, *J* = 8.2 Hz, 1H), 7.21–7.18 (m, 3H), 7.01–6.97 (m, 2H), 6.52 (dd, *J* = 47.9, 3.9 Hz, 1H), 3.22 (dq, *J* = 28.5, 7.2, 3.9 Hz, 1H), 1.52 (d, *J* = 7.2 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) δ 191.43 (d, *J* = 7.0 Hz), 145.06 (d, *J* = 20.6 Hz), 139.83, 132.46 (d, *J* = 3.8 Hz), 130.63 (q, *J* = 33.4 Hz), 130.38 (d, *J* = 4.1 Hz), 129.84–129.53 (m), 128.76 (d, *J* = 6.7 Hz), 128.22–127.80

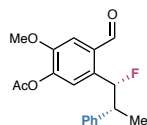
(m), 127.18–126.79 (m), 123.32 (q, $J = 272.3$ Hz), 95.20–91.11 (m), 45.76 (d, $J = 21.5$ Hz), 20.45–16.36 (m). **^{19}F NMR** (376 MHz, CDCl_3) δ -65.53 (s, 3F), -192.32 (dd, $J = 48.1, 28.8$ Hz, 1F). **HRMS** (ESI-TOF) calculated for $\text{C}_{17}\text{H}_{14}\text{F}_3\text{O}^+$ $[\text{M}-\text{F}]^+$ 291.0997, found 291.0999; **SFC** (chiral column) The sample was analyzed on a Waters UPC² SFC with a Daicel IG column (3 μm , 4.6 $\times$ 250 mm) under isocratic conditions (4 mL/min, 2% MeOH / CO_2 , 1600 psi backpressure) at 30 $^\circ\text{C}$. The enantiomers were detected by UV light (212 nm).



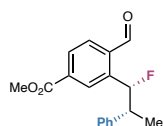
5-Fluoro-2-((1*R*,2*R*)-1-fluoro-2-phenylpropyl)-4-methylbenzaldehyde (**3t**). This compound was prepared according to General Procedure (using **TDG-A**) as a yellow oil (14.3 mg, 52% yield, *d.r.* >20:1, >99% *ee*). **^1H NMR** (600 MHz, CDCl_3) δ 9.96 (s, 1H), 7.43 (dd, $J = 9.4, 1.1$ Hz, 1H), 7.25–7.17 (m, 3H), 7.07–7.03 (m, 2H), 6.98 (d, $J = 7.1$ Hz, 1H), 6.43 (dd, $J = 47.3, 4.8$ Hz, 1H), 3.16 (dq, $J = 26.1, 7.2, 4.8$ Hz, 1H), 2.22–2.19 (m, 3H), 1.41 (d, $J = 7.3$ Hz, 3H). **^{13}C NMR** (150 MHz, CDCl_3) δ 190.96 (d, $J = 1.9$ Hz), 160.57 (d, $J = 247.5$ Hz), 140.65, 136.81 (dd, $J = 20.5, 3.8$ Hz), 132.06 (dd, $J = 5.8, 3.5$ Hz), 131.59 (d, $J = 17.2$ Hz), 130.77 (dd, $J = 11.5, 4.7$ Hz), 128.65, 127.97, 126.85, 119.10 (d, $J = 23.1$ Hz), 93.46 (d, $J = 176.2$ Hz), 46.23 (d, $J = 22.2$ Hz), 17.43 (d, $J = 4.6$ Hz), 14.78 (d, $J = 2.9$ Hz). **^{19}F NMR** (376 MHz, CDCl_3) δ -120.33 (t, $J = 8.6$ Hz, 1F), -187.75 (dd, $J = 47.2, 25.7$ Hz, 1F). **HRMS** (ESI-TOF) calculated for $\text{C}_{17}\text{H}_{16}\text{FO}^+$ $[\text{M}-\text{F}]^+$ 255.1185, found 255.1186; **SFC** (chiral column) The sample was analyzed on a Waters UPC² SFC with a Daicel IG column (3 μm , 4.6 $\times$ 250 mm) under isocratic conditions (4 mL/min, 5% MeOH / CO_2 , 1600 psi backpressure) at 30 $^\circ\text{C}$. The enantiomers were detected by UV light (250 nm).



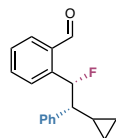
3-((1*R*,2*R*)-1-fluoro-2-phenylpropyl)-4-formylbenzonitrile (**3u**). This compound was prepared according to General Procedure (using **TDG-A**) as a yellow oil (11.0 mg, 41% yield, *d.r.* >20:1, >99% *ee*). **^1H NMR** (600 MHz, CDCl_3) δ 10.09 (s, 1H), 7.91 (dd, $J = 7.9, 1.1$ Hz, 1H), 7.73 (dd, $J = 7.9, 1.6$ Hz, 1H), 7.37–7.34 (m, 1H), 7.23–7.18 (m, 3H), 6.97–6.93 (m, 2H), 6.47 (dd, $J = 47.7, 3.8$ Hz, 1H), 3.20 (dq, $J = 28.7, 7.2, 3.8$ Hz, 1H), 1.52 (d, $J = 7.2$ Hz, 3H). **^{13}C NMR** (150 MHz, CDCl_3) δ 191.33, 142.45 (d, $J = 21.0$ Hz), 139.36, 134.55 (d, $J = 4.7$ Hz), 133.58, 131.46, 130.94 (d, $J = 13.6$ Hz), 128.65, 128.16 (d, $J = 3.1$ Hz), 127.33, 117.35, 116.64, 93.04 (d, $J = 179.3$ Hz), 45.69 (d, $J = 21.6$ Hz), 17.38 (d, $J = 4.3$ Hz). **^{19}F NMR** (376 MHz, CDCl_3) δ -192.52 (dd, $J = 47.7, 28.7$ Hz, 1F). **HRMS** (ESI-TOF) calculated for $\text{C}_{17}\text{H}_{14}\text{NO}^+$ $[\text{M}-\text{F}]^+$ 248.1075, found 248.1081; **SFC** (chiral column) The sample was analyzed on a Waters UPC² SFC with a Daicel IA column (3 μm , 4.6 $\times$ 250 mm) under isocratic conditions (4 mL/min, 10% MeOH / CO_2 , 1600 psi backpressure) at 30 $^\circ\text{C}$. The enantiomers were detected by UV light (250 nm).



5-((1*R*,2*R*)-1-fluoro-2-phenylpropyl)-4-formyl-2-methoxyphenyl acetate (**3v**). This compound was prepared according to General Procedure (using **TDG-A**) as a yellow oil (28.1 mg, 85% yield, *d.r.* >20:1, 96% *ee*). **¹H NMR** (600 MHz, CDCl₃) δ 9.99 (s, 1H), 7.40 (d, *J* = 1.0 Hz, 1H), 7.27–7.19 (m, 4H), 7.07 (dd, *J* = 7.1, 1.9 Hz, 2H), 6.91 (s, 1H), 6.36 (dd, *J* = 46.8, 5.2 Hz, 1H), 3.90 (s, 3H), 3.21 (dq, *J* = 23.3, 7.2, 5.1 Hz, 1H), 2.28 (s, 3H), 1.38 (d, *J* = 7.3 Hz, 3H). **¹³C NMR** (150 MHz, CDCl₃) δ 190.53, 167.91, 151.01, 143.86, 140.50 (d, *J* = 2.4 Hz), 134.68 (d, *J* = 21.2 Hz), 131.26 (d, *J* = 3.3 Hz), 128.53, 128.17, 126.94, 122.33 (d, *J* = 11.5 Hz), 115.08, 93.29 (d, *J* = 177.0 Hz), 56.11, 46.32 (d, *J* = 22.5 Hz), 20.52, 17.17 (d, *J* = 4.5 Hz). **¹⁹F NMR** (376 MHz, CDCl₃) δ -181.76 (dd, *J* = 46.9, 23.2 Hz, 1F). **HRMS** (ESI-TOF) calculated for C₁₉H₁₉O₄⁺ [M-F]⁺ 311.1283, found 311.1286; **SFC** (chiral column) The sample was analyzed on a Waters UPC² SFC with a Daicel IC column (3 μm, 4.6×250 mm) under isocratic conditions (4 mL/min, 7% MeOH / CO₂, 1600 psi backpressure) at 30 °C. The enantiomers were detected by UV light (224 nm).

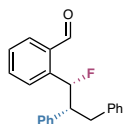


Methyl 3-((1*R*,2*R*)-1-fluoro-2-phenylpropyl)-4-formylbenzoate (**3w**). This compound was prepared according to General Procedure (using **TDG-A**) as a yellow oil (24.0 mg, 80% yield, *d.r.* >20:1, 99% *ee*). **¹H NMR** (600 MHz, CDCl₃) δ 10.11 (s, 1H), 8.11 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.92–7.85 (m, 2H), 7.25–7.17 (m, 3H), 7.09–7.05 (m, 2H), 6.49 (dd, *J* = 47.5, 5.1 Hz, 1H), 3.90 (s, 3H), 3.23 (dq, *J* = 25.1, 7.3, 5.0 Hz, 1H), 1.41 (d, *J* = 7.2 Hz, 3H). **¹³C NMR** (150 MHz, CDCl₃) δ 192.11, 165.69, 141.43 (d, *J* = 20.5 Hz), 140.46, 135.37 (d, *J* = 3.5 Hz), 134.11, 133.20, 129.09, 128.53, 128.45 (d, *J* = 12.0 Hz), 128.13, 126.96, 93.63 (d, *J* = 177.3 Hz), 52.53, 46.21 (d, *J* = 21.9 Hz), 17.40 (d, *J* = 5.0 Hz). **¹⁹F NMR** (376 MHz, CDCl₃) δ -184.41 (dd, *J* = 47.7, 25.0 Hz, 1F). **HRMS** (ESI-TOF) calculated for C₁₈H₁₇O₃⁺ [M-F]⁺ 281.1178, found 281.1182; **SFC** (chiral column) The sample was analyzed on a Waters UPC² SFC with a Daicel IA column (3 μm, 4.6×250 mm) under isocratic conditions (4 mL/min, 7% MeOH / CO₂, 1600 psi backpressure) at 30 °C. The enantiomers were detected by UV light (255 nm).

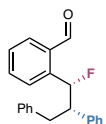


2-((1*R*,2*R*)-2-cyclopropyl-1-fluoro-2-phenylethyl)benzaldehyde (**3x**). This compound was prepared according to General Procedure (using **TDG-A**) as a yellow oil (19.1 mg, 71% yield, *d.r.* >20:1, 98% *ee*). **¹H NMR** (600 MHz, CDCl₃) δ 10.08 (s, 1H), 7.79 (dt, *J* = 7.6, 1.4 Hz, 1H), 7.44 (td, *J* = 7.5, 1.3 Hz, 1H), 7.39 (td, *J* = 7.6, 1.5 Hz, 1H), 7.19 (tdd, *J* = 4.7, 3.4, 1.5 Hz, 3H), 7.12 (d, *J* = 7.7 Hz, 1H), 7.05–7.00 (m, 2H), 6.75 (dd, *J* = 47.7, 4.0 Hz, 1H), 2.19–2.09 (m, 1H), 1.49 (dtt, *J* = 10.2, 7.7, 5.3 Hz, 1H), 0.62–0.55 (m, 1H), 0.52–0.45 (m, 2H), 0.08 (dddd, *J* = 8.7, 6.8, 5.6, 3.5 Hz, 1H). **¹³C NMR** (150 MHz, CDCl₃) δ 193.24, 141.56 (d, *J* = 20.4 Hz), 139.89, 134.34, 133.33, 132.12 (d, *J* = 4.3 Hz), 129.15, 127.88, 127.78, 127.10 (d, *J* = 12.7 Hz), 126.63, 93.30 (d,

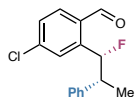
$J = 175.8$ Hz), 56.97 (d, $J = 21.1$ Hz), 13.56 (d, $J = 5.3$ Hz), 5.43, 4.65. **^{19}F NMR** (376 MHz, CDCl_3) δ -187.59 (dd, $J = 47.8, 29.2$ Hz, 1F). **HRMS** (ESI-TOF) calculated for $\text{C}_{18}\text{H}_{17}\text{O}^+$ $[\text{M}-\text{F}]^+$ 249.1279, found 249.1282; **SFC** (chiral column) The sample was analyzed on a Waters UPC² SFC with a Daicel IC column (3 μm , 4.6 $\times$ 250 mm) under isocratic conditions (4 mL/min, 5% MeOH / CO_2 , 1600 psi backpressure) at 30 $^\circ\text{C}$. The enantiomers were detected by UV light (213 nm).



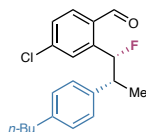
2-((1*R*,2*R*)-1-Fluoro-2,3-diphenylpropyl)benzaldehyde (**3y**). This compound was prepared according to General Procedure (using **TDG-A**) as a yellow oil (20.4 mg, 64% yield, *d.r.* >20:1, 99% *ee*). **^1H NMR** (600 MHz, CDCl_3) δ 9.97 (s, 1H), 7.75 (dt, $J = 7.6, 1.4$ Hz, 1H), 7.38 (td, $J = 7.5, 1.2$ Hz, 1H), 7.31 (td, $J = 7.6, 1.5$ Hz, 1H), 7.26–7.22 (m, 2H), 7.21–7.15 (m, 3H), 7.13–7.09 (m, 3H), 7.02 (d, $J = 7.8$ Hz, 1H), 6.95 (ddd, $J = 7.3, 3.1, 1.2$ Hz, 2H), 6.57 (dd, $J = 47.8, 2.8$ Hz, 1H), 3.38–3.33 (m, 1.5 H), 3.32–3.28 (m, 0.5 H), 3.25 (dt, $J = 13.1, 6.1$ Hz, 1H). **^{13}C NMR** (150 MHz, CDCl_3) δ 193.00, 141.29 (d, $J = 20.4$ Hz), 139.65, 138.43, 134.15, 133.29, 131.81 (d, $J = 4.2$ Hz), 129.50, 129.29, 128.16, 127.81, 127.72, 126.95 (d, $J = 13.1$ Hz), 126.72, 126.10, 92.20 (d, $J = 177.3$ Hz), 53.14 (d, $J = 20.9$ Hz), 38.64 (d, $J = 3.7$ Hz). **^{19}F NMR** (376 MHz, CDCl_3) δ -195.46 (dd, $J = 48.1, 32.6$ Hz, 1F). **HRMS** (ESI-TOF) calculated for $\text{C}_{22}\text{H}_{19}\text{O}^+$ $[\text{M}-\text{F}]^+$ 299.1436, found 299.1441; **SFC** (chiral column) The sample was analyzed on a Waters UPC² SFC with a Daicel IG column (3 μm , 4.6 $\times$ 250 mm) under isocratic conditions (4 mL/min, 20% MeOH / CO_2 , 1600 psi backpressure) at 30 $^\circ\text{C}$. The enantiomers were detected by UV light (212 nm).



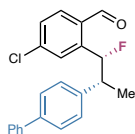
2-((1*R*,2*S*)-1-Fluoro-2,3-diphenylpropyl)benzaldehyde (**3z**). This compound was prepared according to General Procedure (using **TDG-A**) as a yellow oil (19.1 mg, 60% yield, *d.r.* >20:1, 98% *ee*). **^1H NMR** (600 MHz, CDCl_3) δ 10.01 (s, 1H), 7.78 (dt, $J = 7.6, 1.3$ Hz, 1H), 7.73 (d, $J = 7.7$ Hz, 1H), 7.63 (td, $J = 7.6, 1.4$ Hz, 1H), 7.50 (td, $J = 7.5, 1.2$ Hz, 1H), 7.22–7.16 (m, 4H), 7.16–7.12 (m, 1H), 7.08–7.04 (m, 2H), 7.04–7.00 (m, 1H), 6.85–6.82 (m, 2H), 6.56 (dd, $J = 47.7, 4.6$ Hz, 1H), 3.38 (ddt, $J = 25.1, 10.7, 4.5$ Hz, 1H), 3.21–3.11 (m, 2H). **^{13}C NMR** (150 MHz, CDCl_3) δ 192.43, 141.10 (d, $J = 20.1$ Hz), 140.01 (d, $J = 2.7$ Hz), 139.67, 134.05, 133.68, 132.43 (d, $J = 3.8$ Hz), 128.97, 128.90, 128.38, 128.18, 128.01, 127.21 (d, $J = 13.1$ Hz), 126.85, 125.76, 93.85 (d, $J = 178.2$ Hz), 53.27 (d, $J = 21.5$ Hz), 34.96 (d, $J = 5.6$ Hz). **^{19}F NMR** (376 MHz, CDCl_3) δ -190.09 (dd, $J = 47.8, 25.0$ Hz, 1F). **HRMS** (ESI-TOF) calculated for $\text{C}_{22}\text{H}_{19}\text{O}^+$ $[\text{M}-\text{F}]^+$ 299.1436, found 299.1439; **SFC** (chiral column) The sample was analyzed on a Waters UPC² SFC with a Daicel IG column (3 μm , 4.6 $\times$ 250 mm) under isocratic conditions (4 mL/min, 20% MeOH / CO_2 , 1600 psi backpressure) at 30 $^\circ\text{C}$. The enantiomers were detected by UV light (212 nm).



4-Chloro-2-((1*R*,2*R*)-1-fluoro-2-phenylpropyl)benzaldehyde (**4a**). This compound was prepared according to General Procedure (using **TDG-A**) as a yellow oil (90% yield, *d.r.* >20:1, >99% *ee*). **¹H NMR** (600 MHz, CDCl₃) δ 10.02 (s, 1H), 7.74 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.42 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.24–7.18 (m, 3H), 7.11 (d, *J* = 2.1 Hz, 1H), 7.02 (dd, *J* = 6.7, 1.6 Hz, 2H), 6.50 (dd, *J* = 47.8, 4.4 Hz, 1H), 3.18 (dq, *J* = 27.4, 7.3, 4.3 Hz, 1H), 1.47 (d, *J* = 7.2 Hz, 3H). **¹³C NMR** (150 MHz, CDCl₃) δ 191.78, 143.36 (d, *J* = 20.6 Hz), 140.53, 140.33 (d, *J* = 1.4 Hz), 135.39, 130.77 (d, *J* = 3.8 Hz), 128.80, 128.45, 128.18, 127.74 (d, *J* = 12.8 Hz), 127.16, 93.27 (d, *J* = 177.5 Hz), 45.98, 17.66 (d, *J* = 4.8 Hz). **¹⁹F NMR** (376 MHz, CDCl₃) δ -190.77 (dd, *J* = 47.7, 27.2 Hz). **HRMS** (ESI-TOF) calculated for C₁₆H₁₄ClO⁺ [M-F]⁺ 299.1436, found 299.1439; **SFC** (chiral column) The enantiomeric excess was determined by heart-cutting 2D LC-SFC (77). The LC dimension consisted of a Waters I-Class LC with a Waters BEH C18 column (1.7 μm, 2.1×100 mm) using a 0.1% aqueous formic acid:acetonitrile gradient (0.6 mL/min, 15–99% acetonitrile over 2.1 minutes) at 55 °C. The heart cut was performed at 2.18 minutes using a 6-port 2-position valve equipped with a 10 μL transfer loop. The SFC dimension consisted of a Waters UPC² SFC with a Daicel IA column (3 μm, 4.6×250 mm) using isocratic conditions (4 mL/min, 5% MeOH / CO₂, 1600 psi backpressure) at 30 °C. The enantiomers were detected by UV light (214 nm).

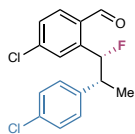


2-((1*R*,2*R*)-2-(4-Butylphenyl)-1-fluoropropyl)-4-chlorobenzaldehyde (**4b**). This compound was prepared according to General Procedure (using **TDG-A**) as a yellow oil (76% yield, *d.r.* >20:1, >99% *ee*). **¹H NMR** (600 MHz, CDCl₃) δ 10.01 (s, 1H), 7.73 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.41 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.08 (d, *J* = 2.0 Hz, 1H), 7.02 (d, *J* = 8.2 Hz, 2H), 6.90 (d, *J* = 7.7 Hz, 2H), 6.47 (dd, *J* = 47.9, 4.2 Hz, 1H), 3.15 (dq, *J* = 27.5, 7.2, 4.3 Hz, 1H), 2.58–2.52 (m, 2H), 1.58–1.54 (m, 2H), 1.45 (d, *J* = 7.2 Hz, 3H), 1.35–1.30 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H). **¹³C NMR** (150 MHz, CDCl₃) δ 191.71, 143.47 (d, *J* = 20.6 Hz), 141.77, 140.45, 137.33, 135.18, 130.76 (d, *J* = 3.8 Hz), 128.63, 128.36, 128.20, 127.82 (d, *J* = 13.1 Hz), 93.35 (d, *J* = 177.8 Hz), 45.65 (d, *J* = 21.7 Hz), 35.34, 33.73, 22.38, 17.60 (d, *J* = 4.7 Hz), 14.11. **¹⁹F NMR** (376 MHz, CDCl₃) δ -190.78 (dd, *J* = 47.7, 27.6 Hz). **HRMS** (ESI-TOF) calculated for C₂₀H₂₂ClO⁺ [M-F]⁺ 313.1354, found 313.1362; **SFC** (chiral column) The sample was analyzed on a Waters UPC² SFC with a Daicel IA column (3 μm, 4.6×250 mm) under isocratic conditions (4 mL/min, 10% MeOH / CO₂, 1600 psi backpressure) at 30 °C. The enantiomers were detected by UV light (212 nm).

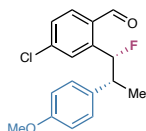


2-((1*R*,2*R*)-2-([1,1'-Biphenyl]-4-yl)-1-fluoropropyl)-4-chlorobenzaldehyde (**4c**). This compound was prepared according to General Procedure (using **TDG-A**) as a yellow oil (36% yield, *d.r.* >20:1, 98% *ee*). **¹H NMR** (600 MHz, CDCl₃) δ 10.05 (s, 1H), 7.75 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.56

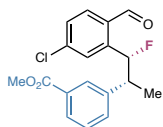
(dd, $J = 8.2, 1.2$ Hz, 2H), 7.46–7.40 (m, 5H), 7.34–7.31 (m, 1H), 7.16 (d, $J = 2.0$ Hz, 1H), 7.10 (d, $J = 8.0$ Hz, 2H), 6.54 (dd, $J = 47.9, 4.4$ Hz, 1H), 3.23 (dq, $J = 26.8, 7.3, 4.4$ Hz, 1H), 1.50 (d, $J = 7.3$ Hz, 3H). **^{13}C NMR** (150 MHz, CDCl_3) δ 191.90, 143.37 (d, $J = 20.4$ Hz), 141.10, 140.62, 140.09, 139.51, 135.55, 130.76 (d, $J = 3.7$ Hz), 129.18, 128.85, 128.49, 127.79 (d, $J = 12.9$ Hz), 127.29, 127.22, 126.92, 93.25 (d, $J = 177.5$ Hz), 45.81 (d, $J = 21.9$ Hz), 17.72 (d, $J = 4.6$ Hz). **^{19}F NMR** (376 MHz, CDCl_3) δ -190.49 (dd, $J = 47.8, 27.1$ Hz). **HRMS** (ESI-TOF) calculated for $\text{C}_{22}\text{H}_{18}\text{ClO}^+ [\text{M}-\text{F}]^+$ 333.1041, found 333.1047; **SFC** (chiral column) The sample was analyzed on a Waters UPC² SFC with a Daicel IC column (3 μm , 4.6 $\times$ 250 mm) under isocratic conditions (4 mL/min, 15% MeOH / CO_2 , 1600 psi backpressure) at 30 $^\circ\text{C}$. The enantiomers were detected by UV light (212 nm).



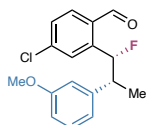
4-Chloro-2-((1*R*,2*R*)-2-(4-chlorophenyl)-1-fluoropropyl)benzaldehyde (**4d**). This compound was prepared according to General Procedure (using **TDG-A**) as a yellow oil (72% yield, *d.r.* >20:1, 97% *ee*). **^1H NMR** (600 MHz, CDCl_3) δ 10.04 (s, 1H), 7.75 (dd, $J = 8.1, 1.2$ Hz, 1H), 7.44 (dd, $J = 8.2, 2.1$ Hz, 1H), 7.19 (d, $J = 8.5$ Hz, 2H), 7.11 (d, $J = 2.0$ Hz, 1H), 6.98–6.93 (m, 2H), 6.49 (dd, $J = 47.9, 4.1$ Hz, 1H), 3.16 (dq, $J = 28.0, 7.3, 4.2$ Hz, 1H), 1.56 (s, 1H), 1.46 (d, $J = 7.2$ Hz, 3H). **^{13}C NMR** (150 MHz, CDCl_3) δ 192.05, 143.16 (d, $J = 20.4$ Hz), 140.74, 138.94, 135.99, 132.87, 130.60 (d, $J = 3.9$ Hz), 130.14, 128.58, 128.29, 127.58 (d, $J = 13.3$ Hz), 93.02 (d, $J = 177.9$ Hz), 45.43 (d, $J = 21.6$ Hz), 17.85 (d, $J = 4.7$ Hz). **^{19}F NMR** (376 MHz, CDCl_3) δ -192.03 (dd, $J = 48.0, 27.9$ Hz). **HRMS** (ESI-TOF) calculated for $\text{C}_{16}\text{H}_{13}\text{Cl}_2\text{O}^+ [\text{M}-\text{F}]^+$ 291.0338, found 291.0337; **SFC** (chiral column) The sample was analyzed on a Waters UPC² SFC with a Daicel IBN column (3 μm , 4.6 $\times$ 250 mm) under isocratic conditions (4 mL/min, 10% MeOH / CO_2 , 1600 psi backpressure) at 30 $^\circ\text{C}$. The enantiomers were detected by UV light (212 nm).



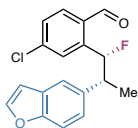
4-Chloro-2-((1*R*,2*R*)-1-fluoro-2-(4-methoxyphenyl)propyl)benzaldehyde (**4e**). This compound was prepared according to General Procedure (using **TDG-A**) as a yellow oil (70% yield, *d.r.* >20:1, 99% *ee*). **^1H NMR** (600 MHz, CDCl_3) δ 10.01 (s, 1H), 7.74 (dd, $J = 8.2, 1.1$ Hz, 1H), 7.42 (dd, $J = 8.2, 2.1$ Hz, 1H), 7.13 (d, $J = 2.1$ Hz, 1H), 6.94–6.91 (m, 2H), 6.78–6.75 (m, 2H), 6.45 (dd, $J = 48.0, 4.3$ Hz, 1H), 3.77 (s, 3H), 3.14 (dq, $J = 27.5, 7.3, 4.2$ Hz, 1H), 1.44 (d, $J = 7.3$ Hz, 3H). **^{13}C NMR** (150 MHz, CDCl_3) δ 191.72, 158.71, 143.49 (d, $J = 20.5$ Hz), 140.50, 135.29, 132.33, 130.76 (d, $J = 3.8$ Hz), 129.73, 128.40, 127.75 (d, $J = 13.2$ Hz), 113.60, 93.43 (d, $J = 177.4$ Hz), 55.40, 45.21 (d, $J = 22.0$ Hz), 17.85 (d, $J = 4.6$ Hz). **^{19}F NMR** (376 MHz, CDCl_3) δ -190.93 (dd, $J = 47.9, 27.3$ Hz). **HRMS** (ESI-TOF) calculated for $\text{C}_{17}\text{H}_{16}\text{ClO}_2^+ [\text{M}-\text{F}]^+$ 287.0833, found 287.0843; **SFC** (chiral column) The sample was analyzed on a Waters UPC² SFC with a Daicel IC column (3 μm , 4.6 $\times$ 250 mm) under isocratic conditions (4 mL/min, 7% MeOH / CO_2 , 1600 psi backpressure) at 30 $^\circ\text{C}$. The enantiomers were detected by UV light (212 nm).



Methyl 3-((1*R*,2*R*)-1-(5-chloro-2-formylphenyl)-1-fluoropropan-2-yl)benzoate (**4f**). This compound was prepared according to General Procedure (using **TDG-A**) as a yellow oil (34% yield, *d.r.* >20:1, 94% *ee*). **¹H NMR** (600 MHz, CDCl₃) δ 10.06 (s, 1H), 7.89 (ddd, *J* = 7.7, 1.7, 1.2 Hz, 1H), 7.76 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.68 (t, *J* = 1.9 Hz, 1H), 7.44 (dd, *J* = 8.1, 2.1 Hz, 1H), 7.30 (td, *J* = 7.7, 0.5 Hz, 1H), 7.24–7.21 (m, 1H), 7.07 (d, *J* = 2.1 Hz, 1H), 6.52 (dd, *J* = 47.9, 4.2 Hz, 1H), 3.89 (s, 3H), 3.25 (dq, *J* = 27.7, 7.2, 4.1 Hz, 1H), 1.51 (d, *J* = 7.3 Hz, 3H). **¹³C NMR** (150 MHz, CDCl₃) δ 192.02, 167.18, 143.11 (d, *J* = 20.4 Hz), 140.78, 140.68, 135.95, 133.41, 130.64 (d, *J* = 4.0 Hz), 130.01 (d, *J* = 2.4 Hz), 128.59, 128.42, 128.21, 127.62 (d, *J* = 13.6 Hz), 93.03 (d, *J* = 178.0 Hz), 52.23, 45.84 (d, *J* = 22.0 Hz), 17.77 (d, *J* = 4.4 Hz). **¹⁹F NMR** (376 MHz, CDCl₃) δ -191.90 (dd, *J* = 48.0, 27.6 Hz). **HRMS** (ESI-TOF) calculated for C₁₈H₁₆ClO₃⁺ [M-F]⁺ 315.0782, found 315.0795; **SFC** (chiral column) The sample was analyzed on a Waters UPC² SFC with a Daicel IG column (3 μm, 4.6×250 mm) under isocratic conditions (4 mL/min, 15% MeOH / CO₂, 1600 psi backpressure) at 30 °C. The enantiomers were detected by UV light (212 nm).

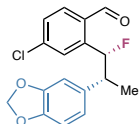


4-Chloro-2-((1*R*,2*R*)-1-fluoro-2-(3-methoxyphenyl)propyl)benzaldehyde (**4g**). This compound was prepared according to General Procedure (using **TDG-A**) as a yellow oil (63% yield, *d.r.* >20:1, 98% *ee*). **¹H NMR** (600 MHz, CDCl₃) δ 10.02 (s, 1H), 7.74 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.43 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.18 (d, *J* = 2.1 Hz, 1H), 7.14 (t, *J* = 7.9 Hz, 1H), 6.76 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1H), 6.62–6.59 (m, 2H), 6.49 (dd, *J* = 47.8, 4.5 Hz, 1H), 3.74 (s, 3H), 3.16 (dq, *J* = 26.6, 7.2, 4.5 Hz, 1H), 1.44 (d, *J* = 7.2 Hz, 3H). **¹³C NMR** (150 MHz, CDCl₃) δ 191.77 (d, *J* = 2.1 Hz), 159.50, 143.32 (d, *J* = 20.5 Hz), 142.04, 140.56, 135.35, 130.82 (d, *J* = 3.8 Hz), 129.12, 128.48, 127.75 (d, *J* = 13.1 Hz), 121.24, 114.73, 112.39, 93.19 (d, *J* = 177.9 Hz), 55.34, 46.10 (d, *J* = 22.0 Hz), 17.66 (d, *J* = 4.8 Hz). **¹⁹F NMR** (376 MHz, CDCl₃) δ -190.16 (dd, *J* = 47.8, 27.0 Hz). **HRMS** (ESI-TOF) calculated for C₁₇H₁₆ClO₂⁺ [M-F]⁺ 287.0833, found 287.0837; **SFC** (chiral column) The sample was analyzed on a Waters UPC² SFC with a Daicel IA column (3 μm, 4.6×250 mm) under isocratic conditions (4 mL/min, 10% MeOH / CO₂, 1600 psi backpressure) at 30 °C. The enantiomers were detected by UV light (212 nm).

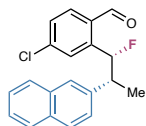


2-((1*R*,2*R*)-2-(Benzofuran-5-yl)-1-fluoropropyl)-4-chlorobenzaldehyde (**4h**). This compound was prepared according to General Procedure (using **TDG-A**) as a yellow oil (50% yield, *d.r.* >20:1, >99% *ee*). **¹H NMR** (600 MHz, CDCl₃) δ 10.04 (s, 1H), 7.74 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.59 (d, *J* = 2.2 Hz, 1H), 7.41 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.36–7.31 (m, 2H), 7.14 (d, *J* = 2.1 Hz, 1H), 6.94 (dd, *J* = 8.5, 1.8 Hz, 1H), 6.69 (dd, *J* = 2.2, 1.0 Hz, 1H), 6.53 (dd, *J* = 47.9, 4.6 Hz, 1H), 3.29 (dq,

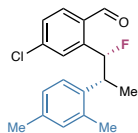
$J = 26.6, 7.3, 4.6$ Hz, 1H), 1.48 (d, $J = 7.3$ Hz, 3H). **^{13}C NMR** (150 MHz, CDCl_3) δ 191.84, 154.24, 145.34, 143.47 (d, $J = 20.5$ Hz), 140.57, 135.43, 135.02, 130.84 (d, $J = 3.8$ Hz), 128.47, 127.70 (d, $J = 12.9$ Hz), 127.45, 125.15, 121.04, 110.88, 106.63, 93.45 (d, $J = 177.4$ Hz), 46.05 (d, $J = 21.9$ Hz), 18.28 (d, $J = 4.7$ Hz). **^{19}F NMR** (376 MHz, CDCl_3) δ -189.72 (dd, $J = 48.1, 27.0$ Hz). **HRMS** (ESI-TOF) calculated for $\text{C}_{18}\text{H}_{14}\text{ClO}_2^+$ $[\text{M}-\text{F}]^+$ 297.0677, found 297.0685; **SFC** (chiral column) The sample was analyzed on a Waters UPC² SFC with a Daicel IA column (3 μm , 4.6 $\times$ 250 mm) under isocratic conditions (4 mL/min, 15% MeOH / CO_2 , 1600 psi backpressure) at 30 $^\circ\text{C}$. The enantiomers were detected by UV light (220 nm).



2-((1*R*,2*R*)-2-(Benzo[*d*][1,3]dioxol-5-yl)-1-fluoropropyl)-4-chlorobenzaldehyde (**4i**). This compound was prepared according to General Procedure (using **TDG-A**) as a yellow oil (37% yield, *d.r.* >20:1, 94% *ee*). **^1H NMR** (600 MHz, CDCl_3) δ 10.02 (s, 1H), 7.74 (dd, $J = 8.2, 1.2$ Hz, 1H), 7.44 (dd, $J = 8.2, 2.1$ Hz, 1H), 7.18 (d, $J = 2.1$ Hz, 1H), 6.64 (d, $J = 8.0$ Hz, 2H), 6.49–6.37 (m, 2H), 5.92 (dd, $J = 8.0, 1.6$ Hz, 2H), 3.11 (dq, $J = 27.5, 7.2, 4.2$ Hz, 1H), 1.42 (d, $J = 7.2$ Hz, 3H). **^{13}C NMR** (150 MHz, CDCl_3) δ 191.84, 147.57, 146.54, 143.45, 143.31, 140.59, 135.52, 134.23, 130.73 (d, $J = 4.0$ Hz), 128.49, 127.69 (d, $J = 13.3$ Hz), 122.05, 109.03, 107.90, 101.02, 93.34 (d, $J = 177.5$ Hz), 45.73 (d, $J = 21.6$ Hz), 18.01 (d, $J = 4.6$ Hz). **^{19}F NMR** (376 MHz, CDCl_3) δ -191.21 (dd, $J = 48.0, 27.6$ Hz). **HRMS** (ESI-TOF) calculated for $\text{C}_{17}\text{H}_{14}\text{ClO}_3^+$ $[\text{M}-\text{F}]^+$ 301.0626, found 301.0627; **SFC** (chiral column) The sample was analyzed on a Waters UPC² SFC with a Daicel IA column (3 μm , 4.6 $\times$ 250 mm) under isocratic conditions (4 mL/min, 15% MeOH / CO_2 , 1600 psi backpressure) at 30 $^\circ\text{C}$. The enantiomers were detected by UV light (212 nm).



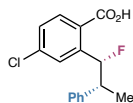
4-Chloro-2-((1*R*,2*R*)-1-fluoro-2-(naphthalen-2-yl)propyl)benzaldehyde (**4j**). This compound was prepared according to General Procedure (using **TDG-A**) as a yellow oil (60% yield, *d.r.* >20:1, 99% *ee*). **^1H NMR** (600 MHz, CDCl_3) δ 10.07 (s, 1H), 7.80–7.71 (m, 4H), 7.51–7.50 (m, 1H), 7.45–7.40 (m, 3H), 7.22 (dt, $J = 8.4, 1.4$ Hz, 1H), 7.19 (d, $J = 2.1$ Hz, 1H), 6.60 (dd, $J = 47.7, 4.8$ Hz, 1H), 3.36 (dq, $J = 26.4, 7.2, 4.7$ Hz, 1H), 1.52 (d, $J = 7.2$ Hz, 3H). **^{13}C NMR** (150 MHz, CDCl_3) δ 191.92, 143.38 (d, $J = 20.4$ Hz), 140.67, 138.17, 135.58, 133.36, 132.69, 130.87 (d, $J = 3.8$ Hz), 128.56, 127.82, 127.76, 127.71, 127.67, 127.50, 126.92, 126.06, 125.72, 93.29 (d, $J = 177.4$ Hz), 46.36 (d, $J = 22.0$ Hz), 17.95 (d, $J = 4.9$ Hz). **^{19}F NMR** (376 MHz, CDCl_3) δ -189.11 (dd, $J = 47.3, 26.4$ Hz). **HRMS** (ESI-TOF) calculated for $\text{C}_{20}\text{H}_{16}\text{ClO}^+$ $[\text{M}-\text{F}]^+$ 307.0884, found 307.0892; **SFC** (chiral column) The sample was analyzed on a Waters UPC² SFC with a Daicel IBN column (3 μm , 4.6 $\times$ 250 mm) under isocratic conditions (4 mL/min, 25% MeOH / CO_2 , 1600 psi backpressure) at 30 $^\circ\text{C}$. The enantiomers were detected by UV light (220 nm).



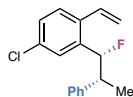
4-Chloro-2-((1*R*,2*R*)-2-(2,4-dimethylphenyl)-1-fluoropropyl)benzaldehyde (**4k**). This compound was prepared according to General Procedure (using **TDG-A**) as a yellow oil (45% yield, *d.r.* >20:1, 99% *ee*). **¹H NMR** (600 MHz, CDCl₃) δ 9.98 (s, 1H), 7.72 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.44 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.29 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.21 (d, *J* = 2.1 Hz, 1H), 7.05–7.02 (m, 1H), 6.86–6.83 (m, 1H), 6.50 (dd, *J* = 47.6, 5.0 Hz, 1H), 3.53 (dq, *J* = 25.9, 7.2, 4.9 Hz, 1H), 2.28 (s, 3H), 1.87 (s, 3H), 1.35 (d, *J* = 7.2 Hz, 3H). **¹³C NMR** (150 MHz, CDCl₃) δ 191.49, 143.30, 143.17, 140.49, 136.34, 136.19, 135.78, 134.76, 131.27 (d, *J* = 3.8 Hz), 130.92, 128.58, 128.00–127.63 (m), 126.95, 93.15 (d, *J* = 177.0 Hz), 40.07 (d, *J* = 21.7 Hz), 21.05, 19.53, 17.73 (d, *J* = 4.9 Hz). **¹⁹F NMR** (376 MHz, CDCl₃) δ -187.71. **HRMS** (ESI-TOF) calculated for C₁₈H₁₈ClO⁺ [M-F]⁺ 285.1041, found 285.1044; **SFC** (chiral column) The sample was analyzed on a Waters UPC² SFC with a Daicel IC column (3 μm, 4.6×250 mm) under isocratic conditions (4 mL/min, 7% IPA / CO₂, 1600 psi backpressure) at 30 °C. The enantiomers were detected by UV light (255 nm).

Synthetic Diversifications of **4a**

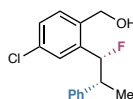
Procedures and Full Characterization of Reaction Products



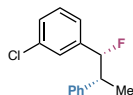
4-Chloro-2-((1*R*,2*R*)-1-fluoro-2-phenylpropyl)benzoic acid (**5a**). To a culture tube containing a stir bar were added **4a** (55.3 mg, 0.2 mmol), KH₂PO₄ (54.4 mg, 0.4 mmol), H₂O (0.15 mL), MeCN (0.15 mL) and 30% H₂O₂ (33.9 mg, 0.3 mmol). The mixture was cooled to 0 °C, and a solution of 80% NaClO₂ (35.9 mg, 0.32 mmol) in H₂O (0.15 mL) was added dropwise (71). After stirring overnight, the reaction was quenched with saturated NaHSO₃ solution and extracted with EtOAc. The combined organic phases were concentrated *in vacuo* and purified by silica gel column chromatography (DCM/EtOAc = 3/2) to give a white solid (50.9 mg, 87% yield, *d.r.* >20:1, >99% *ee*). **¹H NMR** (600 MHz, CDCl₃) δ 8.08 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.33 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.27–7.19 (m, 3H), 7.08–7.02 (m, 3H), 6.63 (dd, *J* = 48.1, 4.1 Hz, 1H), 3.27 (dq, *J* = 28.2, 7.2, 4.1 Hz, 1H), 1.50 (d, *J* = 7.3 Hz, 3H). **¹³C NMR** (150 MHz, CDCl₃) δ 171.67, 144.81, 144.68, 140.14 (d, *J* = 19.2 Hz), 132.71, 128.76, 127.98, 127.91, 127.64 (d, *J* = 14.1 Hz), 126.94, 123.88 (d, *J* = 4.4 Hz), 93.29 (d, *J* = 176.6 Hz), 46.01 (d, *J* = 21.9 Hz), 17.74 (d, *J* = 4.4 Hz). **¹⁹F NMR** (376 MHz, CDCl₃) δ -190.32 (dd, *J* = 48.3, 28.0 Hz, 1F). **HRMS** (ESI-TOF) calculated for C₁₆H₁₄ClO₂⁺ [M-F]⁺ 273.0677, found 273.0680; **SFC** (chiral column) The sample was analyzed on a Waters UPC² SFC with a Daicel IG column (3 μm, 4.6×250 mm) under isocratic conditions (4 mL/min, 10% MeOH / CO₂, 1600 psi backpressure) at 30 °C. The enantiomers were detected by UV light (212 nm).



4-Chloro-2-((1*R*,2*R*)-1-fluoro-2-phenylpropyl)-1-vinylbenzene (**5b**). To a culture tube containing a stir bar was added methyltriphenylphosphonium bromide (142.9 mg, 0.4 mmol). Next, the tube was evacuated and backfilled with N₂ three times. Anhydrous THF (2 mL) and ⁿBuLi solution (0.18 mL, 0.44 mmol, 2.5 M in hexane) were added in sequence at 0 °C followed by **4a** (55.3 mg, 0.2 mmol) in THF (0.5 mL) before the mixture was allowed to warm to room temperature. After stirring overnight, the reaction was quenched with saturated NH₄Cl solution and extracted with EtOAc. The combined organic phases were concentrated *in vacuo* and purified by preparatory TLC (Hexane) to give a colorless oil (36.3 mg, 66% yield, *d.r.* >20:1, 99% *ee*). **¹H NMR** (600 MHz, CDCl₃) δ 7.39 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.30–7.26 (m, 2H), 7.25–7.21 (m, 2H), 7.15–7.11 (m, 3H), 6.86 (dd, *J* = 17.2, 10.9 Hz, 1H), 5.74 (dd, *J* = 46.3, 6.8 Hz, 1H), 5.62 (dd, *J* = 17.2, 1.1 Hz, 1H), 5.36 (dd, *J* = 10.9, 1.1 Hz, 1H), 3.21 (dp, *J* = 19.5, 7.1 Hz, 1H), 1.25 (d, *J* = 7.2 Hz, 3H). **¹³C NMR** (150 MHz, CDCl₃) δ 141.08 (d, *J* = 1.9 Hz), 137.74 (d, *J* = 19.9 Hz), 134.30 (d, *J* = 4.5 Hz), 133.54, 132.80, 128.37 (d, *J* = 1.7 Hz), 128.23, 128.15, 127.49, 126.94, 126.60 (d, *J* = 9.5 Hz), 117.61, 94.23 (d, *J* = 177.2 Hz), 45.63 (d, *J* = 22.7 Hz), 17.33 (d, *J* = 5.4 Hz). **¹⁹F NMR** (376 MHz, CDCl₃) δ -182.19 (dd, *J* = 46.2, 19.6 Hz, 1F). **HRMS** (ESI-TOF) calculated for C₁₇H₁₆Cl⁺ [M-F]⁺ 255.0935, found 255.0939; **SFC** (chiral column) The sample was analyzed on a Waters UPC² SFC with a Daicel IA column (3 μm, 4.6×250 mm) under isocratic conditions (4 mL/min, 5% MeOH / CO₂, 1600 psi backpressure) at 30 °C. The enantiomers were detected by UV light (212 nm).



(4-Chloro-2-((1*R*,2*R*)-1-fluoro-2-phenylpropyl)phenyl)methanol (**5c**). To a culture tube containing a stir bar were added **4a** (55.3 mg, 0.2 mmol) and anhydrous MeOH (2 mL). NaBH₄ (11.3 mg, 0.3 mmol) was added slowly at 0 °C, and the mixture was allowed to warm to room temperature. After stirring for an additional 2 hours, the reaction was quenched with 1N HCl solution and extracted with EtOAc. The combined organic phases were concentrated *in vacuo* and purified by preparatory TLC (Hexane/EtOAc = 2/1) to give a colorless oil (51.3 mg, 92% yield, *d.r.* >20:1, 99% *ee*). **¹H NMR** (600 MHz, CDCl₃) δ 7.32–7.23 (m, 5H), 7.20 (d, *J* = 2.2 Hz, 1H), 7.17 (dd, *J* = 7.0, 1.8 Hz, 2H), 5.79 (dd, *J* = 46.2, 6.9 Hz, 1H), 4.61–4.48 (m, 2H), 3.29 (dp, *J* = 18.4, 7.1 Hz, 1H), 1.26 (d, *J* = 7.3 Hz, 3H). **¹³C NMR** (150 MHz, CDCl₃) δ 141.11 (d, *J* = 2.1 Hz), 138.55 (d, *J* = 19.9 Hz), 136.14 (d, *J* = 4.3 Hz), 133.76, 129.99, 128.51 (d, *J* = 1.8 Hz), 128.30, 128.23, 127.27 (d, *J* = 8.2 Hz), 127.05, 94.16 (d, *J* = 175.9 Hz), 62.08, 45.63 (d, *J* = 23.2 Hz), 17.21 (d, *J* = 5.2 Hz). **¹⁹F NMR** (376 MHz, CDCl₃) δ -178.06 (dd, *J* = 46.1, 18.3 Hz, 1F). **HRMS** (ESI-TOF) calculated for C₁₈H₁₉ClNO⁺ [M-F+MeCN]⁺ 300.1155, found 300.1157; **SFC** (chiral column) The sample was analyzed on a Waters UPC² SFC with a Daicel IA column (3 μm, 4.6×250 mm) under isocratic conditions (4 mL/min, 20% MeOH / CO₂, 1600 psi backpressure) at 30 °C. The enantiomers were detected by UV light (212 nm).



1-Chloro-3-((1*R*,2*R*)-1-fluoro-2-phenylpropyl)benzene (**5d**). To a culture tube containing a stir bar were added **4a** (55.3 mg, 0.2 mmol), RhCl(PPh₃)₃ (185.0 mg, 0.2 mmol) and *m*-xylene (2 mL) under inert atmosphere. The reaction was stirred vigorously at 140 °C for 16 hours, then quenched with H₂O and extracted with EtOAc (**17**). The combined organic phases were concentrated *in vacuo* and purified by preparatory TLC (Hexane/EtOAc = 50/1) and prep-HPLC in sequence to give a colorless oil (37.8 mg, 76% yield, *d.r.* >20:1, >99% *ee*). **¹H NMR** (600 MHz, CDCl₃) δ 7.33–7.21 (m, 6H), 7.20–7.16 (m, 3H), 7.04 (dq, *J* = 7.4, 1.3 Hz, 1H), 5.43 (dd, *J* = 46.4, 7.0 Hz, 1H), 3.21 (dp, *J* = 17.5, 7.1 Hz, 1H), 1.22 (d, *J* = 7.1 Hz, 3H). **¹³C NMR** (150 MHz, CDCl₃) δ 141.24 (d, *J* = 2.7 Hz), 140.64 (d, *J* = 21.0 Hz), 134.12, 129.38, 128.41 (d, *J* = 1.6 Hz), 128.30, 128.12, 126.92, 126.44 (d, *J* = 7.2 Hz), 124.48 (d, *J* = 7.0 Hz), 97.24 (d, *J* = 178.0 Hz), 45.94 (d, *J* = 22.8 Hz), 17.00 (d, *J* = 5.5 Hz). **¹⁹F NMR** (376 MHz, CDCl₃) δ -179.05 (dd, *J* = 46.6, 17.4 Hz, 1F). **HRMS** (ESI-TOF) calculated for C₁₅H₁₄Cl⁺ [M-F]⁺ 229.0784, found 229.0784; **SFC** (chiral column) The enantiomeric excess was determined by heart-cutting 2D LC-SFC (**77**). The LC dimension consisted of a Waters I-Class LC with a Waters BEH C18 column (1.7 μm, 2.1×100 mm) using a 0.1% aqueous formic acid:acetonitrile gradient (0.6 mL/min, 15–99% acetonitrile over 2.1 minutes) at 55 °C. The heart cut was performed at 2.22 minutes using a 6-port 2-position valve equipped with a 10 μL transfer loop. The SFC dimension consisted of a Waters UPC² SFC with a Daicel IG column (3 μm, 4.6×250 mm) using isocratic conditions (4 mL/min, 5% MeOH / CO₂, 1600 psi backpressure) at 30 °C. The enantiomers were detected by UV light (220 nm).

Preparation of MCJ001F

Previous Syntheses for Comparison

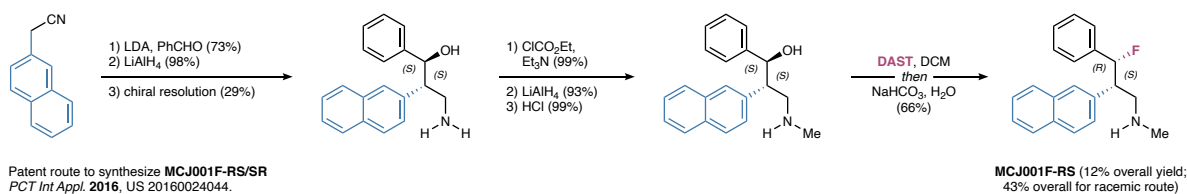
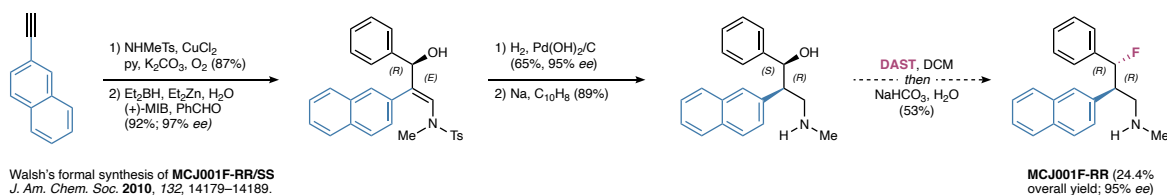
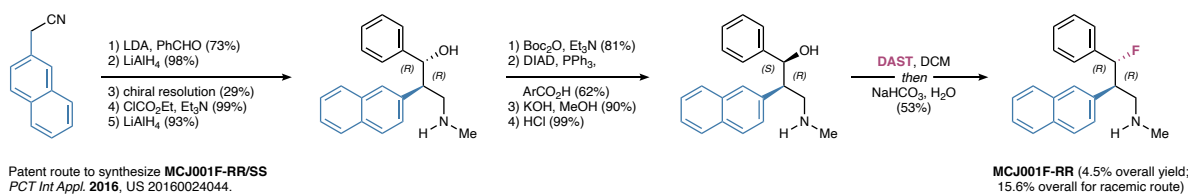


Figure S7. Summary of previous syntheses of MCJ001F (50, 51).

Procedure for Preparation of MCJ001F-RR

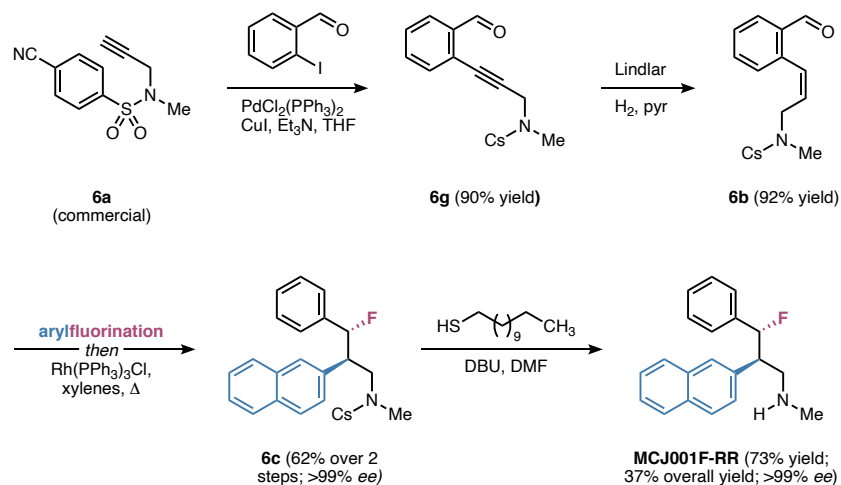


Figure S8. Synthesis of MCJ001F-RR.

Pd(PPh₃)₂Cl₂ (71.9 mg, 10 mol%) and CuI (38.1 mg, 20 mol%) were added to a stirring solution of 2-iodobenzaldehyde (2.32 g, 10 mmol) in triethylamine (40 mL) at room temperature under

inert atmosphere. The mixture was allowed to stir for 10 minutes, at which point 4-cyano-*N*-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide **6a** (2.81 g, 12 mmol) in degassed THF (20 mL) was added. After stirring overnight, the reaction was quenched with saturated NH₄Cl solution and extracted with EtOAc. The combined organic phases were concentrated *in vacuo* and purified by silica gel column chromatography to give a yellow solid in 90% yield (3.05 g) (72).

4-Cyano-*N*-(3-(2-formylphenyl)prop-2-yn-1-yl)-*N*-methylbenzenesulfonamide **6g** (1.0 g, 3 mmol) was dissolved in pyridine (12 mL). To this solution was added Lindlar's catalyst (622 mg, 0.3 mmol). The flask was purged with hydrogen gas then equipped with a hydrogen balloon. The mixture was allowed to stir at room temperature for 3 days and was then filtered through Celite. The filtrate was concentrated *in vacuo* and purified by silica gel column chromatography to give the yellow solid in 92% yield (929 mg) (17).

To a culture tube were added PhB(OH)₂ (227.8 mg, 1.87 mmol), [F⁺] (256.6 mg, 0.90 mmol), **TDG-A** (45.3 mg, 0.20 mmol), Pd(MeCN)₄(BF₄)₂ (17.8 mg, 0.04 mmol), and AgF (50.7 mg, 0.40 mmol) in a glovebox. The tube was then removed from the glovebox and a solution of **6c** (0.40 mmol) dissolved in DCM (0.67 mL), MeCN (0.33 mL), and H₂O (21.6 μL, 1.20 mmol) was added under inert atmosphere and stirred at 35 °C. After stirring at 35 °C for 72 hours, the reaction was quenched with 1N HCl aqueous solution and extracted with EtOAc. The combined organic phases were concentrated *in vacuo* and purified by silica gel chromatography to give a mixture of product (66% yield) and starting material (4%) by ¹H NMR.

To a culture tube were added the arylfluorination product, RhCl(PPh₃)₃ (20.4 mg, 0.22 mmol), and *m*-xylene (4 mL) under inert atmosphere. The reaction was stirred vigorously at 140 °C for 16 hours, then quenched with H₂O and extracted with EtOAc. The combined organic phases were concentrated *in vacuo* and purified by silica gel chromatography to afford **6f** in 62% yield (113.7 mg) over two steps.

To a culture tube in a glovebox were added **6f** (0.1 mmol), DMF (0.3 mL), and 1-dodecanethiol (120 μL, 0.5 mmol). The reaction was stirred for 5 minutes before addition of DBU (72 μL, 0.48 mmol) in one portion. After stirring under argon for 12 hours at room temperature, the reaction was quenched with water and extracted with EtOAc. The combined organic phases were concentrated *in vacuo* and purified by silica gel column chromatography to give **MCJ001F-RS** in 72% yield (21.4 mg) (73).

Procedure for Preparation of MCJ001F-RS

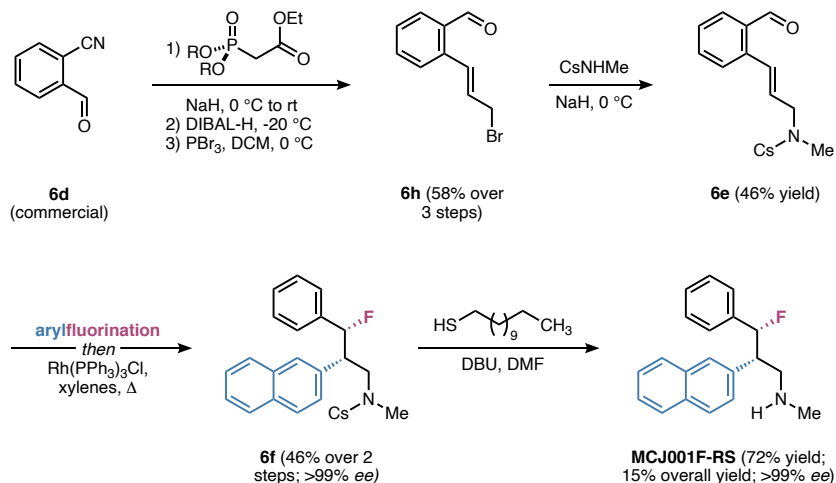


Figure S9. Synthesis of MCJ001F-RS.

A round-bottomed flask was charged with NaH (60% in oil, 3.4 g, 85 mmol) and anhydrous THF (50 mL) under inert atmosphere. After cooling to 0°C , triethyl phosphonoacetate (16.8 mL, 85 mmol) was slowly added and the reaction left to stir for 30 minutes, after which 2-cyanobenzaldehyde (6.56 g, 50 mmol) was slowly added. After stirring for 60 minutes at 0°C , the mixture was quenched with saturated NH_4Cl and extracted with diethyl ether. The combined organic phases were washed with saturated NaHCO_3 and brine, then dried over anhydrous Na_2SO_4 . The combined organic phases were concentrated *in vacuo* and purified by silica gel column chromatography to afford a white solid in 97% yield (9.82 g) (74).

To a suspension of (*E*)-ethyl-3-(2-cyanophenyl)acrylate (4.02 g, 20 mmol) in DCM (50 mL) at -20°C was added dropwise DIBAL-H (70 mL, 70 mmol, 1.0 M solution in cyclohexane) over 30 minutes. The reaction was then allowed to warm to room temperature and left to stir for 3 hours. The reaction was quenched with ice containing dilute HCl, the organic layer separated, and the aqueous layer further extracted with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4 , then concentrated *in vacuo* and purified by silica gel column chromatography to afford (*E*)-2-(3-hydroxyprop-1-enyl)benzaldehyde as a colorless oil in 90% yield (2.92 g) (74).

To an oven dried 250 mL flask were added (*E*)-2-(3-hydroxyprop-1-enyl)benzaldehyde (1.62g, 10 mmol) and anhydrous ether (30 mL) under inert atmosphere. PBr_3 (1.35 g, 5 mmol) was added slowly at 0°C and the reaction was stirred until the alcohol was consumed. The reaction was then quenched with saturated NaHCO_3 solution and extracted with DCM. The combined organic phases were concentrated *in vacuo* and purified by silica gel column chromatography to give **6h** as a yellow oil in 67% yield (1.51 g) (75).

To an oven dried 100 mL round-bottom flask were added NaH (150 mg, 3.8 mmol) and anhydrous THF (10 mL) under inert atmosphere. 4-Cyano-*N*-methylbenzenesulfonamide (706 mg, 3.6 mmol) in anhydrous THF (5 mL) was slowly added at 0°C , and the mixture was allowed to warm to room temperature. After stirring for 30 minutes, **6h** (675 mg, 3.0 mmol) was added, and the reaction was heated to 45°C . After full consumption of the starting material, the reaction was quenched with

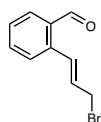
saturated NH₄Cl solution and extracted with DCM. The combined organic phases were concentrated *in vacuo* and purified by silica gel column chromatography to give **6e** as a yellow solid in 78% yield (796 mg).

To a culture tube were added PhB(OH)₂ (227.8 mg, 1.87 mmol), [F⁺] (256.6 mg, 0.90 mmol), **TDG-A** (45.3 mg, 0.20 mmol), Pd(MeCN)₄(BF₄)₂ (17.8 mg, 0.04 mmol), and AgF (50.7 mg, 0.40 mmol) in a glovebox. The tube was then removed from the glovebox and a solution of **6e** (0.40 mmol) dissolved in DCM (0.67 mL), MeCN (0.33 mL), and H₂O (21.6 μL, 1.20 mmol) was added under inert atmosphere and stirred at 35 °C. After stirring at 35 °C for 72 hours, the reaction was quenched with 1N HCl aqueous solution and extracted with EtOAc. The combined organic phases were concentrated *in vacuo* and purified by silica gel chromatography to give a mixture of product (48% yield) and starting material (4%) by ¹H NMR.

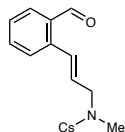
To a culture tube were added the arylfluorination product, RhCl(PPh₃)₃ (20.4 mg, 0.22 mmol), and *m*-xylene (4 mL) under inert atmosphere. The reaction was stirred vigorously at 140 °C for 16 hours, then quenched with H₂O and extracted with EtOAc. The combined organic phases were concentrated *in vacuo* and purified by silica gel chromatography to afford **6f** in 46% yield (84.4 mg) over two steps.

To a culture tube in a glovebox were added **6f** (0.1 mmol), DMF (0.3 mL), and 1-dodecanethiol (120 μL, 0.5 mmol). The reaction was stirred for 5 minutes before addition of DBU (72 μL, 0.48 mmol) in one portion. After stirring under argon for 12 hours at room temperature, the reaction was quenched with water and extracted with EtOAc. The combined organic phases were concentrated *in vacuo* and purified by silica gel column chromatography to give **MCJ001F-RS** in 72% yield (21.1 mg) (73).

Full Characterization of Reaction Products

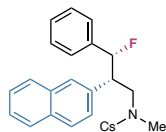


(*E*)-2-(3-bromoprop-1-en-1-yl)benzaldehyde (**6h**). ¹H NMR (600 MHz, CDCl₃) δ 10.23 (d, *J* = 1.5 Hz, 1H), 7.82 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.62–7.54 (m, 3H), 7.47 (ddt, *J* = 8.3, 6.7, 1.7 Hz, 1H), 6.36 (dtd, *J* = 15.4, 7.7, 1.5 Hz, 1H), 4.20 (dt, *J* = 7.7, 1.3 Hz, 2H). ¹³C NMR (150 MHz, CDCl₃) δ 192.47, 138.06, 133.75, 132.91, 132.58, 130.59, 130.25, 128.34, 127.66, 32.59.

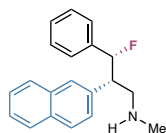


(*E*)-4-Cyano-*N*-(3-(2-formylphenyl)allyl)-*N*-methylbenzenesulfonamide (**6e**). ¹H NMR (600 MHz, CDCl₃) δ 10.15 (s, 1H), 7.97–7.94 (m, 2H), 7.86–7.83 (m, 2H), 7.79 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.57 (td, *J* = 7.5, 1.4 Hz, 1H), 7.51–7.47 (m, 2H), 7.47–7.43 (m, 1H), 6.02 (dt, *J* = 15.7, 6.6 Hz, 1H), 3.93–3.90 (m, 2H), 2.83 (d, *J* = 0.8 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) δ 192.80, 142.11, 138.00, 133.83, 133.52, 132.98, 132.76, 131.87, 128.33, 128.02, 127.62 (d, *J* = 1.9 Hz),

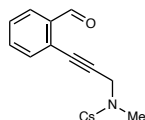
117.26, 116.45, 52.54, 34.45. **HRMS** (ESI-TOF) calculated for $C_{18}H_{17}N_2O_3S^+$ $[M+H]^+$ 341.0960, found 341.0959.



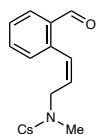
4-Cyano-*N*-((2*S*,3*R*)-3-fluoro-2-(naphthalen-2-yl)-3-phenylpropyl)-*N*-methylbenzenesulfonamide (**6f**). **1H NMR** (600 MHz, $CDCl_3$) δ 7.81–7.77 (m, 1H), 7.72–7.65 (m, 4H), 7.61–7.58 (m, 2H), 7.51 (d, J = 1.8 Hz, 1H), 7.49–7.45 (m, 2H), 7.23 (td, J = 3.7, 1.7 Hz, 4H), 7.10–7.06 (m, 2H), 5.92 (dd, J = 46.5, 3.8 Hz, 1H), 3.60–3.53 (m, 2.5H), 3.53–3.48 (m, 0.5H), 2.76 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 141.80, 137.70 (d, J = 20.5 Hz), 133.67, 133.08, 132.66, 128.59, 128.26, 128.18, 127.98, 127.71, 127.66, 127.53, 126.84 (d, J = 2.0 Hz), 126.17, 126.08, 125.57 (d, J = 7.3 Hz), 117.17, 116.14, 93.82 (d, J = 178.8 Hz), 52.48 (d, J = 4.8 Hz), 51.88 (d, J = 21.9 Hz), 36.25. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -189.25 (dd, J = 46.8, 26.4 Hz, 1F). **HRMS** (ESI-TOF) calculated for $C_{27}H_{24}FN_2O_2S^+$ $[M+H]^+$ 459.1543, found 459.1544. **SFC** (chiral column) The sample was analyzed on a Waters UPC² SFC with a Daicel IG column (3 μ m, 4.6 $\times$ 250 mm) under isocratic conditions (4 mL/min, 40% MeOH / CO_2 , 1600 psi backpressure) at 30 $^{\circ}C$. The enantiomers were detected by UV light (225 nm).



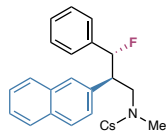
(2*S*,3*R*)-3-fluoro-*N*-methyl-2-(naphthalen-2-yl)-3-phenylpropan-1-amine (**MCJ001F-RS**). **1H NMR** (600 MHz, $CDCl_3$) δ 7.82–7.79 (m, 1H), 7.77 (dd, J = 8.7, 4.4 Hz, 2H), 7.65 (d, J = 1.7 Hz, 1H), 7.47–7.43 (m, 2H), 7.35–7.32 (m, 1H), 7.27 (qd, J = 5.0, 1.5 Hz, 3H), 7.19 (dd, J = 7.3, 2.4 Hz, 2H), 5.81 (dd, J = 46.6, 6.0 Hz, 1H), 3.46 (ddt, J = 22.2, 9.2, 5.7 Hz, 1H), 3.02 (dd, J = 11.9, 9.2 Hz, 1H), 2.92 (dd, J = 11.9, 5.4 Hz, 1H), 2.34 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 138.48 (d, J = 20.7 Hz), 135.54, 133.32, 132.68, 128.30, 128.21, 128.19, 128.11, 127.77, 127.57, 126.68, 126.00, 125.96, 125.72, 95.46 (d, J = 176.6 Hz), 53.14 (d, J = 4.9 Hz), 52.46 (d, J = 22.6 Hz), 36.33. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -183.28 (dd, J = 46.5, 22.1 Hz, 1F). **HRMS** (ESI-TOF) calculated for $C_{20}H_{21}FN^+$ $[M+H]^+$ 294.1658, found 294.1657. **SFC** (chiral column) The sample was analyzed on a Waters UPC² SFC with a Phenomenex AMY1 column (3 μ m, 4.6 $\times$ 250 mm) under isocratic conditions (4 mL/min, 10% MeOH containing 0.5 vol% 7M methanolic NH_3 / CO_2 , 1600 psi backpressure) at 30 $^{\circ}C$. The enantiomers were detected by UV light (220 nm).



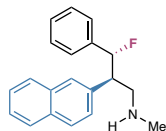
4-Cyano-*N*-(3-(2-formylphenyl)prop-2-yn-1-yl)-*N*-methylbenzenesulfonamide (**6g**). ^1H NMR (600 MHz, CDCl_3) δ 10.06–10.05 (m, 1H), 8.01–7.96 (m, 2H), 7.87 (dd, J = 7.7, 1.4 Hz, 1H), 7.75–7.71 (m, 2H), 7.55 (td, J = 7.5, 1.4 Hz, 1H), 7.48 (td, J = 7.6, 1.1 Hz, 1H), 7.21 (d, J = 7.7 Hz, 1H), 4.41 (s, 2H), 3.00 (s, 3H). ^{13}C NMR (150 MHz, CDCl_3) δ 190.39, 141.83, 135.87, 133.80, 133.26, 132.69, 129.41, 128.43, 128.31, 124.37, 117.00, 116.60, 87.87, 82.44, 40.73, 34.87. **HRMS** (ESI-TOF) calculated for $\text{C}_{18}\text{H}_{15}\text{N}_2\text{O}_3\text{S}^+$ $[\text{M}+\text{H}]^+$ 339.0803, found 339.0805.



(*Z*)-4-cyano-*N*-(3-(2-formylphenyl)allyl)-*N*-methylbenzenesulfonamide (**6b**). ^1H NMR (600 MHz, CDCl_3) δ 10.16 (s, 1H), 7.88 (dd, J = 7.7, 1.4 Hz, 1H), 7.86–7.82 (m, 2H), 7.81–7.78 (m, 2H), 7.58 (td, J = 7.5, 1.4 Hz, 1H), 7.49 (td, J = 7.4, 1.0 Hz, 1H), 7.18 (d, J = 7.6 Hz, 1H), 7.14–7.10 (m, 1H), 5.79 (dt, J = 11.5, 6.8 Hz, 1H), 3.79 (dd, J = 6.8, 1.7 Hz, 2H), 2.67 (s, 3H). ^{13}C NMR (150 MHz, CDCl_3) δ 191.87, 142.19, 137.69, 133.69 (d, J = 2.3 Hz), 132.94, 131.70, 131.23, 130.37, 128.34, 127.88, 127.73, 117.23, 116.41, 47.62, 34.36. **HRMS** (ESI-TOF) calculated for $\text{C}_{18}\text{H}_{17}\text{N}_2\text{O}_3\text{S}^+$ $[\text{M}+\text{H}]^+$ 341.0960, found 341.0958.



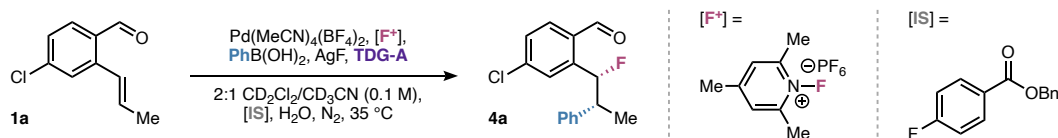
4-cyano-*N*-((2*R*,3*R*)-3-fluoro-2-(naphthalen-2-yl)-3-phenylpropyl)-*N*-methylbenzenesulfonamide (**6c**). ^1H NMR (600 MHz, CDCl_3) δ 7.82–7.78 (m, 1H), 7.72 (d, J = 8.5 Hz, 1H), 7.68 (dt, J = 8.0, 2.7 Hz, 1H), 7.52–7.46 (m, 7H), 7.29–7.24 (m, 4H), 7.18 (dd, J = 7.1, 2.6 Hz, 2H), 5.70 (dd, J = 46.9, 6.8 Hz, 1H), 3.81 (dd, J = 14.1, 10.6 Hz, 1H), 3.70–3.56 (m, 2H), 2.59 (s, 3H). ^{13}C NMR (150 MHz, CDCl_3) δ 142.19, 137.65 (d, J = 20.3 Hz), 135.04 (d, J = 4.6 Hz), 133.21, 132.67, 132.49, 128.47, 128.42, 128.31, 128.14, 127.69, 127.60, 127.54, 126.37, 126.25, 126.19, 125.79 (d, J = 7.4 Hz), 117.23, 115.89, 95.82 (d, J = 178.7 Hz), 51.60 (d, J = 21.4 Hz), 51.25 (d, J = 6.0 Hz), 35.73. ^{19}F NMR (376 MHz, CDCl_3) δ -183.72 (dd, J = 46.9, 17.6 Hz, 1F). **HRMS** (ESI-TOF) calculated for $\text{C}_{27}\text{H}_{24}\text{FN}_2\text{O}_2\text{S}^+$ $[\text{M}+\text{H}]^+$ 459.1543, found 459.1528. **SFC** (chiral column) The sample was analyzed on a Waters UPC² SFC with a Daicel IBN column (3 μm , 4.6×250 mm) under isocratic conditions (4 mL/min, 35% MeOH / CO_2 , 1600 psi backpressure) at 30 °C. The enantiomers were detected by UV light (225 nm).



(2*R*,3*R*)-3-fluoro-*N*-methyl-2-(naphthalen-2-yl)-3-phenylpropan-1-amine (**MCJ001F-RR**). **¹H NMR** (600 MHz, CDCl₃) δ 7.79–7.75 (m, 1H), 7.73 (dd, *J* = 8.6, 2.6 Hz, 2H), 7.57–7.54 (m, 1H), 7.47–7.40 (m, 2H), 7.25–7.19 (m, 4H), 7.17–7.13 (m, 2H), 5.69 (dd, *J* = 47.0, 7.7 Hz, 1H), 3.56 (dddd, *J* = 14.8, 9.4, 7.7, 4.7 Hz, 1H), 3.24 (dd, *J* = 12.0, 4.7 Hz, 1H), 3.17 (dd, *J* = 12.0, 9.4 Hz, 1H), 2.38 (s, 3H). **¹³C NMR** (150 MHz, CDCl₃) δ 138.35 (d, *J* = 20.2 Hz), 136.08 (d, *J* = 6.2 Hz), 133.34, 132.60, 128.31, 128.21 (d, *J* = 2.1 Hz), 128.12, 127.78, 127.70, 127.57, 126.46, 126.12, 126.08, 125.79, 96.62 (d, *J* = 177.2 Hz), 52.64 (d, *J* = 4.9 Hz), 52.47, 36.46. **¹⁹F NMR** (376 MHz, CDCl₃) δ -180.56 (dd, *J* = 46.7, 14.7 Hz, 1F). **HRMS** (ESI-TOF) calculated for C₂₀H₂₁FN⁺ [M+H]⁺ 294.1658, found 294.1658. **SFC** (chiral column) The sample was analyzed on a Waters UPC² SFC with a Phenomenex AMY1 column (3 μm, 4.6×250 mm) under isocratic conditions (4 mL/min, 25% MeOH containing 0.5 vol% 7M methanolic NH₃ / CO₂, 1600 psi backpressure) at 30 °C. The enantiomers were detected by UV light (225 nm).

Kinetics Experiments

General Kinetics Procedure



To a culture tube were added PhB(OH)₂, [F⁺], and AgF in a glovebox. Under inert atmosphere, the appropriate amount of alkene (0.15 mmol scale), internal standard (benzyl 4-fluorobenzoate, 0.075 mmol), and **TDG-A** were added via stock solutions in CD₂Cl₂ (1.00 mL total) followed by the appropriate amount of H₂O and Pd(MeCN)₄(BF₄)₂ via stock solutions in CD₃CN (0.50 mL total). The reaction was then stirred at 35 °C, and aliquots were removed at each time interval using a microsyringe. Each aliquot (~25 μL) was diluted with CD₃CN and analyzed by ¹H NMR and ¹⁹F NMR to determine yield (based on the benzyl 4-fluorobenzoate internal standard). Concentrations were calculated given the total volume of liquids in parent reaction (1.5 mL), and the changes in this value between experiments were deemed negligible.

Same-Excess Experiments

Experiments at same-excess were designed using Reaction Progress Kinetic Analysis protocols (52–54) and were conducted as described by the *General Kinetics Procedure* using the reaction component concentrations in **Table S2**.

[reactant]	Standard Conditions	Same-Excess	Same-Ex. + Product
[1a]	0.100 M	0.070 M	0.070 M
[4a]	0.000 M	0.000 M	0.030 M
[PhB(OH) ₂]	0.467 M	0.437 M	0.437 M
[F ⁺]	0.225 M	0.195 M	0.195 M
[AgF]	0.100 M	0.100 M	0.100 M
[H ₂ O]	0.300 M	0.300 M	0.300 M
[Pd]	0.010 M	0.010 M	0.010 M
[TDG]	0.050 M	0.050 M	0.050 M

Table S2. Starting concentrations for same-excess experiments.

To normalize the data, both same-excess experiments were time shifted by 1.2 hours (the point at which the reaction reaches ~30% conversion). The [product] vs. time data is outlined in **Table S3** along with the kinetic profile of the experiments performed at same-excess. Each data point represents the average of two discrete runs.

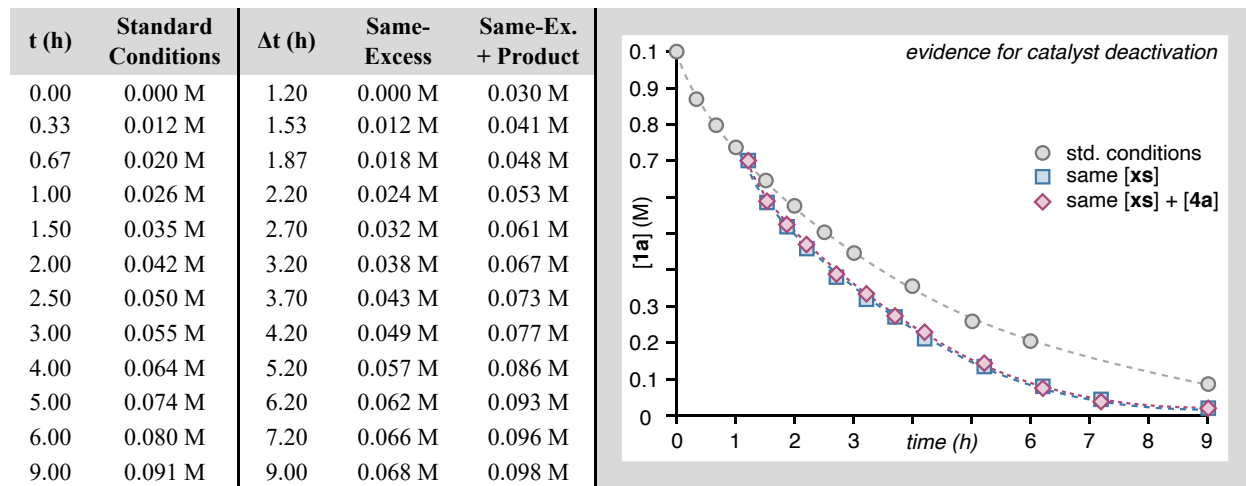


Table S3. Raw data for concentration of the product ([4a]) over time in the same-excess experiments and the kinetic profile of the experiments. The value of [1a] = (0.100 M) – [4a] in the kinetic profile.

Different-Excess Experiments

Experiments at different-excess were designed using Reaction Progress Kinetic Analysis protocol (52–54) and were conducted as described by the *General Kinetics Procedure* using the reaction component concentrations in **Table S4**.

[reactant]	Standard Conditions	Lower [PhB(OH) ₂]	Higher [PhB(OH) ₂]	Lower [F ⁺]	Higher [F ⁺]	Lower [AgF]	Lower [1a]	Lower [H ₂ O]	Lower [Pd]	Higher [TDG]
[1a]	0.100 M	0.100 M	0.100 M	0.100 M	0.100 M	0.100 M	0.070 M	0.100 M	0.100 M	0.100 M
[4a]	0.000 M	0.000 M	0.000 M	0.000 M	0.000 M	0.000 M	0.000 M	0.000 M	0.000 M	0.000 M
[PhB(OH) ₂]	0.467 M	0.350 M	0.550 M	0.467 M	0.467 M	0.467 M	0.467 M	0.467 M	0.467 M	0.467 M
[F ⁺]	0.225 M	0.225 M	0.225 M	0.150 M	0.275 M	0.225 M	0.225 M	0.225 M	0.225 M	0.225 M
[AgF]	0.100 M	0.100 M	0.100 M	0.100 M	0.100 M	0.050 M	0.100 M	0.100 M	0.100 M	0.100 M
[H ₂ O]	0.300 M	0.300 M	0.300 M	0.300 M	0.300 M	0.300 M	0.300 M	0.000 M	0.300 M	0.300 M
[Pd]	0.010 M	0.010 M	0.010 M	0.010 M	0.010 M	0.010 M	0.010 M	0.010 M	0.005 M	0.010 M
[TDG]	0.050 M	0.050 M	0.050 M	0.050 M	0.050 M	0.050 M	0.050 M	0.050 M	0.050 M	0.075 M

Table S4. Starting concentrations for different-excess experiments.

The [product] vs. time data for each of the experiments performed at different-excess is outlined in **Table S5**.

t (h)	Standard Conditions	Lower [PhB(OH) ₂]	Higher [PhB(OH) ₂]	Lower [F ⁺]	Higher [F ⁺]	Lower [AgF]	Lower [1a]	Lower [H ₂ O]	Lower [Pd]	Higher [TDG]
0.00	0.000 M	0.000 M	0.000 M	0.000 M	0.000 M	0.000 M	0.000 M	0.000 M	0.000 M	0.000 M
0.33	0.012 M	0.009 M	0.015 M	0.009 M	0.014 M	0.014 M	0.012 M	0.010 M	0.007 M	0.011 M
0.67	0.020 M	0.014 M	0.022 M	0.014 M	0.021 M	0.021 M	0.020 M	0.016 M	0.010 M	0.016 M
1.00	0.026 M	0.019 M	0.0290 M	0.019 M	0.028 M	0.028 M	0.026 M	0.024 M	0.014 M	0.021 M
1.50	0.035 M	0.024 M	0.038 M	0.024 M	0.036 M	0.036 M	0.035 M	0.033 M	0.018 M	0.028 M
2.00	0.042 M	0.030 M	0.046 M	0.030 M	0.043 M	0.042 M	0.044 M	0.038 M	0.021 M	0.034 M
2.50	0.050 M	0.035 M	0.055 M	0.035 M	0.048 M	0.049 M	0.050 M	0.045 M	0.024 M	0.041 M
3.00	0.055 M	0.038 M	0.062 M	0.040 M	0.055 M	0.054 M	0.057 M	0.051 M	0.026 M	0.045 M
4.00	0.064 M	0.045 M	0.072 M	0.048 M	0.065 M	0.064 M	0.063 M	0.063 M	0.033 M	0.052 M
5.00	0.074 M	0.050 M	0.079 M	0.056 M	0.072 M	0.069 M	0.068 M	0.068 M	0.037 M	0.058 M
6.00	0.080 M	0.055 M	0.086 M	0.061 M	0.079 M	0.075 M	0.069 M	0.074 M	0.042 M	0.064 M
9.00	0.091 M	0.066 M	0.099 M	0.078 M	0.091 M	0.085 M	0.070 M	0.085 M	0.051 M	0.080 M

Table S5. Raw data for concentration of the product ([4a]) over time in the different-excess experiments.

The initial rates of reaction as shown in the main manuscript were calculated based on the linear slope of the first 3 recorded times points in each run. The full reaction profiles are included in **Figure S10**.

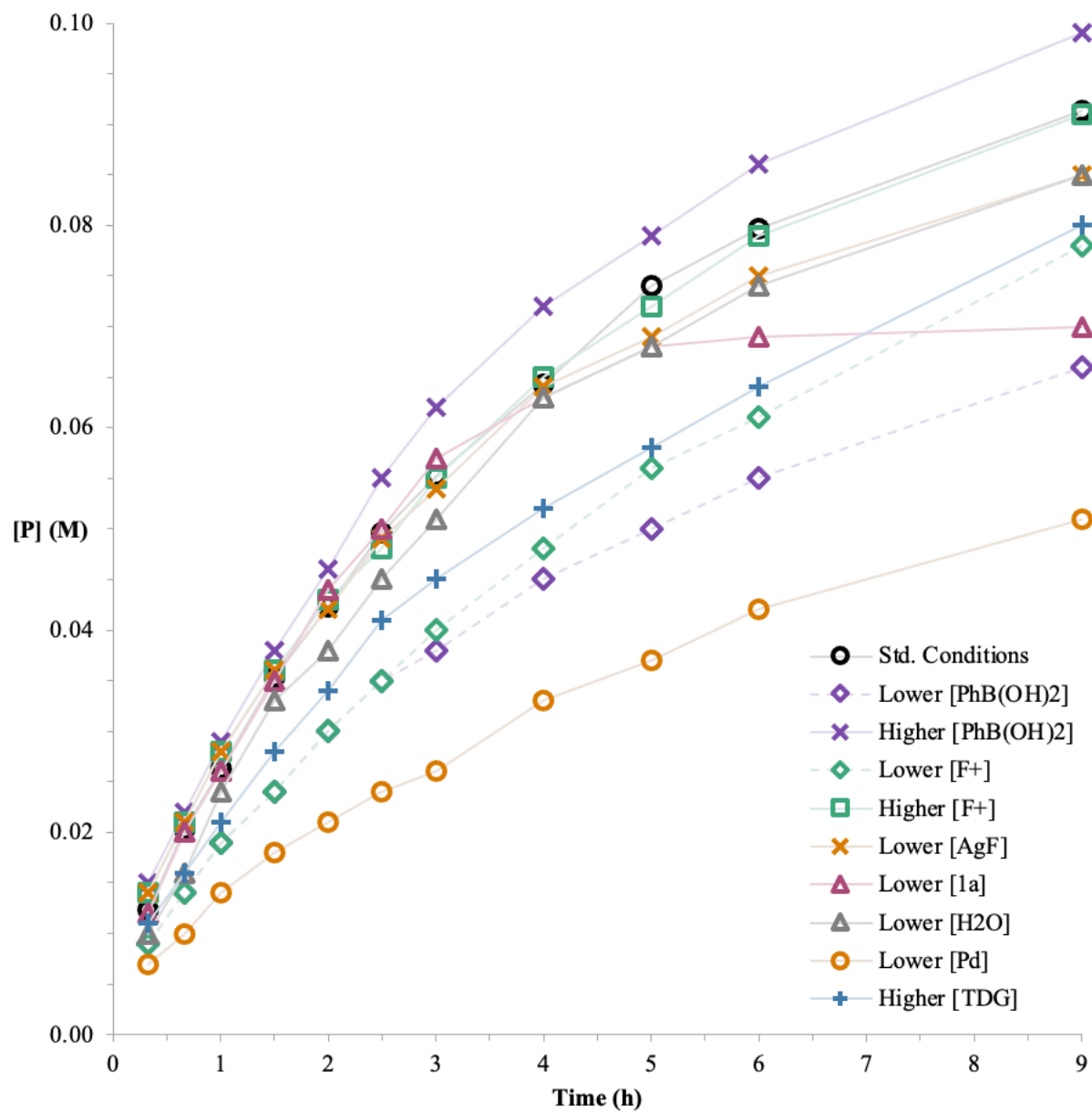


Figure S10. Kinetic profiles for experiments performed at different-excess.

Nonlinear Experiments

Procedure and Data

To a culture tube were added PhB(OH)₂ (56.9 mg, 0.467 mmol), [F⁺] (64.2 mg, 0.225 mmol), Pd(MeCN)₄(BF₄)₂ (4.4 mg, 0.01 mmol), and AgF (12.7 mg, 0.1 mmol) in a glovebox. The tube was then removed from the glovebox and a solution of alkene (0.1 mmol) dissolved in DCM (0.33 mL), MeCN (0.33 mL), and H₂O (5.4 μL, 0.3 mmol) was added under inert atmosphere. Finally, a solution of **TDG-A** with a given *ee* value (-100.0%, -66.67%, -33.33%, 33.33%, 66.67%, 100.0%) which was prepared by mixing stock solutions of (*R*)-**TDG-A** and (*S*)-**TDG-A** in DCM, was added and the reaction stirred at 35 °C. After stirring at 35 °C for 16 hours, the reaction was quenched with 1N HCl aqueous solution (3 mL) and extracted with EtOAc (5 mL × 3). The combined organic phases were concentrated *in vacuo* and *ee* measured as previously described.

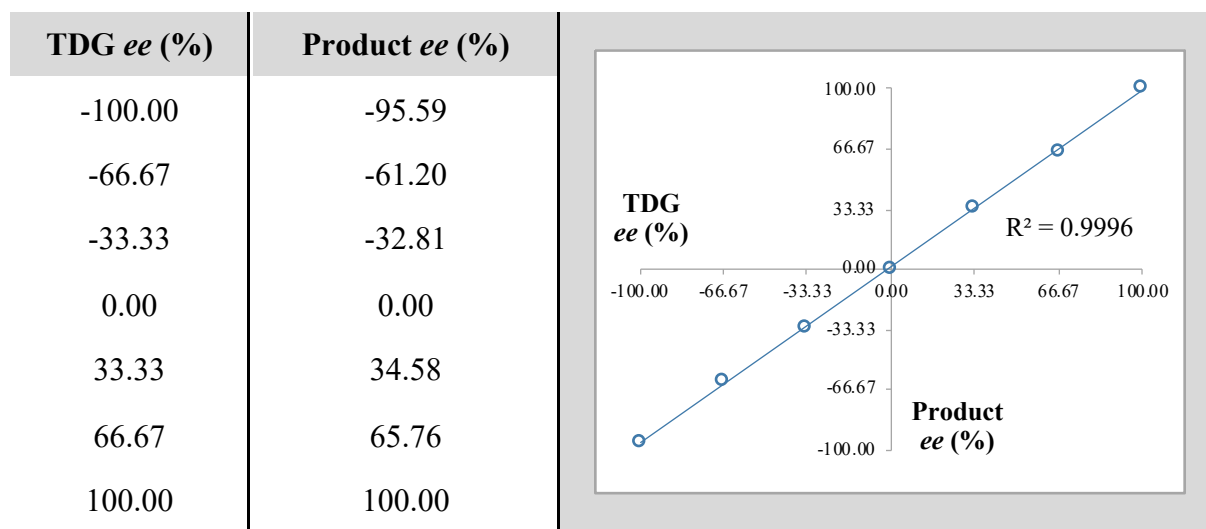
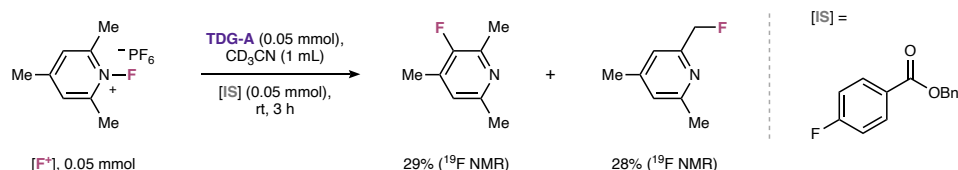


Table S6. TDG enantiomeric excess vs. product enantiomeric excess data.

Control Experiments

Procedure for Investigating Decomposition of [F⁺]



A culture tube was charged with [F⁺], **TDG-A**, and CD₃CN. The solution was stirred at room temperature for 3 hours, then analyzed by ¹H NMR and ¹⁹F NMR. All [F⁺] was consumed over the course of the reaction, generating the fluorinated pyridine derivatives depicted. This process is consistent with what has been previously observed (76).

Annotated Spectral Data

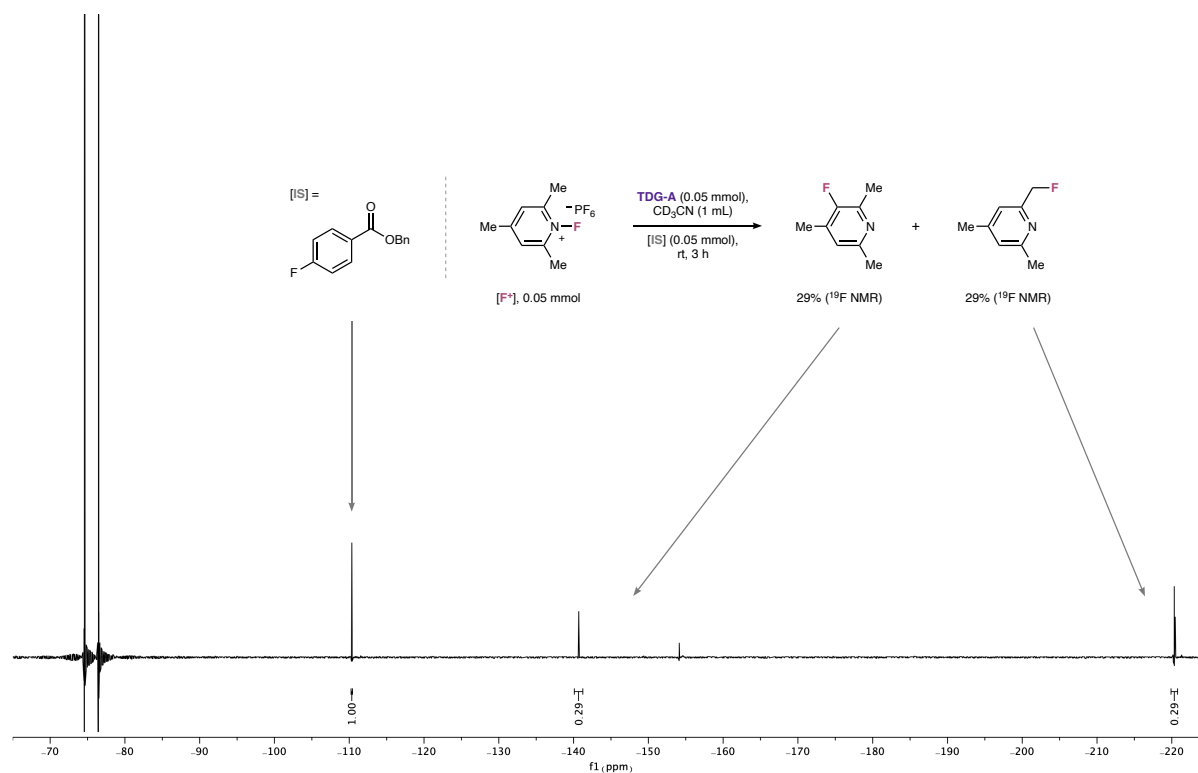


Figure S11. ^{19}F NMR spectrum of the reaction mixture.

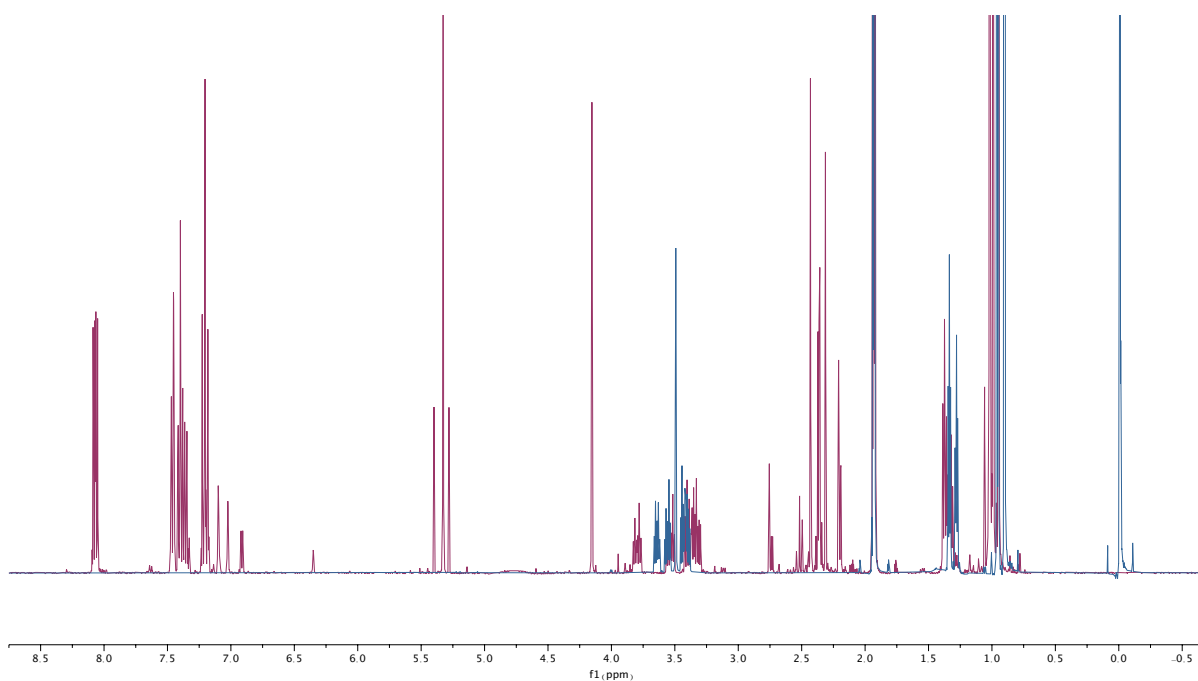


Figure S12. ^1H NMR spectrum of the reaction mixture (red) overlaid with ^1H NMR spectrum of pure TDG-A (blue).

Procedure for Investigating Potential Off-Cycle Species

A culture tube was charged with **TDG-A** (0.1 mmol), $\text{Pd}(\text{MeCN})_4(\text{BF}_4)_2$ (0.1 mmol), and CD_3CN (1 mL). The solution was stirred at 35 °C for 1 hour, then analyzed by ^1H NMR

Spectral Data

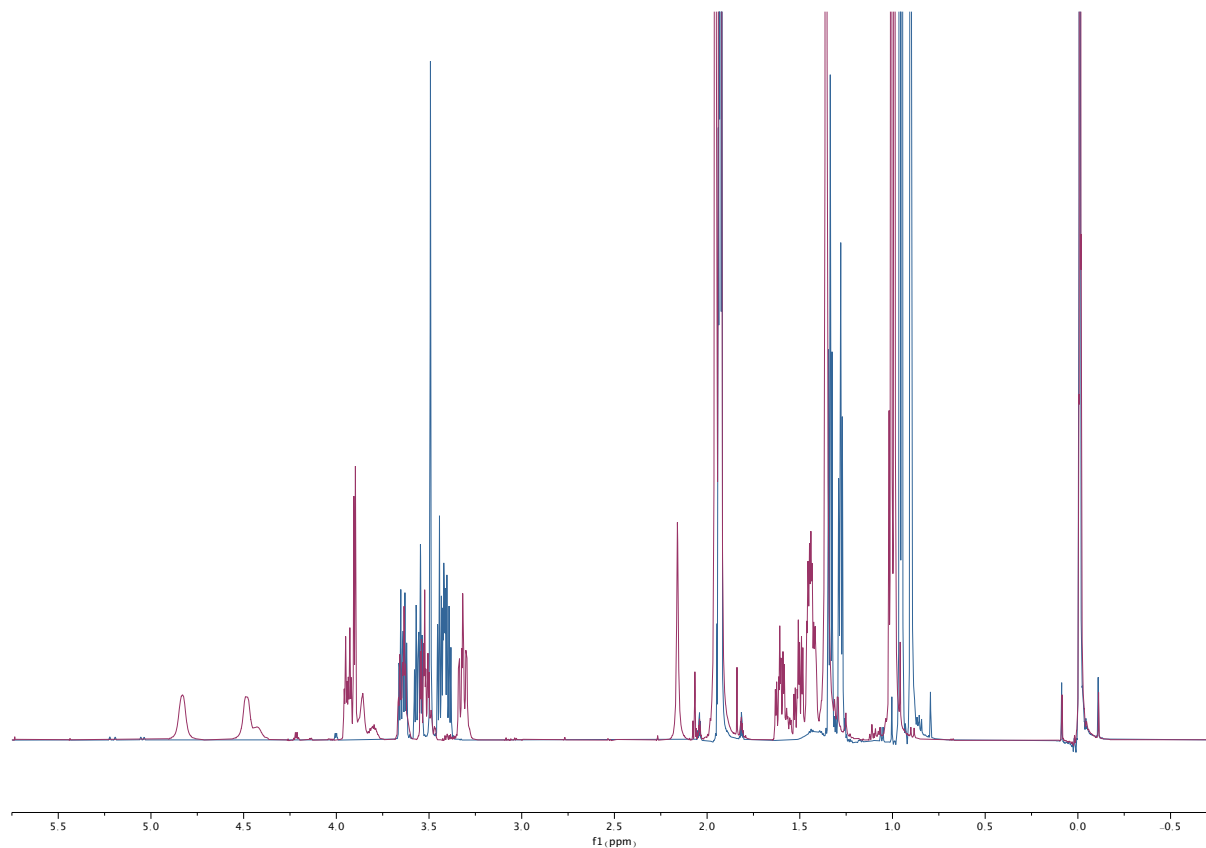
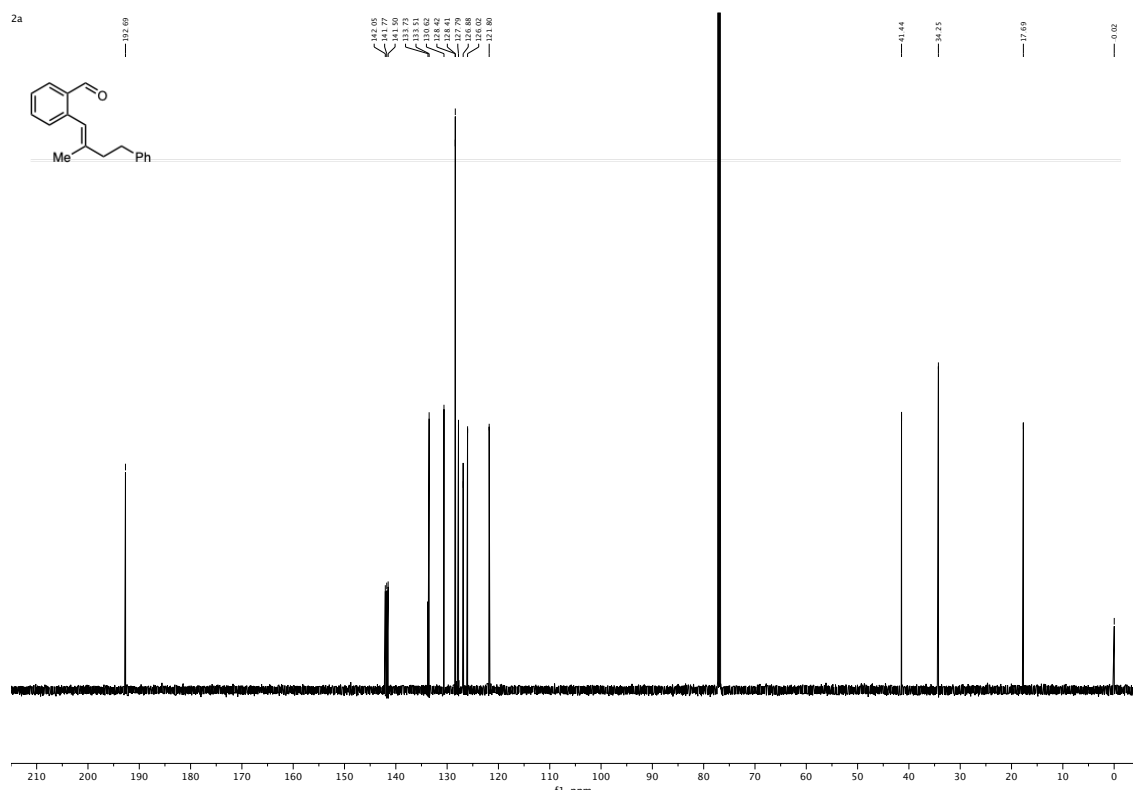
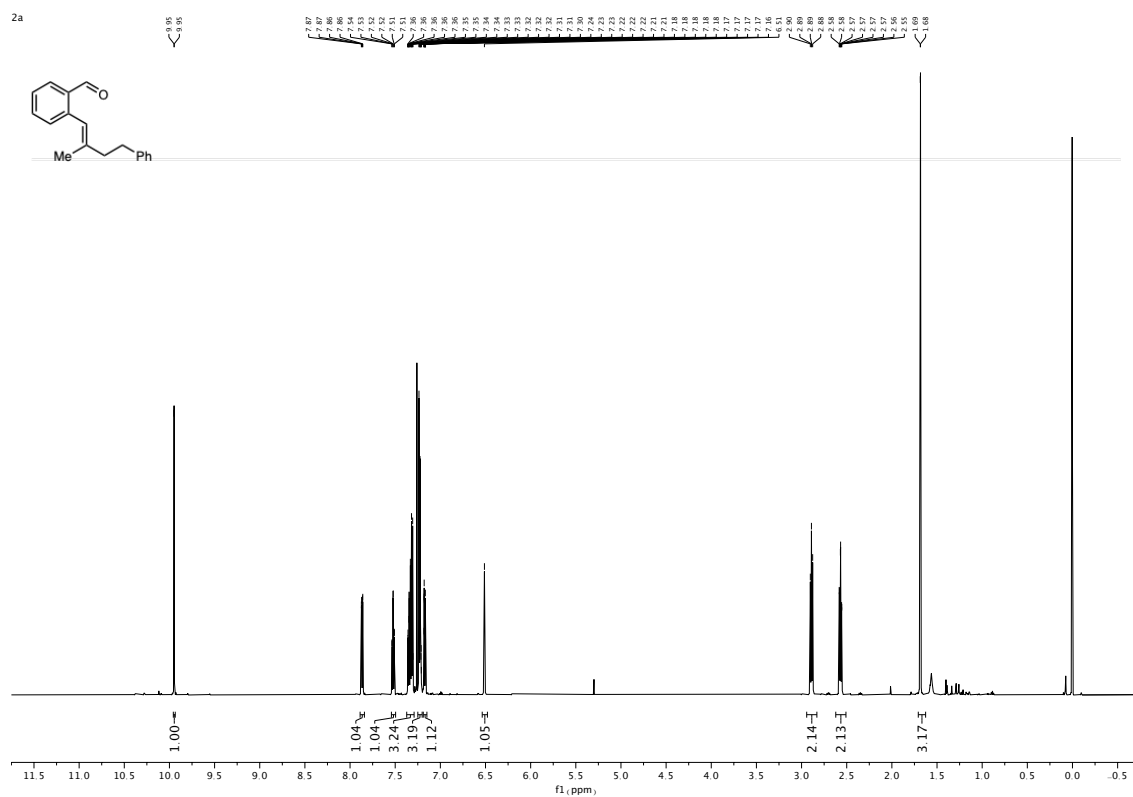
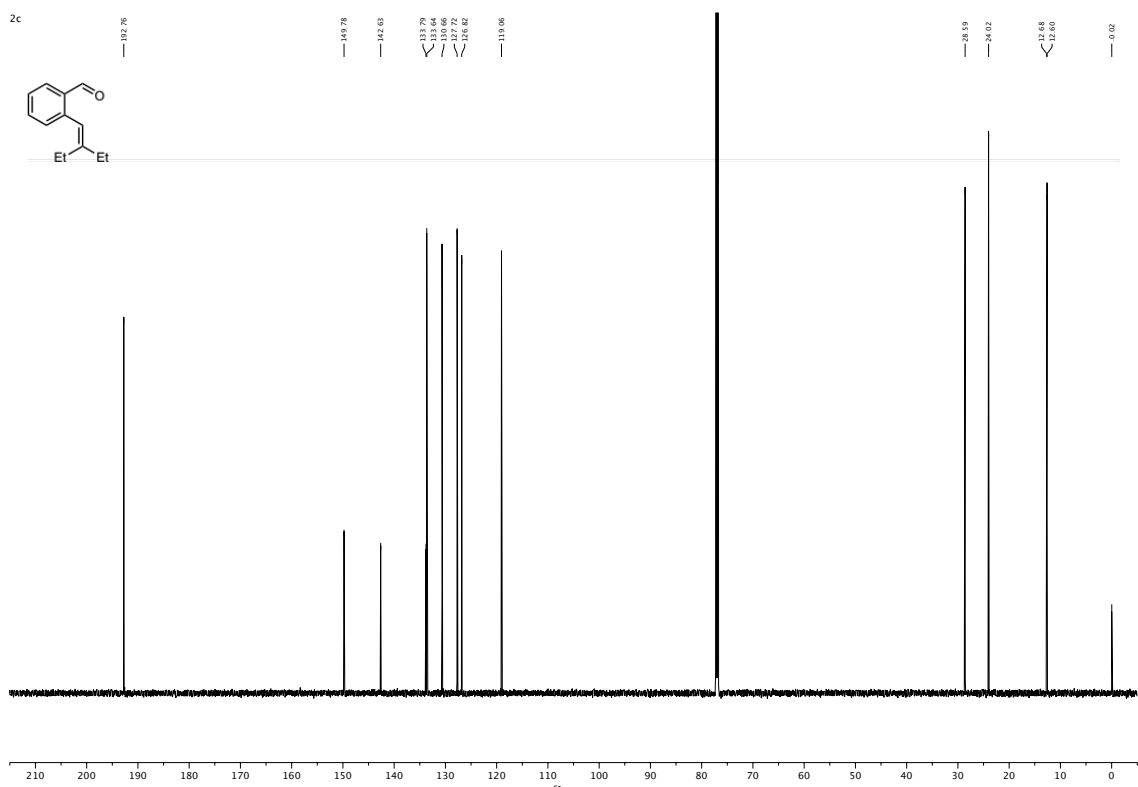
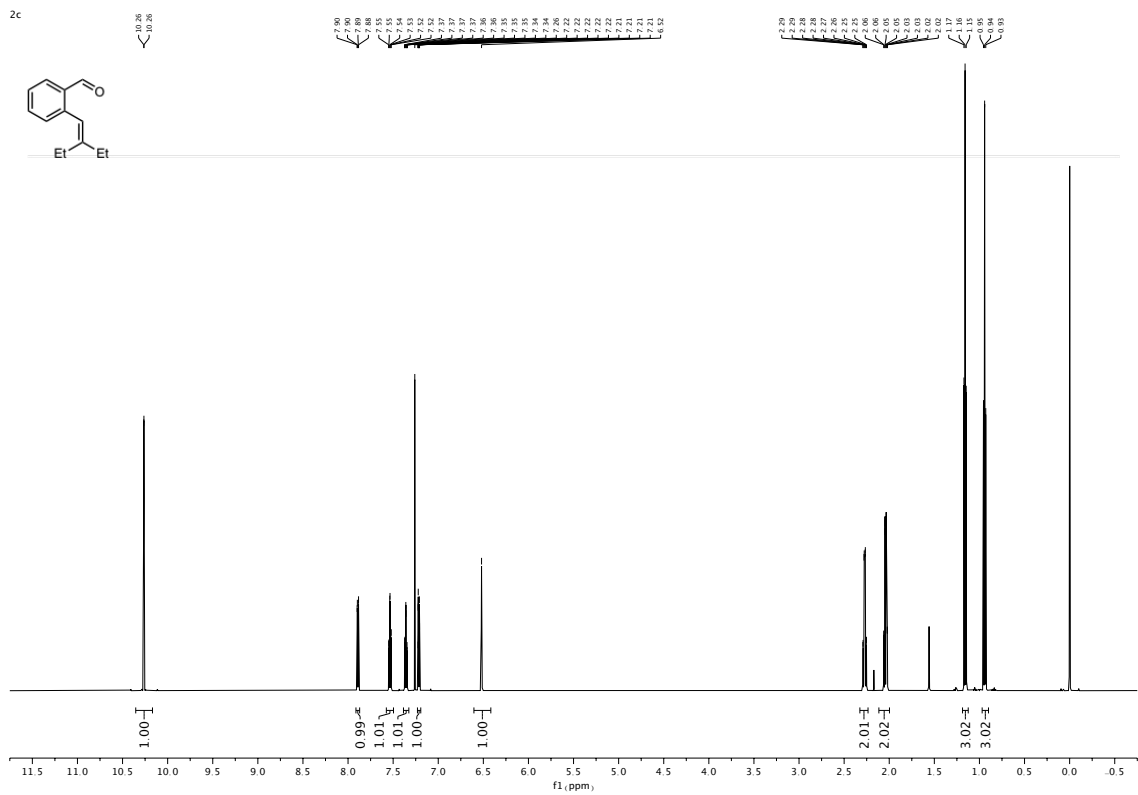
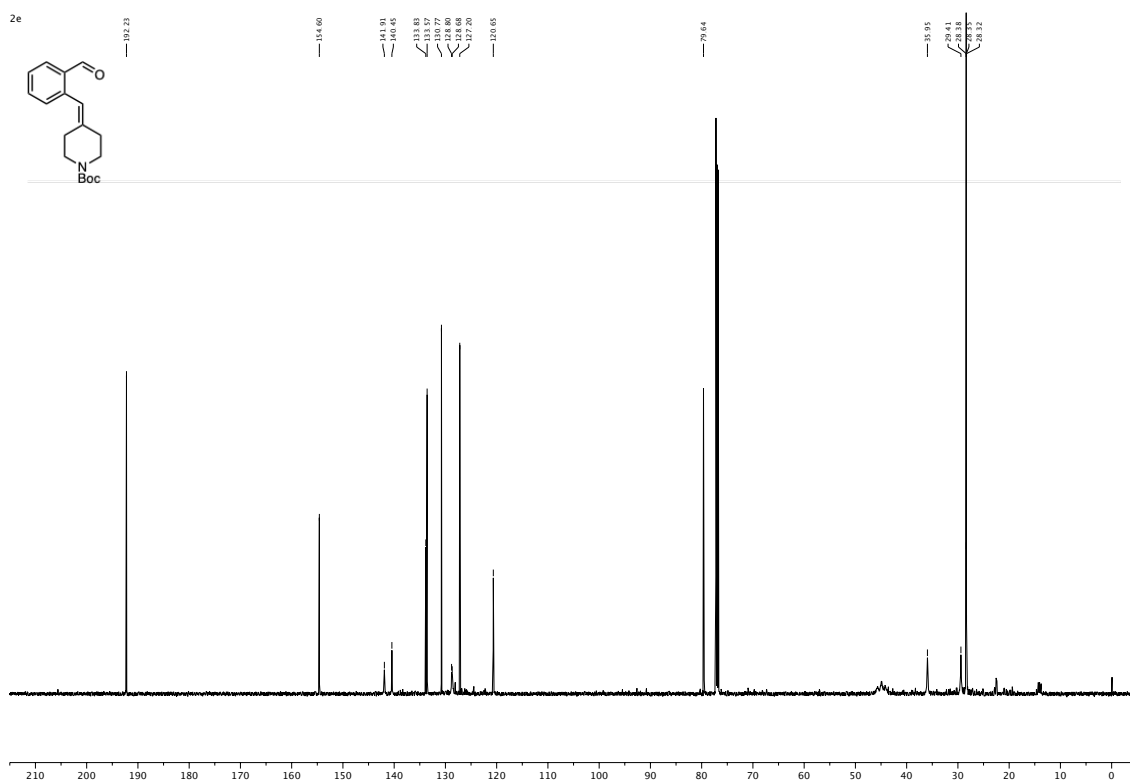
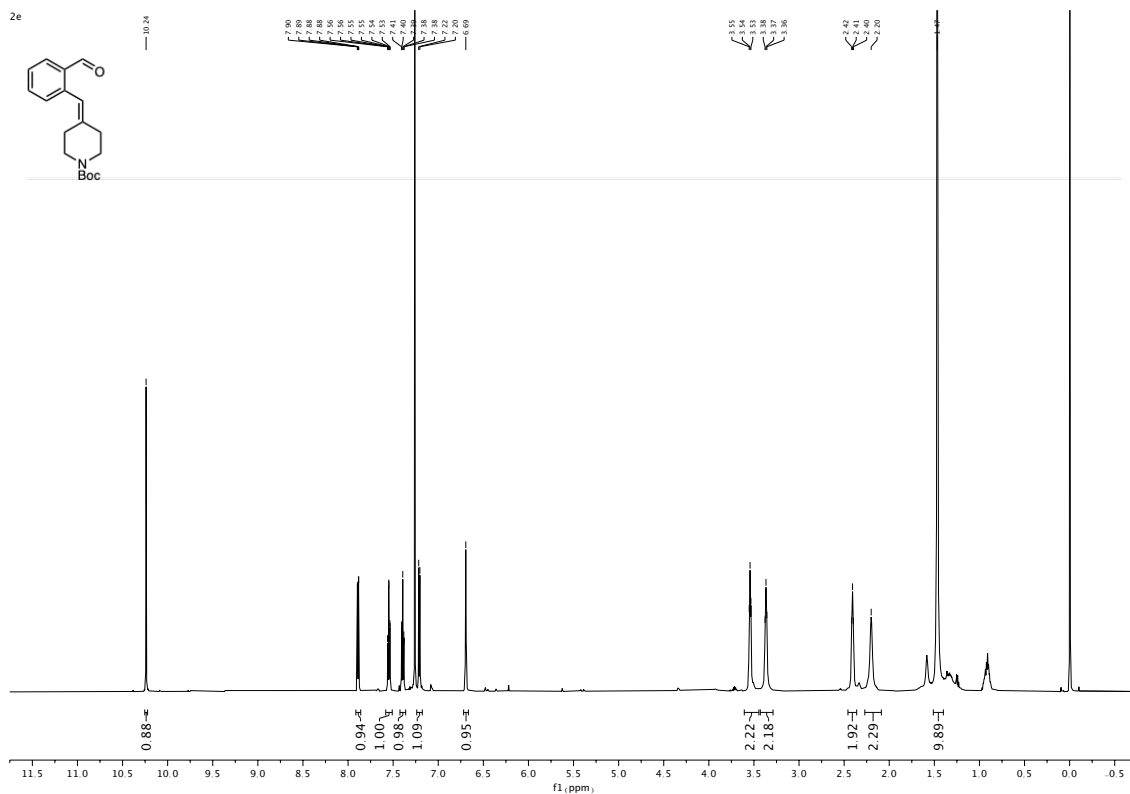


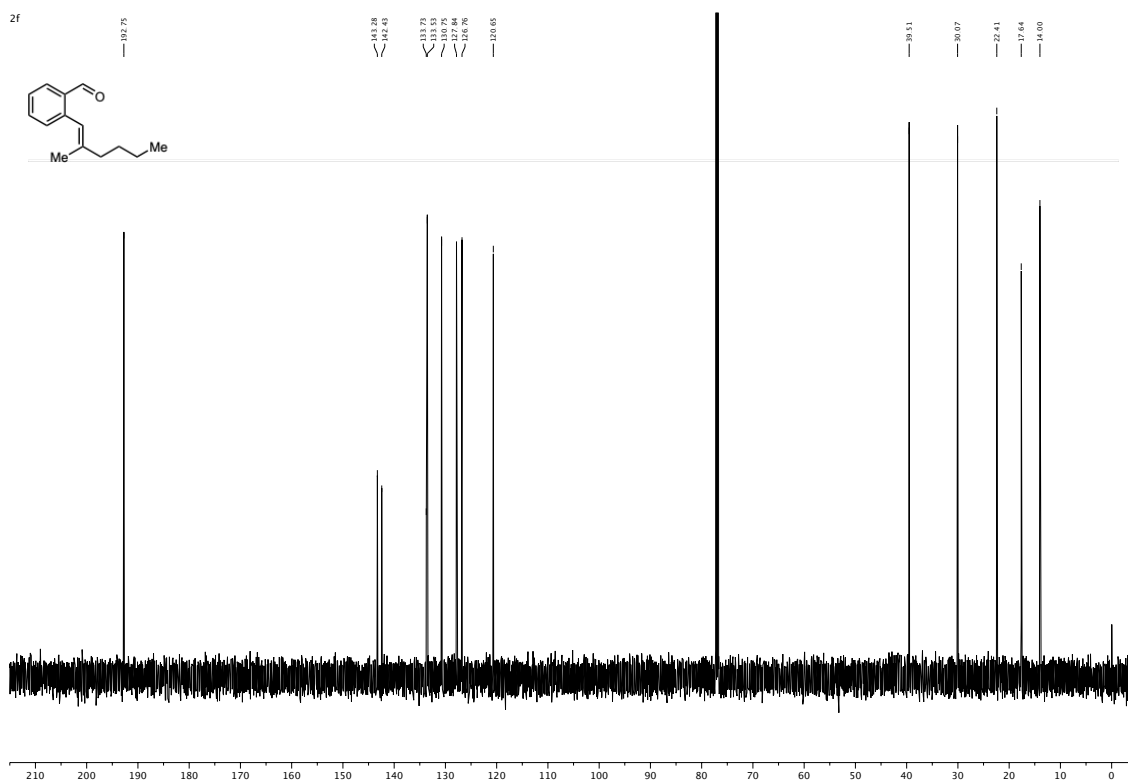
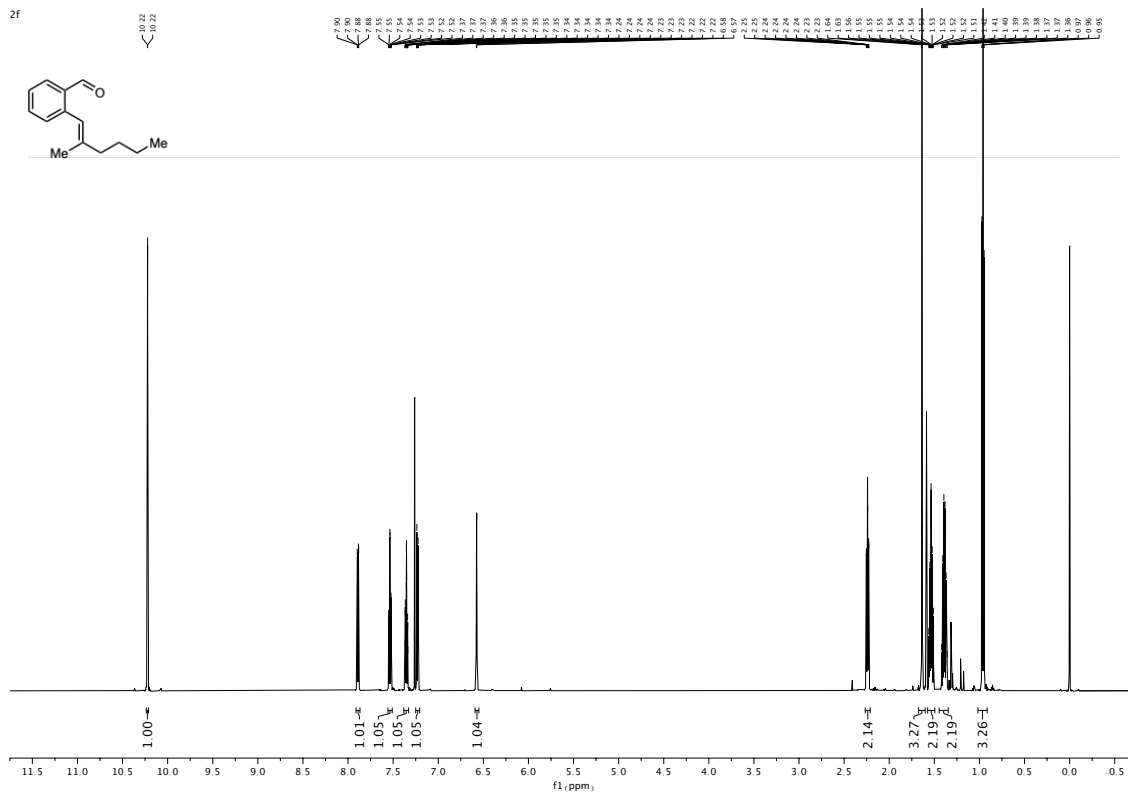
Figure S13. ^1H NMR spectrum of the reaction mixture (red) overlaid with ^1H NMR spectrum of pure **TDG-A** (blue).

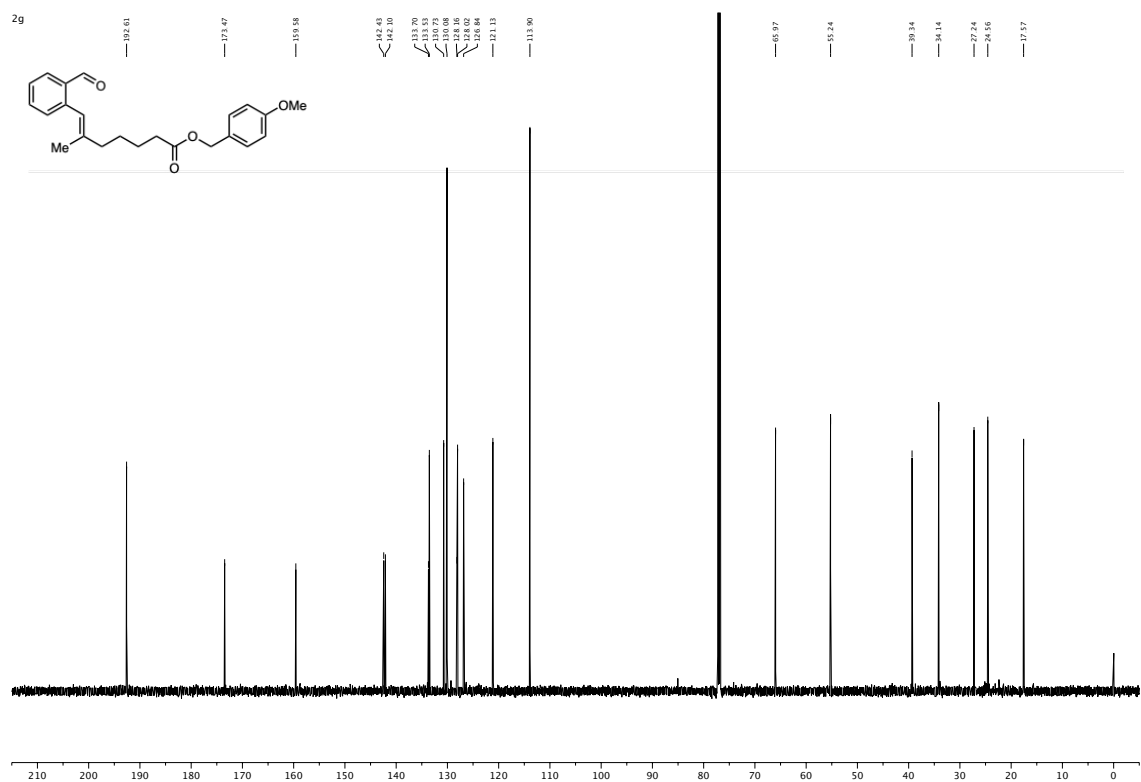
NMR Spectra.

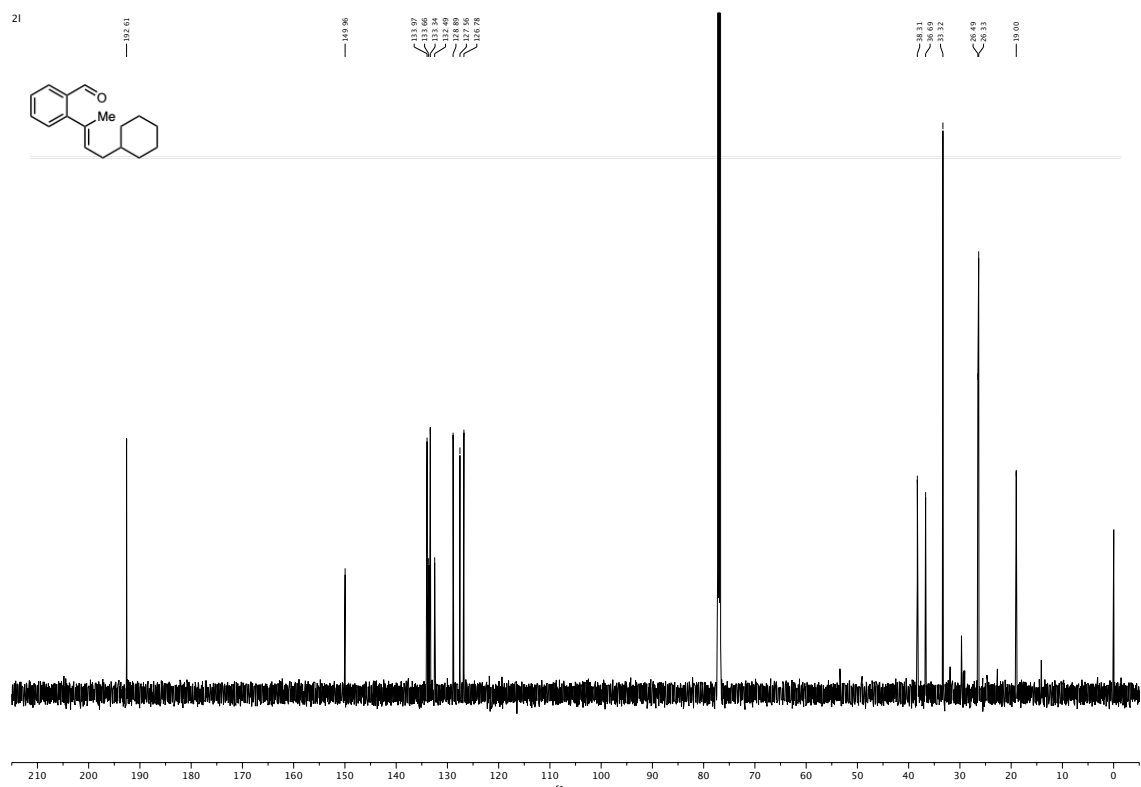
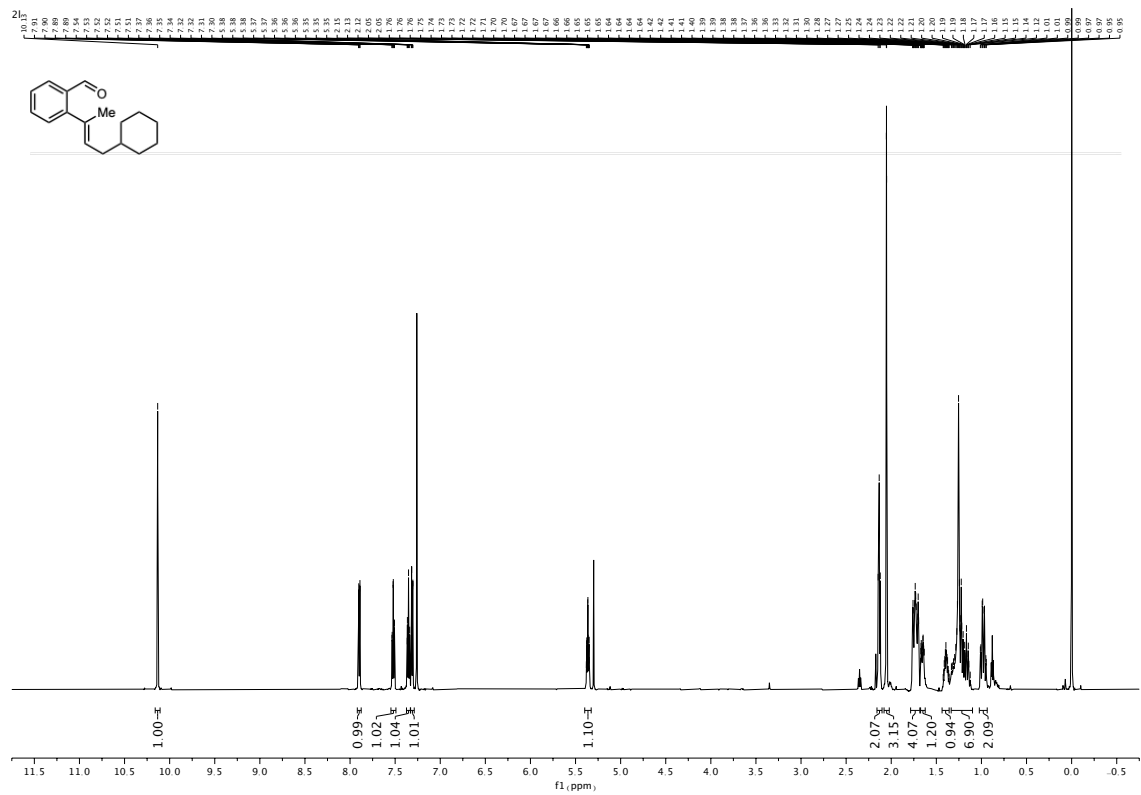


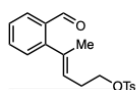
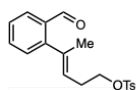


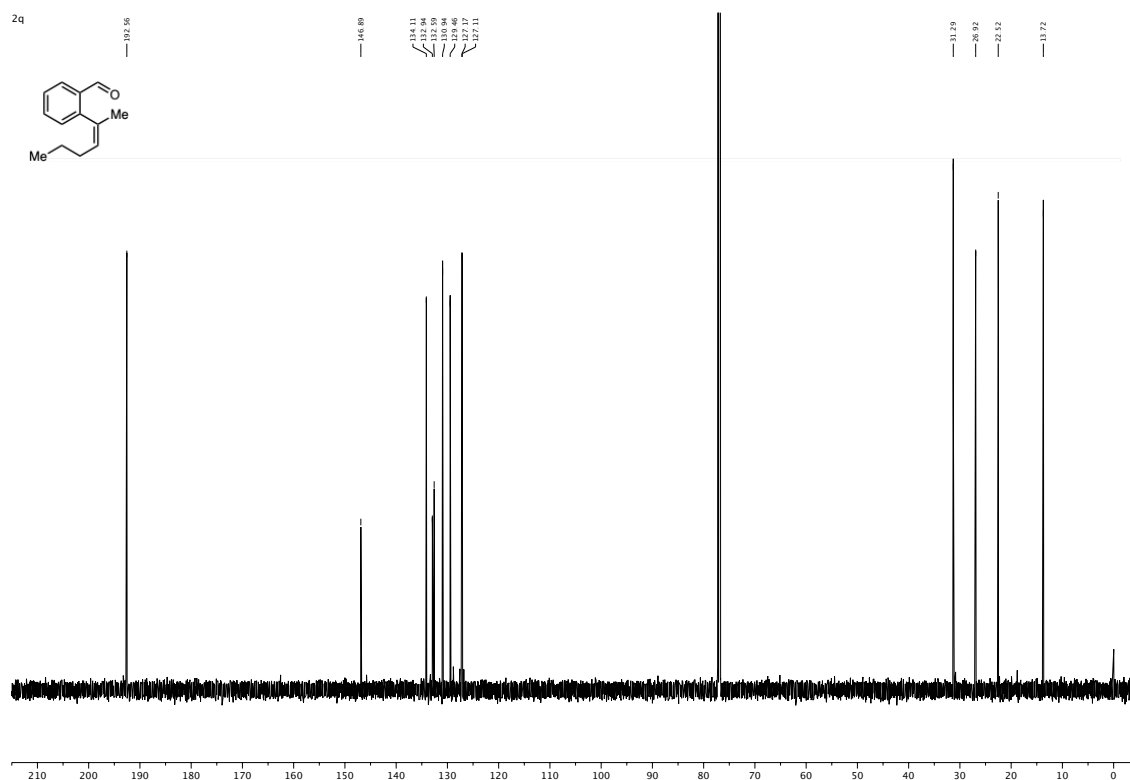
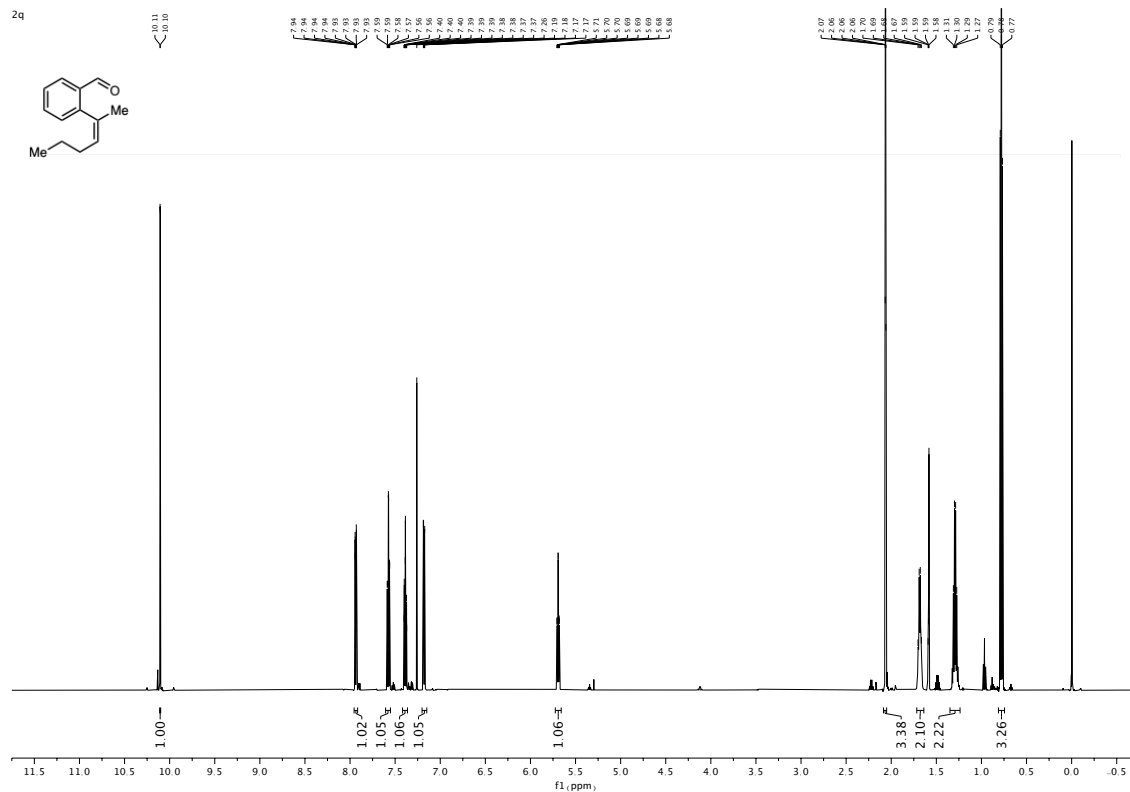


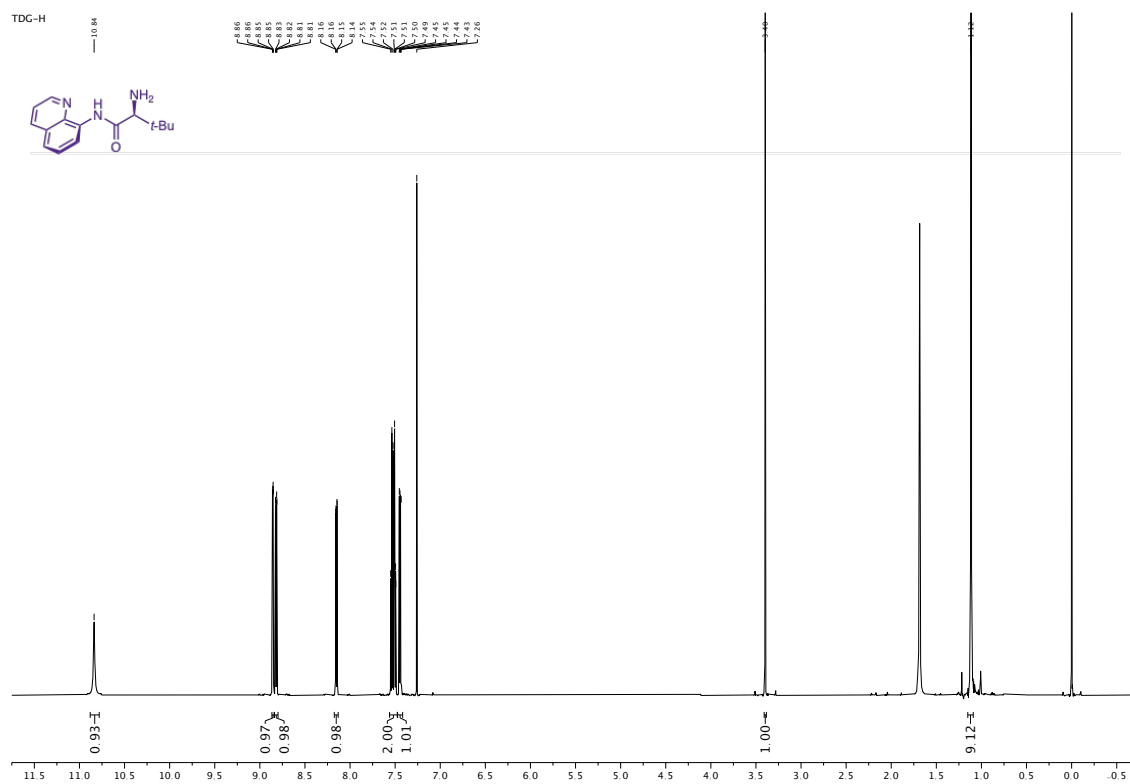
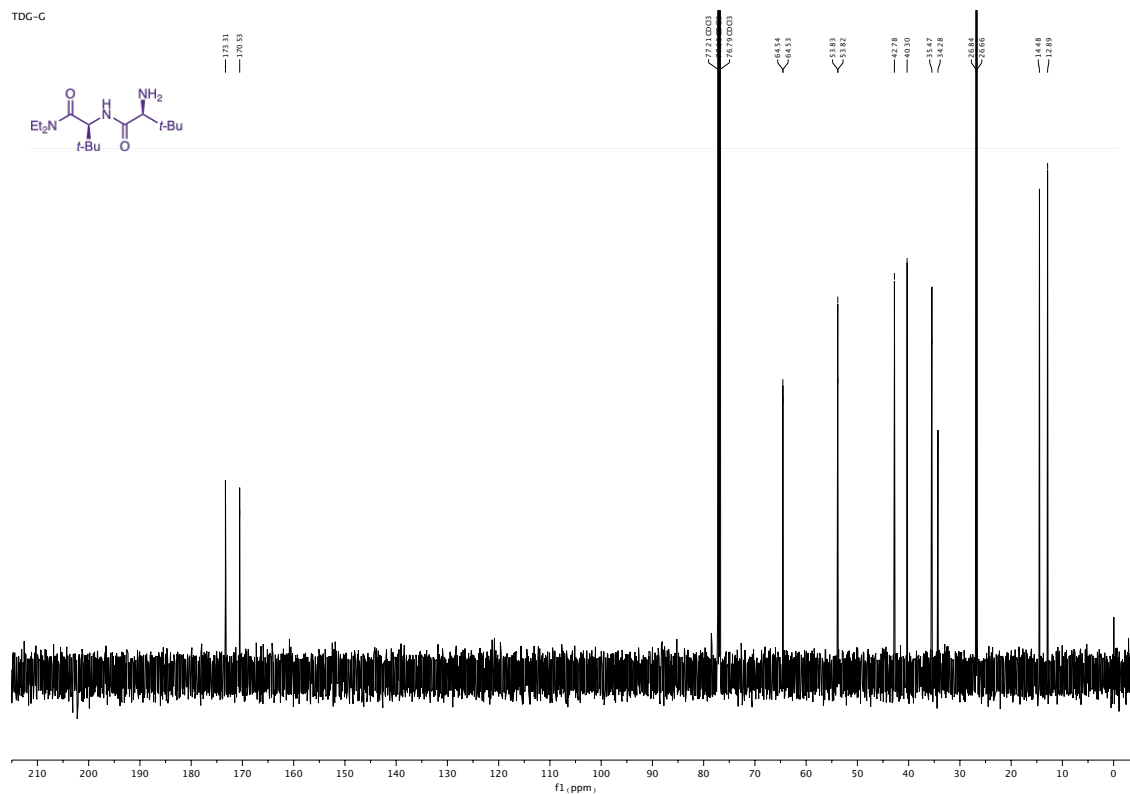


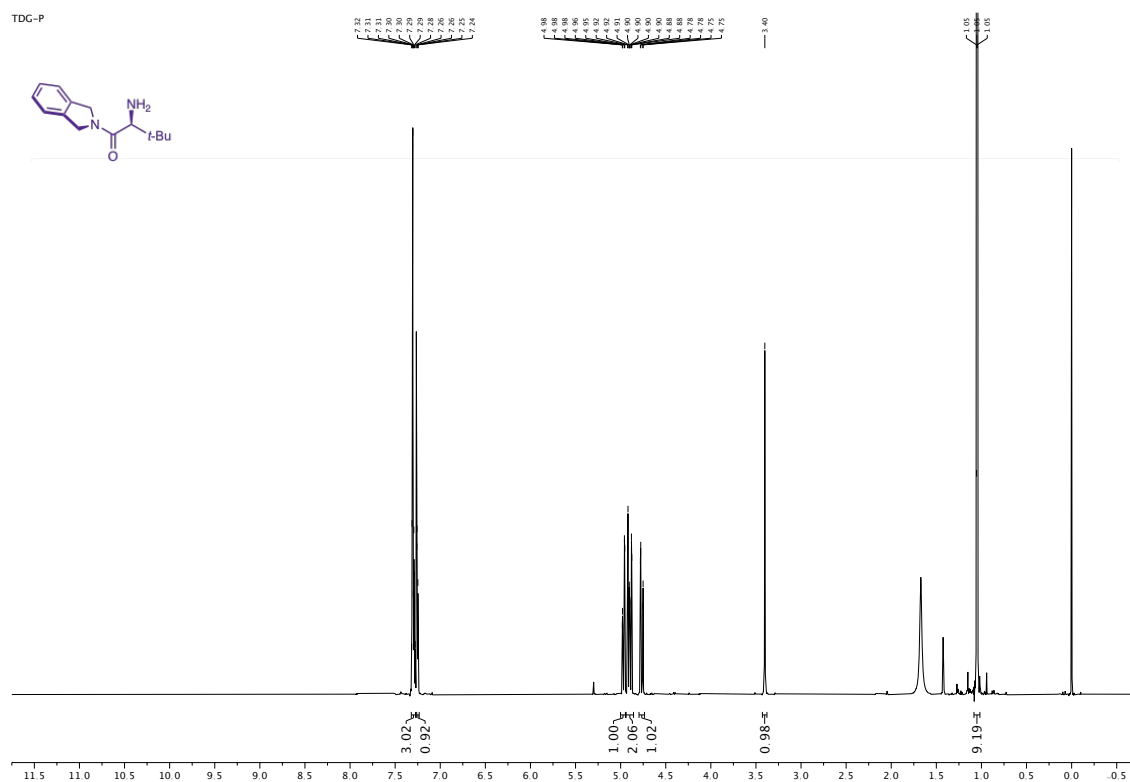
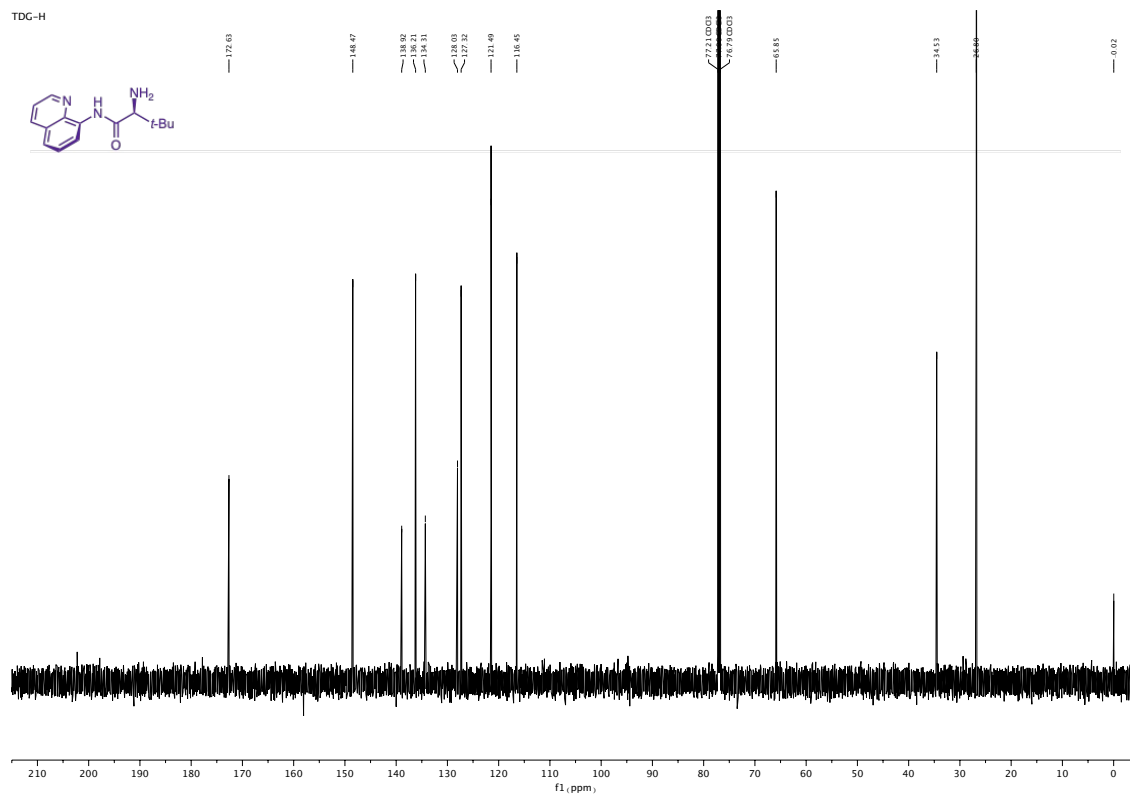


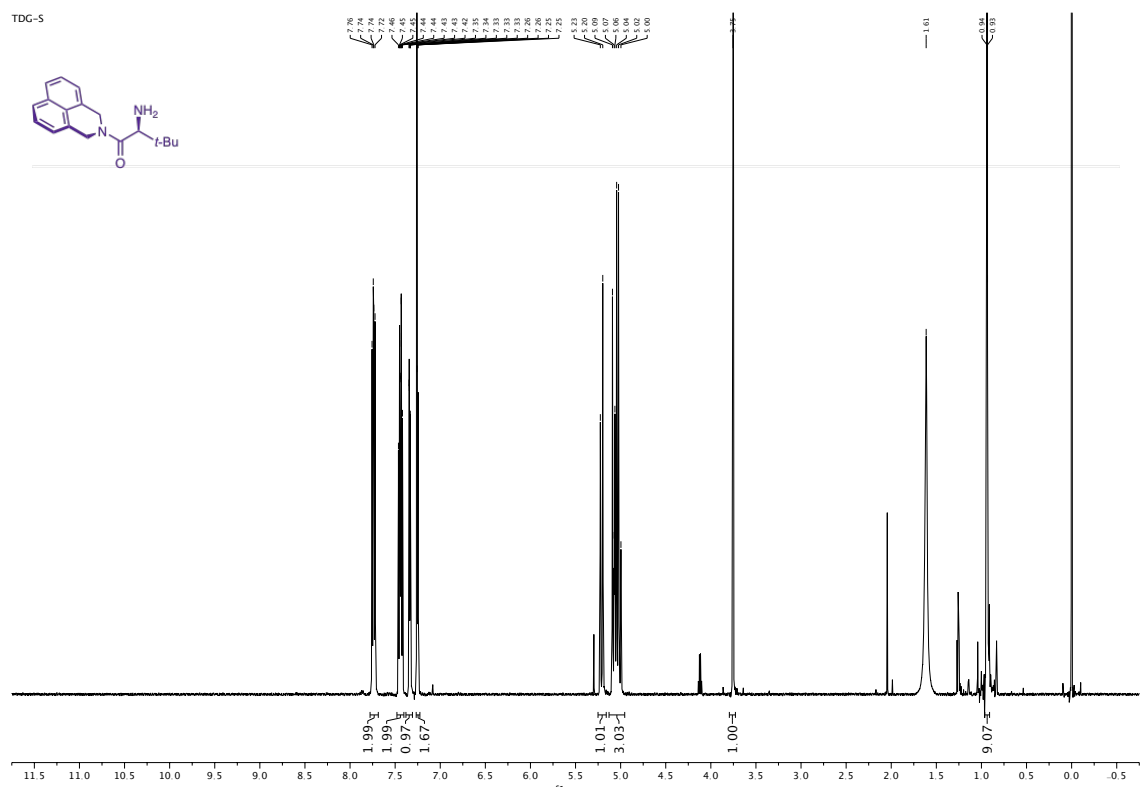
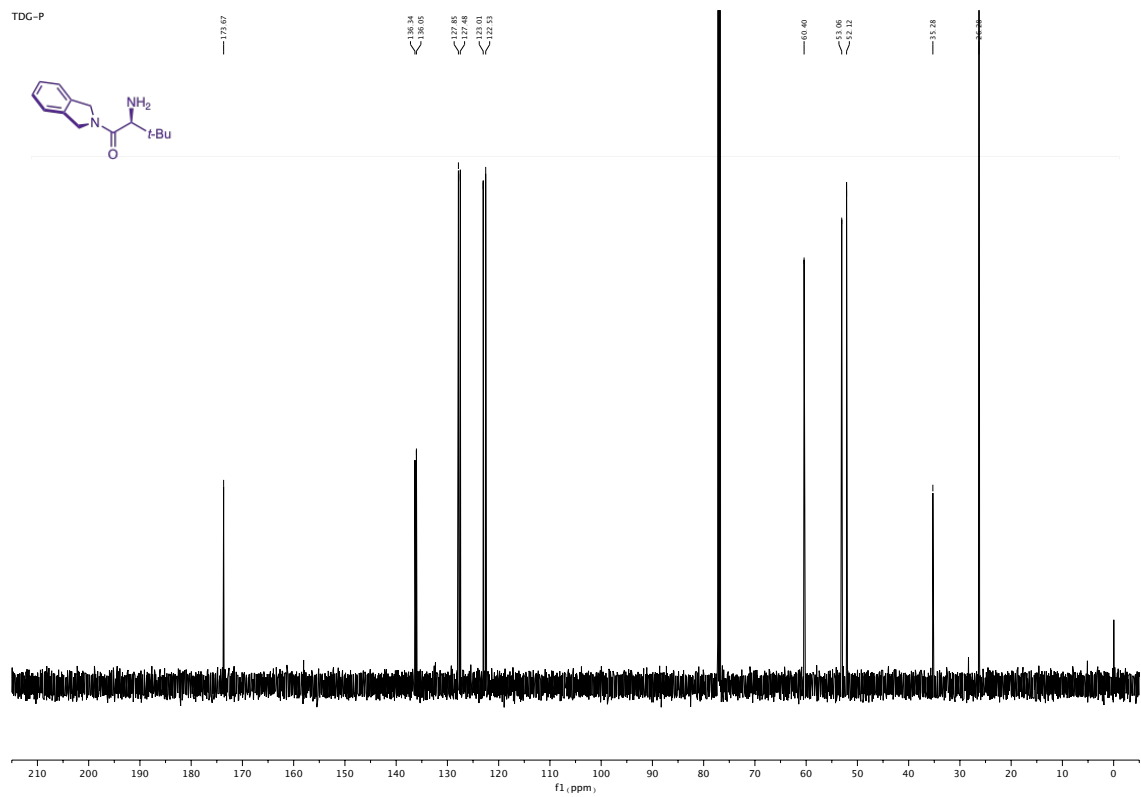


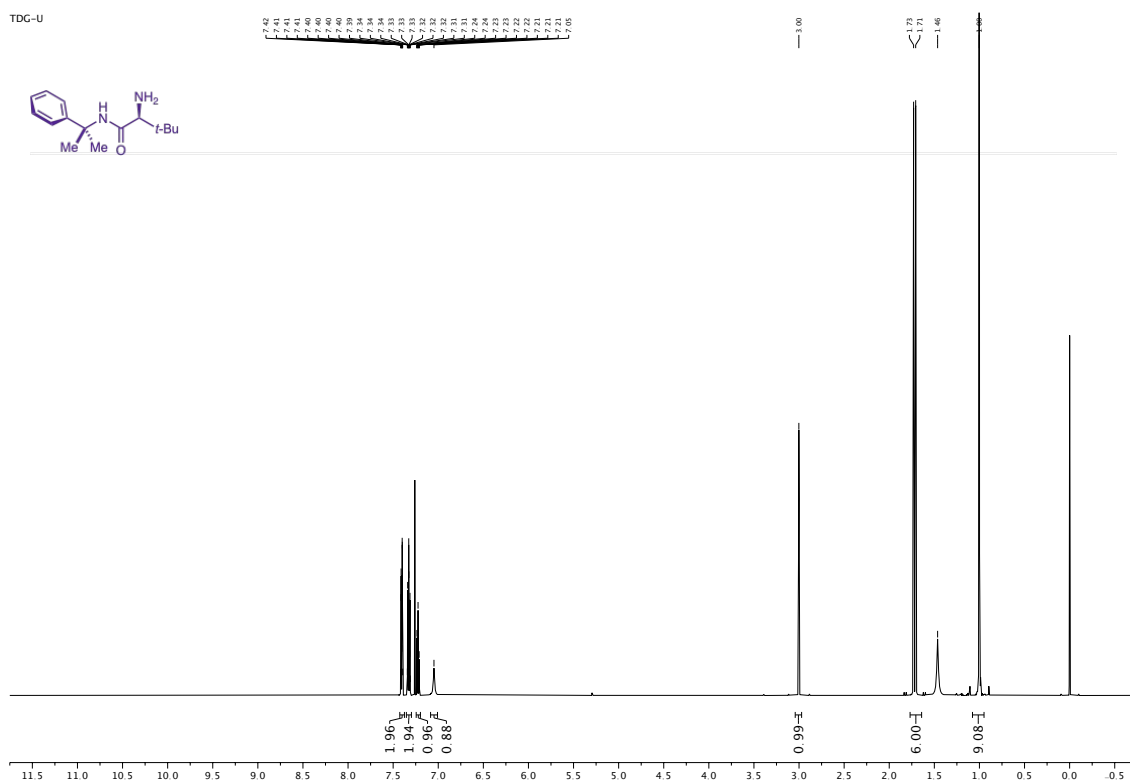
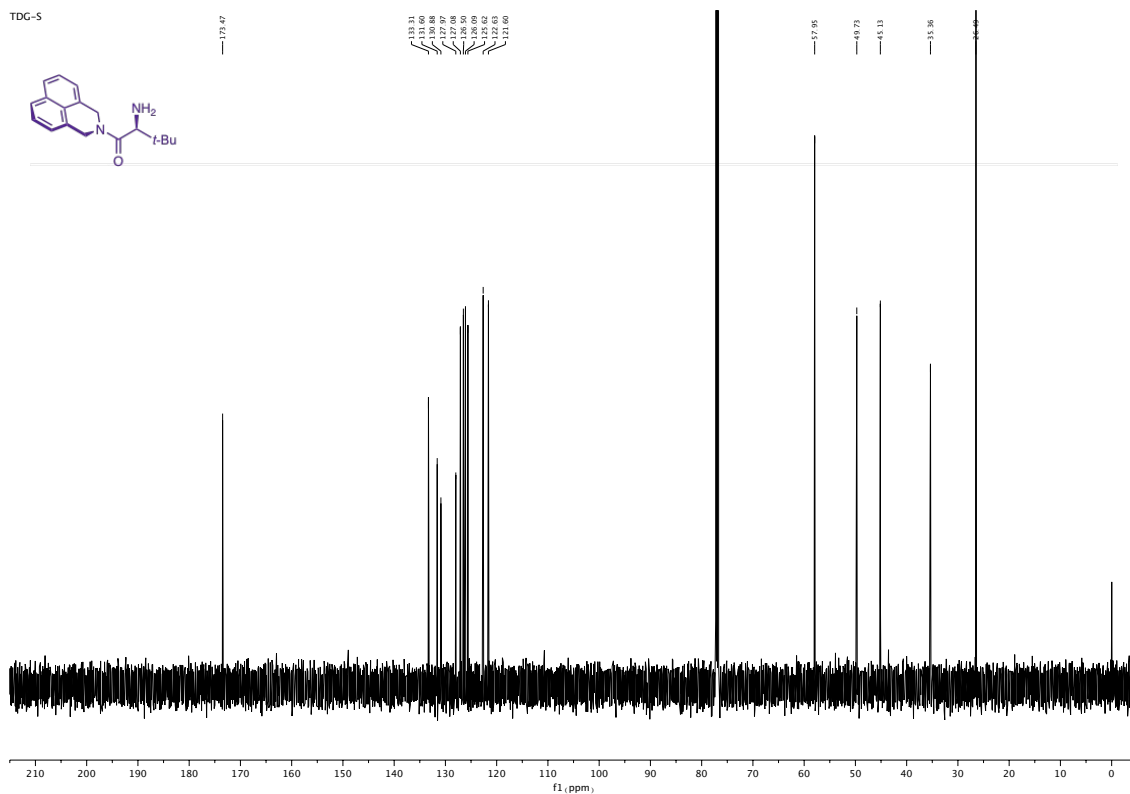


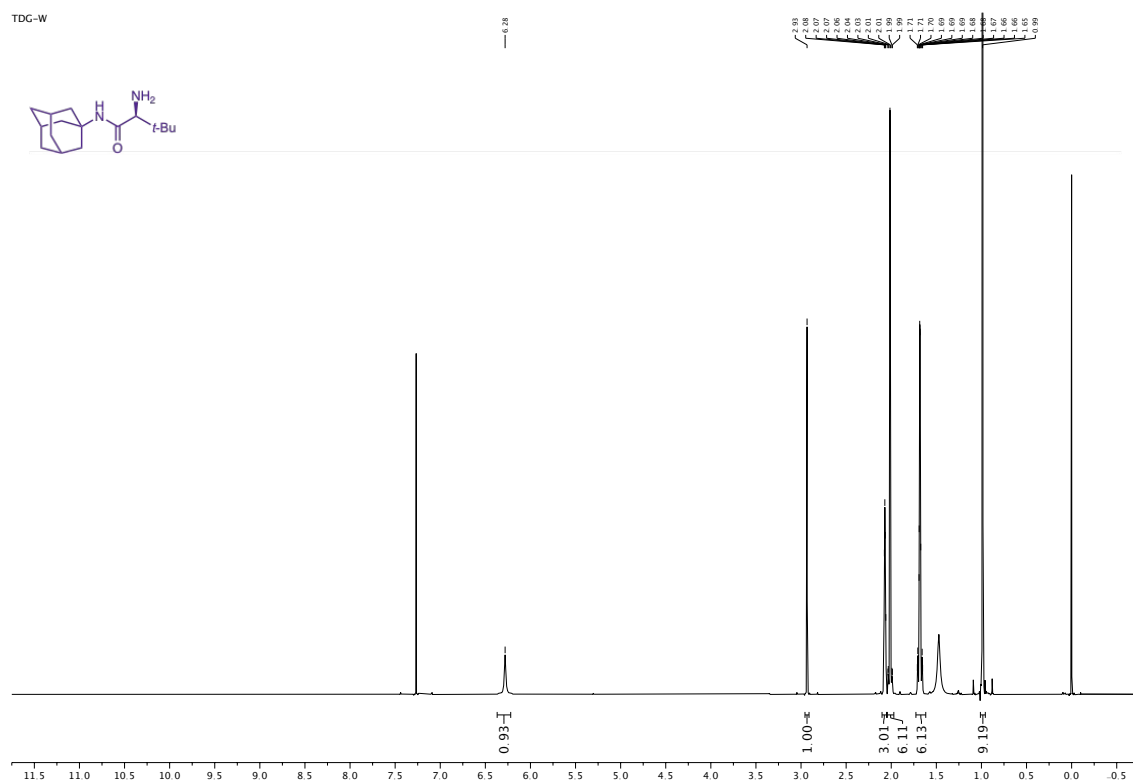
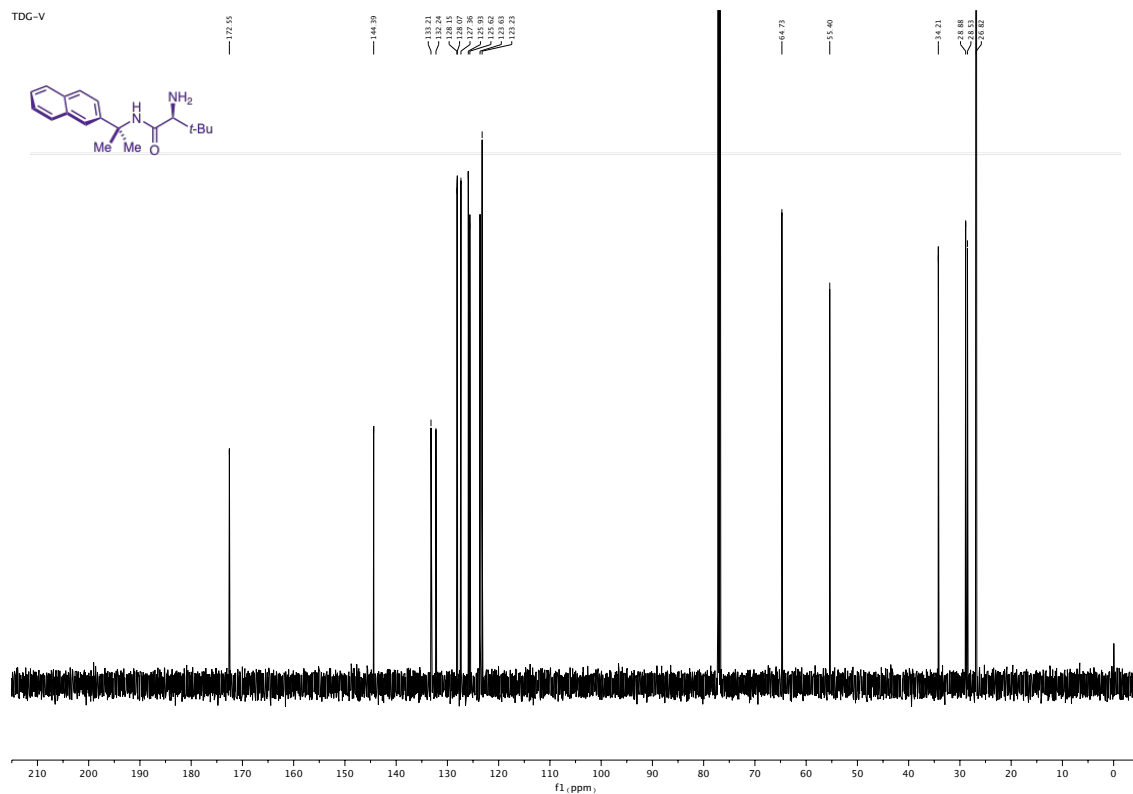


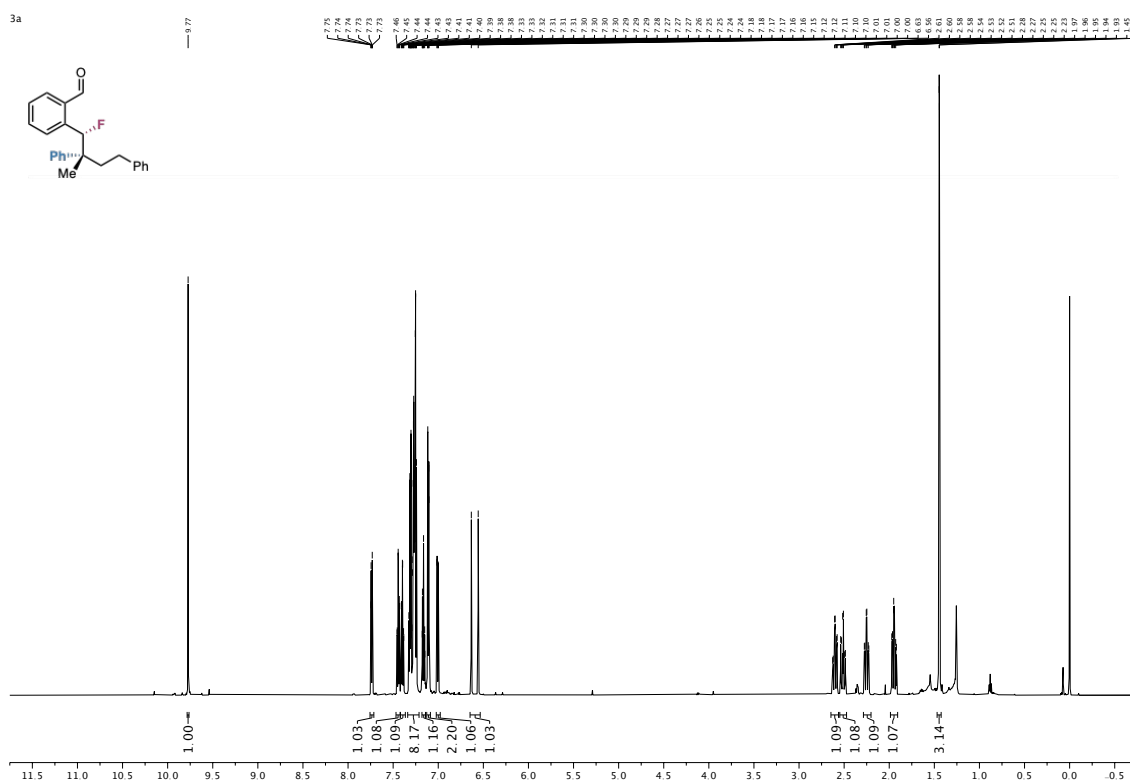


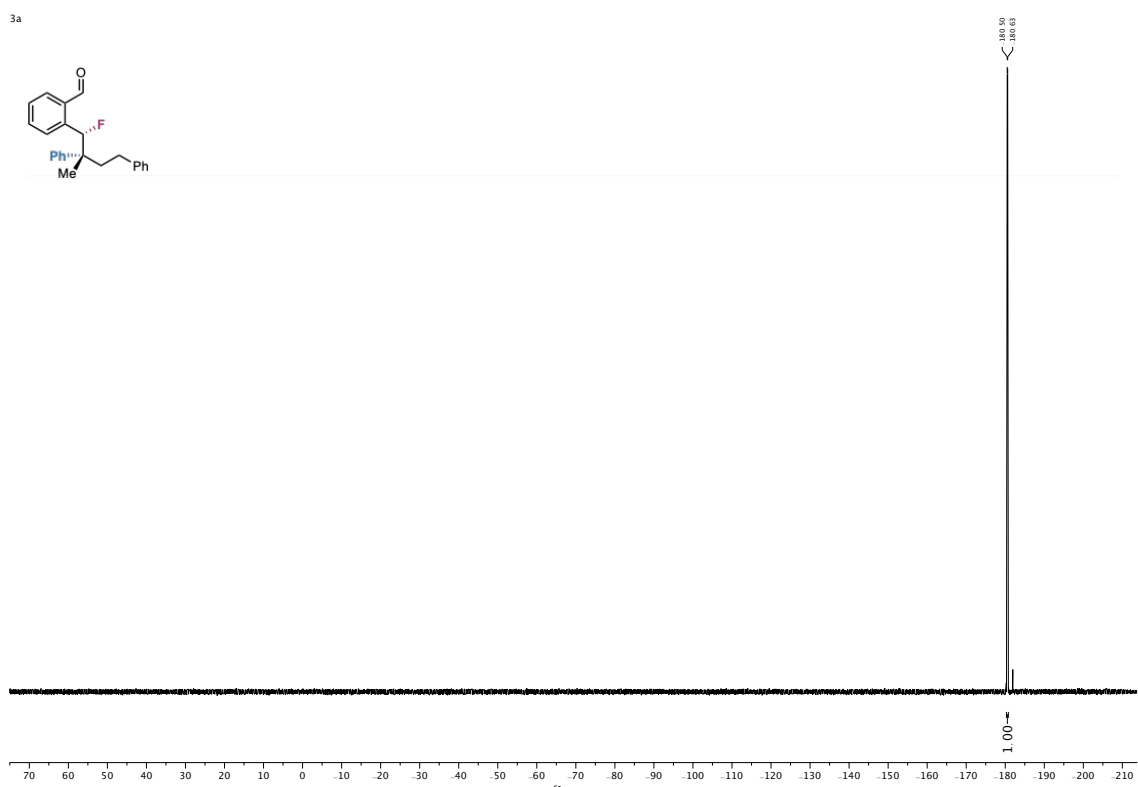
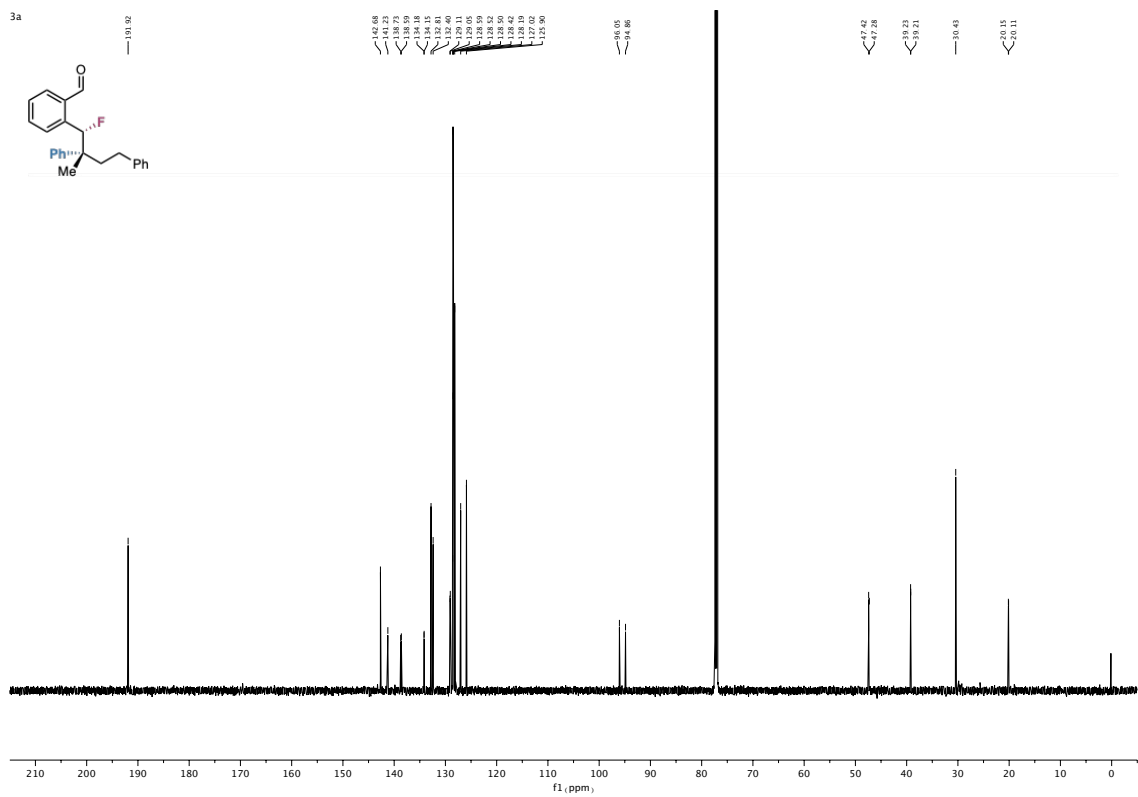


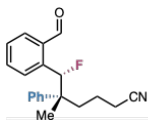
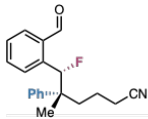




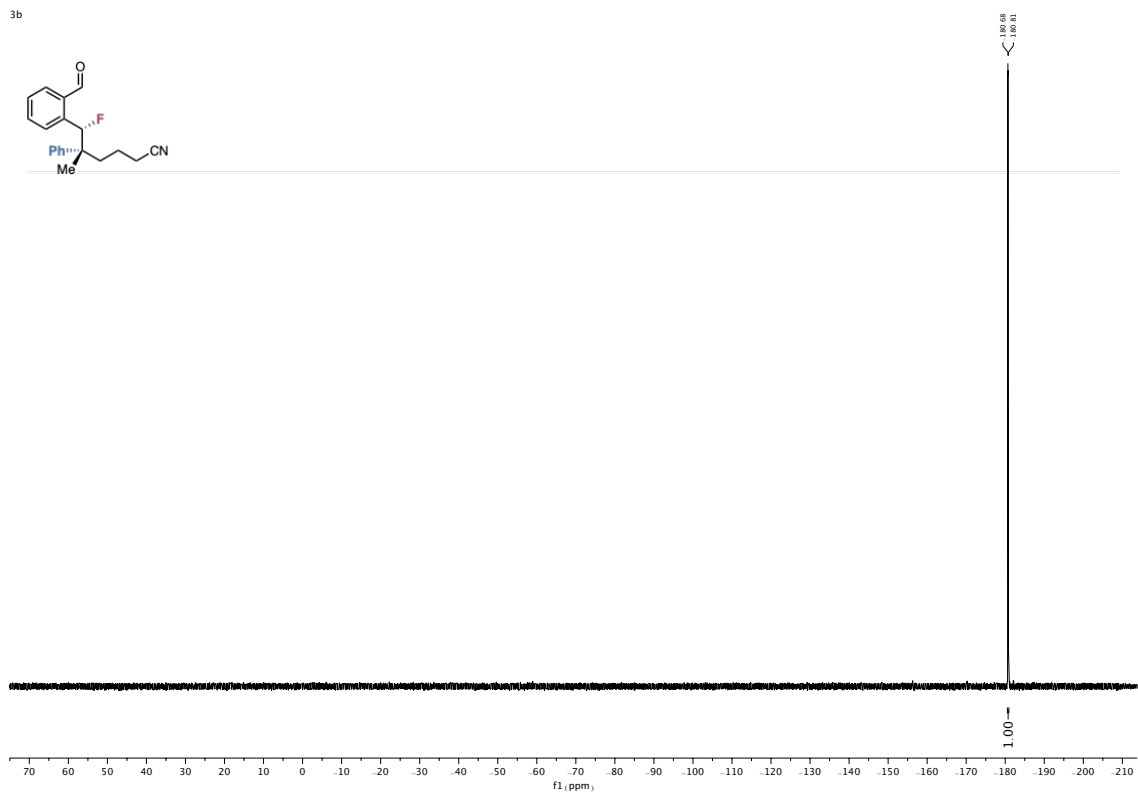


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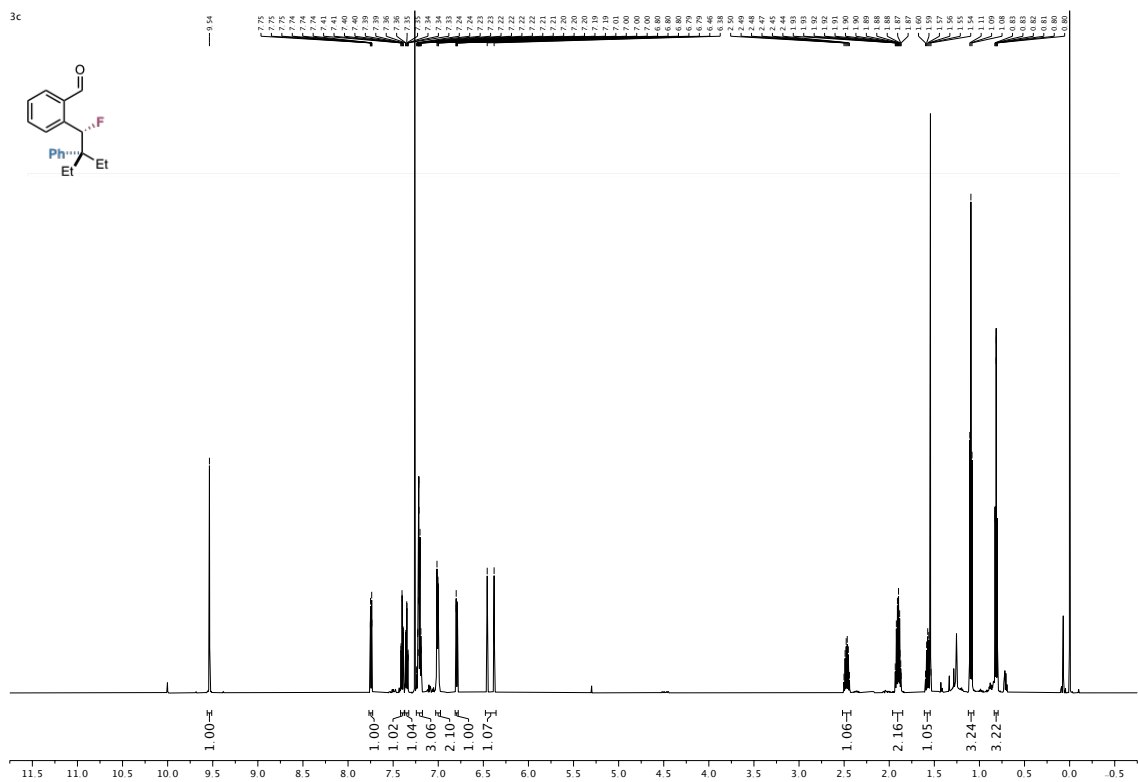


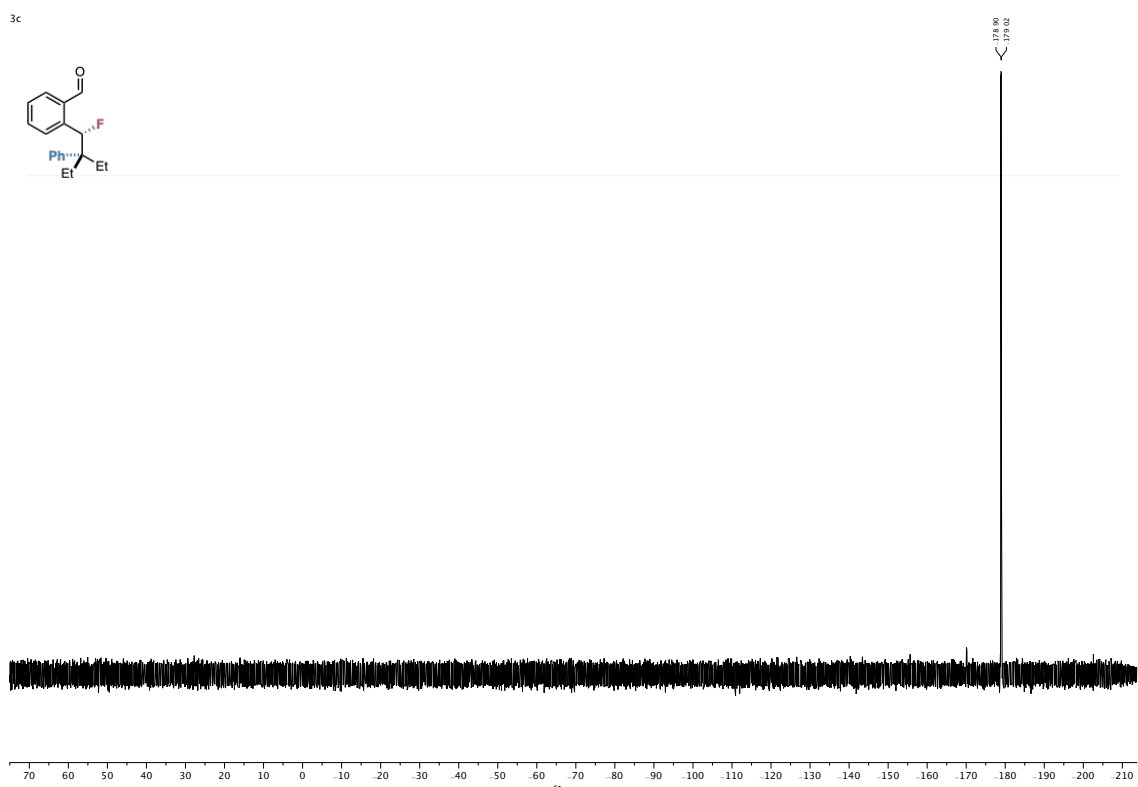
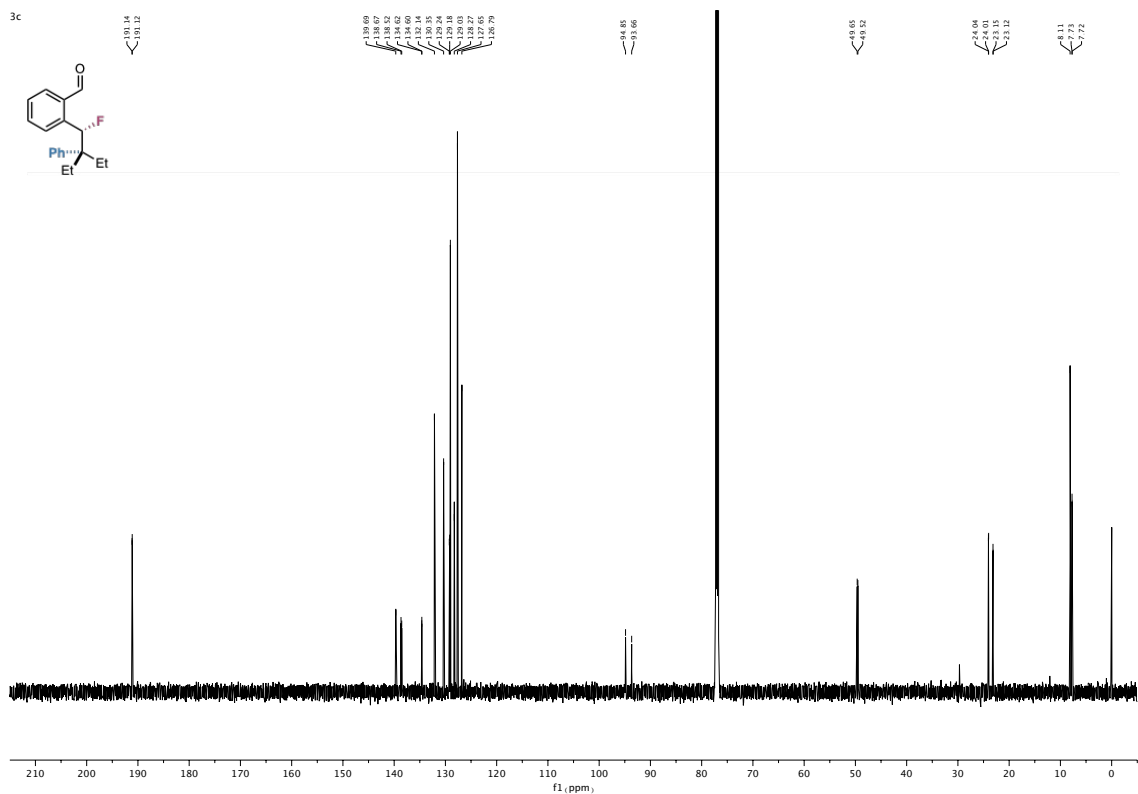


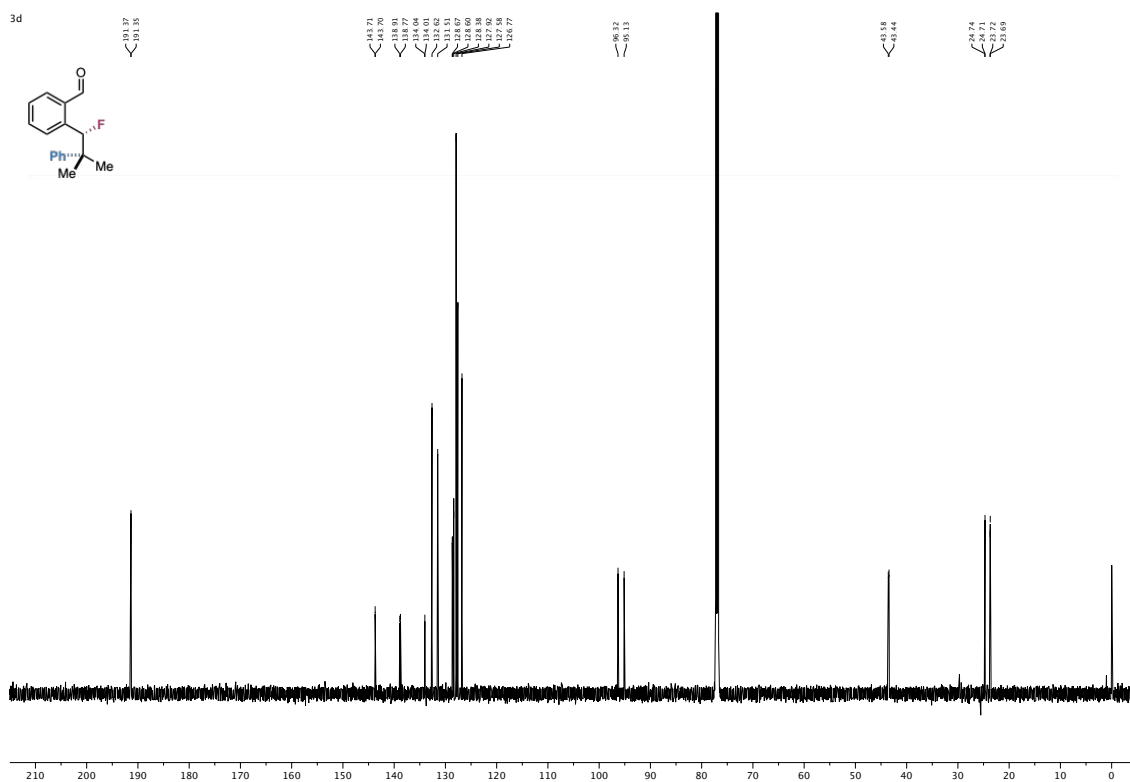
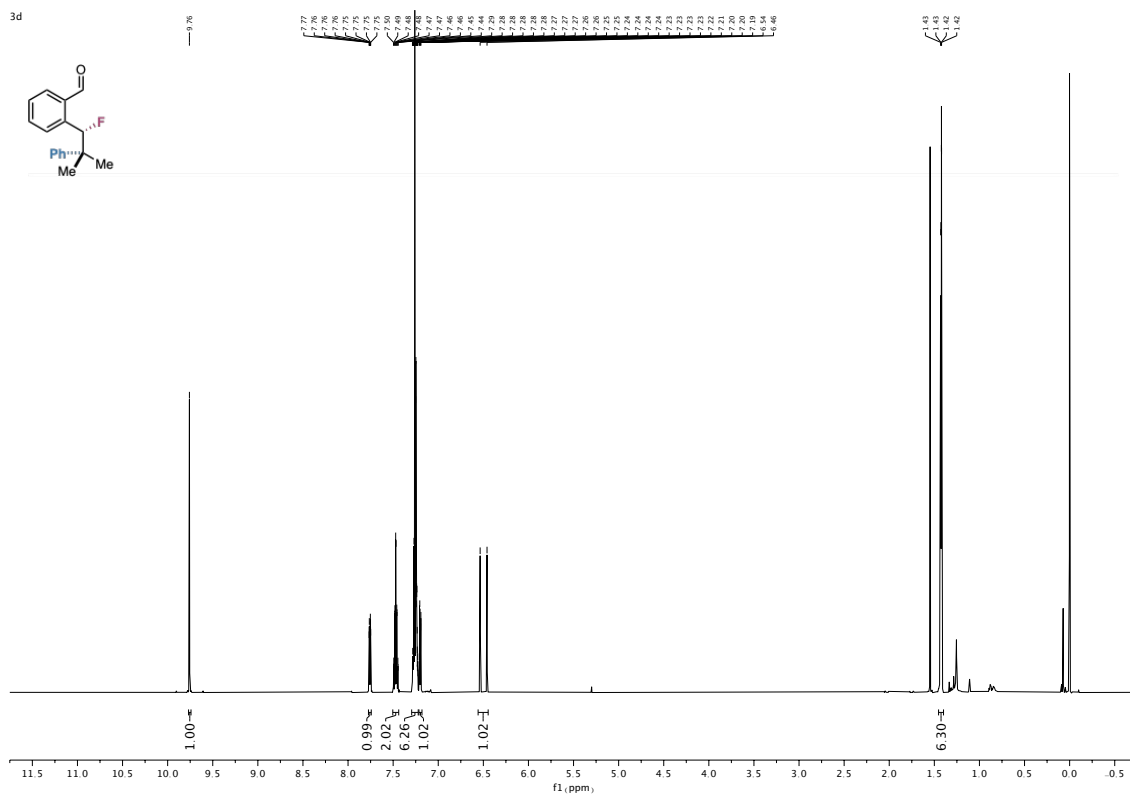
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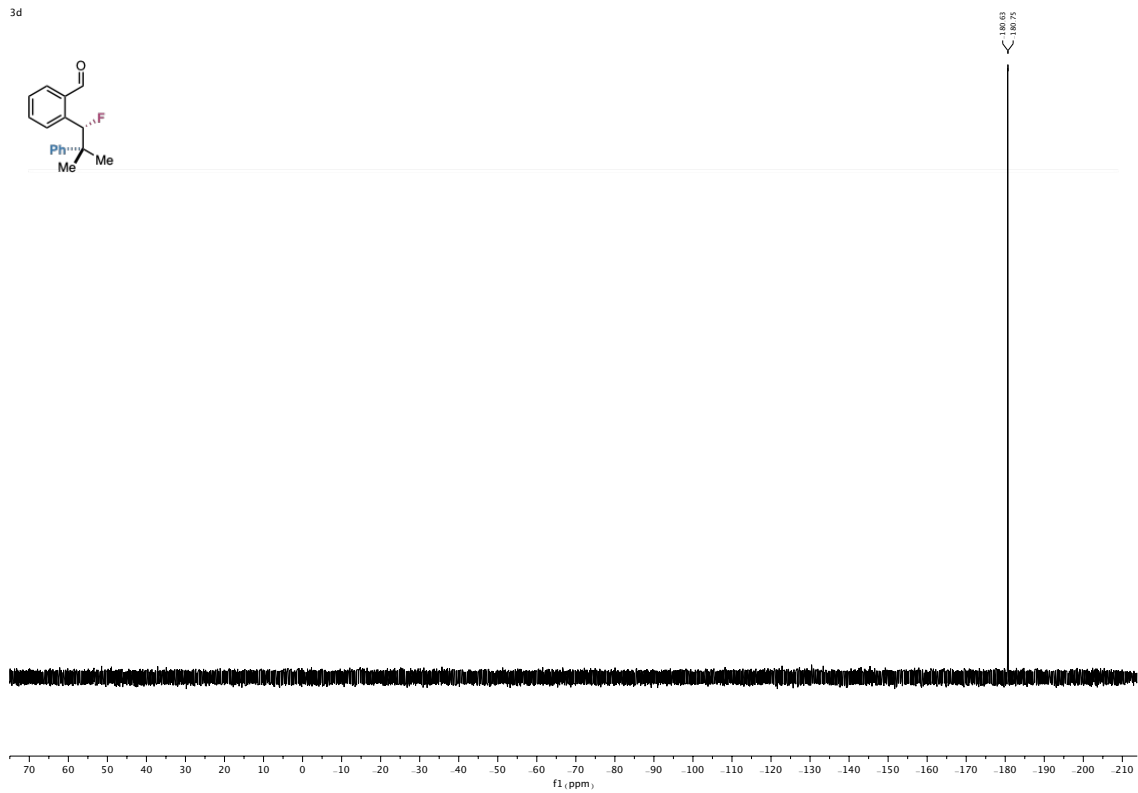
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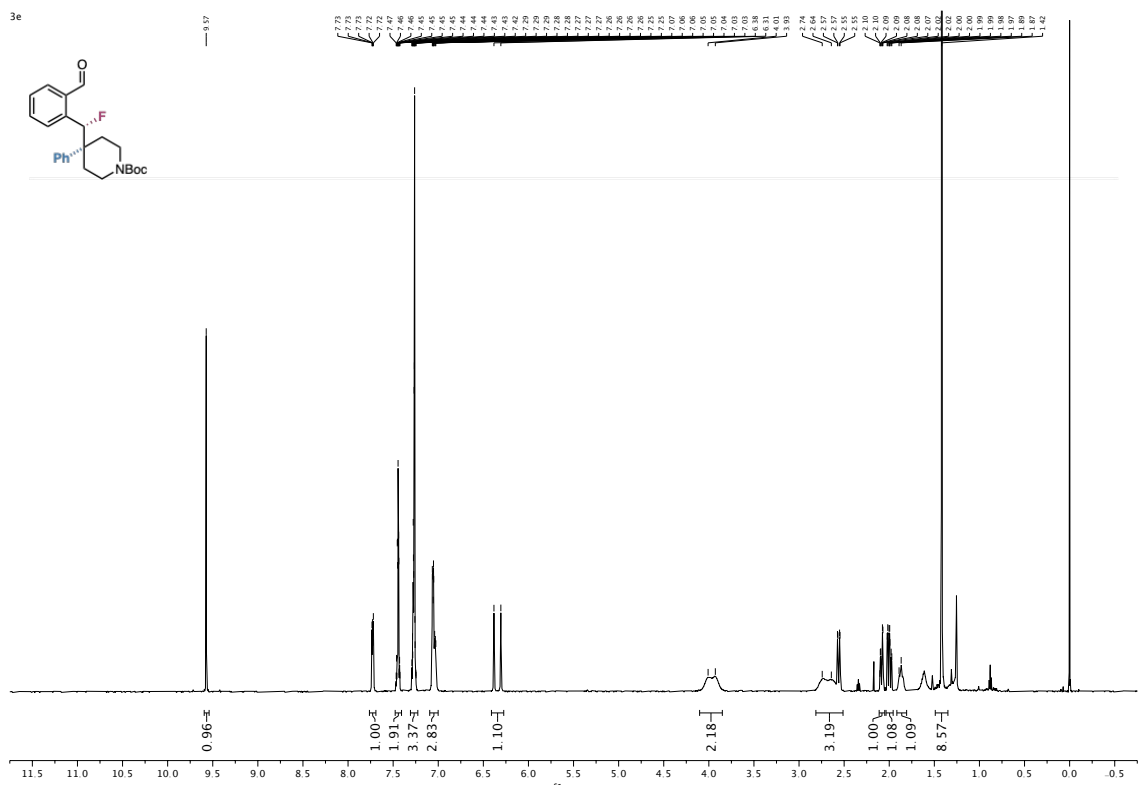


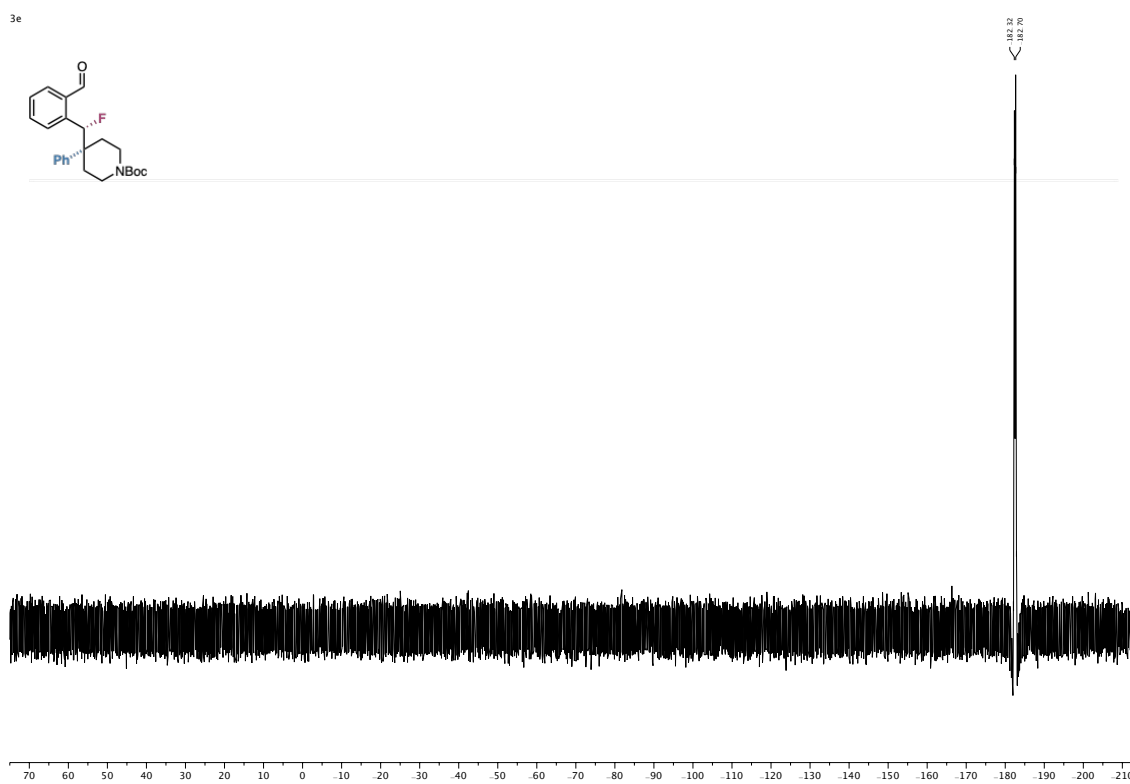
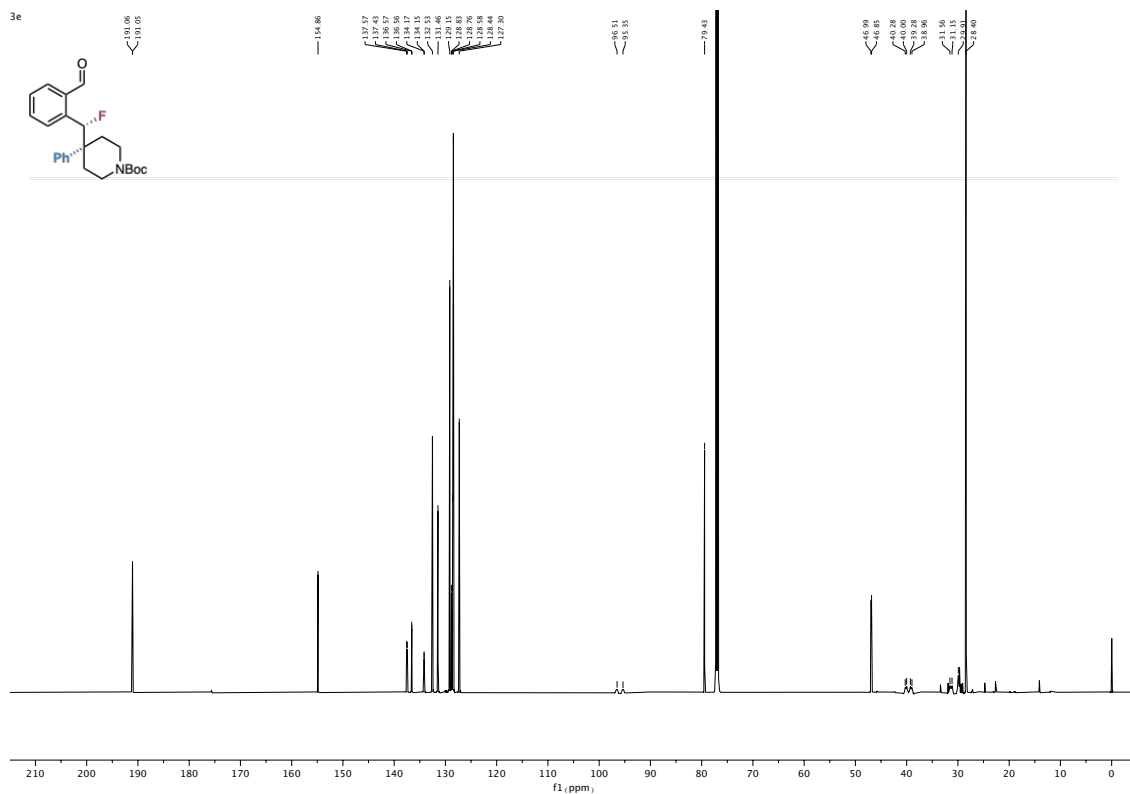


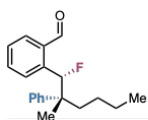
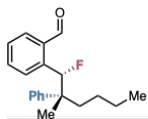
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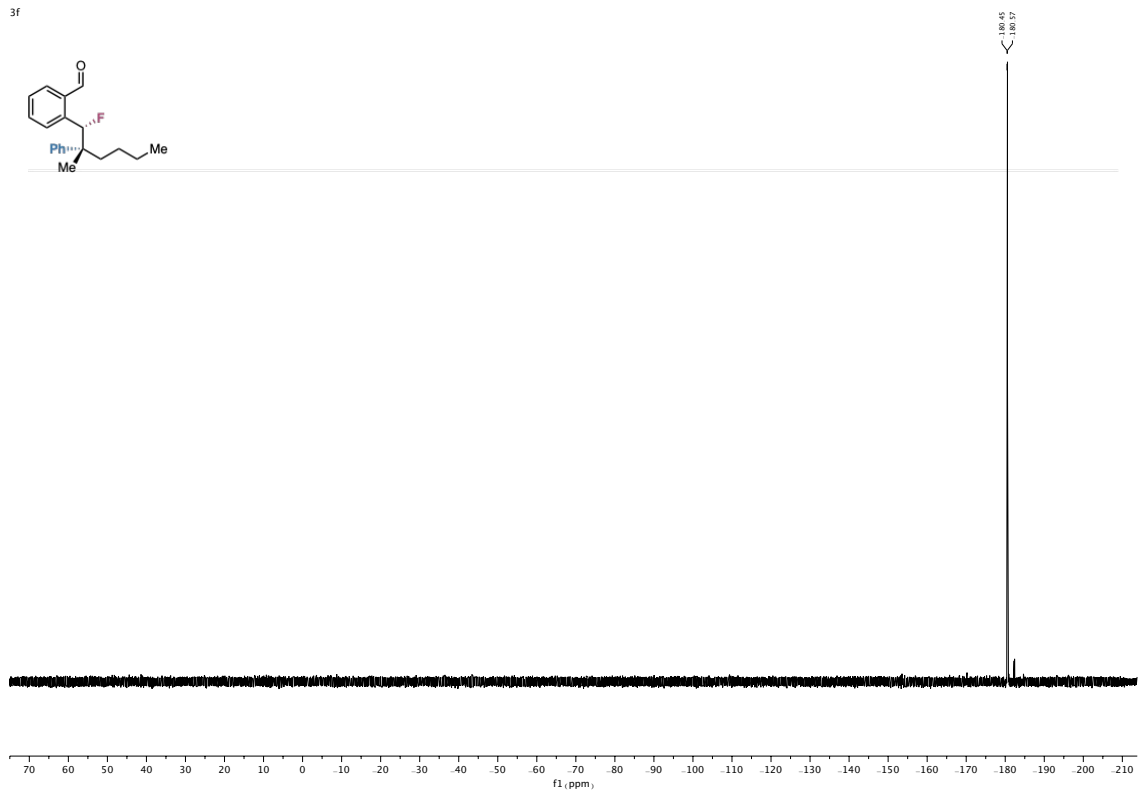
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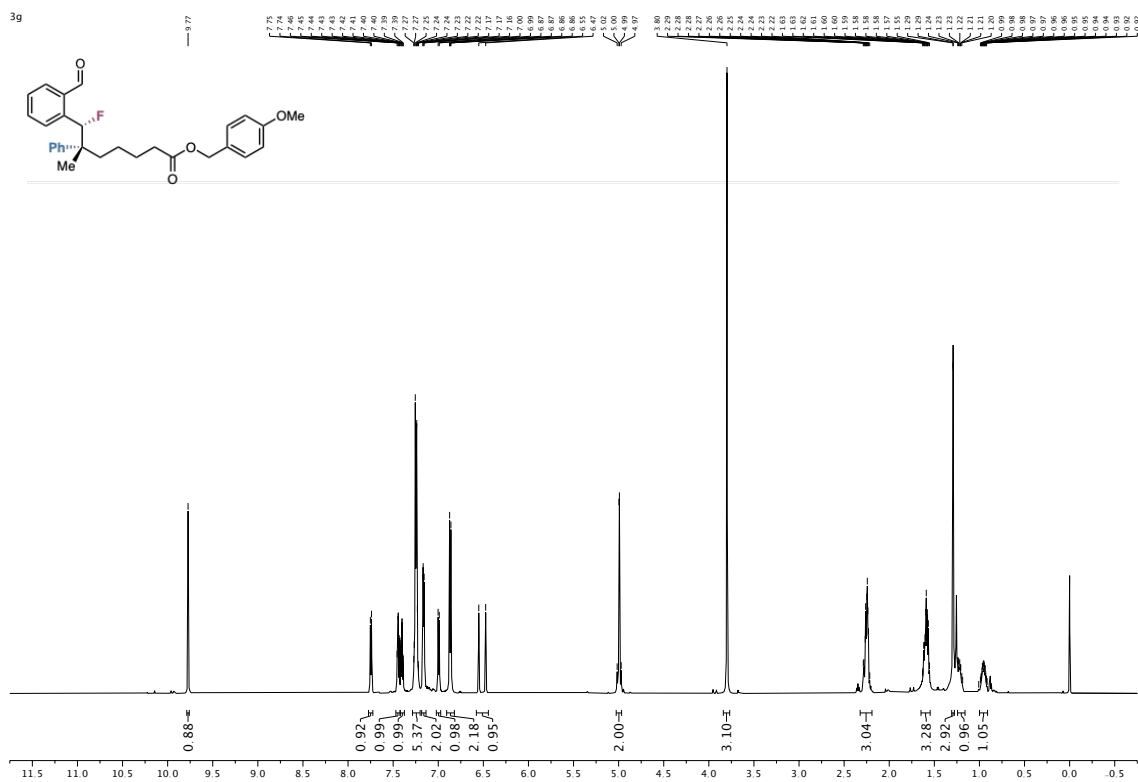


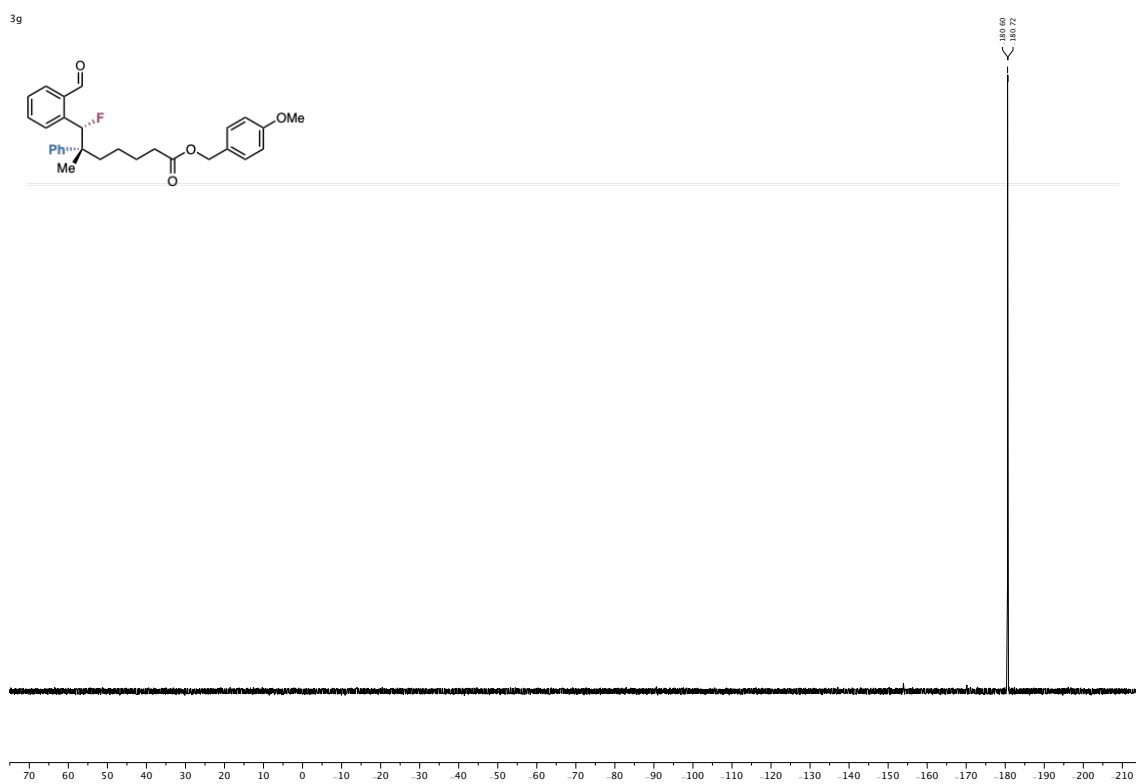
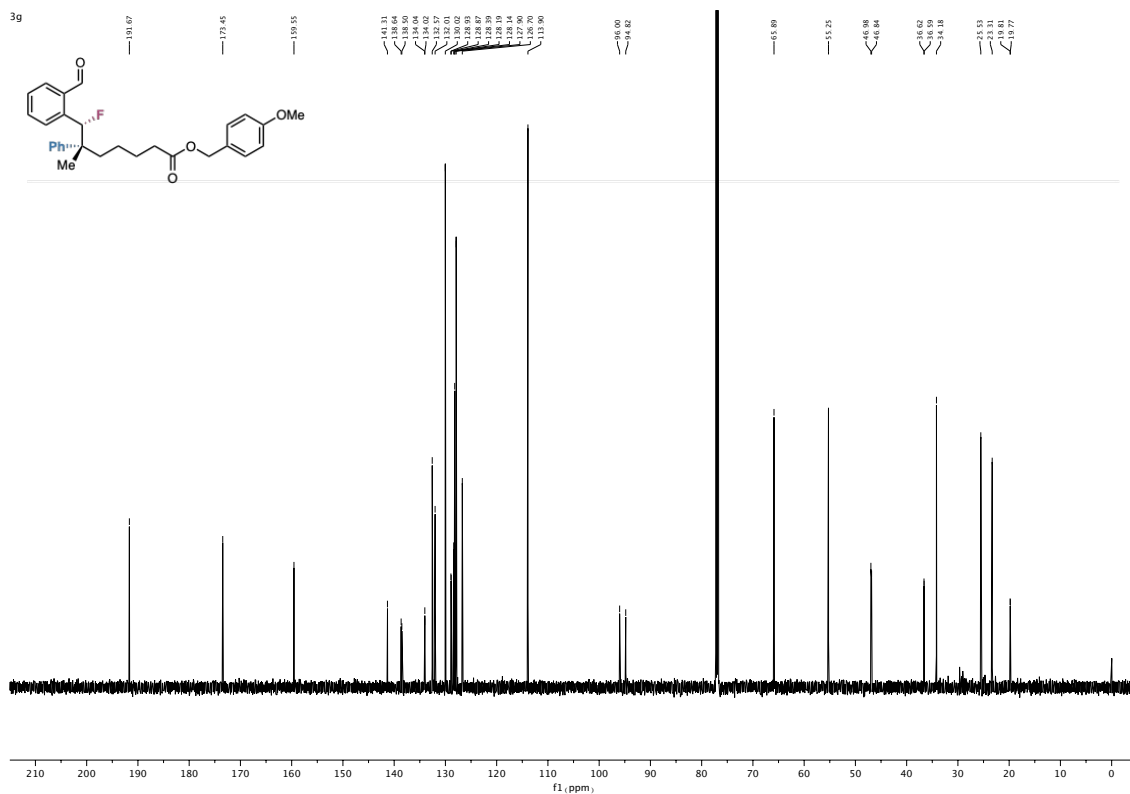


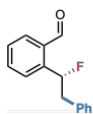
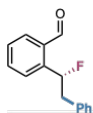
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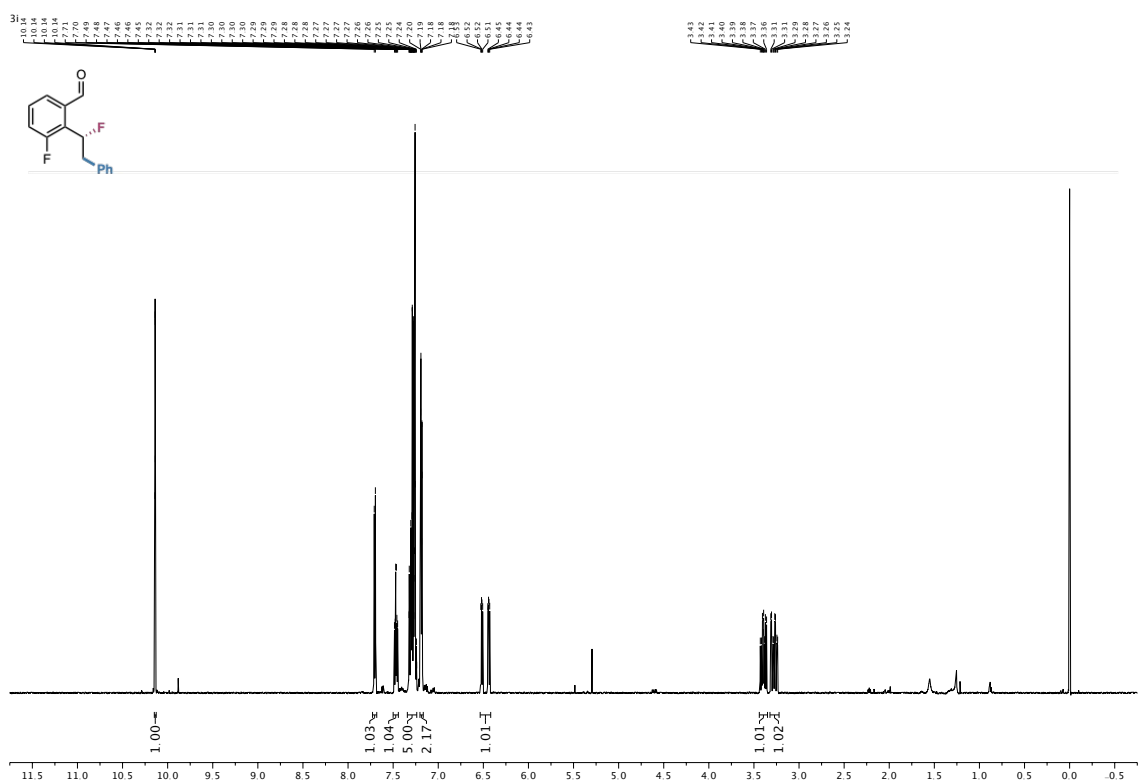


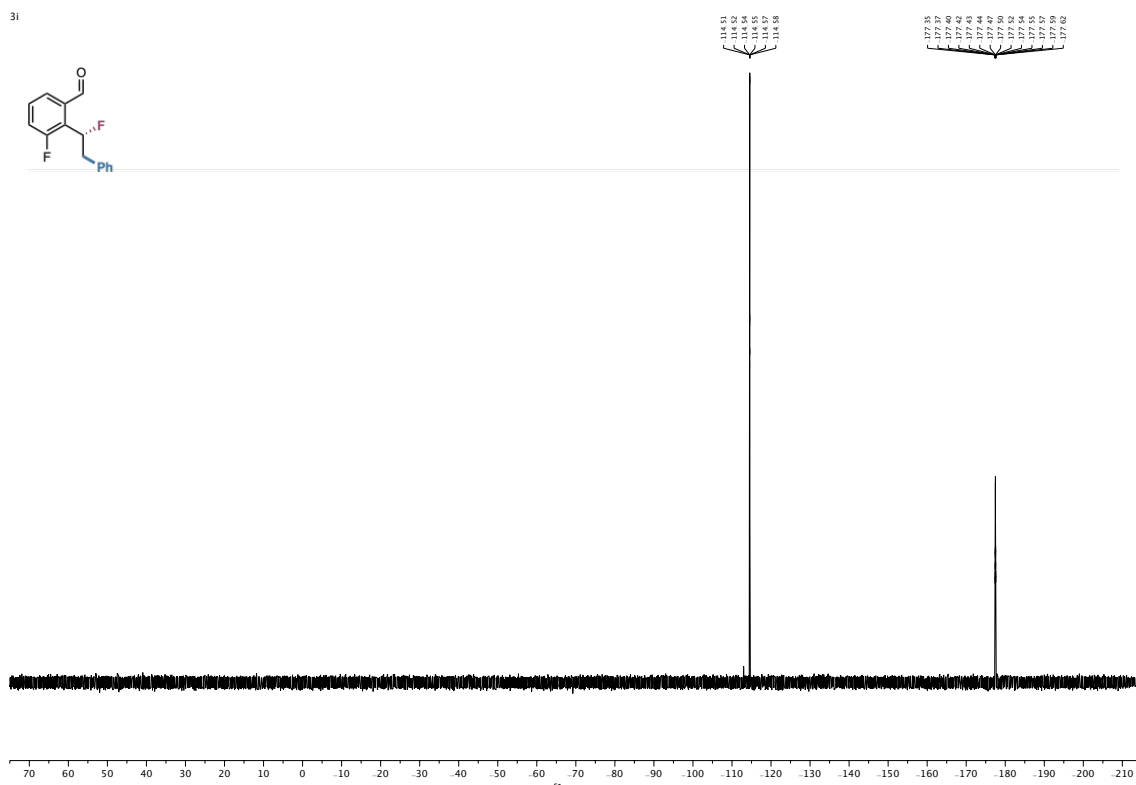
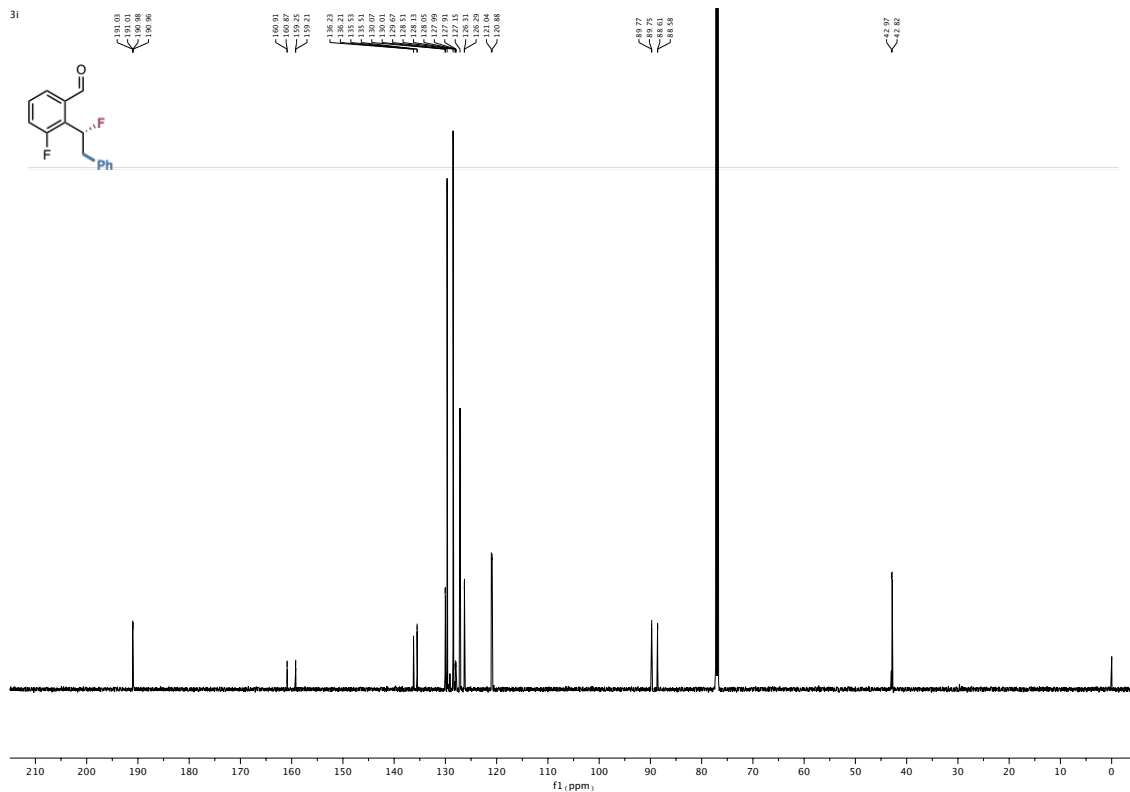
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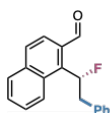
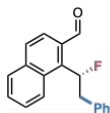




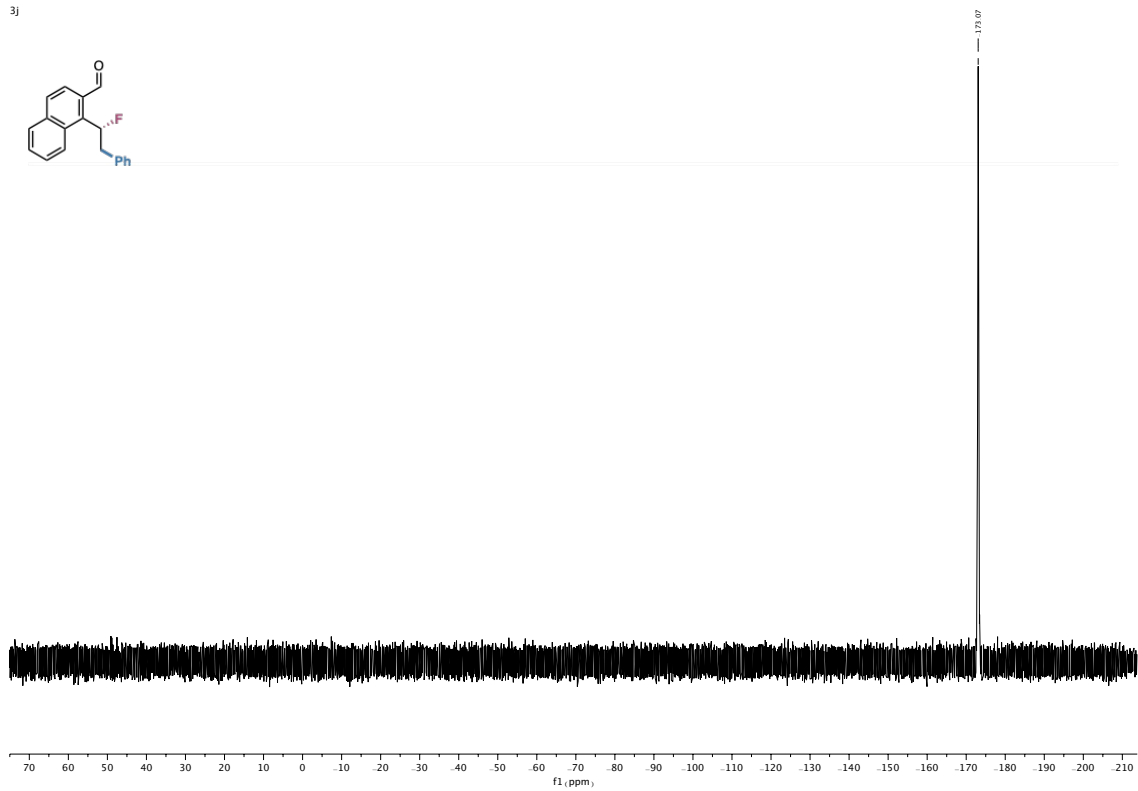


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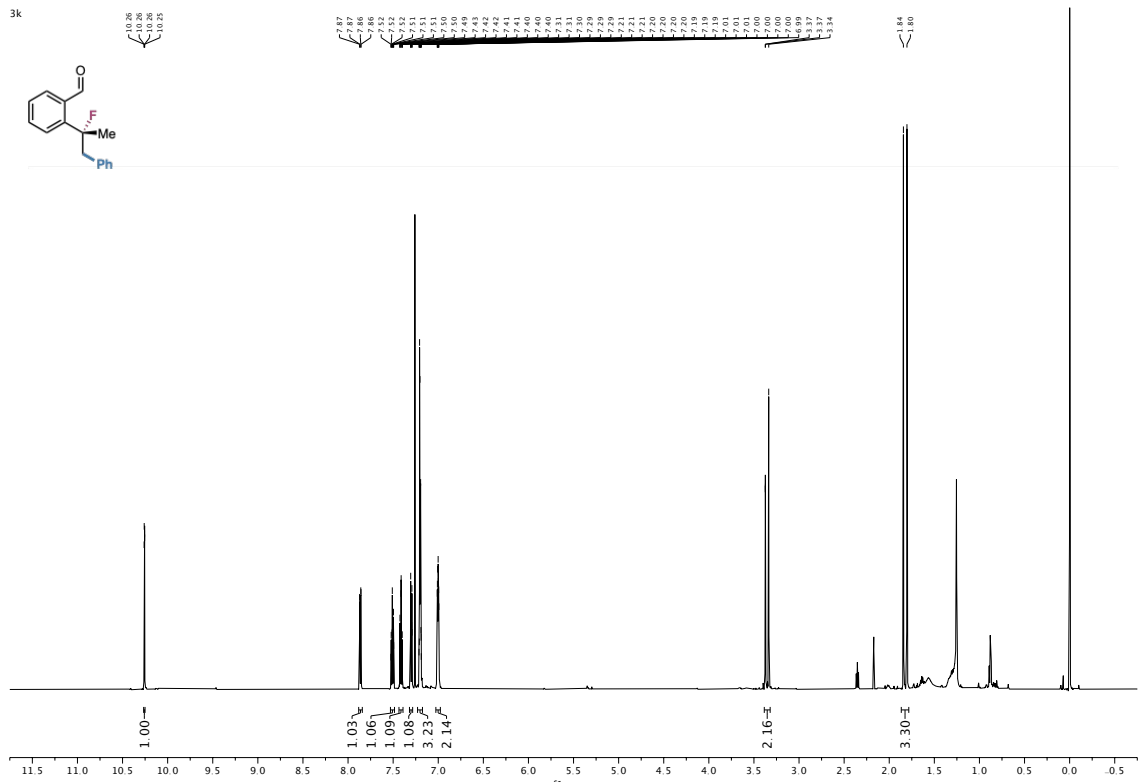


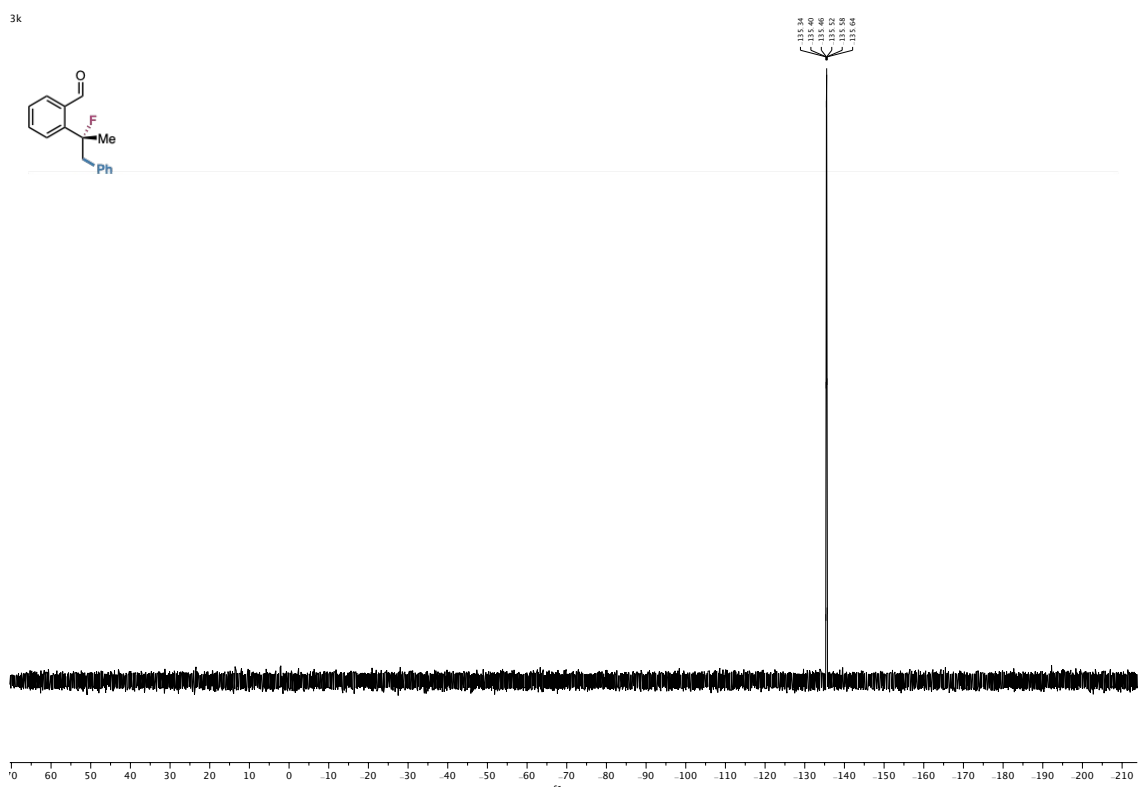
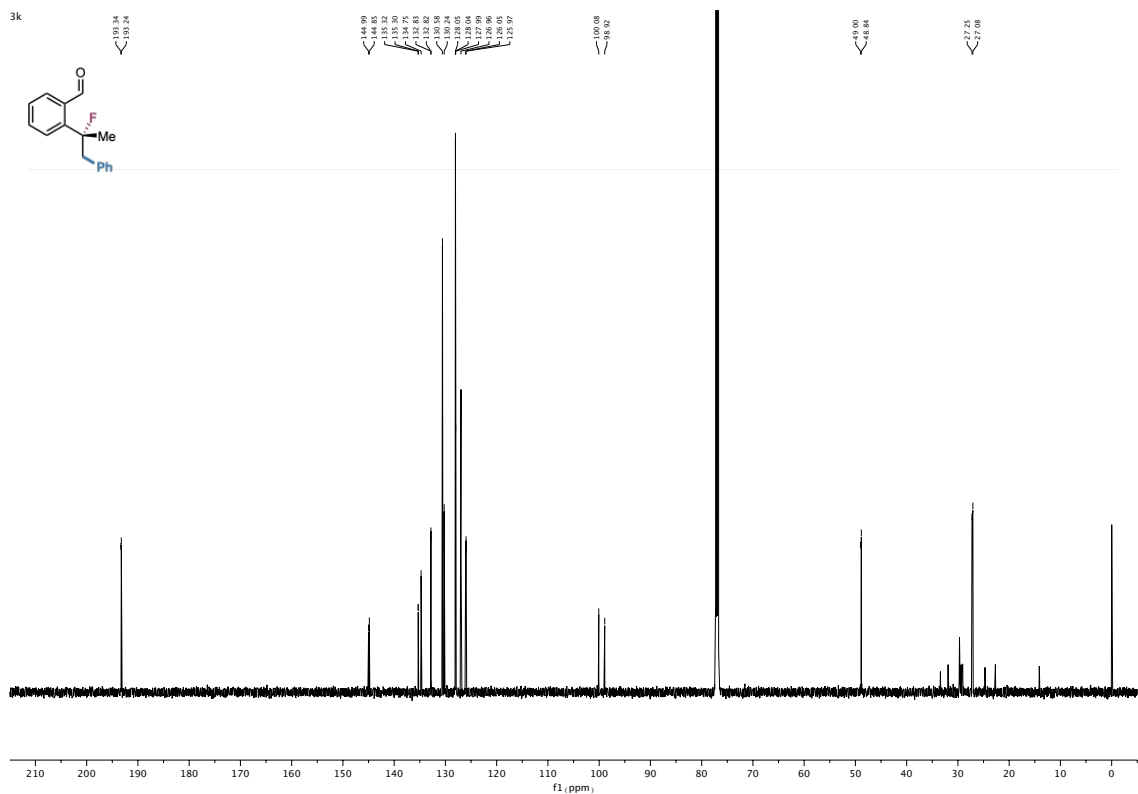


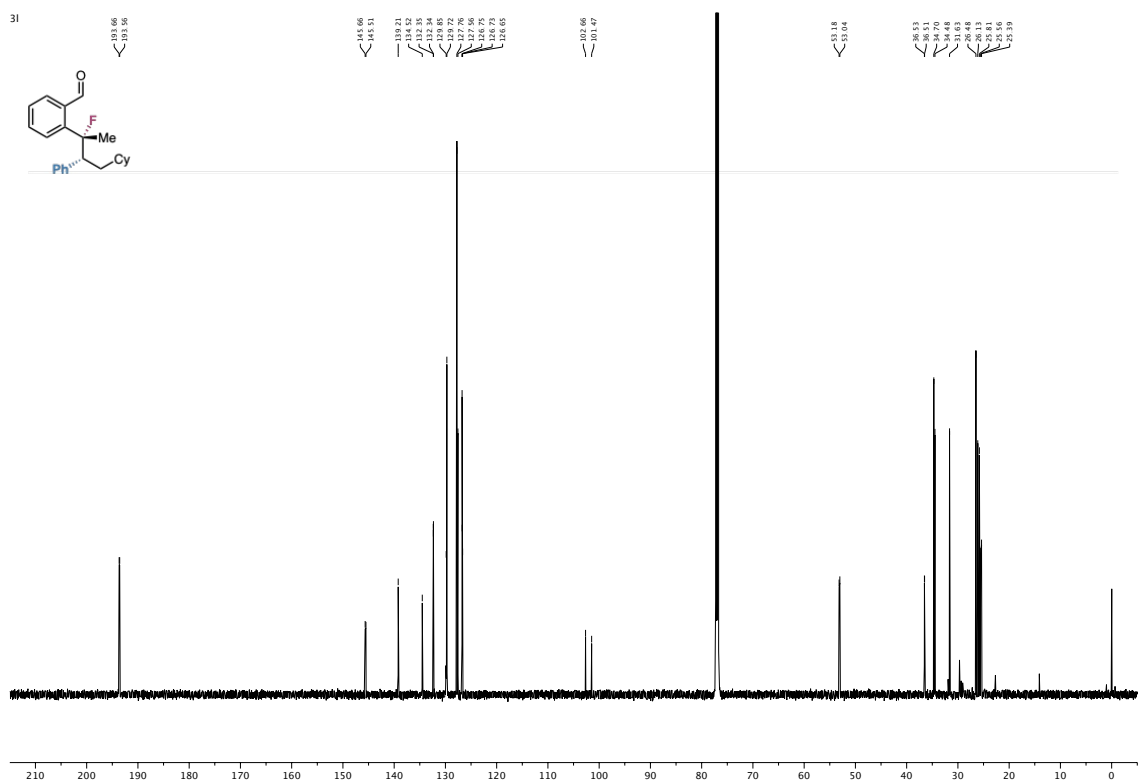
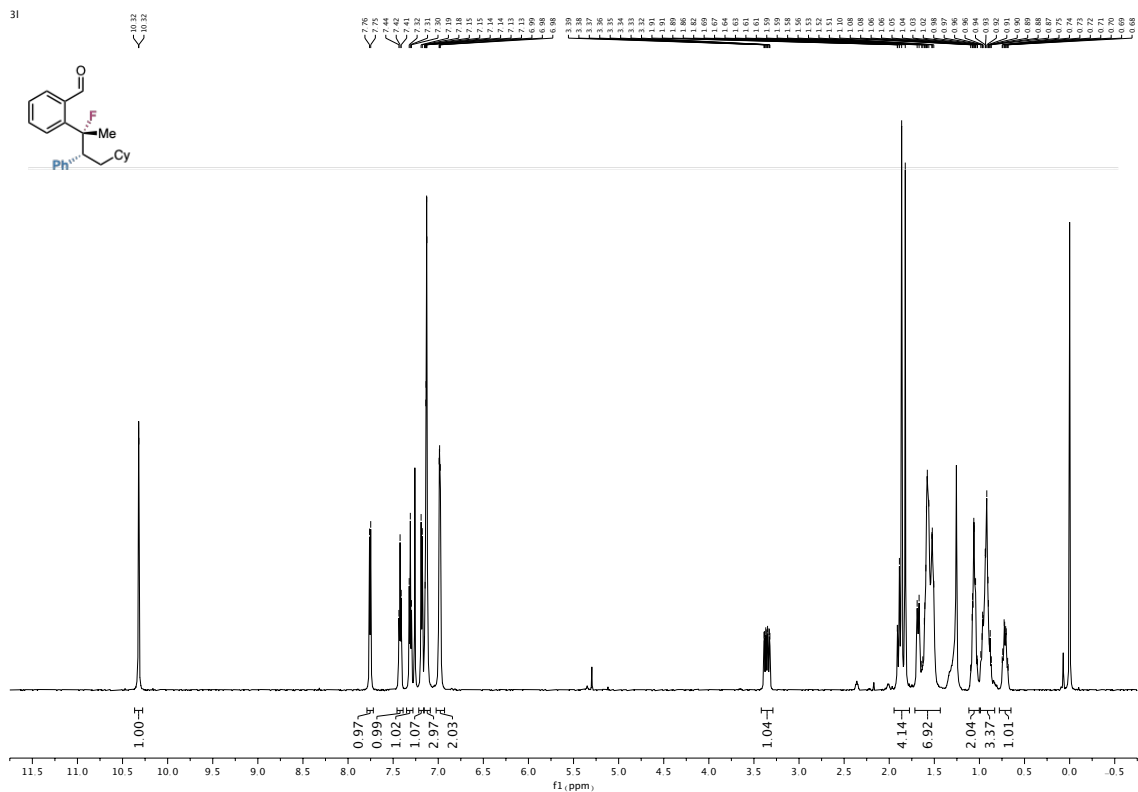
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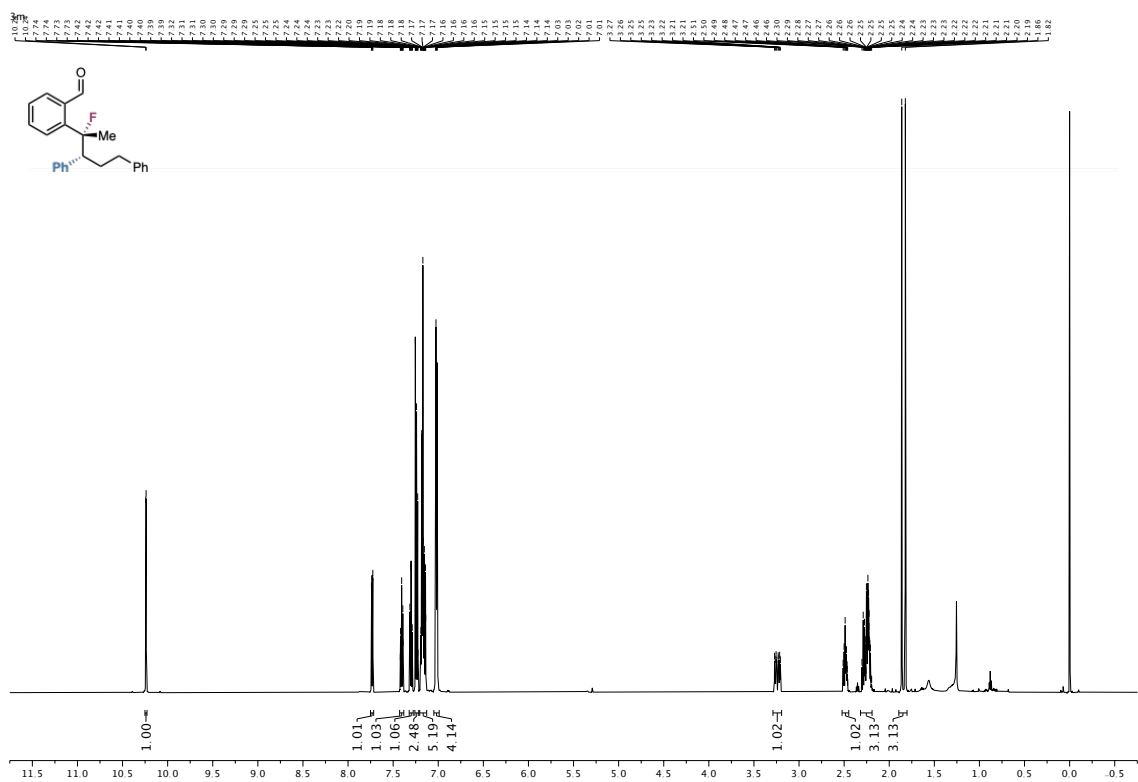
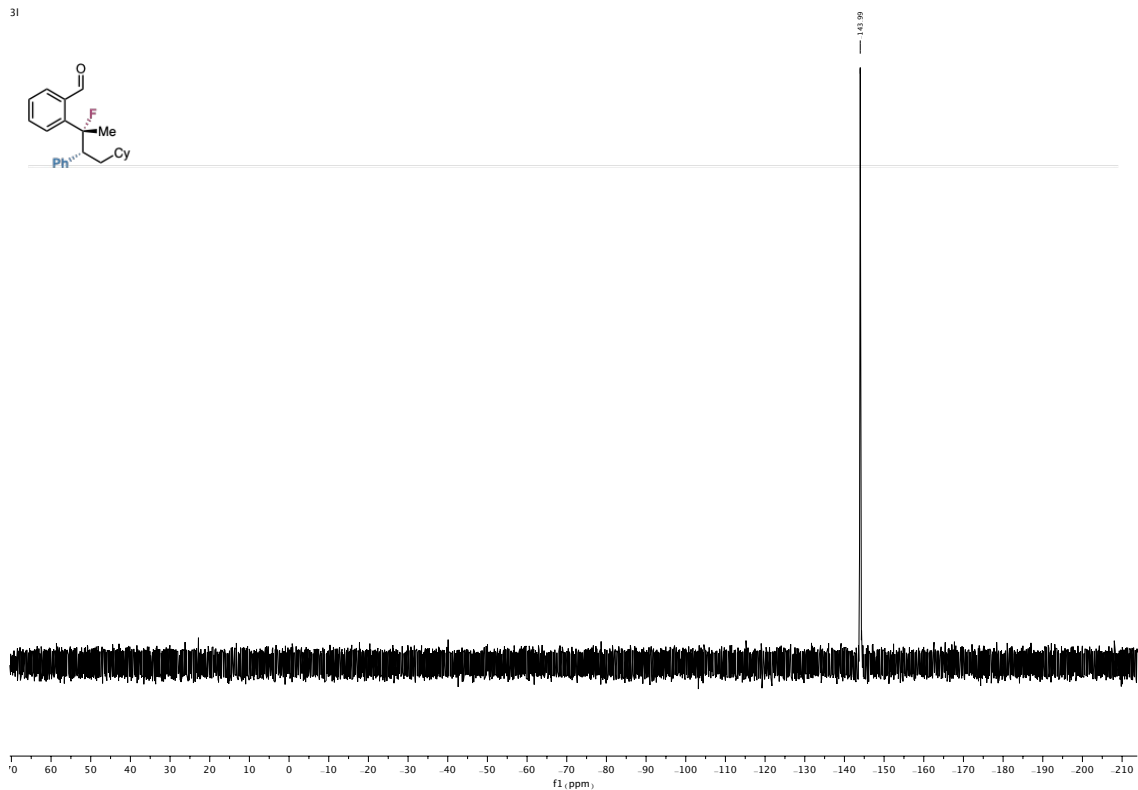


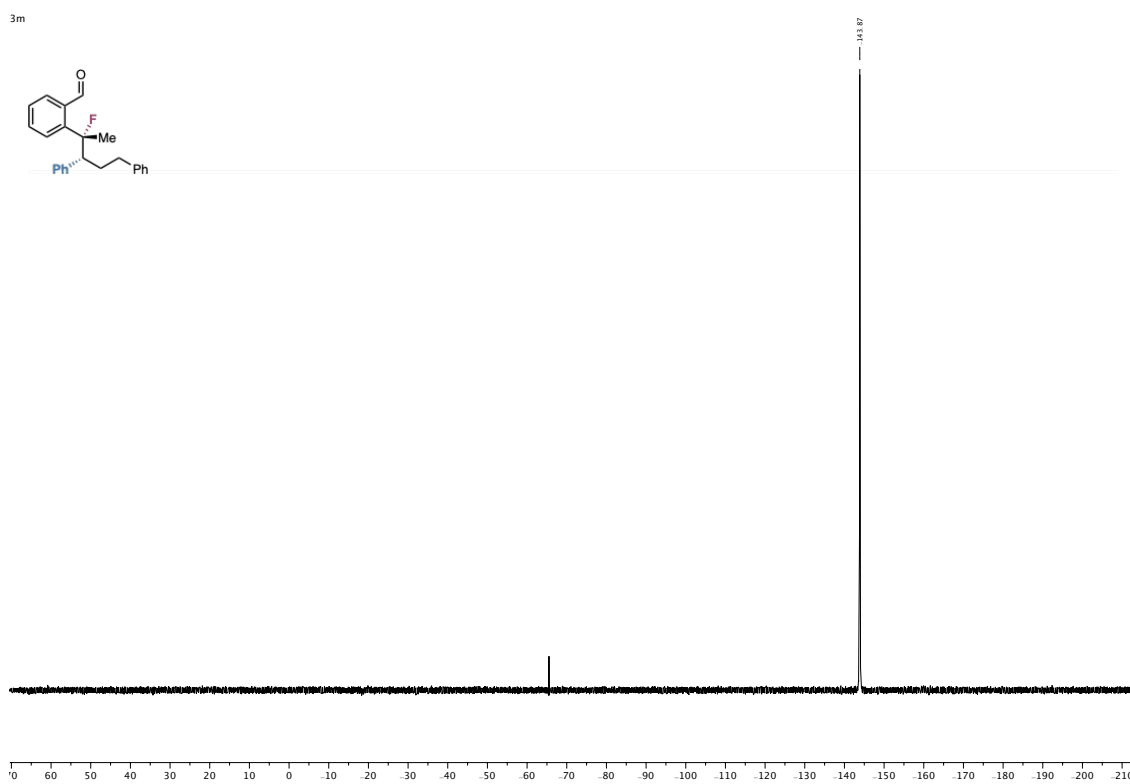
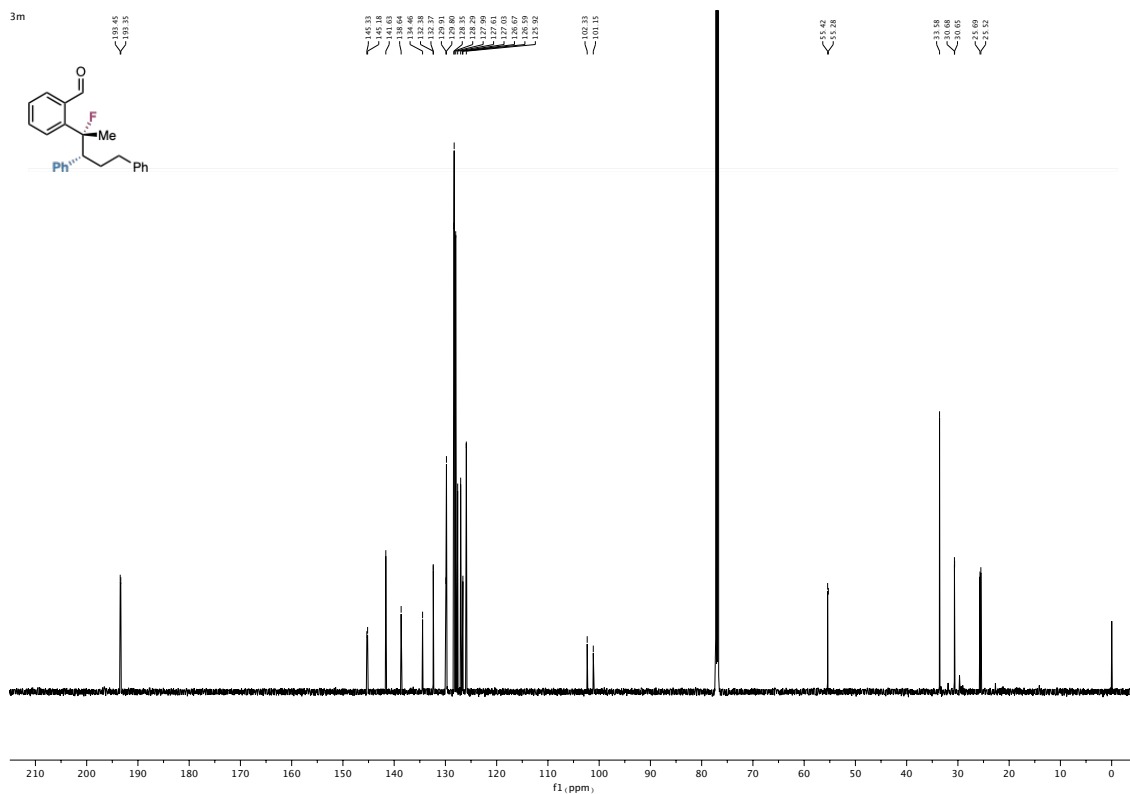
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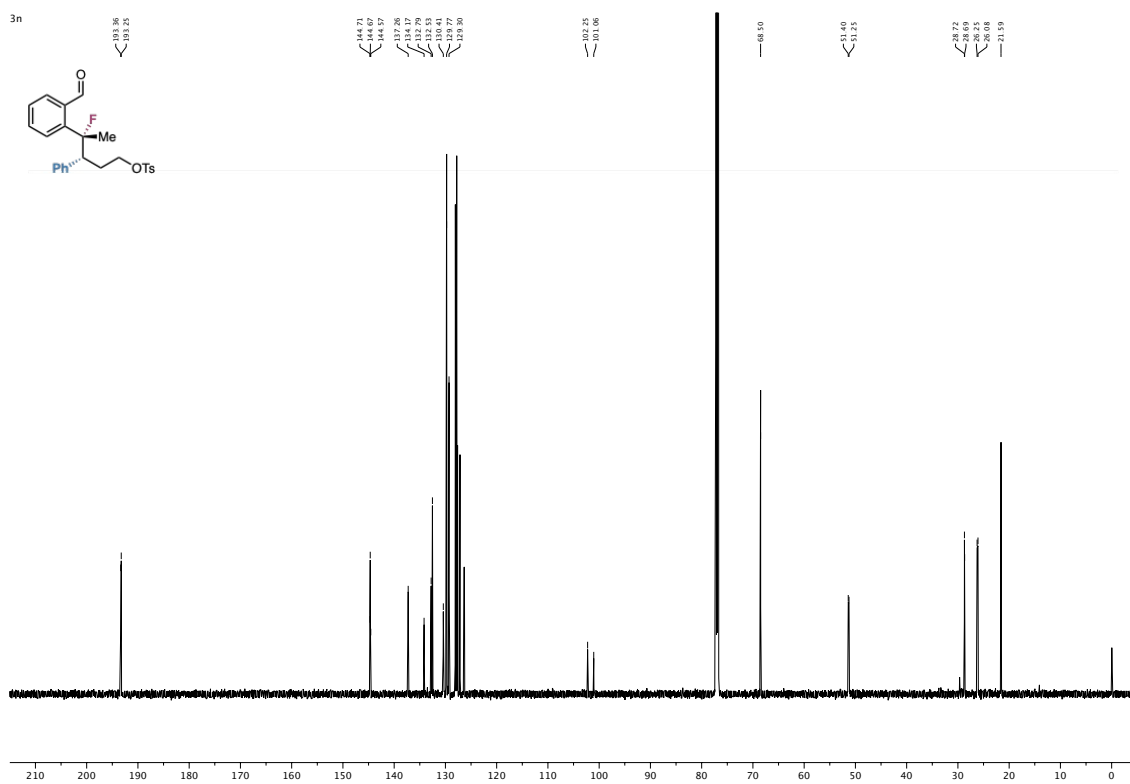
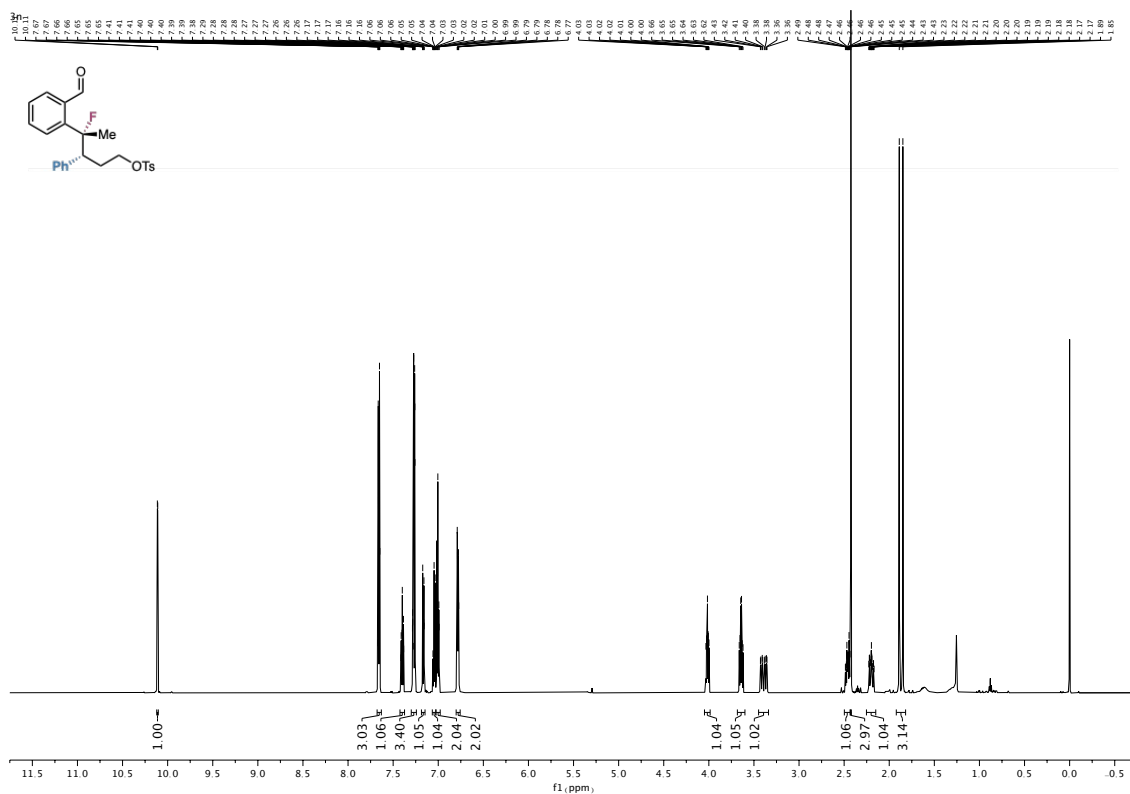




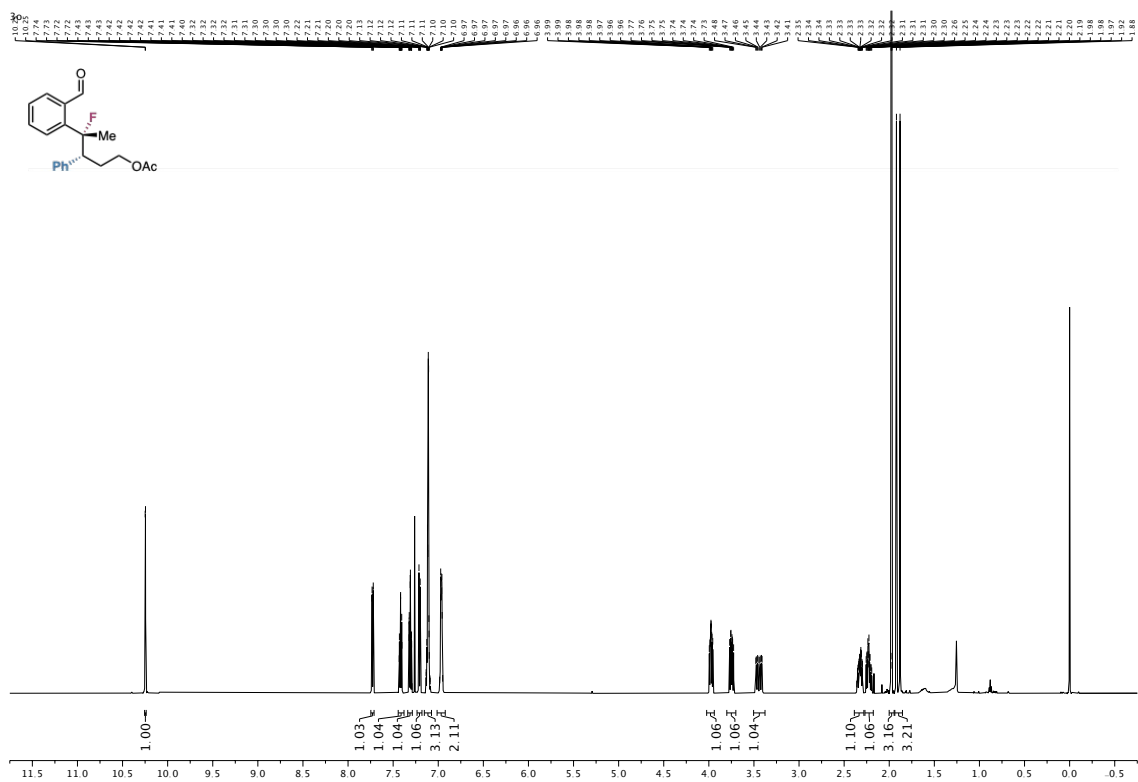
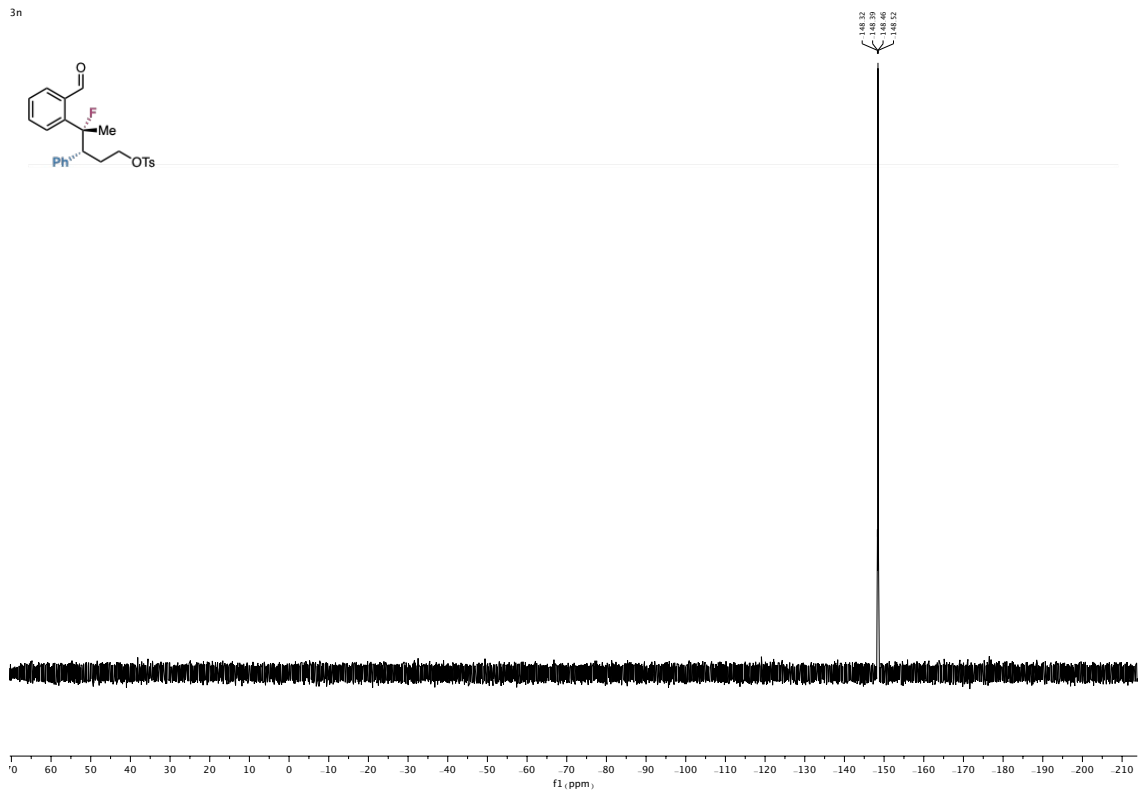


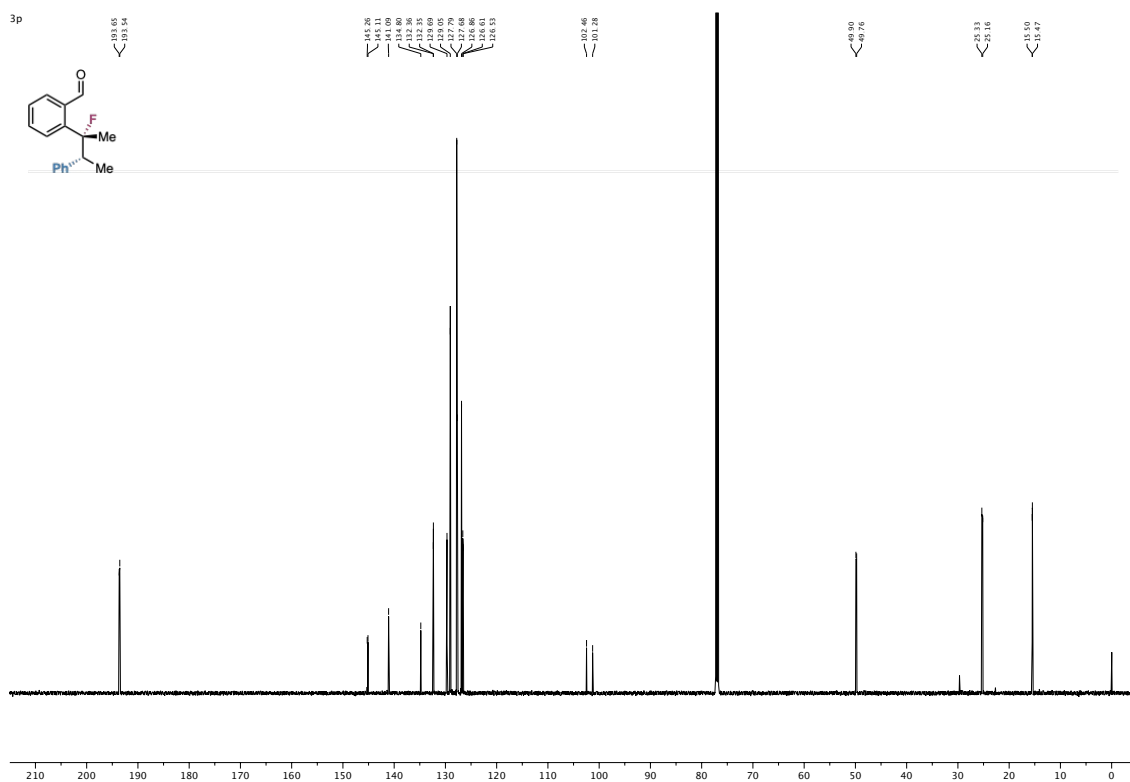
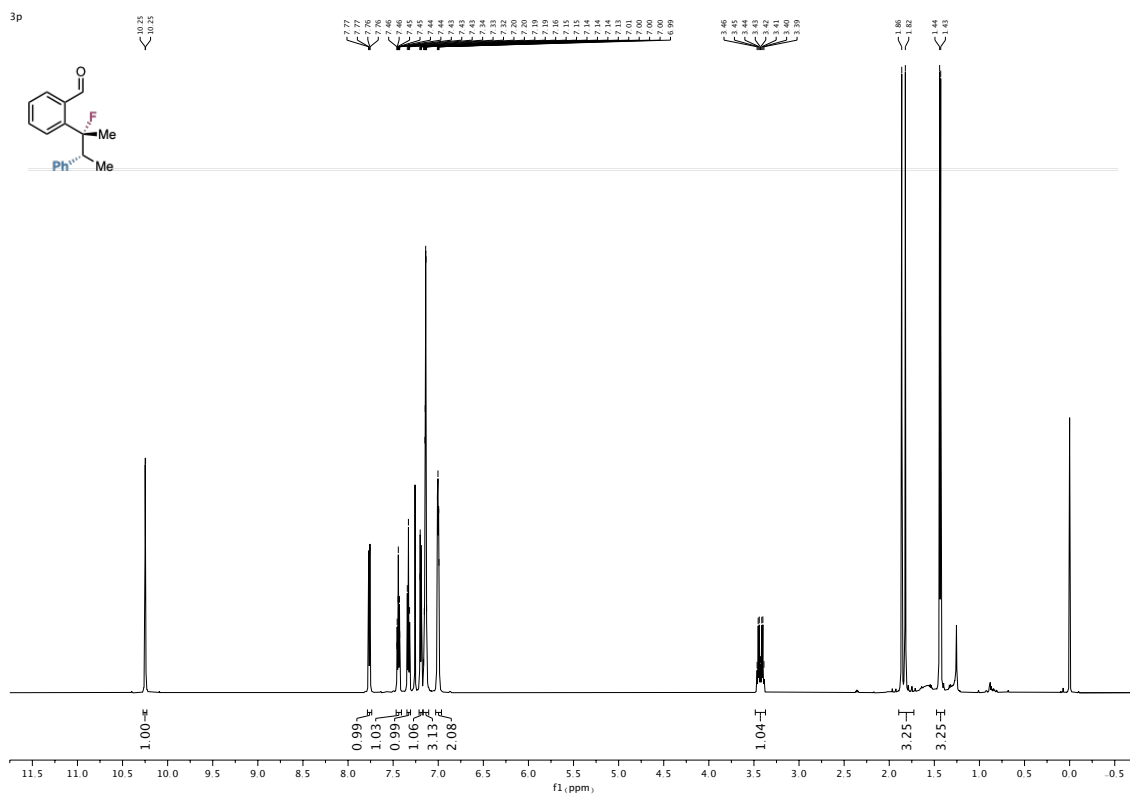




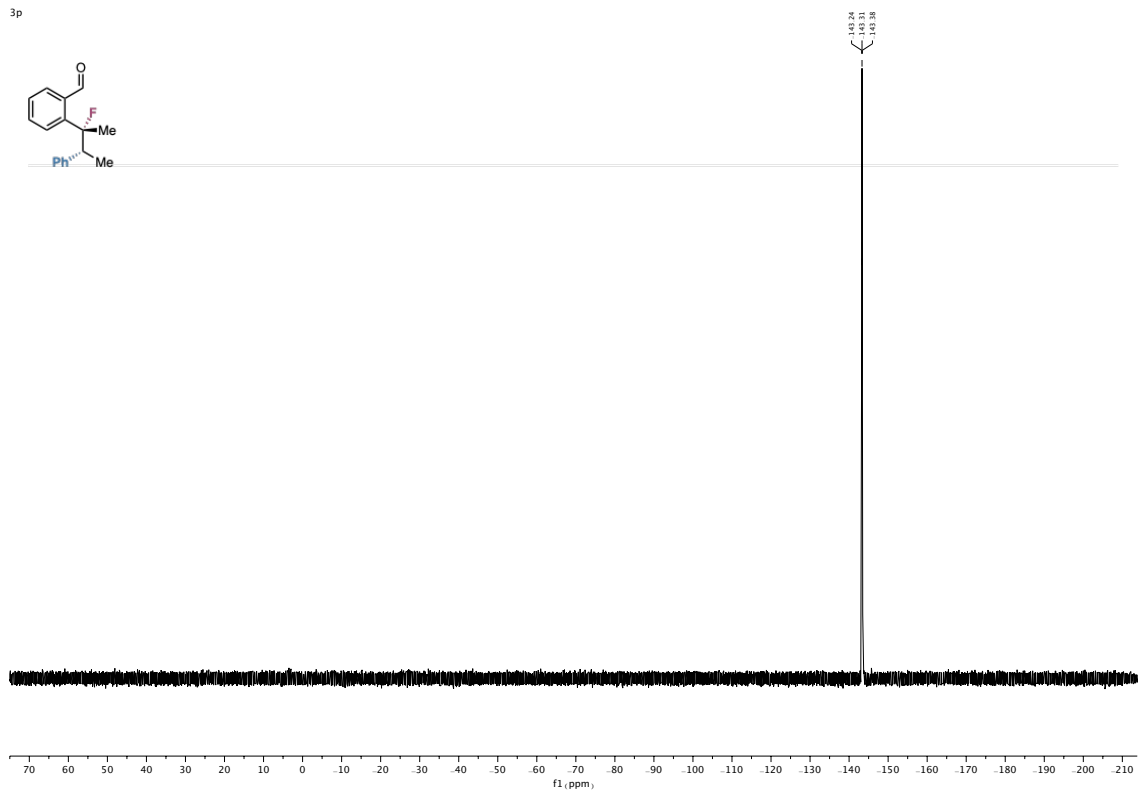


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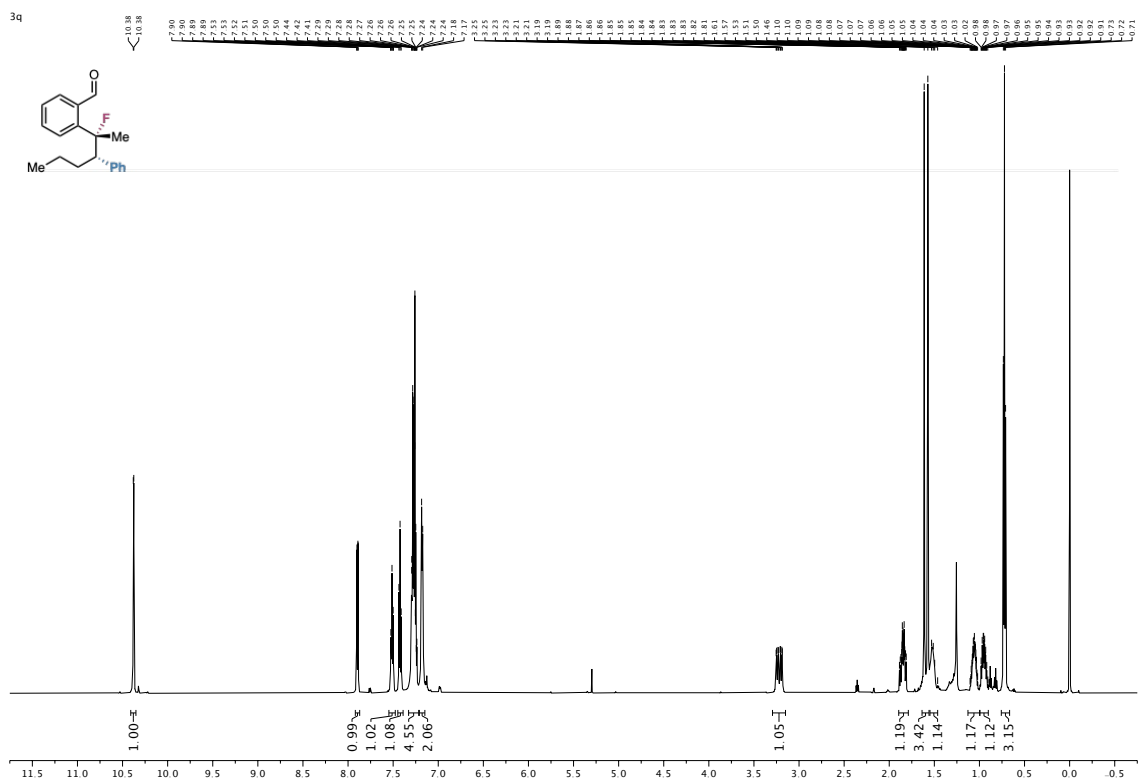


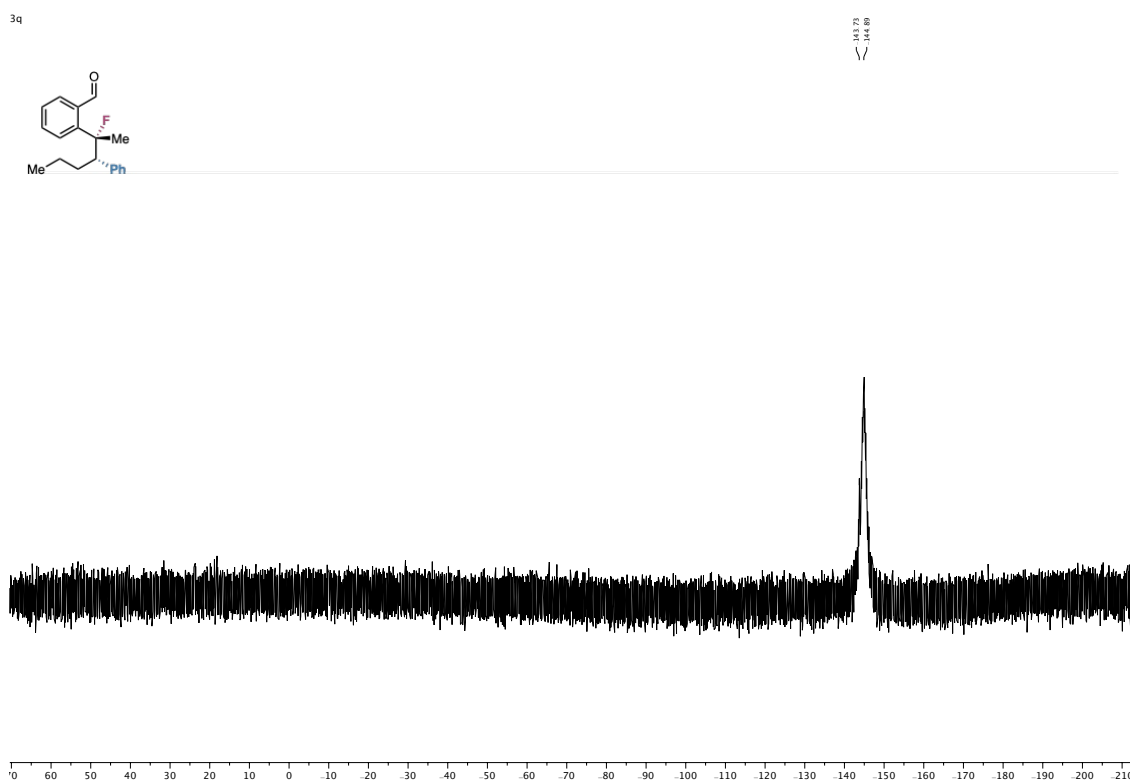
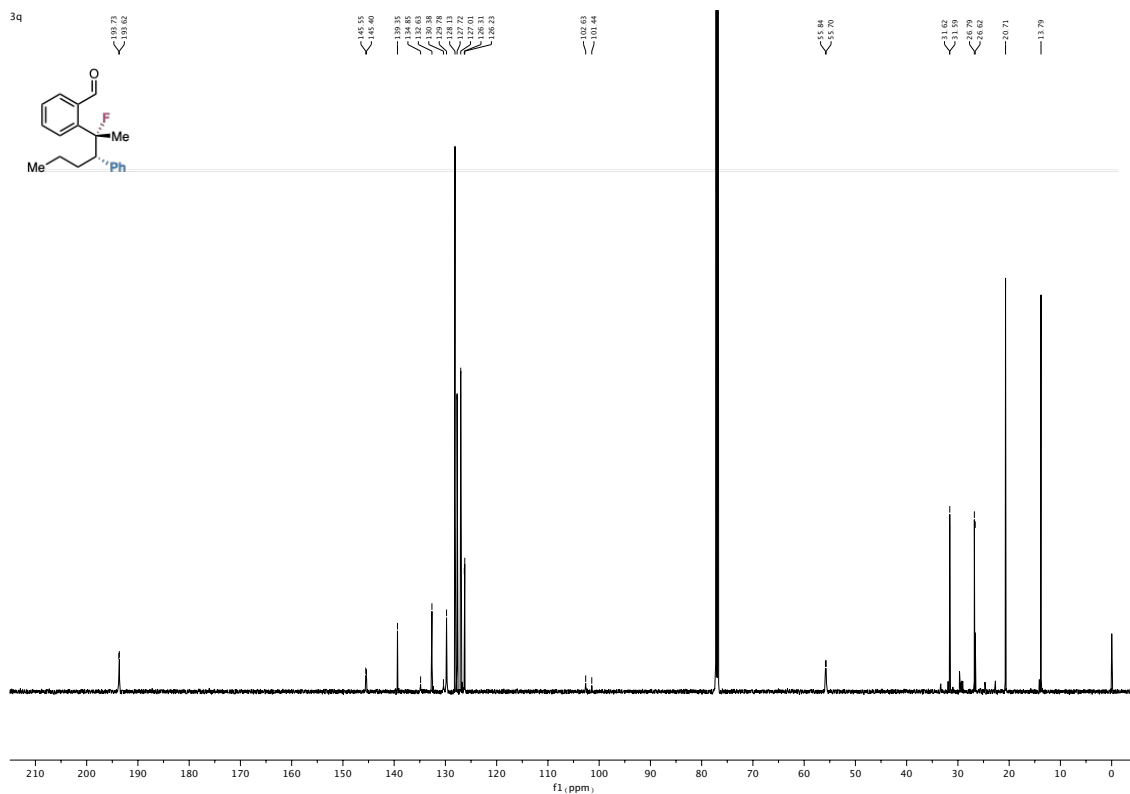


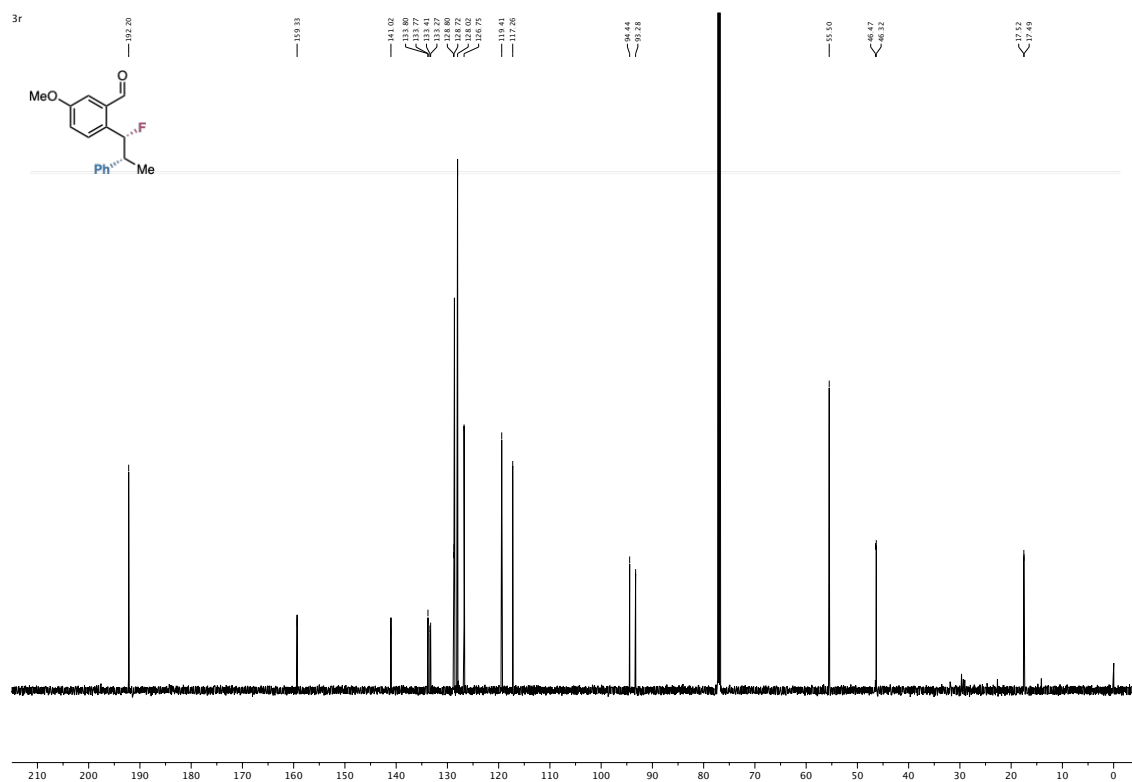
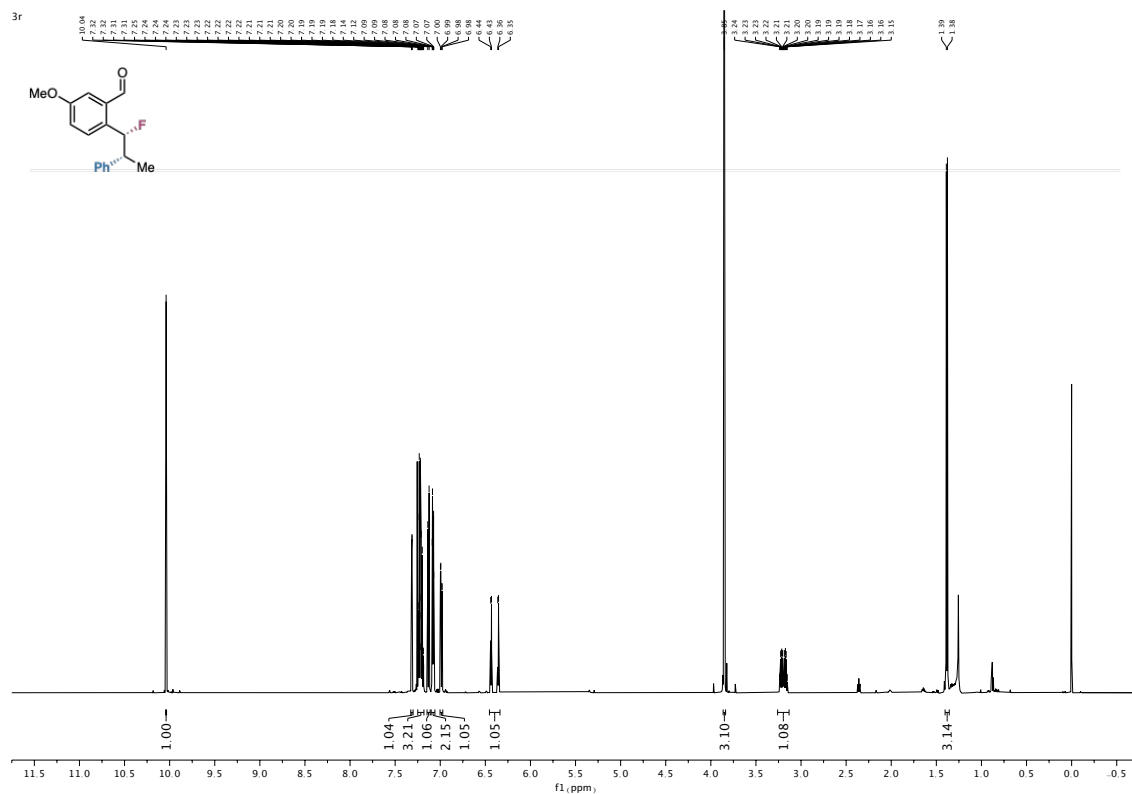
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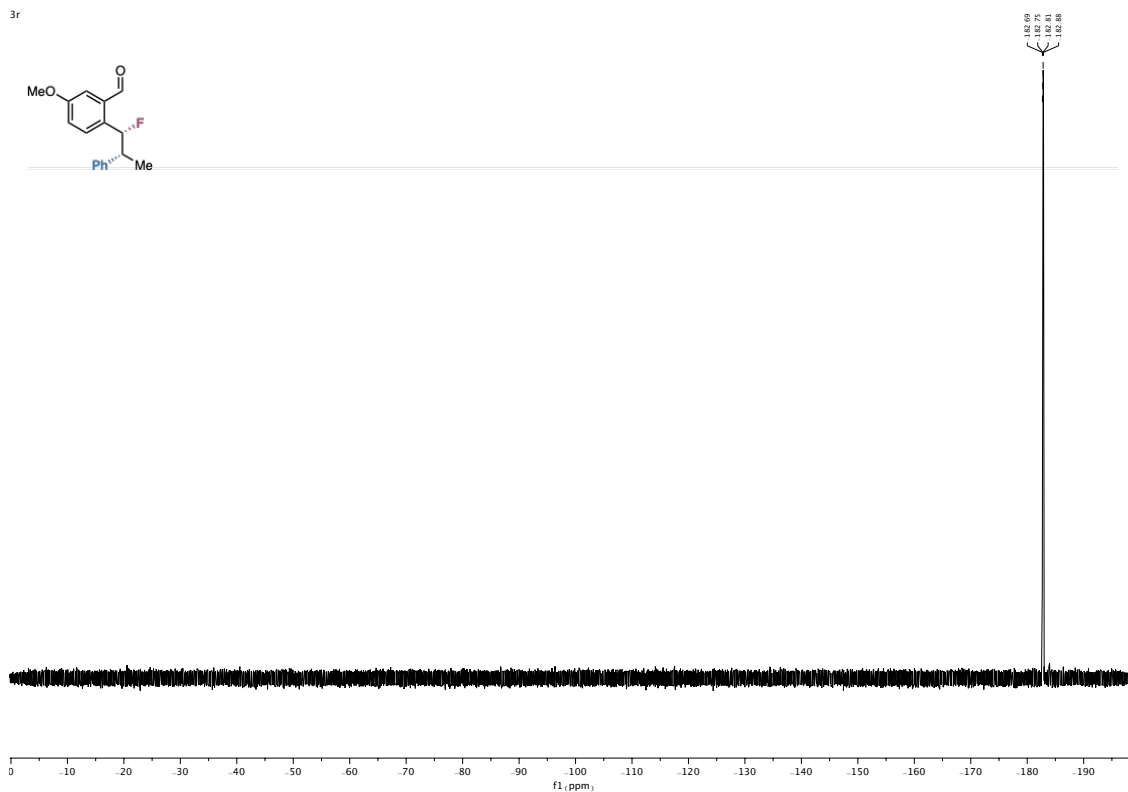
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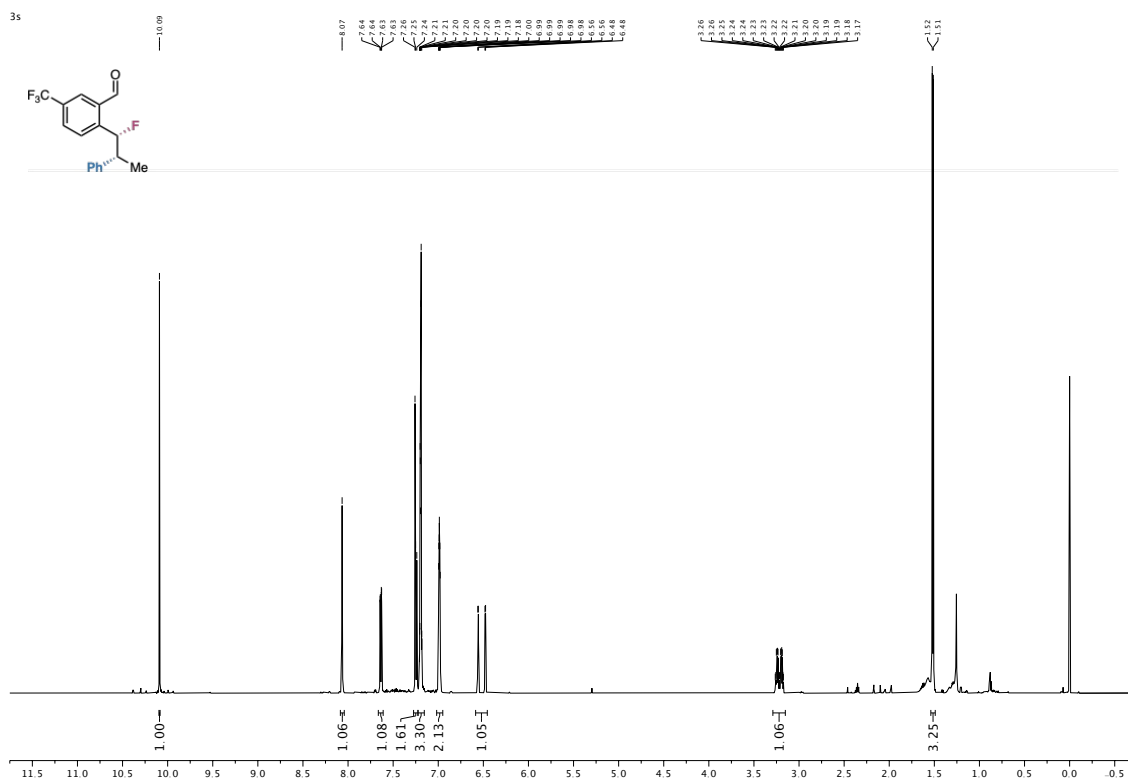


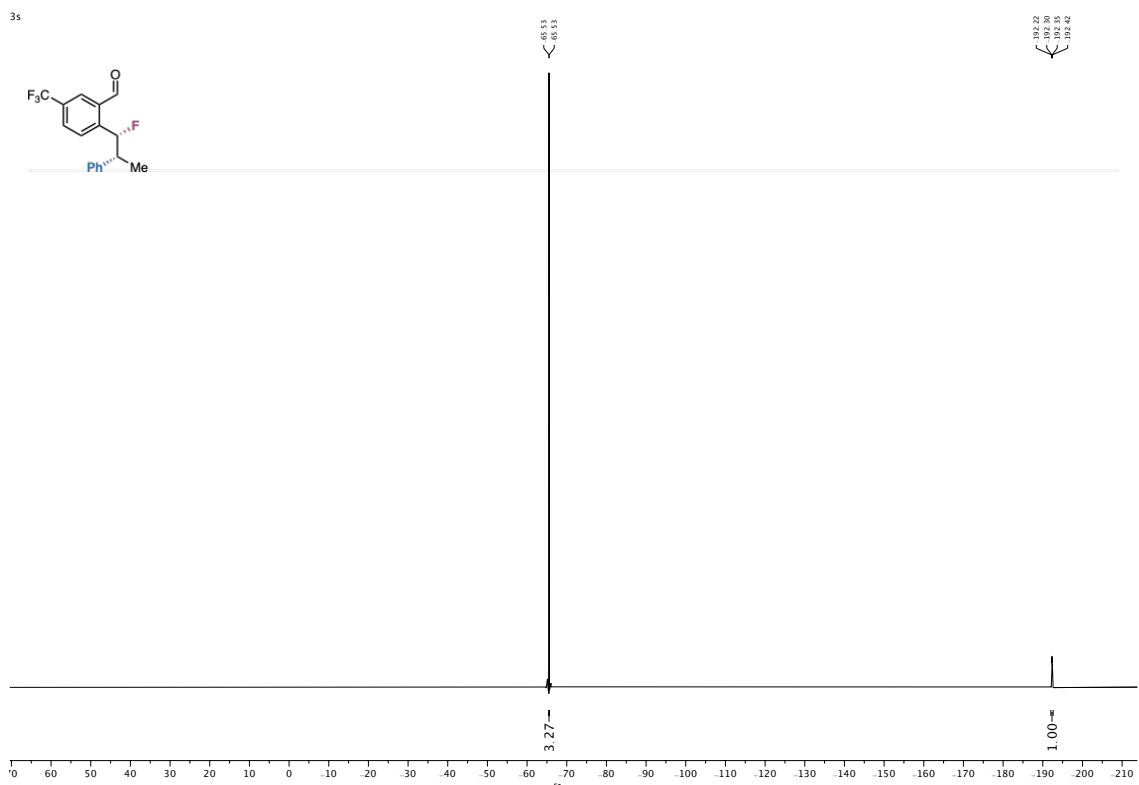
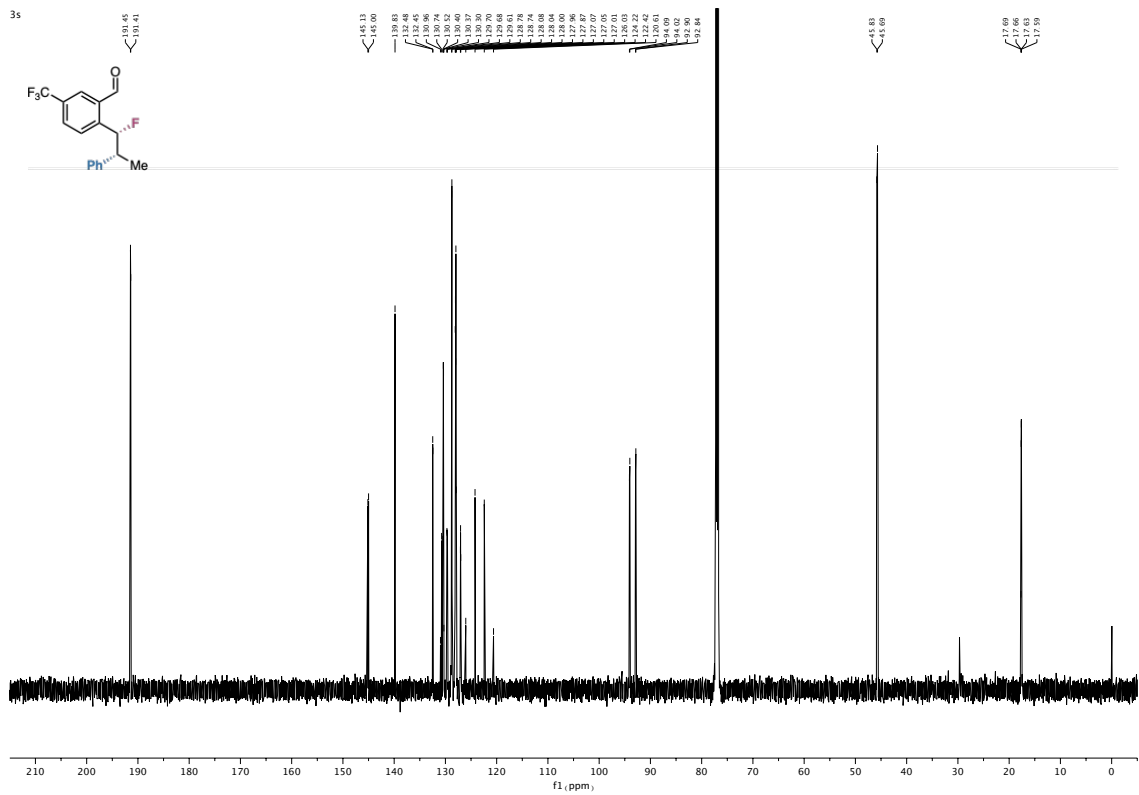


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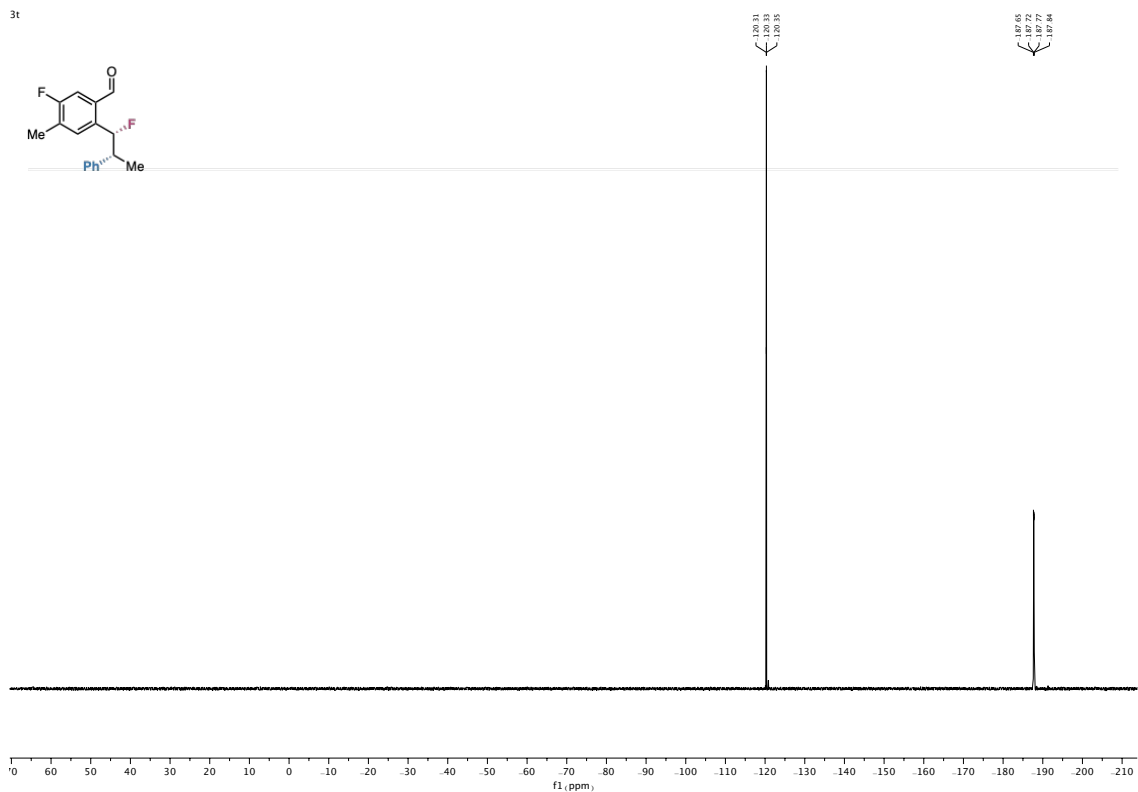


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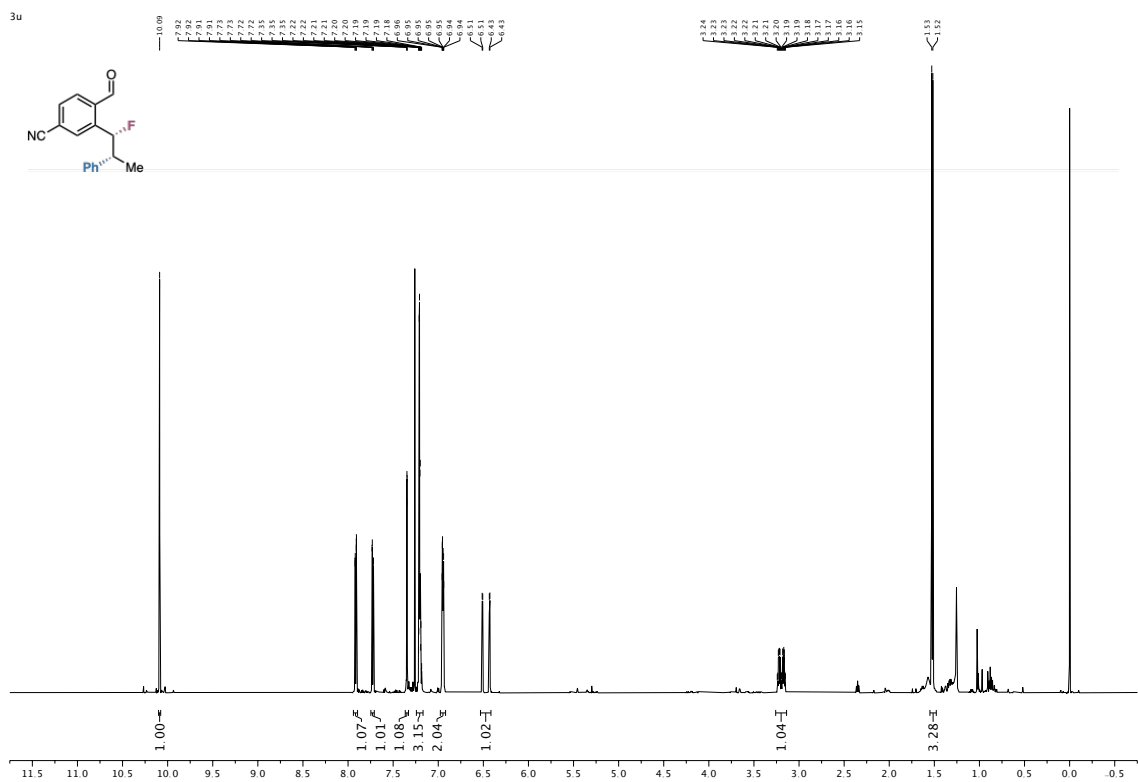


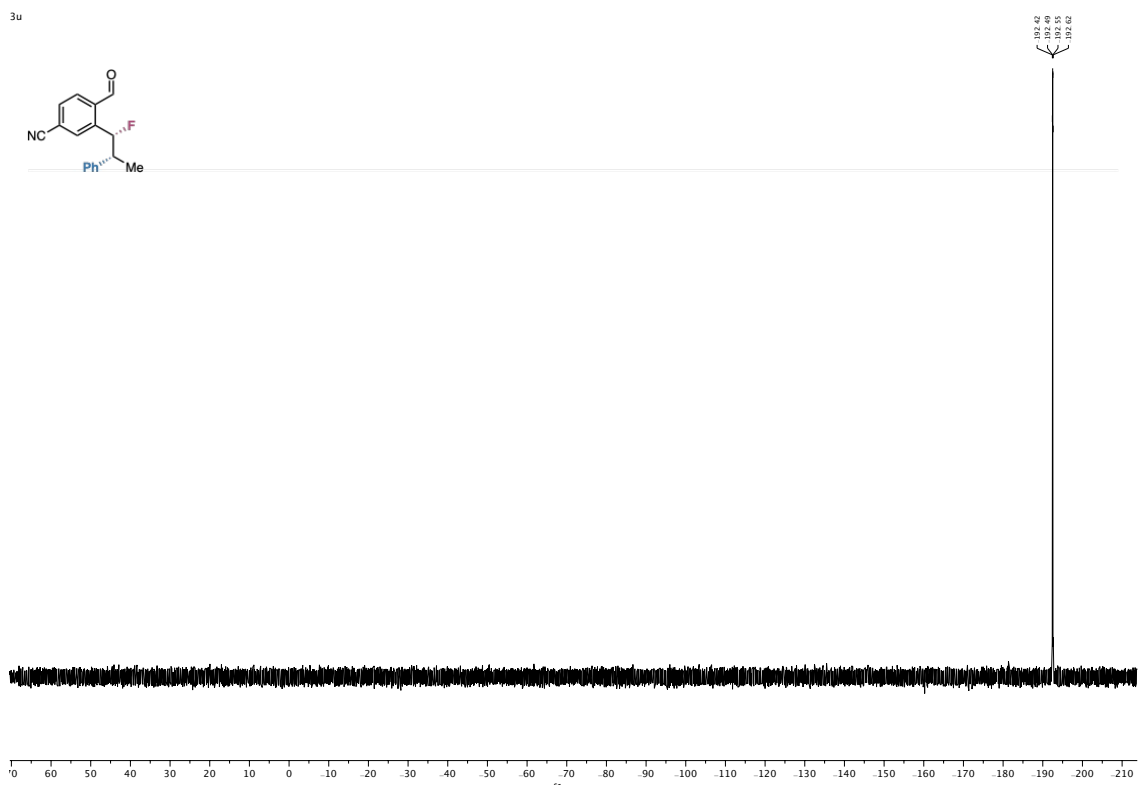
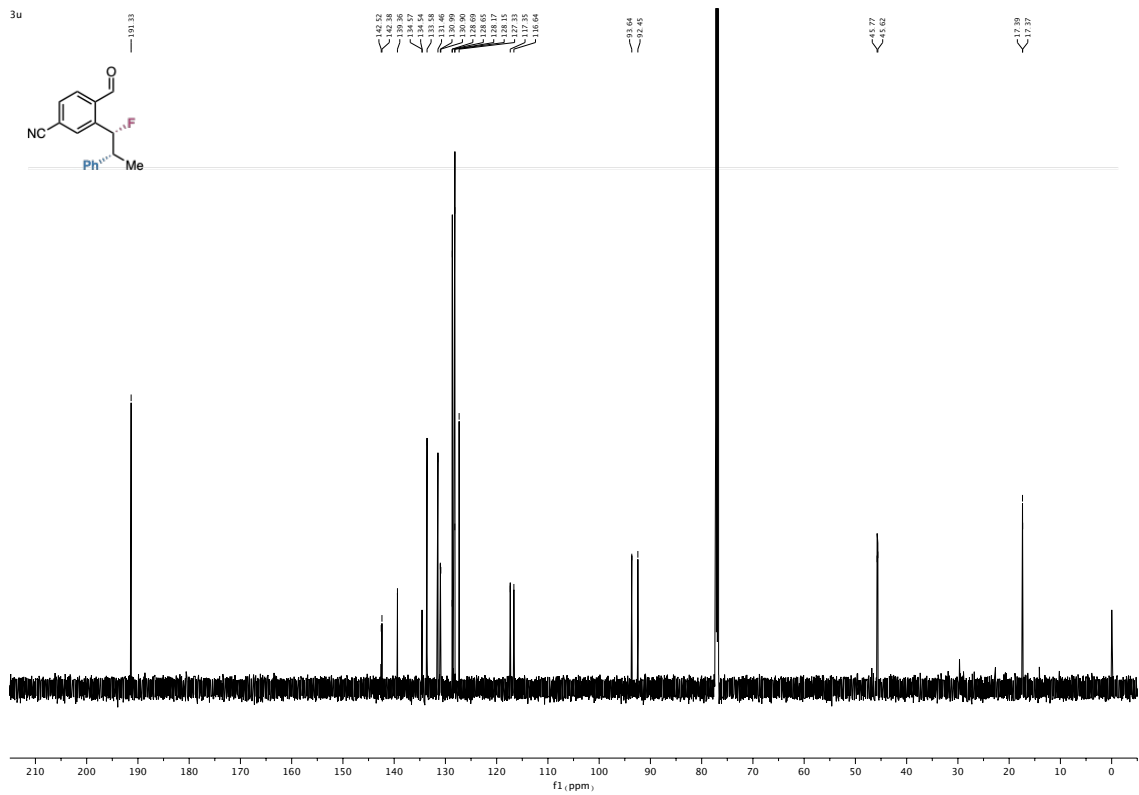


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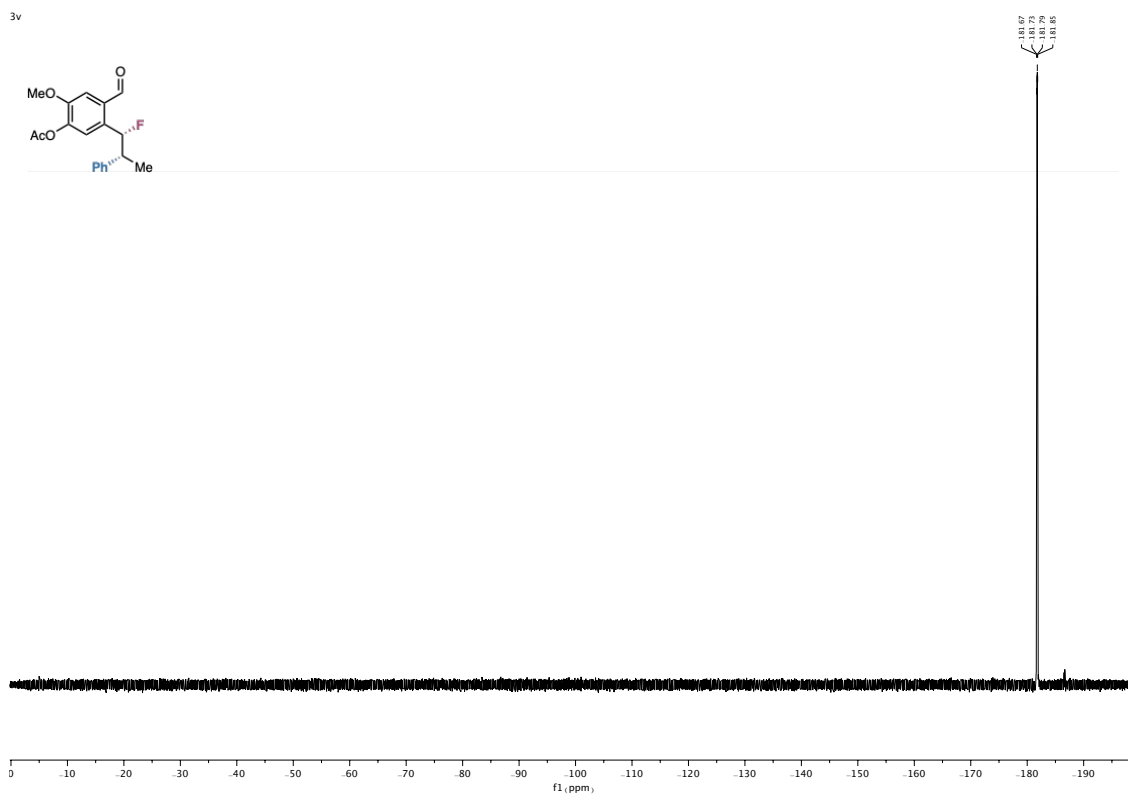


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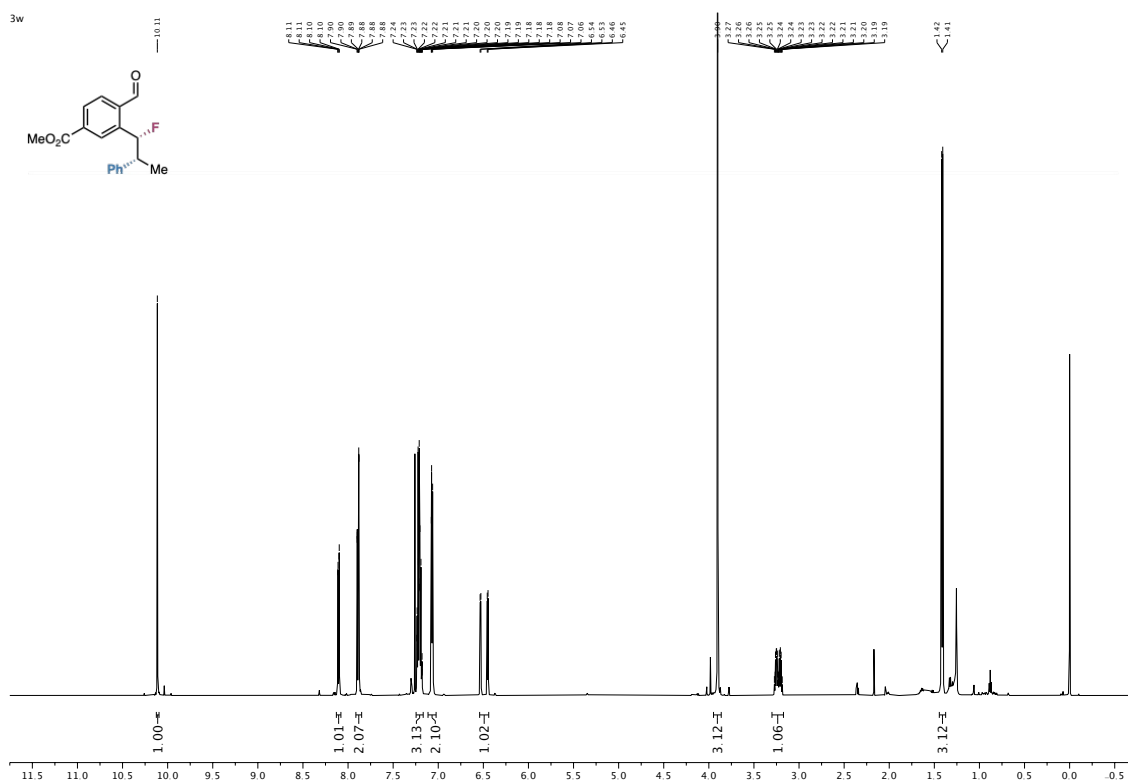


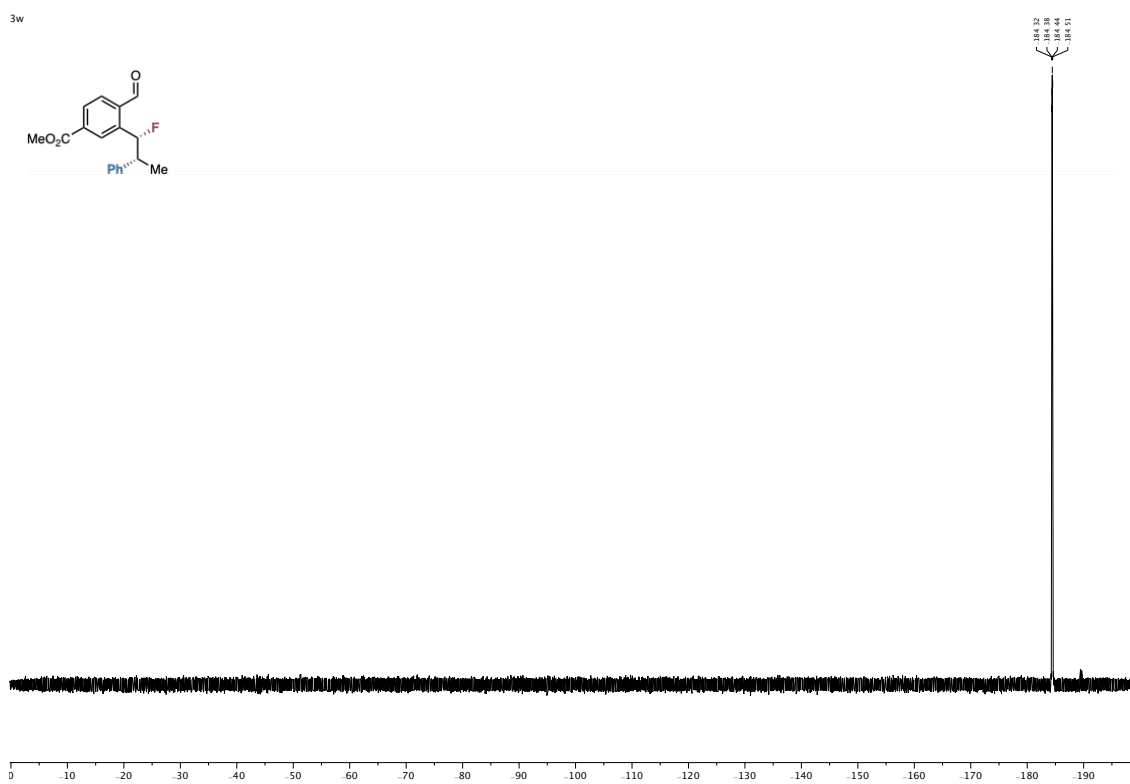
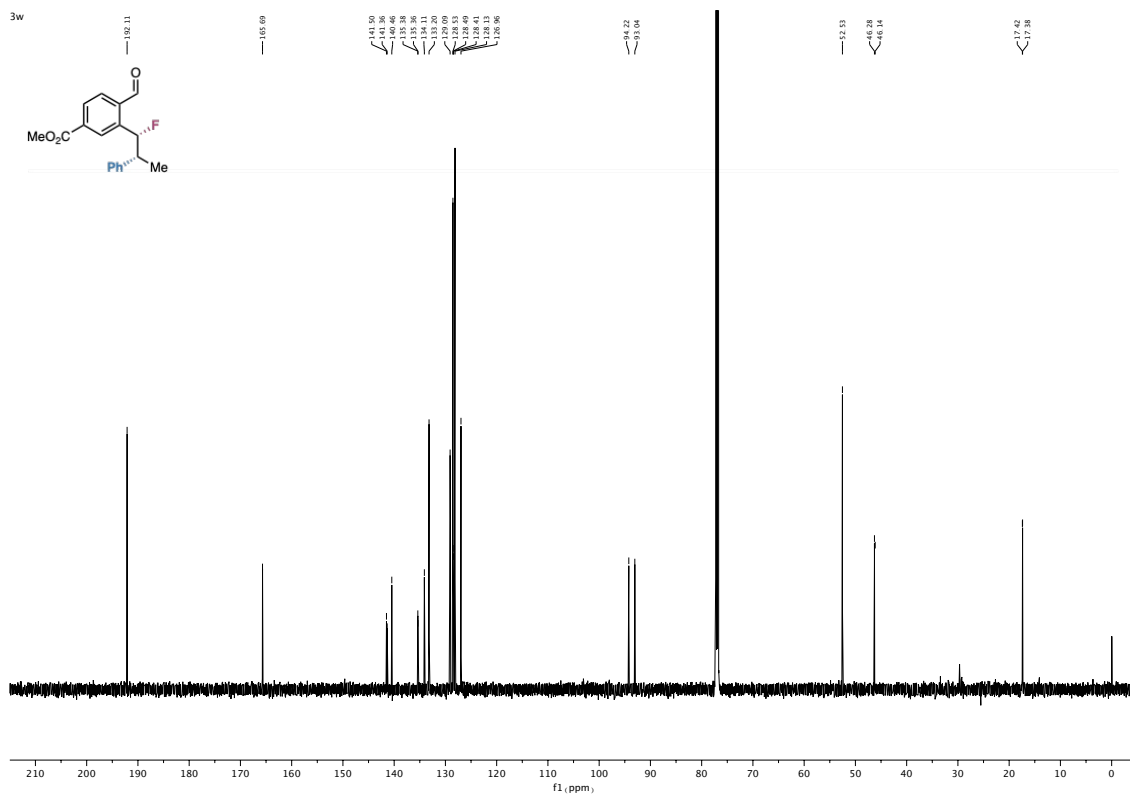


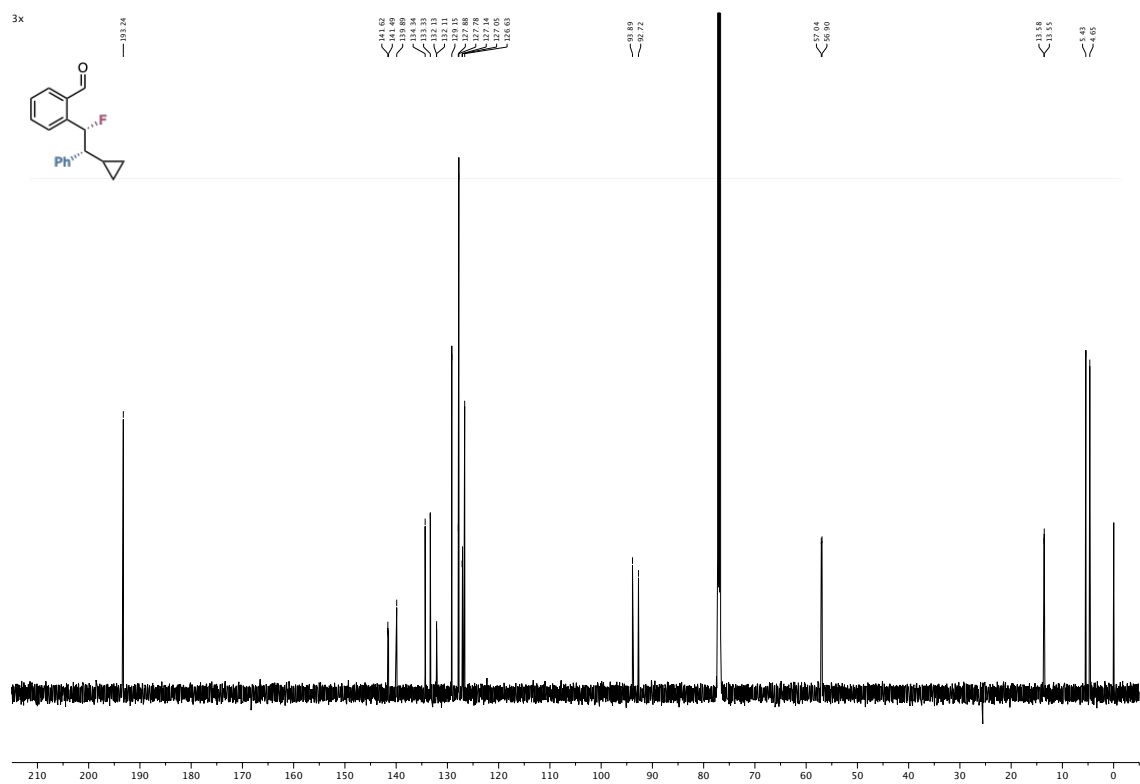
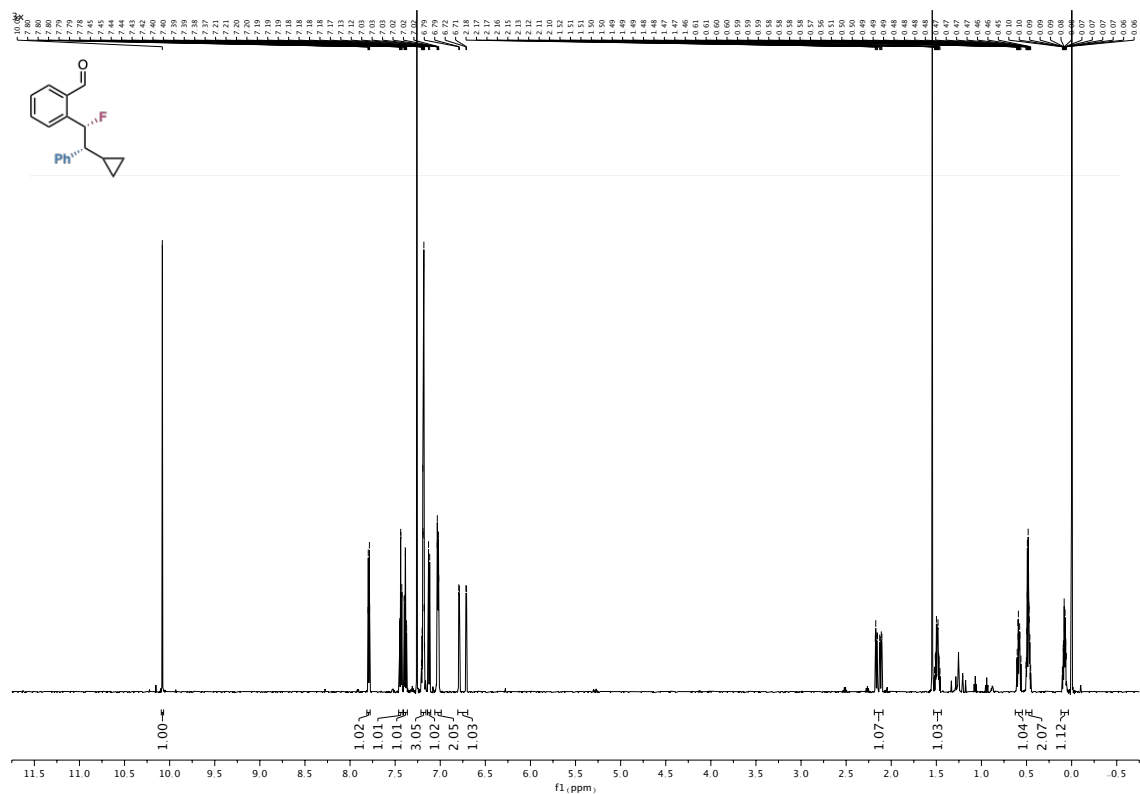
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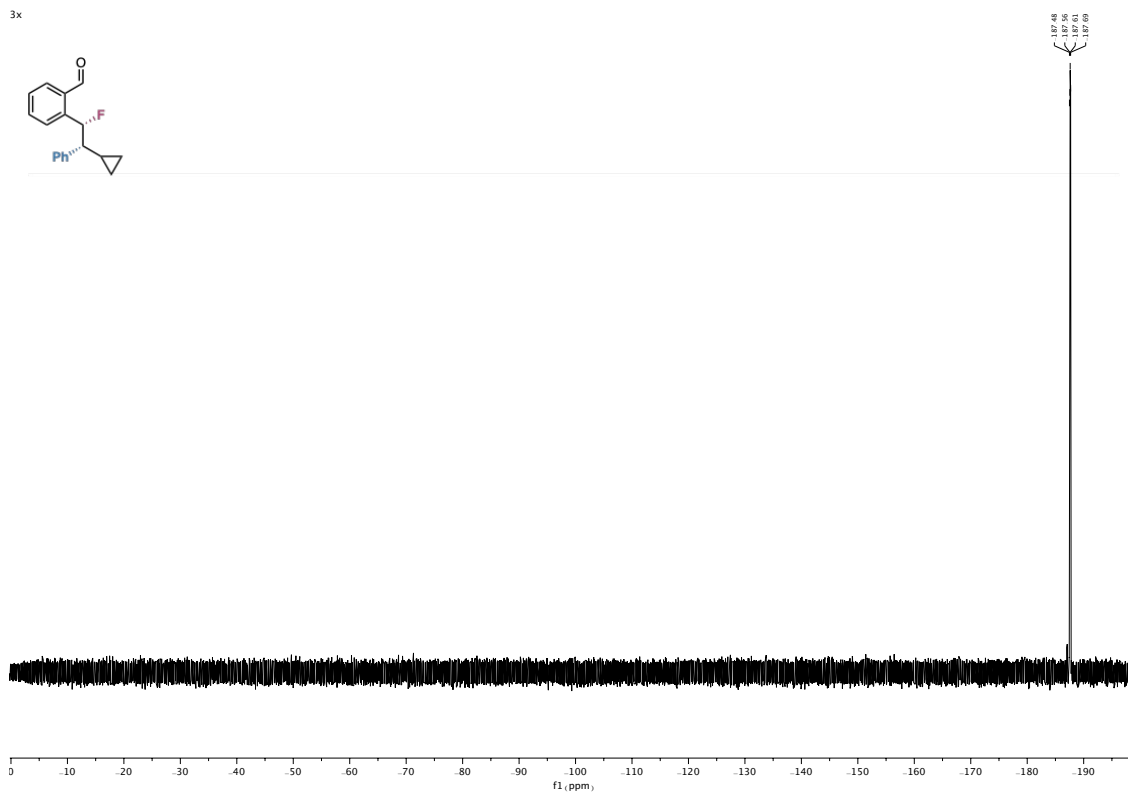
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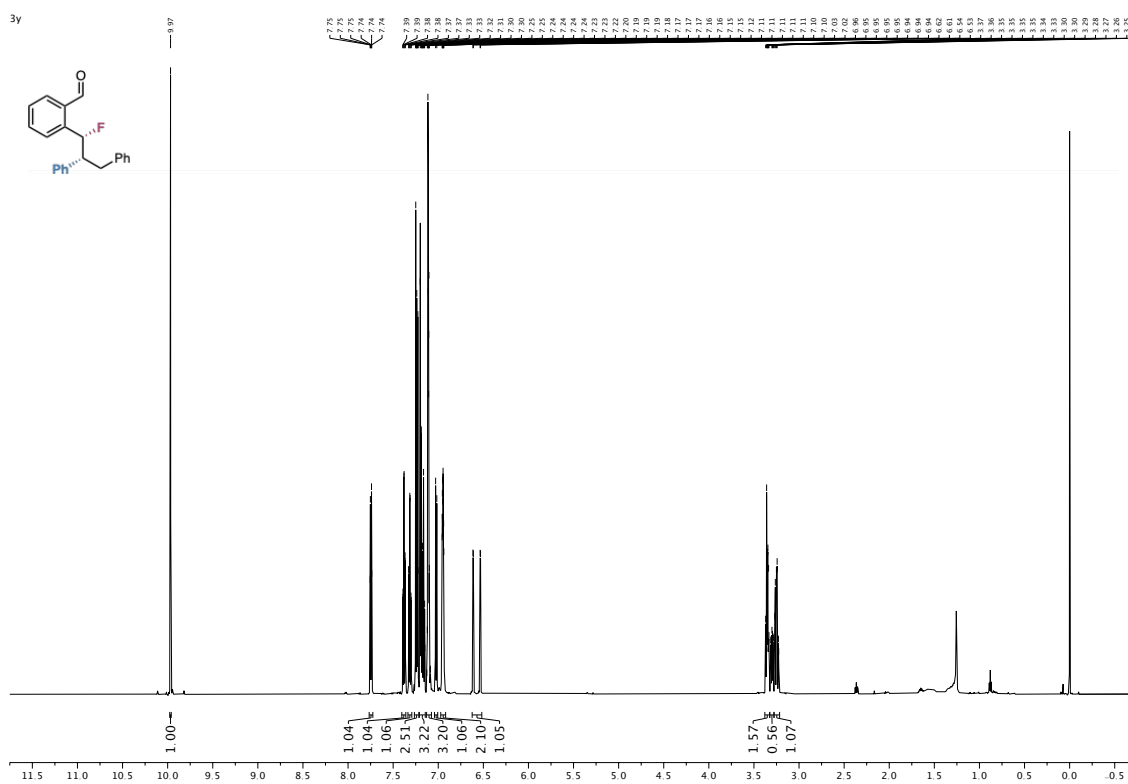


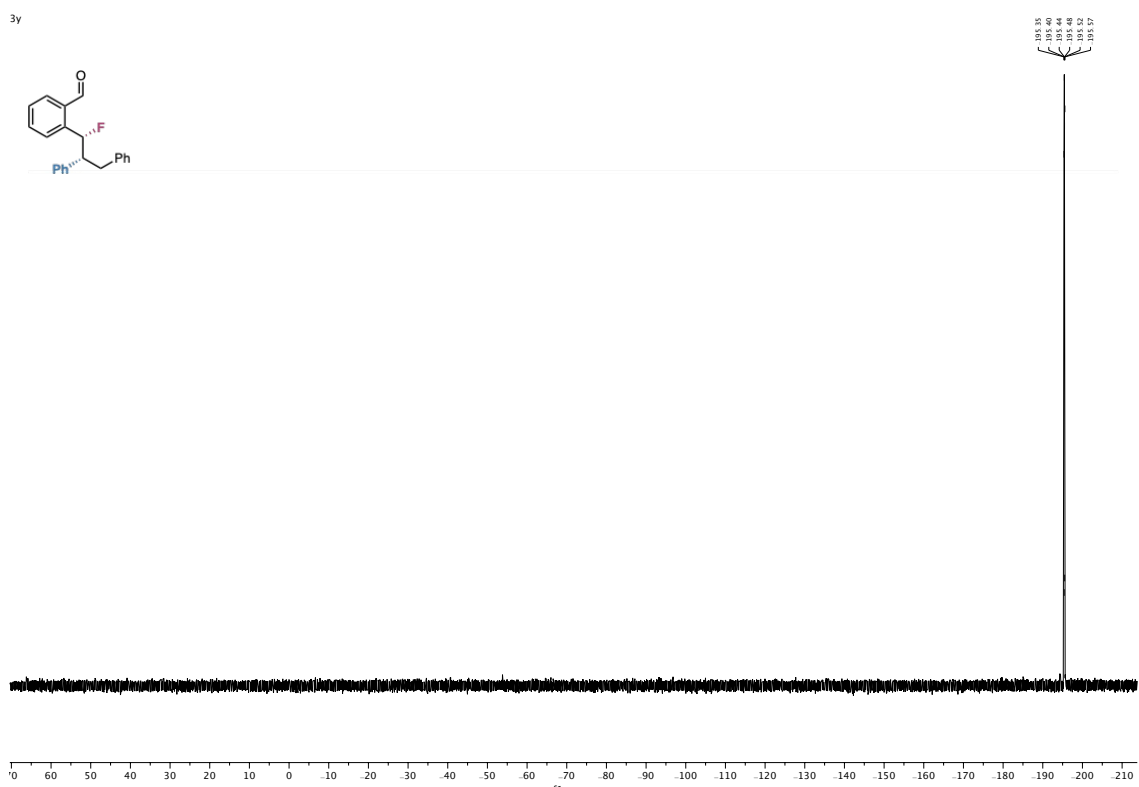
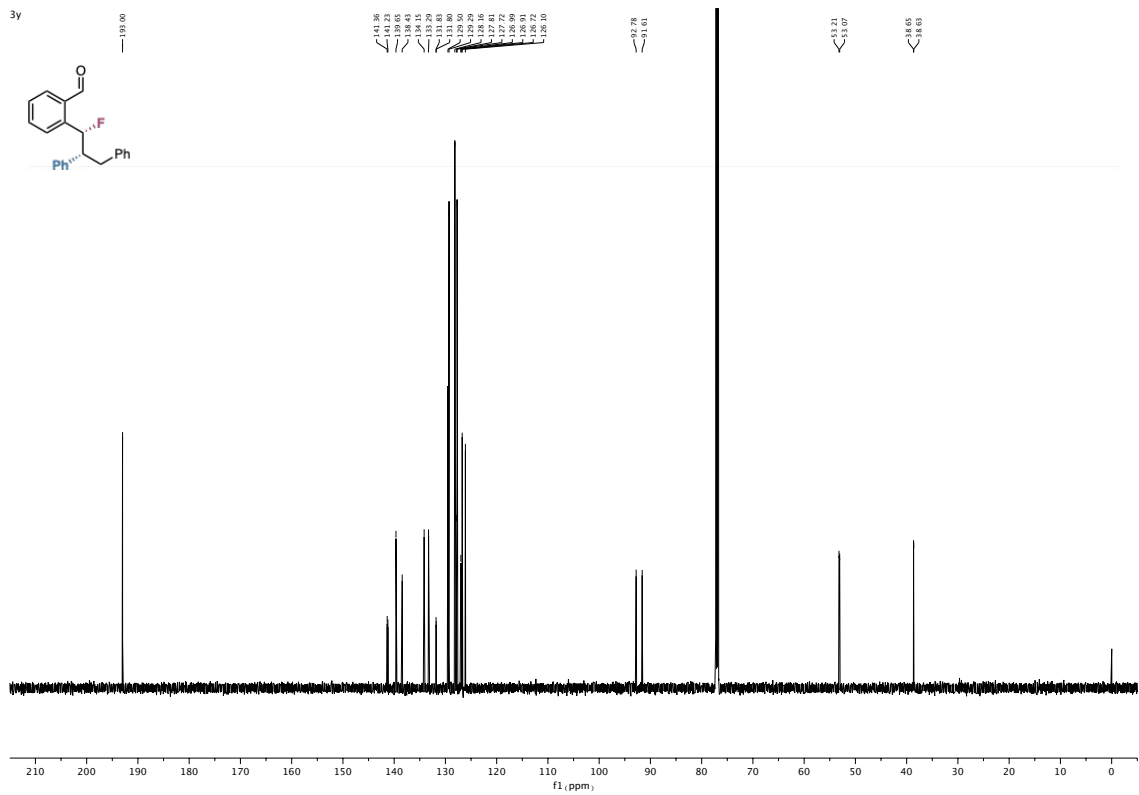


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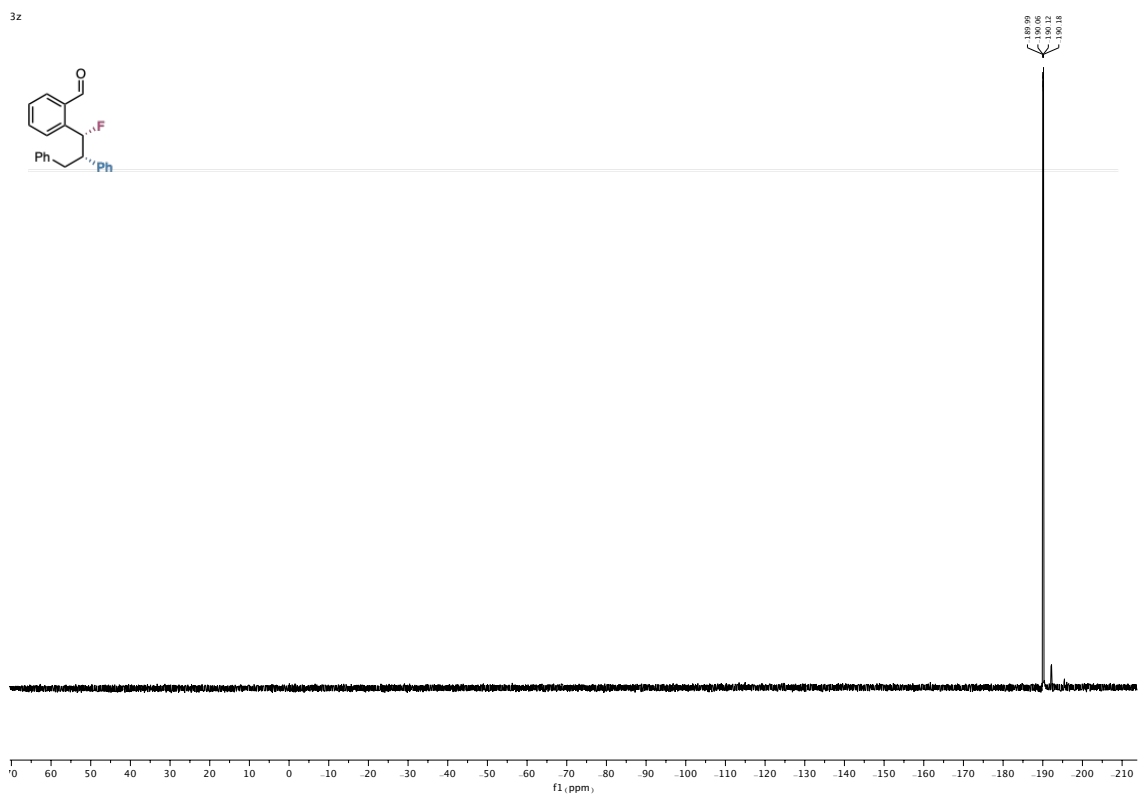


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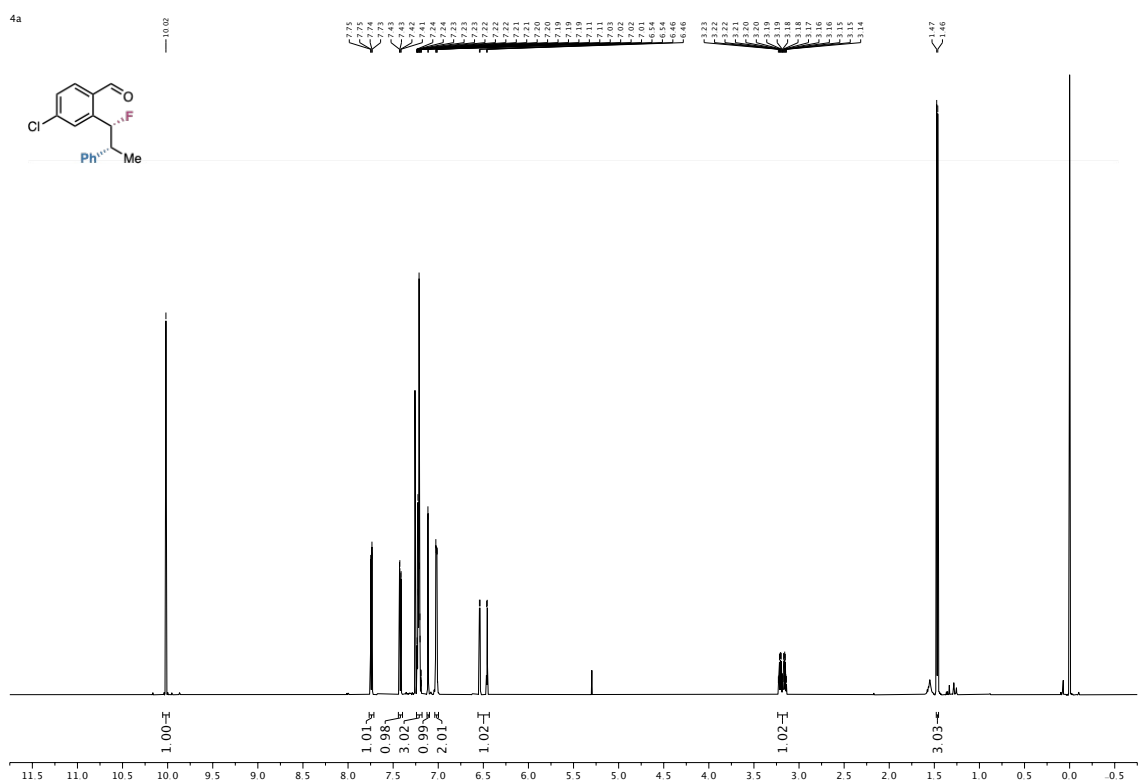


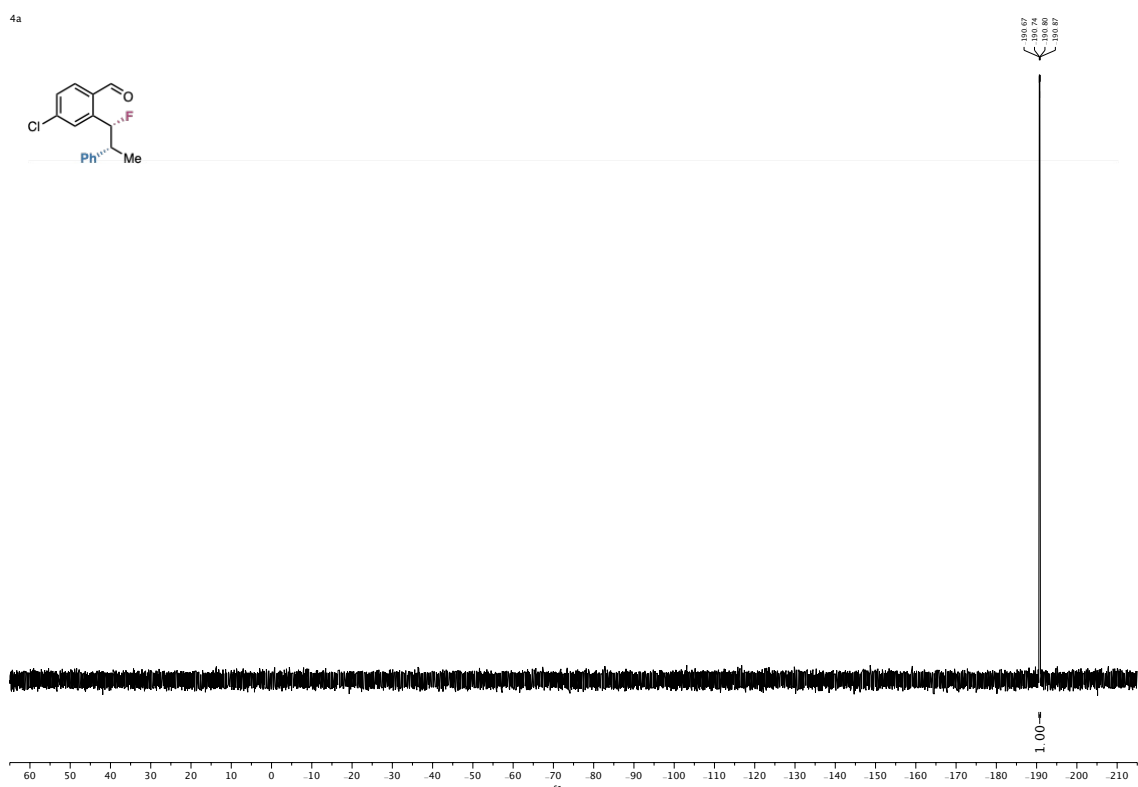
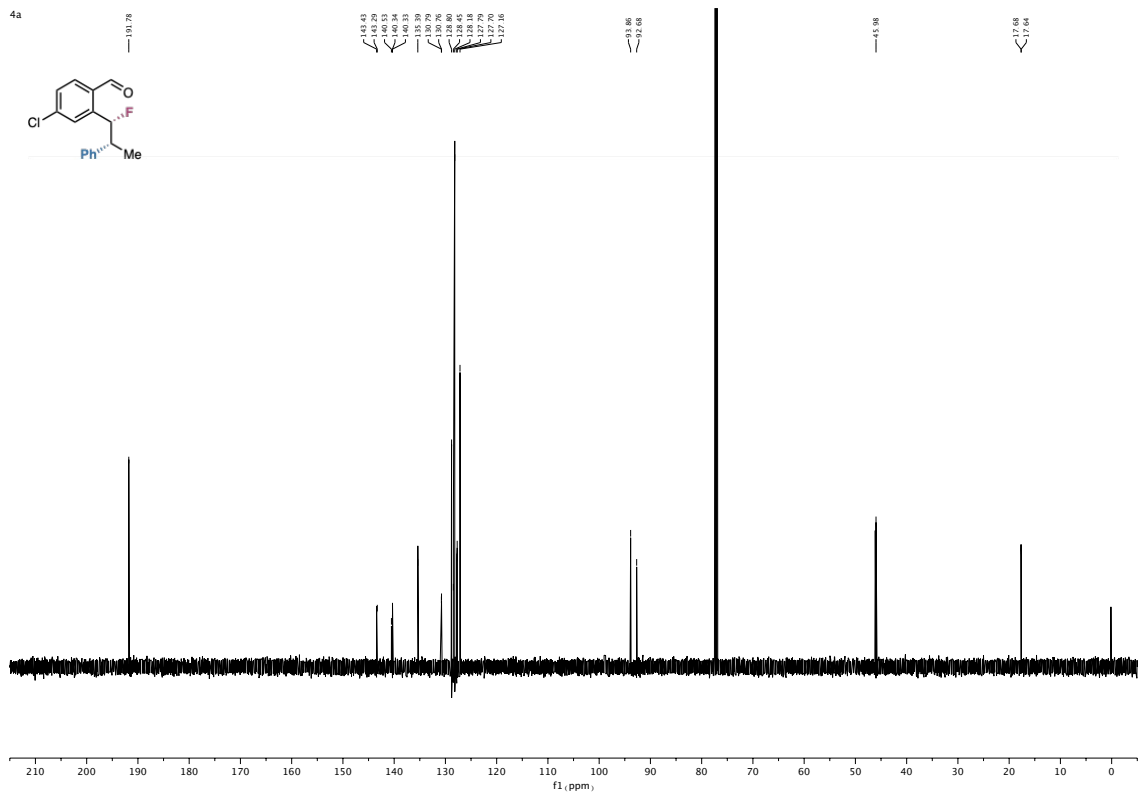


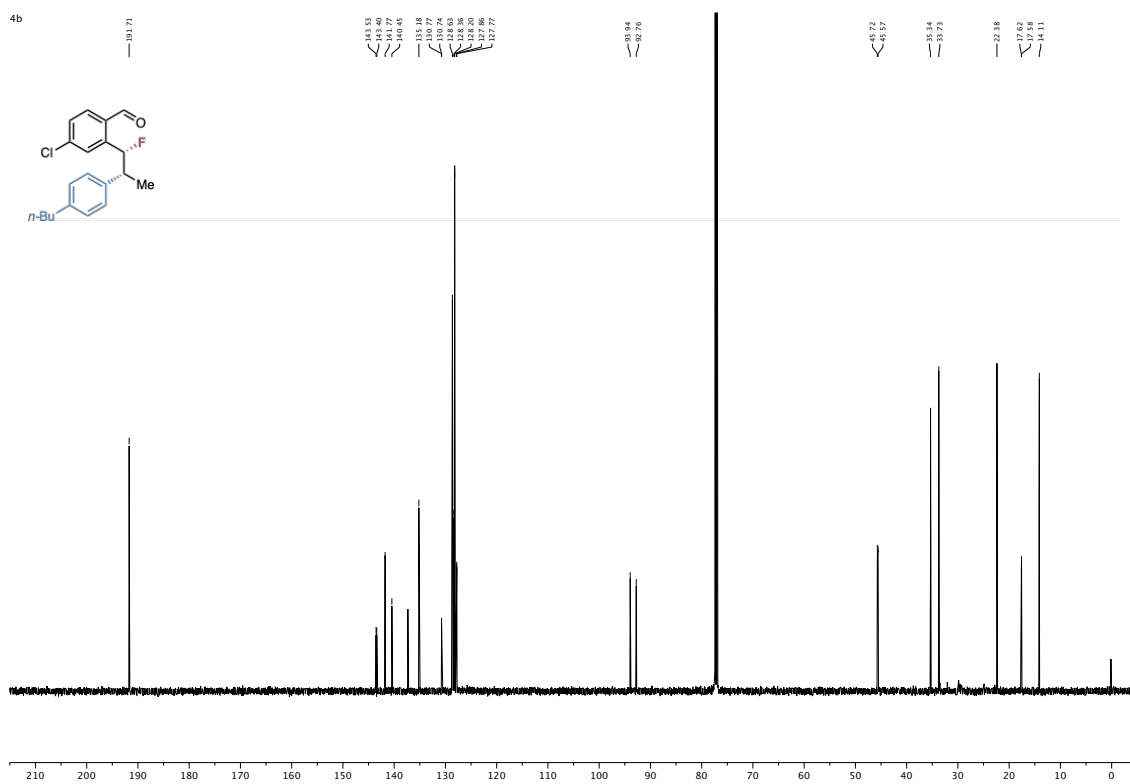
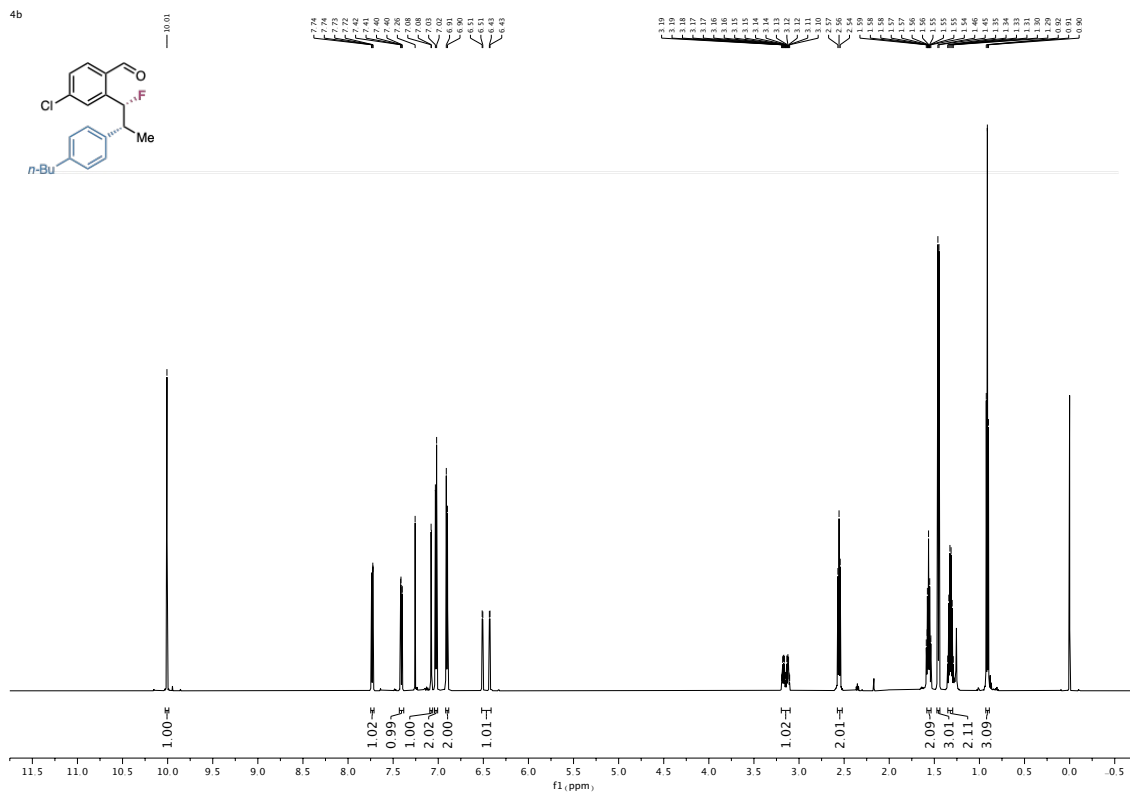
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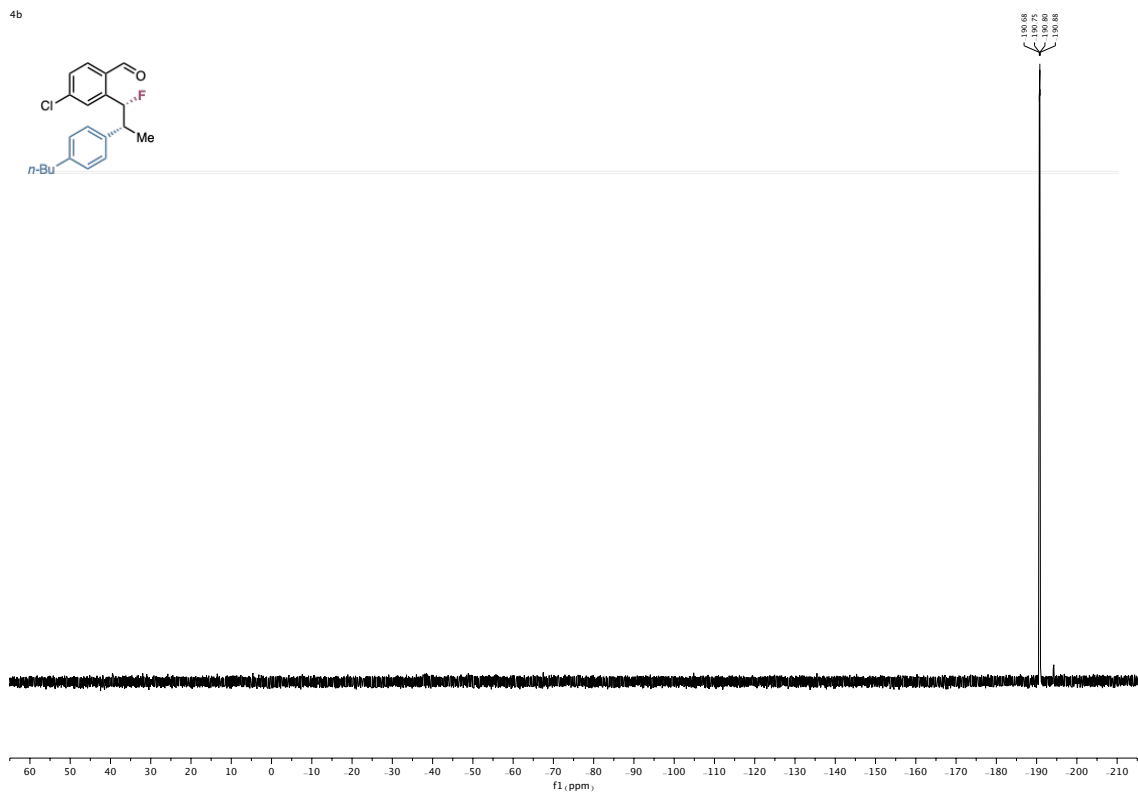
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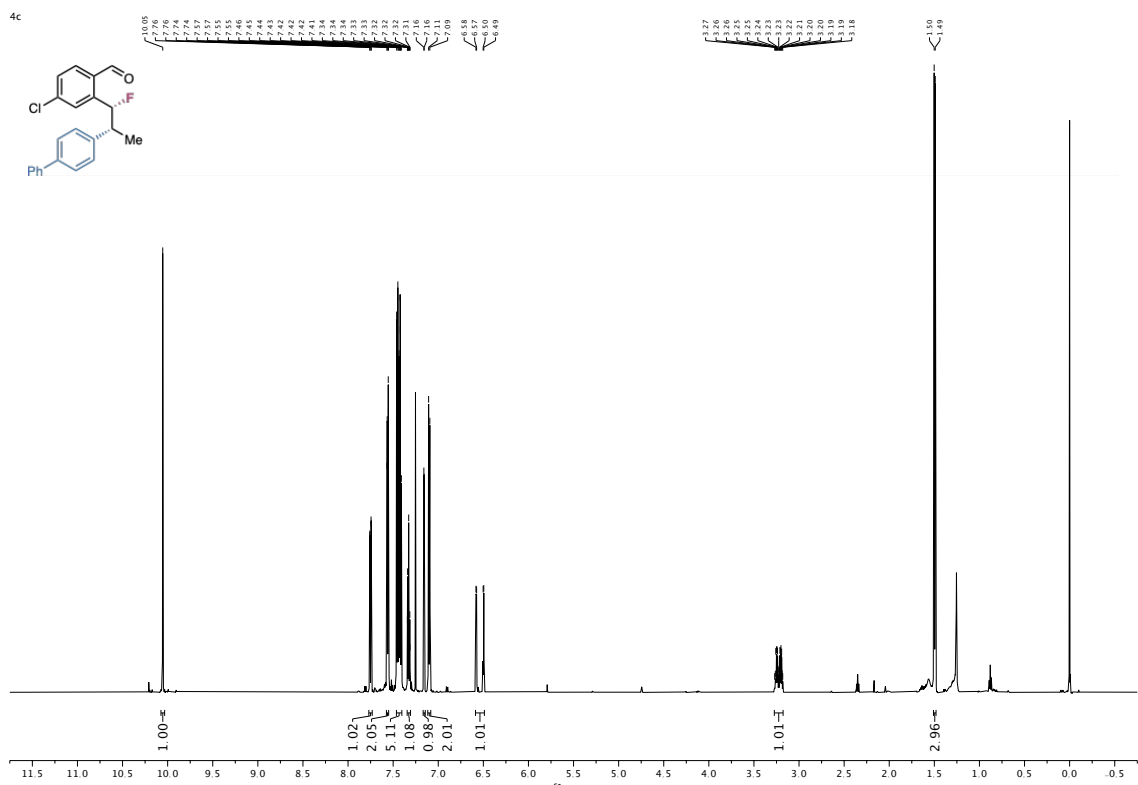


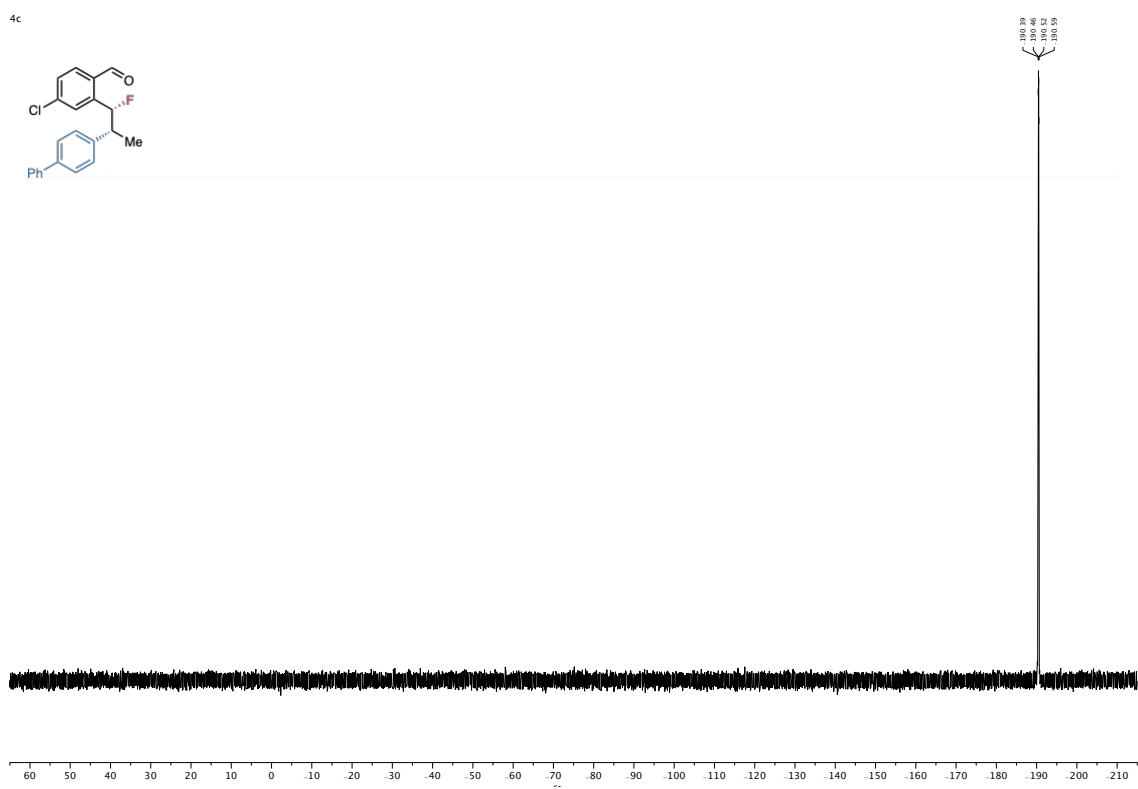
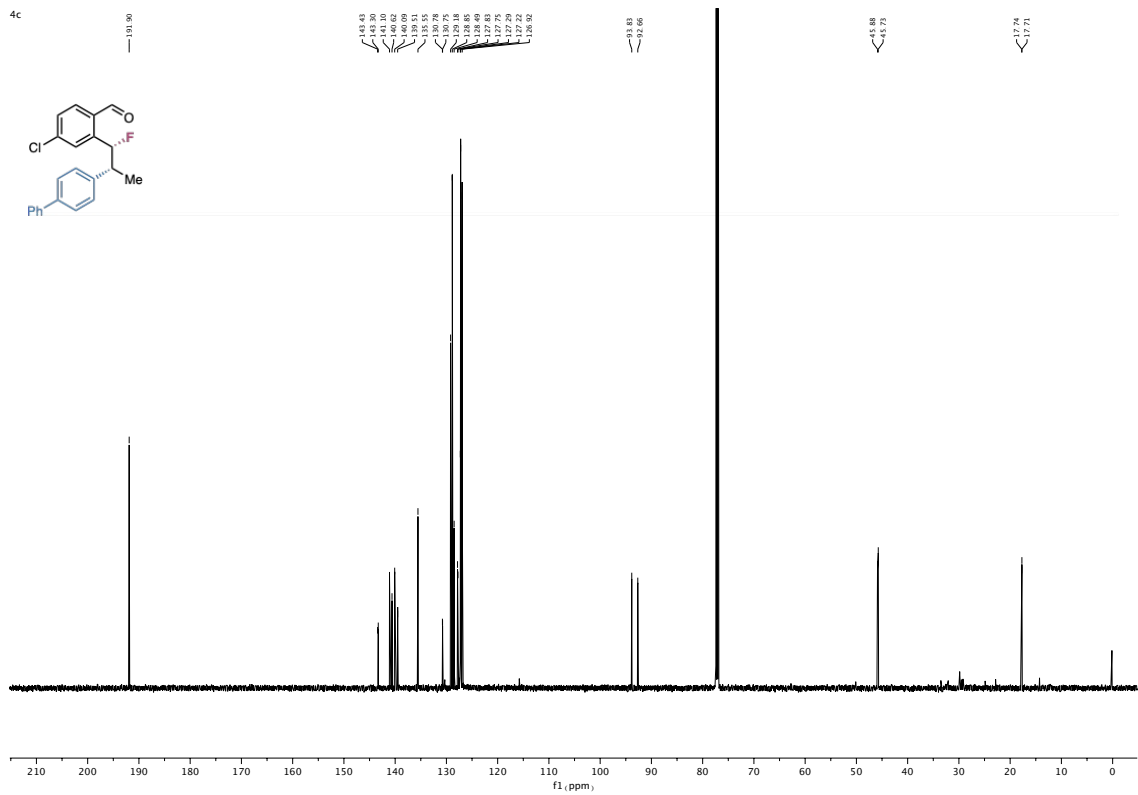


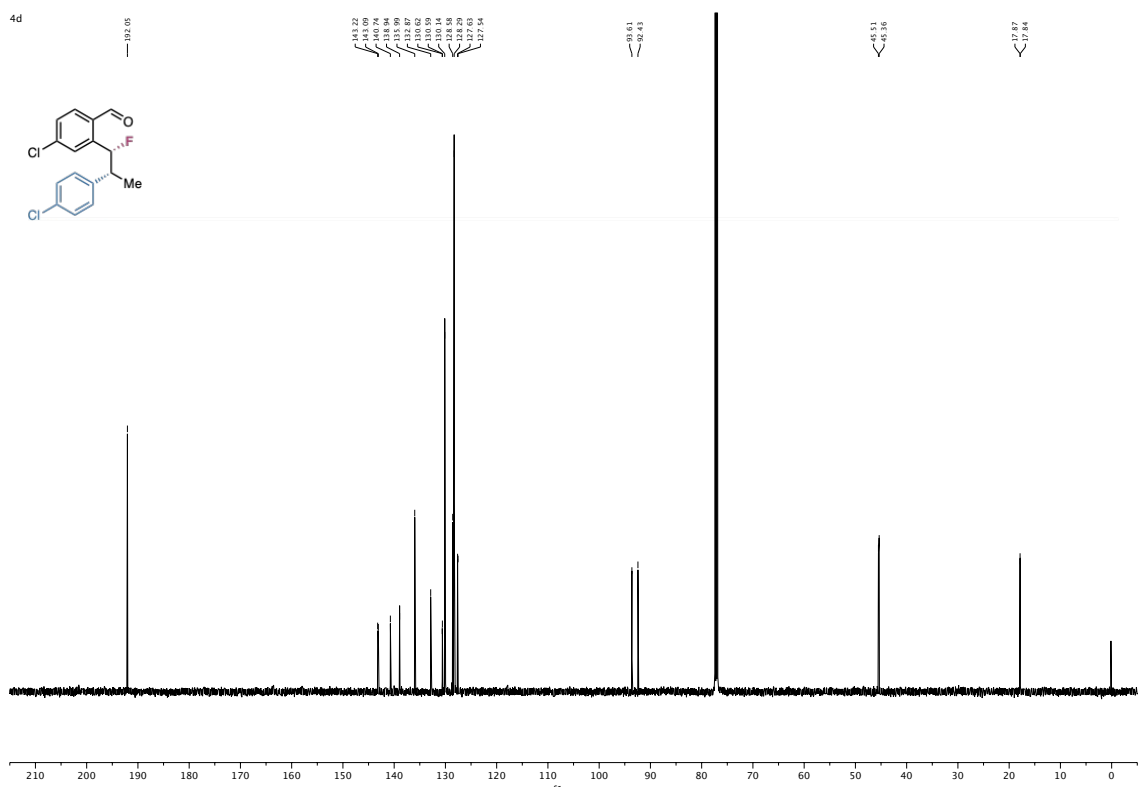
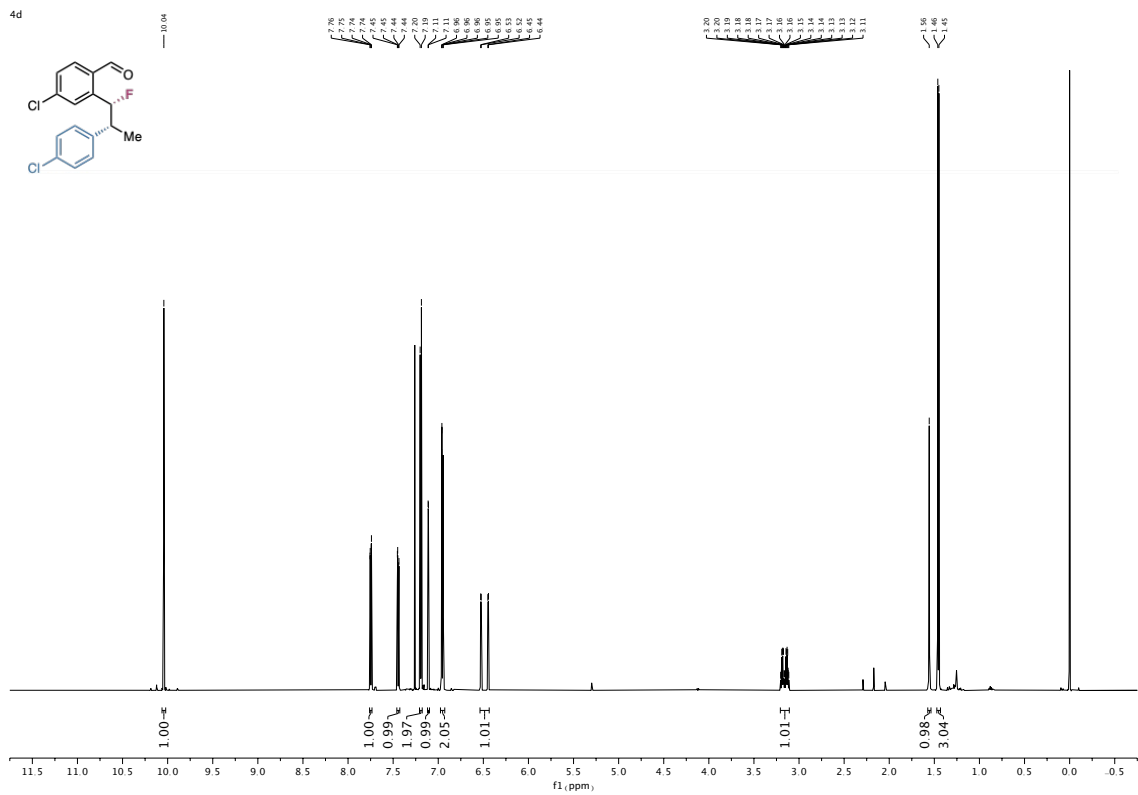
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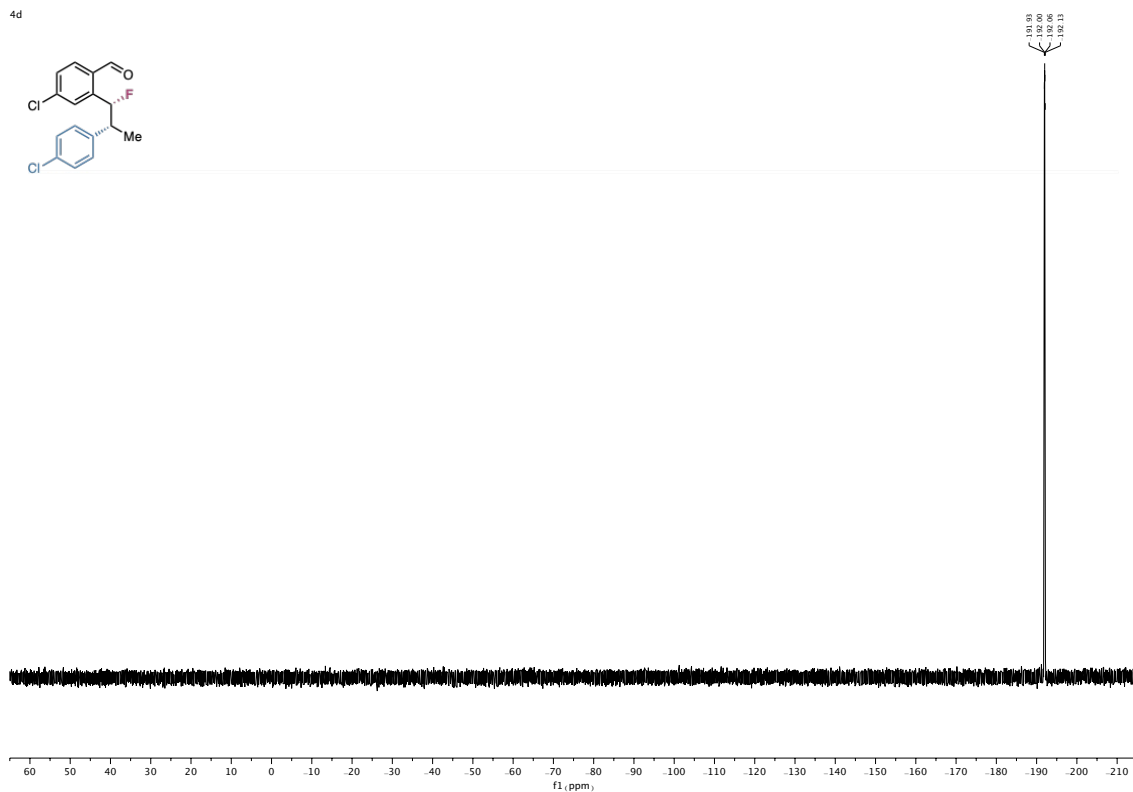
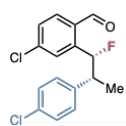
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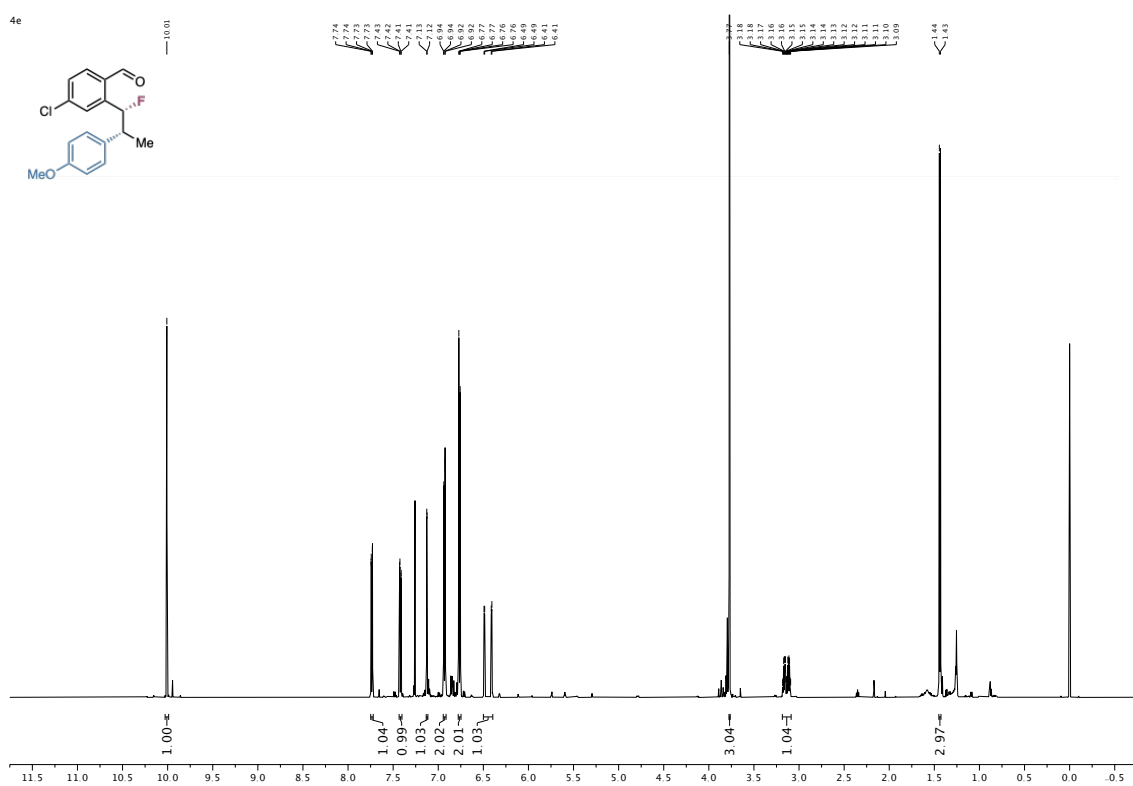
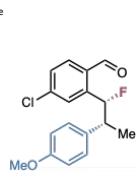


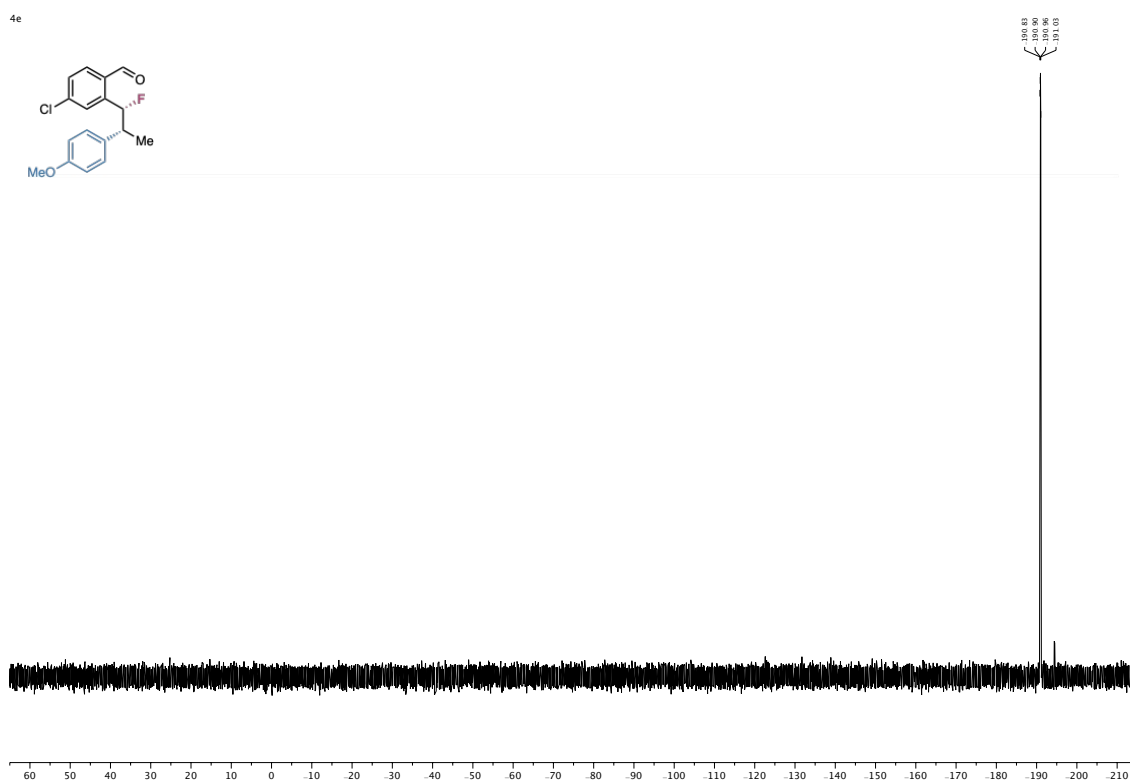
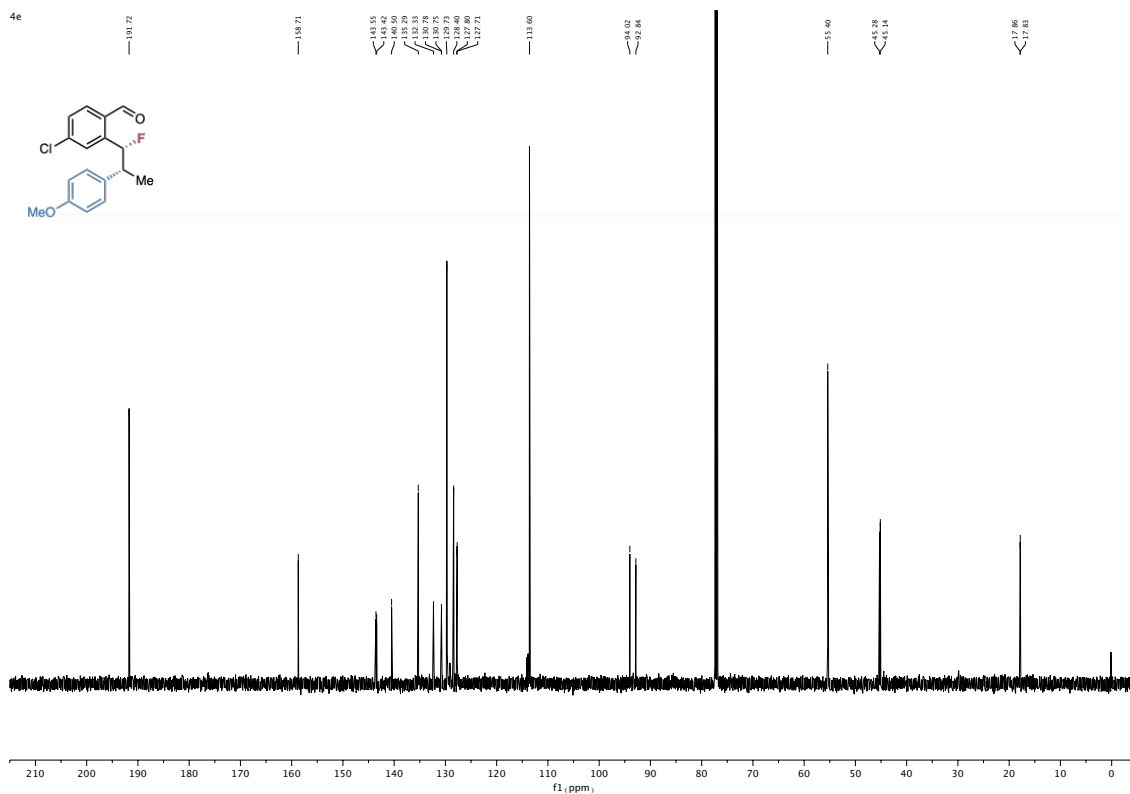


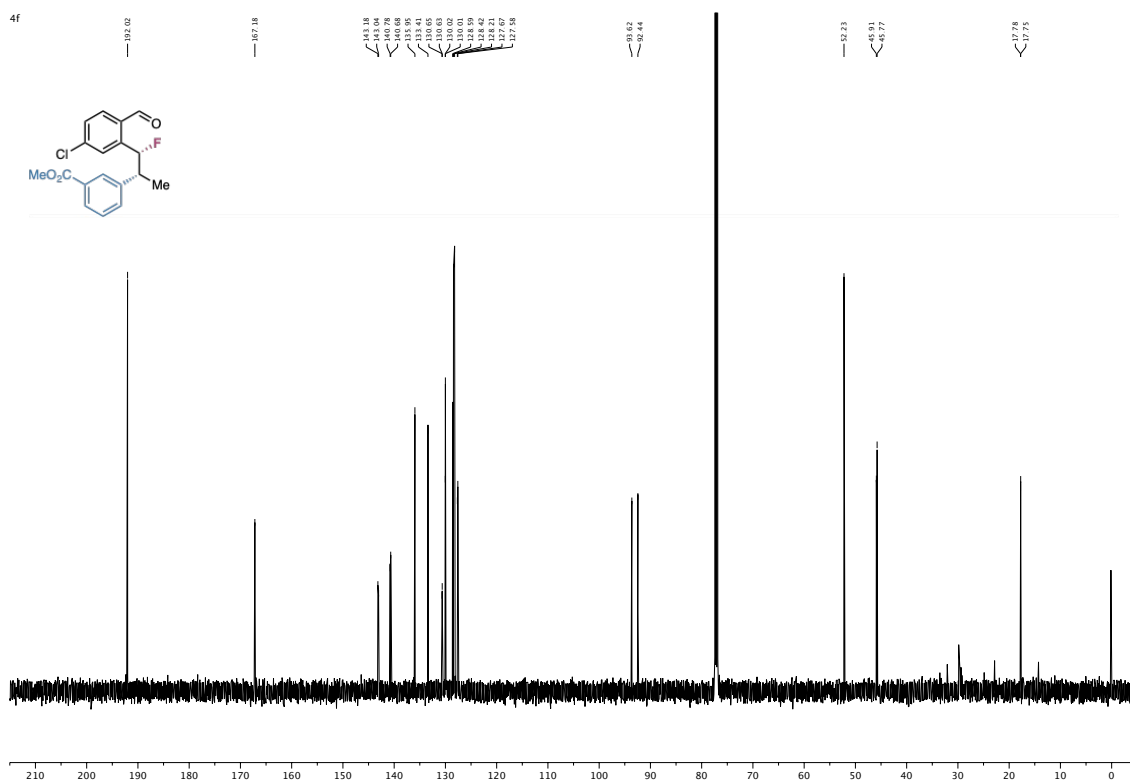
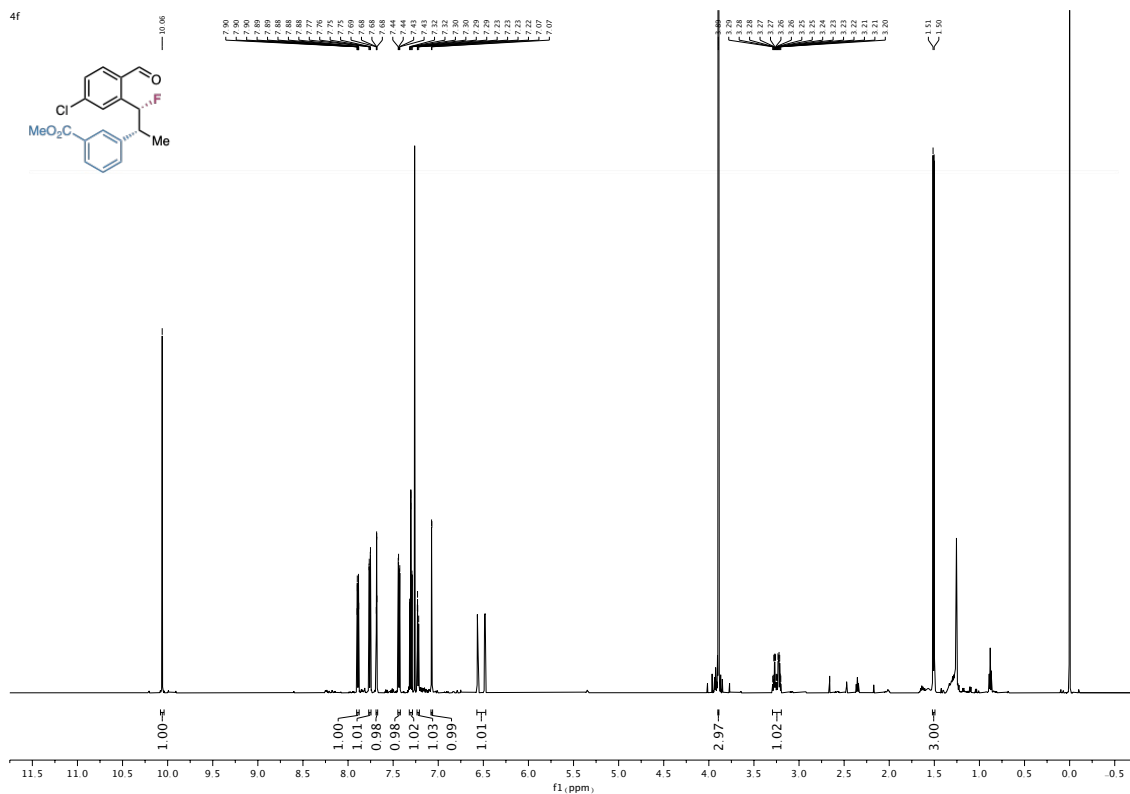
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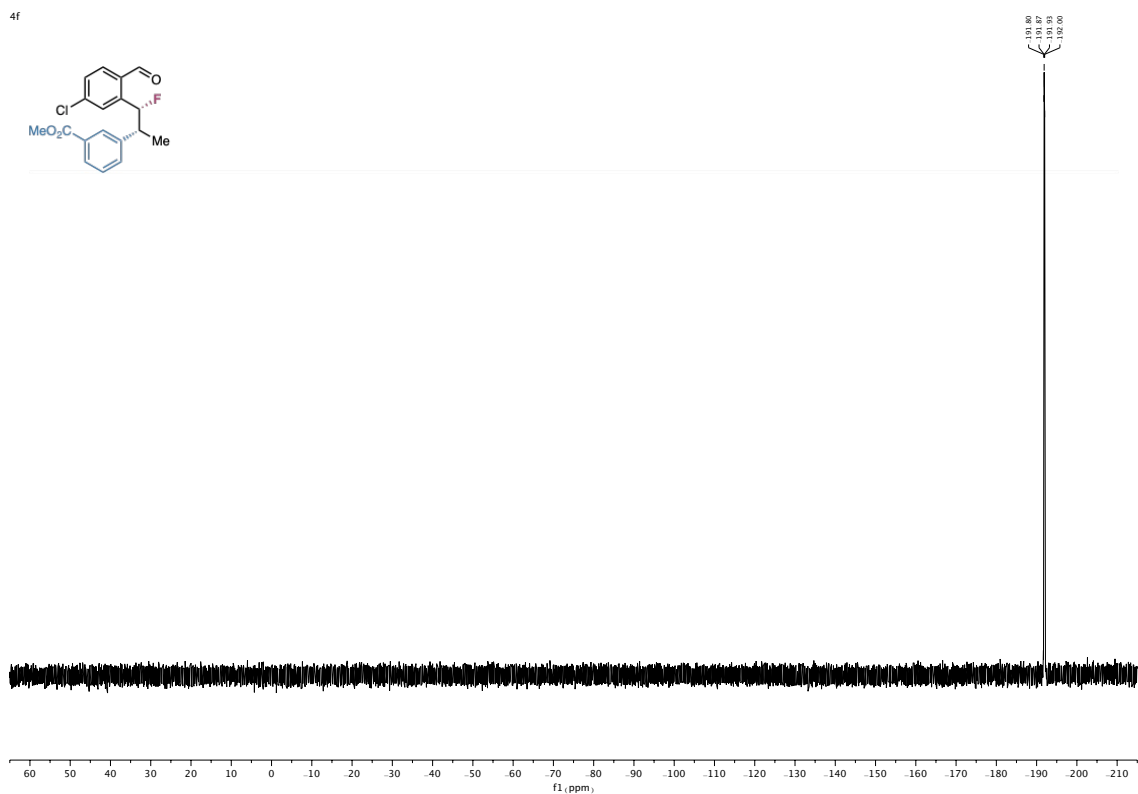
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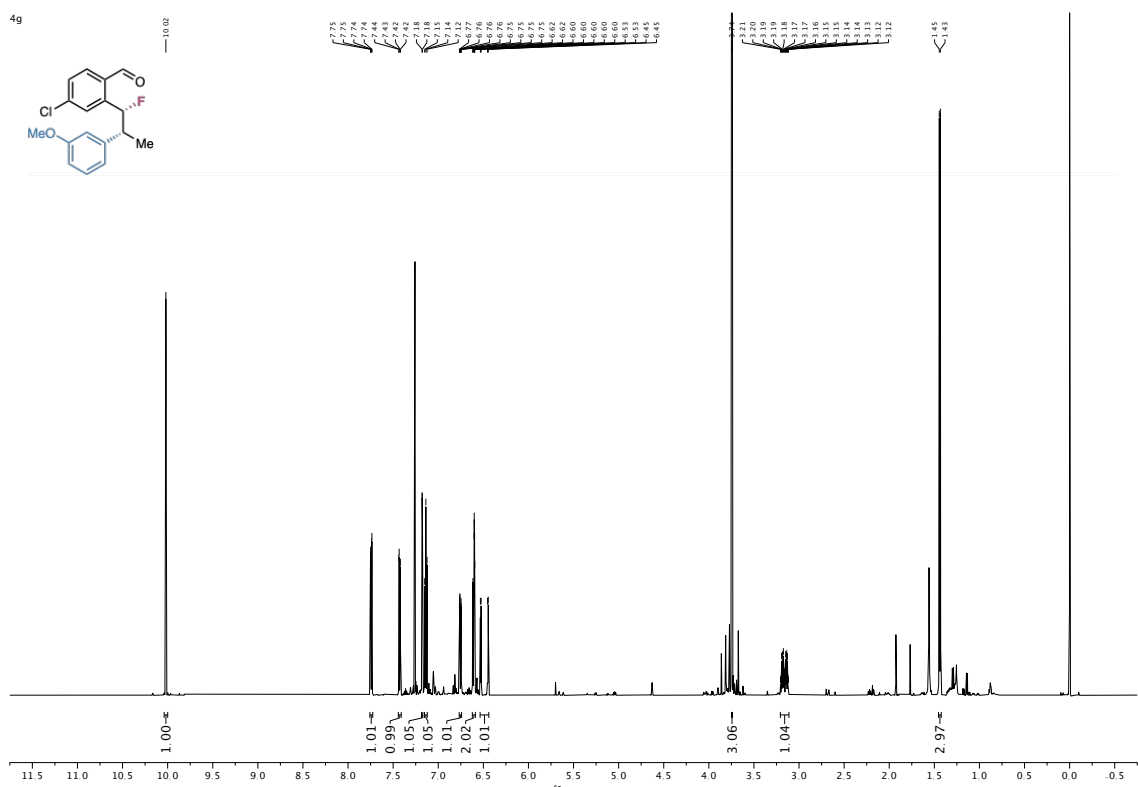


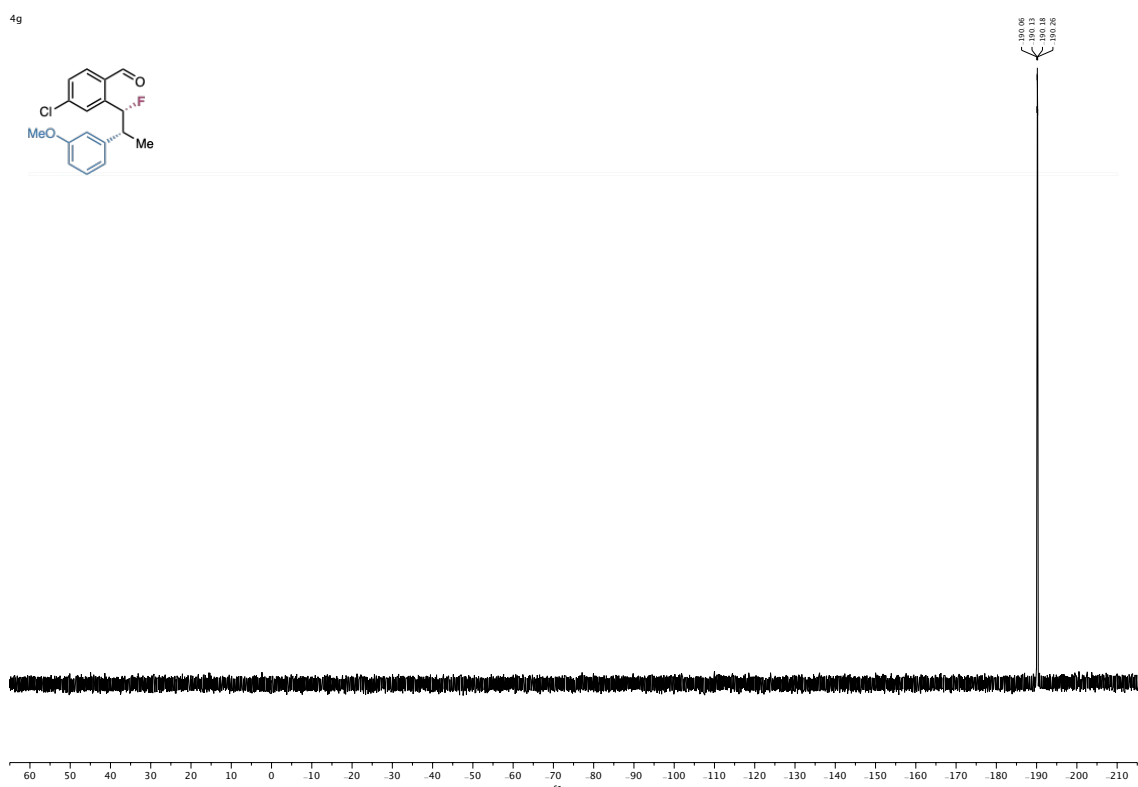
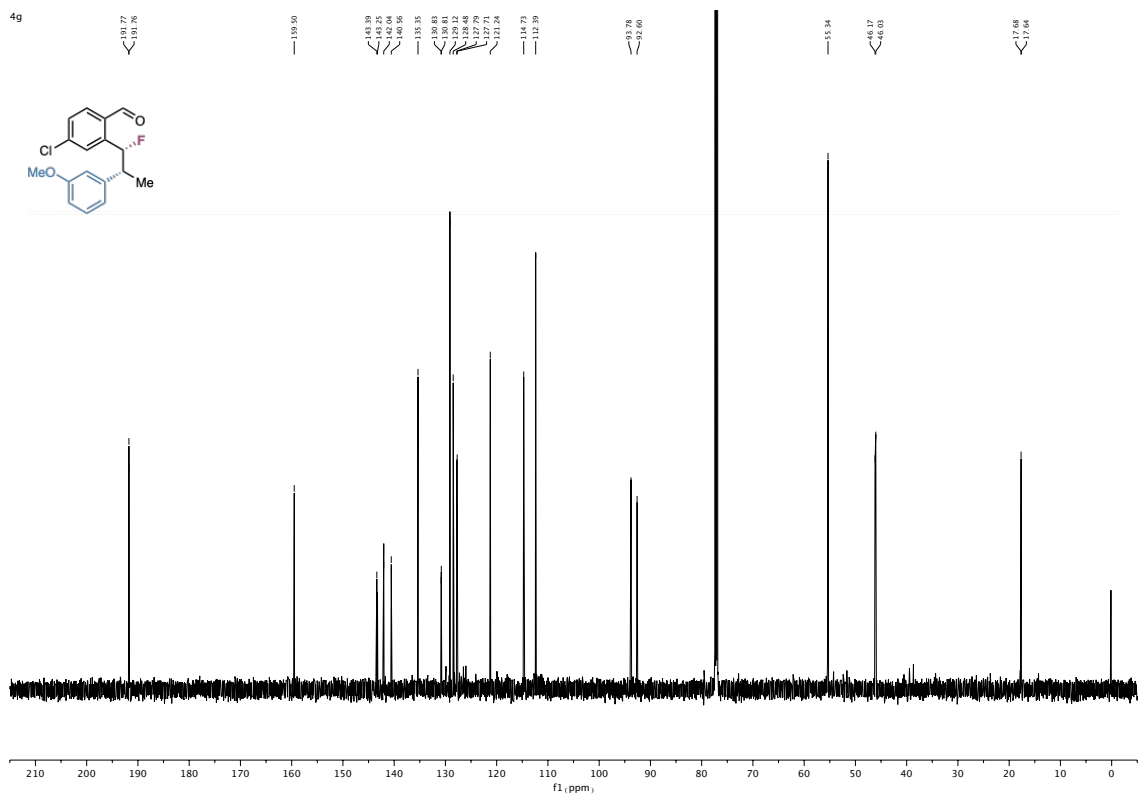


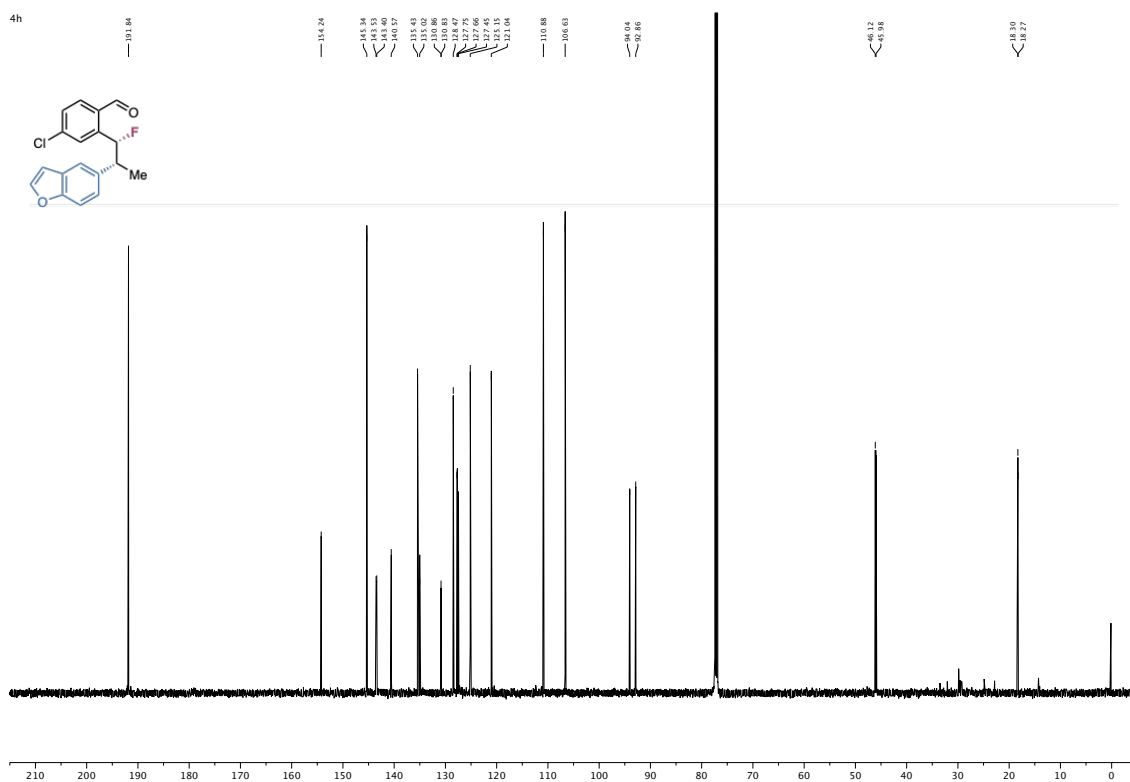
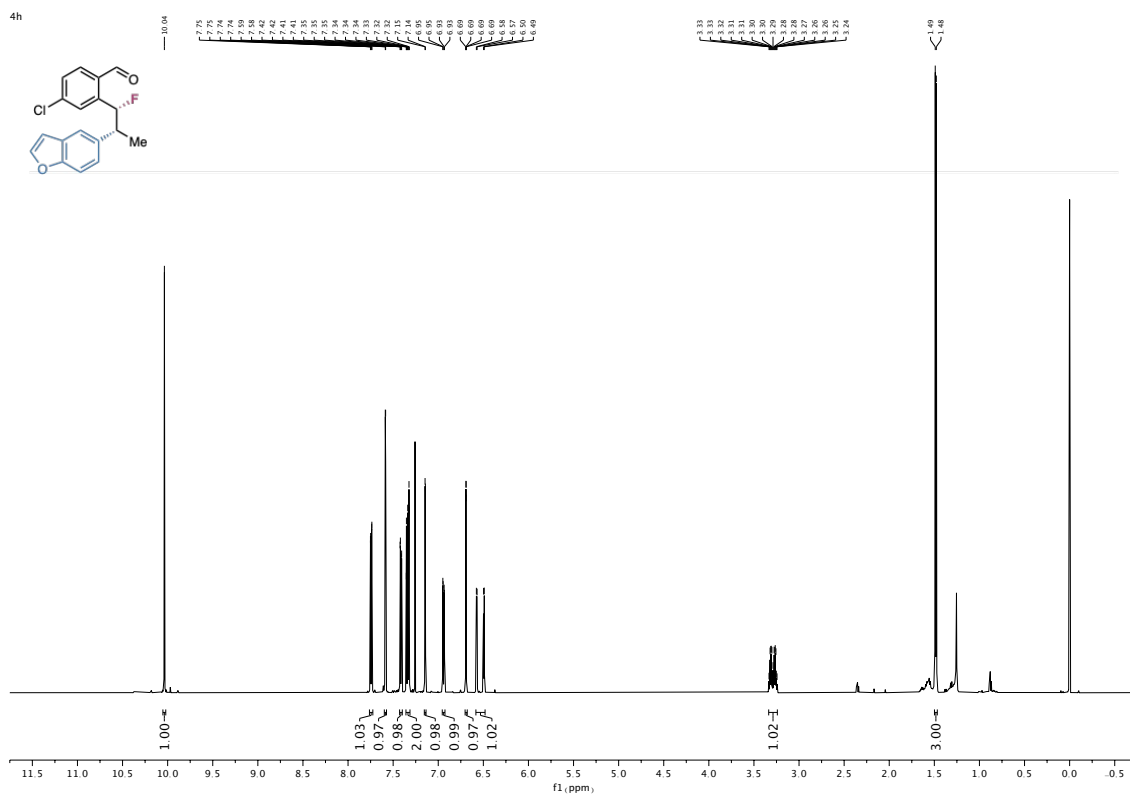
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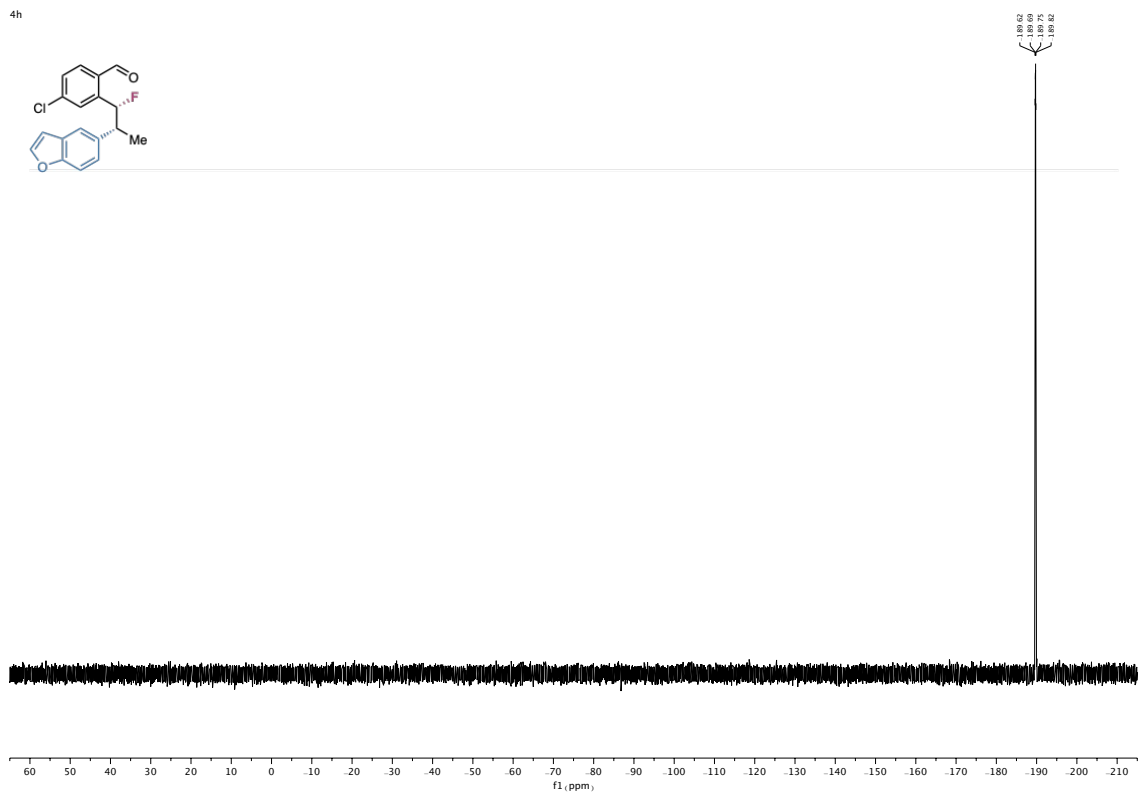
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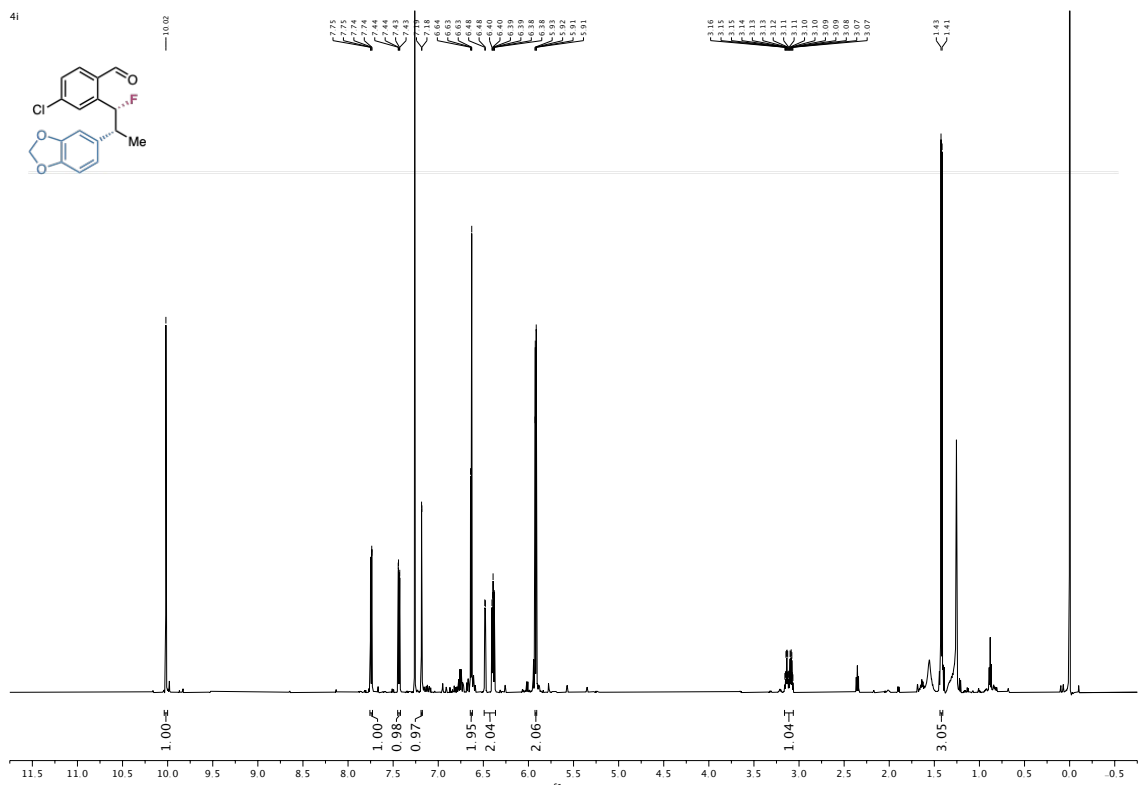


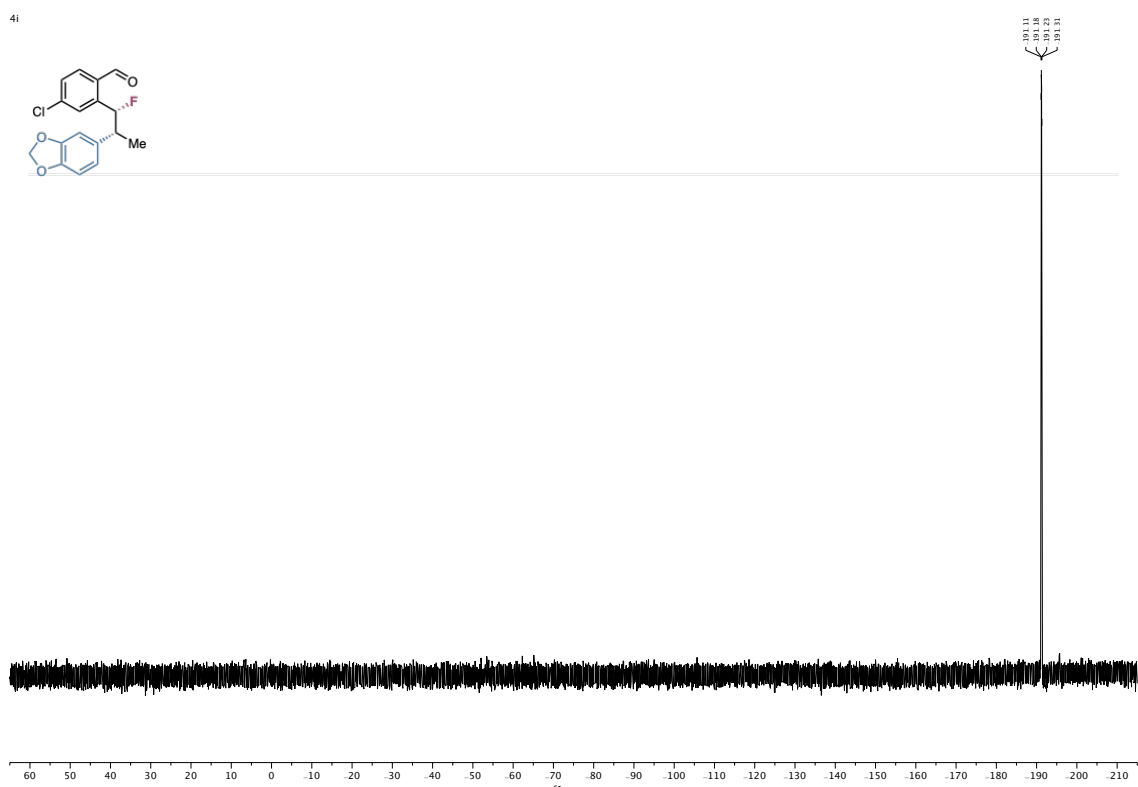
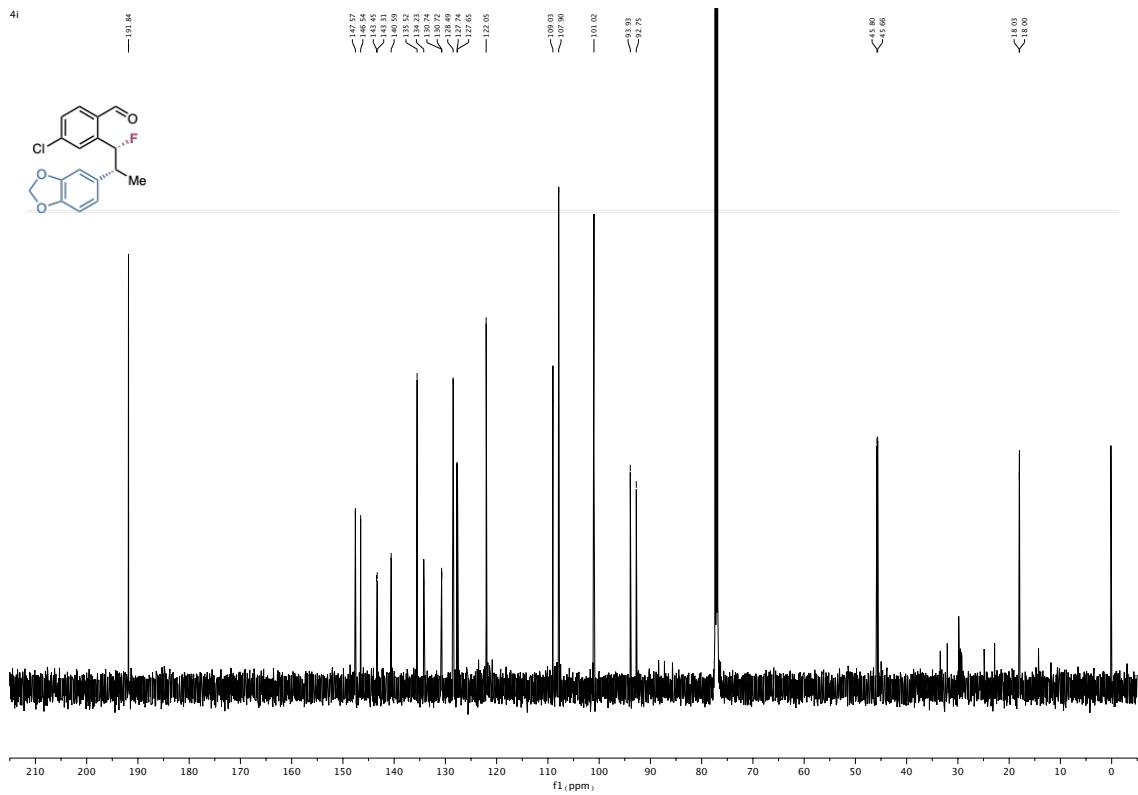


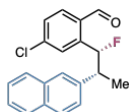
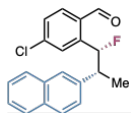
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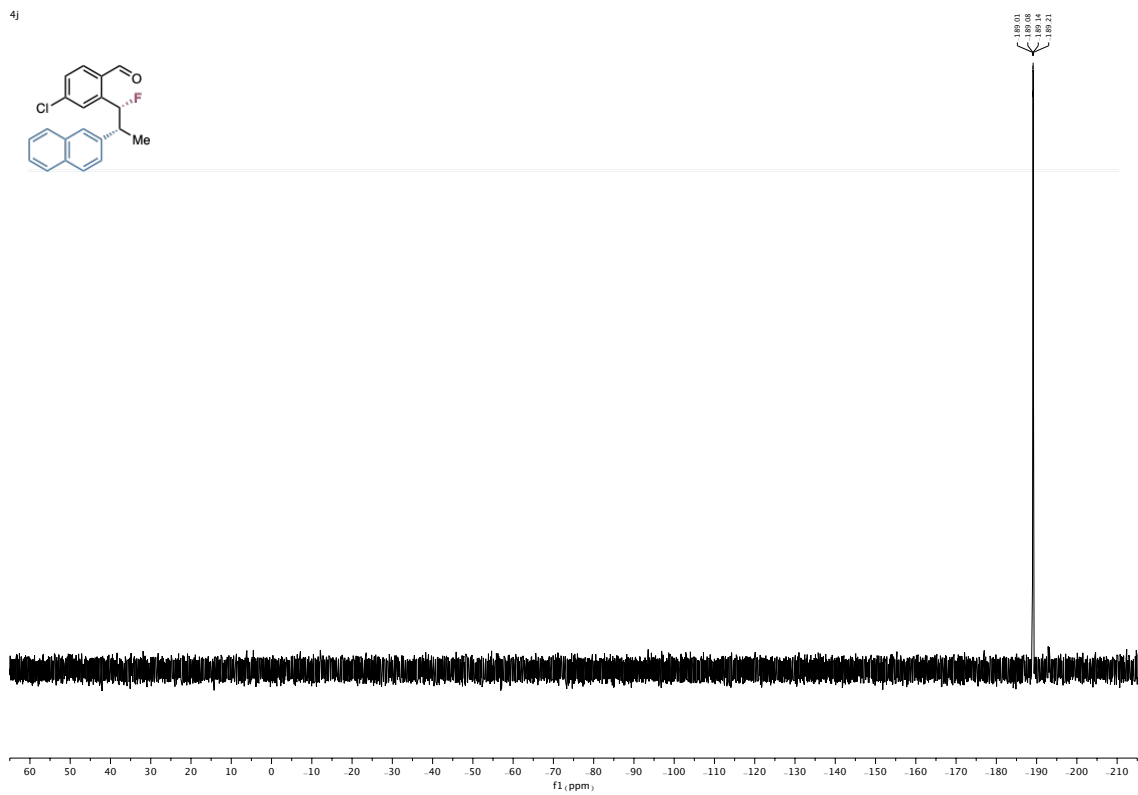
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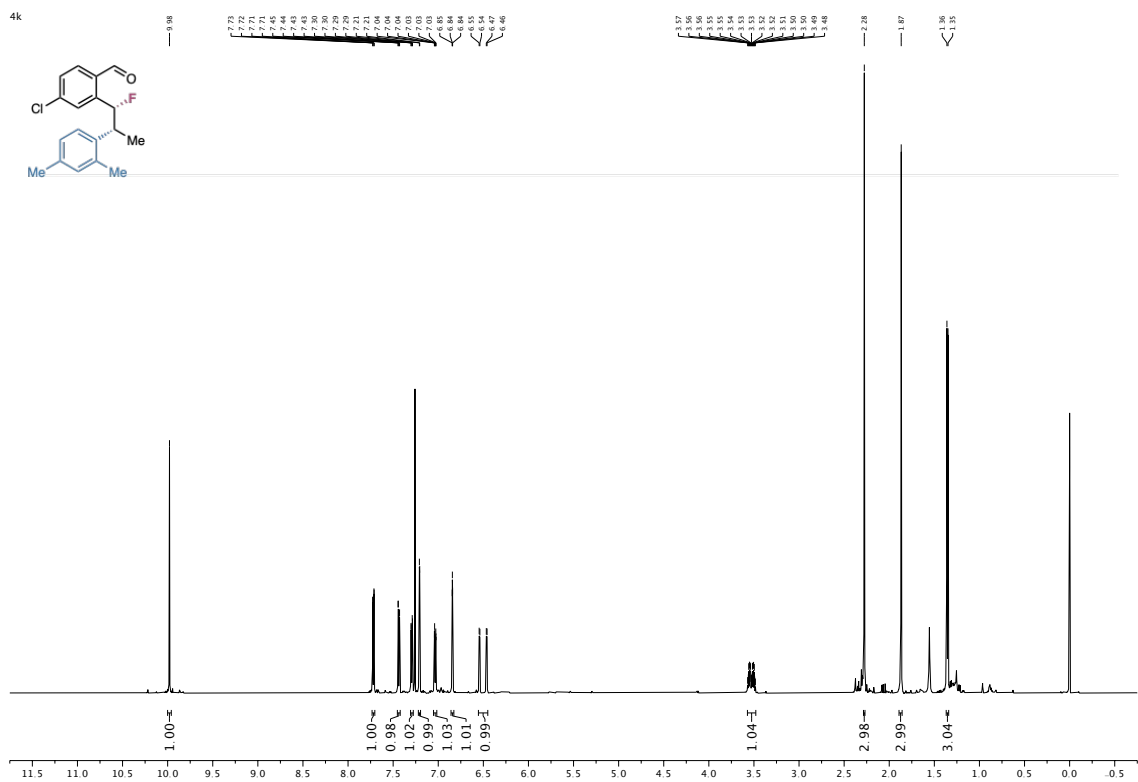


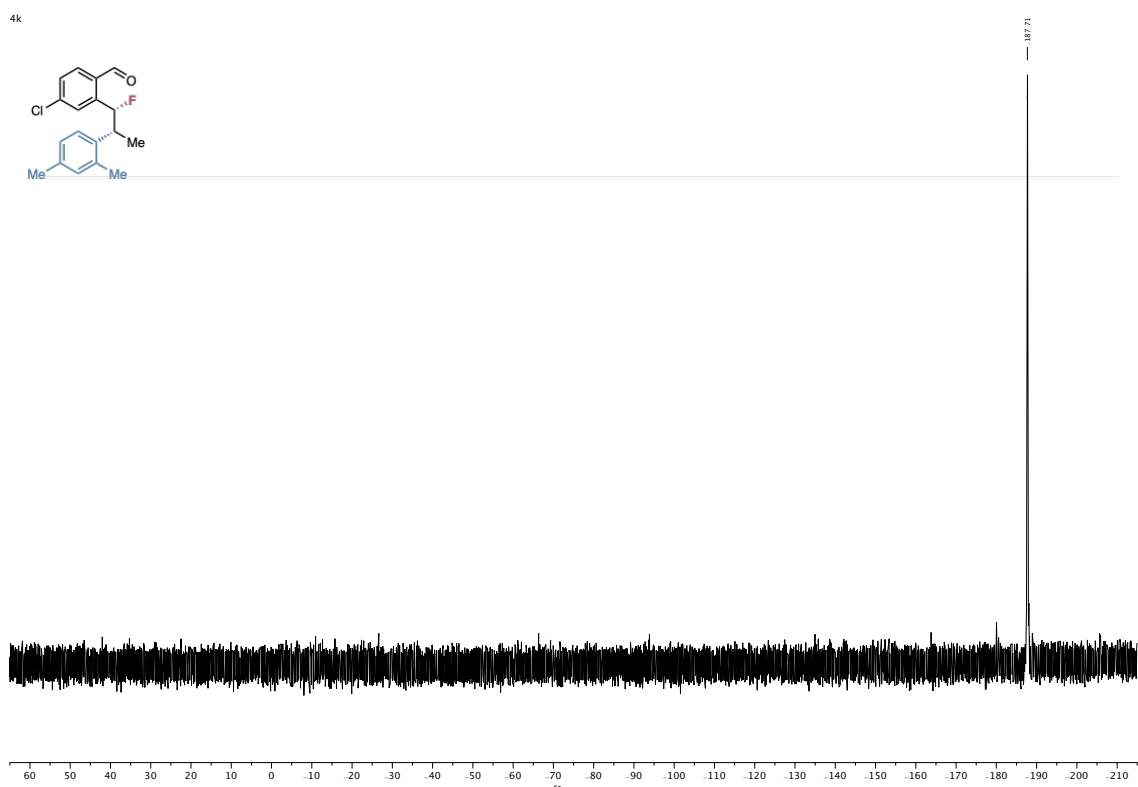
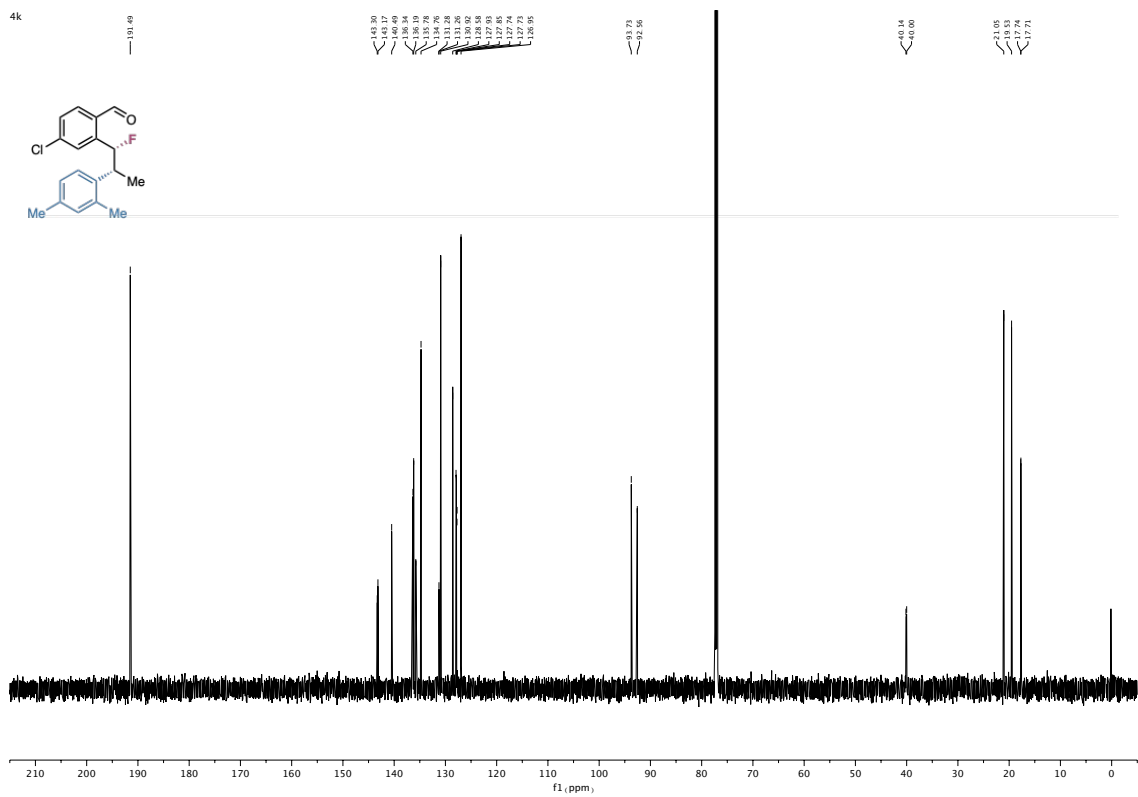


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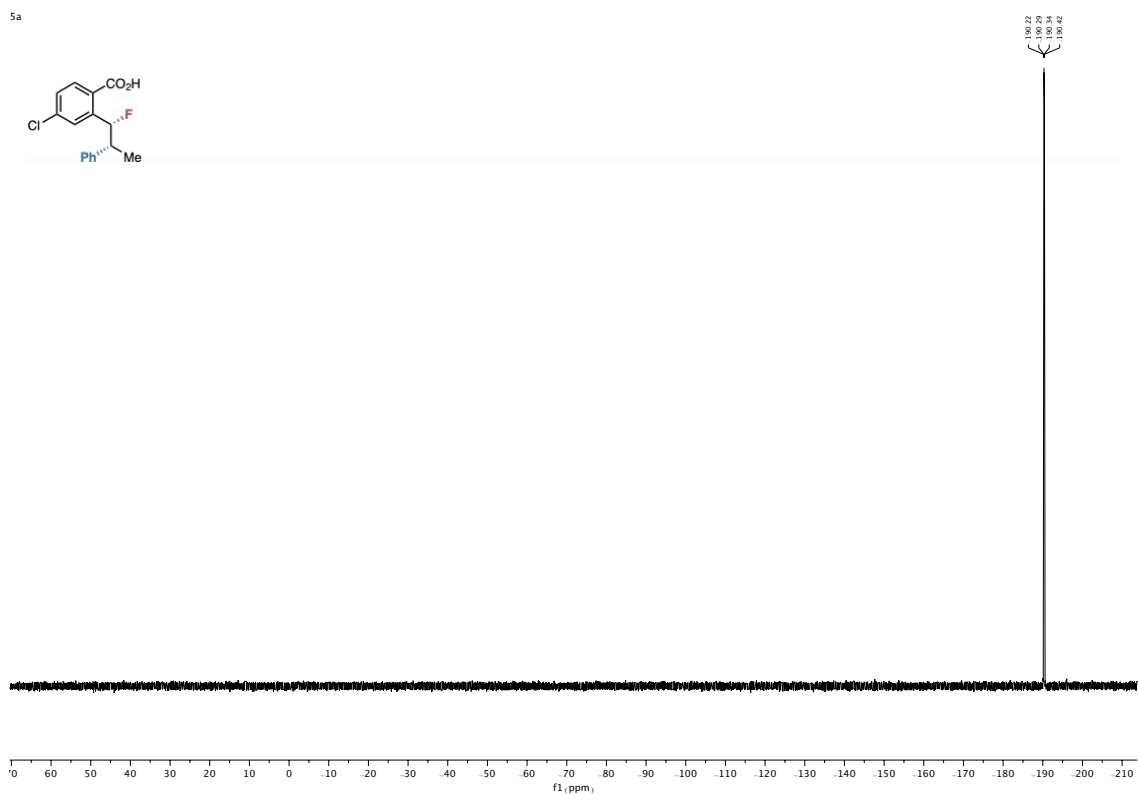


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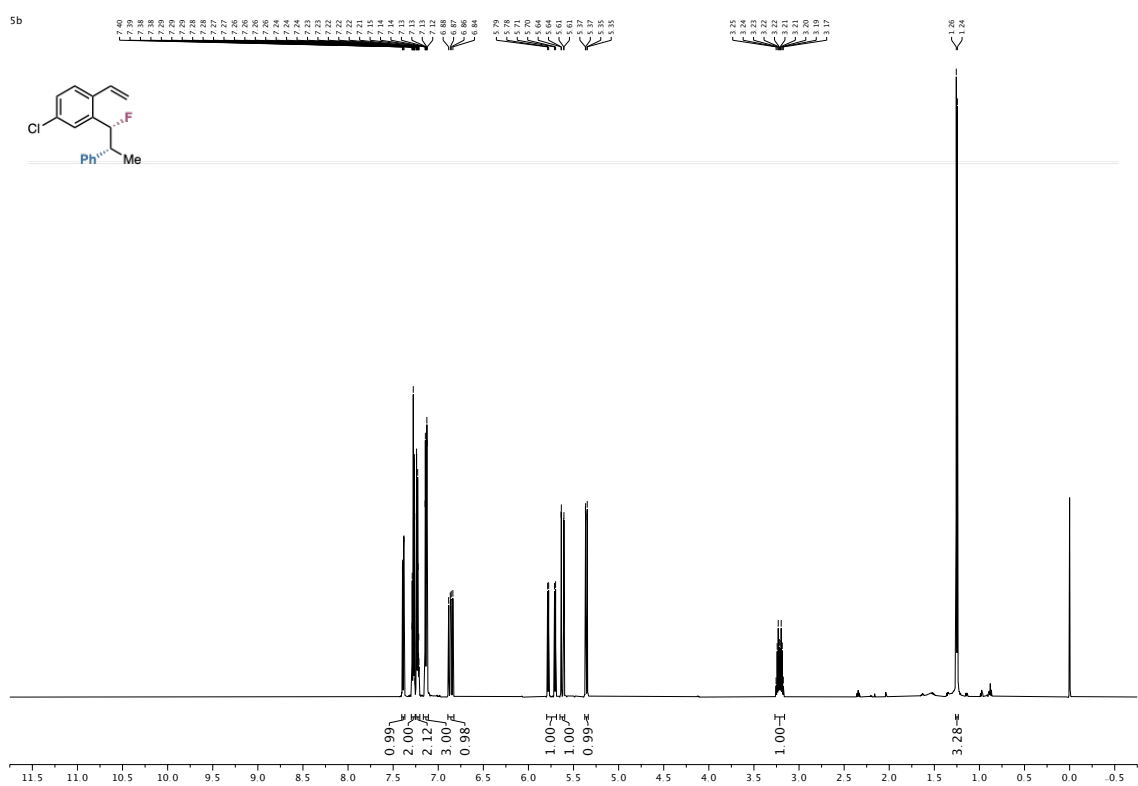




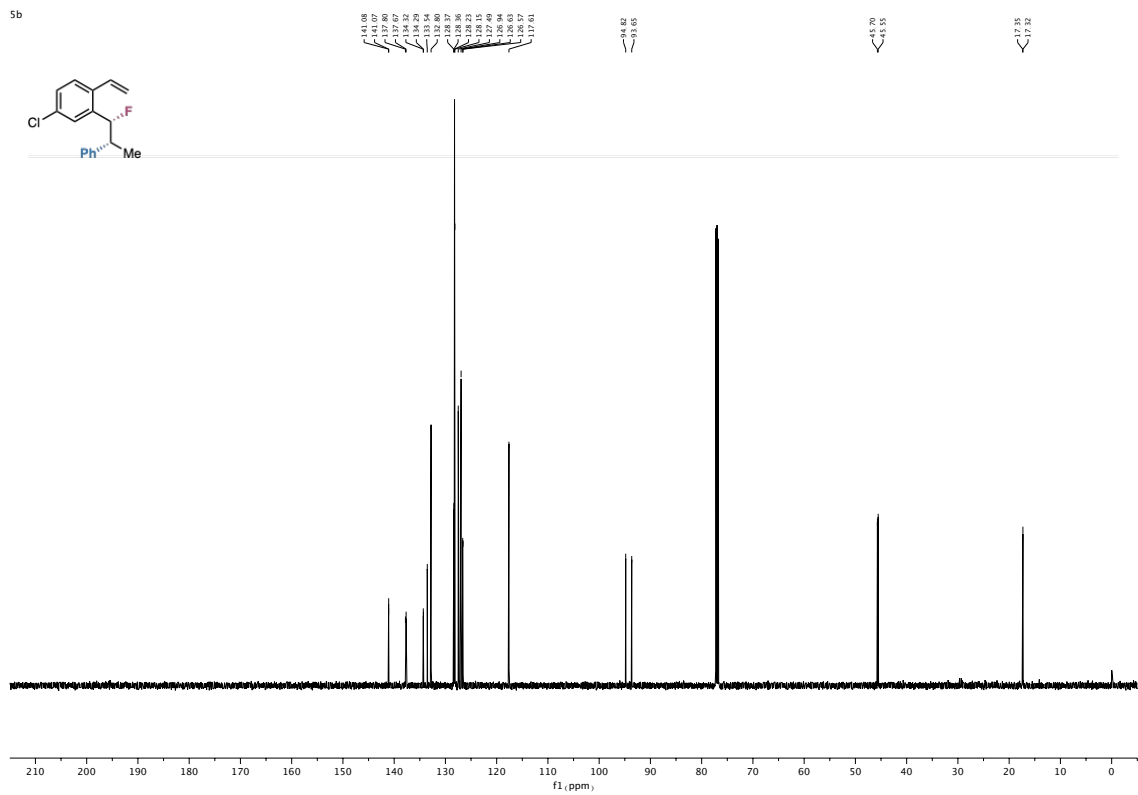
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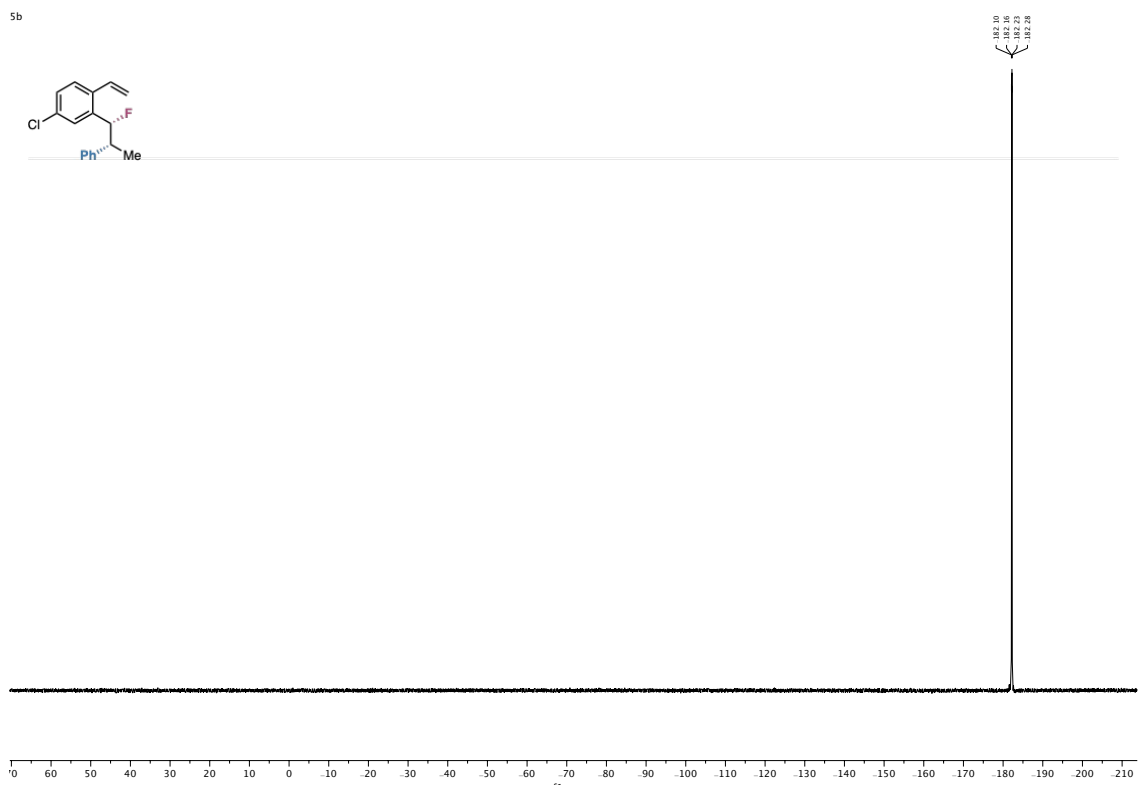
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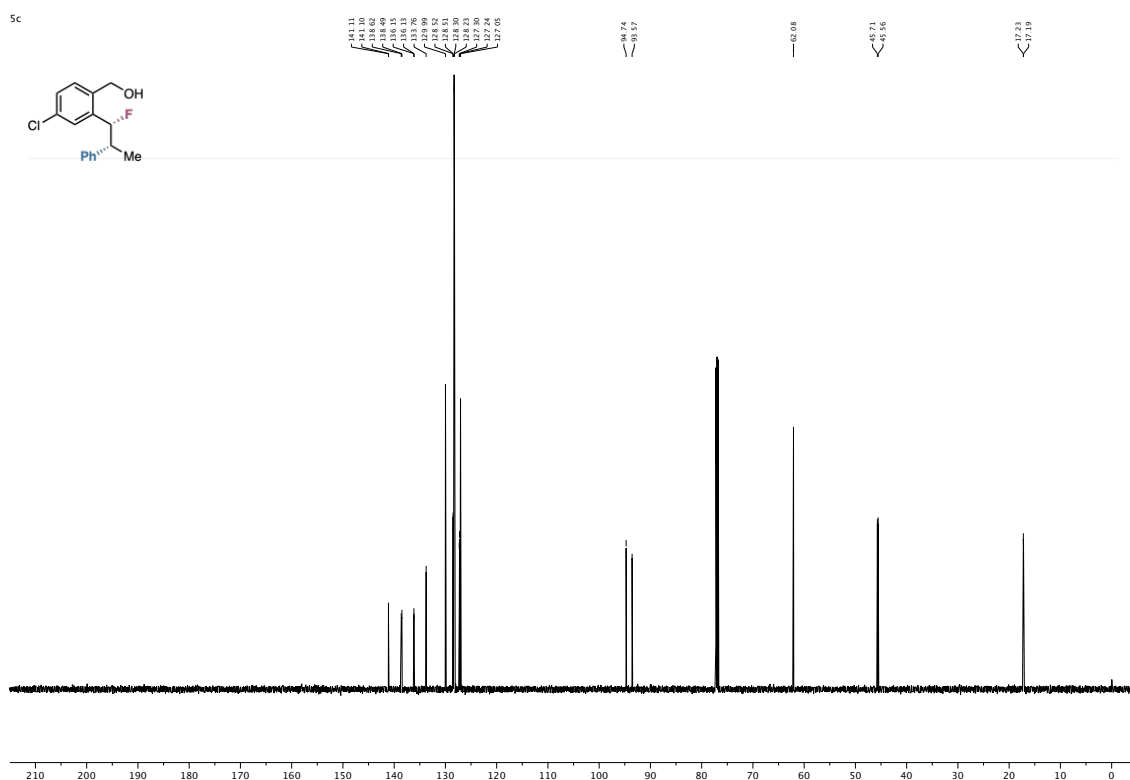
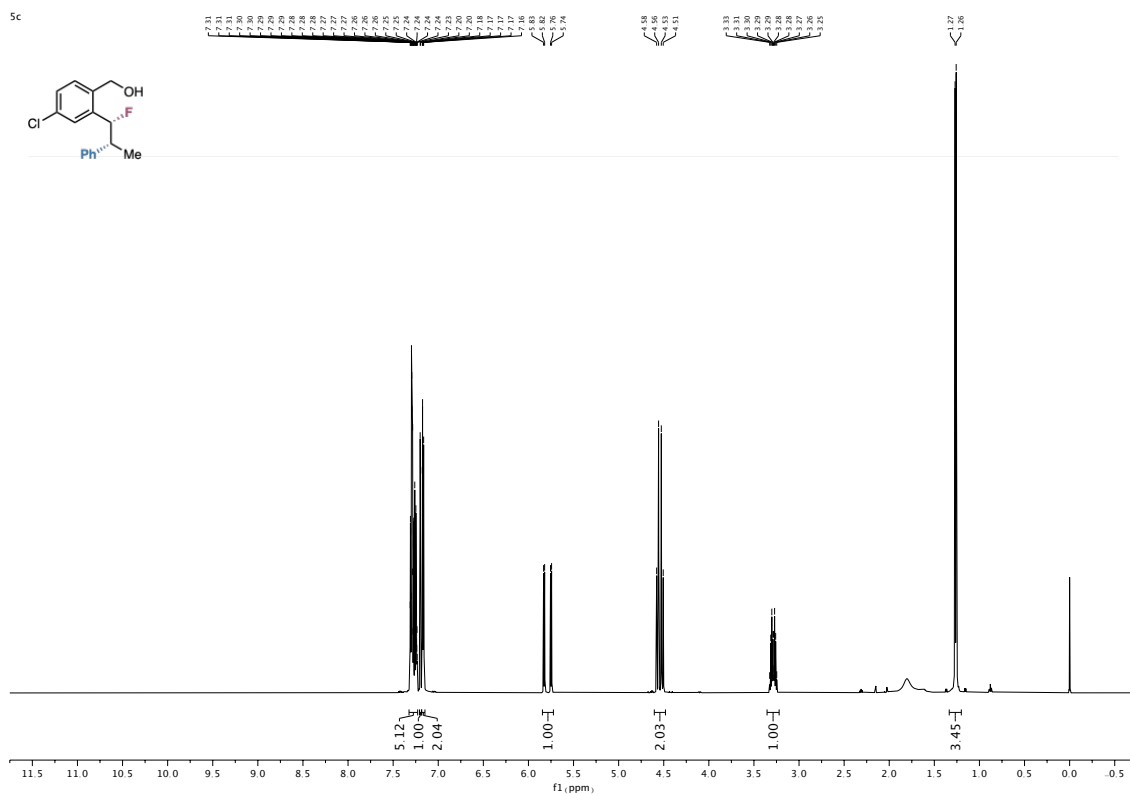


5b

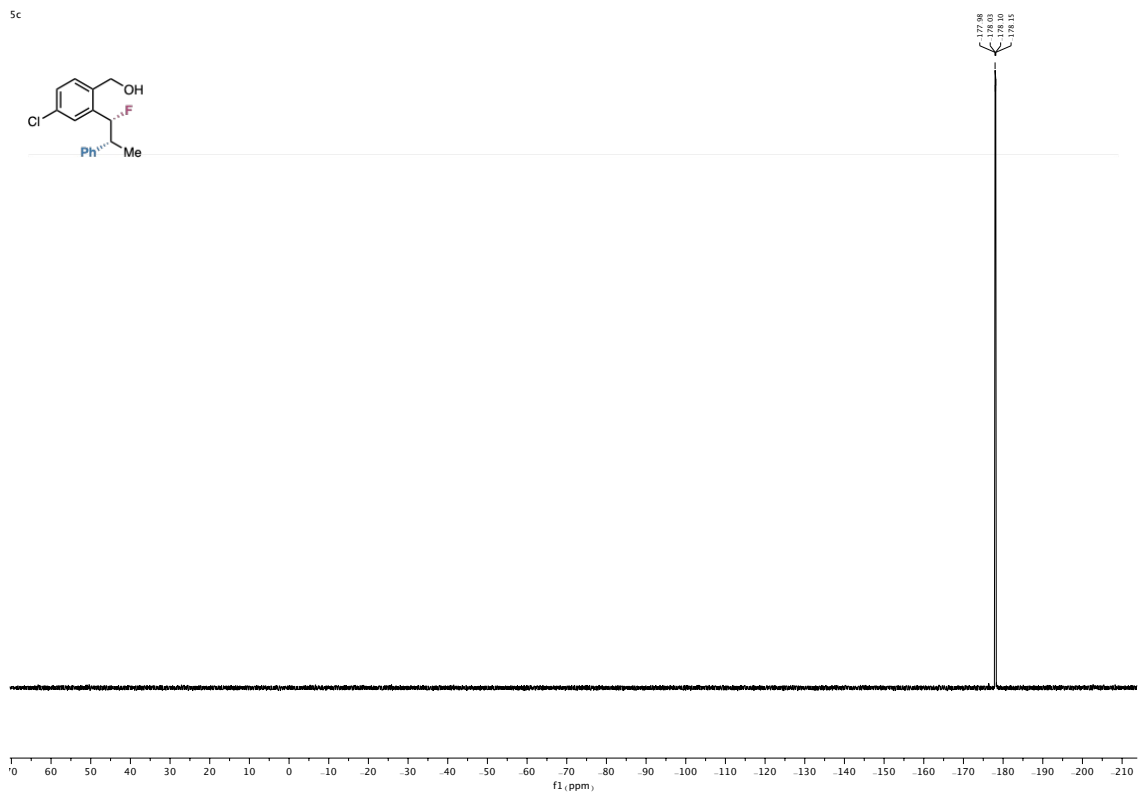


5b

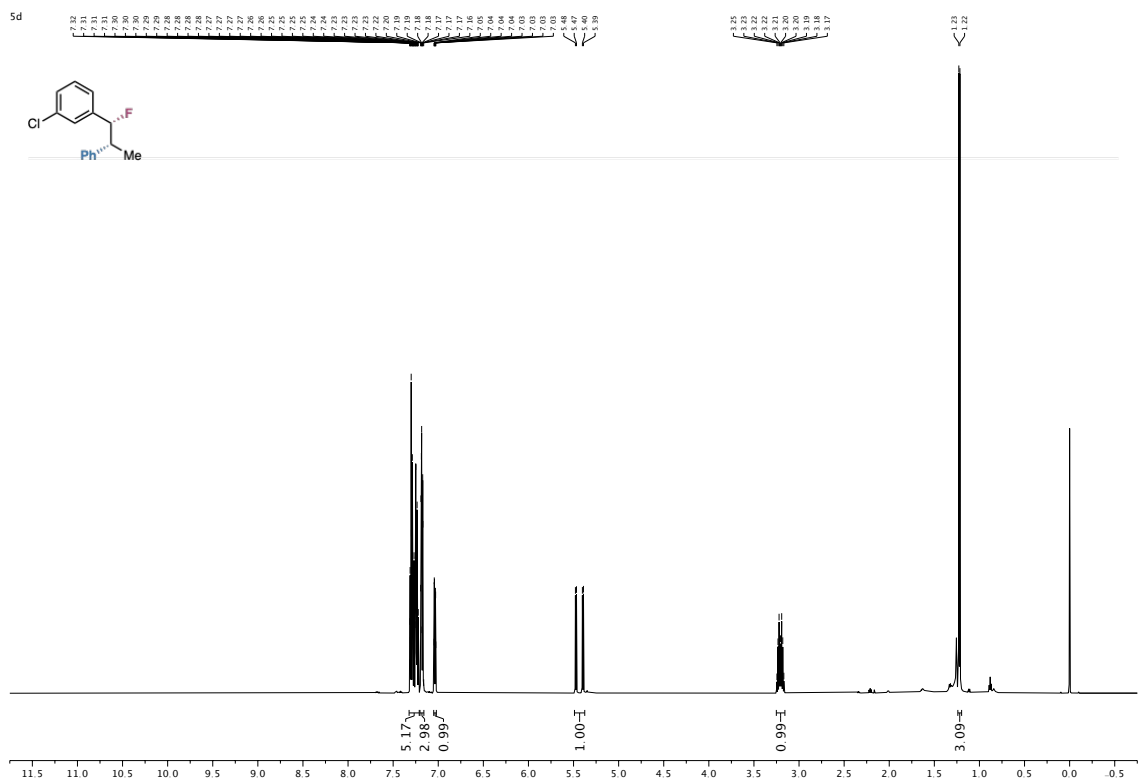


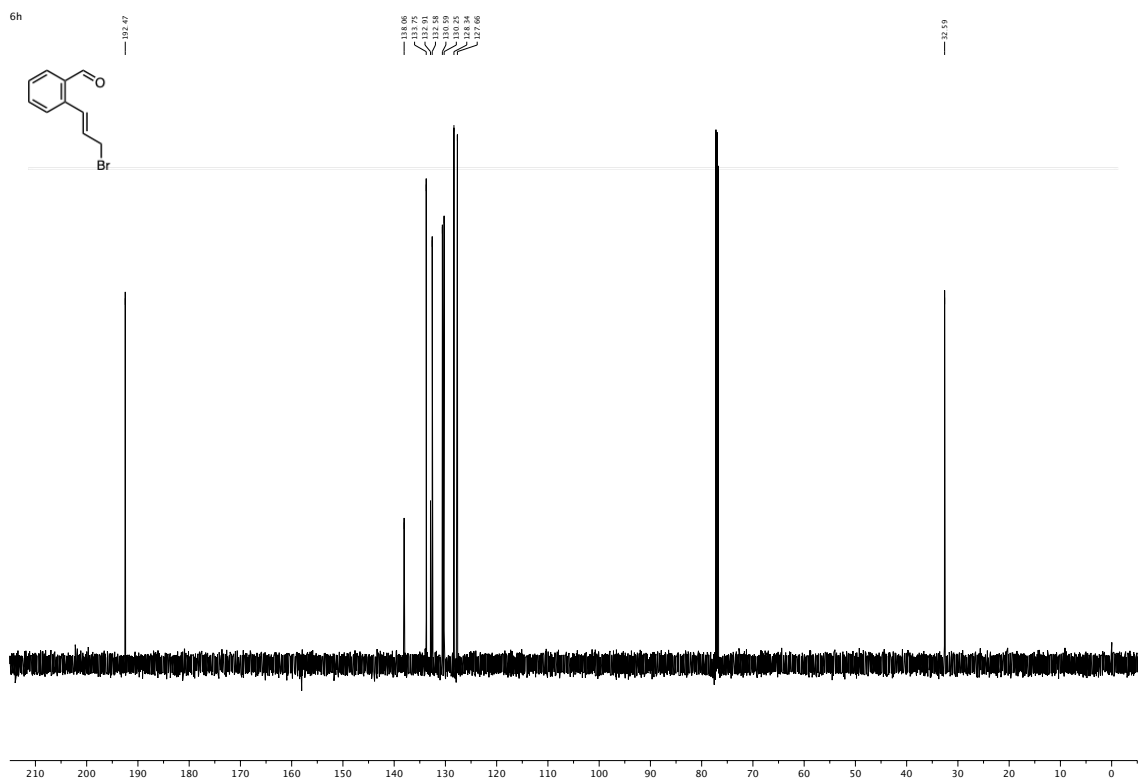
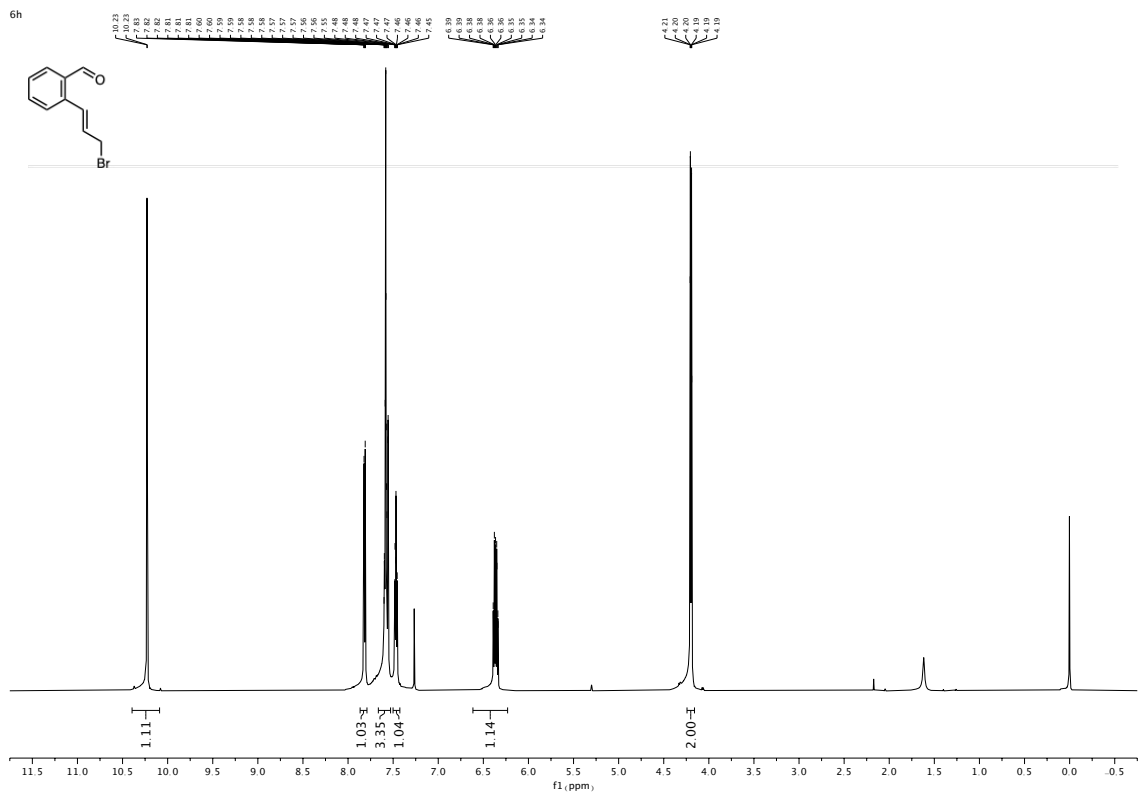


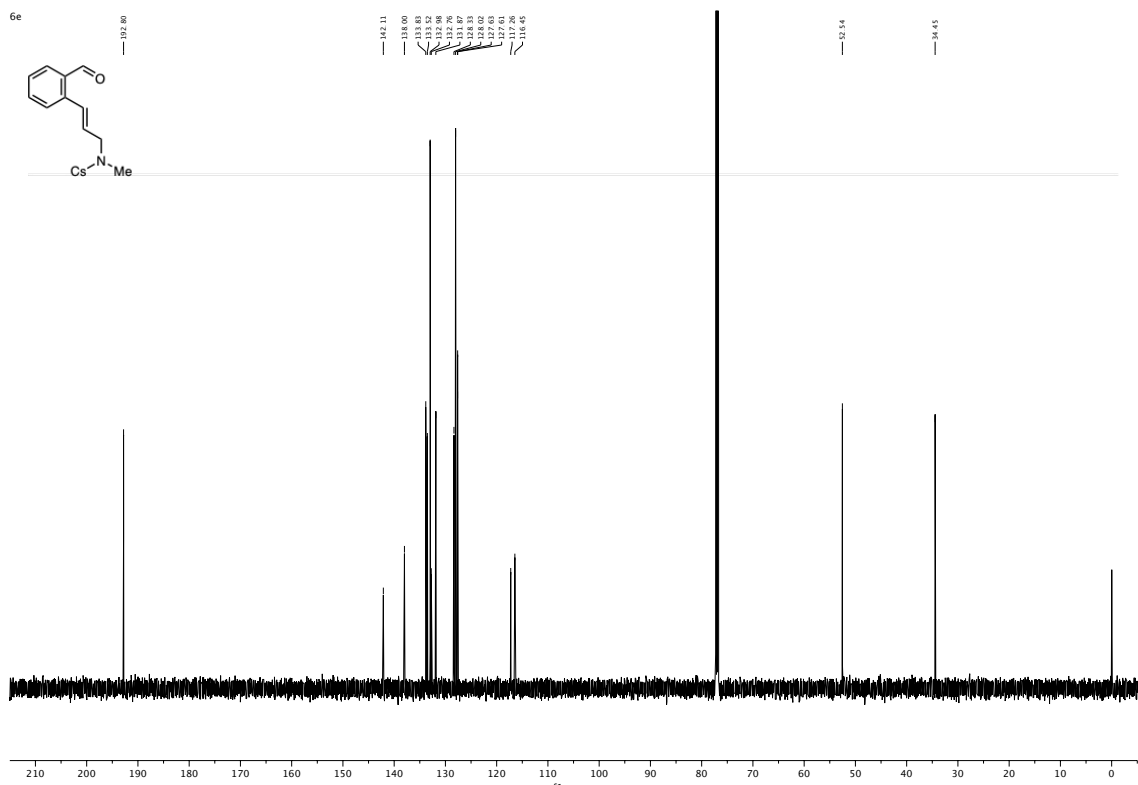
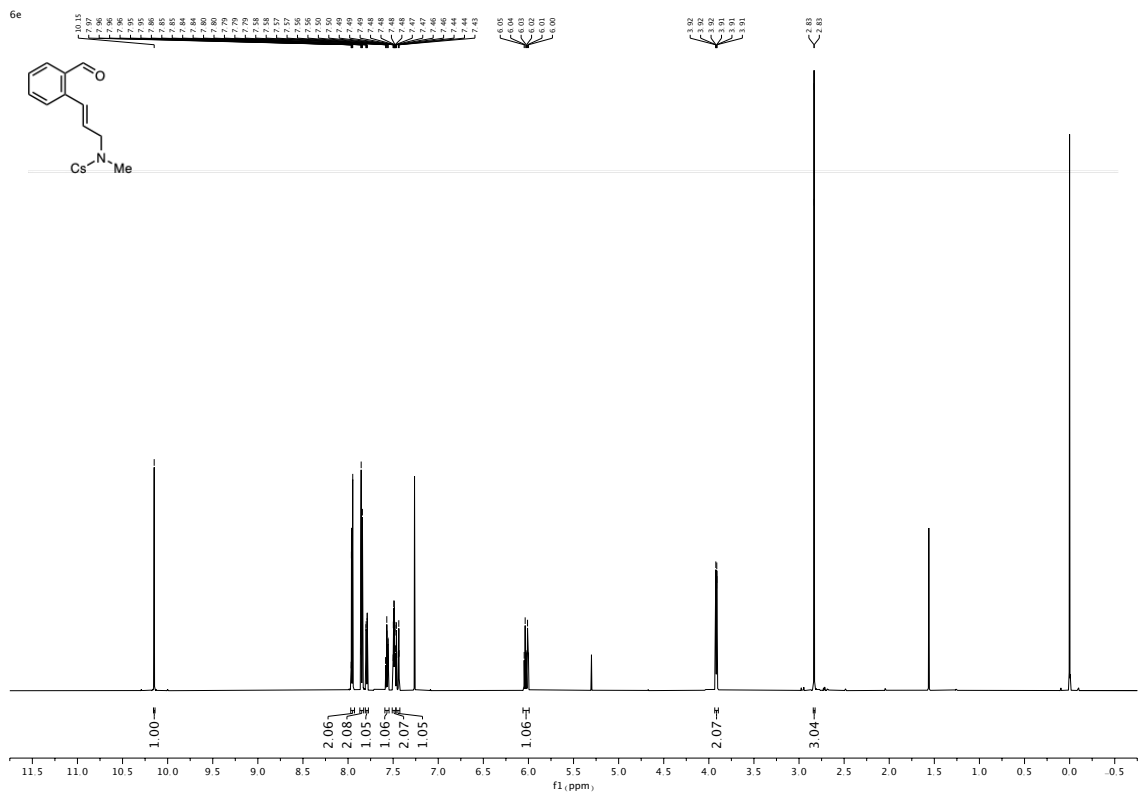
5c

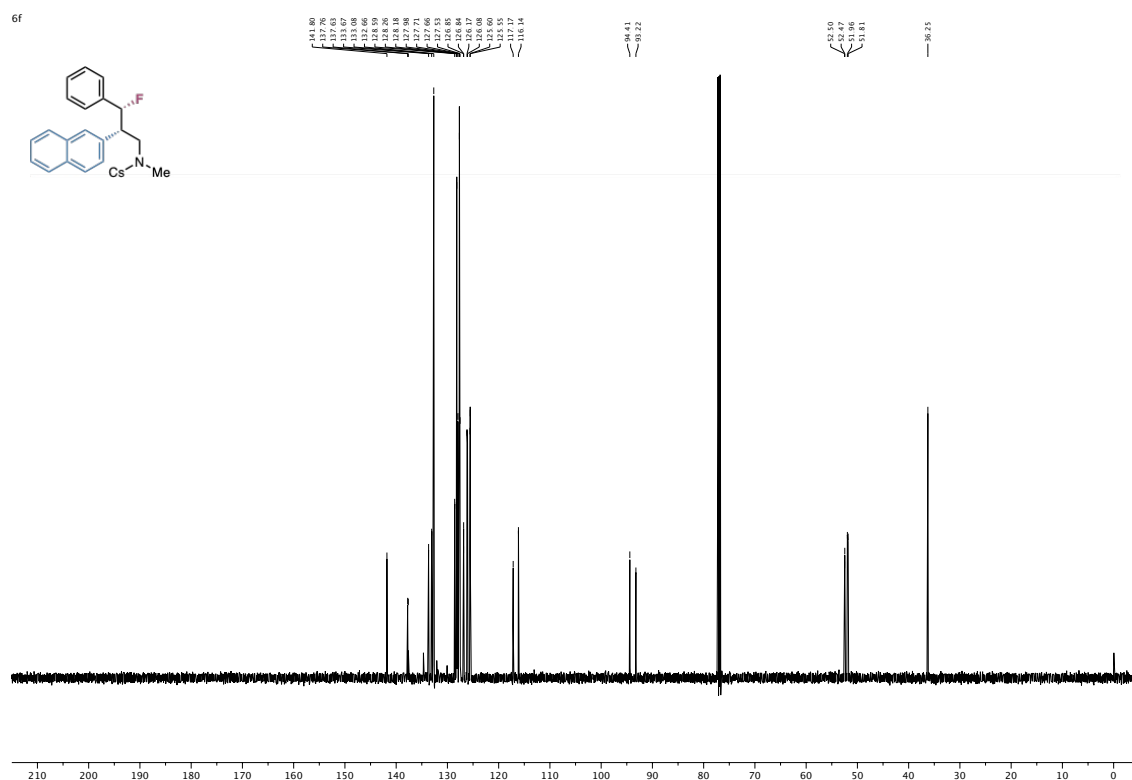
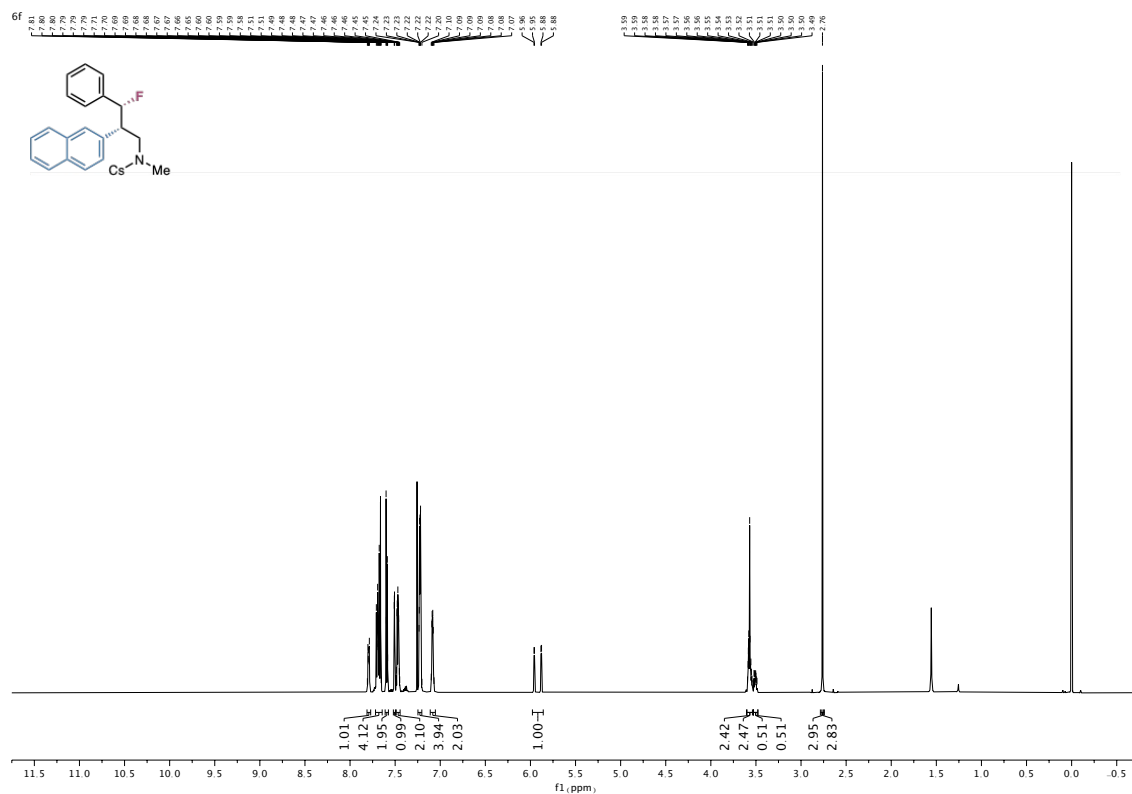


5d

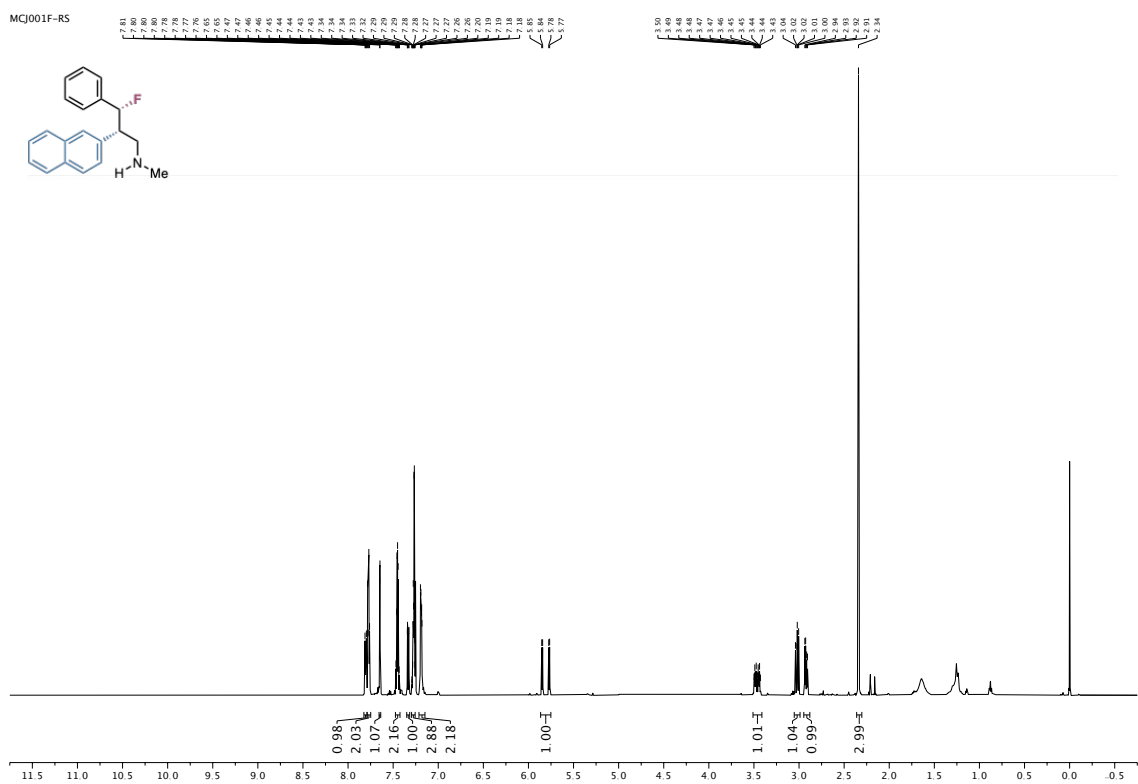
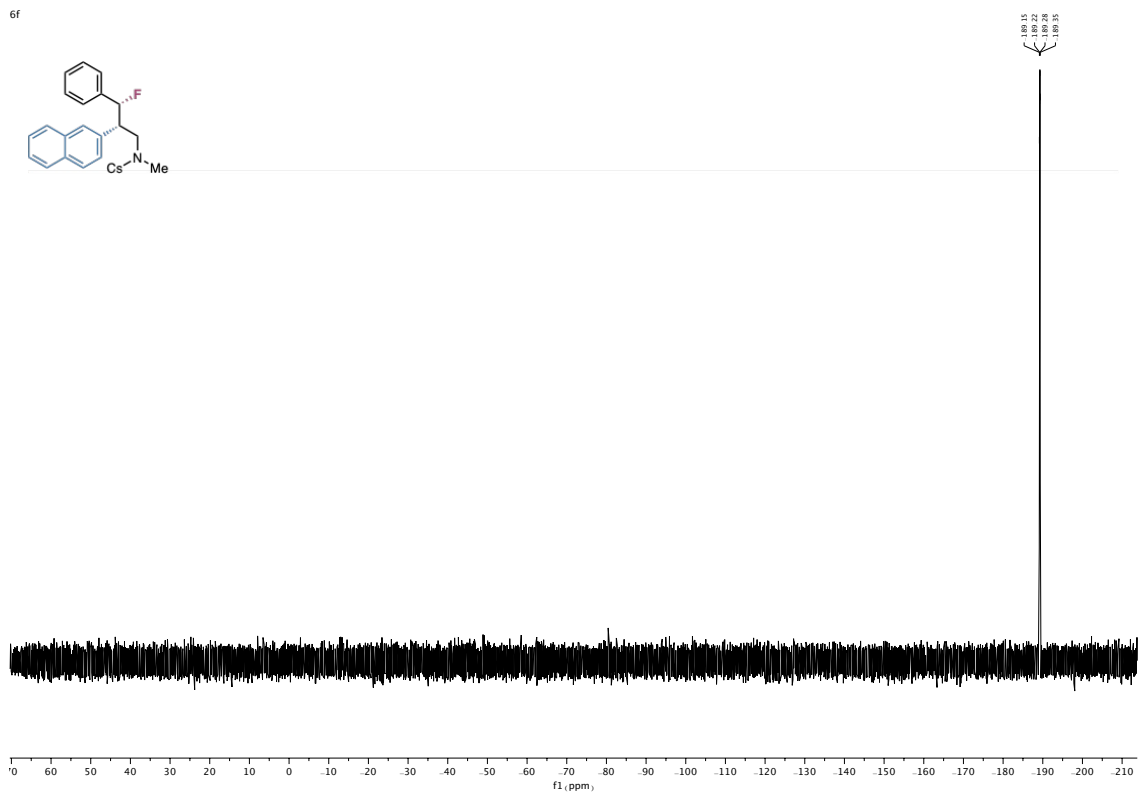


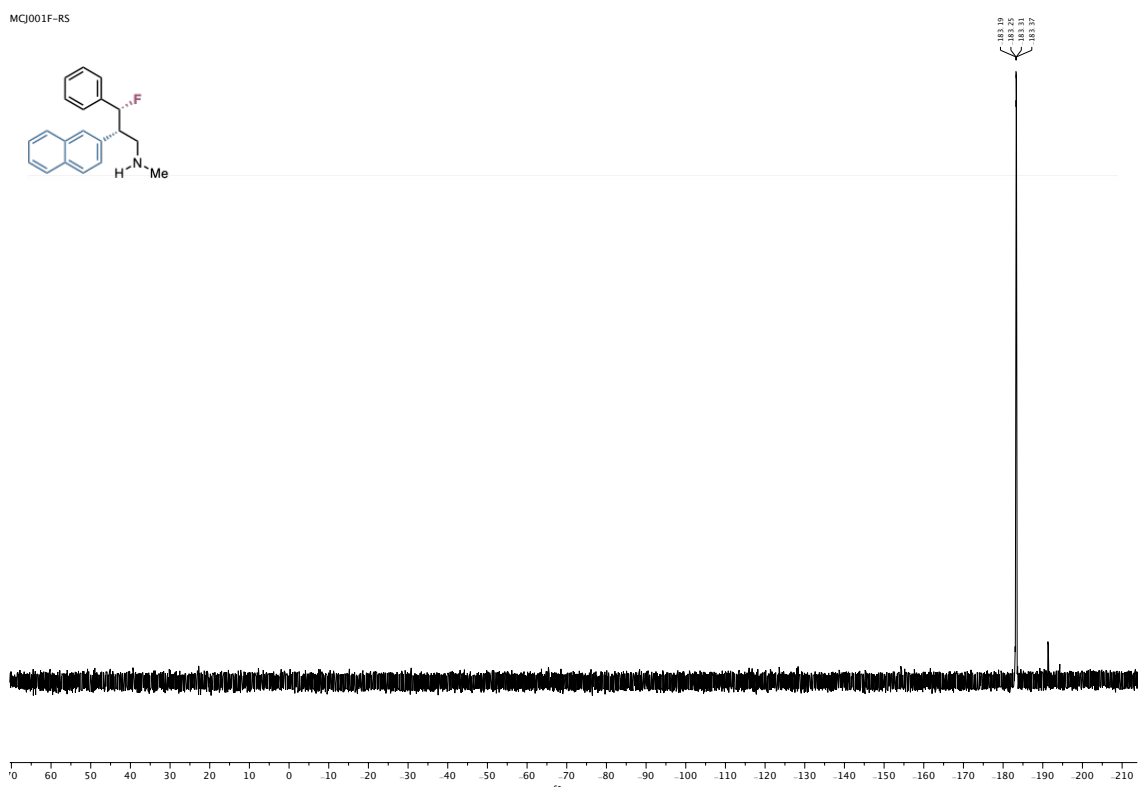
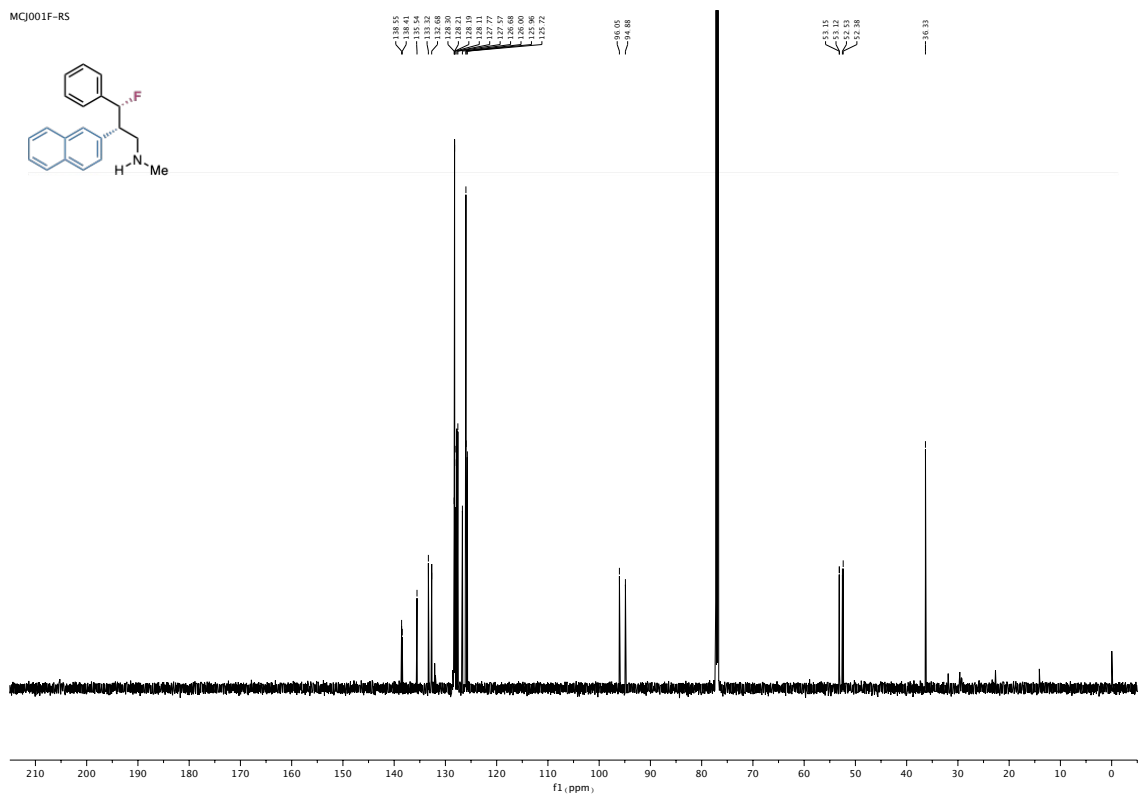


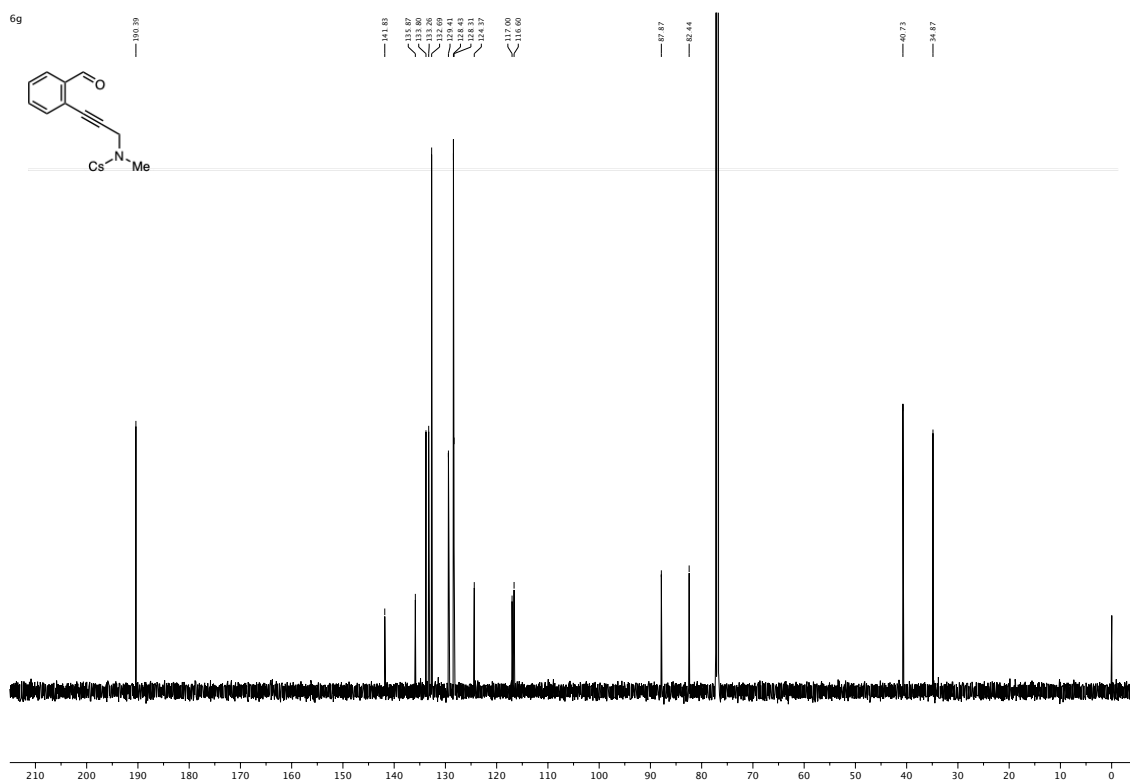
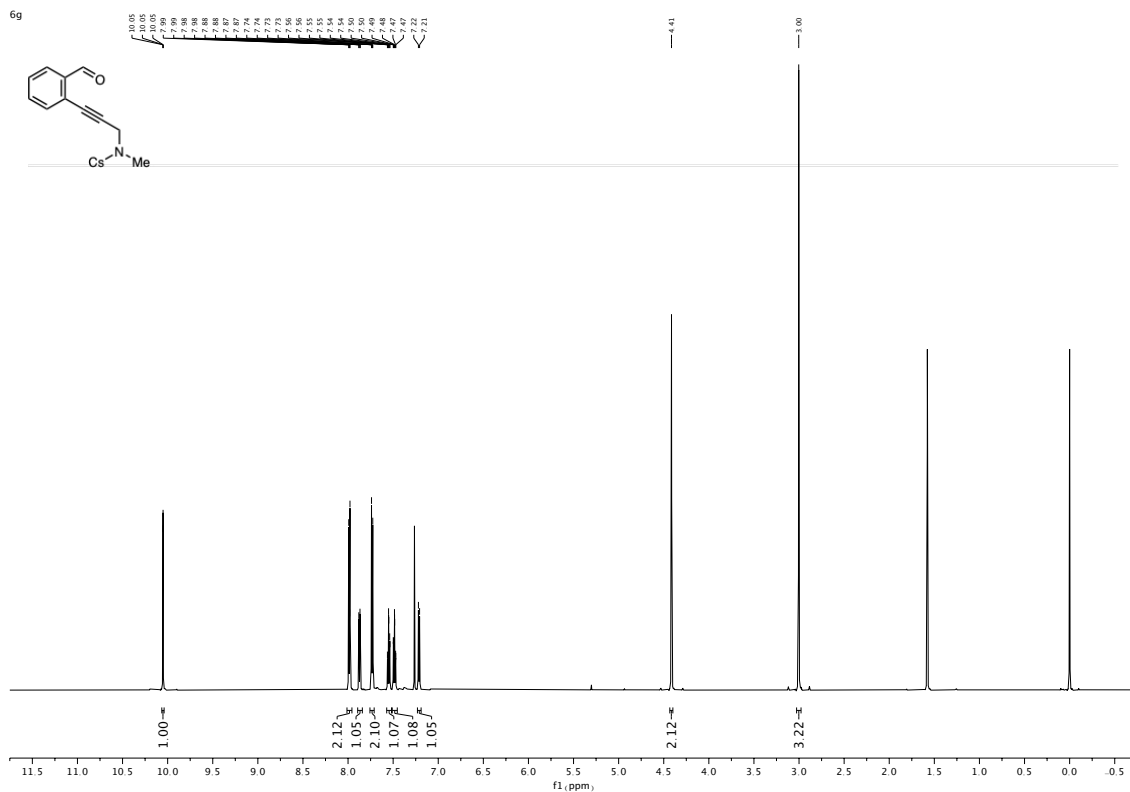


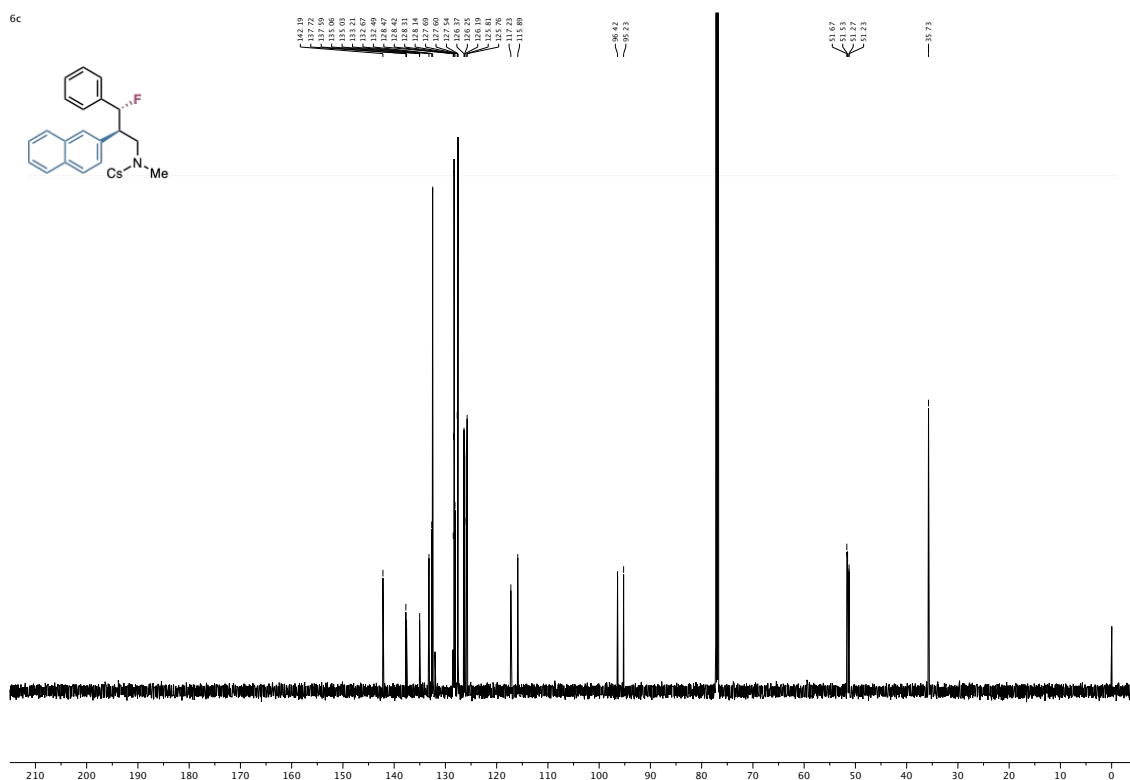
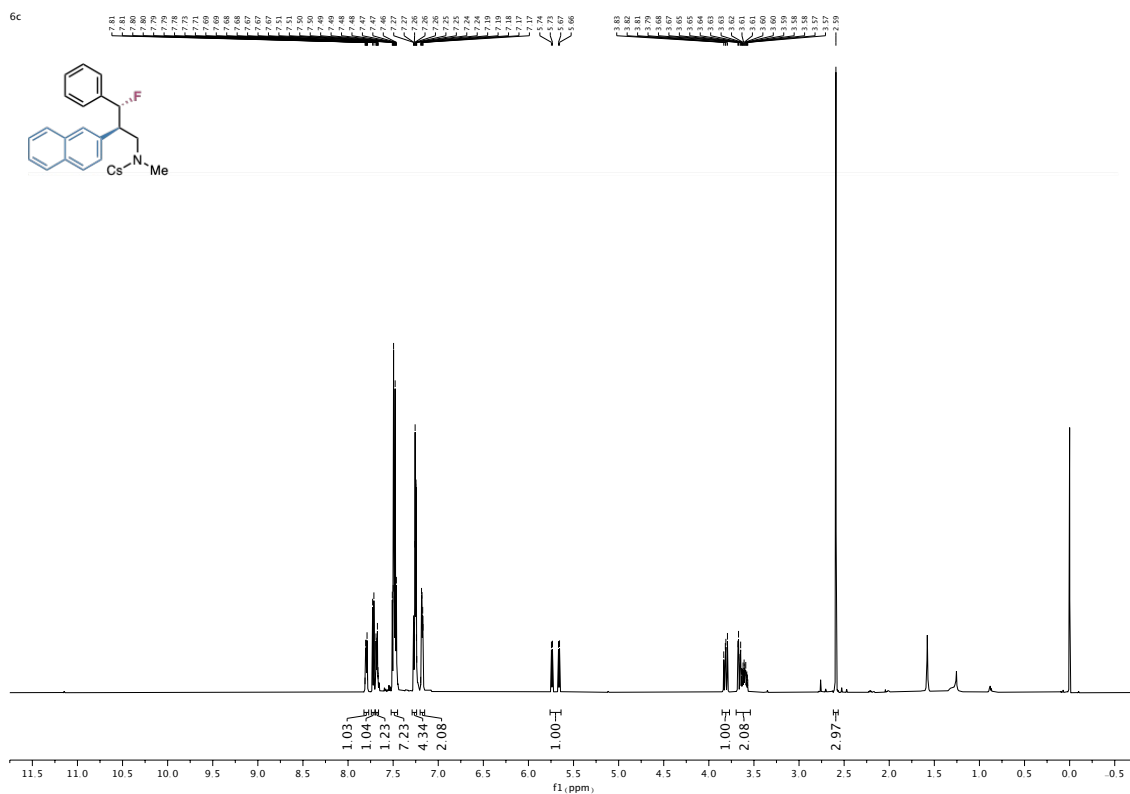


6f

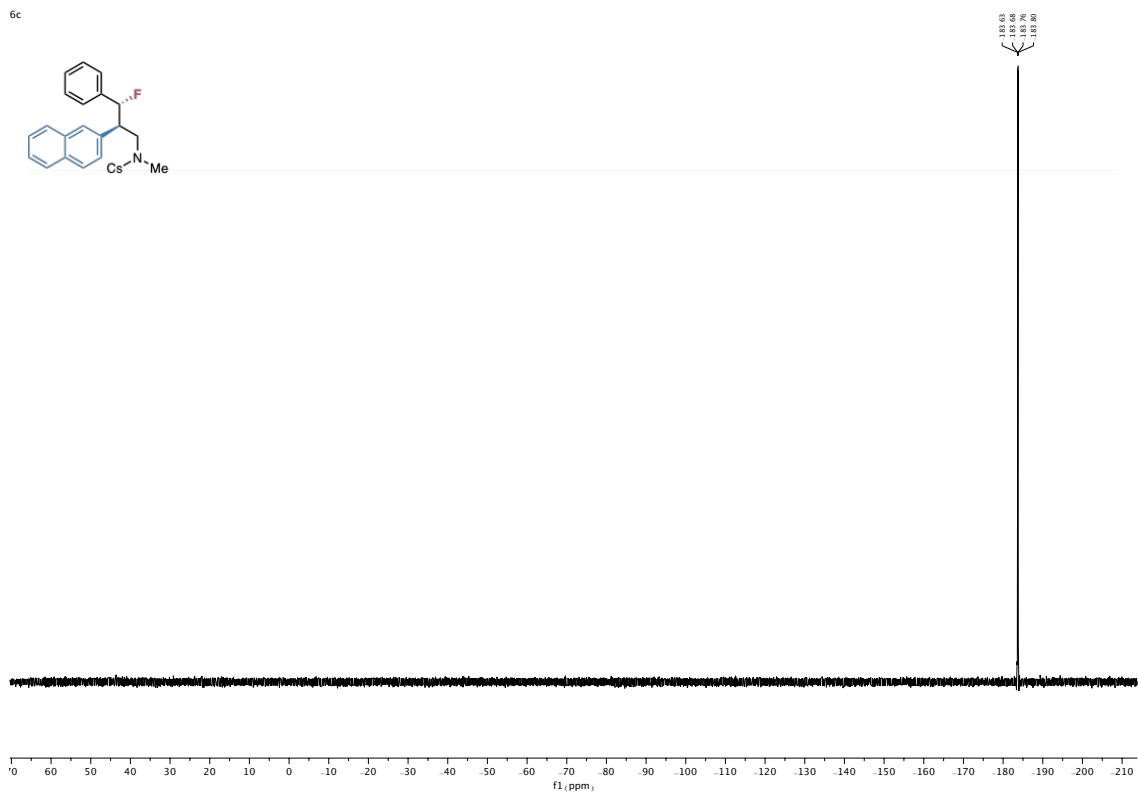
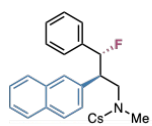




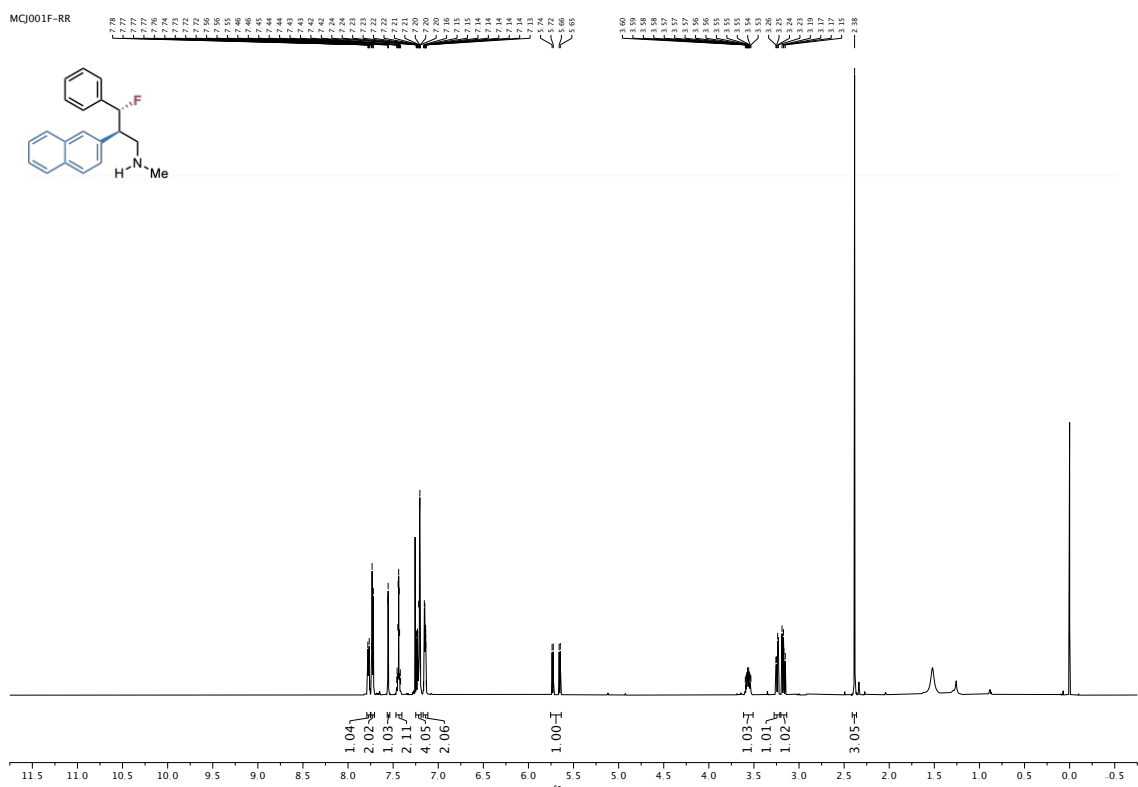
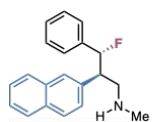




6c

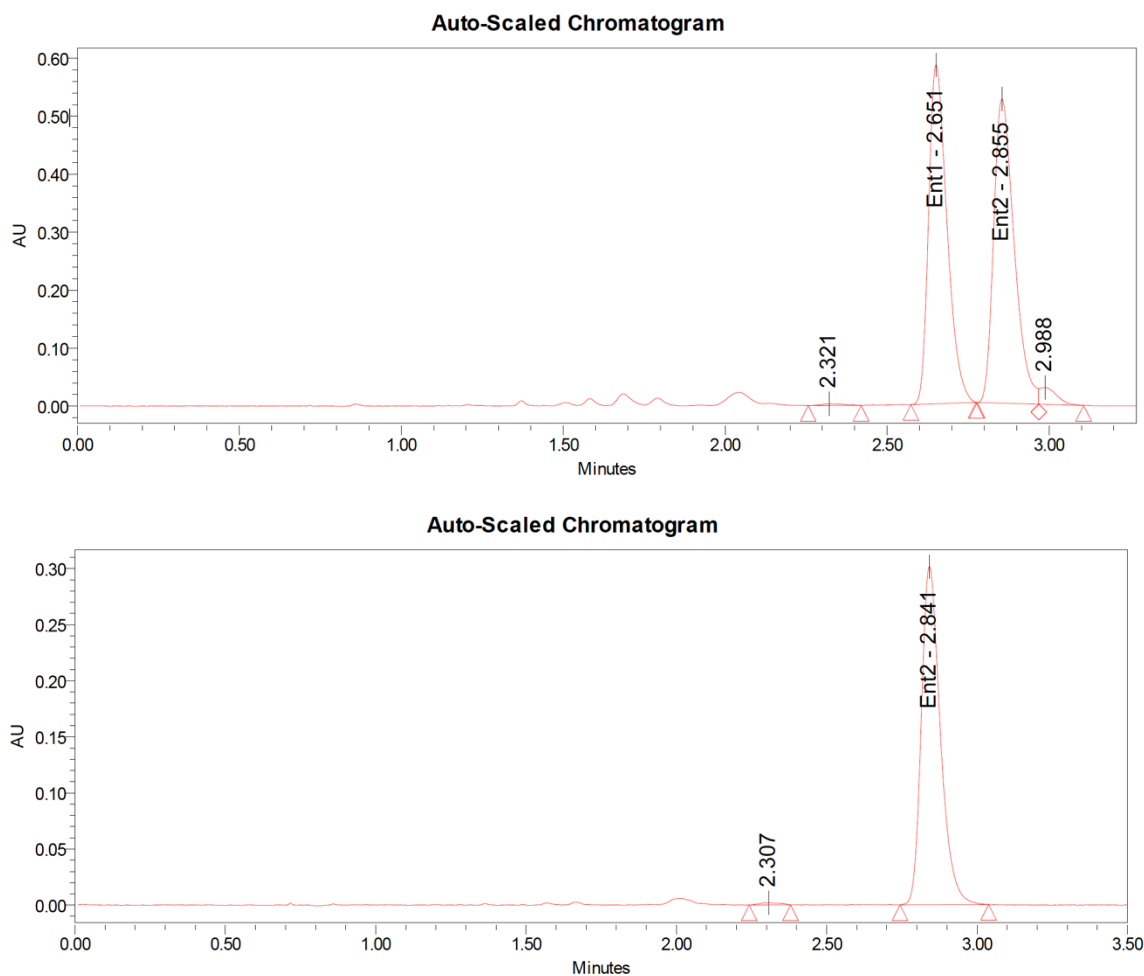


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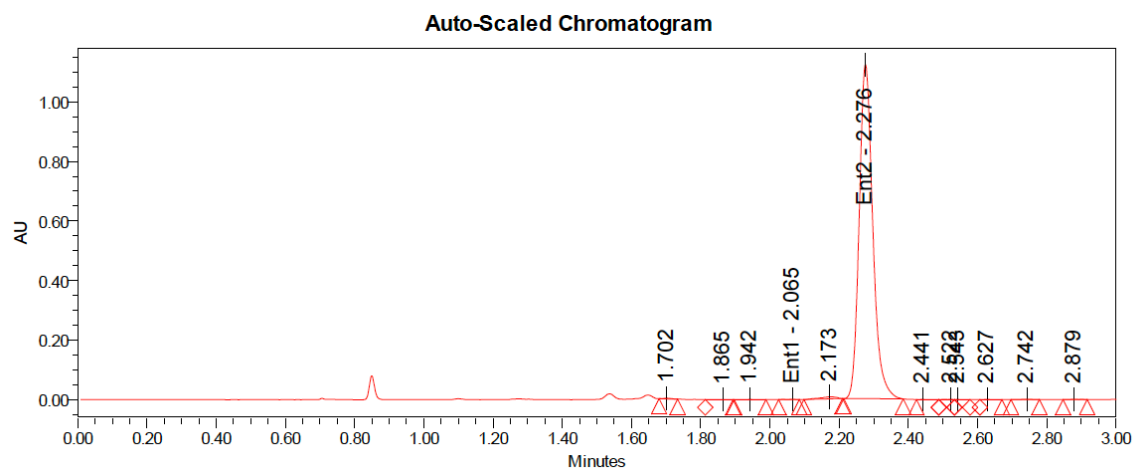
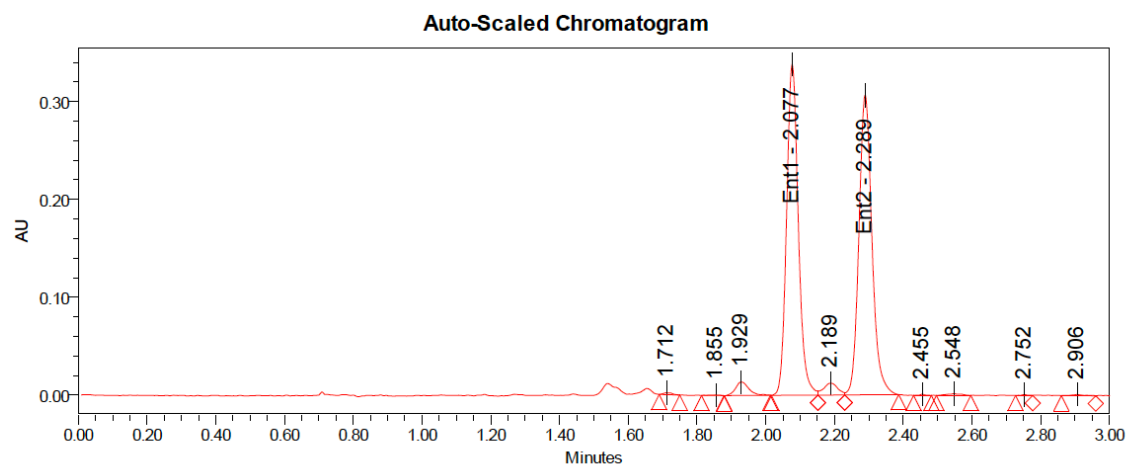
SFC Chromatograms

2-((1*R*,2*R*)-1-Fluoro-2-methyl-2,4-diphenylbutyl)benzaldehyde (**3a**)



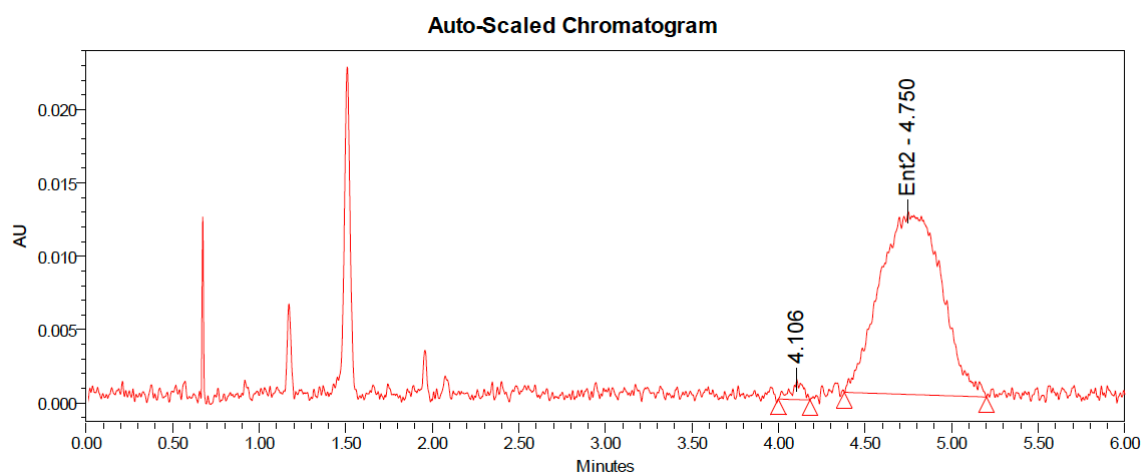
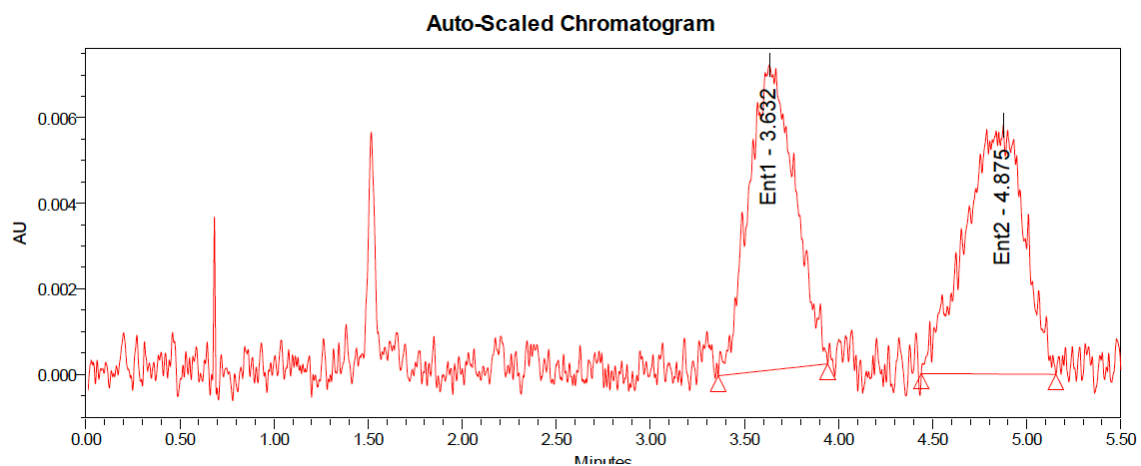
Sample	ent1	ent2	ee	Ent1	Ent2
racemic	49.95	50.05	-0.11	2308298	2313344
scalemic	-	100.00	-100.00	-	1321123

(5*R*,6*R*)-6-Fluoro-6-(2-formylphenyl)-5-methyl-5-phenylhexanenitrile (**3b**).



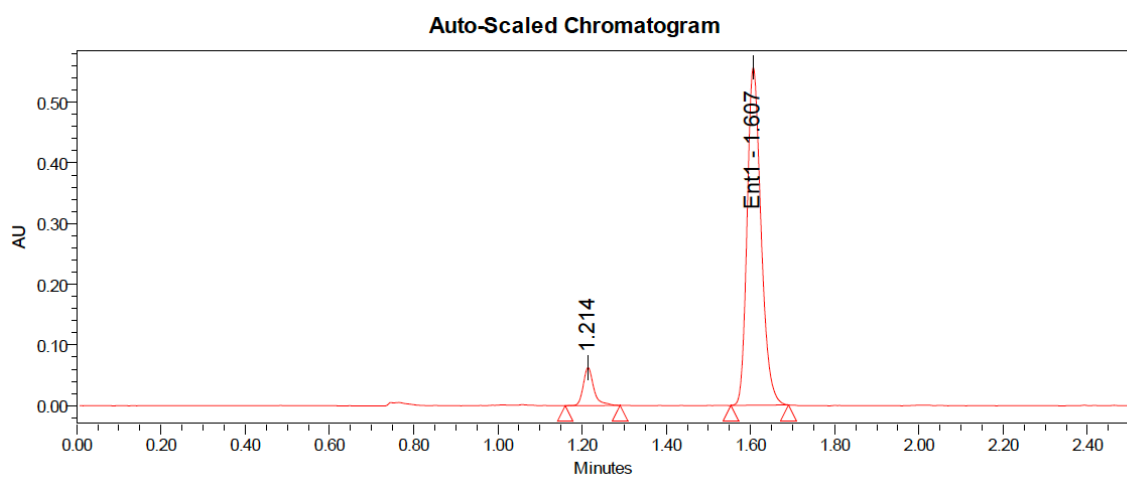
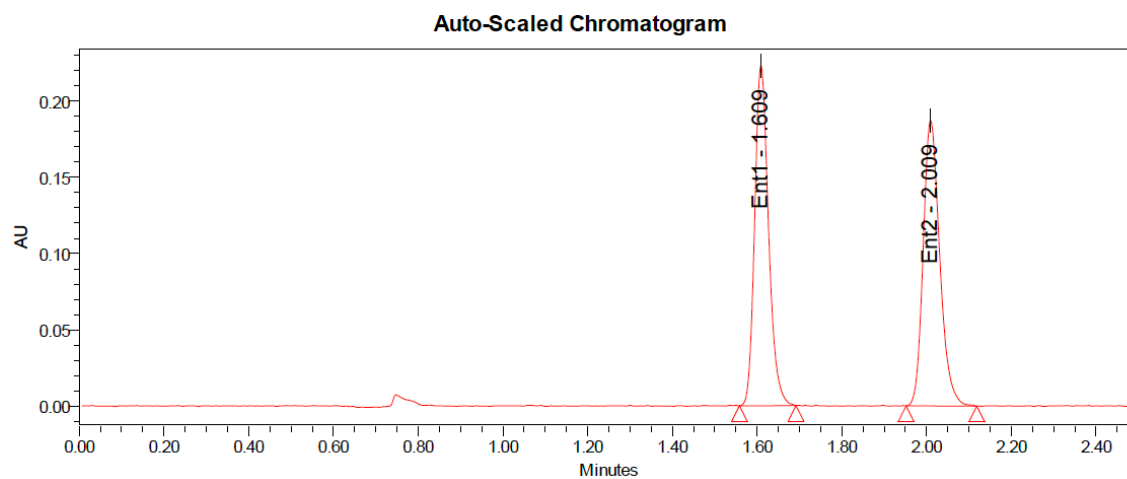
Sample	ent1	ent2	ee	Ent1	Ent2
racemic	49.77	50.23	-0.47	801201	808727
scalemic	0.06	99.94	-99.88	1854	3060896

(*R*)-2-(2-Ethyl-1-fluoro-2-phenylbutyl)benzaldehyde (**3c**).



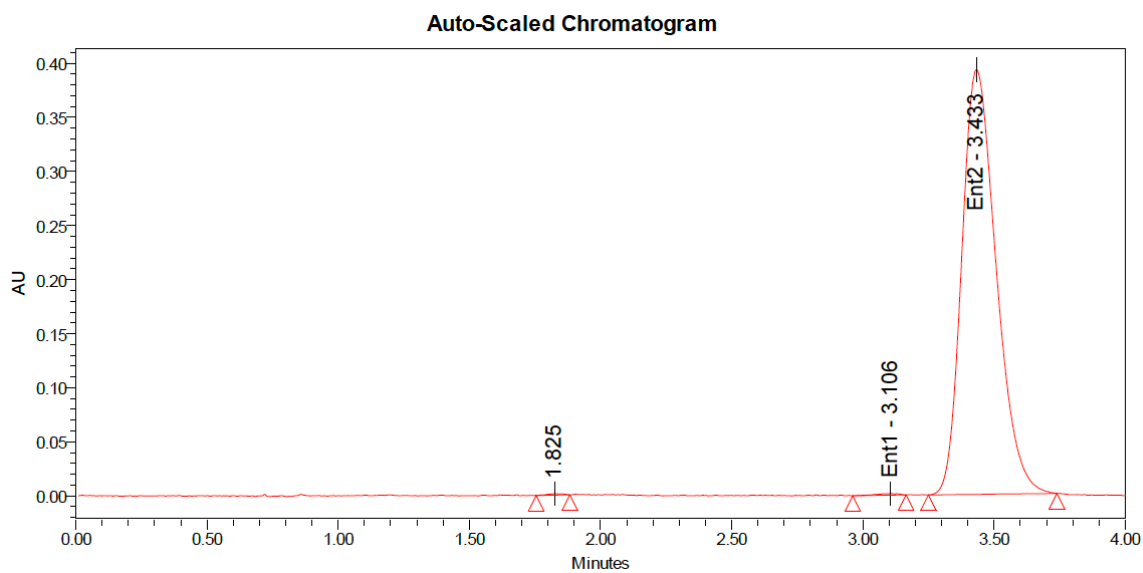
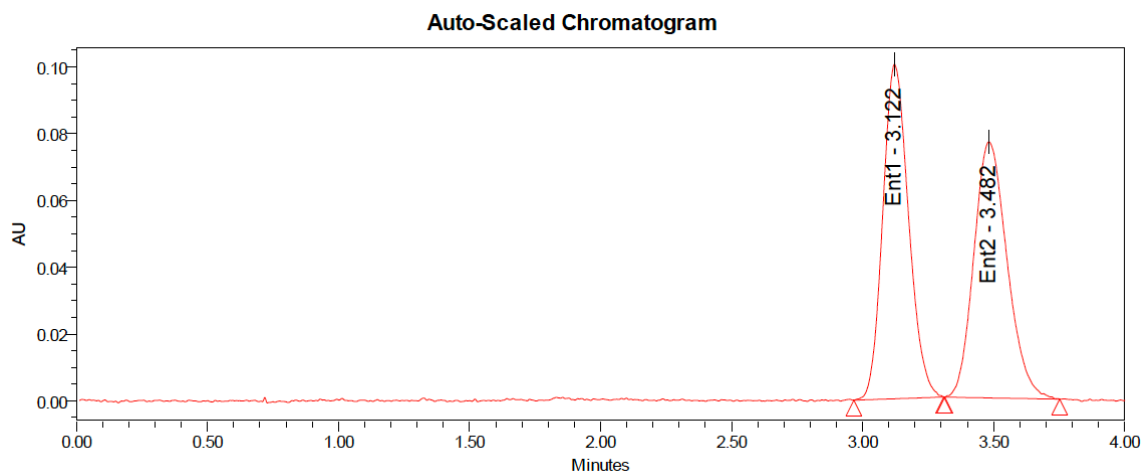
Sample	ent1	ent2	ee	Ent1	Ent2
racemic	49.00	51.00	-1.99	122349	127322
scalemic	-	100.00	-100.00	-	309294

(*R*)-2-(1-Fluoro-2-methyl-2-phenylpropyl)benzaldehyde (**3d**).



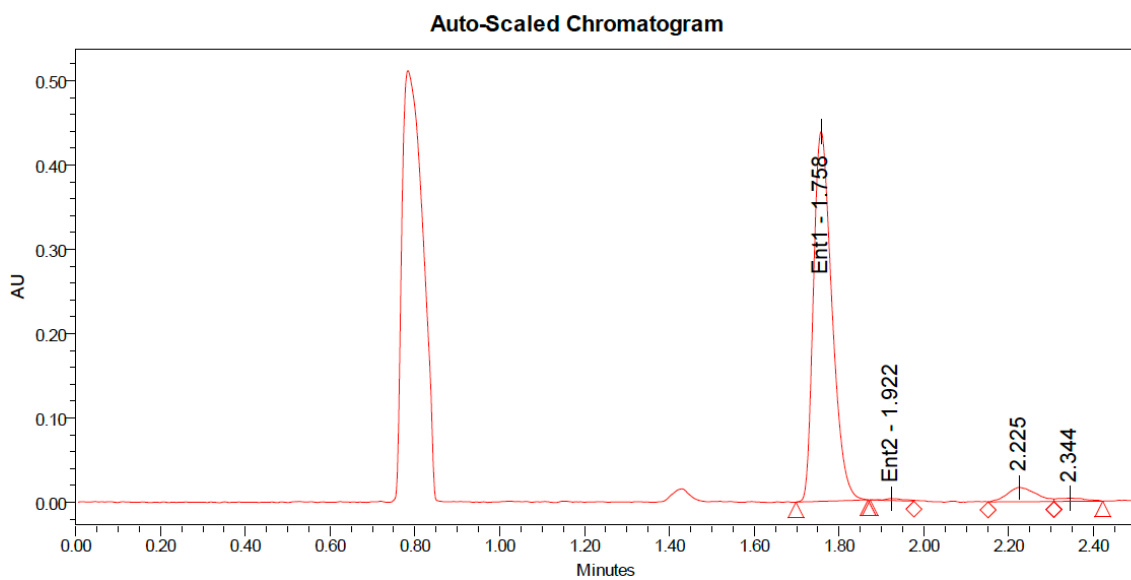
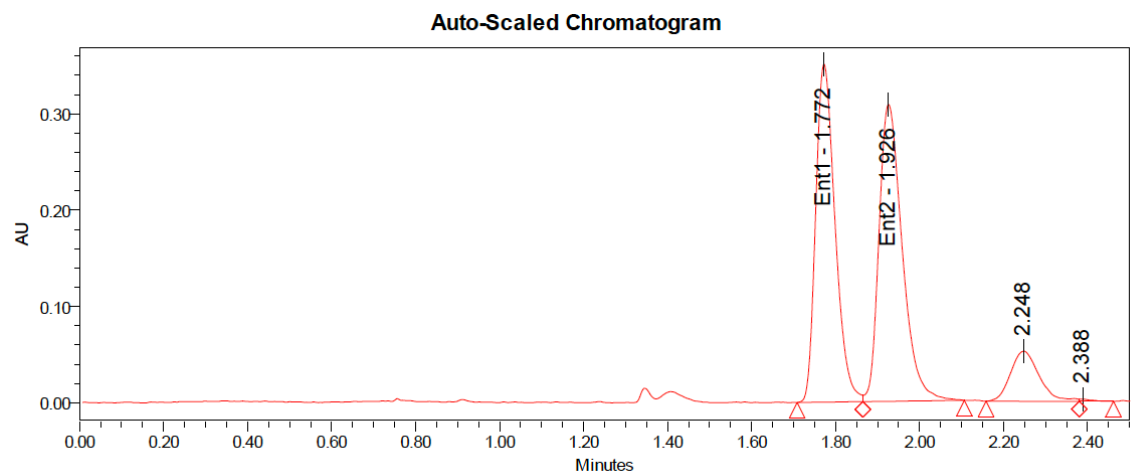
Sample	ent1	ent2	ee	Ent1	Ent2
racemic	49.93	50.07	-0.15	506766	508268
scalemic	100.00	-	100.00	1277262	-

tert-Butyl (*R*)-4-(fluoro(2-formylphenyl)methyl)-4-phenylpiperidine-1-carboxylate (**3e**).



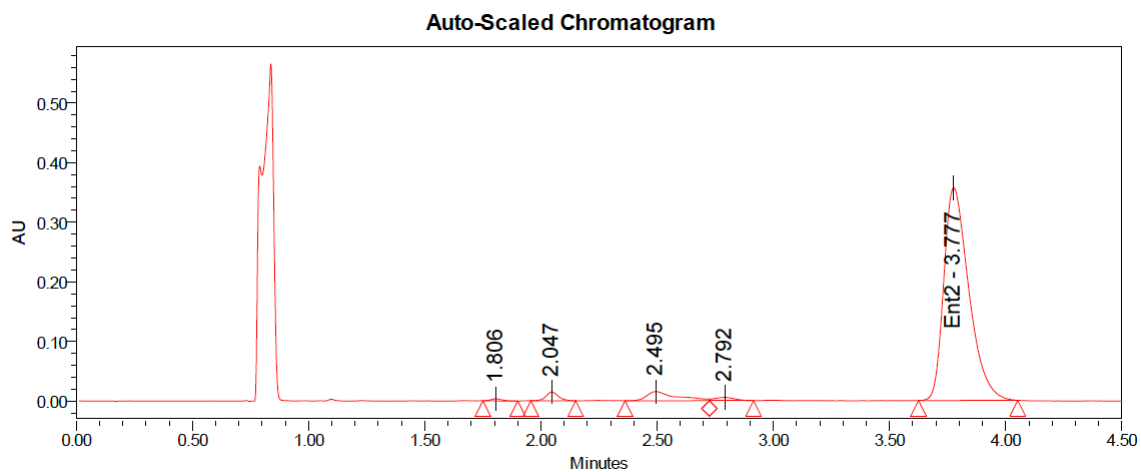
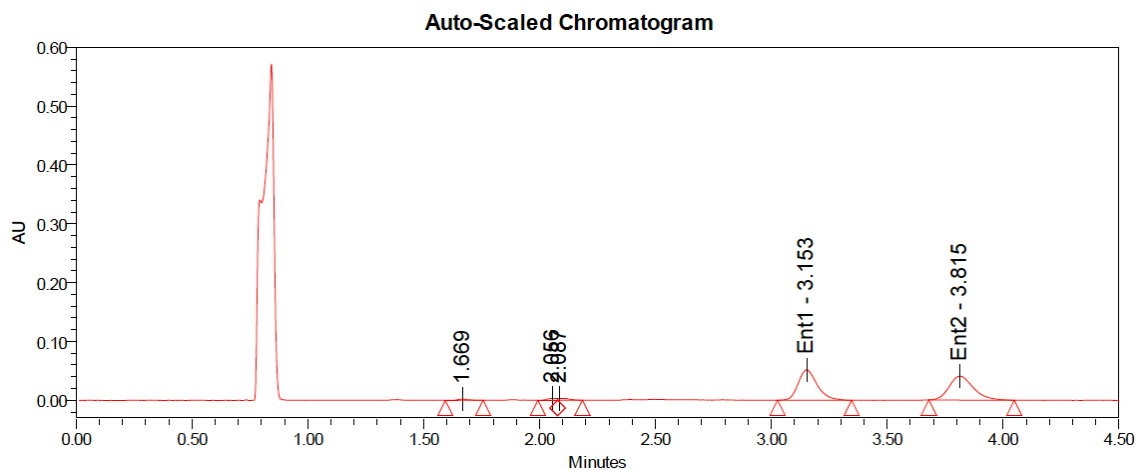
Sample	ent1	ent2	ee	Ent1	Ent2
racemic	50.36	49.64	0.71	686939	677252
scalemic	0.24	99.76	-99.51	8775	3577111

2-((1*R*,2*R*)-1-Fluoro-2-methyl-2-phenylhexyl)benzaldehyde (**3f**).



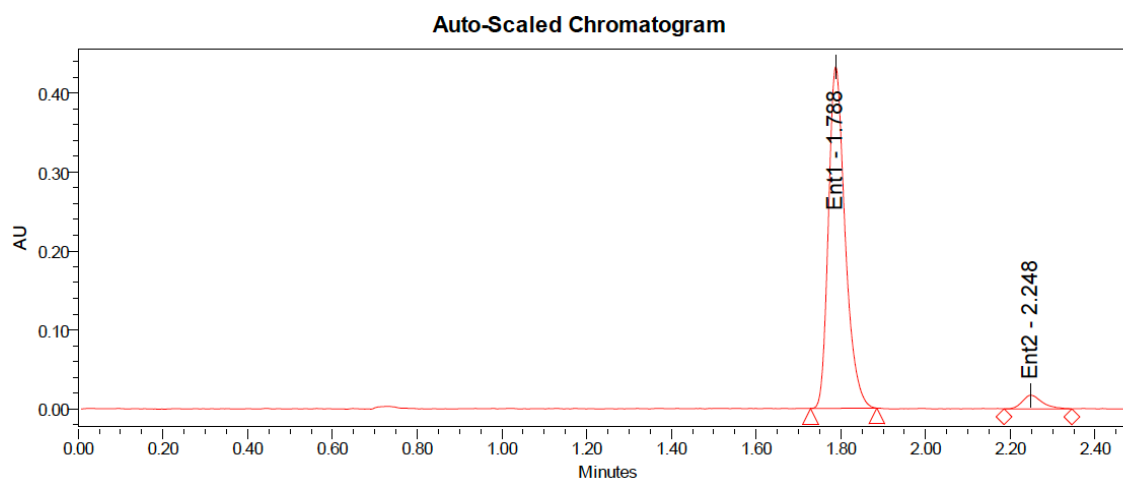
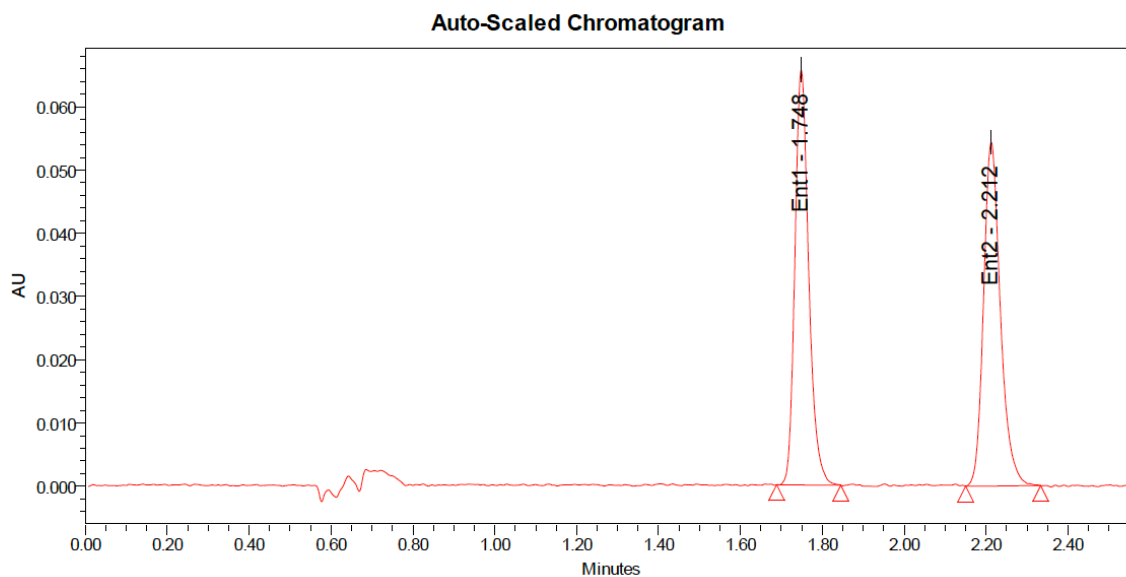
Sample	ent1	ent2	ee	Ent1	Ent2
racemic	48.71	51.29	-2.58	1124209	1183752
scalemic	99.43	0.57	98.87	1327084	7559

4-Methoxybenzyl (6*R*,7*R*)-7-fluoro-7-(2-formylphenyl)-6-methyl-6-phenylheptanoate
(**3g**).



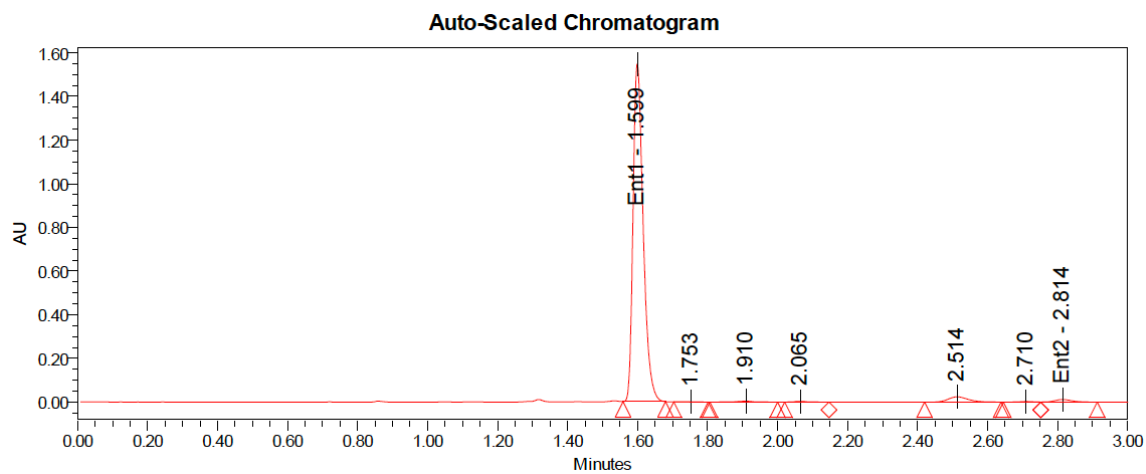
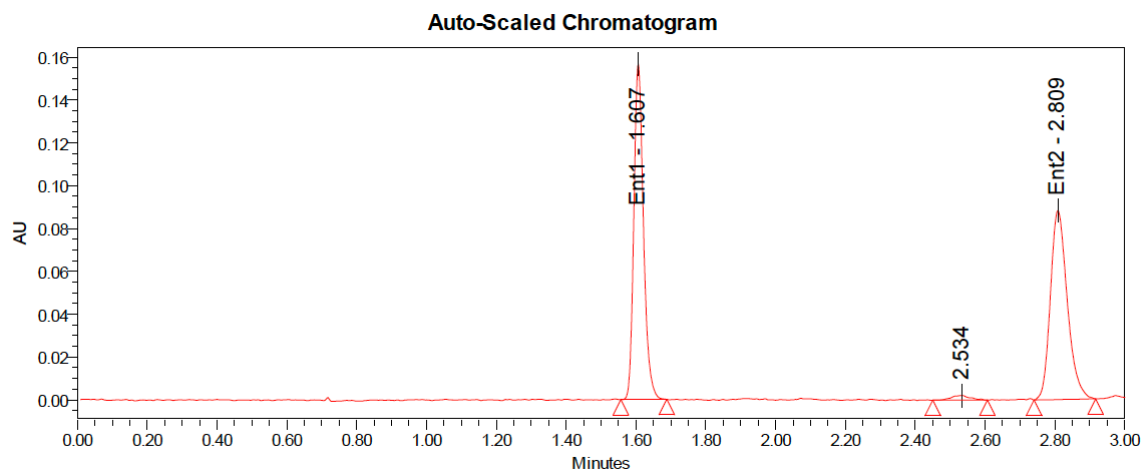
Sample	ent1	ent2	ee	Ent1	Ent2
racemic	49.89	50.11	-0.22	294203	295472
scalemic	-	100.00	-100.00	-	2675911

(*R*)-2-(1-Fluoro-2-phenylethyl)benzaldehyde (**3h**).



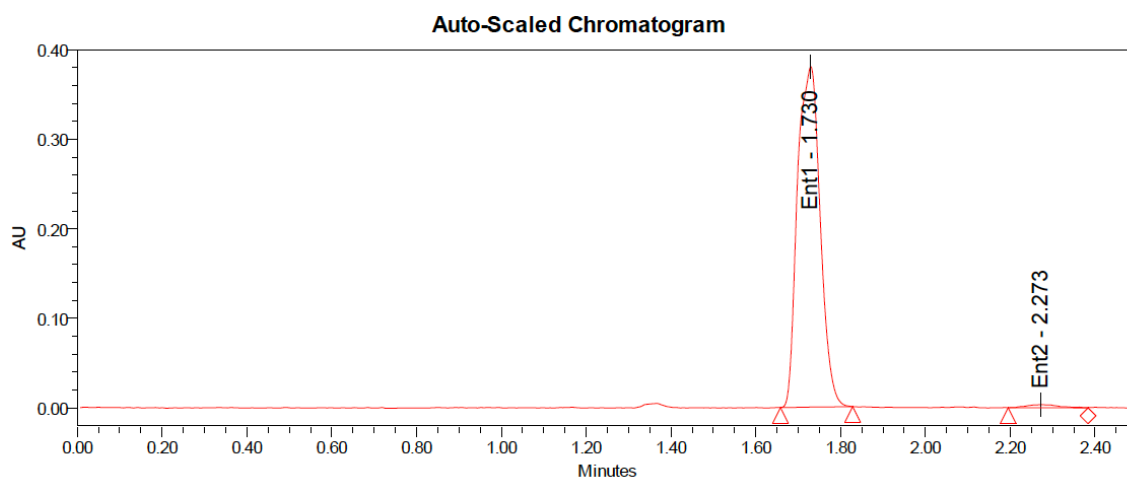
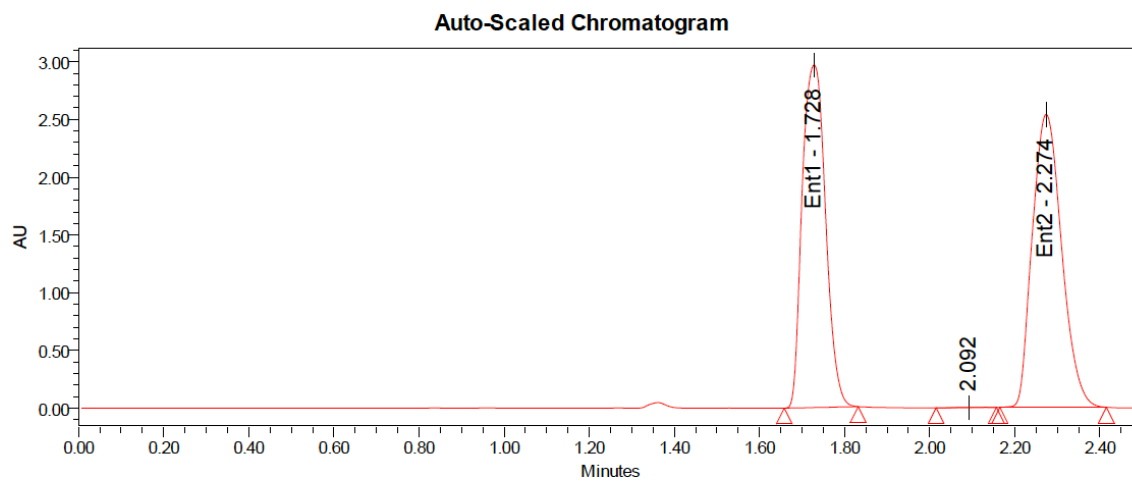
Sample	ent1	ent2	ee	Ent1	Ent2
racemic	49.78	50.22	-0.43	154239	155574
scalemic	95.43	4.57	90.86	1184861	56734

(*R*)-3-Fluoro-2-(1-fluoro-2-phenylethyl)benzaldehyde (**3i**).



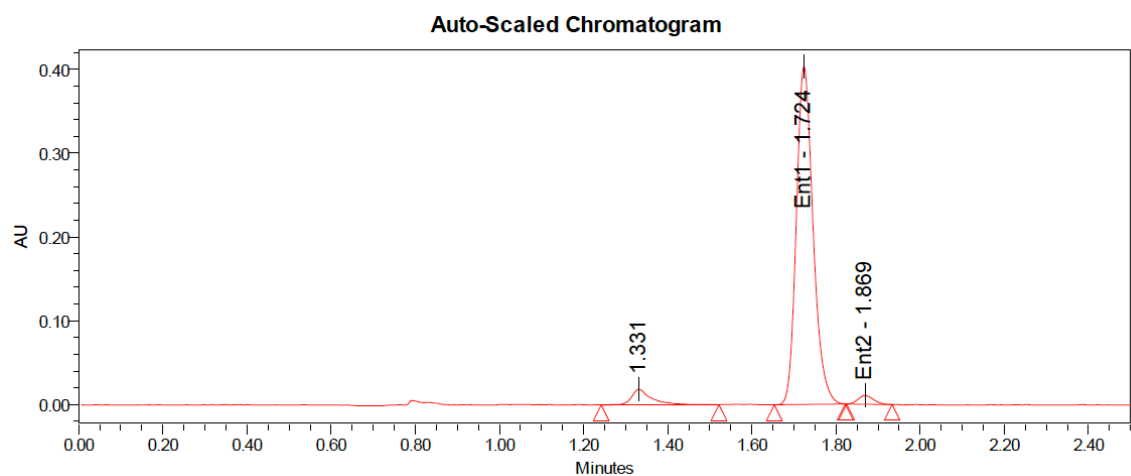
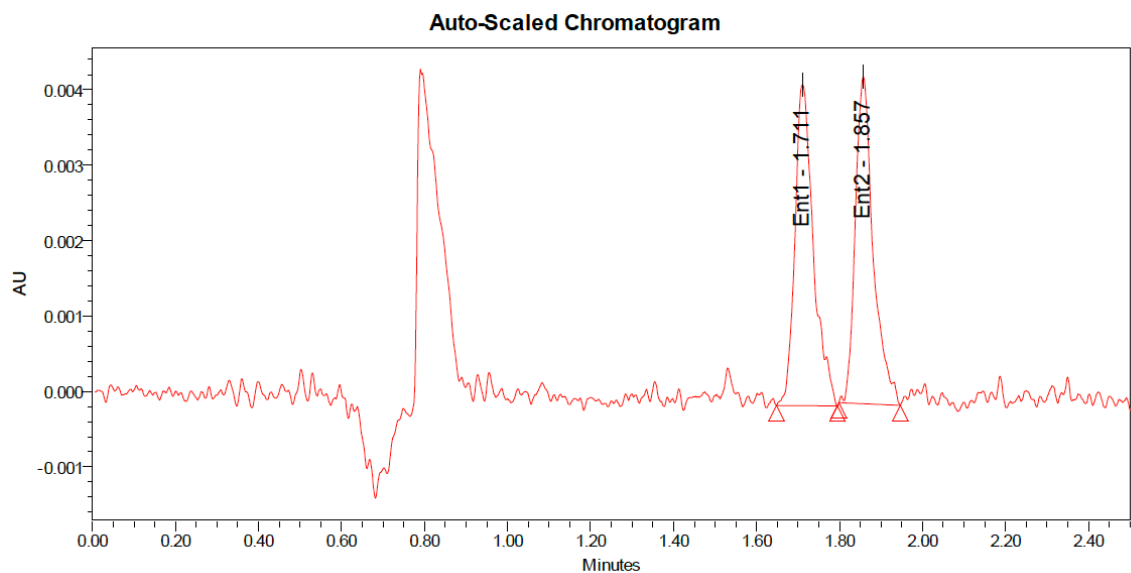
Sample	ent1	ent2	ee	Ent1	Ent2
racemic	50.23	49.77	0.46	299640	296884
scalemic	98.68	1.32	97.36	3109088	41660

(*R*)-1-(1-Fluoro-2-phenylethyl)-2-naphthaldehyde (**3j**).



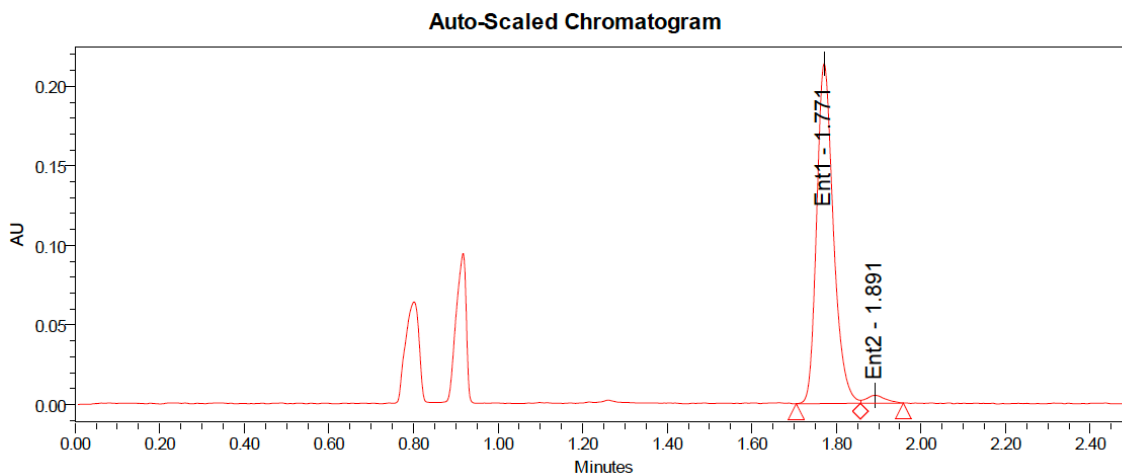
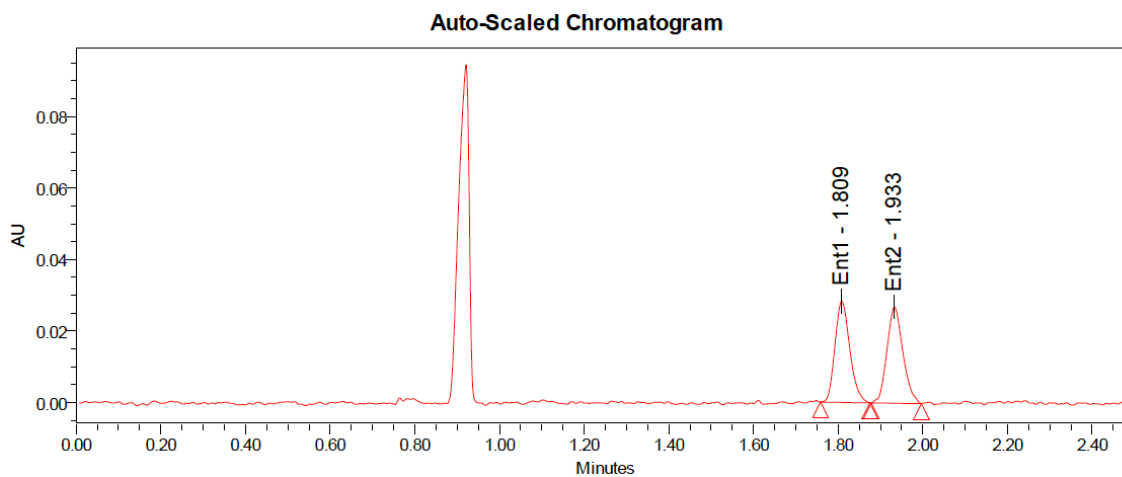
Sample	ent1	ent2	ee	Ent1	Ent2
racemic	48.21	51.79	-3.59	11289402	12129356
scalemic	98.70	1.30	97.41	1410553	18529

(*R*)-2-(2-Fluoro-1-phenylpropan-2-yl)benzaldehyde (**3k**).



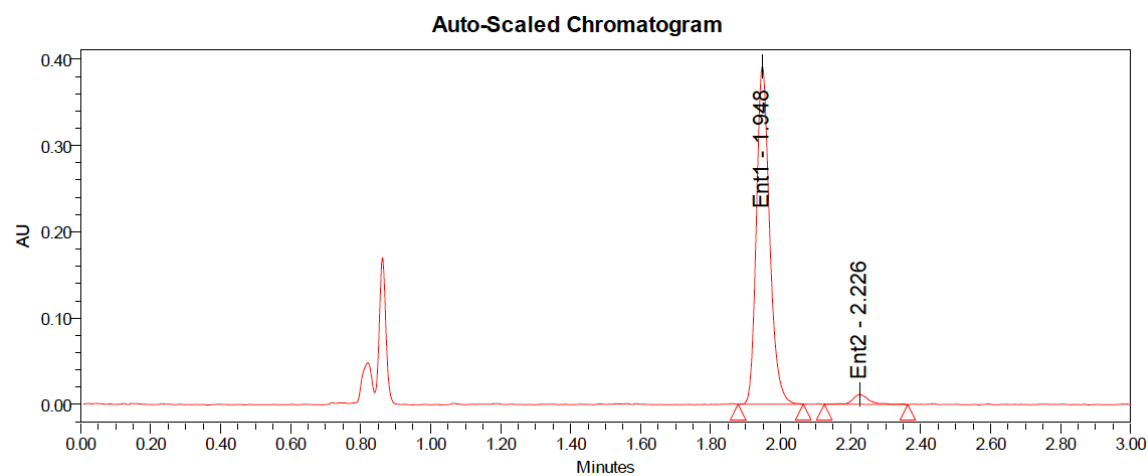
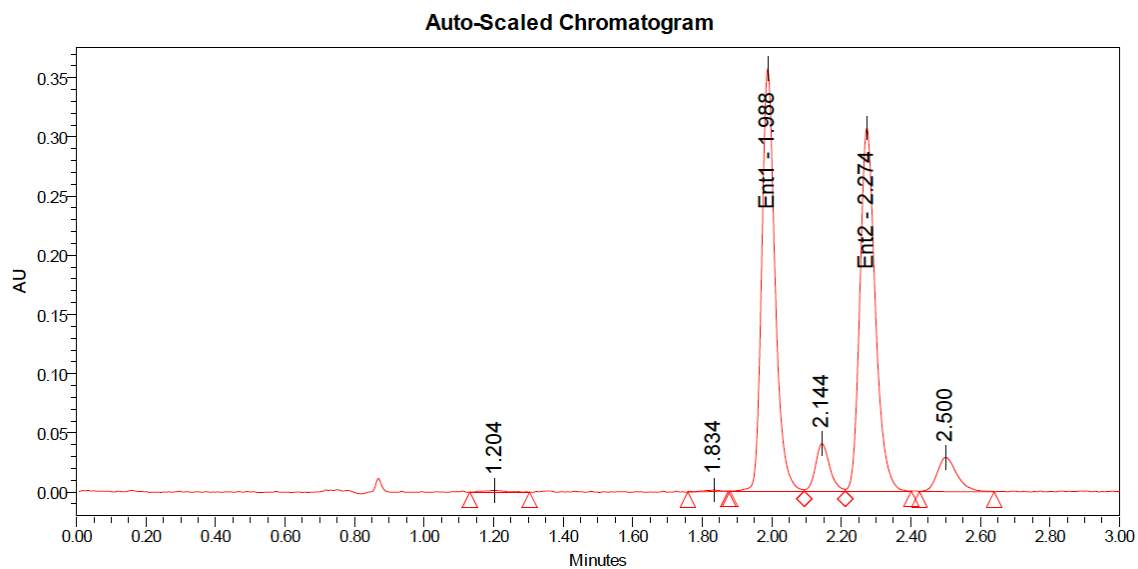
Sample	ent1	ent2	ee	Ent1	Ent2
racemic	50.37	49.63	0.74	13211	13015
scalemic	97.66	2.34	95.31	1114017	26745

2-((2*R*,3*R*)-4-Cyclohexyl-2-fluoro-3-phenylbutan-2-yl)benzaldehyde (**31**).



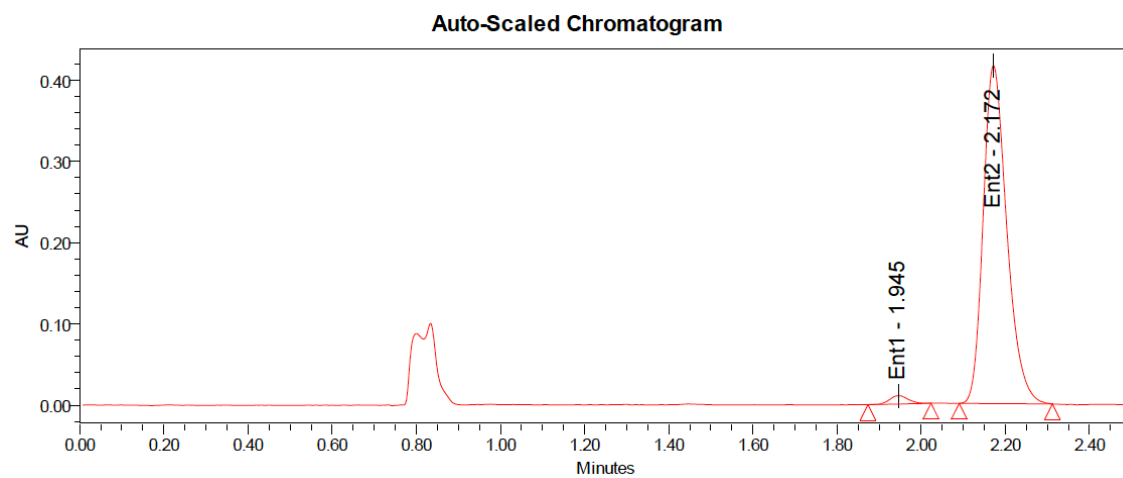
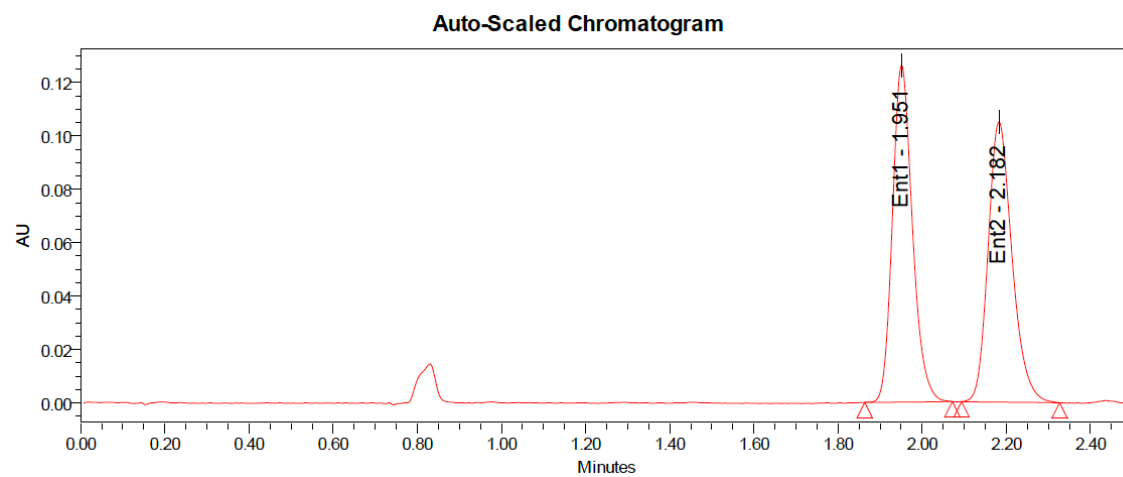
Sample	ent1	ent2	ee	Ent1	Ent2
racemic	49.54	50.46	-0.91	69227	70504
scalemic	97.40	2.60	94.80	586232	15652

2-((2*R*,3*R*)-2-Fluoro-3,5-diphenylpentan-2-yl)benzaldehyde (**3m**).



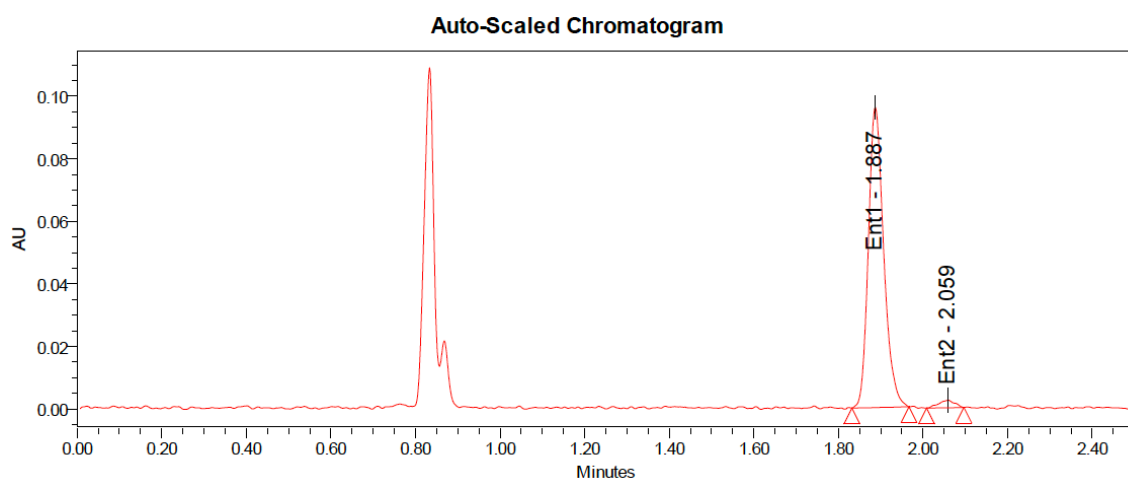
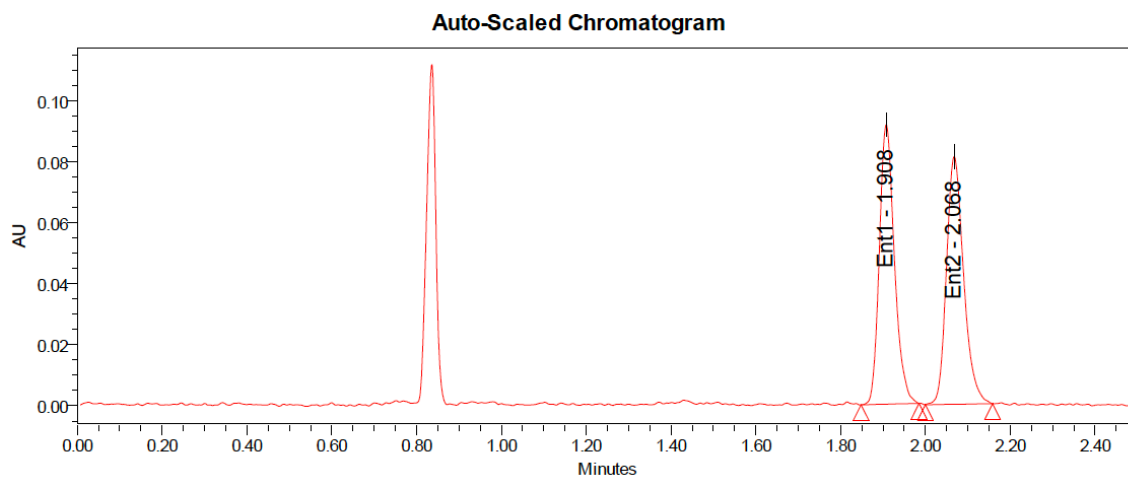
Sample	ent1	ent2	ee	Ent1	Ent2
racemic	50.27	49.73	0.53	954313	944235
scalemic	96.53	3.47	93.06	1029329	36993

(3*R*,4*R*)-4-Fluoro-4-(2-formylphenyl)-3-phenylpentyl 4-methylbenzenesulfonate (**3n**).



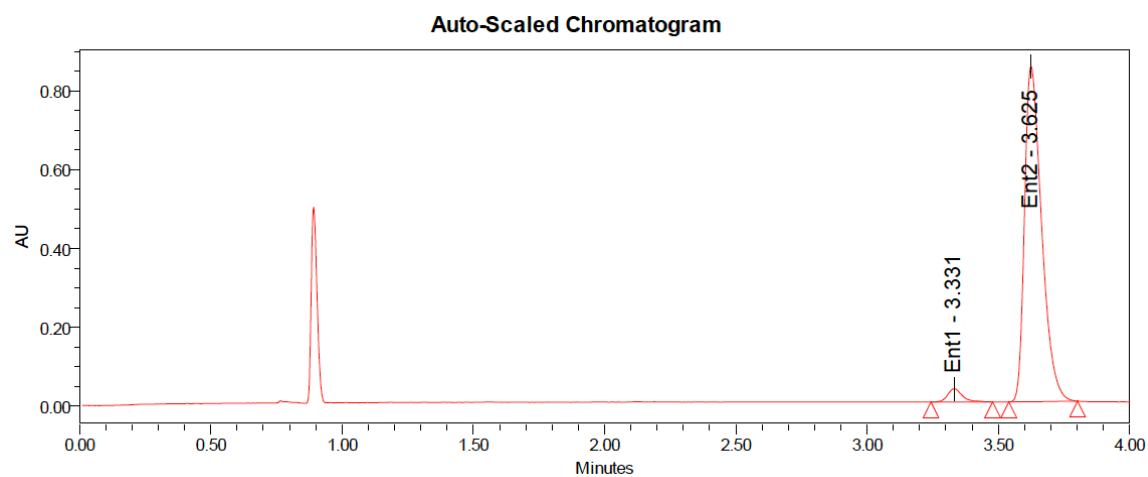
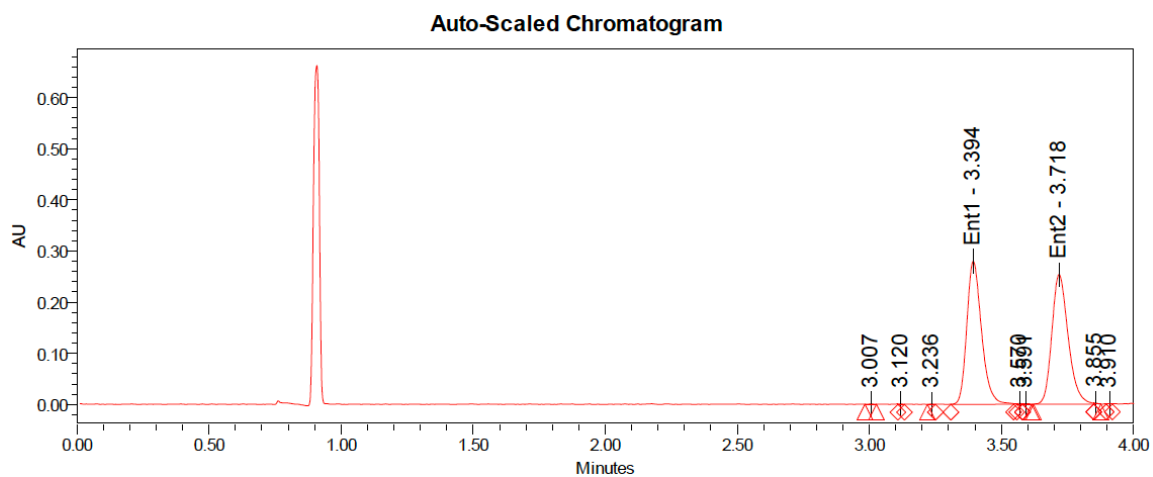
Sample	ent1	ent2	ee	Ent1	Ent2
racemic	50.03	49.97	0.05	415571	415123
scalemic	1.93	98.07	-96.15	31851	1621425

(3*R*,4*R*)-4-Fluoro-4-(2-formylphenyl)-3-phenylpentyl acetate (**30**).



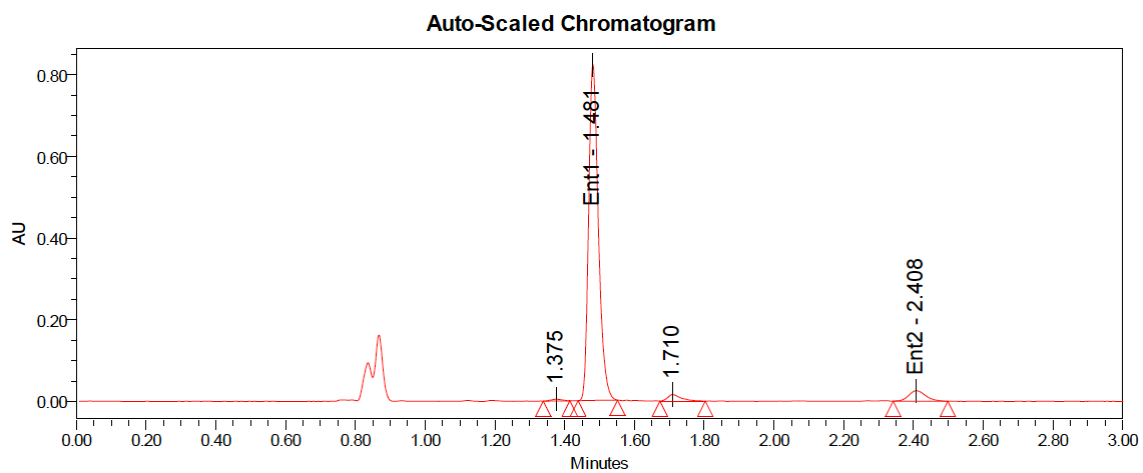
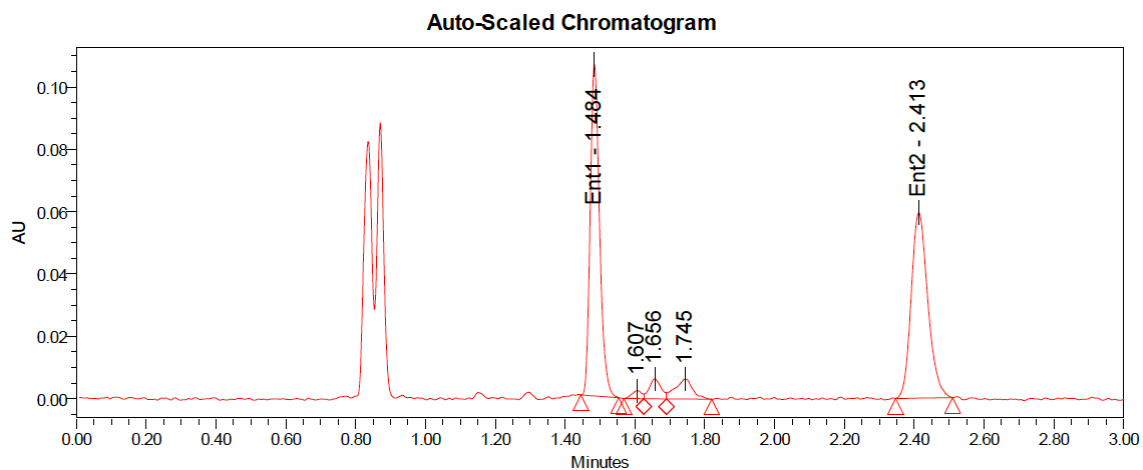
Sample	ent1	ent2	ee	Ent1	Ent2
racemic	49.73	50.27	-0.53	225964	228373
scalemic	97.43	2.57	94.86	241601	6371

2-((2*R*,3*R*)-2-Fluoro-3-phenylbutan-2-yl)benzaldehyde (**3p**).



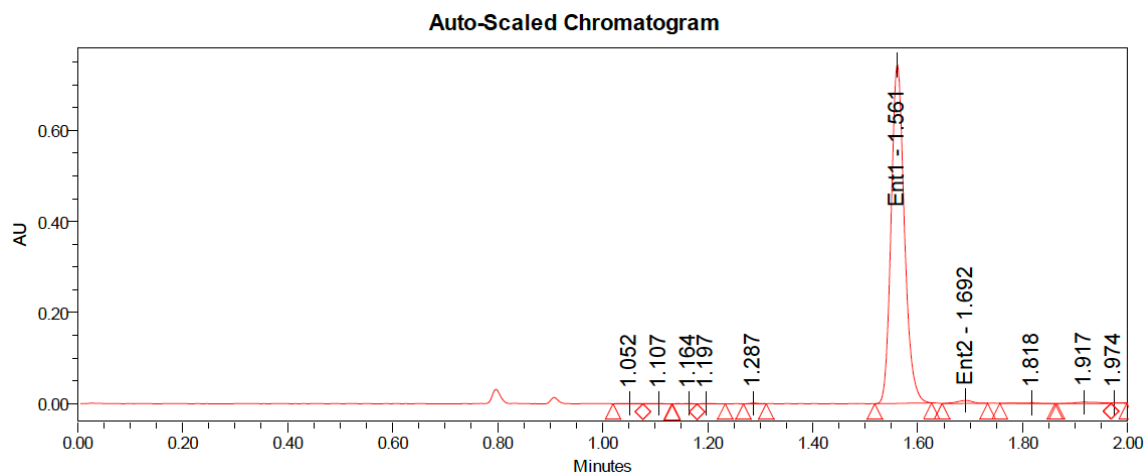
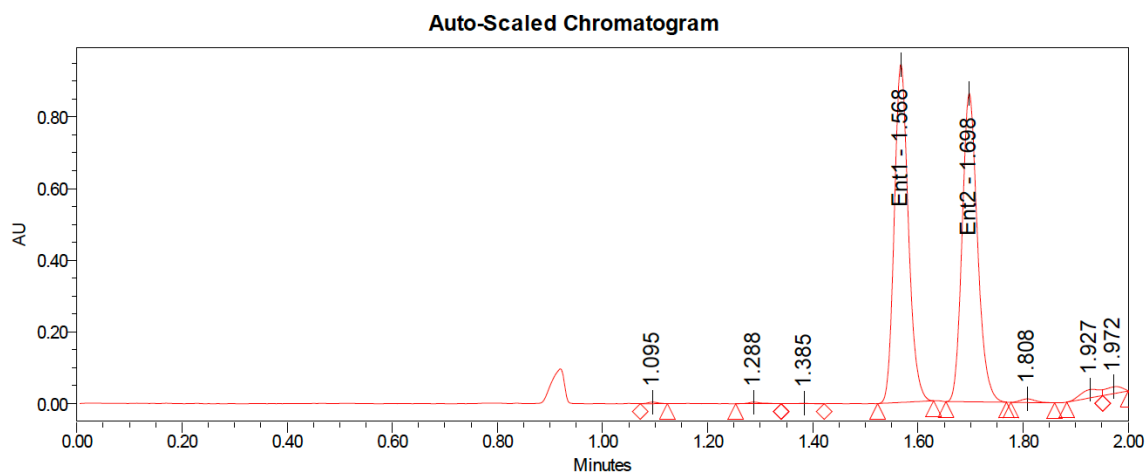
Sample	ent1	ent2	ee	Ent1	Ent2
racemic	49.89	50.11	-0.23	1083172	1088072
scalemic	3.35	96.65	-93.31	133591	3857421

2-((2*R*,3*S*)-2-Fluoro-3-phenylhexan-2-yl)benzaldehyde (**3q**).



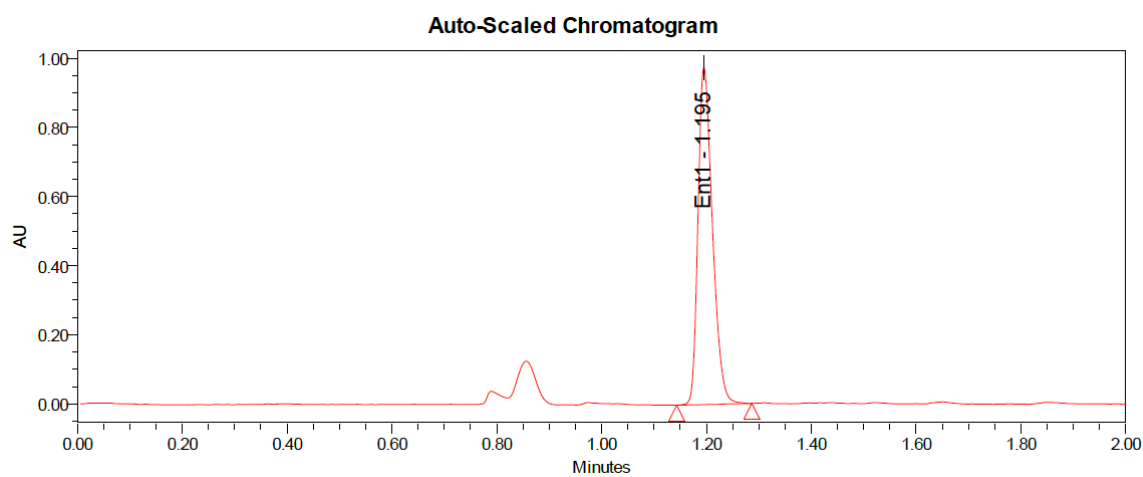
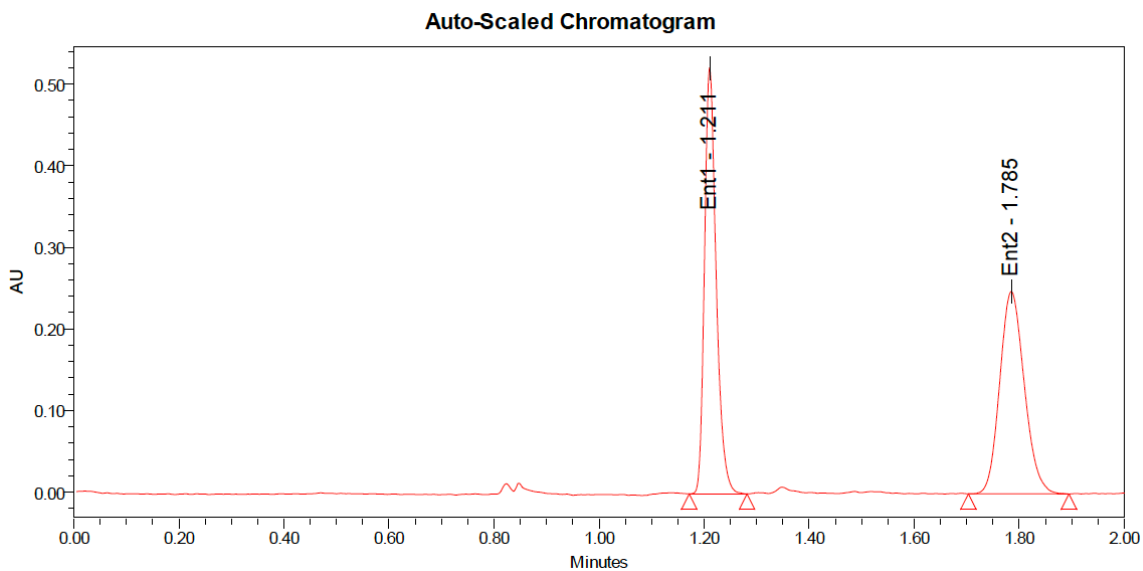
Sample	ent1	ent2	ee	Ent1	Ent2
racemic	50.06	49.94	0.12	197559	197093
scalemic	94.79	5.21	89.59	1598400	87805

2-((1*R*,2*R*)-1-Fluoro-2-phenylpropyl)-5-methoxybenzaldehyde (**3r**).



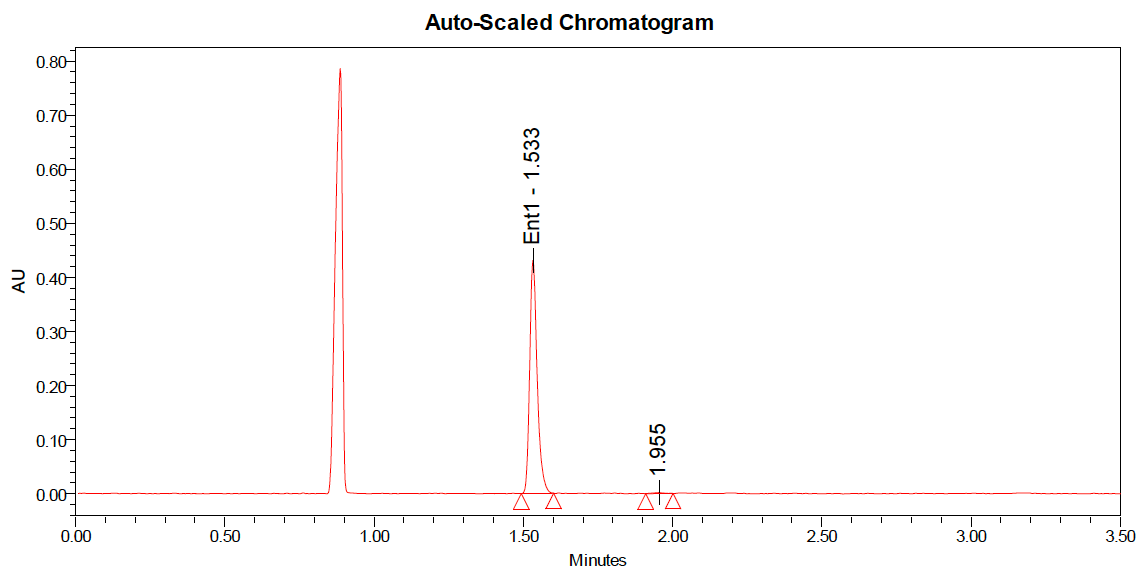
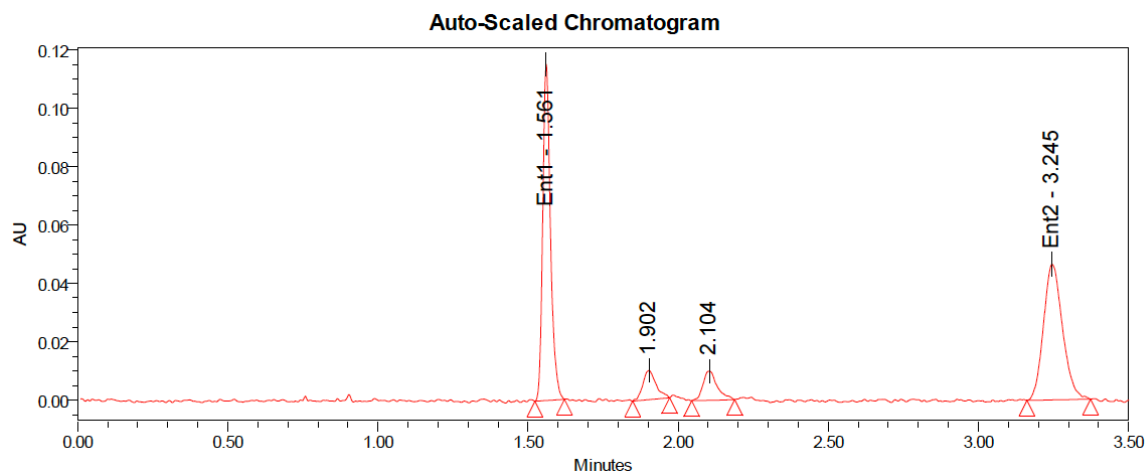
Sample	ent1	ent2	ee	Ent1	Ent2
racemic	50.11	49.89	0.22	1755877	1748104
scalemic	99.01	0.99	98.01	1304574	13107

2-((1*R*,2*R*)-1-Fluoro-2-phenylpropyl)-5-(trifluoromethyl)benzaldehyde (**3s**).



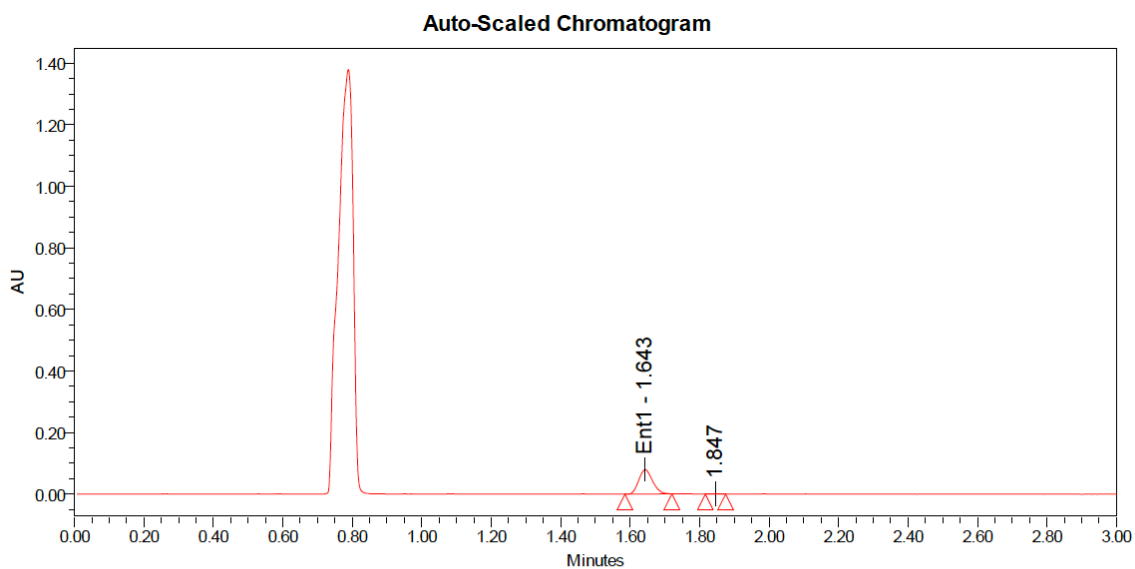
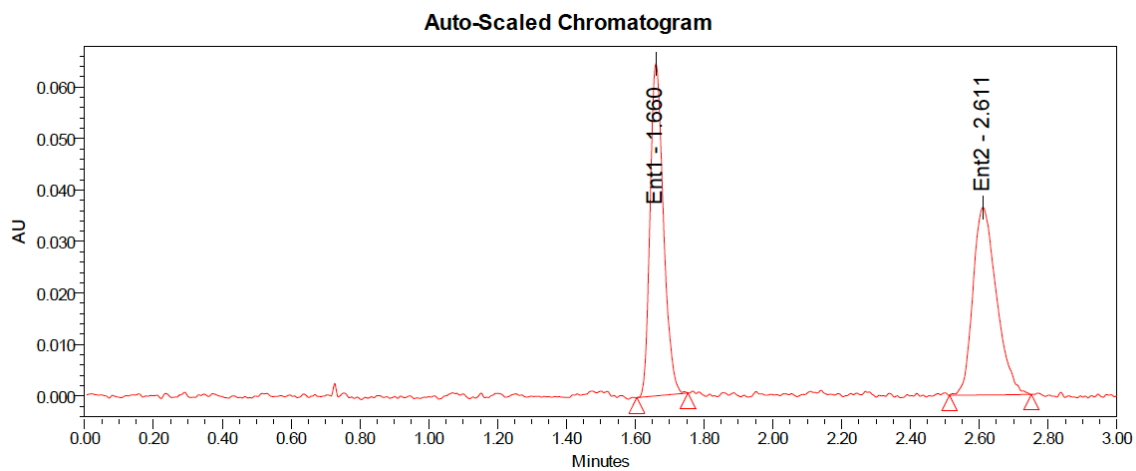
Sample	ent1	ent2	ee	Ent1	Ent2
racemic	49.95	50.05	-0.09	804801	806312
scalemic	100.00	-	100.00	1859473	-

5-Fluoro-2-((1*R*,2*R*)-1-fluoro-2-phenylpropyl)-4-methylbenzaldehyde (**3t**).



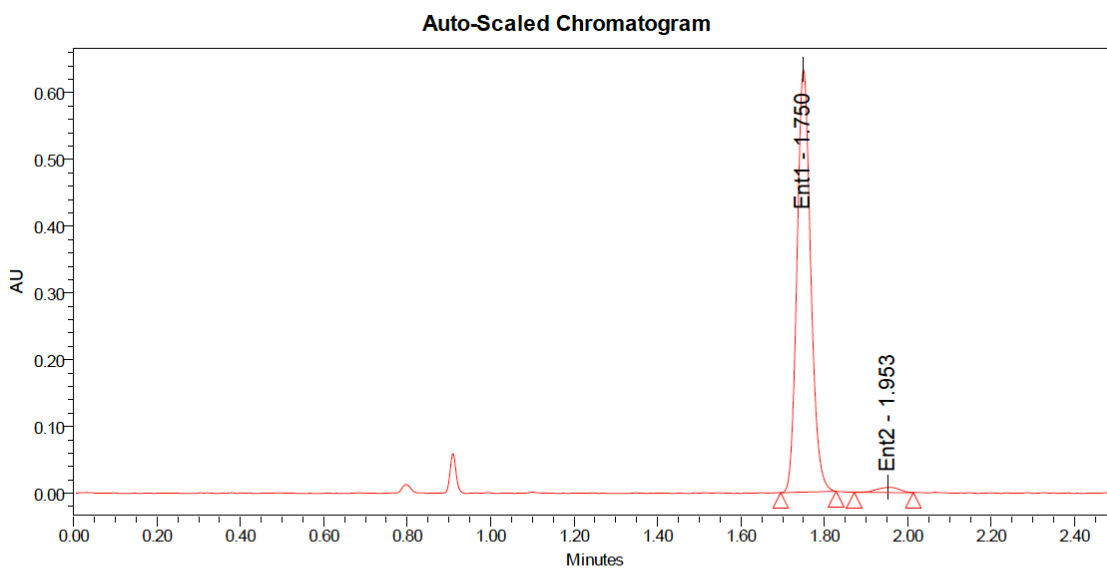
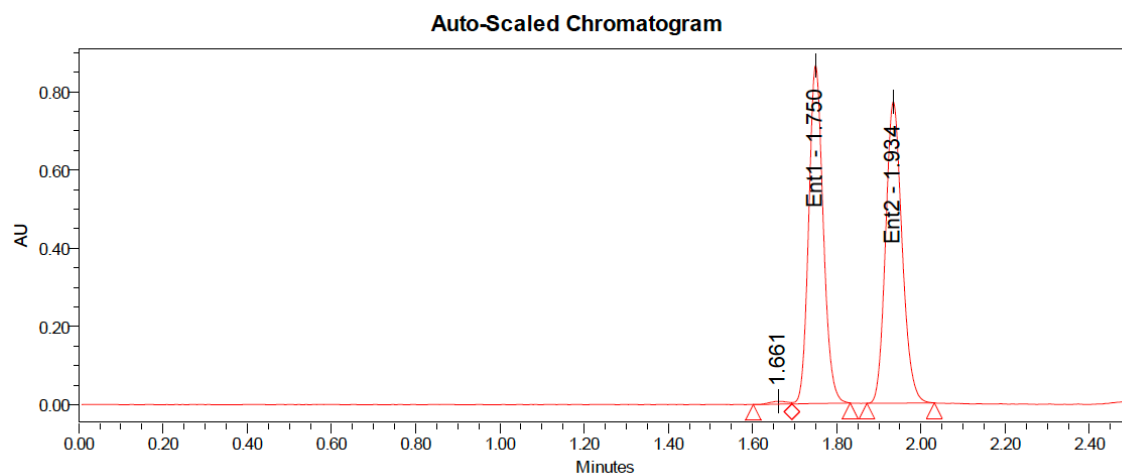
Sample	ent1	ent2	ee	Ent1	Ent2
racemic	50.11	49.89	0.22	206175	205258
scalemic	100.00	-	100.00	753675	-

3-((1*R*,2*R*)-1-Fluoro-2-phenylpropyl)-4-formylbenzonitrile (**3u**).



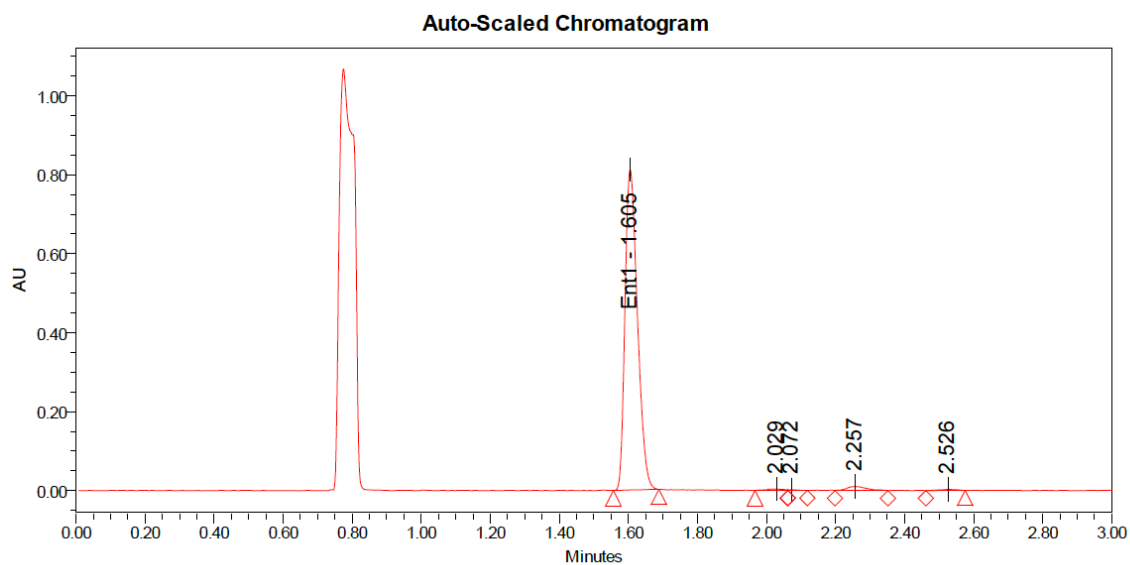
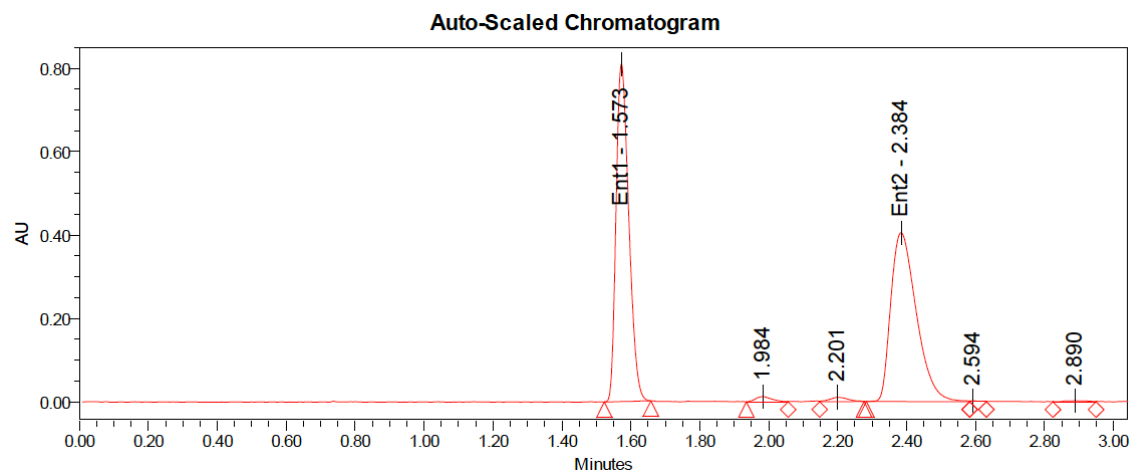
Sample	ent1	ent2	ee	Ent1	Ent2
racemic	50.15	49.85	0.31	174210	173135
scalemic	100.00	-	100.00	217552	-

5-((1*R*,2*R*)-1-Fluoro-2-phenylpropyl)-4-formyl-2-methoxyphenyl acetate (**3v**).



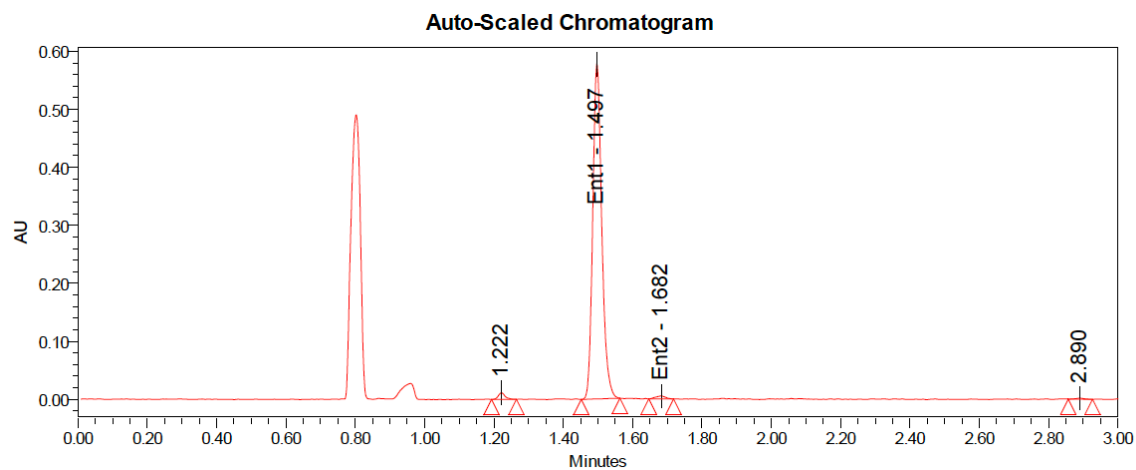
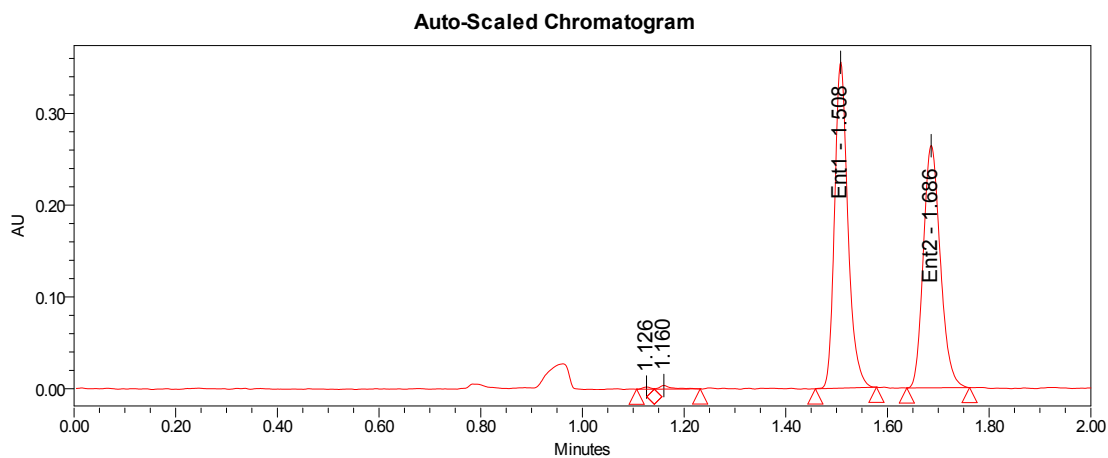
Sample	ent1	ent2	ee	Ent1	Ent2
racemic	49.68	50.32	-0.63	2071543	2098006
scalemic	97.98	2.02	95.96	1444492	29816

Methyl 3-((1*R*,2*R*)-1-fluoro-2-phenylpropyl)-4-formylbenzoate (**3w**).



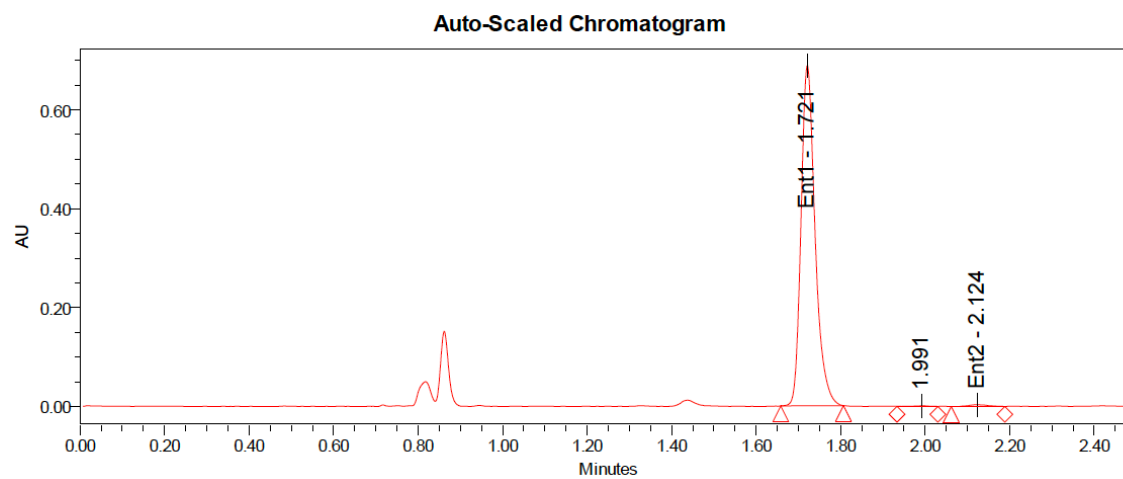
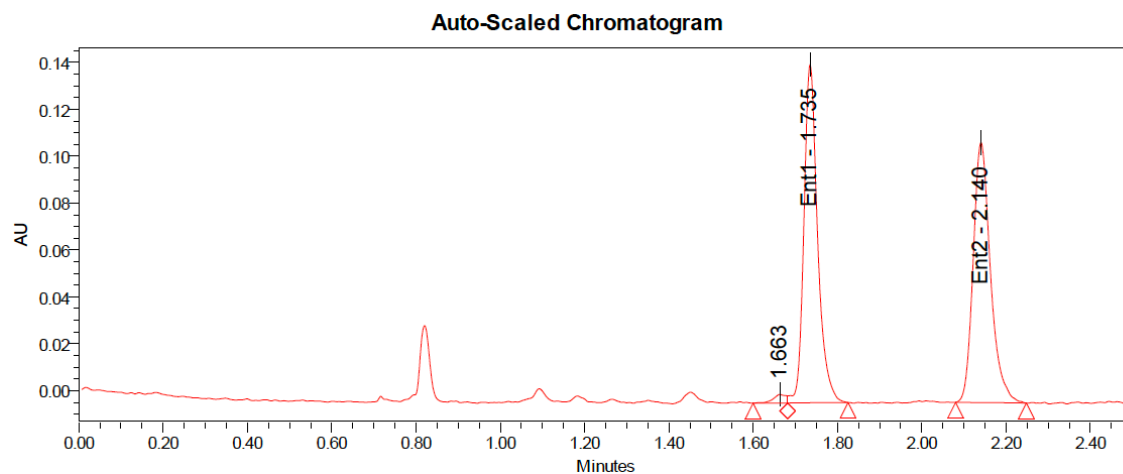
Sample	ent1	ent2	ee	Ent1	Ent2
racemic	49.88	50.12	-0.25	2073763	2084141
scalemic	100.00	-	100.00	2026261	-

2-((1*R*,2*R*)-2-Cyclopropyl-1-fluoro-2-phenylethyl)benzaldehyde (**3x**).



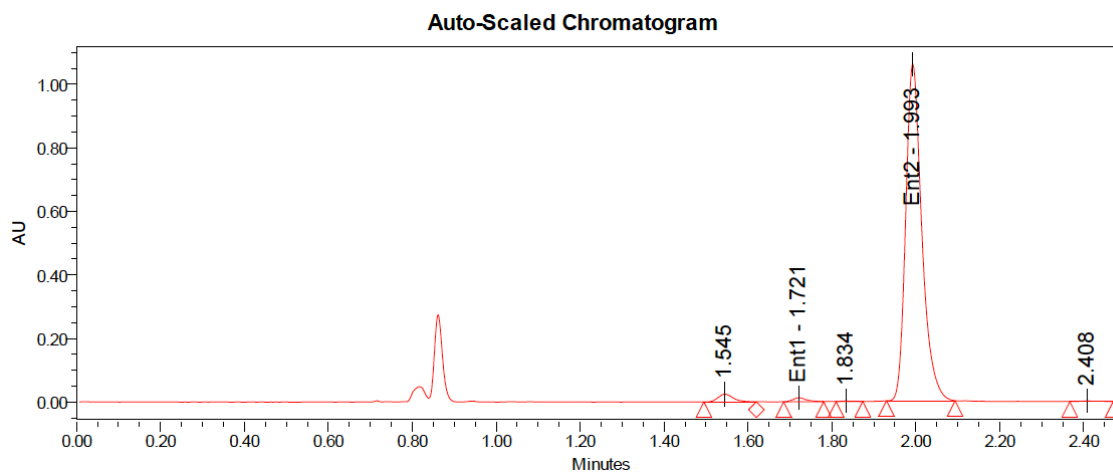
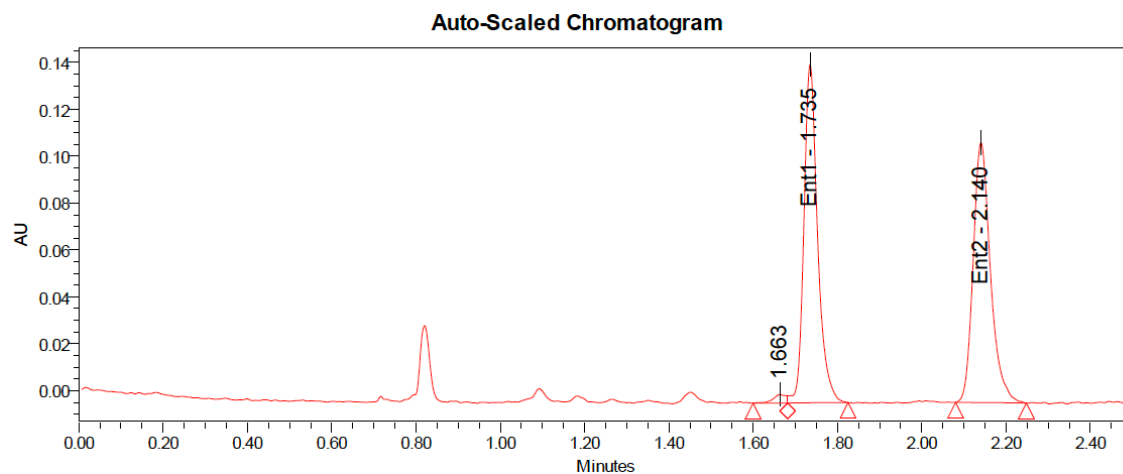
Sample	ent1	ent2	ee	Ent1	Ent2
racemic	51.36	48.64	2.72	646861	612611
scalemic	99.08	0.92	98.16	1046732	9726

2-((1*R*,2*R*)-1-Fluoro-2,3-diphenylpropyl)benzaldehyde (**3y**).



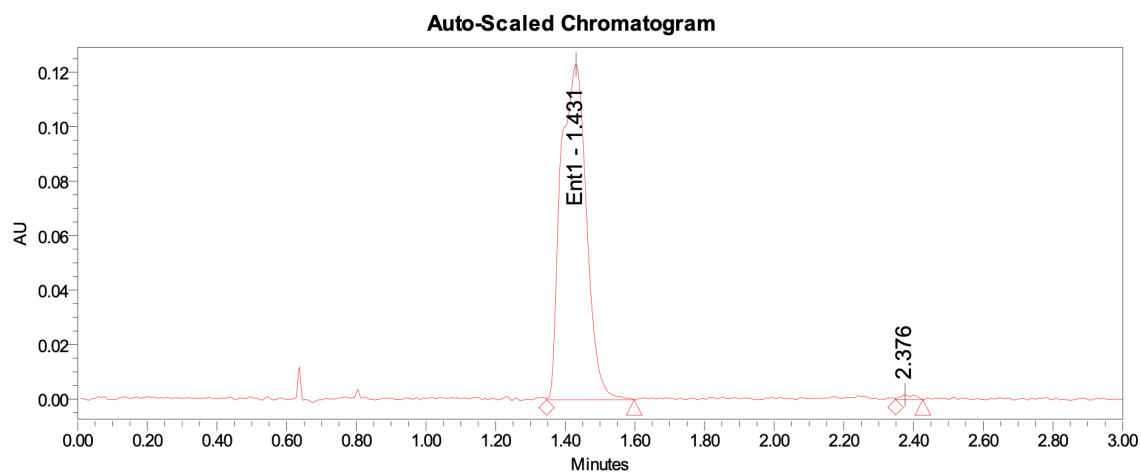
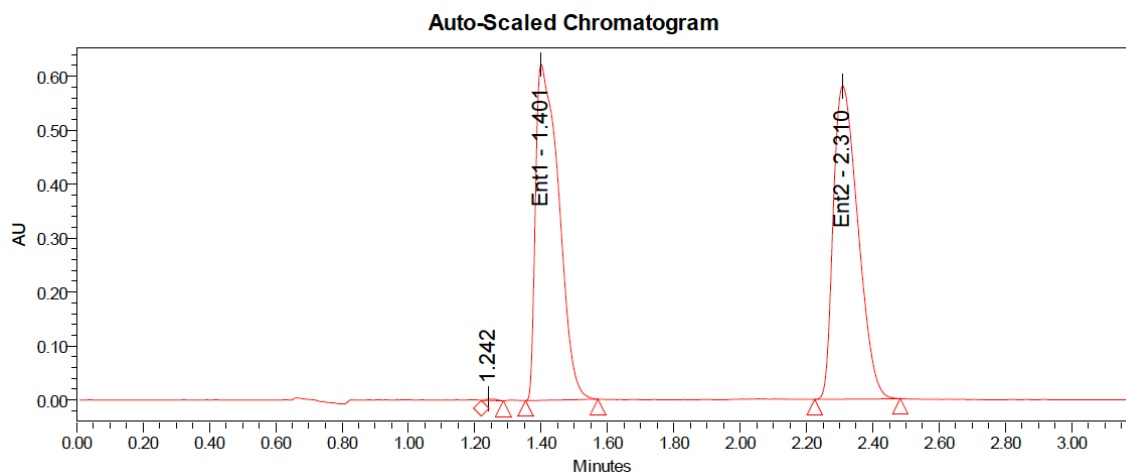
Sample	ent1	ent2	ee	Ent1	Ent2
racemic	50.74	49.26	1.49	326057	316511
scalemic	99.27	0.73	98.54	1589388	11681

2-((1*R*,2*S*)-1-Fluoro-2,3-diphenylpropyl)benzaldehyde (**3z**).



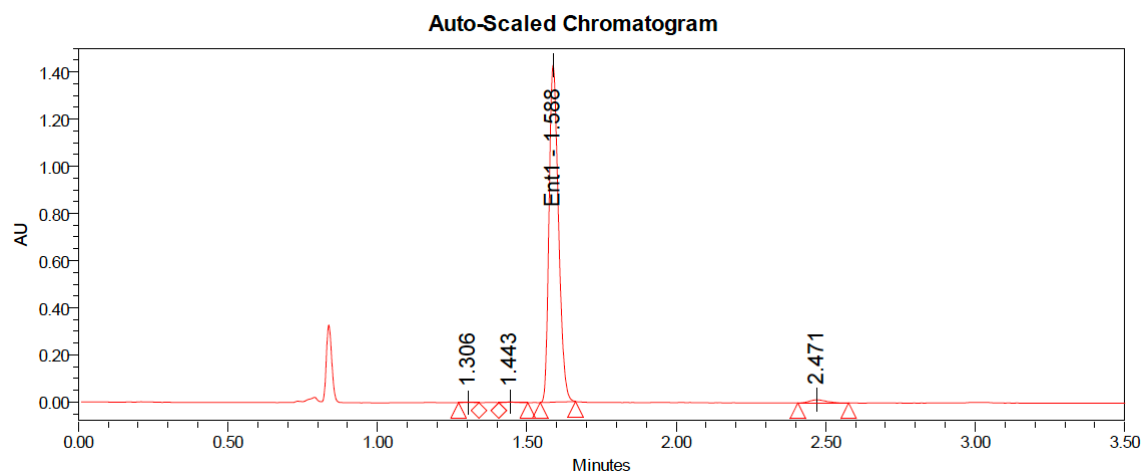
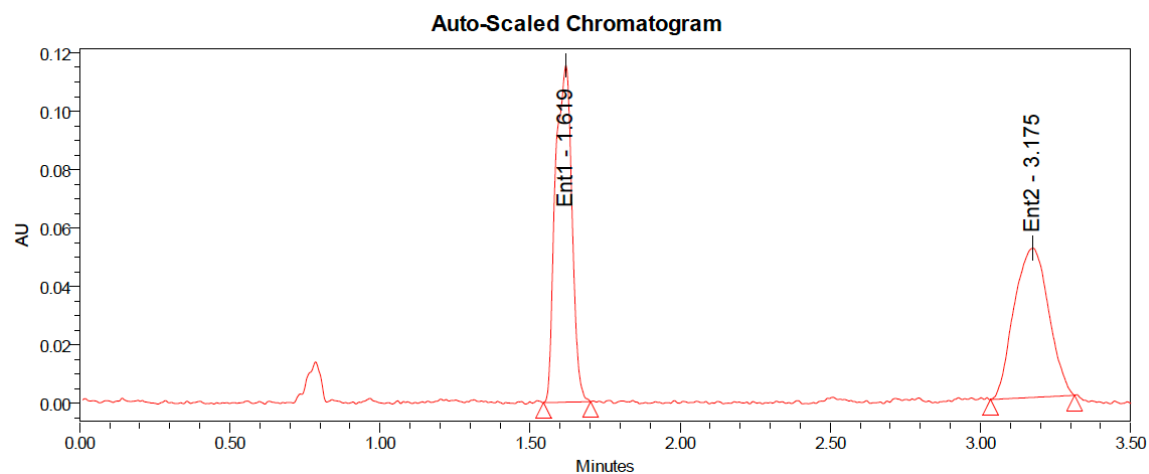
Sample	ent1	ent2	ee	Ent1	Ent2
racemic	50.74	49.26	1.49	326057	316511
scalemic	0.98	99.02	-98.04	28017	2829971

4-Chloro-2-((1*R*,2*R*)-1-fluoro-2-phenylpropyl)benzaldehyde (**4a**).



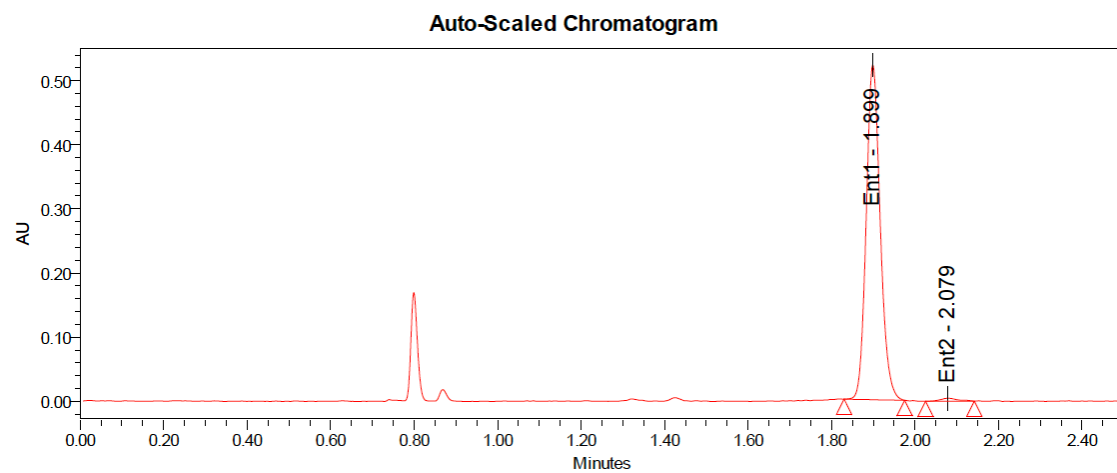
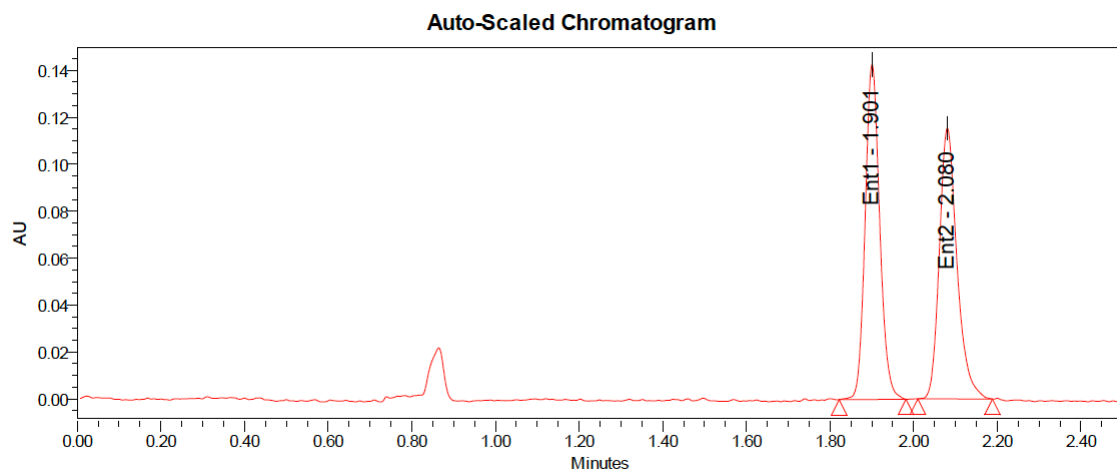
Sample	ent1	ent2	ee	Ent1	Ent2
racemic	50.14	49.86	0.29	3008744	2991546
scalemic	100.00	-	100.00	627772	-

2-((1*R*,2*R*)-2-(4-Butylphenyl)-1-fluoropropyl)-4-chlorobenzaldehyde (**4b**).



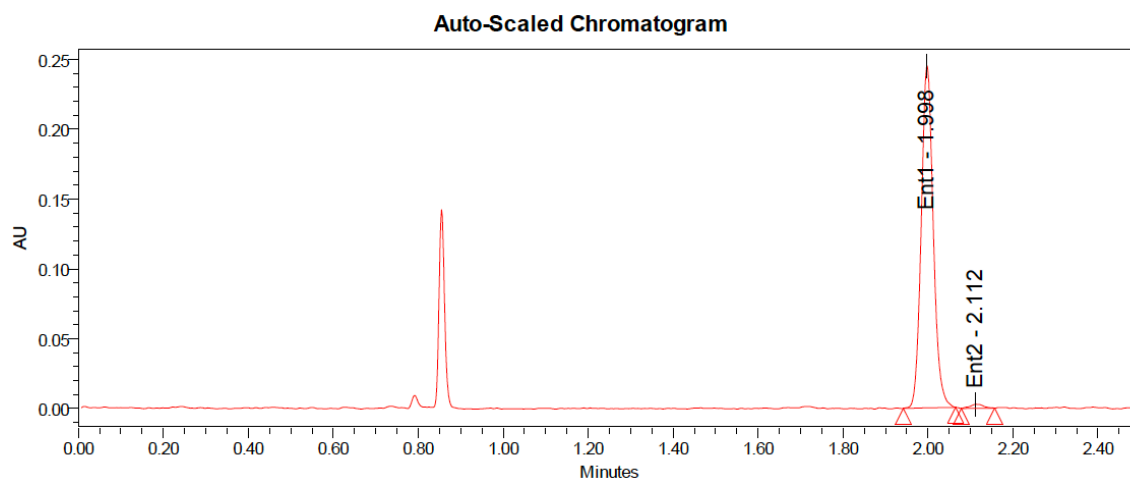
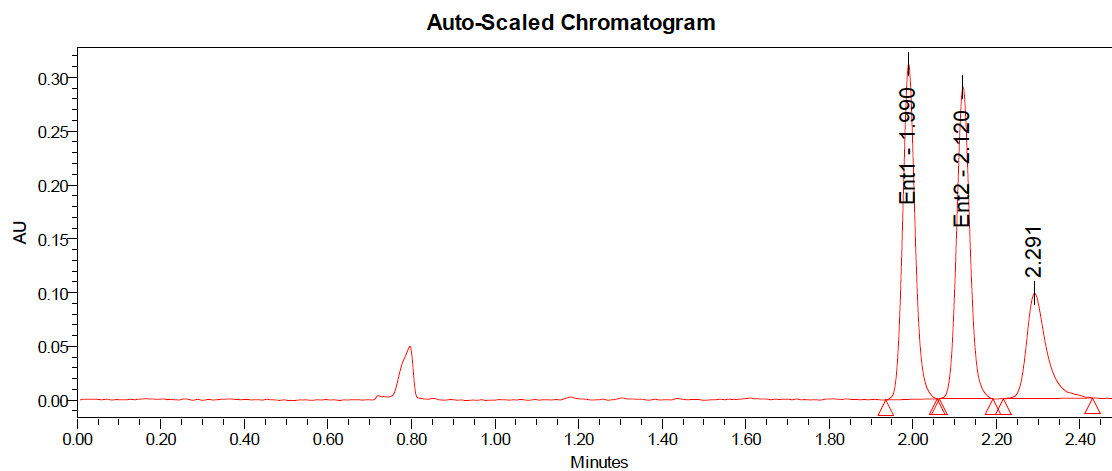
Sample	ent1	ent2	ee	Ent1	Ent2
racemic	51.75	48.25	3.49	439193	409543
scalemic	100.00	-	100.00	3129364	-

2-((1*R*,2*R*)-2-([1,1'-Biphenyl]-4-yl)-1-fluoropropyl)-4-chlorobenzaldehyde (**4c**).



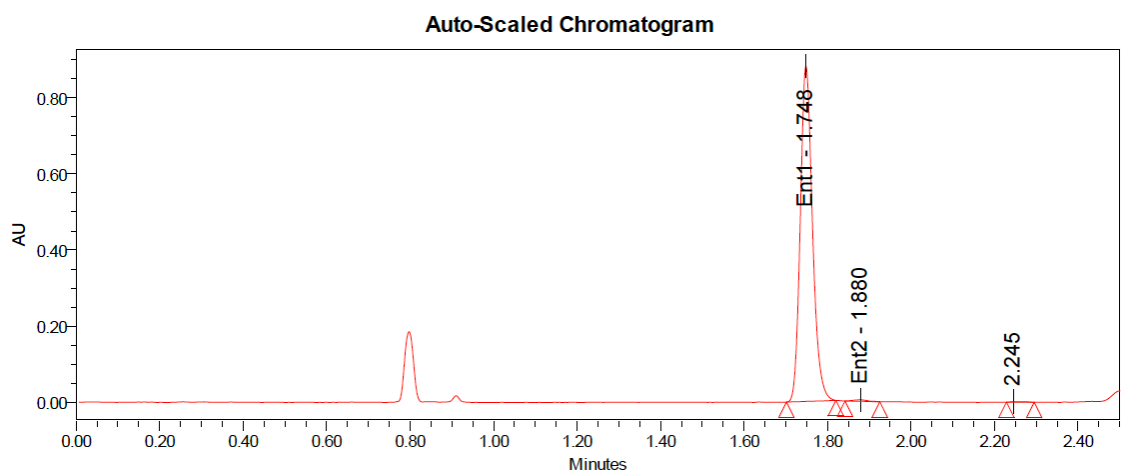
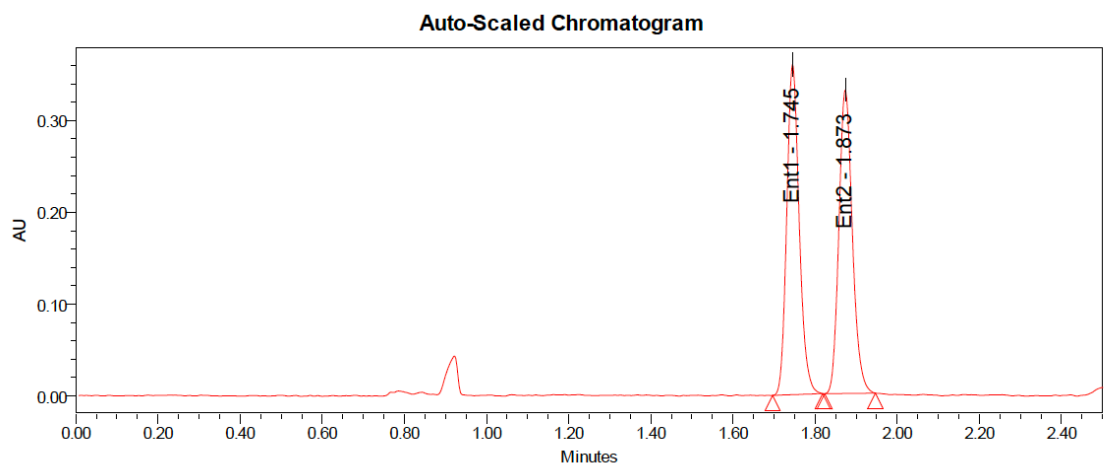
Sample	ent1	ent2	ee	Ent1	Ent2
racemic	50.54	49.46	1.08	345237	337864
scalemic	98.91	1.09	97.81	1219433	13473

4-Chloro-2-((1*R*,2*R*)-2-(4-chlorophenyl)-1-fluoropropyl)benzaldehyde (**4d**).



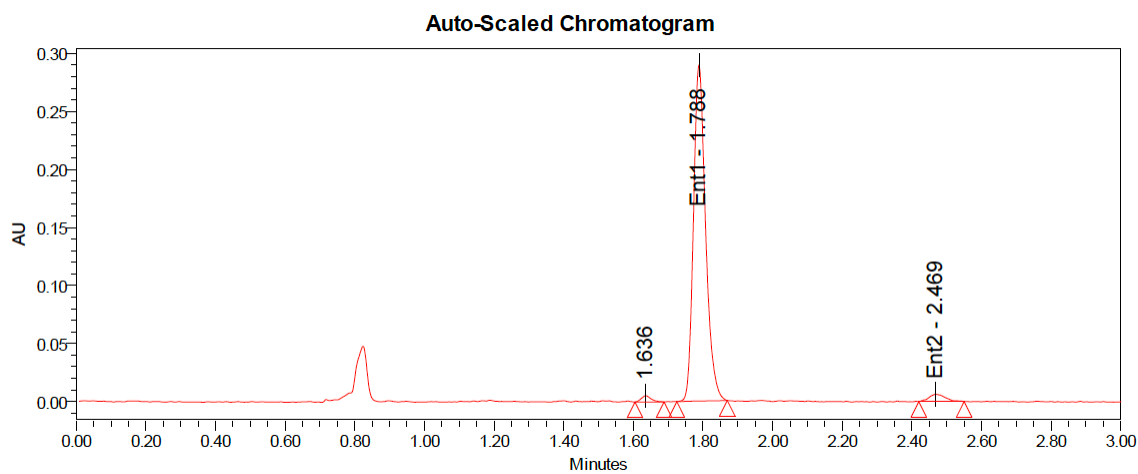
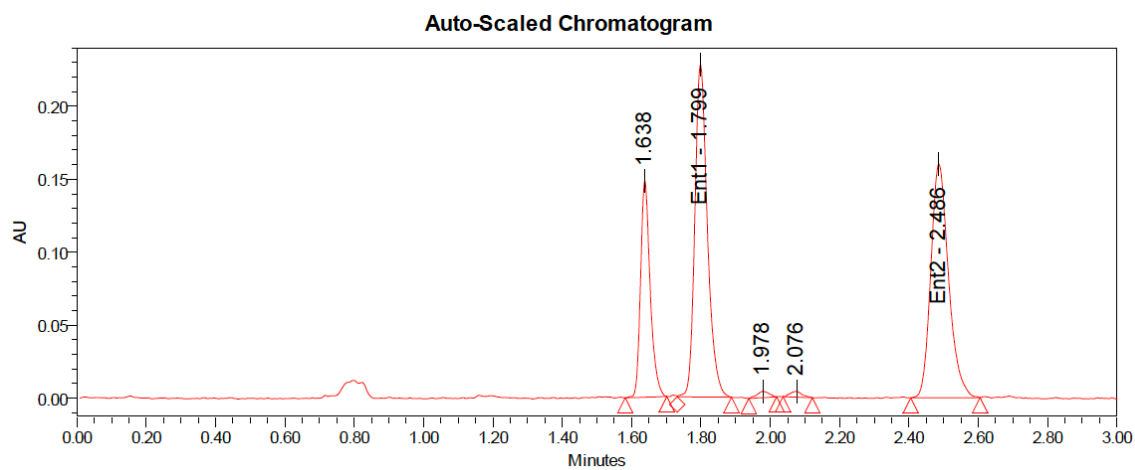
Sample	ent1	ent2	ee	Ent1	Ent2
racemic	50.13	49.87	0.26	635077	631823
scalemic	98.70	1.30	97.39	482900	6377

4-Chloro-2-((1*R*,2*R*)-1-fluoro-2-(4-methoxyphenyl)propyl)benzaldehyde (**4e**).



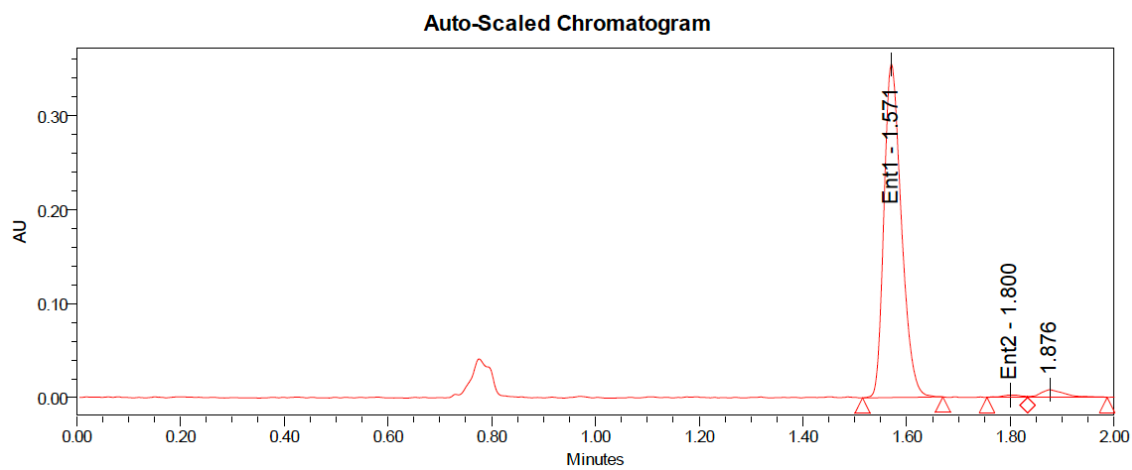
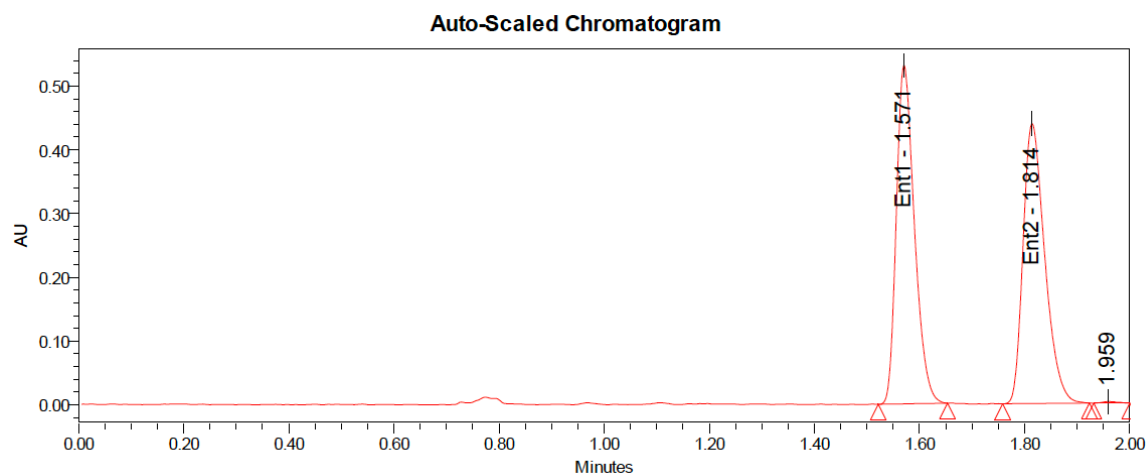
Sample	ent1	ent2	ee	Ent1	Ent2
racemic	50.17	49.83	0.34	759062	753913
scalemic	99.49	0.51	98.98	1787880	9175

Methyl 3-((1*R*,2*R*)-1-(5-chloro-2-formylphenyl)-1-fluoropropan-2-yl)benzoate (**4f**).



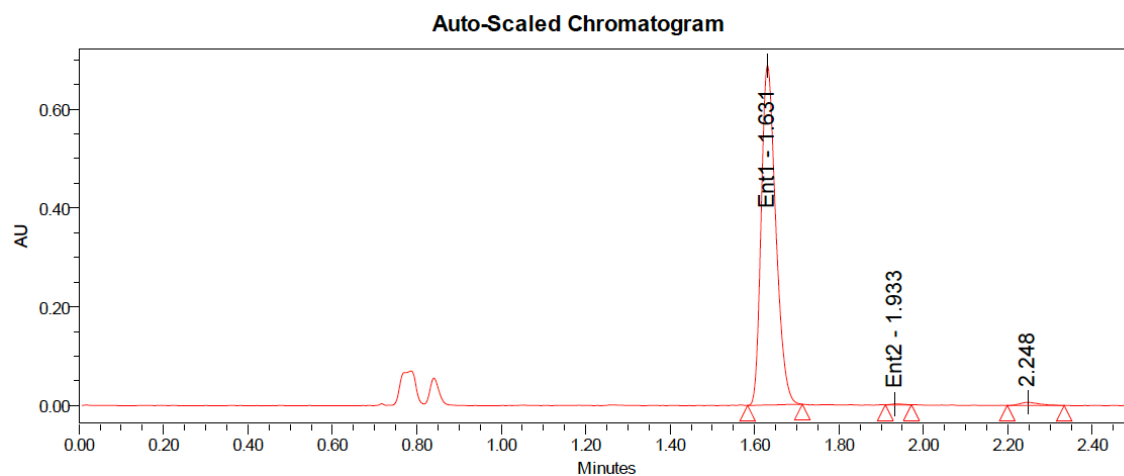
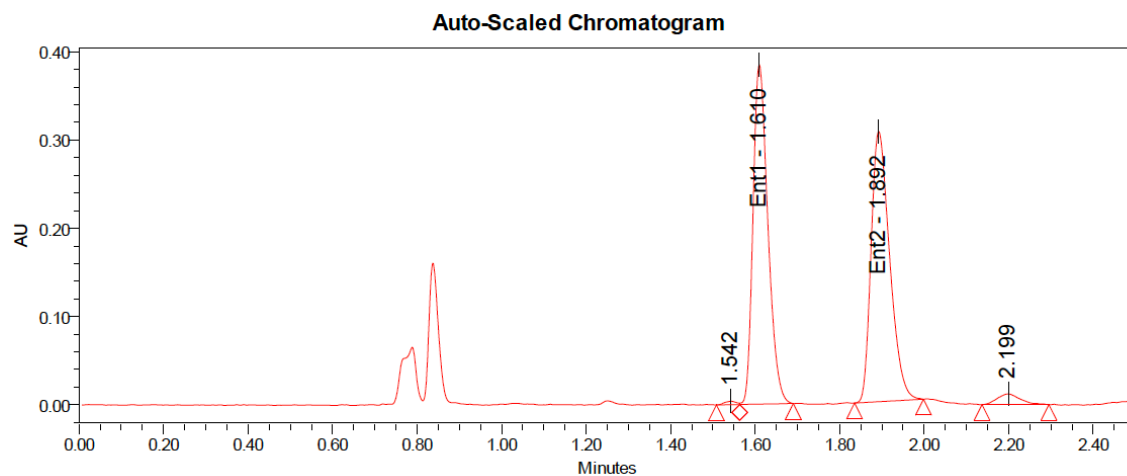
Sample	ent1	ent2	ee	Ent1	Ent2
racemic	50.08	49.92	0.16	571415	569558
scalemic	97.10	2.90	94.21	700471	20895

4-Chloro-2-((1*R*,2*R*)-1-fluoro-2-(3-methoxyphenyl)propyl)benzaldehyde (**4g**).



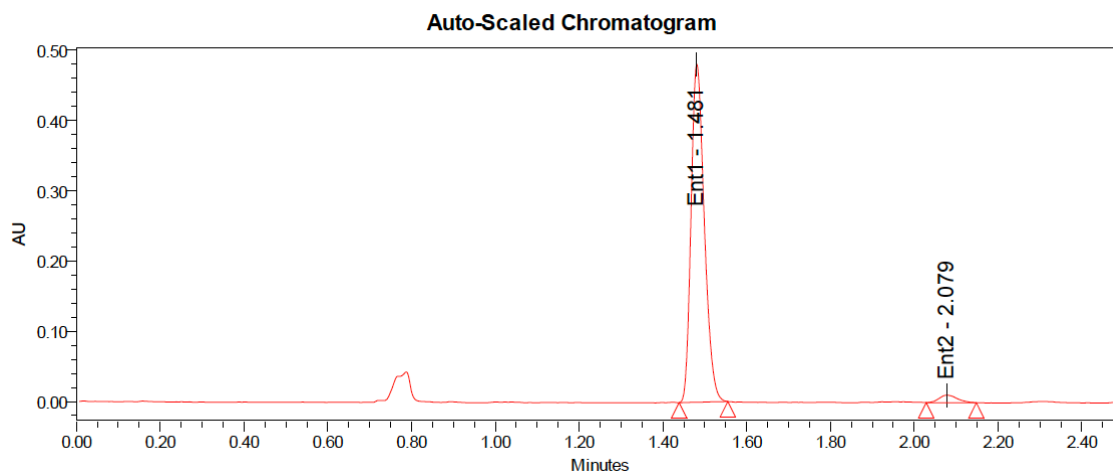
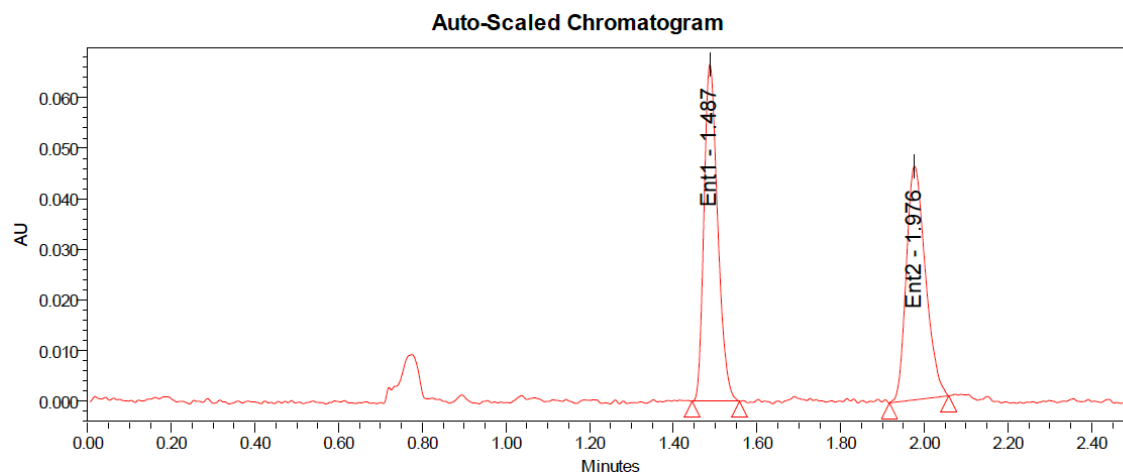
Sample	ent1	ent2	ee	Ent1	Ent2
racemic	50.12	49.88	0.23	1265844	1259910
scalemic	99.18	0.82	98.37	827909	6811

2-((1*R*,2*R*)-2-(Benzofuran-5-yl)-1-fluoropropyl)-4-chlorobenzaldehyde (**4h**).



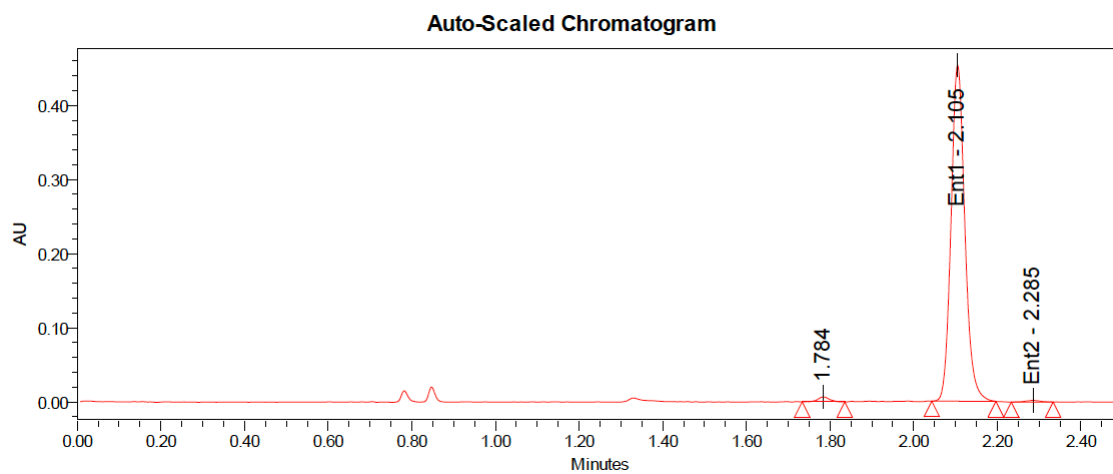
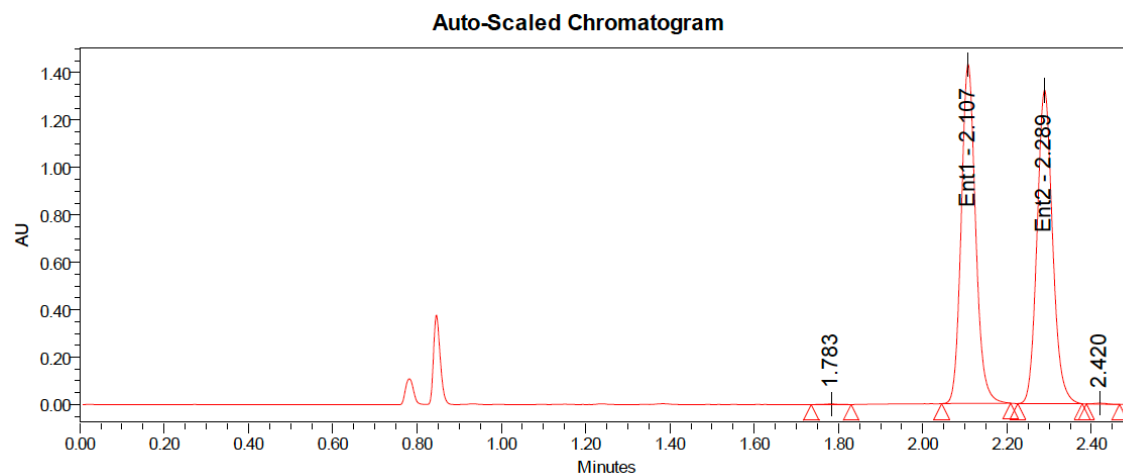
Sample	ent1	ent2	ee	Ent1	Ent2
racemic	50.13	49.87	0.25	938594	933845
scalemic	99.77	0.23	99.55	1649970	3730

2-((1*R*,2*R*)-2-(Benzo[d][1,3]dioxol-5-yl)-1-fluoropropyl)-4-chlorobenzaldehyde (**4i**).



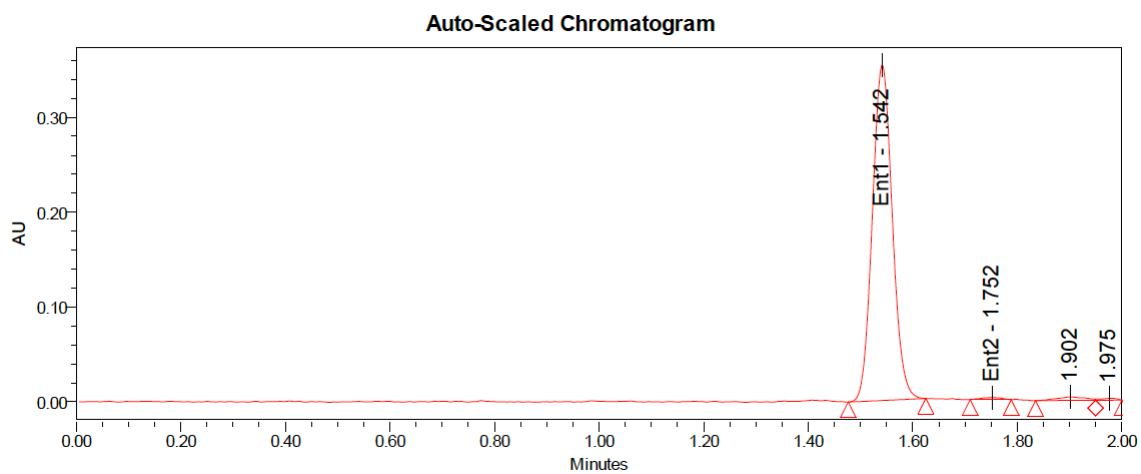
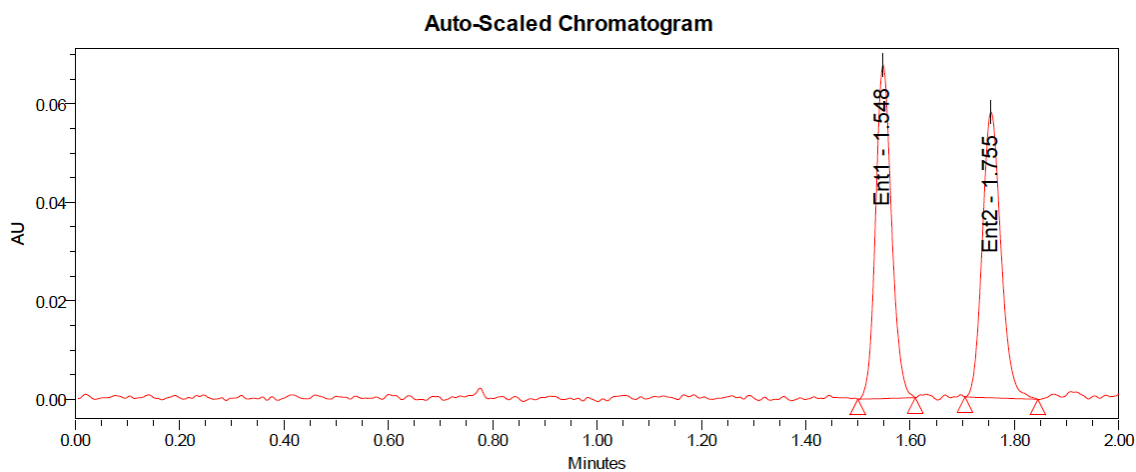
Sample	ent1	ent2	ee	Ent1	Ent2
racemic	50.77	49.23	1.53	151679	147104
scalemic	97.05	2.95	94.09	1056530	32155

4-Chloro-2-((1*R*,2*R*)-1-fluoro-2-(naphthalen-2-yl)propyl)benzaldehyde (**4j**).



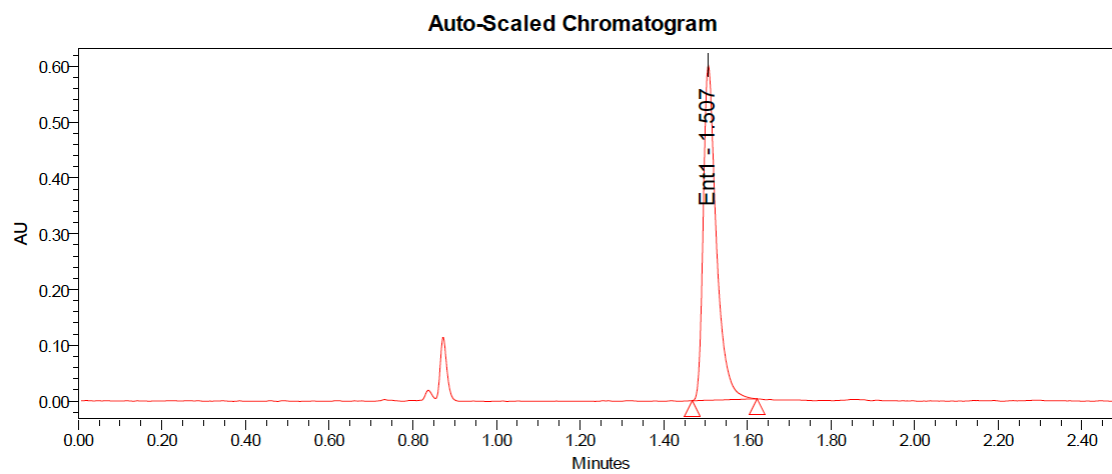
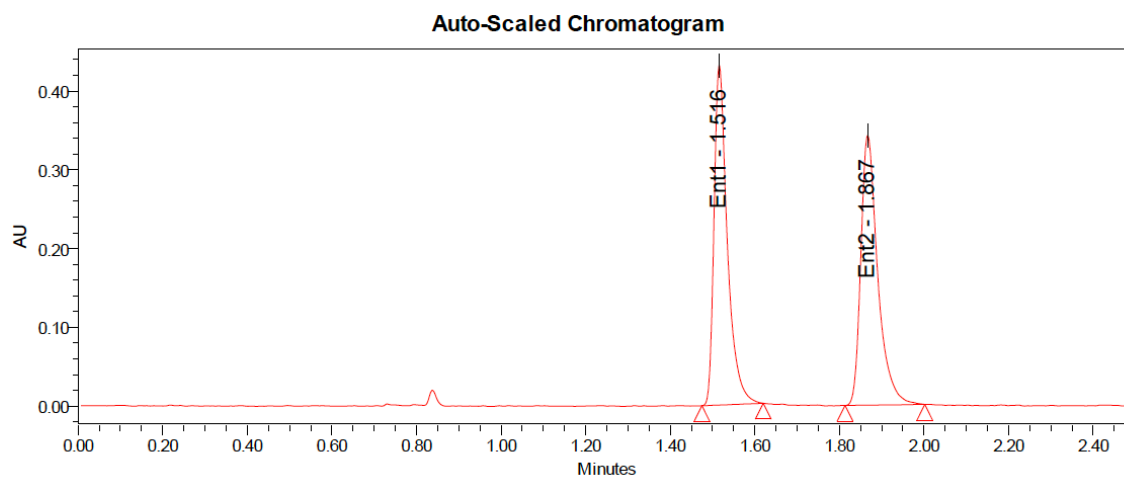
Sample	ent1	ent2	ee	Ent1	Ent2
racemic	50.07	49.93	0.13	3400486	3391573
scalemic	99.46	0.54	98.93	1041822	5616

4-Chloro-2-((1*R*,2*R*)-2-(2,4-dimethylphenyl)-1-fluoropropyl)benzaldehyde (**4k**).



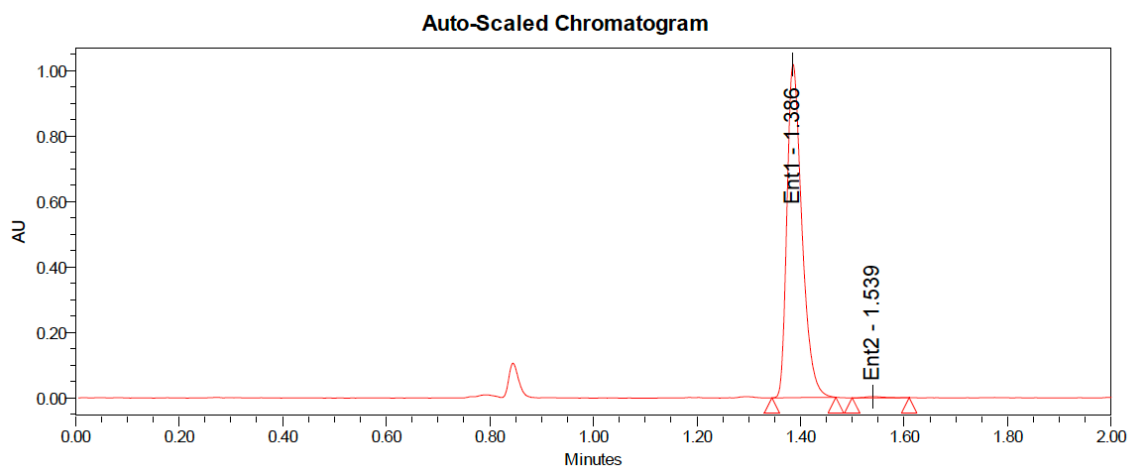
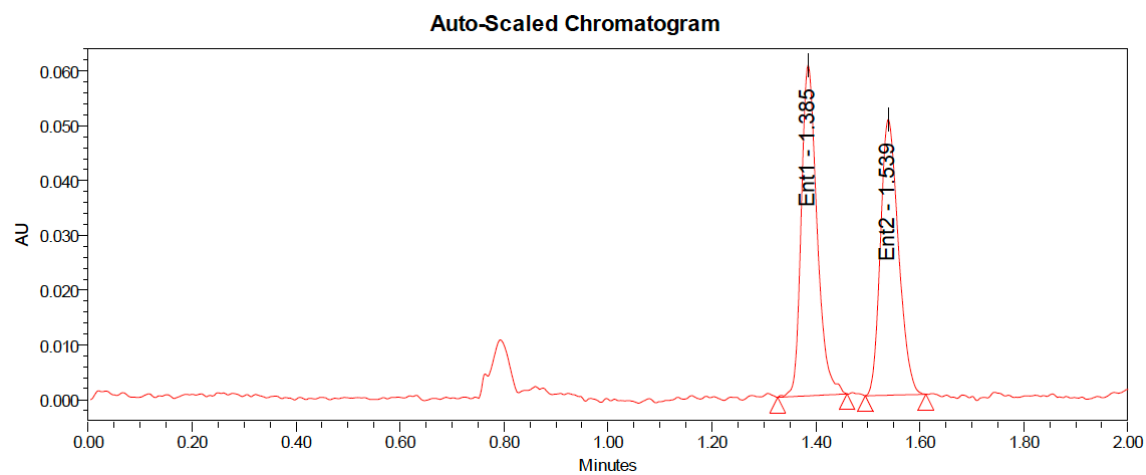
Sample	ent1	ent2	ee	Ent1	Ent2
racemic	50.10	49.90	0.20	144553	143975
scalemic	99.35	0.65	98.71	937768	6095

4-Chloro-2-((1*R*,2*R*)-1-fluoro-2-phenylpropyl)benzoic acid (**5a**).



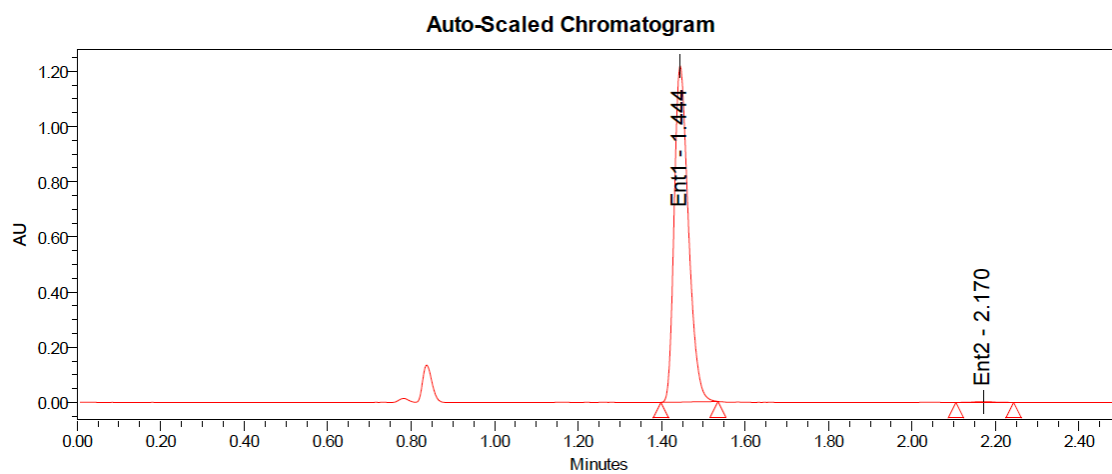
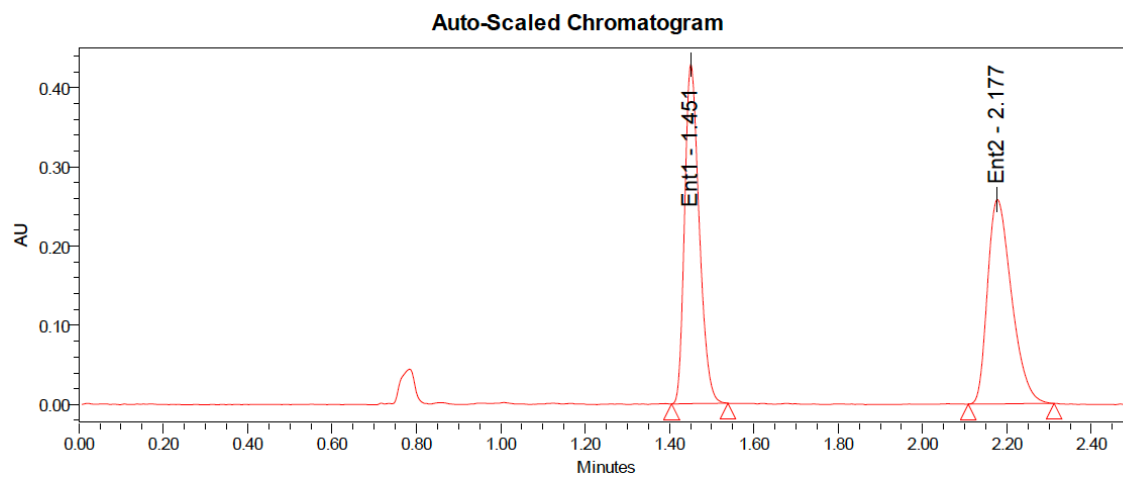
Sample	ent1	ent2	ee	Ent1	Ent2
racemic	49.66	50.34	-0.68	938520	951343
scalemic	100.00	-	100.00	1306245	-

4-chloro-2-((1*R*,2*R*)-1-fluoro-2-phenylpropyl)-1-vinylbenzene (**5b**).



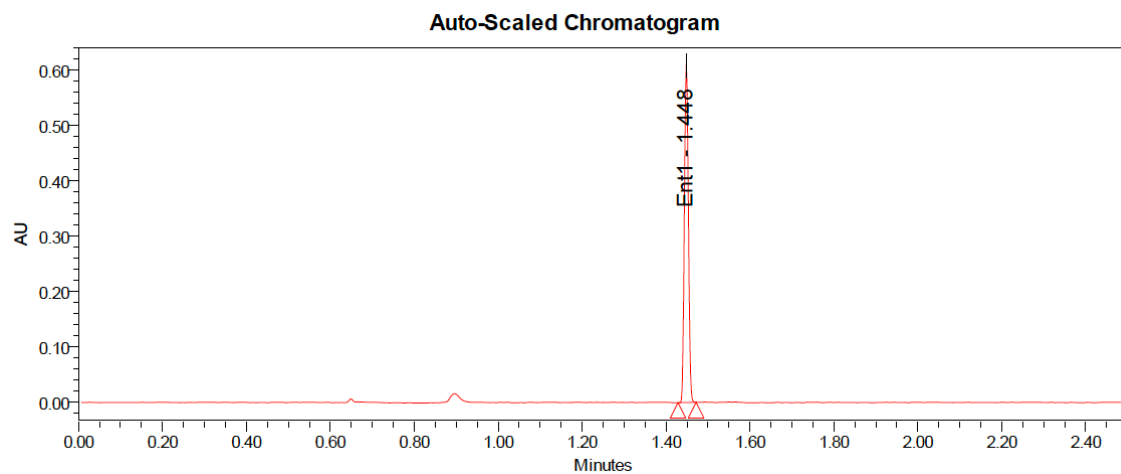
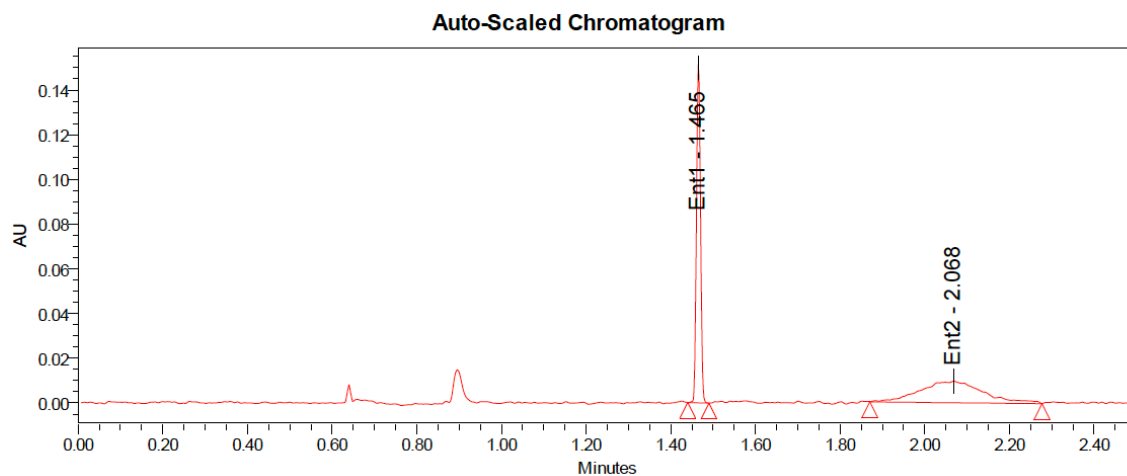
Sample	ent1	ent2	ee	Ent1	Ent2
racemic	51.27	48.73	2.54	127579	121270
scalemic	99.57	0.43	99.14	2044531	8836

(4-Chloro-2-((1*R*,2*R*)-1-fluoro-2-phenylpropyl)phenyl)methanol (**5c**).



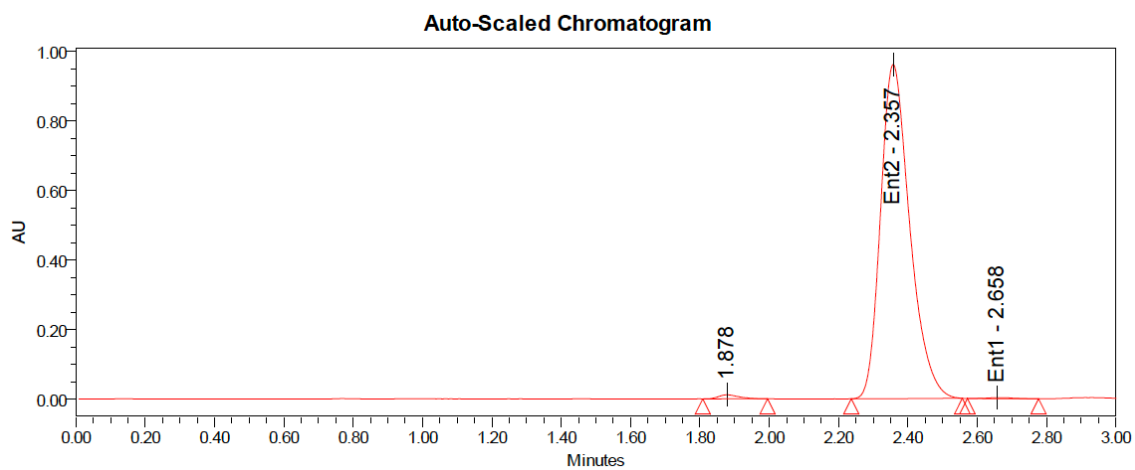
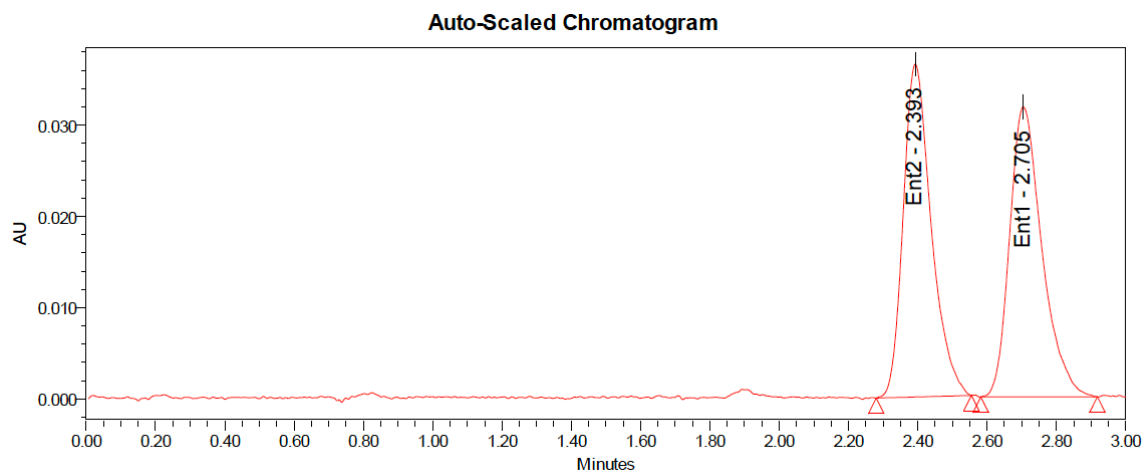
Sample	ent1	ent2	ee	Ent1	Ent2
racemic	50.20	49.80	0.40	1028705	1020586
scalemic	99.57	0.43	99.14	2897273	12564

1-chloro-3-((1*R*,2*R*)-1-fluoro-2-phenylpropyl)benzene (**5d**).



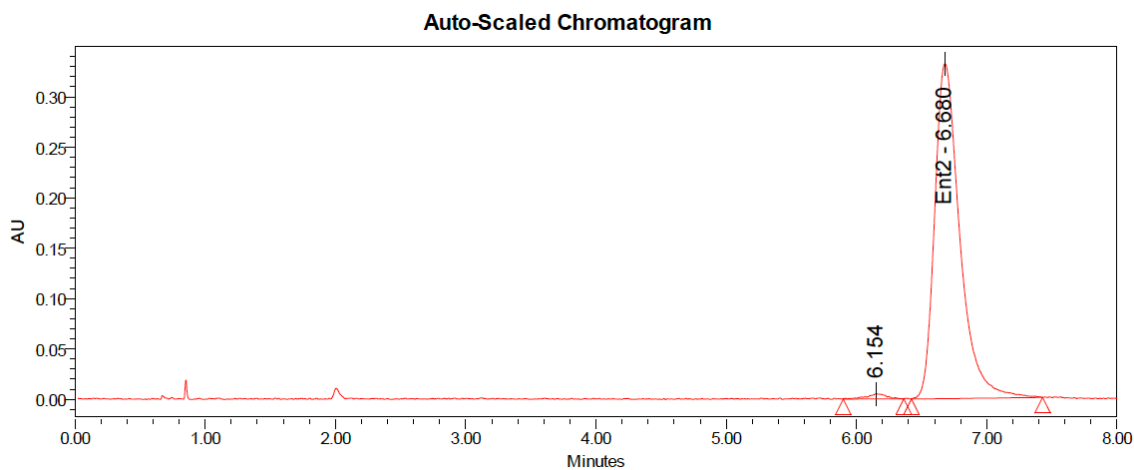
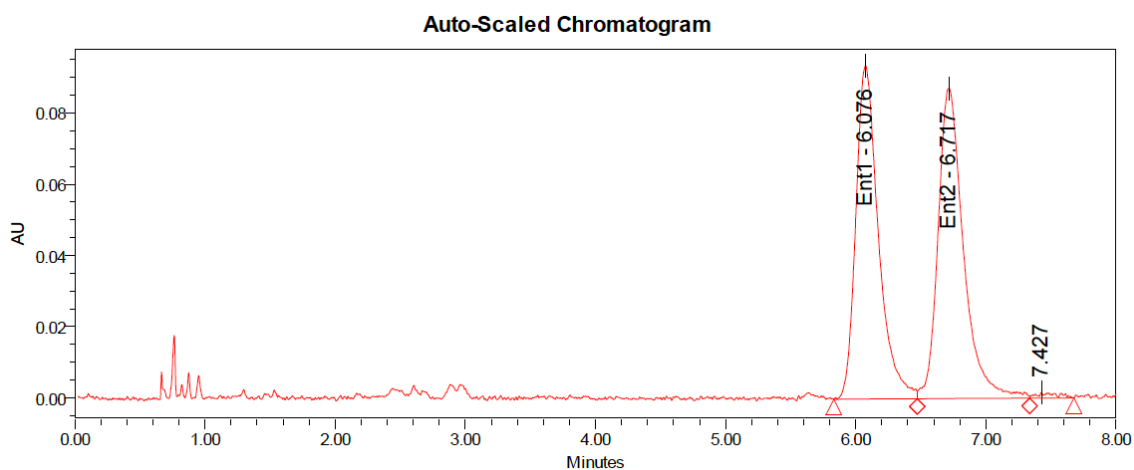
Sample	ent1	ent2	ee	Ent1	Ent2
racemic	50.34	49.66	0.67	101198	99849
scalemic	100.00	-	100.00	410622	-

4-Cyano-*N*-((2*S*,3*R*)-3-fluoro-2-(naphthalen-2-yl)-3-phenylpropyl)-*N*-methylbenzenesulfonamide (**6f**).



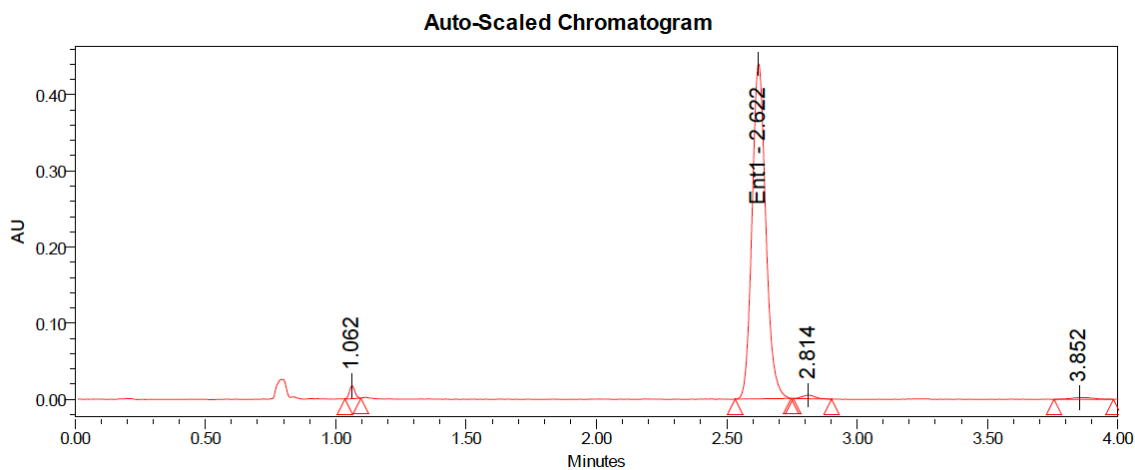
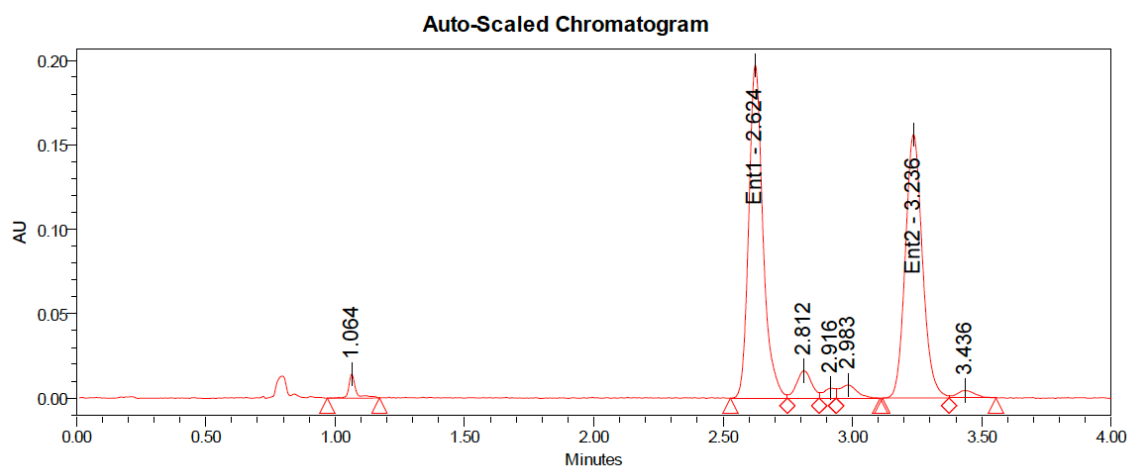
Sample	ent1	ent2	ee	Ent1	Ent2
racemic	50.11	49.89	0.21	205049	205920
scalemic	0.26	99.74	-99.49	5625203	14402

(2*S*,3*R*)-3-fluoro-*N*-methyl-2-(naphthalen-2-yl)-3-phenylpropan-1-amine
(MCJ001F-RS).



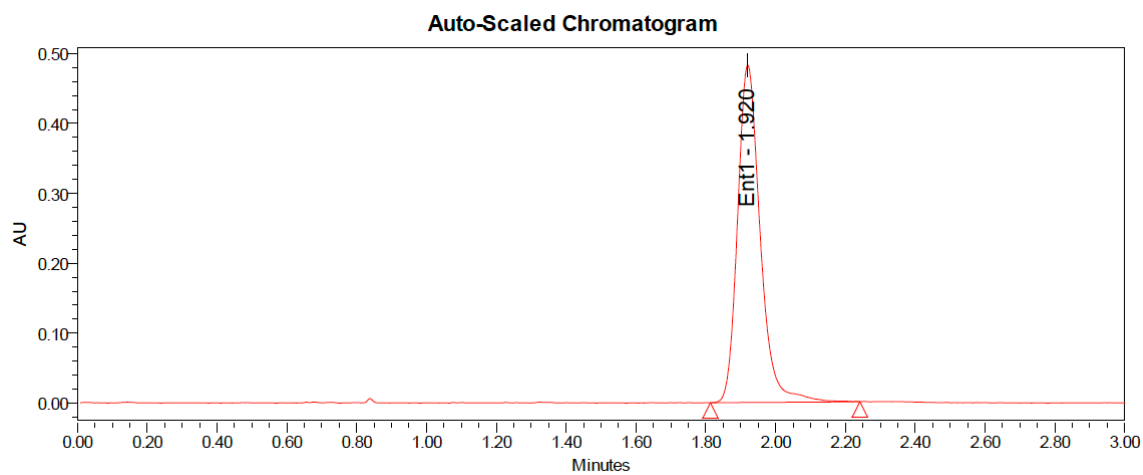
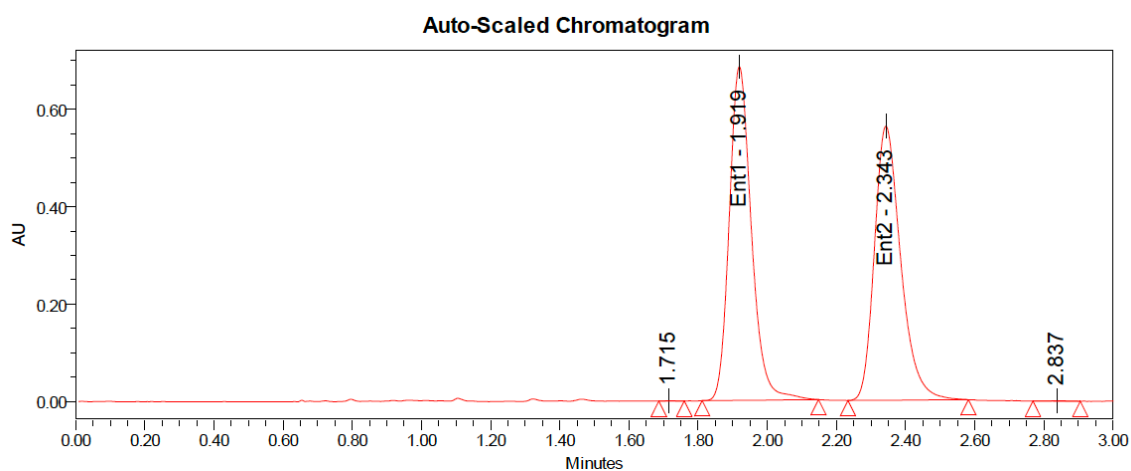
Sample	ent1	ent2	ee	Ent1	Ent2
racemic	48.92	51.08	-2.16	1130071	1180050
scalemic	-	100.00	-100.00	-	4454713

4-cyano-*N*-((2*R*,3*R*)-3-fluoro-2-(naphthalen-2-yl)-3-phenylpropyl)-*N*-methylbenzenesulfonamide (**6c**).



Sample	ent1	ent2	ee	Ent1	Ent2
racemic	51.17	48.83	2.35	753682	719106
scalemic	100.00	-	100.00	1612160	-

(2*R*,3*R*)-3-fluoro-*N*-methyl-2-(naphthalen-2-yl)-3-phenylpropan-1-amine
(MCJ001F-RR).



Sample	ent1	ent2	ee	Ent1	Ent2
racemic	50.62	49.38	1.23	3041238	2967238
scalemic	100.00	-	100.00	2176018	-

X-Ray Crystallography Data

Procedure for Crystal Preparation

A sample of **3u** (20 mg) was dissolved in a minimal volume of boiling hexane to afford a saturated solution in a 1-dram vial. The organic solvent was then allowed to slowly evaporate until crystals precipitated.

Experimental Summary

The single crystal X-ray diffraction studies were carried out on a Bruker SMART APEX II CCD diffractometer equipped with Cu K α radiation (λ = 1.54178). Crystals of the subject compound were used as received. A 0.27 x 0.25 x 0.23 mm colorless block crystal was mounted on a Cryoloop with Paratone oil.

Data were collected in a nitrogen gas stream at 100(2)K. Crystal-to-detector distance was 40 mm using variable exposure times (depending on the 2θ position) with a scan width of 1.00°. Data collection was 99.9% complete to 68.522° in θ . A total of 5278 reflections were collected. 2493 reflections were found to be symmetry independent, with a R_{int} of 0.0257. Indexing and unit cell refinement indicated a Primitive Orthorhombic lattice. The space group was found to be $P2_12_12_1$. The data were integrated using the Bruker SAINT Software program and scaled using the SADABS software program. Solution by direct methods (SHELXT) produced a complete phasing model consistent with the proposed structure.

All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All carbon bonded hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014.

Notes: Excellent data and refinement (CCDC 2048393)

Absolute stereochemistry conclusive: Absolute structure parameter -0.05(6).

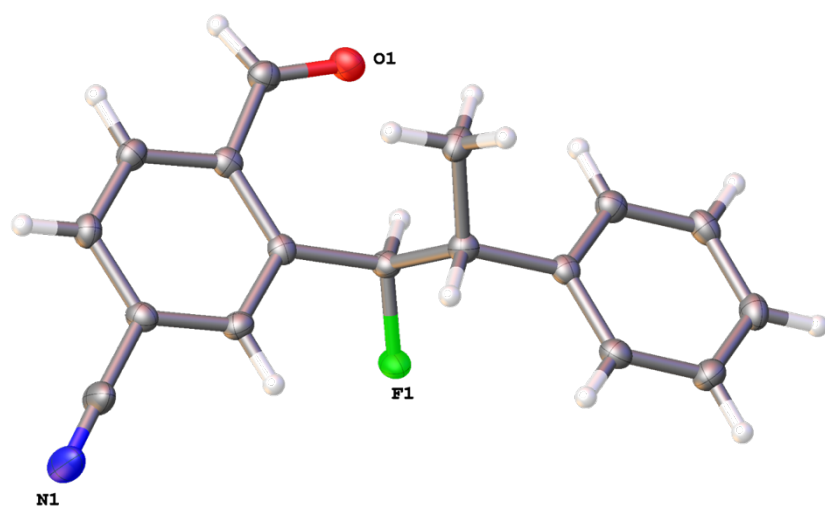


Figure S14. X-ray crystal structure of **3u**.

Table S7. Crystal data and structure refinement for **3u**.

Identification code	B-071-38	
Empirical formula	C ₁₇ H ₁₄ F N O	
Formula weight	267.29	
Temperature	100.15 K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P2 ₁ 2 ₁ 2 ₁	
Unit cell dimensions	a = 7.8323(4) Å	$\alpha = 90^\circ$.
	b = 11.5783(5) Å	$\beta = 90^\circ$.
	c = 15.0718(6) Å	$\gamma = 90^\circ$.
Volume	1366.78(11) Å ³	
Z	4	
Density (calculated)	1.299 Mg/m ³	
Absorption coefficient	0.735 mm ⁻¹	
F(000)	560	
Crystal size	0.27 x 0.25 x 0.23 mm ³	
Theta range for data collection	4.816 to 68.522°.	
Index ranges	-8 ≤ h ≤ 9, -13 ≤ k ≤ 13, -15 ≤ l ≤ 18	
Reflections collected	5278	
Independent reflections	2493 [R(int) = 0.0257]	
Completeness to theta = 67.679°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7530 and 0.6585	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	2493 / 0 / 182	
Goodness-of-fit on F ²	1.056	
Final R indices [I > 2σ(I)]	R1 = 0.0316, wR2 = 0.0808	
R indices (all data)	R1 = 0.0319, wR2 = 0.0812	
Absolute structure parameter	-0.05(6)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.252 and -0.158 e.Å ⁻³	

Table S8. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **3u**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
F(1)	5997(1)	2431(1)	2017(1)	22(1)
O(1)	3807(2)	5515(1)	1192(1)	24(1)
N(1)	3544(3)	2214(2)	5609(1)	42(1)
C(1)	2863(2)	5467(2)	1829(1)	21(1)
C(2)	3123(2)	4748(2)	2633(1)	18(1)
C(3)	1972(2)	4936(2)	3326(1)	20(1)
C(4)	2039(2)	4302(2)	4104(1)	20(1)
C(5)	3310(2)	3461(2)	4186(1)	20(1)
C(6)	3431(3)	2775(2)	4983(1)	28(1)
C(7)	4483(2)	3267(2)	3504(1)	19(1)
C(8)	4405(2)	3900(1)	2719(1)	17(1)
C(9)	5716(2)	3638(1)	2009(1)	18(1)
C(10)	7459(2)	4208(2)	2184(1)	18(1)
C(11)	7317(2)	5526(2)	2256(1)	23(1)
C(12)	8730(2)	3854(1)	1472(1)	17(1)
C(13)	8608(2)	4277(2)	603(1)	21(1)
C(14)	9776(2)	3943(2)	-39(1)	22(1)
C(15)	11090(3)	3184(2)	166(1)	24(1)
C(16)	11226(3)	2759(2)	1027(1)	24(1)
C(17)	10052(2)	3095(2)	1672(1)	21(1)

Table S9. Bond lengths [Å] and angles [°] for **3u**.

F(1)-C(9)	1.4146(19)
O(1)-C(1)	1.213(2)
N(1)-C(6)	1.149(3)
C(1)-H(1)	0.9500
C(1)-C(2)	1.484(2)
C(2)-C(3)	1.398(2)
C(2)-C(8)	1.411(3)
C(3)-H(3)	0.9500
C(3)-C(4)	1.383(2)
C(4)-H(4)	0.9500
C(4)-C(5)	1.398(3)
C(5)-C(6)	1.443(3)
C(5)-C(7)	1.397(2)
C(7)-H(7)	0.9500
C(7)-C(8)	1.392(2)
C(8)-C(9)	1.514(2)
C(9)-H(9)	1.0000
C(9)-C(10)	1.539(2)
C(10)-H(10)	1.0000
C(10)-C(11)	1.534(2)
C(10)-C(12)	1.520(2)
C(11)-H(11A)	0.9800
C(11)-H(11B)	0.9800
C(11)-H(11C)	0.9800
C(12)-C(13)	1.403(2)
C(12)-C(17)	1.392(3)
C(13)-H(13)	0.9500
C(13)-C(14)	1.387(3)
C(14)-H(14)	0.9500
C(14)-C(15)	1.388(3)
C(15)-H(15)	0.9500
C(15)-C(16)	1.391(3)
C(16)-H(16)	0.9500
C(16)-C(17)	1.393(3)
C(17)-H(17)	0.9500
O(1)-C(1)-H(1)	117.0
O(1)-C(1)-C(2)	126.07(17)
C(2)-C(1)-H(1)	117.0
C(3)-C(2)-C(1)	115.78(15)
C(3)-C(2)-C(8)	119.93(15)
C(8)-C(2)-C(1)	124.27(15)
C(2)-C(3)-H(3)	119.1
C(4)-C(3)-C(2)	121.74(16)
C(4)-C(3)-H(3)	119.1
C(3)-C(4)-H(4)	120.9
C(3)-C(4)-C(5)	118.15(16)
C(5)-C(4)-H(4)	120.9
C(4)-C(5)-C(6)	120.24(16)
C(7)-C(5)-C(4)	121.00(16)
C(7)-C(5)-C(6)	118.76(17)
N(1)-C(6)-C(5)	178.7(2)
C(5)-C(7)-H(7)	119.6
C(8)-C(7)-C(5)	120.78(16)
C(8)-C(7)-H(7)	119.6

C(2)-C(8)-C(9)	123.85(15)
C(7)-C(8)-C(2)	118.40(15)
C(7)-C(8)-C(9)	117.75(15)
F(1)-C(9)-C(8)	107.28(13)
F(1)-C(9)-H(9)	109.9
F(1)-C(9)-C(10)	106.48(14)
C(8)-C(9)-H(9)	109.9
C(8)-C(9)-C(10)	113.22(13)
C(10)-C(9)-H(9)	109.9
C(9)-C(10)-H(10)	107.7
C(11)-C(10)-C(9)	111.96(14)
C(11)-C(10)-H(10)	107.7
C(12)-C(10)-C(9)	110.14(14)
C(12)-C(10)-H(10)	107.7
C(12)-C(10)-C(11)	111.44(15)
C(10)-C(11)-H(11A)	109.5
C(10)-C(11)-H(11B)	109.5
C(10)-C(11)-H(11C)	109.5
H(11A)-C(11)-H(11B)	109.5
H(11A)-C(11)-H(11C)	109.5
H(11B)-C(11)-H(11C)	109.5
C(13)-C(12)-C(10)	121.41(16)
C(17)-C(12)-C(10)	120.36(15)
C(17)-C(12)-C(13)	118.22(16)
C(12)-C(13)-H(13)	119.7
C(14)-C(13)-C(12)	120.65(17)
C(14)-C(13)-H(13)	119.7
C(13)-C(14)-H(14)	119.7
C(13)-C(14)-C(15)	120.67(17)
C(15)-C(14)-H(14)	119.7
C(14)-C(15)-H(15)	120.4
C(14)-C(15)-C(16)	119.25(18)
C(16)-C(15)-H(15)	120.4
C(15)-C(16)-H(16)	120.0
C(15)-C(16)-C(17)	120.09(18)
C(17)-C(16)-H(16)	120.0
C(12)-C(17)-C(16)	121.12(16)
C(12)-C(17)-H(17)	119.4
C(16)-C(17)-H(17)	119.4

Symmetry transformations used to generate equivalent atoms:

Table S10. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **3u**. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
F(1)	28(1)	15(1)	22(1)	-2(1)	6(1)	0(1)
O(1)	29(1)	26(1)	18(1)	4(1)	0(1)	1(1)
N(1)	50(1)	45(1)	30(1)	17(1)	19(1)	24(1)
C(1)	20(1)	21(1)	21(1)	1(1)	-2(1)	0(1)
C(2)	17(1)	18(1)	18(1)	-1(1)	-3(1)	-3(1)
C(3)	17(1)	21(1)	22(1)	-2(1)	-2(1)	1(1)
C(4)	19(1)	22(1)	18(1)	-3(1)	2(1)	-1(1)
C(5)	24(1)	18(1)	17(1)	0(1)	1(1)	-1(1)
C(6)	33(1)	28(1)	23(1)	3(1)	10(1)	9(1)
C(7)	21(1)	16(1)	20(1)	-2(1)	0(1)	2(1)
C(8)	18(1)	17(1)	16(1)	-2(1)	0(1)	-3(1)
C(9)	22(1)	14(1)	16(1)	-1(1)	2(1)	1(1)
C(10)	20(1)	19(1)	16(1)	-1(1)	-1(1)	0(1)
C(11)	19(1)	20(1)	29(1)	-6(1)	2(1)	-2(1)
C(12)	19(1)	16(1)	17(1)	-2(1)	0(1)	-3(1)
C(13)	20(1)	21(1)	22(1)	1(1)	-1(1)	-2(1)
C(14)	26(1)	24(1)	16(1)	1(1)	1(1)	-7(1)
C(15)	25(1)	23(1)	22(1)	-4(1)	7(1)	-3(1)
C(16)	24(1)	20(1)	27(1)	-1(1)	3(1)	3(1)
C(17)	24(1)	18(1)	20(1)	1(1)	1(1)	-2(1)

Table S11. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **3u**.

	x	y	z	U(eq)
H(1)	1865	5932	1812	25
H(3)	1120	5514	3263	24
H(4)	1244	4434	4569	24
H(7)	5345	2697	3576	23
H(9)	5273	3882	1415	21
H(10)	7892	3911	2765	22
H(11A)	8438	5851	2402	34
H(11B)	6500	5725	2724	34
H(11C)	6923	5842	1689	34
H(13)	7716	4797	452	25
H(14)	9677	4237	-626	26
H(15)	11887	2957	-276	28
H(16)	12121	2240	1175	28
H(17)	10157	2800	2257	25

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