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The enantioselective hydrocyanation of olefins represents a conceptually straightforward approach to prepare enantiomerically enriched nitriles. These, in turn, comprise or are intermediates in the synthesis of many pharmaceuticals and their synthetic derivatives. Herein, we report a cyanide-free dual Pd/CuH-catalyzed protocol for the asymmetric Markovnikov hydrocyanation of vinyl arenes and the anti-Markovnikov hydrocyanation of terminal olefins in which oxazoles function as nitrile equivalents. After an initial hydroarylation process, the oxazole substructure was deconstructed using a [4+2]/retro-[4+2] sequence to afford the enantioenriched nitrile product under mild reaction conditions.

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Enantioselective Olefin Hydrocyanation Without Cyanide

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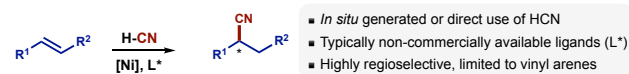
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ABSTRACT: The enantioselective hydrocyanation of olefins represents a conceptually straightforward approach to prepare enantiomerically enriched nitriles. These, in turn, comprise or are intermediates in the synthesis of many pharmaceuticals and their synthetic derivatives. Herein, we report a cyanide-free dual Pd/CuH-catalyzed protocol for the asymmetric Markovnikov hydrocyanation of vinyl arenes and the anti-Markovnikov hydrocyanation of terminal olefins in which oxazoles function as nitrile equivalents. After an initial hydroarylation process, the oxazole substructure was deconstructed using a [4+2]/retro-[4+2] sequence to afford the enantioenriched nitrile product under mild reaction conditions.

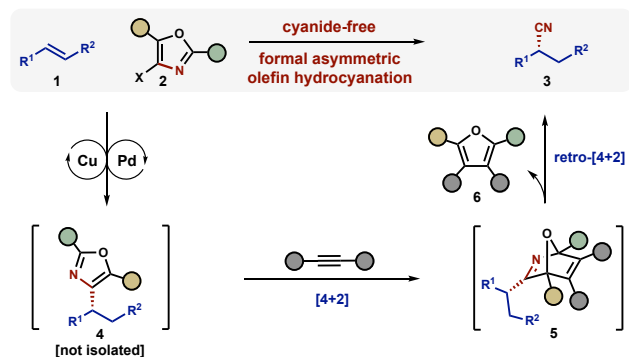
Nitriles are a ubiquitous class of compounds present in many pharmaceuticals,¹ secondary metabolites,² and polymers.³ Owing to their unique chemical reactivity, nitriles often serve as precursors to numerous additional important functional groups in organic synthesis, including *N*-heterocycles, carbonyl compounds, and amines.⁴ Although nitriles can be accessed by many methods, the conversion of olefins to alkyl nitriles via transition metal-catalyzed olefin hydrocyanation represents one of the most conceptually straightforward processes. While hydrocyanation of feedstock olefins is conducted on a million-metric ton scale annually to produce nitrile precursors to polymers,³ these protocols employ hydrogen cyanide and form almost exclusively achiral products. Despite the numerous improvements in the racemic hydrocyanation of olefin feedstocks⁵ and fine chemicals,⁶ the reaction conditions and substrates employed in the analogous asymmetric variant of this transformation have advanced minimally since the seminal work by Jackson^{7a} and RajanBabu.^{7b–7d,7g}

Asymmetric olefin hydrocyanation is typically achieved through the formal addition of hydrogen cyanide, either generated *in situ* or employed directly in gaseous form, across an olefin facilitated by a chiral phosphine-ligated metal catalyst (Scheme 1A).^{7–8} Aside from the potential safety concerns of working with hydrogen cyanide,⁹ many of these asymmetric methods are limited to vinyl arenes and employ non-commercially available ligands.^{7,10–11} Alternative methods to access enantioenriched nitriles, including C–H cyanation,¹² α -arylation of prefunctionalized nitriles¹³ and enantioselective protonation of silyl ketene imines,¹⁴ have also been developed employing various precursors.¹⁵

A. Prototypical Asymmetric Olefin Hydrocyanation



B. This Approach



C. Proposed Dual Catalytic Cycle

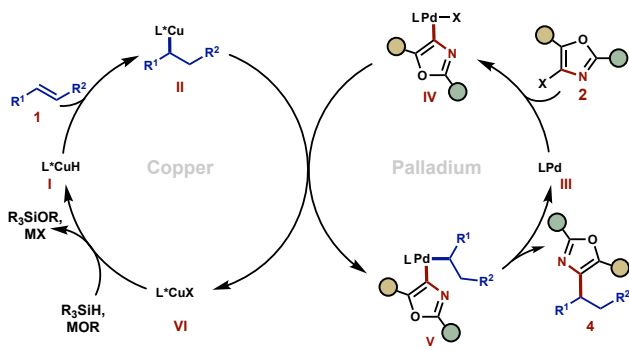


Figure 1. A. Traditional approaches to asymmetric olefin hydrocyanation. B. Our dual Pd/CuH-catalyzed asymmetric olefin hydrocyanation using oxazoles as masked nitriles, followed by a thermal deconstruction of **4** to the enantioenriched nitrile. C. Proposed dual Pd/CuH catalytic cycles for the hydrofunctionalization process involving a 2-halo-oxazole (**2**).

Our continued interest in enantioselective alkene hydrofunctionalization reactions led us to envision the development of a catalytic protocol to access enantioenriched α -alkyl- α -arylnitriles, represented by **3** (Figure 1B).^{16–18} We proposed that the critical C–CN bond of the nitrile could be forged through an initial dual Pd/CuH-catalyzed asymmetric olefin hydroarylation¹⁷ reaction using a *N*-heterocyclic compound as a nitrile surrogate, thus obviating the

need to employ cyanide either directly or transiently formed. A subsequent thermal-[4+2]/retro-[4+2] sequence with the appropriate dienophile could furnish the enantioenriched nitrile. However, at the outset, it was unclear to us which *N*-heterocycle would best serve as a masked nitrile, since pyrimidines, pyrazines, oxazoles and several other heterocycles have all been shown to expel nitriles as byproducts in cycloaddition reactions with alkynes.^{19–21} We reasoned that an oxazole, despite its limited precedent in forming nitriles,¹⁹ would be an ideal nitrile precursor for this transformation as it does not introduce any regiochemical complications and is an electron-rich aza-diene.²¹

Figure 1C details our proposed dual Pd/CuH catalytic cycle for the aforementioned approach. Enantioselective hydrocupration of an olefinic substrate (**1**) by a CuH catalyst (**I**), generated *in situ* through the use of a Cu(I) salt, chiral phosphine ligand, and silane, would form an enantioenriched Cu(I) alkyl intermediate (**II**). Meanwhile, the Pd catalytic cycle would begin with oxidative addition of a ligated Pd(0) species (**III**) into a 2-halo-oxazole (**2**) forming complex **IV**. Stereospecific transmetalation of **II** with Pd species **IV** would result in an alkyl Pd(II) complex (**V**), which following reductive elimination furnishes an intermediate enantioenriched oxazole (**4**). The formed copper(I) halide (**VI**) could regenerate the active CuH catalyst after a σ -bond metathesis reaction in the presence of an appropriate base and silane.^{17–18} For this approach to be successful, the rates of both catalytic cycles would need to be well aligned to prevent any deleterious side pathways or the racemization of the alkyl copper species **II**.¹⁷ After this hydroarylation process, as depicted in Figure 1B, a subsequent thermal [4+2] cycloaddition between oxazole **4** and an alkyne would form a highly strained 7-oxa-2-azabicyclo[2.2.1]heptadiene derivative (**5**), and upon a retro-[4+2] cycloaddition the nitrile product is liberated along with an electron deficient furan (**6**). Thus, we reasoned that the judicious choice of a 2,5-disubstituted-4-halo-oxazole (**2**) coupling partner would be paramount to achieving both a highly enantioselective hydroarylation step and an efficient [4+2]/retro-[4+2] sequence.

Accordingly, we focused on finding a suitable halo-oxazole coupling partner (**2**) and a set of experimental reaction conditions for the asymmetric olefin hydrocyanation using styrene (**1a**) as a model substrate (Table 1). Our investigation of the optimal reaction conditions identified oxazole **2a** as an excellent nitrile surrogate and the commercially available alkyne **7a** as a suitable dienophile. When **2a** and **7a** were utilized in conjunction with [Pd(cinnamyl)Cl]₂, BrettPhos (**L3**), **P1**, NaOTMS, and Me₂(Ph)SiH, the desired nitrile **3a** was formed in high yield and enantioselectivity (entry 1, 96% ¹H NMR yield and 97:3 er), without isolation of the alkyl oxazole intermediate (**4**). Evaluation of a series of Cu salts and chiral biphosphines (entries 1–5) led us to discover the air-stable Cu(I) precatalyst **P1**, which enabled the reaction to be set up without the use of an inert-atmosphere glovebox.²² Use of the previously described (*S*)-DTBM-SEGPHOS-ligated CuCl precatalyst **P2**^{18b} formed the desired product in similar yield but with considerably lower enantioselectivity (entry 2). Variation of the biarylphosphine backbone (entries 6–7) or the absence of a Pd-catalyst (entry 8) resulted in diminished yield or no product formation respectively. Examination of an alternative to **2a** as the nitrile surrogate highlighted the crucial role of the oxazole substituents in this transformation. Modification of the substituent at the 5-position from methyl to phenyl (**2b**) delivered nitrile **3a** in considerably lower yield and enantioselectivity, presumably due to the electron-poor nature of the corresponding alkyl oxazole intermediate (entry 9). While our previous reports on enantioselective olefin hydroarylation^{18b} suggested that a 2-chloro-*N*-heterocycle was more efficient in the hydrofunctionalization reaction than the corresponding heteroaryl bromide, use of **2c** in the current process resulted in minimal olefin hydrocyanation (entry 10). A variety of acetylene diester derivatives, such as the di-*n*-octyl substituted ester (**7b**),

Table 1. Optimization of the enantioselective hydrocyanation of styrene (**1a**).^a

entry	variation from standard conditions	% yield	er
1	none, 2a (X=Br, R=Me)	96%	97:3
2	P2	88%	80:20
3	6.0 mol% CuOAc + 7.0 mol% L1	94%	97:3
4	6.0 mol% Cu(OAc) ₂ + 7.0 mol% L1	82%	72:28
5	6.0 mol% CuOAc + 7.0 mol% L2	81%	99:1
6	XPhos (L4)	61%	87:13
7	<i>t</i> -BuBrettPhos (L5)	14%	nd
8	no Pd and BrettPhos	0%	nd
9	2b (X=Br, R=Ph)	35%	90:10
10	2c (X=Cl, R=Me)	5%	nd

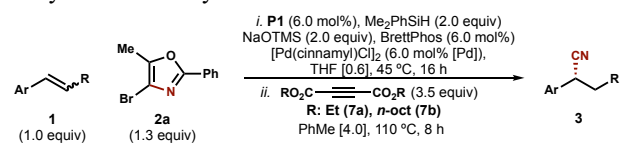
Ar = 3,5-(*t*-Bu)₂-4-MeOC₆H₂ (*S*)-DTBM-SEGPHOS (**L1**)
Ar = 3,5-(*t*-Bu)₂-4-MeOC₆H₂ (*R*)-DTBM-OME-BIPHEP (**L2**)
L3: BrettPhos (R¹: OMe, R²: Cy)
L4: XPhos (R¹: H, R²: Cy)
L5: *t*-BuBrettPhos (R¹: OMe, R²: *t*-Bu)

^aReaction conditions: 0.2 mmol styrene (1.0 equiv), yields were determined by ¹H NMR spectroscopy of the crude reaction mixture, using 1,1,2,2-tetrachloroethane as internal standard. Enantiomeric ratio (er) was determined by chiral SFC. nd: not determined

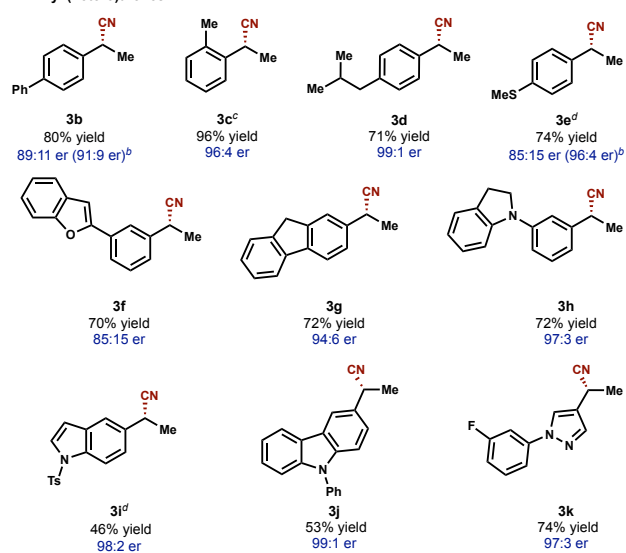
performed well as dienophiles. Notably, the judicious choice of dienophile coupling partner aided in the purification of the nitrile products (see below and the Supporting Information for details).

Having established appropriate reaction conditions for the asymmetric olefin hydrocyanation reaction, we investigated the scope of vinyl arene substrates (Scheme 1). Vinyl arenes bearing a substituent at the *para*-position, such as phenyl (**3b**), isobutyl (**3d**), or thiomethyl (**3e**), were well tolerated under the reaction conditions, resulting in good yields and enantioselectivity of the nitrile product. Facile enantiospecific hydrolysis could convert nitrile **3d** and **3g** to ibuprofen¹⁰ and cicloprofen,¹⁴ respectively, both of which are non-steroidal anti-inflammatory drugs (NSAIDs).²³ A vinyl arene containing *ortho*-substitution was effectively converted to the nitrile (**3c**) in high yield and enantiopurity. Moreover, substrates containing heterocycles, including benzofuran (**3f**), indoline (**3h**), *N*-tosyl-indole (**3i**), carbazole (**3j**), pyrazole (**3k**), morpholine (**3m**), and *N*-Boc-piperazine (**3o**), were smoothly transformed to the nitrile product with excellent selectivity. Additionally, 1,2-disubstituted alkenes (Scheme 1B), a problematic substrate class for complementary Ni-catalyzed asymmetric olefin hydrocyanation methods,^{7h} performed well under our reaction conditions (**3l** and **3m**). However, cyclic olefins were difficult substrates for this transformation. Nitrile **3n** was isolated in moderate yield and enantioselectivity when **1n** was subjected to the standard catalytic system. We hypothesized that this diminished yield may reflect a slower rate of transmetalation between the proposed organometallic species **II** and **IV**, potentially due to a more sterically congested transition state, or a slower rate of hydrocupration of **1n**. To further highlight the applicability of this formal olefin hydrocyanation method to access medicinally relevant molecules, we synthesized an intermediate (**3o**) en route to **8**, a USP28 inhibitor (Scheme 1C). Conversion of **3o** to **8** could be achieved via reduction of the nitrile (**3o**) and acylation of the resulting primary amine.²⁴

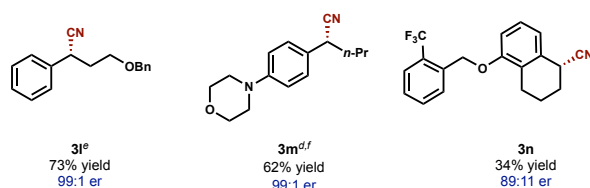
Scheme 1. Substrate scope of the asymmetric Markovnikov hydrocyanation of vinyl arenes.^a



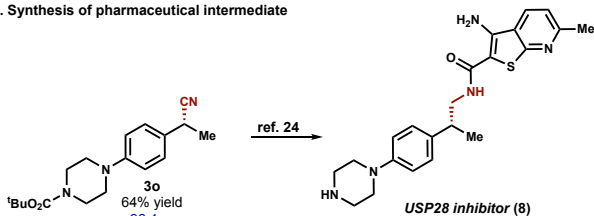
A. Vinyl (hetero)arenes



B. 1,2-disubstituted alkenes



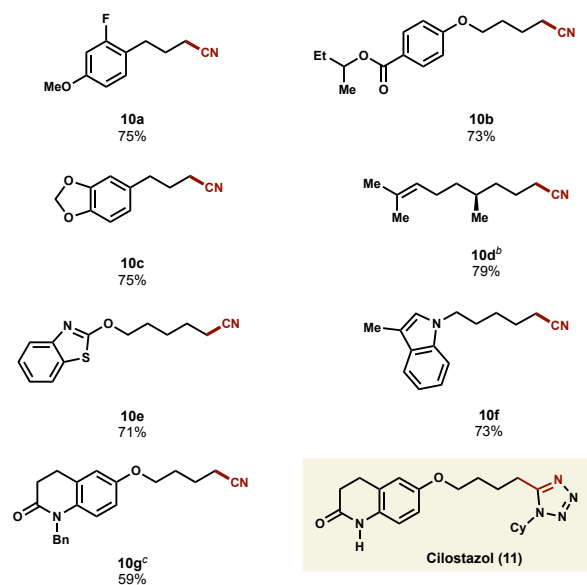
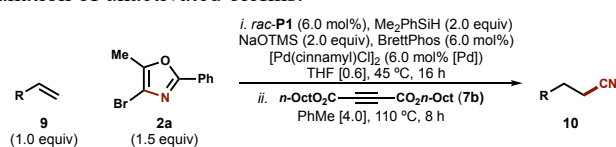
C. Synthesis of pharmaceutical intermediate



^aAll yields represent the average of isolated yields from two runs purified by silica flash chromatography with 0.5 mmol alkene; alkyne (**7b**) was used unless otherwise noted, enantioselectivity determined by chiral SFC or HPLC. ^bAlternative purification was used, see supporting information for details. ^cYield was determined by ¹H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard due to the volatility of the product. ^dAlkyne (**7a**) was used. ^eIntermediate oxazole **4l** was purified, isolated yield reported over two steps. ^f1.5 equiv of **2a** and 24 h at 45 °C

We were interested in extending this chemistry toward the anti-Markovnikov hydrocyanation of unactivated olefins. In line with our previous work,^{18b} we anticipated the anti-Markovnikov hydrocyanation to be more challenging due to the higher hydrocyanation barrier.²⁵ However, we were able to perform the hydrocyanation of terminal olefins without significantly modifying the standard reaction conditions (Scheme 2). Overall, this process tolerates the presence of a variety of important structural elements (**10a–10g**), including an ester (**10b**), dioxolane (**10c**), benzothiazole (**10e**), indole (**10f**) and an amide (**10g**). Furthermore, the corresponding alkyl

Scheme 2. Substrate scope for the anti-Markovnikov hydrocyanation of unactivated olefins.^a

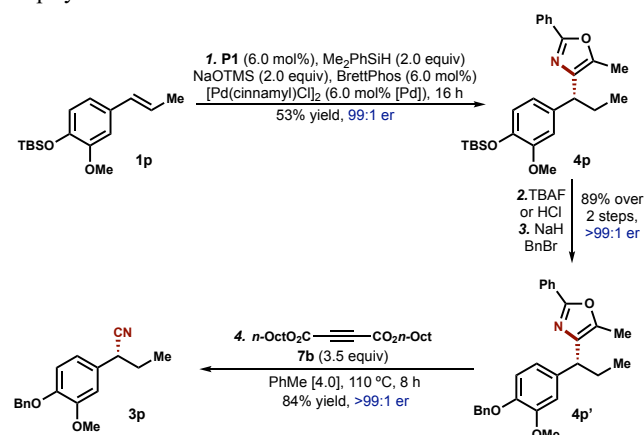


^aAll yields represent the average of isolated yields from two runs purified by silica flash chromatography with 0.5 mmol alkene. ^bYield was determined by ¹H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard ^c4.0 mol% **P1**

nitriles were isolated in high yield and regioselectivity. Hydrocyanation of terminal alkene (**9d**) accentuated the degree of chemoselectivity for this process, which generated **10d** in good yield without any detectable hydrocyanation of the trisubstituted alkene. We further demonstrated the utility of this method by synthesizing the nitrile derivative (**10g**) of the cardiovascular drug Cilostazol (**11**), which could conceivably be converted to **11** following deprotection and tetrazole formation.²⁶ As previously mentioned, reduction of the halo-oxazole (**2**) and the olefinic coupling partner represents potential side reactions for this transformation. Formation of a significant amount of reduced **9g** was observed when the olefin was subjected to the standard reaction conditions. A decrease in the amount of **P1** utilized, from 6.0 to 4.0 mol%, was necessary to improve the efficiency of the dual CuH/Pd catalytic system and deliver amide **10g** as the major product.

Enantioenriched alkyl nitriles (**3**) often undergo epimerization or decomposition under a variety of acidic, basic and oxidative conditions, thus making further manipulation of the resulting nitrile product potentially challenging.^{7f,27} To obviate these degradation pathways, we envisioned that the chiral alkyl oxazole (**4**) may serve as a stable masked nitrile in multistep organic synthesis, which could be revealed at a later stage under neutral reaction conditions (Scheme 3). To illustrate this concept, we employed 1,2-disubstituted olefin **1p** as a simple representative example. An initial asymmetric olefin hydroarylation reaction installed the oxazole substructure (**4p**), which was followed by silyl group removal, either under acid or fluoride-mediated conditions, and basic functionalization of the resulting phenol to yield oxazole **4p'** without any erosion of the enantioselectivity. A subsequent thermal cycloaddition sequence with alkyne **7b** revealed the nitrile (**3p**) with complete enantiospecificity. We believe that this strategy will be further

Scheme 3. Enantioenriched oxazoles as masked nitriles in multi-step synthesis



^aReagents and conditions: (1) Average of isolated yields from two runs on 0.5 mmol scale; (2) TBAF (1.5 equiv), THF [0.45], rt, 1.5 h or aq. 6 M HCl (5.0 equiv), THF [0.5], rt, 16 h; (3) NaH (1.2 equiv), BnBr (1.2 equiv), rt, 18 h, 89% or 81% over two steps, respectively >99:1 er; (4) **7b** (3.5 equiv), PhMe [4.0], 110 °C, 8 h, 84%, >99:1 er

applicable in more sophisticated contexts and numerous reaction manifolds that would otherwise result in decomposition of the nitrile substructure.

In summary, we have developed an asymmetric olefin hydrocyanation sequence that relies on an oxazole as surrogate for a nitrile, thus avoiding the use of any sources of cyanide in the reaction mixture. These reaction conditions developed were broadened to the anti-Markovnikov hydrocyanation of unactivated olefins. We anticipate that this strategy of employing an enantioenriched alkyl oxazole as a masked nitrile in multistep synthesis will find further utility in a variety of scenarios.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures, and characterization data for all new compounds including ¹H- and ¹³C-NMR spectra, SFC and HPLC traces (PDF).

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Notes

The authors declare the following competing financial interest(s): MIT has obtained patents for some of the ligands that are described in this Communication from which S.L.B. and former/current co-workers receive royalty payments.

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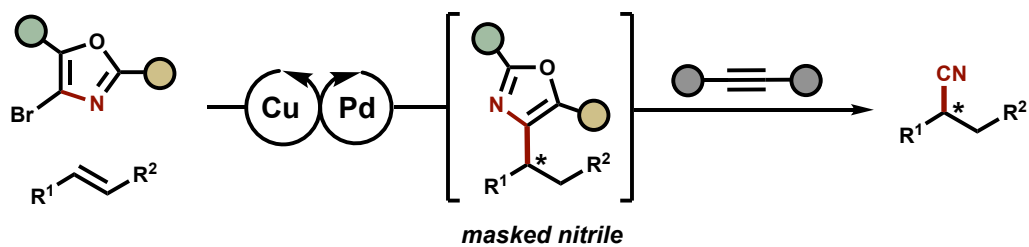
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column chromatography, which could be avoided by altering the method of purification, see supporting information for details.



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Enantioselective Olefin Hydrocyanation Without Cyanide

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1. General Experimental Details

General Experimental Procedures: All reactions were performed in flame-dried or oven-dried glassware fitted with rubber or PTFE/silicone septa under a positive pressure of nitrogen, unless otherwise noted. Standard reactions were performed in glass culture tubes with threaded ends (Fisherbrand, 16 × 125 mm, catalog no. 1495935A; oven-dried at 140 °C) that were sealed with screw-thread caps (Kimble Chase Open Top S/T Closure, catalog no. 73804-15425) fitted with Teflon/SIL septa (Thermo Scientific, catalog no. B7995-15). Air- and moisture-sensitive liquids were transferred via syringe or stainless steel cannula through rubber or PTFE/silicone septa. Solids were added under inert gas counter flow or were dissolved in the appropriate solvent. Reactions carried out at temperatures above room temperature (rt) were conducted in a pre-heated oil bath. All reactions were magnetically stirred and monitored by NMR spectroscopy or analytical thin-layer chromatography (TLC), using glass-backed plates pre-coated with silica gel (250 µm, 60-Å pore size, Extra Hard Layer, *SiliaPlate*) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV), were stained by submersion in iodine dispersed in sand (I₂), an acidic solution of cerium ammonium molybdate (CAM) or in aqueous potassium permanganate solution (KMnO₄) and were developed by heating with a heat gun. Preparative thin-layer chromatography was performed using glass-backed plates pre-coated with silica gel (1000 µm, 60-Å pore size, Extra Hard Layer, *SiliaPlate*) impregnated with a fluorescent indicator (254 nm). Flash column chromatography was performed using SiliCycle SiliaFlash® F60 silica gel (40-63 µm, 230-400 mesh, 60 Å pore diameter) or with the aid of a Biotage Isolera or a Teledyne ISCO CombiFlash Automated Flash Chromatography System using prepacked SNAP silica cartridges (10-100 g).

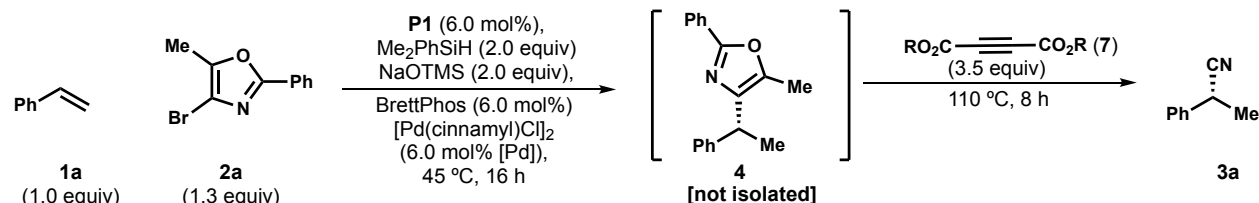
Materials: Unless noted otherwise, all reagents and starting materials were purchased from commercial sources and used as received (Sigma Aldrich, Alfa Aesar, Strem, TCI-America, Combi-Blocks, or Matrix Scientific). CDCl₃ was purchased from Cambridge Isotope Laboratories. Tetrahydrofuran (THF), diethyl ether (Et₂O), toluene (PhMe) and dichloromethane (CH₂Cl₂) were obtained from J.T. Baker in CYCLE-TAINER® delivery kegs and purified by successive filtrations through packed columns of neutral alumina and CuO under Ar pressure. Solvents for extraction, crystallization and flash column chromatography were purchased in A.C.S. reagent grade from Sigma Aldrich, with the exception of hexane, which was purchased in HPLC grade. The yields refer to chromatographically and spectroscopically (¹H and ¹³C NMR) pure material.

Instrumentation: NMR spectra were measured on Bruker Avance III HD 400, 500, or 600 MHz, spectrometer. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to the residual proton in the NMR solvent (CDCl₃: δ 7.26,). All ¹³C spectra recorded are proton-decoupled. The carbon chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to the carbon resonance of the NMR solvent (CDCl₃: δ 77.16). ¹H NMR spectroscopic data are reported as follows: Chemical shift in ppm (multiplicity, coupling constants *J* (Hz), integration intensity, assigned proton). The multiplicities are abbreviated with s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), hept (heptet) m (multiplet), a (apparent). ¹³C NMR spectroscopic data are reported as follows: Chemical shift in ppm (multiplicity, coupling constants *J* (Hz), assigned carbon). All ¹⁹F and ³¹P chemical shifts are expressed in parts per million (ppm, δ scale. All raw fid files were processed and the spectra analyzed using the program *MestReNOVA 10.0* from *Mestrelab Research S. L.* High-resolution

Supporting Information

mass spectra were recorded on a JEOL AccuTOF LC-Plus 46 DART system and on an *Agilent Technologies* 6545 Q-TOF LC/MS system or JEOL AccuTOF 4G with an ionSense DART. IR spectra were recorded on a Nicolet iS5 spectrometer equipped with an iD5 diamond laminate ATR accessory from *Thermo Scientific*. IR spectra were acquired from neat samples. If required, substances were dissolved in CH₂Cl₂ prior to direct application on the ATR unit. Data are reported as follows: frequency of absorption (cm⁻¹). Melting points were determined on an EZ-Melt capillary melting point apparatus from *SRS Stanford Research System*. The values are uncorrected. Elemental analyses were performed by *Atlantic Microlabs Inc.*, Norcross, GA, USA. Specific optical rotations were recorded for chloroform solutions at a standard concentration of 10 mg/mL using a Jasco 1010 polarimeter operating at 589 nm and 23 °C. Enantiomeric ratio (er) was determined either by chiral HPLC analysis using Agilent 1200 Series chromatographs or by Chiral SFC using a Waters Acquity UPC2 instrument; specific columns and analytic methods are provided in the experimental details for individual compounds; the wavelengths of light used for chiral analyses are provided with the associated chromatograms

2. Reaction Optimization



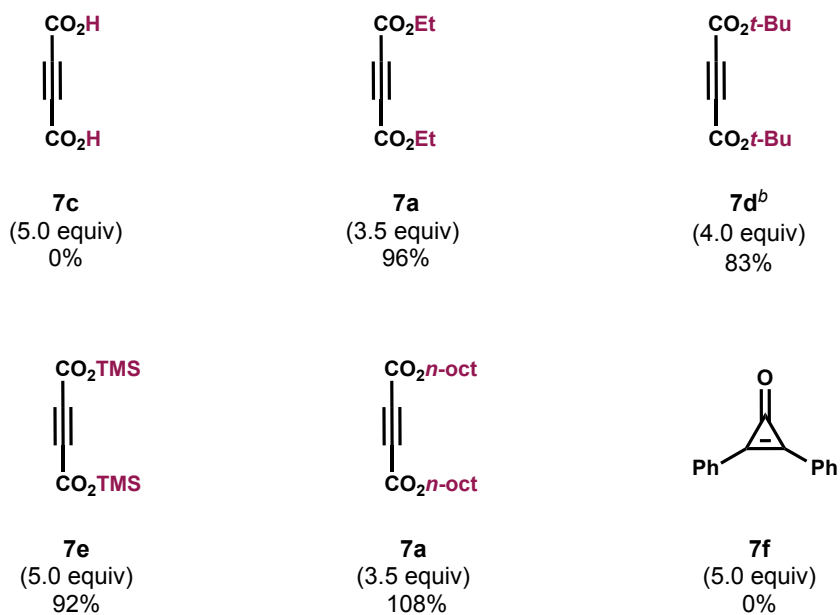
Inside a nitrogen-filled glovebox, an oven-dried reaction tube, labelled as “**A**”, (Fisherbrand, 13x100 mm, 1495935C) equipped with a magnetic stir bar was charged with the corresponding Cu salt (0.012 mmol, 6.0 mol%), chiral ligand (0.014 mmol, 7.0 mol%), 4-bromo-5-methyl-2-phenyloxazole **2a** (61.9 mg, 0.260 mmol, 1.3 equiv), NaOTMS (44.9 mg, 0.60 mmol, 2.0 equiv) and THF (0.20 mL). Simultaneously, in another oven-dried reaction tube, labelled as “**B**”, (Fisherbrand, 13x100 mm, 1495935C) equipped with a magnetic stir bar was charged with $[\text{Pd}(\text{cinnamyl})\text{Cl}]_2$ (3.3 mg, 0.012 mmol, 6.0 mol%), BrettPhos (6.4 mg, 0.012 mmol, 6.0 mol%) and THF (0.15 mL).

After the reaction mixture had stirred for 5 min at room temperature, Me_2PhSiH (61.3 μL , 0.60 mmol, 2.0 equiv) was added dropwise to the test tube “**A**” using a glass air-tight syringe (Caution: gas evolution!) and the reaction mixture was allowed to stir for 10 min.

The palladium-catalyst solution, in reaction tube “**B**”, and the corresponding alkene (**1a**) (0.2 mmol, 1.0 equiv) were simultaneously added to reaction tube “**A**” using glass syringes, and if the alkene was a solid it was added following the addition of “**B**” to “**A**”. Test tube “**A**” was sealed with a screw cap containing a Teflon septum, taken outside the glovebox and the reaction tube was placed in a preheated 45 °C oil bath.

After the reaction mixture had stirred for 15 h at 45 °C, the reaction vessel was removed from the oil bath and the reaction mixture was allowed cool to room temperature. Once at room temperature, the reaction mixture was filtered through a short pad of SiO_2 (rinsed with ca. 5 mL of Et_2O) directly to a reaction tube labelled as “**C**” (Fisherbrand, 13x100 mm, 1495935C). The volatiles were carefully concentrated under reduced pressure with the aid of a rotary evaporator and then using a high vacuum Schlenk line by using a 24/40 glass adapter and a double threaded connector.

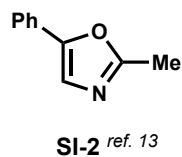
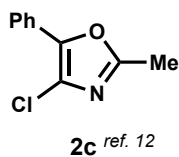
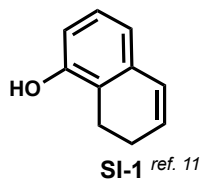
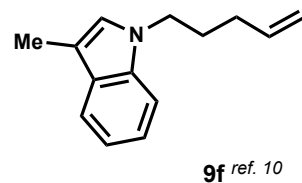
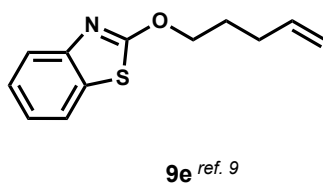
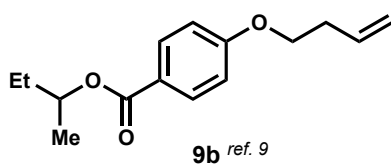
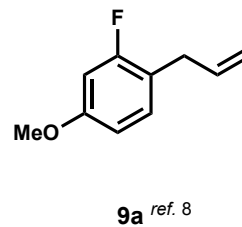
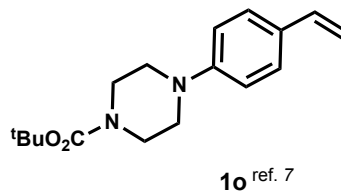
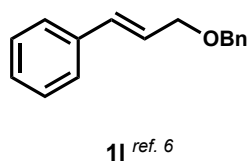
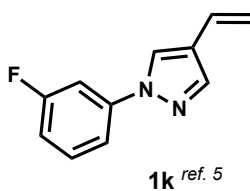
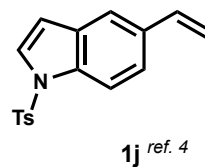
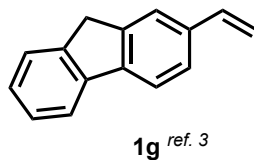
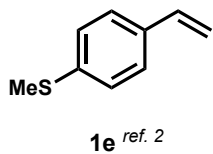
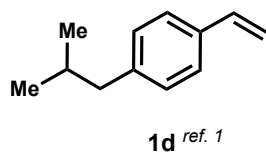
To the reaction tube “**C**” was added a magnetic stir bar, toluene (0.02 mL, 4.0 M) and the corresponding dienophile (**7**) (0.7 mmol, 3.5 or 5.0 equiv). Test tube “**C**” was flushed with N_2 , sealed with a screw cap containing a Teflon septum and moved to a preheated 110 °C oil bath. After the reaction mixture had stirred for 8 h at 110 °C, the reaction vessel was removed from the oil bath and allowed to cool to room temperature. The crude reaction yield was evaluated by ^1H NMR with 1,1,2,2-tetrachloroethane as internal standard. A small portion of the crude reaction mixture was purified by prep silica thin layer chromatography, and the resulting pure sample was analyzed by chiral SFC to determine enantioselectivity.

Figure SI1: Optimization of the alkyne component using procedure for reaction optimization^a

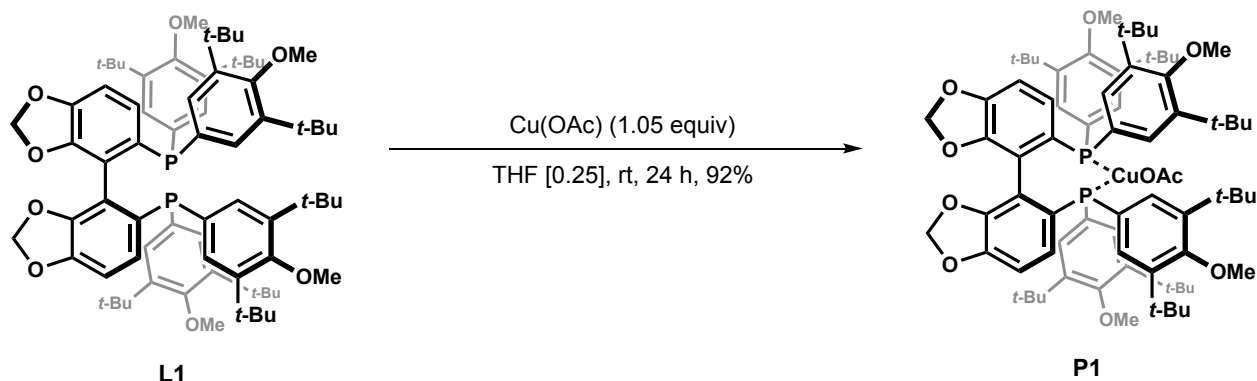
^aReaction conditions: 0.2 mmol styrene (**1a**) (1.0 equiv), yields were determined by ¹H NMR spectroscopy of the crude reaction mixture, using 1,1,2,2-tetrachloroethane as internal standard. ^b0.2 mmol **1l** (1.0 equiv) was used in place of **1a**, incomplete conversion of intermediate alkyl oxazole **4l** was observed when **7d** was used as a dienophile.

3. Synthesis and Characterization of Starting Materials

The following starting materials and substrates were prepared by known protocols:



3.1. Synthesis and Characterization of CuOAc-[(S)-DTBM-SEGPPOS] (P1)

**CuOAc-[(S)-DTBM-SEGPPOS] (P1)**

Inside a nitrogen filled glovebox, a reaction tube (Fisherbrand, 20x150 mm, 1495937C) equipped with a egg-shaped magnetic stir bar was charged with Cu(OAc) (0.257 g, 2.1 mmol, 1.05 equiv), (S)-DTBM-SEGPPOS (2.359 g, 2.0 mmol, 1.0 equiv) and dry THF (8.0 mL, [0.25]). The test tube was capped with a phenolic screw cap/septa (Cap: Fisher Scientific, Closure OT S/T 18-400, Cat. No. 033407G; Septa: Thermo Scientific, Septa T/S for 18-400Cap, Cat. No. B7995-18) and removed from the glovebox, and allowed to stir at room temperature. After the reaction mixture had stirred at room temperature for 24 h, the reaction mixture was concentrated in vacuo with the aid of a rotary evaporator. The resulting beige solid was washed with hexanes (3 x 15 mL) to give complex **P1** as a beige solid in 92% yield (2.4 g).

CuOAc-[rac-DTBM-SEGPPOS] (rac-P1) was obtained following the aforementioned procedure using *rac*-DTBM-SEGPPOS.

¹H NMR (CDCl₃, 600 MHz): δ 7.82–7.75 (m, 4H), 7.56–7.46 (m, 4H), 6.44 (d, *J* = 8.0 Hz, 2H), 6.37–6.32 (m, 2H), 5.55 (s, 2H), 5.43 (s, 2H), 3.70 (s, 6H), 3.60 (s, 6H), 2.01 (s, 3H), 1.43 (s, 36H), 1.29 (s, 36H).

¹³C NMR (CDCl₃, 151 MHz): δ 161.7, 161.3, 147.1, 147.0 (t, *J* = 6.2 Hz), 144.2 (t, *J* = 5.2 Hz), 143.2 (t, *J* = 5.2 Hz), 134.3 (m), 133.3 (m), 129.6 (t, *J* = 13.8 Hz), 126.6 (t, *J* = 16.6 Hz), 125.2 (t, *J* = 20.2 Hz), 124.9, 118.5 (t, *J* = 11.0 Hz), 107.7, 100.3, 64.4, 64.2, 36.2, 35.8, 32.3, 32.1. The observed complexity is due to C-P scalar couplings.

³¹P NMR (CDCl₃, 161 MHz): – 4.5.

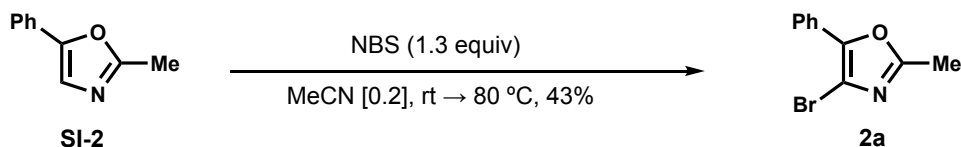
IR (Diamond-ATR, neat) $\tilde{\nu}_{\text{max}}$: 2956, 1435, 1256, 1140, 1053, 1008, 940, 806, 667, 617.

Melting Point (°C): 175 (decomposition).

Specific Rotation [α]_D²³: – 69.7 (c 1.0, CHCl₃).

EA calc. for C₇₆H₁₀₃CuO₁₀P₂: C, 69.59; H, 7.97. Found: C, 69.52; H, 7.95.

3.2. Synthesis and Characterization of 4-bromo-5-methyl-2-phenyloxazole (2a)



To an oven-dried 500 mL round bottomed flask equipped with a magnetic stir bar was added oxazole **SI-2** (7.5 g, 4.7 mmol, 1.0 equiv) and MeCN (220 mL, 0.2 M). To the stirred reaction mixture was added *N*-bromosuccinimide (11 g, 61 mmol, 1.3 equiv) in one portion at room temperature. The reaction vessel was fitted with an oven-dried reflux condenser and placed under a nitrogen atmosphere. The reaction apparatus was moved to a room temperature oil bath, which was then heated to 80 °C.

After the reaction mixture had stirred at 80 °C for 1 h, the reaction apparatus was removed from the oil bath and allowed to cool to room temperature. The reaction mixture was diluted with water (250 mL) and EtOAc (150 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 150 mL). The combined organic layers were washed with sat. aq. NaHCO₃ (200 mL), brine (200 mL), dried over Na₂SO₄, filtered and concentrated in vacuo with the aid of a rotary evaporator. Purification by automated flash column chromatography using Biotage Isolera 100 g silica cartridge (gradient elution: 0% to 10% EtOAc in hexanes) afforded **2a** as an off-white solid (4.85 g, 43%).

TLC (10% EtOAc in hexanes): R_f = 0.34 (UV).

¹H NMR (CDCl₃, 400 MHz): δ 7.99–7.96 (m, 2H), 7.44–7.42 (m, 3H), 2.38 (s, 3H).

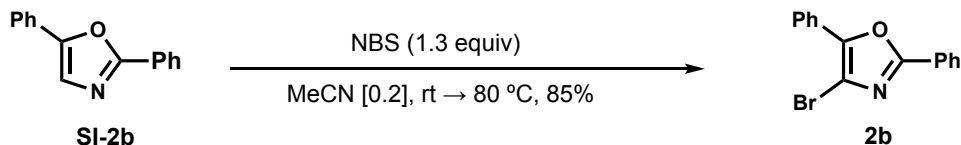
¹³C NMR (CDCl₃, 101 MHz): δ 160.2, 146.0, 130.6, 128.9, 126.9, 126.1, 113.8, 10.5.

IR (Diamond-ATR, neat) $\tilde{\nu}_{\text{max}}$: 1604, 1546, 1480, 1452, 1094, 1076, 1025, 777, 707, 654.

Melting Point (°C): 66 – 67.

HRMS (ESI) calc. C₁₀H₉BrNO [M+H]⁺: 237.9868. Found: 237.9864

3.3. Synthesis and Characterization of 4-bromo-5-methyl-2-phenyloxazole (2b)



To an oven-dried 250 mL round bottomed flask equipped with a magnetic stir bar was added oxazole **SI-2b** (2.6 g, 11.75 mmol, 1.0 equiv) and MeCN (60 mL, 0.2 M). To the stirred reaction mixture was added *N*-bromosuccinimide (2.7 g, 15.28 mmol, 1.3 equiv) in one portion at room temperature. The reaction vessel was fitted with an oven dried reflux condenser and placed under a nitrogen atmosphere. The reaction apparatus was moved to a room temperature oil bath, which was then heated to 80 °C.

After the reaction mixture had stirred at 80 °C for 1 h, the reaction apparatus was removed from the oil bath and allowed to cool to room temperature. The reaction mixture was diluted with water (100 mL) and EtOAc (100 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with sat. aq. NaHCO₃ (100 mL), brine (100 mL), dried over Na₂SO₄, filtered and concentrated in vacuo with the aid of a rotary evaporator. Purification by automated flash column chromatography using Biotage Isolera 100 g silica cartridge (gradient elution: 0% to 10% EtOAc in hexanes) afforded **2b** as an off-white solid (3.0 g, 85%).

TLC (10% EtOAc in hexanes): R_f = 0.70 (UV).

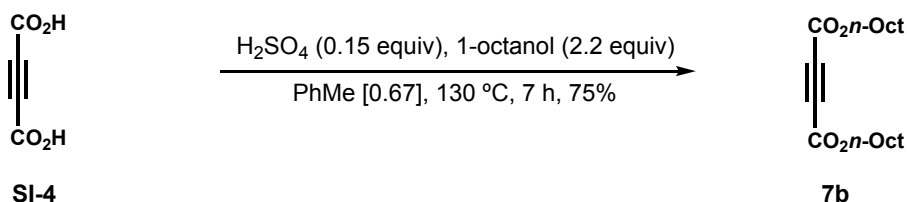
¹H NMR (CDCl₃, 400 MHz): δ 8.11–8.08 (m, 2H), 8.02 (d, J = 7.5 Hz, 2H), 7.51–7.47 (m, 5H), 7.42–7.38 (m, 1H).

¹³C NMR (CDCl₃, 101 MHz): δ 160.2, 146.3, 132.1, 131.1, 129.0, 128.9, 128.9, 127.2, 126.5, 125.5, 112.9.

IR (Diamond-ATR, neat) $\tilde{\nu}_{\text{max}}$: 1482, 1449, 1260, 1206, 1085, 1066, 973, 770, 758, 705, 684, 674.

Melting Point (°C): 71 – 72.

HRMS (ESI) calc. C₁₅H₁₁BrNO [M+H]⁺: 300.0019. Found: 300.0017

3.4. Synthesis and Characterization of dioctyl but-2-ynedioate (**7b**)

To an oven-dried 250 mL round-bottomed flask equipped with a magnetic stir bar was added carboxylic acid **SI-4** (5.70 g, 50.0 mmol, 1.0 equiv), PhMe (75 mL, 0.67M), and 1-octanol (17 mL, 110 mmol, 2.2 equiv). To the stirred reaction mixture was added concentrated sulfuric acid (400 μL , 7.5 mmol, 0.15 equiv). The reaction vessel was fitted with a Dean-Stark trap, which was connected to a reflux condenser, and placed under a nitrogen atmosphere. The reaction apparatus was moved to a room temperature oil bath, which was then heated to 130 $^\circ\text{C}$.

After the reaction mixture had stirred at 130 $^\circ\text{C}$ for 7 h, the reaction apparatus was removed from the oil bath and allowed to cool to room temperature. Once at room temperature, the reaction mixture was diluted with water (100 mL) and hexanes (150 mL). The layers were separated and the aqueous layer was extracted with hexanes (2 x 150 mL). The combined organic layers were washed with aq. 3 M NaOH (100 mL), brine (300 mL), dried over Na_2SO_4 , filtered and concentrated in vacuo with the aid of a rotary evaporator. Purification by flash column chromatography (gradient elution: 100% hexane to 5% EtOAc in hexane) afforded **7b** as a colorless oil (12.7 g, 75%).

TLC (10% EtOAc in hexanes): R_f = 0.75 (weak UV, I_2).

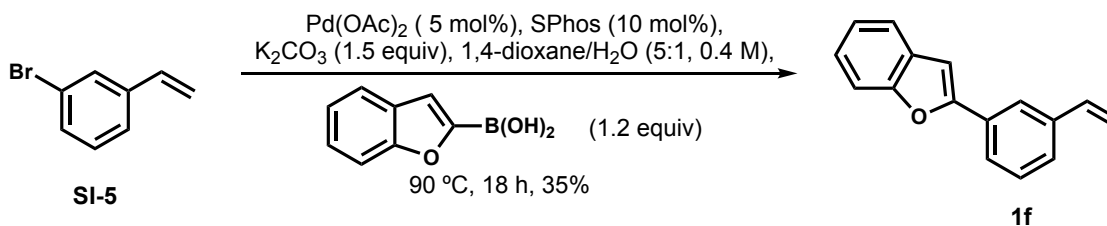
^1H NMR (CDCl_3 , 400 MHz): δ 4.22 (t, J = 6.7 Hz, 4H), 1.71–1.64 (m, 4H), 1.41–1.22 (m, 20H), 0.88 (t, J = 7.0 Hz, 6H).

^{13}C NMR (CDCl_3 , 101 MHz): δ 152.1, 74.8, 67.2, 31.9, 29.2, 29.2, 28.4, 25.8, 22.7, 14.2.

IR (Diamond-ATR, neat) $\tilde{\nu}_{\text{max}}$: 2925, 2856, 1720, 1466, 1241, 1027, 746.

HRMS (DART) calc. $\text{C}_{20}\text{H}_{38}\text{NO}_4$ $[\text{M}+\text{H}]^+$: 356.2795. Found: 356.2796.

3.5 Synthesis and Characterization of Vinyl Arenes and Terminal Olefins



2-(3-vinylphenyl)benzofuran (**1f**)

To a reaction tube (Fisherbrand, 20x150 mm, 1495937C) equipped with a magnetic stir bar was charged with $\text{Pd}(\text{OAc})_2$ (33.7 mg, 0.15 mmol, 5.0 mol%), SPhos (123.2 mg, 0.30 mmol, 10.0 mol%), K_2CO_3 (1.24 g, 9.0 mmol, 3.0 equiv), 1-bromo-3-vinylbenzene **SI-5** (549 mg, 3.0 mmol, 1.0 equiv,) and benzofuran-2-ylboronic acid (583.0 mg, 3.6 mmol, 1.2 equiv). The reaction tube was sealed with a screw cap containing a Teflon septum and then evacuated/backfilled with N_2 (this process was repeated a total of three times) using a dual manifold Schlenk line. The reaction mixture was then diluted with 1,4-dioxane (7.5 mL) and H_2O (1.5 mL), and the resulting mixture was moved to a preheated 90 °C oil bath. After the reaction mixture had stirred at 90 °C for 18 h, the reaction vessel was removed from the oil bath and was allowed to cool to room temperature. Once at room temperature, the reaction mixture was diluted with Et_2O (5 mL) and H_2O (5 mL). The aqueous phase was extracted with Et_2O (3 x 15 mL). The combined organic layers were washed with brine (75 mL), dried with MgSO_4 and then the volatiles were evaporated in vacuo with the aid of a rotary evaporator. The residue was purified by flash column chromatography on silica gel (hexane:acetone 40:1) to yield **1f** as a colorless solid (180.5 mg, 35% yield).

TLC (hexane:acetone 40:1): R_f = 0.70 (UV).

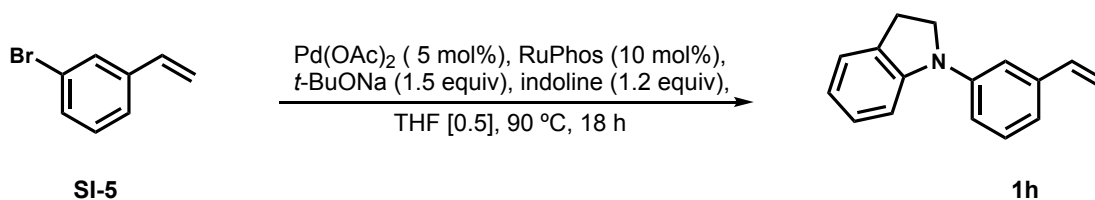
^1H NMR (CDCl_3 , 400 MHz): δ 7.95 (s, 1H), 7.79 (ddd, J = 5.5, 3.8, 1.8 Hz, 1H), 7.63 (d, J = 7.6, Hz, 1H), 7.58 (d, J = 7.6, Hz, 1H), 7.46–7.43 (m, 2H), 7.35–7.26 (m, 2H), 7.08 (s, 1H), 6.83 (dd, J = 17.6, 10.9 Hz, 1H), 5.90 (d, J = 17.6 Hz, 1H), 5.38 (d, J = 10.9 Hz, 1H).

^{13}C NMR (CDCl_3 , 101 MHz): δ 155.9, 155.0, 138.3, 136.6, 130.9, 129.3, 129.1, 126.4, 124.5, 123.1, 122.9, 121.1, 114.8, 111.3, 101.7.

IR (Diamond-ATR, neat) $\tilde{\nu}_{\text{max}}$: 1452, 1255, 1041, 991, 934, 913, 902, 812, 744, 684.

Melting Point (°C): 42 – 44.

HRMS (DART) calc. $\text{C}_{16}\text{H}_{13}\text{O}$ $[\text{M}+\text{H}]^+$: 221.0961. Found: 221.0961.

**1-(3-vinylphenyl)indoline (1h)**

Inside a nitrogen filled glovebox, an oven-dried reaction tube (Fisherbrand, 20x150 mm, 1495937C) equipped with a magnetic stir bar was charged with Pd(OAc)₂ (22.4 mg, 0.1 mmol, 5.0 mol%), RuPhos (93.3 mg, 0.2 mmol, 10 mol%) and dry THF (4.0 mL, 0.5 M).

After the reaction mixture had stirred at room temperature for 15 min, indoline (269 μ L, 2.4 mmol, 1.2 equiv), *t*-BuONa (288 mg, 3.0 mmol, 1.5 equiv) and 1-bromo-3-vinylbenzene **SI-5** (262 μ L, 2.0 mmol, 1.0 equiv) were added sequentially to the palladium-catalyst solution. The reaction tube was sealed with a screw cap containing a Teflon septum, taken outside the glovebox and the reaction vessel was placed in a preheated 90 $^{\circ}$ C oil bath. After the reaction mixture had stirred at 90 $^{\circ}$ C for 18 h, the reaction vessel was removed from the oil bath and the reaction mixture was allowed cool to room temperature. Once at room temperature, the reaction mixture was filtered through a short pad of SiO₂ (rinsed with ca. 30 mL of Et₂O) and the volatiles were carefully concentrated in vacuo with the aid of a rotary evaporator. The residue was purified by flash column chromatography on silica gel (pentane:Et₂O 10:1) to yield **1h** as a pale yellow oil (413.0 mg, 93% yield).

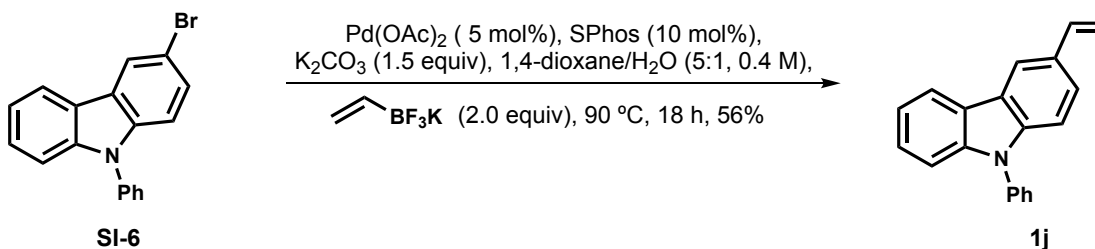
TLC (pentane:Et₂O 10:1): *R*_f = 0.80 (UV, I₂).

¹H NMR (CDCl₃, 400 MHz): δ 7.32–7.25 (m, 2H), 7.18–7.13 (m, 3H), 7.10–7.02 (m, 2H), 6.77–6.68 (m, 2H), 5.76 (d, *J* = 17.6 Hz, 1H), 5.26 (d, *J* = 10.8 Hz, 1H), 3.97 (t, *J* = 8.4 Hz, 2H), 3.13 (t, *J* = 8.4 Hz, 2H).

¹³C NMR (CDCl₃, 101 MHz): δ 147.1, 144.5, 138.7, 137.2, 131.4, 129.4, 127.2, 125.2, 119.1, 119.0, 117.3, 115.6, 114.2, 108.3, 52.3, 28.3.

IR (Diamond-ATR, neat) $\tilde{\nu}_{\text{max}}$: 1587, 1481, 1458, 1385, 1261, 1232, 987, 739, 707, 672.

EA: calc. for C₁₆H₁₅N: C, 86.84; H, 6.83. Found: C, 86.80; H, 6.82.

**9-phenyl-3-vinyl-9H-carbazole (1j)**

To a reaction tube (Fisherbrand, 20x150 mm, 1495937C) equipped with a magnetic stir bar was charged with Pd(OAc)₂ (33.7 mg, 0.15 mmol, 5.0 mol%) SPhos (123.2 mg, 0.30 mmol,

10.0 mol%), K_2CO_3 (1.24 g, 9.0 mmol, 3.0 equiv), trifluoro(vinyl)-*l*-4-borane salt (803.7 mg, 6.0 mmol, 2.0 equiv), methyl 3-bromo-9-phenyl-9H-carbazole **SI-5** (966.6 mg, 3.0 mmol, 1.0 equiv). The reaction tube was sealed with a screw cap containing a Teflon septum and then evacuated/backfilled with N_2 (this process was repeated a total of three times) using a dual manifold Schlenk line. The reaction mixture was then diluted 1,4-Dioxane (7.5 mL) and H_2O (1.5 mL) and the reaction vessel was moved to a preheated 90 °C oil bath.

After the reaction mixture had stirred at 90 °C for 18 h, the reaction vessel was removed from the oil bath, and the reaction mixture was allowed to cool to room temperature. Once at room temperature, the reaction mixture was diluted with Et_2O (5 mL) and H_2O (5 mL). The layers were separated and aqueous phase was extracted with Et_2O (3 x 15 mL). The combined organic phases were washed with brine (50 mL), dried with $MgSO_4$ and then the volatiles were carefully concentrated in vacuo with the aid of a rotary evaporator. The residue was purified by flash column chromatography on silica gel (pentane:EtOAc 20:1) to yield **1j** (450 mg, 56% yield) as a thick yellow oil.

Note: Substrate **1j** was immediately employed in the olefin hydrocyanation reaction due to its instability at ambient temperature, half-life ca. 48 h.

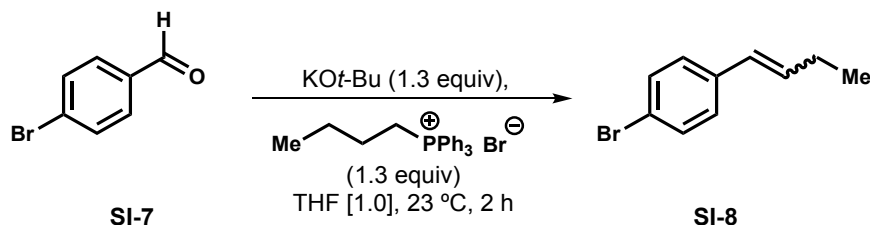
TLC (pentane: EtOAc 20:1): R_f = 0.60 (UV).

1H NMR ($CDCl_3$, 400 MHz): δ 8.17–8.14 (m, 3H), 7.63–7.59 (m, 3H), 7.58–7.55 (m, 3H), 7.52 (dd, J = 8.5, 1.7 Hz, 1H), 7.47 (ddt, J = 7.2, 5.1, 1.6 Hz, 1H), 7.42–7.40 (m, 4H), 7.35 (d, J = 8.6 Hz, 1H), 7.29 (ddd, J = 8.0, 4.9, 3.3 Hz, 2H), 6.93 (dd, J = 17.5, 10.9 Hz, 1H), 5.79 (dd, J = 17.5, 1.0 Hz, 1H), 5.23 (dd, J = 10.9, 1.0 Hz, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 141.4, 141.0, 140.8, 137.9, 137.7, 137.5, 130.1, 130.0, 130.0, 127.6, 127.6, 127.3, 126.2, 126.0, 124.4, 123.7, 123.5, 123.5, 120.5, 120.4, 120.2, 120.0, 118.4, 111.6, 110.0, 109.9, 109.9.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 1595, 1500, 1477, 1450, 1229, 811, 759, 744, 734, 724, 697, 642.

HRMS (DART) calc. $C_{20}H_{16}O$ $[M+H]^+$: 270.1277. Found: 270.1270.



1-bromo-4-(but-1-en-1-yl)benzene (SI-8)

To a reaction tube equipped (Fisherbrand, 20x150 mm, 1495937C) with a magnetic stir bar was added propyl triphenylphosphonium bromide (2.0 g, 6.5 mmol, 1.3 equiv) and the reaction vial was capped with a screw cap. Following this, the reaction mixture was diluted with THF (10 mL, 0.5 M). To the stirred reaction mixture was added potassium *tert*-butoxide (0.73 g, 6.5 mmol, 1.3 equiv) at room temperature. After the reaction mixture had stirred at room

temperature for 30 min, aldehyde **SI-7** (0.93 g, 5.0 mmol, 1.0 equiv) was added to the reaction mixture.

After the resulting reaction mixture had stirred at room temperature for an additional 1 h, the reaction mixture was diluted with sat. aq. NH_4Cl (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4 , filtered and concentrated in vacuo by rotary evaporation. Purification by automated flash column chromatography using a Biotage Isolera 50 g cartridge (gradient elution: 100% hexane to 10% EtOAc/hexane) afforded **SI-8** (892 mg, 85%. 1:2 *E:Z* mixture) as a colorless oil.

TLC (10% EtOAc in hexane): R_f = 0.74 (UV).

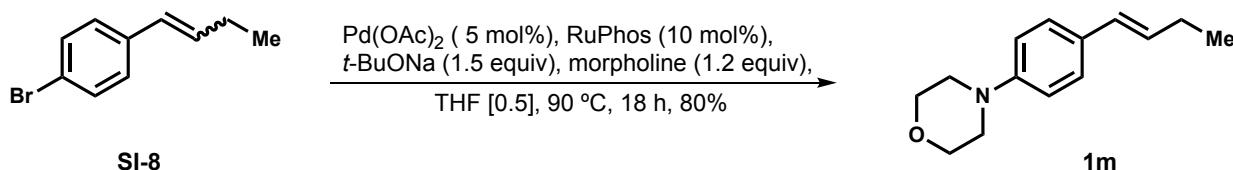
^1H NMR (CDCl_3 , 400 MHz) for the ***E*-isomer**: δ 7.44 (d, J = 8.1 Hz, 2H), 7.14 (d, J = 8.1 Hz, 2H), 6.34–6.26 (m, 1H), 5.68 (dt, J = 11.4, 7.3 Hz, 1H), 2.34–2.27 (m, 2H), 1.06 (t, J = 7.4 Hz, 3H).

^1H NMR (CDCl_3 , 400 MHz) for the ***Z*-isomer**: δ 7.40 (d, J = 8.2 Hz, 2H), 7.20 (d, J = 8.1 Hz, 2H), 6.25–6.22 (m, 1H), 5.56–5.50 (m, 1H), 2.25–2.19 (m, 2H), 1.09 (t, J = 7.4 Hz, 3H).

^{13}C NMR (CDCl_3 , 101 MHz) for the ***E*- and *Z*-isomers**: δ 137.0, 136.8, 135.7, 133.7, 131.7, 131.5, 131.4, 130.5, 130.4, 129.5, 127.8, 127.6, 127.3, 127.1, 120.5, 120.4, 38.5, 26.2, 22.1, 21.3, 18.0, 14.5, 13.6.

IR (Diamond-ATR, neat) $\tilde{\nu}_{\text{max}}$: 2963, 1485, 1071, 1008, 964, 801, 785, 736.

EA calc. for $\text{C}_{10}\text{H}_{11}\text{Br}$: C, 56.9; H, 5.25. Found: C, 57.20; H, 5.32.



4-(4-(but-1-en-1-yl)phenyl)morpholine (**1m**)

Inside a nitrogen filled glovebox, an oven-dried reaction tube (Fisherbrand, 20x150 mm, 1495937C) equipped with a magnetic stir bar was charged with $\text{Pd}(\text{OAc})_2$ (22.4 mg, 0.1 mmol, 5.0 mol%), RuPhos (93.3 mg, 0.2 mmol, 10.0 mol%) and THF (4.0 mL, 0.5 M).

After the reaction mixture had stirred at room temperature for 15 min, morpholine (209 mg, 2.4 mmol, 1.2 equiv), $t\text{-BuONa}$ (288 mg, 3.0 mmol, 1.5 equiv) and 1-bromo-4-(but-1-en-1-yl)benzene (**SI-8**) (422 mg, 2.0 mmol, 1.0 equiv) were added sequentially to the palladium-catalyst solution. The reaction tube was sealed with a screw cap containing a Teflon septum, taken outside the glovebox and the reaction vessel was placed in a preheated 90 °C oil bath. After the reaction mixture had stirred at 90 °C for 18 h, the reaction vessel was removed from the oil bath and allowed cool to room temperature. Once at room temperature, the reaction mixture was filtered through a short pad of SiO_2 (rinsed with ca. 30 mL of Et_2O) and the volatiles were carefully concentrated in vacuo with the aid of a rotary evaporator. The residue was purified by flash column chromatography on silica gel (pentane:EtOAc 20:1) to yield **1m** in 80% yield (410.5 mg) as a colorless solid (1:10 *Z:E* mixture by ^1H NMR).

TLC (pentane:EtOAc 20:1): R_f = 0.65 (UV, I_2).

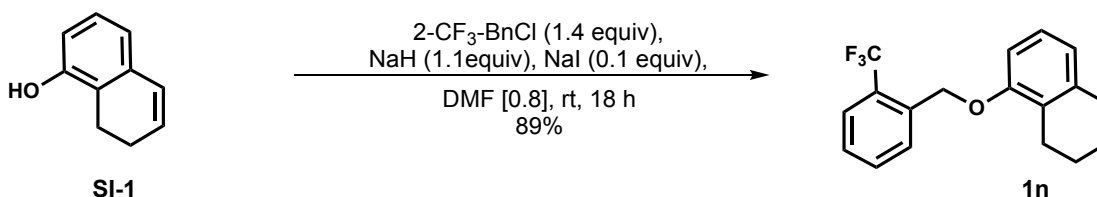
^1H NMR (CDCl_3 , 400 MHz) for the **E-isomer**: δ 7.27 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 8.3 Hz, 2H), 6.31 (d, J = 15.9 Hz, 1H), 6.13 (dt, J = 15.6, 6.4 Hz, 1H), 3.87–3.85 (m, 4H), 3.16–3.14 (m, 4H), 2.21 (p, J = 7.2 Hz, 2H), 1.08 (t, J = 7.4 Hz, 3H).

^{13}C NMR (CDCl_3 , 101 MHz) for the **E-isomer**: δ 150.3, 130.3, 130.2, 128.3, 126.9, 115.8, 67.1, 49.5, 26.2, 14.0.

IR (Diamond-ATR, neat) $\tilde{\nu}_{\text{max}}$: 2960, 1605, 1512, 1447, 1378, 1331, 1230, 1120, 1068, 1050, 966, 924, 808.

Melting Point ($^\circ\text{C}$): 75 – 76.

EA: calc. for $\text{C}_{14}\text{H}_{19}\text{NO}$: C, 77.38; H, 8.81. Found: C, 77.55; H, 8.99.



8-((2-(trifluoromethyl)benzyl)oxy)-1,2-dihydronaphthalene (**1n**)

To an oven-dried reaction tube (Fisherbrand, 20x150 mm, 1495937C) equipped with a magnetic stir bar and sealed with a Teflon screw cap was added sodium hydride (160 mg, 6.8 mmol, 1.1 equiv) and DMF (4 mL, 1.7 M). To the stirred reaction mixture was added a solution of alcohol **SI-1** (0.9 g, 6.2 mmol, 1.0 equiv) in DMF (4 mL, 1.6 M) dropwise over 5 min at room temperature (CAUTION! gas evolution), to achieve a final reaction concentration of 0.8 M. After the reaction mixture had stirred at room temperature for 10 min, 2-(trifluoromethyl)benzyl chloride (1.3 mL, 8.6 mmol, 1.4 equiv) and sodium iodide (92 mg, 0.62 mmol, 0.1 equiv) was added to the reaction mixture sequentially.

After the reaction mixture had stirred at room temperature for 18 h, sat. aq. NH_4Cl (10 mL) and EtOAc (7 mL) was added to the reaction mixture. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over Na_2SO_4 , filtered and concentrated in vacuo by rotary evaporation. Purification by automated flash column chromatography using a Biotage Isolera 50 g silica cartridge (gradient elution: 100% hexane to 10% EtOAc in hexane) afforded **1n** as a colorless solid (1.66 g, 89%).

TLC (10% EtOAc in hexanes): R_f = 0.55 (UV).

^1H NMR (CDCl_3 , 400 MHz): δ 7.80 (d, J = 7.8 Hz, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.59 (t, J = 7.6 Hz, 1H), 7.43 (t, J = 7.7 Hz, 1H), 7.11 (t, J = 7.9 Hz, 1H), 6.77 (d, J = 8.2 Hz, 1H), 6.73 (d, J = 7.5 Hz, 1H), 6.46 (d, J = 9.6 Hz, 1H), 6.06 (dt, J = 9.3, 4.4 Hz, 1H), 5.30 (s, 2H), 2.92 (t, J = 8.5 Hz, 2H), 2.34 (dt, J = 8.4, 6.1, 2.6 Hz, 2H).

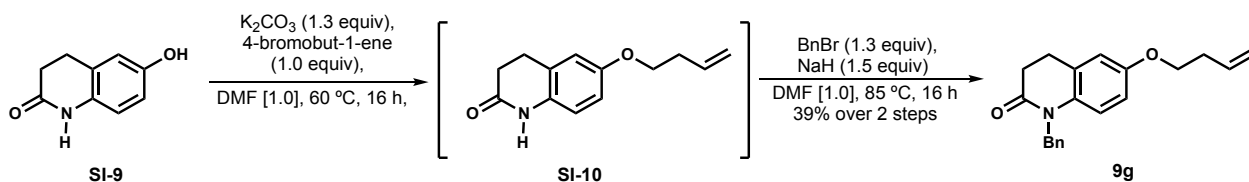
^{13}C NMR (CDCl_3 , 101 MHz): δ 155.0, 136.3 (q, $J = 1.5$ Hz), 135.5, 132.3, 129.1, 128.4, 127.7, 127.7, 127.5, 127.2, 126.9, 126.0 (q, $J = 5.8$ Hz), 125.9, 123.7, 123.2, 119.7, 111.2, 66.3 (q, $J = 3.2$ Hz), 22.8, 19.9. The observed complexity is due to C-F scalar couplings.

^{19}F NMR (CDCl_3 , 376 MHz): δ – 60.4.

IR (Diamond-ATR, neat) $\tilde{\nu}_{\text{max}}$: 1572, 1450, 1311, 1280, 1263, 1235, 1155, 1112, 1093, 1035, 804, 745, 698.

Melting Point ($^{\circ}\text{C}$): 51 – 52.

HRMS (ESI) calc. $\text{C}_{18}\text{H}_{16}\text{F}_3\text{O}$ $[\text{M}+\text{H}]^+$: 305.1153. Found: 305.1145.



1-benzyl-6-(but-3-en-1-yloxy)-3,4-dihydroquinolin-2(1H)-one (**9g**)

To an oven dried reaction tube equipped (Fisherbrand, 20x150 mm, 1495937C) with a magnetic stir bar and sealed with a Teflon screw cap was added amide **SI-9** (1.63 g, 10.0 mmol, 1.0 equiv) as a solution in DMF (1.0 mL, 0.5 M). The reaction tube was then evacuated and backfilled with nitrogen. To the reaction mixture was added K_2CO_3 (1.79 g, 13.0 mmol, 1.3 equiv). The reaction mixture was allowed to stir for 10 min at room temperature before 4-bromobut-1-ene (1.02 mL, 10.0 mmol, 1.0 equiv) was added dropwise to the reaction mixture over 2 min. The reaction vessel was moved to a preheated 60 $^{\circ}\text{C}$ oil bath.

After the reaction mixture had stirred at 60 $^{\circ}\text{C}$ for 16 h, the reaction vessel was removed from the oil bath and allowed to cool to room temperature. Once at room temperature, the reaction mixture was diluted with sat. aq. NH_4Cl (30 mL), water (25 mL) and EtOAc (35 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (2 x 25 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure by rotary evaporation. The crude material was used in the next step without further purification.

To an oven dried reaction tube equipped (Fisherbrand, 20x150 mm, 1495937C) with a magnetic stir bar and sealed with a Teflon screw cap was added crude amide **SI-10** as a solution in DMF (6.0 mL, 0.5 M). The reaction tube was then evacuated and backfilled with nitrogen. To the reaction mixture was added sodium hydride (360.0 mg, 13.0 mmol, 1.5 equiv), CAUTION! gas evolution. The reaction mixture was allowed to stir for 10 min at room temperature before benzyl bromide (1.54 mL, 13.0 mmol, 1.3 equiv) was added dropwise to the reaction mixture over 2 min. The reaction vessel was moved to a preheated 85 $^{\circ}\text{C}$ oil bath.

Supporting Information

After the reaction mixture had stirred at 85 °C for 16 h, the reaction vessel was removed from the oil bath and allowed to cool to room temperature. Once at room temperature, the reaction mixture was diluted with sat. aq. NH₄Cl (10 mL), water (15 mL) and EtOAc (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (2 x 15 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure by rotary evaporation. Purification by automated flash column chromatography using a Biotage Isolera 100 g silica cartridge (10% to 75% EtOAc/hexanes) afforded **9g** as a colorless solid (1.2 g, 39% over 2 steps).

TLC (50% EtOAc in hexanes): R_f = 0.46 (UV).

¹H NMR (CDCl₃, 400 MHz): δ 7.30 (at, J = 7.3 Hz, 2H), 7.22 (at, J = 8.0 Hz, 3H), 6.77 (d, J = 8.8 Hz, 1H), 6.74 (d, J = 2.8 Hz, 1H), 6.62 (dd, J = 8.8, 2.8 Hz, 1H), 5.87 (ddt, J 17.0, 10.3, 6.7 Hz, 1H), 5.17–5.12 (m, 4H), 5.11–5.08 (m, 1H), 3.94 (t, J = 6.7 Hz, 2H), 2.94 (dd, J = 8.8, 5.8 Hz, 2H), 2.77 (dd, J = 8.8, 5.8 Hz, 2H), 2.50 (qt, J = 6.7, 1.4 Hz, 2H)

¹³C NMR (CDCl₃, 101 MHz): δ ¹³C NMR (101 MHz, CDCl₃) δ 170.2, 154.7, 137.2, 134.5, 133.5, 128.8, 128.0, 127.1, 126.5, 117.1, 116.6, 114.7, 112.7, 67.6, 46.3, 33.7, 32.0, 25.9

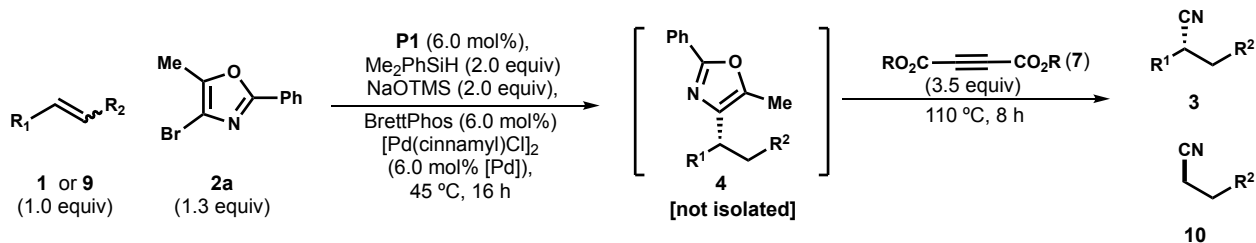
IR (Diamond-ATR, neat) $\tilde{\nu}_{\text{max}}$: 2924, 1663, 1501, 1471, 1380, 1189, 724.

Melting Point (°C): 66 – 67.

HRMS (ESI) calc. C₂₁H₂₃N₂O₂ [M+H]⁺: 308.1645. Found: 308.1655

4. Synthesis and Characterization of Hydrocyanation products

4.1. General Procedure A for Hydrocyanation of Olefins



Inside a nitrogen filled glovebox, an oven-dried reaction tube, labelled as “**A**”, (Fisherbrand, 20x125 mm, 1495937A) equipped with a magnetic stir bar was charged with (*S*)-DTBM-SEGPBOS·CuOAc **P1** (39.0 mg, 0.030 mmol, 6.0 mol%), 4-bromo-5-methyl-2-phenyloxazole **2a** (155 mg, 0.65 mmol, 1.3 equiv), NaOTMS (112 mg, 1.0 mmol, 2.0 equiv) and THF (0.50 mL). Simultaneously, in another oven-dried reaction tube, labelled as “**B**”, (Fisherbrand, 13x100 mm, 1495935C) equipped with a magnetic stir bar was charged with $[\text{Pd}(\text{cinnamyl})\text{Cl}]_2$ (7.7 mg, 0.015 mmol, 6.0 mol%), BrettPhos (16.1 mg, 0.030 mmol, 6.0 mol%) and THF (0.37 mL) (Photo **A–B**).

After the reaction mixture had stirred for 5 min at room temperature, Me_2PhSiH (153.0 μL , 1.0 mmol, 2.0 equiv) was added dropwise to the test tube “**A**” using a glass air-tight syringe (Caution: gas evolution!) and the reaction mixture was allowed to stir for 10 min (Photo **C**).

The palladium catalyst stock solution, in reaction tube “**B**”, and the corresponding alkene (**1** or **9**) (0.5 mmol, 1.0 equiv) were simultaneously added to reaction tube “**A**” using glass syringes (photo **D**), and if the alkene was a solid it was added following the addition of “**B**” to “**A**”. Test tube “**A**” was sealed with a screw cap containing a Teflon septum (cap: Kimble Chase Open Top S/T Closure catalog no. 73804-15425; Septum: Thermo Scientific 1.3 mm silicone/PTFE catalog no. B7995-18), taken outside the glovebox and the reaction tube was placed in a preheated 45 °C oil bath.

After the reaction mixture had stirred for 16 h at 45 °C, the reaction vessel was removed from the oil bath and the reaction mixture was allowed cool to room temperature. (Photo **E**) Once at room temperature, the reaction mixture was filtered through a short pad of SiO_2 (rinsed with ca. 15 mL of Et_2O) directly to a reaction tube labelled as “**C**” (Fisherbrand, 20x125 mm, 1495937A) (Photo **F–G**). The volatiles were carefully concentrated in vacuo with the aid of a rotary evaporator and then dried under high vacuum Schlenk line (ca. 10 min) by using a 24/40 glass adapter and a double threaded connector (Photo **H**).

To the reaction tube “**C**” was added a magnetic stir bar, toluene (0.125 mL, 4.0 M) and the corresponding acetylene, **7a** or **7b**, (1.75 mmol, 3.5 equiv) (Photo **I**). Test tube “**C**” was flushed with N_2 , sealed with a screw cap containing a Teflon septum and moved to a preheated 110 °C oil bath. After the reaction mixture had stirred for 8 h at 110 °C, the reaction vessel was removed from the oil bath and allowed to cool to room temperature. The crude reaction mixture was directly purified by silica flash column chromatography.

For unactivated olefins (**9**) *rac*-**P1** was used in place of **P1**.

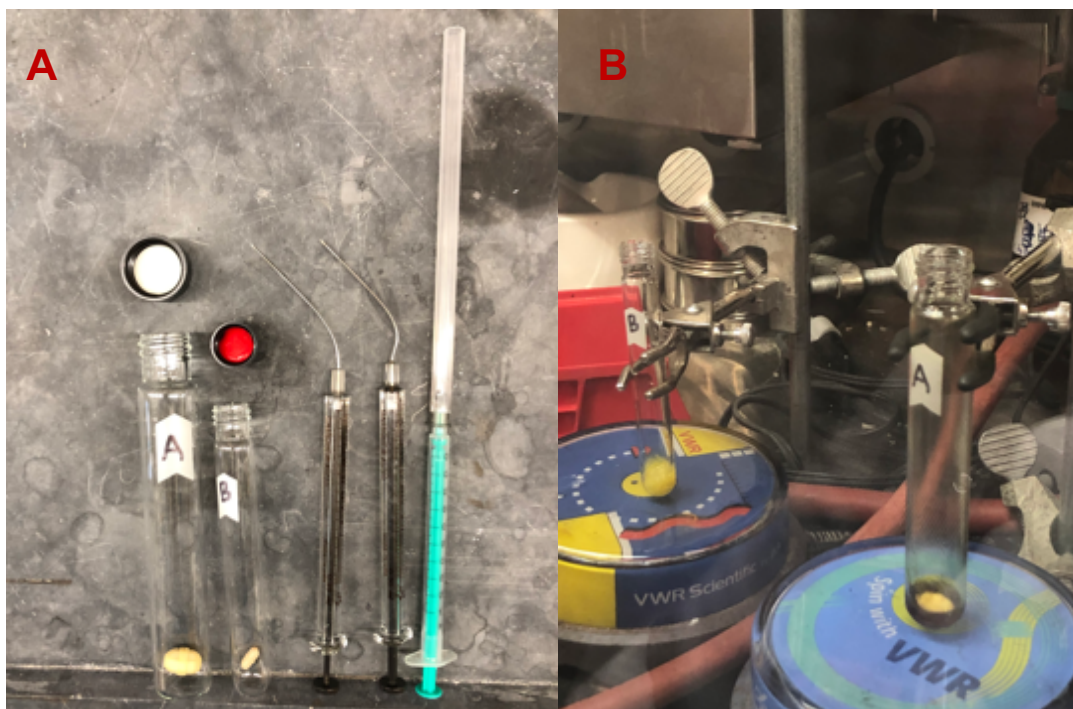


Figure SI2: A. Reactions vessels and syringes used in reaction set up. B. Reaction tube "A": following addition of **2a**, **P1**, NaOTMS and THF; reaction tube "B": [Pd(cinnamyl)Cl]₂, BrettPhos, and THF.

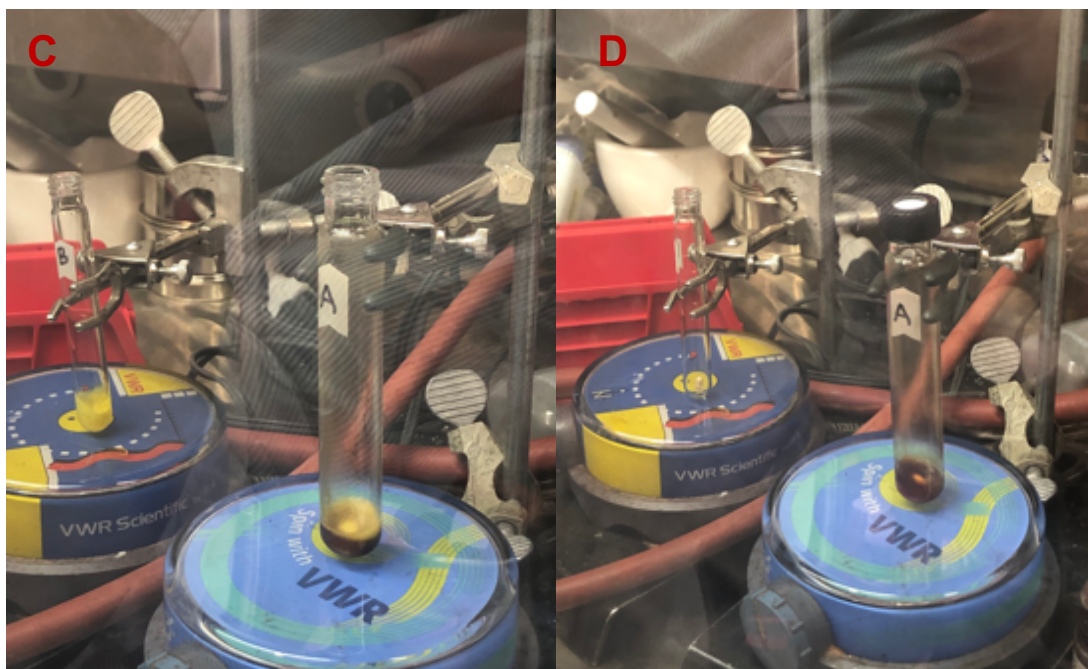


Figure SI2: C. After addition of silane to reaction tube "A". D. Following the addition of the entirety of reaction tube "B" and starting olefin to reaction tube "A"

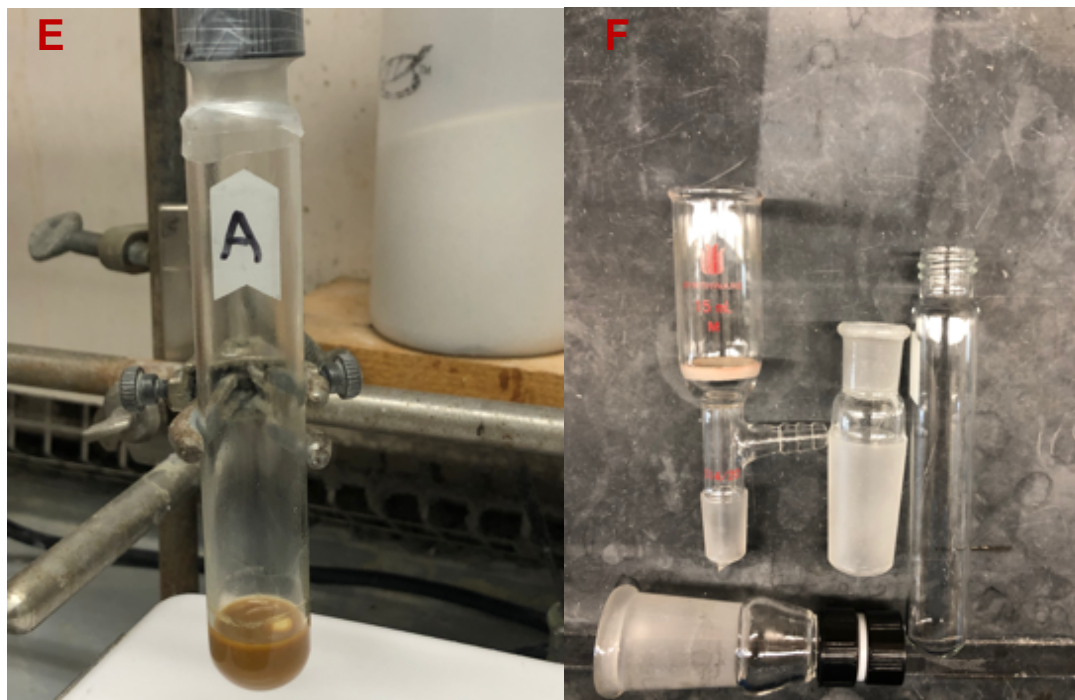


Figure S12: E. The appearance of the reaction mixture following the dual Pd/CuH hydrofunctionalization. F. The necessary glassware for the cycloaddition step.

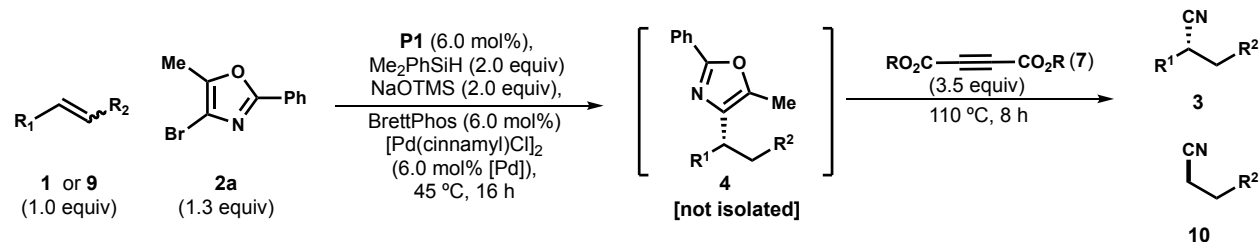


Figure S12: G. Setup for the filtration of the crude reaction mixture into reaction tube "C". H. Concentration of volatiles in vacuo by rotary evaporation.



Figure SI2 I. Appearance of reaction mixture in tube “C” following the addition of toluene and alkyne, but prior to heating in a 110 °C oil bath.

4.2. General Procedure B for Hydrocyanation of Olefins: Benchtop Reaction Setup



Note: All chemicals were removed from a nitrogen-filled glovebox and stored in a desiccator prior to use.

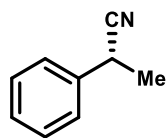
An oven-dried reaction tube labelled as “**A**” (Fisherbrand, 20x125 mm, 1495937A) equipped with a magnetic stir bar was charged with (*S*)-DTBM-SEGPBOS-CuOAc **P1** (39.0 mg, 0.030 mmol, 6.0 mol%), 4-bromo-5-methyl-2-phenyloxazole **2a** (155 mg, 0.65 mmol, 1.3 equiv) and NaOTMS (112.0 mg, 1.0 mmol, 2.0 equiv). Simultaneously, a separate oven-dried reaction tube labelled as “**B**” (Fisherbrand, 13x100 mm, 1495935C) equipped with a magnetic stir bar was charged with $[\text{Pd}(\text{cinnamyl})(\text{Cl})]_2$ (7.7 mg, 0.015 mmol, 6.0 mol%) and BrettPhos (16.1 mg, 0.030 mmol, 6.0 mol%).

Test tubes “**A**” and “**B**” were sealed with a screw cap containing a Teflon septum (cap: Kimble Chase Open Top S/T Closure catalog no. 73804-15425; Septum: Thermo Scientific 1.3 mm silicone/PTFE catalog no. B7995-18) and then evacuated and backfilled with N_2 (this process was repeated a total of three times). The N_2 inlet needles were left in the septa and 0.5 mL and 0.37 mL of dry THF were added to test tubes “**A**” and “**B**”, respectively. After the reaction mixtures had stirred for 5 min at room temperature, a needle was inserted into the septum of test tube “**A**” with a constant flow of N_2 prior to the dropwise addition of dimethylphenylsilane (153 μL , 1.0 mmol, 2.0 equiv) using a glass air-tight syringe. (Caution: gas evolution!). Both solutions were stirred for 10 min under a positive pressure of N_2 . Following this, the purging needle was removed from test tube “**A**”. The entirety of the palladium-catalyst solution in reaction tube “**B**” and alkene (**1** or **9**) (0.5 mmol, 1.0 equiv) were sequentially added to reaction tube “**A**” via syringe. Test tube “**A**” was then placed in a preheated 45 °C oil bath.

After the reaction mixture had stirred for 15 h at 45 °C, the reaction vessel was removed from the oil bath and the reaction mixture was allowed cool to room temperature. Once at room temperature, the reaction mixture was filtered through a short pad of SiO_2 (rinsed with ca. 15 mL of Et_2O) directly to a reaction tube labelled as “**C**” (Fisherbrand, 20x125 mm, 1495937A). The volatiles were carefully concentrated under reduced pressure with the aid of a rotary evaporator and then a high vacuum Schlenk line by using a 24/40 glass adapter and a double threaded connector.

To the reaction tube “**C**” was added toluene (0.125 mL, 4.0 M) and alkyne **7** (1.75 mmol, 3.5 equiv). Test tube “**C**” was flushed with N_2 , sealed with a screw cap containing a Teflon septum and moved to a preheated 110 °C oil bath. After the reaction mixture had stirred for 8 h at 110 °C, the reaction vessel was removed from the oil bath and allowed to cool to room temperature. The crude reaction mixture was purified by silica flash column chromatography.

4.3. Characterization of Hydrocyanation Products



3a

(R)-2-phenylpropanenitrile (3a)

Prepared according to **General Procedure A** using styrene (**1a**) (57.4 μ L, 0.50 mmol, 1.00 equiv), 4-bromo-5-methyl-2-phenyloxazole (**2a**) (154.7 mg, 0.65 mmol, 1.3 equiv) and diethyl acetylenedicarboxylate (**7a**) (280.0 μ L, 1.75 mmol, 3.5 equiv). NMR yield was determined by ^1H NMR spectroscopy of the crude reaction mixture, using 1,1,2,2-tetrachloroethane as internal standard. An analytically pure sample of **3a** was purified by silica preparative TLC (10:1 hexanes:acetone) (1st run: 98%, 97:3 er; 2nd run: 93%, 97:3 er) and isolated as a colorless oil.

^1H NMR yield was determined using **General Procedure B** (benchtop setup) on 0.5 mmol scale and 1,1,2,2-tetrachloroethane as internal standard: 88% yield, 97:3 er.

TLC (hexanes:acetone 10:1): R_f = 0.60 (low UV activity).

^1H NMR (CDCl_3 , 400 MHz): δ 7.42–7.30 (m, 5H), 3.90 (q, J = 7.3 Hz, 1H), 1.65 (d, J = 7.3 Hz, 3H).

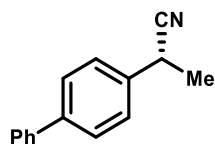
^{13}C NMR (CDCl_3 , 101 MHz): δ 137.2, 129.2, 128.2, 126.8, 121.7, 31.4, 21.6.

IR (Diamond-ATR, neat) $\tilde{\nu}_{\text{max}}$: 2985, 2241, 1493, 1451, 755, 696, 572.

HRMS (DART) calc. $\text{C}_9\text{H}_{10}\text{N}$ $[\text{M}+\text{H}]^+$: 132.0808. Found: 132.0817.

Specific Rotation $[\alpha]^{23}_{\text{D}}$: + 19.7 (c 0.5, CHCl_3).¹⁴

Chiral SFC: Chiralcel OD-H (scCO₂/IPA = 99/1 to 98/2 over 16 minutes, 2.5 mL/min, 210–400 nm, 45 °C), 3.52 and 3.69 min.



3b

(R)-2-([1,1'-biphenyl]-4-yl)propanenitrile (3b)

Prepared according to **General Procedure A** using 4-vinyl-1,1'-biphenyl (**1b**) (90.1 mg, 0.50 mmol, 1.00 equiv), 4-bromo-5-methyl-2-phenyloxazole (**2a**) (154.7 mg, 0.65 mmol, 1.3 equiv) and dioctyl but-2-ynedioate (**7b**) (592.3 mg, 1.75 mmol, 3.5 equiv). The residue was purified by flash column chromatography on silica gel (gradient elution: 10% CH_2Cl_2 in hexanes (100 mL) to 20% CH_2Cl_2 in hexanes (500 mL) to 30% CH_2Cl_2 in hexanes (200 mL), to 35% CH_2Cl_2 in

Supporting Information

hexanes (500 mL), to 45% CH₂Cl₂ in hexanes (150 mL) 2.5 cm diameter x 13 cm height of silica) to yield **3b** (1st run: 81.6 mg, 79%, 87:13 er; 2nd run: 83.0 mg, 80%, 90:10 er) as a colorless solid.

When **3b** was purified by preparative TLC on silica gel (hexanes:acetone 10:1), it was isolated with 91:9 er.

TLC (30% CH₂Cl₂ in hexanes): *R*_f = 0.24 (UV).

¹H NMR (CDCl₃, 400 MHz): δ 7.63–7.57 (m, 4H), 7.48–7.42 (m, 4H), 7.37 (t, *J* = 7.3 Hz, 1H), 3.95 (q, *J* = 7.3 Hz, 1H), 1.69 (d, *J* = 7.3 Hz, 3H).

¹³C NMR (CDCl₃, 101 MHz): 141.3, 140.4, 136.1, 129.0, 128.0, 127.7, 127.3, 127.2, 121.5, 31.1, 21.6.

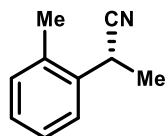
IR (Diamond-ATR, neat) $\tilde{\nu}_{\text{max}}$: 2985, 2240, 1486, 1449, 1406, 1085, 1005, 836, 762, 726, 689.

Melting Point (°C): 83 – 84.

HRMS (DART) calc. C₁₅H₁₇N₂ [M+NH₄]⁺: 225.1392. Found: 225.1384

Specific Rotation [α]_D²³: + 7.3 (c 1.0, CHCl₃).

Chiral SFC: Chiralcel AD-H (scCO₂/IPA = 95/5 to 90/10 over 12 min, 2.5 mL/min, 210–400 nm, 45 °C), 7.02 and 7.96 min.



3c

(*R*)-2-(*o*-tolyl)propanenitrile (**3c**)

Prepared according to **General Procedure A** using 1-methyl-2-vinylbenzene (**1c**) (59.0 mg, 0.50 mmol, 1.00 equiv), 4-bromo-5-methyl-2-phenyloxazole (**2a**) (154.7 mg, 0.65 mmol, 1.3 equiv) and dioctyl but-2-ynedioate (**7b**) (592.3 mg, 1.75 mmol, 3.5 equiv). NMR yield was determined by ¹H NMR spectroscopy of the crude reaction mixture, using 1,1,2,2-tetrachloroethane as internal standard. An analytically pure sample of **3c** was purified by preparative TLC (10:1 hexanes:acetone) (1st run: 98%, 96:4 er; 2nd run: 93%, 96:4 er) and isolated as a colorless oil.

Note: **3c** was volatile under high vacuum (ca. 100 mtorr)

TLC (10% acetone in hexanes): *R*_f = 0.57 (weak UV, I₂ + CAM).

¹H NMR (CDCl₃, 400 MHz): δ 7.46 (dd, *J* = 7.2, 1.9 Hz, 1H), 7.26–7.17 (m, 3H), 4.04 (q, *J* = 7.2 Hz, 1H), 2.37 (s, 3H), 1.62 (d, *J* = 7.2 Hz, 3H).

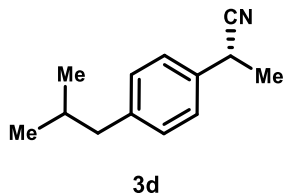
¹³C NMR (CDCl₃, 101 MHz): δ 135.4, 134.9, 131.1, 128.3, 127.1, 126.9, 121.9, 28.3, 20.2, 19.1.

IR (Diamond-ATR, neat) $\tilde{\nu}_{\text{max}}$: 2985, 2933, 2872, 2239, 1609, 1498, 1460, 1385, 1290, 1087

HRMS (DART) calc. $C_{10}H_{12}N$ $[M+H]^+$: 146.0970. Found: 146.0971

Specific Rotation $[\alpha]^{23}_D$: + 6.7 (c 0.55, $CHCl_3$).

Chiral HPLC (AD-H, 210 nm, hexane:IPA 99.2:0.8, 1 mL/min, 7.9 and 8.2 min).



(R)-2-(4-isobutylphenyl)propanenitrile (3d)

Prepared according to **General Procedure A** using 1-isobutyl-4-vinylbenzene (**1d**) (80.1 mg, 0.50 mmol, 1.00 equiv), 4-bromo-5-methyl-2-phenyloxazole (**2a**) (154.7 mg, 0.65 mmol, 1.3 equiv) and dioctyl but-2-ynedioate (**7b**) (592.3 mg, 1.75 mmol, 3.5 equiv). The residue was purified by flash column chromatography on silica gel (gradient elution: 100% hexane to 25% CH_2Cl_2 in hexane) to yield **3d** (1st run: 69.3 mg, 74%, 99:1 er; 2nd run: 62.8 mg, 67%, 99:1 er) as a colorless oil.

TLC (30% CH_2Cl_2 in hexanes): R_f = 0.34 (weak UV, I_2 + CAM).

1H NMR ($CDCl_3$, 400 MHz): δ 7.25 (d, J = 7.9 Hz, 2H), 7.15 (d, J = 7.9 Hz, 2H), 3.87 (q, J = 7.3 Hz, 1H), 2.47 (d, J = 7.2 Hz, 2H), 1.91–1.81 (m, 1H), 1.63 (d, J = 7.3 Hz, 3H), 0.90 (d, J = 6.6 Hz, 7H).

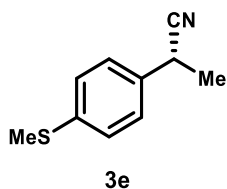
^{13}C NMR ($CDCl_3$, 101 MHz): δ 141.8, 134.4, 129.9, 126.6, 121.9, 45.1, 31.0, 30.3, 22.4, 21.6.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2955, 2925, 2240, 1512, 1565, 1366, 1167, 1086, 844, 796.

HRMS (DART) calc. $C_{13}H_{18}N$ $[M+H]^+$: 188.1434. Found: 188.1427

Specific Rotation $[\alpha]^{23}_D$: + 7.79 (c 1.0, $CHCl_3$).¹⁴

Chiral SFC: Chiralcel AD-H (scCO₂/IPA = 95/5 to 90/10, 2.5 mL/min, 210–400 nm, 45 °C), 2.39 and 2.67 min.



(R)-2-(4-(methylthio)phenyl)propanenitrile (3e)

Prepared according to **General Procedure A** using methyl(4-vinylphenyl)sulfane (**1e**) (75.1 mg, 0.50 mmol, 1.0 equiv), 4-bromo-5-methyl-2-phenyloxazole (**2a**) (154.7 mg, 0.65 mmol, 1.3 equiv) and diethyl acetylenedicarboxylate (**7a**) (280.0 μ L, 1.75 mmol, 3.5 equiv). The residue was

purified by flash column chromatography on silica gel (hexane:acetone 50:1, 4 cm diameter x 17.5 cm height of silica) to yield **3e** (1st run: 65.0 mg, 73%, 85:15 er; 2nd run: 67.3 mg, 74%, 85:15 er) as colorless solid.

When **3e** was purified by preparative TLC on silica gel (hexane:acetone 10:1), it was isolated with 96:4 er (0.5 mmol scale).

TLC (hexane:acetone 10:1): R_f = 0.45 (UV).

¹H NMR (CDCl₃, 400 MHz): δ 7.26 (m, 4H), 3.86 (q, J = 7.3 Hz, 1H), 2.48 (s, 3H), 1.62 (d, J = 7.3 Hz, 3H).

¹³C NMR (CDCl₃, 101 MHz): δ 138.9, 133.8, 127.3, 127.2, 121.6, 30.9, 21.5, 15.8.

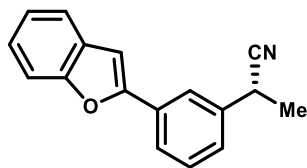
IR (Diamond-ATR, neat) $\tilde{\nu}_{\text{max}}$: 2238, 1492, 1434, 1096, 1014, 956, 814, 718.

Melting Point (°C): 91 – 92.

EA: calc. for C₁₀H₁₁NS: C, 67.76; H, 6.26. Found: C, 66.75; H, 6.32.

Specific Rotation [α]_D²³: + 14.13 (c 1.0, CHCl₃).

Chiral SFC: Chiralcel OD-H (scCO₂/IPA = 99/1 to 98/2 over 16 min, 2.5 mL/min, 210–400 nm, 45 °C), 8.70 and 9.00 min.



3f

(R)-2-(3-(benzofuran-2-yl)phenyl)propanenitrile (3f)

Prepared according to **General Procedure A** using 2-(3-vinylphenyl)benzofuran (**1f**) (110.1 mg, 0.50 mmol, 1.00 equiv), 4-bromo-5-methyl-2-phenyloxazole (**2a**) (154.7 mg, 0.65 mmol, 1.3 equiv) and dioctyl but-2-ynedioate (**7b**) (592.3 mg, 1.75 mmol, 3.5 equiv). The residue was purified by flash column chromatography on silica gel (pentane:acetone 50:1) to yield **3f** (1st run: 83.0 mg, 67%, 82:18 er; 2nd run: 90.0 mg, 73%, 87:13 er) as a colorless solid.

TLC (pentane:acetone 10:1): R_f = 0.45 (UV).

¹H NMR (CDCl₃, 400 MHz): δ 7.86 (t, J = 1.8 Hz, 1H), 7.82 (dt, J = 7.8, 1.4 Hz, 1H), 7.60 (dd, J = 7.3, 1.3 Hz, 1H), 7.54 (d, J = 8.1 Hz, 1H), 7.48 (t, J = 7.7 Hz, 1H), 7.37–7.29 (m, 2H), 7.27–7.23 (m, 1H), 7.08 (s, 1H), 3.97 (q, J = 7.3 Hz, 1H), 1.72 (d, J = 7.3 Hz, 3H).

¹³C NMR (CDCl₃, 101 MHz): δ 155.1, 137.9, 131.6, 129.8, 129.1, 126.8, 124.8, 124.7, 123.2, 121.5, 121.2, 111.4, 102.3, 31.5, 21.6.

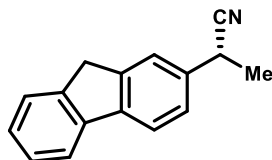
IR (Diamond-ATR, neat) $\tilde{\nu}_{\text{max}}$: 2924, 2242, 1484, 1450, 1257, 1214, 1108, 1042, 792, 749.

Melting Point (°C): 88 – 89.

HRMS (DART) calc. C₁₇H₁₄NO [M+H]⁺: 248.1070. Found: 248.1074.

Specific Rotation [α]_D²³: + 21.4 (c 1.0, CHCl₃).

Chiral SFC: Chiralcel OD-H (scCO₂/IPA = 95/5 to 80/20, 2.5 mL/min, 210-400 nm, 45 °C), 6.68 and 6.94 min.



3g

(R)-2-(9H-fluoren-2-yl)propanenitrile (3g)

Prepared according to **General Procedure A** using 2-vinyl-9H-fluorene (**1g**) (96.1 mg, 0.50 mmol, 1.00 equiv), 4-bromo-5-methyl-2-phenyloxazole (**2a**) (154.7 mg, 0.65 mmol, 1.3 equiv) and dioctyl but-2-ynedioate (**7b**) (592.3 mg, 1.75 mmol, 3.5 equiv). The residue was purified by flash column chromatography on silica gel (hexane:acetone 40:1) to yield **3g** (1st run: 74.6 mg, 68%, 92:8 er; 2nd run: 82.2 mg, 75%, 95:5 er) as a colorless solid.

TLC (hexane:acetone 10:1): *R*_f = 0.40 (UV).

¹H NMR (CDCl₃, 400 MHz): δ 7.80–7.76 (m, 2H), 7.56 (ddt, *J* = 4.2, 2.1, 1.1 Hz, 2H), 7.41–7.31 (m, 3H), 3.98 (q, *J* = 7.3 Hz, 1H), 3.92 (s, 2H), 1.70 (d, *J* = 7.3 Hz, 3H).

¹³C NMR (CDCl₃, 101 MHz): δ 144.4, 143.4, 141.9, 141.0, 135.6, 127.2, 127.0, 125.6, 125.3, 123.6, 122.0, 120.5, 120.2, 37.0, 31.5, 21.9.

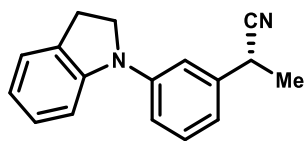
IR (Diamond-ATR, neat) $\tilde{\nu}_{\text{max}}$: 2981, 2925, 2238, 1732, 1455, 1083, 833, 769, 736.

Melting Point (°C): 118 – 119.

HRMS (DART) calc. C₁₆H₁₄N [M+H]⁺: 220.1121. Found: 220.1118.

Specific Rotation [α]_D²³: + 16.9 (c 1.0, CHCl₃).¹⁴

Chiral SFC: Chiralcel OJ-H (scCO₂/IPA = 95/5 to 60/40, 2.5 mL/min, 210-400 nm, 45 °C), 5.45 and 5.72 min.



3h

(R)-2-(3-(indolin-1-yl)phenyl)propanenitrile (3h)

Prepared according to **General Procedure A** using 1-(3-vinylphenyl)indoline (**1h**) (110.6 mg, 0.50 mmol, 1.00 equiv), 4-bromo-5-methyl-2-phenyloxazole (**2a**) (178.5 mg, 0.75 mmol, 1.5 equiv) and dioctyl but-2-ynedioate (**7b**) (592.3 mg, 1.75 mmol, 3.5 equiv). The residue was purified by flash column chromatography on silica gel (hexane:acetone 40:1) to yield **3h** (1st run: 94.1 mg, 76%, 97:3 er; 2nd run: 83.0 mg, 67%, 97:3 er) as a pale-yellow oil.

TLC (hexane:acetone 10:1): R_f = 0.45 (UV, I_2).

^1H NMR (CDCl_3 , 400 MHz): δ 7.34 (t, J = 7.8 Hz, 1H), 7.21–7.07 (m, 5H), 6.92 (dt, J = 7.5, 1.3 Hz, 1H), 6.78 (td, J = 7.3, 1.2 Hz, 1H), 3.98 (t, J = 8.4 Hz, 2H), 3.89 (q, J = 7.3 Hz, 1H), 3.15 (t, J = 8.4 Hz, 2H), 1.67 (d, J = 7.3 Hz, 3H).

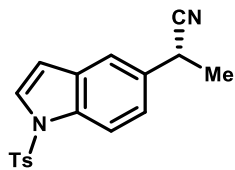
^{13}C NMR (CDCl_3 , 101 MHz): δ 146.5, 145.0, 138.3, 131.5, 130.1, 127.3, 125.3, 121.8, 119.5, 118.9, 117.0, 115.5, 108.5, 52.2, 31.6, 28.2, 21.6.

IR (Diamond-ATR, neat) $\tilde{\nu}_{\text{max}}$: 2926, 2240, 1732, 1591, 1482, 1337, 1228, 995, 741, 696.

EA calc. for $\text{C}_{17}\text{H}_{16}\text{N}_2$: C, 82.22; H, 6.49. Found: C, 82.23; H, 6.61.

Specific Rotation $[\alpha]_{\text{D}}^{23}$: + 16.9 (c 1.0, CHCl_3).

Chiral SFC: Chiralcel OJ-H (scCO_2/IPA = 95/5 to 80/20, 2.5 mL/min, 210–400 nm, 45 °C), 6.56 and 6.84 min.



3i

(R)-2-(1-tosyl-1H-indol-5-yl)propanenitrile (3i)

Prepared according to **General Procedure A** using 1-tosyl-5-vinyl-1H-indole (**1i**) (148.6 mg, 0.50 mmol, 1.00 equiv), 4-bromo-5-methyl-2-phenyloxazole (**2a**) (178.5 mg, 0.75 mmol, 1.5 equiv) and diethyl but-2-ynedioate (**7a**) (298 mg, 1.75 mmol, 3.5 equiv). The residue was purified by preparative TLC on silica gel (20% acetone in hexane, 5 plates) to yield **3i** (1st run: 74.9 mg, 46%, 98:2 er; 2nd run: 75.2 mg, 46%, 98:2 er) as a pale-yellow oil.

TLC (15% acetone in hexanes): R_f = 0.15 (UV).

^1H NMR (CDCl_3 , 400 MHz): δ 7.98 (d, J = 8.6 Hz, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 3.7 Hz, 1H), 7.53 (d, J = 1.9 Hz, 1H), 7.28–7.22 (m, 3H), 6.64 (d, J = 3.6 Hz, 1H), 3.95 (q, J = 7.3 Hz, 1H), 2.35 (s, 3H), 1.65 (d, J = 7.3 Hz, 3H).

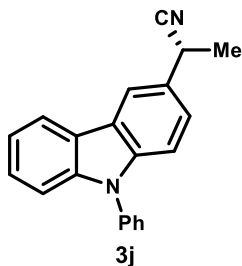
^{13}C NMR (CDCl_3 , 101 MHz): δ 145.3, 135.3, 134.4, 132.3, 131.4, 130.1, 127.5, 127.0, 123.4, 121.9, 119.7, 114.3, 108.9, 31.3, 21.9, 21.7.

IR (Diamond-ATR, neat) $\tilde{\nu}_{\text{max}}$: 2985, 2240, 1595, 1461, 1369, 1270, 1172, 1129, 995, 812, 674, 609.

HRMS (DART) calc. $\text{C}_{18}\text{H}_{17}\text{N}_2\text{O}_2\text{S}$ $[\text{M}+\text{H}]^+$: 325.1005. Found: 325.0098.

Specific Rotation $[\alpha]^{23}_{\text{D}}$: – 4.5 (c 1.0, CHCl_3).

Chiral SFC: Chiralcel OJ-H (scCO_2/IPA = 95/5 to 60/40, 2.5 mL/min, 210–400 nm, 45 °C), 5.76 and 5.89 min.



(R)-2-(9-phenyl-9H-carbazol-3-yl)propanenitrile (3j)

Prepared according to **General Procedure A** using 9-phenyl-3-vinyl-9H-carbazole (**1j**) (134.6 mg, 0.50 mmol, 1.00 equiv), 4-bromo-5-methyl-2-phenyloxazole (**2a**) (154.7 mg, 0.65 mmol, 1.3 equiv) and dioctyl but-2-ynedioate (**7b**) (592.3 mg, 1.75 mmol, 3.5 equiv). The residue was purified by flash column chromatography on silica gel (hexane:acetone 40:1) to yield **3j** (1st run: 74.0 mg, 50%, 99:1 er; 2nd run: 82.1 mg, 55%, 98:2 er) as a thick yellow oil.

Note: freshly prepared **1j** was used when conducting this reaction.

TLC (hexane:acetone 10:1): R_f = 0.3 (UV, I_2).

^1H NMR (CDCl_3 , 400 MHz): δ 8.17 (d, J = 7.8 Hz, 1H), 8.14 (d, J = 1.7 Hz, 1H), 7.64–7.60 (m, 2H), 7.57–7.53 (m, 2H), 7.49 (dt, J = 8.0, 1.4 Hz, 1H), 7.46–7.35 (m, 4H), 7.32 (dddd, J = 8.0, 6.4, 1.7, 1.7 Hz, 1H), 4.11 (q, J = 7.3 Hz, 1H), 1.76 (d, J = 7.3 Hz, 3H).

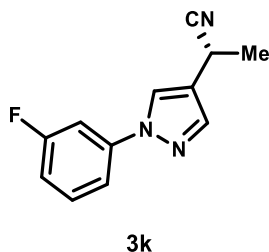
^{13}C NMR (CDCl_3 , 101 MHz): δ 141.5, 140.5, 137.5, 130.1, 128.8, 127.8, 127.2, 126.6, 124.6, 123.9, 122.9, 122.4, 120.5, 120.4, 118.6, 110.5, 110.1, 31.5, 22.3.

IR (Diamond-ATR, neat) $\tilde{\nu}_{\text{max}}$: 2928, 2854, 2239, 1732, 1597, 1501, 1451, 1263, 568.

HRMS (DART) calc. $\text{C}_{21}\text{H}_{17}\text{N}_2$ $[\text{M}+\text{H}]^+$: 297.1386. Found: 297.1379.

Specific Rotation $[\alpha]^{23}_{\text{D}}$: + 20.4 (c 1.0, CHCl_3).

Chiral SFC: Chiralcel OJ-H (scCO₂/IPA = 98/2 to 60/40, 2.5 mL/min, 210-400 nm, 45 °C), 5.77 and 5.94 min.



(R)-2-(1-(3-fluorophenyl)-1H-pyrazol-4-yl)propanenitrile (3k)

Prepared according to **General Procedure A** using 1-(3-fluorophenyl)-4-vinyl-1H-pyrazole (**1k**) (94.1 mg, 0.50 mmol, 1.00 equiv), 4-bromo-5-methyl-2-phenyloxazole (**2a**) (154.7 mg, 0.65 mmol, 1.3 equiv) and di-octyl but-2-ynedioate (**7b**) (592.3 mg, 1.75 mmol, 3.5 equiv). The residue was purified by flash column chromatography on silica gel (gradient elution: 100% hexane to 10% acetone in hexane) to yield **3k** (1st run: 81.8 mg, 76%, 97:3 er; 2nd run: 74.9 mg, 70%, 97:3 er) as a yellow oil.

Note: freshly prepared **1k** was used when conducting this reaction.

TLC (15% acetone in hexanes): R_f = 0.28 (UV, I₂).

¹H NMR (CDCl₃, 500 MHz): δ 7.93 (s, 1H), 7.68 (s, 1H), 7.48–7.40 (m, 3H), 7.05–6.99 (m, 1H), 3.96 (q, J = 7.3 Hz, 1H), 1.70 (d, J = 7.3 Hz, 3H).

¹³C NMR (CDCl₃, 126 MHz): δ 163.4 (d, J = 247.2 Hz), 141.2 (d, J = 8.0 Hz), 139.5, 131.0 (d, J = 9.1 Hz), 125.1, 121.3, 120.5, 114.4 (d, J = 3.2 Hz), 113.9 (d, J = 21.4 Hz), 107.1 (d, J = 26.5 Hz), 21.9, 20.4. The observed complexity is due to C-F scalar couplings.

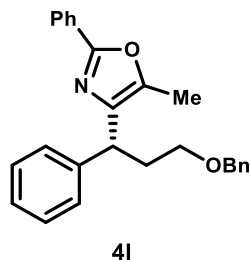
¹⁹F NMR (CDCl₃, 471 MHz): δ – 110.5.

IR (Diamond-ATR, neat) $\tilde{\nu}_{\text{max}}$: 2985, 2245, 1722, 1612, 1601, 1497, 1397, 1257, 1151, 969, 865, 771, 677.

HRMS (ESI) calc. C₁₂H₁₁FN₃ [M+H]⁺: 216.0931. Found: 216.0932

Specific Rotation [α]_D²³: + 1.88 (c 1.0, CHCl₃).

Chiral SFC: CEL2 (scCO₂/IPA = 99/1 to 95/5, 2.5 mL/min, 210-400 nm, 45 °C), 4.33 and 4.60 min.



(R)-4-(3-(benzyloxy)-1-phenylpropyl)-5-methyl-2-phenyloxazole (4I)

Prepared according to **General Procedure A** using (*E*)-(3-(benzyloxy)prop-1-en-1-yl)benzene (**1I**) (112.1 mg, 0.50 mmol, 1.0 equiv) and 4-bromo-5-methyl-2-phenyloxazole (**2a**) (178.5 mg, 0.75 mmol, 1.5 equiv). After the standard workup the residue was purified by flash column chromatography on silica gel (hexane:acetone 25:1) to yield **4I** (1st run: 160.0 mg, 85%; 2nd run: 150.5 mg, 80%) as a yellow oil.

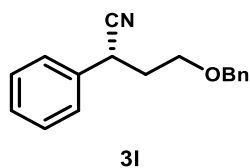
TLC (hexane:acetone 10:1): R_f = 0.5 (UV).

¹H NMR (CDCl₃, 400 MHz): δ 8.03 (dd, J = 8.0, 1.8 Hz, 2H), 7.51–7.39 (m, 5H), 7.38–7.30 (m, 7H), 7.25–7.21 (m, 1H), 4.49 (s, 2H), 4.14 (dd, J = 8.6, 7.0 Hz, 1H), 3.48 (dd, J = 6.8, 5.3 Hz, 2H), 2.53 (ddt, J = 14.3, 8.7, 5.7 Hz, 1H), 2.42–2.33 (m, 1H), 2.30 (s, 3H).

¹³C NMR (CDCl₃, 101 MHz): δ 159.3, 144.0, 143.8, 138.7, 137.9, 129.7, 128.7, 128.5, 128.4, 128.3, 128.1, 127.8, 127.6, 126.4, 126.1, 73.0, 68.2, 38.6, 35.5, 10.4.

IR (Diamond-ATR, neat) $\tilde{\nu}_{\text{max}}$: 2855, 1632, 1553, 1487, 1066, 948, 734, 691.

HRMS (DART) calc. C₂₆H₂₆NO₂ [M+H]⁺: 384.1958. Found: 384.1961



(R)-4-(benzyloxy)-2-phenylbutanenitrile (3I)

To an oven dried reaction tube (Fisherbrand, 13x100 mm, 1495935C) equipped with a magnetic stir bar was added toluene (0.125 mL, 3.3 M), alkyne **7b** (592.3 mg, 1.75 mmol, 4.2 equiv) and oxazole **4I** (160.0 mg, 0.41 mmol, 1.0 equiv). The reaction tube was flushed with N₂, sealed with a screw cap containing a Teflon septum and moved to a preheated 110 °C oil bath. After the reaction mixture had stirred for 8 h at 110 °C, the reaction vessel was removed from the oil bath and allowed to cool to room temperature. The crude reaction mixture was purified by flash column chromatography on silica gel (hexane:acetone 30:1) to yield **3I** (1st run: 94.1 mg, 75% over two steps, 99:1 er; 2nd run: 87.2 mg, 70% over two steps, 99:1 er) as a thick yellow oil.

TLC (hexane:acetone 10:1): R_f = 0.45 (weak UV, I₂).

Supporting Information

¹H NMR (CDCl₃, 400 MHz): δ 7.41–7.30 (m, 10H), 4.56 (d, *J* = 11.8 Hz, 1H), 4.51 (d, *J* = 11.8 Hz, 1H), 4.10 (dd, *J* = 8.7, 6.9 Hz, 1H), 3.66 (ddd, *J* = 9.8, 7.8, 4.4 Hz, 1H), 3.50 (ddd, *J* = 9.8, 6.1, 4.7 Hz, 1H), 2.27–2.09 (m, 2H).

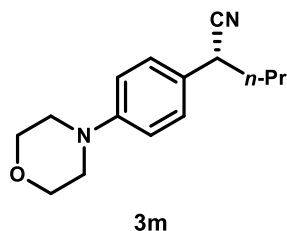
¹³C NMR (CDCl₃, 101 MHz): δ 138.0, 135.6, 129.2, 128.6, 128.2, 128.0, 127.9, 127.6, 120.9, 73.5, 66.4, 36.2, 34.0.

IR (Diamond-ATR, neat) $\tilde{\nu}_{\text{max}}$: 2861, 2239, 1453, 1104, 1364, 1072, 736, 714.

HRMS (ESI) calc. C₁₇H₂₁N₂O [M+NH₄]⁺: 269.1648. Found: 269.1647.

Specific Rotation [α]_D²³: + 6.7 (c 1.0, CHCl₃).

Chiral SFC: Chiralcel OJ-H (scCO₂/IPA = 95/5 to 80/20, 2.5 mL/min, 210–400 nm, 45 °C), 5.12 and 5.72 min.



(*R*)-2-(4-morpholinophenyl)pentanenitrile (**3m**)

Prepared according to a variation of **General Procedure A** (24 h long stirring at 45 °C) using 4-(4-(but-1-en-1-yl)phenyl)morpholine (**1m**) (108.6 mg, 0.50 mmol, 1.00 equiv) as a 1:10 *Z:E* mixture, 4-bromo-5-methyl-2-phenyloxazole (**2a**) (178.5 mg, 0.75 mmol, 1.5 equiv) and diethyl but-2-ynedioate (**7a**) (297.7 mg, 1.75 mmol, 3.5 equiv). The residue was purified by flash column chromatography on silica gel (hexane:acetone 20:1) to yield **3m** (1st run: 74.1 mg, 61%, 99:1 er; 2nd run: 76.4 mg, 62%, 99:1 er) as a solid.

TLC (hexane:acetone 10:1): *R*_f = 0.4 (UV, I₂).

¹H NMR (CDCl₃, 400 MHz): δ 7.22 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.2 Hz, 2H), 3.87–3.85 (m, 4H), 3.71 (dd, *J* = 8.5, 6.4 Hz, 1H), 3.17–3.15 (m, 4H), 1.94–1.75 (m, 2H), 1.55–1.41 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H).

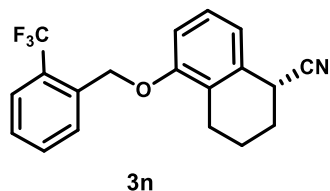
¹³C NMR (CDCl₃, 101 MHz): δ 151.0, 128.2, 127.2, 121.4, 116.0, 67.0, 49.2, 38.0, 36.4, 20.4, 13.6.

IR (Diamond-ATR, neat) $\tilde{\nu}_{\text{max}}$: 2957, 2855, 2235, 1611, 1515, 1449, 1231, 1120, 925, 822.

EA calc. for C₁₅H₂₀N₂O: C, 73.74; H, 8.25. Found: C, 72.76; H, 8.56.

Specific Rotation [α]_D²³: −1.1 (c 1.0, CHCl₃).

Chiral SFC: Chiralcel OJ-H (scCO₂/IPA = 95/5 to 80/20, 2.5 mL/min, 210–400 nm, 45 °C), 4.60 and 5.38 min.



(R)-5-((2-(trifluoromethyl)benzyl)oxy)-1,2,3,4-tetrahydronaphthalene-1-carbonitrile (3n)

Prepared according to **General Procedure A** using 8-((2-(trifluoromethyl)benzyl)oxy)-1,2-dihydronaphthalene (**1n**) (152.0 mg, 0.50 mmol, 1.0 equiv), 4-bromo-5-methyl-2-phenyloxazole (**2a**) (154.7 mg, 0.65 mmol, 1.3 equiv) and dioctyl but-2-ynedioate (**7b**) (592.3 mg, 1.75 mmol, 3.5 equiv). The residue was purified by flash column chromatography on silica gel (pentane:acetone 40:1) to yield **3n** (1st run: 50.0 mg, 30%, 89:11 er; 2nd run: 63.1 mg, 38%, 89:11 er) as a pale yellow oil.

TLC (pentane:acetone 10:1): R_f = 0.3 (UV).

¹H NMR (CDCl₃, 400 MHz): δ 7.72 (t, J = 8.3 Hz, 2H), 7.59 (t, J = 7.4 Hz, 1H), 7.44 (t, J = 7.6 Hz, 1H), 7.18 (t, J = 8.0 Hz, 1H), 7.02 (d, J = 7.8 Hz, 1H), 6.80 (d, J = 8.2 Hz, 1H), 5.28 (s, 2H), 3.99 (t, J = 6.0 Hz, 1H), 2.90–2.73 (m, 2H), 2.16–2.00 (m, 3H), 1.88 (ddd, J = 10.7, 9.1, 5.4 Hz, 1H).

¹³C NMR (CDCl₃, 101 MHz): δ 156.3, 135.7, 132.3, 131.4, 128.4, 127.9, 127.6, 127.2, 127.1, 126.1 (q, J = 5.7 Hz), 126.0, 125.8, 123.1, 121.8, 121.5, 110.5, 66.2 (q, J = 3.2 Hz), 31.1, 27.0, 22.7, 20.4. The observed complexity is due to C-F scalar couplings.

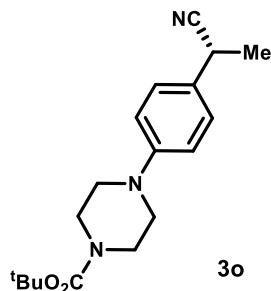
¹⁹F NMR (CDCl₃, 376 MHz): δ – 60.4.

IR (Diamond-ATR, neat) $\tilde{\nu}_{\text{max}}$: 2929, 2237, 1586, 1313, 1261, 1118, 1037, 768, 731.

HRMS (DART) calc. C₁₉H₁₇F₃NO [M+H]⁺: 332.1257. Found: 332.1255.

Specific Rotation [α]_D²³: + 1.5 (c 1.0, CHCl₃).

Chiral SFC: Chiralcel OJ-H (scCO₂/IPA = 95/5 to 90/10, 2.5 mL/min, 210–400 nm, 45 °C), 4.17 and 4.47 min.



tert-butyl (R)-4-(4-(1-cyanoethyl)phenyl)piperazine-1-carboxylate (3o)

Prepared according to **General Procedure A** using tert-butyl 4-(4-vinylphenyl)piperazine-1-carboxylate (**1o**) (144.1 mg, 0.50 mmol, 1.0 equiv), 4-bromo-5-methyl-2-phenyloxazole (**2a**) (154.7 mg, 0.65 mmol, 1.3 equiv) and dioctyl but-2-ynedioate (**7b**) (592.3 mg, 1.75 mmol, 3.5 equiv). The residue was purified by flash column chromatography on silica gel (gradient elution: 20:1 hexane:acetone to 10:1 hexane:acetone) to yield **3o** (1st run: 95.9 mg, 61%, 92:8 er; 2nd run: 103.5 mg, 66%, 99:1 er) as a brown solid.

TLC (15% EtOAc in hexanes): R_f = 0.21 (UV, I_2).

¹H NMR (CDCl₃, 500 MHz): δ 7.24 (d, J = 8.7 Hz, 2H), 6.91 (d, J = 8.7 Hz, 2H), 3.83 (q, J = 7.3 Hz, 1H), 3.59–3.56 (m, 4H), 3.15–3.12 (m, 4H), 1.61 (d, J = 7.3 Hz, 3H), 1.48 (s, 9H).

¹³C NMR (CDCl₃, 126 MHz): δ 154.8, 151.1, 128.4, 127.7, 122.0, 116.9, 80.1, 49.2, 30.6, 28.6, 21.5.

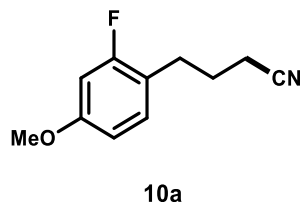
IR (Diamond-ATR, neat) $\tilde{\nu}_{\text{max}}$: 2927, 2250, 1689, 1453, 1230, 1161, 1123, 825, 769.

Melting Point (°C): 110 – 111.

HRMS (ESI) calc. C₁₈H₂₆N₃O₂ [M+H]⁺: 316.2020. Found: 316.2021

Specific Rotation [α]_D²³: + 5.0 (c 1.0, CHCl₃).

Chiral SFC: Chiralpak AD-H (scCO₂/IPA = 95/5 to 80/20, 2.5 mL/min, 210–400 nm, 45 °C), 6.53 and 6.66 min.



4-(2-fluoro-4-methoxyphenyl)butanenitrile (10a)

Prepared according to **General Procedure A** using 1-allyl-2-fluoro-4-methoxybenzene (**9a**) (83.1 mg, 0.50 mmol, 1.00 equiv), 4-bromo-5-methyl-2-phenyloxazole (**2a**) (178.6 mg, 0.75 mmol, 1.5 equiv) and dioctyl but-2-ynedioate (**7b**) (592 mg, 1.75 mmol, 3.5 equiv). The residue

was purified by flash column chromatography on silica gel (hexane:acetone 30:1) to yield **10a** (1st run: 70.6 mg, 72%; 2nd run: 75.1 mg, 78%) as a yellow oil.

TLC (hexane:acetone 30:1): R_f = 0.3 (weak UV, I_2).

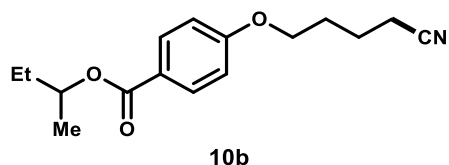
^1H NMR (CDCl_3 , 400 MHz): δ 7.08 (t, J = 8.5 Hz, 1H), 6.66–6.59 (m, 2H), 3.78 (s, 3H), 2.74 (t, J = 7.2 Hz, 2H), 2.32 (t, J = 7.2 Hz, 2H), 1.95 (p, J = 7.2 Hz, 2H).

^{13}C NMR (CDCl_3 , 101 MHz): δ 161.8 (d, J = 244.9 Hz), 159.8 (d, J = 11.0 Hz), 131.1 (d, J = 6.8 Hz), 119.6, 118.6 (d, J = 16.5 Hz), 110.0 (d, J = 3.2 Hz), 102.1 (d, J = 25.7 Hz), 55.7, 27.6 (d, J = 1.9 Hz), 26.0 (d, J = 1.5 Hz), 16.6. The observed complexity is due to C-F scalar couplings.

^{19}F NMR (CDCl_3 , 376 MHz): δ – 116.4.

IR (Diamond-ATR, neat) $\tilde{\nu}_{\text{max}}$: 2929, 2245, 1736, 1625, 1583, 1444, 1148, 1111, 1030, 948, 834.

HRMS (DART) calc. $\text{C}_{11}\text{H}_{13}\text{FNO}$ $[\text{M}+\text{H}]^+$: 194.0976. Found: 194.0980.



sec-butyl 4-(4-cyanobutoxy)benzoate (**10b**)

Prepared according to **General Procedure A** using sec-butyl 4-(but-3-en-1-yloxy)benzoate (**9b**) (124.2 mg, 0.50 mmol, 1.00 equiv), 4-bromo-5-methyl-2-phenyloxazole (**2a**) (178.6 mg, 0.75 mmol, 1.5 equiv) and dioctyl but-2-ynedioate (**7b**) (592 mg, 1.75 mmol, 3.5 equiv). The residue was purified by flash column chromatography on silica gel (10% acetone in pentane) to yield **10b** (1st run: 99.1 mg, 72%; 2nd run: 102.3 mg, 74%) as a thick pale-yellow oil.

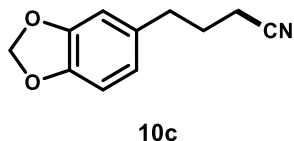
TLC (10% acetone in pentane): R_f = 0.3 (UV).

^1H NMR (CDCl_3 , 400 MHz): δ 7.99 (dt, J = 8.9, 4.0 Hz, 2H), 6.89 (dt, J = 8.9, 4.0 Hz, 1H), 5.07 (h, J = 6.3 Hz, 1H), 4.06 (t, J = 5.7 Hz, 2H), 2.45 (t, J = 6.9 Hz, 2H), 2.03–1.94 (m, 2H), 1.94–1.86 (m, 2H), 1.77–1.63 (m, 2H), 1.32 (d, J = 6.2 Hz, 3H), 0.96 (t, J = 7.4 Hz, 3H).

^{13}C NMR (CDCl_3 , 101 MHz): δ 166.1, 162.4, 131.7, 123.7, 119.5, 114.0, 72.6, 66.9, 29.1, 28.2, 22.5, 19.7, 17.2, 9.9.

IR (Diamond-ATR, neat) $\tilde{\nu}_{\text{max}}$: 2969, 2876, 2245, 1703, 1605, 1580, 1509, 1247, 1166, 1100, 847, 770.

HRMS (DART) calc. $\text{C}_{16}\text{H}_{22}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 276.1594. Found: 276.1593.

**4-(benzo[d][1,3]dioxol-5-yl)butanenitrile (10c)**

Prepared according to **General Procedure A** using 5-allylbenzo[d][1,3]dioxole (**9c**) (81.0 mg, 0.50 mmol, 1.00 equiv), 4-bromo-5-methyl-2-phenyloxazole (**2a**) (178.6 mg, 0.75 mmol, 1.5 equiv) and dioctyl but-2-ynedioate (**7b**) (592 mg, 1.75 mmol, 3.5 equiv). The residue was purified by flash column chromatography on silica gel (gradient elution: 25:1 hexane:acetone to 20:1 hexane:acetone) to yield **10c** (1st run: 73.2 mg, 77%; 2nd run: 69.1 mg, 73%) as a thick yellow oil.

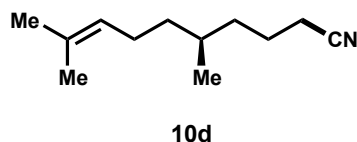
TLC (15% EtOAc in hexanes): R_f = 0.39 (weak UV, I_2).

¹H NMR (CDCl₃, 400 MHz): δ 6.74 (d, J = 7.8 Hz, 1H), 6.67–6.63 (m, 2H), 5.93 (s, 2H), 2.69 (t, J = 7.1 Hz, 2H), 2.31 (t, J = 7.1 Hz, 2H), 1.93 (p, J = 7.1 Hz, 2H).

¹³C NMR (CDCl₃, 101 MHz): δ 148.0, 146.3, 133.5, 121.5, 119.6, 108.9, 108.5, 101.1, 34.2, 27.2, 16.4.

IR (Diamond-ATR, neat) $\tilde{\nu}_{\text{max}}$: 2925, 2855, 2245, 1716, 1503, 1488, 1442, 1037, 808, 731.

HRMS (ESI) calc. C₁₁H₁₂NO₂ [M+H]⁺: 190.0863. Found: 190.0865.

**(R)-5,9-dimethyldec-8-enenitrile (10d)**

Prepared according to **General Procedure A** using (*R*)-4,8-dimethylnona-1,7-diene (**9d**) (76.1 mg, 0.50 mmol, 1.00 equiv), 4-bromo-5-methyl-2-phenyloxazole (**2a**) (178.5 mg, 0.65 mmol, 1.5 equiv) and dioctyl but-2-ynedioate (**7b**) (592.3 mg, 1.75 mmol, 3.5 equiv). NMR yield was determined by ¹H NMR spectroscopy of the crude reaction mixture, using 1,1,2,2-tetrachloroethane as an internal standard. Due to lack of UV activity, an analytically pure sample of **10d** was purified by preparative TLC (20:1 hexane:acetone) (1st run: 79%; 2nd run: 78%) and isolated as a colorless oil.

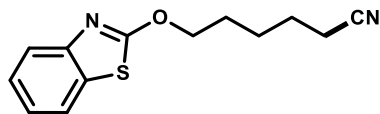
TLC (10% EtOAc in hexanes): R_f = 0.34 (weak UV activity, weak KMnO₄).

¹H NMR (CDCl₃, 500 MHz): δ 5.08 (t, J = 6.7 Hz, 1H), 2.32 (t, J = 7.1 Hz, 2H), 2.04–1.90 (m, 2H), 1.74–1.62 (m, 2H), 1.68 (s, 3H), 1.60 (s, 3H), 1.49–1.42 (m, 2H), 1.36–1.25 (m, 2H), 1.20–1.13 (m, 1H), 0.90 (d, J = 6.2 Hz, 3H).

¹³C NMR (CDCl₃, 126 MHz): δ 131.6, 124.7, 120.0, 36.9, 36.1, 31.9, 25.9, 25.5, 23.2, 19.4, 17.8, 17.6.

IR (Diamond-ATR, neat) $\tilde{\nu}_{\text{max}}$: 2924, 2854, 2361, 2157, 1720, 1451, 1258.

HRMS (DART) calc. C₁₂H₂₂N [M+H]⁺: 180.1747. Found: 180.1735.

**10e****6-(benzo[d]thiazol-2-yloxy)hexanenitrile (10e)**

Prepared according to **General Procedure A** using 2-(pent-4-en-1-yloxy)benzo[d]thiazole (**9e**) (109.7 mg, 0.50 mmol, 1.00 equiv), 4-bromo-5-methyl-2-phenyloxazole (**2a**) (178.6 mg, 0.75 mmol, 1.5 equiv) and dioctyl but-2-ynedioate (**7b**) (592 mg, 1.75 mmol, 3.5 equiv). The residue was purified by flash column chromatography on silica gel (10% acetone in pentane) to yield **10e** (1st run: 90.0 mg, 69%; 2nd run: 85.4 mg, 73%) as a thick pale-yellow oil.

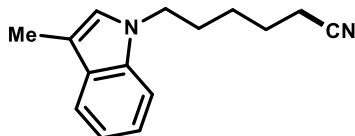
TLC (10% acetone in pentane): R_f = 0.3 (UV).

¹H NMR (CDCl₃, 400 MHz): δ 7.67 (dd, J = 8.1, 1.1 Hz, 1H), 7.63 (dd, J = 8.1, 1.2 Hz, 1H), 7.36 (td, J = 7.7, 1.2 Hz, 1H), 7.22 (td, J = 7.7, 1.2 Hz, 1H), 4.57 (t, J = 6.4 Hz, 2H), 2.37 (t, J = 7.0 Hz, 2H), 1.89 (p, J = 6.6 Hz, 2H), 1.75 (dt, J = 14.1, 6.9 Hz, 2H), 1.68–1.62 (m, 2H).

¹³C NMR (CDCl₃, 101 MHz): δ 172.9, 149.4, 131.9, 126.1, 123.6, 121.4, 120.8, 120.5, 119.6, 71.3, 28.1, 25.2, 17.2.

IR (Diamond-ATR, neat) $\tilde{\nu}_{\text{max}}$: 2937, 2244, 1729, 1532, 1442, 1249, 1216, 1066, 1016, 755, 726.

HRMS (DART) calc. C₁₃H₁₅N₂OS [M+H]⁺: 247.0900. Found: 247.0900.

**10f****5-(3-methyl-1H-indol-1-yl)pentanenitrile (10f)**

Prepared according to a **General Procedure A** using recently synthesized 3-methyl-1-(pent-4-en-1-yl)-1H-indole (**9f**) (99.6 mg, 0.50 mmol, 1.00 equiv), 4-bromo-5-methyl-2-phenyloxazole (**2a**) (178.6 mg, 0.75 mmol, 1.5 equiv) and dioctyl but-2-ynedioate (**7b**) (592 mg, 1.75 mmol, 3.5 equiv). The residue was purified by flash column chromatography on silica gel (gradient elution: 5% to 15% EtOAc in hexane) to yield **10f** (1st run: 81.1 mg, 72%; 2nd run: 82.8 mg, 73%) as a yellow-orange oil.

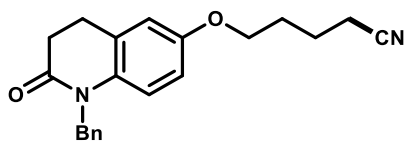
TLC (10% acetone in hexanes): R_f = 0.25 (UV, I₂).

¹H NMR (CDCl₃, 400 MHz): δ 7.58 (d, J = 7.9 Hz, 1H), 7.28 (d, J = 8.2 Hz, 1H), 7.21 (t, J = 7.5 Hz, 1H), 7.11 (t, J = 7.4 Hz, 1H), 6.85 (s, 1H), 4.09 (t, J = 6.9 Hz, 2H), 2.33 (s, 3H), 2.30 (t, J = 7.1 Hz, 2H), 1.85 (dt, J = 14.9, 7.0 Hz, 2H), 1.65 (dt, J = 14.8, 7.2 Hz, 2H), 1.50–1.42 (m, 2H).

¹³C NMR (CDCl₃, 101 MHz): δ 136.3, 128.9, 125.4, 121.5, 119.6, 119.2, 118.7, 110.5, 109.1, 45.8, 29.8, 26.3, 25.2, 17.2, 9.7.

IR (Diamond-ATR, neat) $\tilde{\nu}_{\text{max}}$: 2927, 2856, 2239, 1732, 1481, 1360, 1198, 1012, 736.

HRMS (DART) calc. $\text{C}_{15}\text{H}_{19}\text{N}_2$ $[\text{M}+\text{H}]^+$: 227.1543. Found: 227.1545.



10g

5-((1-benzyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)oxy)pentanenitrile (10g)

Prepared according to a modification of **General Procedure A** using CuOAc -[(*S*)-DTBM-SEGPPOS] (**P1**) (26.0 mg, 0.02 mmol, 4.0 mol%), 1-benzyl-6-(but-3-en-1-yloxy)-3,4-dihydroquinolin-2(1H)-one (**9g**) (153.6 mg, 0.50 mmol, 1.00 equiv), 4-bromo-5-methyl-2-phenyloxazole (**2a**) (178.6 mg, 0.75 mmol, 1.5 equiv) and dioctyl but-2-ynedioate (**7b**) (592 mg, 1.75 mmol, 3.5 equiv). The residue was purified by flash column chromatography on silica gel (gradient elution: 10% to 35% acetone in hexane) to yield **10g** (1st run: 96.1 mg, 56%; 101.3 mg, 2nd run: 61%) as a tan solid.

TLC (30% acetone in hexanes): R_f = 0.28 (UV, I_2).

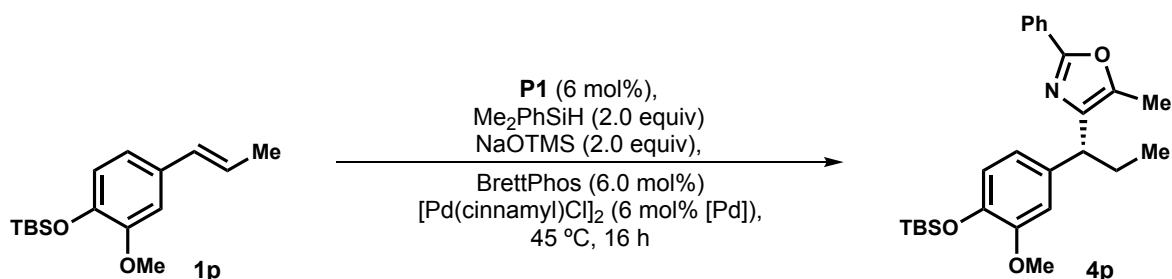
^1H NMR (CDCl_3 , 400 MHz): δ 7.30 (t, J = 7.5 Hz, 2H), 7.24–7.18 (m, 3H), 6.77 (d, J = 8.8 Hz, 1H), 6.72 (d, J = 2.8 Hz, 1H), 6.60 (dd, J = 8.8, 2.9 Hz, 1H), 5.15 (s, 2H), 3.93 (t, J = 5.6 Hz, 2H), 2.94 (dd, J = 8.7, 6.0 Hz, 2H), 2.77 (dd, J = 8.7, 5.9 Hz, 2H), 2.43 (t, J = 6.9 Hz, 2H), 1.94–1.82 (m, 4H).

^{13}C NMR (CDCl_3 , 101 MHz): δ 170.2, 154.5, 137.2, 133.8, 128.9, 128.1, 127.2, 126.5, 119.6, 116.7, 114.6, 112.6, 67.1, 46.3, 32.0, 28.3, 26.0, 22.6, 17.1.

IR (Diamond-ATR, neat) $\tilde{\nu}_{\text{max}}$: 2927, 2856, 2239, 1732, 1481, 1360, 1198, 1012, 736.

Melting Point ($^\circ\text{C}$): 101 – 103.

HRMS (ESI) calc. $\text{C}_{21}\text{H}_{23}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 335.1760. Found: 335.1758



(R)-4-(1-(4-((tert-butyl(dimethyl)silyloxy)-3-methoxyphenyl)propyl)-5-methyl-2-phenyloxazole (4p)

Prepared according to a **General Procedure A** using *tert*-butyl(2-methoxy-4-(prop-1-en-1-yl)phenoxy)dimethylsilane (**1p**) (139.2 mg, 0.50 mmol, 1.00 equiv) as a 1:15 *Z:E* mixture and 4-bromo-5-methyl-2-phenyloxazole (**2a**) (178.6 mg, 0.75 mmol, 1.5 equiv). The residue was purified by flash column chromatography on silica gel (First column chromatography hexane:acetone 10:1; Second column chromatography from hexane:CH₂Cl₂ 10:1 to CH₂Cl₂) to yield **4p** (1st run: 109.6 mg, 50%, 99:1 er; 2nd run: 115.1 mg, 53%, 99:1 er) as a yellow oil.

TLC (hexane:acetone 10:1): *R*_f = 0.80 (UV)

TLC (CH₂Cl₂): *R*_f = 0.65 (UV)

¹H NMR (CDCl₃, 400 MHz): δ 8.01 (dd, *J* = 8.0, 1.7 Hz, 2H), 7.46–7.35 (m, 3H), 6.99 (d, *J* = 2.0 Hz, 1H), 6.80 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.75 (d, *J* = 8.1 Hz, 1H), 3.80 (s, 3H), 3.60 (t, *J* = 7.7 Hz, 1H), 2.23 (s, 3H), 2.19–2.11 (m, 1H), 2.04–1.93 (m, 1H), 0.98 (s, 9H), 0.88 (t, *J* = 7.3 Hz, 3H), 0.14 (s, 6H).

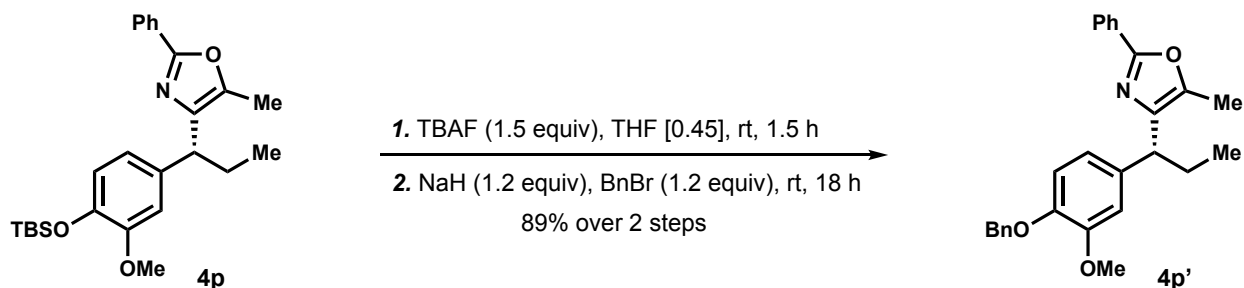
¹³C NMR (CDCl₃, 101 MHz): δ 159.2, 150.8, 143.7, 143.5, 138.7, 137.6, 134.2, 129.6, 128.7, 128.3, 126.1, 120.5, 120.3, 112.3, 55.7, 44.3, 28.9, 25.9, 18.6, 12.8, 10.5, -4.5, -2.2.

IR (Diamond-ATR, neat) $\tilde{\nu}_{\text{max}}$: 2956, 2927, 1488, 1282, 1039, 807, 779, 691.

HRMS (ESI) calc. C₂₆H₃₆NO₃Si [M+H]⁺: 238.2459. Found: 438.2467.

Specific Rotation [α]_D²³: – 91.1 (c 1.0, CHCl₃).

Chiral SFC: Chiralpak AD-H (scCO₂/IPA = 95/5 to 80/20, 2.5 mL/min, 210–400 nm, 45 °C), 4.58 and 5.14 min.



To an oven dried reaction tube (Fisherbrand, 13x100 mm, 1495935C) equipped with a magnetic stir bar was added a solution of oxazole **4p** (80.0 mg, 0.182 mmol, 1.0 equiv) in THF (0.4 mL, 0.45 M) and the reaction vessel was sealed with a Teflon screw cap. To the stirred

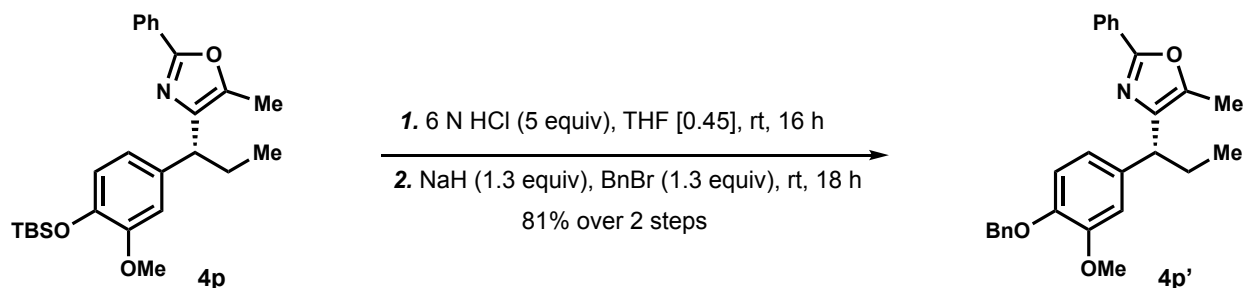
Supporting Information

reaction mixture was added a solution of TBAF (0.27 mL, 0.28 mmol, 1.5 equiv, 1.0 M in THF) at room temperature, which resulted in a yellow reaction mixture.

After the reaction mixture had stirred at room temperature for 1.5 h, the reaction mixture was diluted with water (5 mL) and EtOAc (3 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 3 mL). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuo with the aid of a rotary evaporator. The crude phenol material was used without further purification in the next step.

To an oven dried reaction tube (Fisherbrand, 13x100 mm, 1495935C) equipped with a magnetic stir bar was added a solution of crude phenol in DMF (0.4 mL, 0.45 M). To the stirred reaction mixture was added sodium hydride (5.3 mg, 0.22 mmol, 1.2 equiv) at room temperature. The reaction mixture was allowed to stir for an additional 5 min before benzyl bromide (26 μ L, 0.22 mmol, 1.2 equiv) was added.

After the reaction mixture had stirred at room temperature for 18 h, the reaction mixture was diluted with sat. aq. NH₄Cl (5 mL) and EtOAc (3 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 3 mL). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuo by rotary evaporation. Purification by automated flash column chromatography 10 g silica cartridge (gradient elution: 100% hexane to 25% EtOAc in hexane) yielded **4p'** (67.2 mg, 89% over 2 steps, >99:1 er) as a pale-yellow oil.



To an oven dried reaction tube (Fisherbrand, 13x100 mm, 1495935C) equipped with a magnetic stir bar was added a solution of oxazole **4p** (50.0 mg, 0.11 mmol, 1.0 equiv) in THF (0.4 mL, 0.45 M) and the reaction vessel was sealed with a Teflon screw cap. To the stirred reaction mixture was added aq. 6 M HCl (95 μ L, 0.57 mmol, 5.0 equiv) at room temperature, which resulted in a yellow reaction mixture.

After the reaction mixture had stirred at room temperature for 16 h, the reaction mixture was diluted with water (5 mL) and EtOAc (3 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 3 mL). The combined organic layers were washed with sat. aq. NaHCO₃ (5 mL), brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuo with the aid of a rotary evaporator. The crude phenol material was used without further purification in the next step.

To an oven-dried reaction tube (Fisherbrand, 13x100 mm, 1495935C) equipped with a magnetic stir bar was added a solution of crude phenol in DMF (0.4 mL, 0.45 M). To the stirred reaction mixture was added sodium hydride (3.56 mg, 0.148 mmol, 1.2 equiv) at room

temperature. The reaction mixture was allowed to stir for an additional 5 min before benzyl bromide (17.6 μ L, 0.148 mmol, 1.2 equiv) was added.

After the reaction mixture had stirred at room temperature for 18 h, the reaction mixture was diluted with sat. aq. NH_4Cl (5 mL) and EtOAc (3 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 3 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4 , filtered and concentrated in vacuo with the aid of a rotary evaporator. Purification by automated flash column chromatography 10 g silica cartridge (gradient elution: 100% hexane to 25% EtOAc in hexane) yielded **4p'** (38.8 mg, 81% over 2 steps, >99:1 er) as a pale-yellow oil.

(R)-4-(1-(4-(benzyloxy)-3-methoxyphenyl)propyl)-5-methyl-2-phenyloxazole (4p')

TLC (10% EtOAc in hexanes): R_f = 0.23 (UV)

^1H NMR (CDCl_3 , 400 MHz): δ 8.02 (dd, J = 8.1, 1.6 Hz, 2H), 7.46–7.40 (m, 5H), 7.39–7.34 (m, 2H), 7.32–7.27 (m, 1H), 7.11 (d, J = 1.9 Hz, 1H), 6.87 (dd, J = 8.2, 2.0 Hz, 1H), 6.82 (d, J = 8.2 Hz, 1H), 5.13 (s, 2H), 3.91 (s, 3H), 3.62 (dd, J = 8.4, 7.0 Hz, 1H), 2.28 (s, 3H), 2.24–2.13 (m, 1H), 2.02 (td, J = 13.8, 13.2, 6.2 Hz, 1H), 0.90 (t, J = 7.3 Hz, 3H).

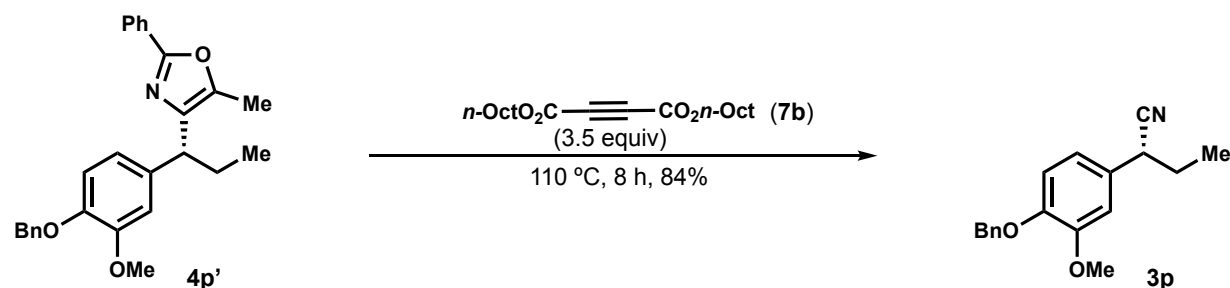
^{13}C NMR (CDCl_3 , 101 MHz): δ 159.3, 149.6, 146.8, 143.7, 138.5, 137.6, 137.5, 129.6, 128.7, 128.6, 128.3, 127.8, 127.4, 126.1, 120.0, 113.9, 112.0, 71.2, 56.1, 44.2, 29.0, 12.8, 10.5.

IR (Diamond-ATR, neat) $\tilde{\nu}_{\text{max}}$: 2956, 2927, 1488, 1282, 1039, 807, 779, 691.

HRMS (ESI) calc. $\text{C}_{27}\text{H}_{28}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 414.2064. Found: 414.2075.

Specific Rotation $[\alpha]^{23}_{\text{D}}$: – 103.1 (c 1.0, CHCl_3).

Chiral SFC: Chiralpak AD-H (sc CO_2 /IPA = 95/5 to 60/40, 2.5 mL/min, 210–400 nm, 45 $^\circ\text{C}$), 6.86 and 7.28 min.



(R)-2-(4-(benzyloxy)-3-methoxyphenyl)butanenitrile (3p)

To an oven dried reaction tube (Fisherbrand, 13x100 mm, 1495935C) equipped with a magnetic stir bar was added toluene (0.02 mL, 4.0 M), alkyne **7b** (71.6 mg, 0.21 mmol, 3.5 equiv) and oxazole **4p'** (25.0 mg, 0.07 mmol, 1.0 equiv). The reaction tube was flushed with N_2 , sealed with a screw cap containing a Teflon septum and moved to a preheated 110 $^\circ\text{C}$ oil bath. After the reaction mixture had stirred for 8 h at 110 $^\circ\text{C}$, the reaction vessel was removed from the oil bath and allowed to cool to room temperature. The crude reaction mixture was directly purified by automated silica flash column chromatography 10 g silica cartridge (gradient elution:

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100% hexane to 20% EtOAc in hexane) yielded **3p** (14.2 mg, 84%, >99:1 er) as a pale-yellow oil.

TLC (15% EtOAc in hexane): R_f = 0.21 (UV)

^1H NMR (CDCl_3 , 400 MHz): δ 7.43 (d, J = 6.9 Hz, 2H), 7.37 (t, J = 7.2 Hz, 2H), 7.30 (t, J = 7.1 Hz, 1H), 6.86 (d, J = 8.3 Hz, 1H), 6.84 (d, J = 2.1 Hz, 1H), 6.79 (dd, J = 8.2, 2.2 Hz, 1H), 5.15 (s, 2H), 3.91 (s, 3H), 3.66 (t, J = 7.2 Hz, 1H), 1.98–1.86 (m, 2H), 1.07 (t, J = 7.4 Hz, 3H).

^{13}C NMR (CDCl_3 , 101 MHz): δ 150.1, 148.0, 137.0, 128.8, 128.7, 128.1, 127.4, 121.1, 119.7, 114.2, 111.0, 71.2, 56.2, 38.7, 29.3, 11.7.

IR (Diamond-ATR, neat) $\tilde{\nu}_{\text{max}}$: 2934, 2237, 1592, 1514, 1220, 1024, 766, 696.

HRMS (DARTI) calc. $\text{C}_{18}\text{H}_{20}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 282.1489. Found: 282.1482.

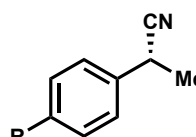
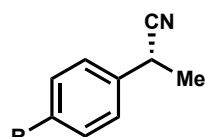
Specific Rotation $[\alpha]^{23}_{\text{D}}$: + 3.66 (c 0.69, CHCl_3).

Chiral SFC: Chiralpak AD-H (sc CO_2 /IPA = 95/5 to 60/40, 2.5 mL/min, 210–400 nm, 45 °C), 4.85 and 5.30 min.

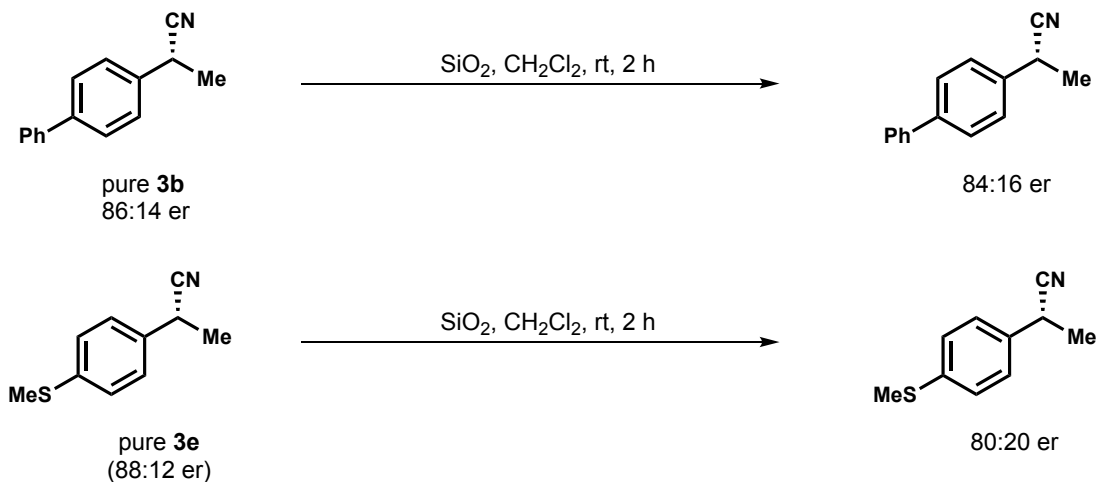
5. Studies on Racemization of Nitrile Products

In some cases, while purifying the enantioenriched nitrile products we observed racemization of **3**. To further understand this phenomenon, we investigated various purification conditions to try to avoid this undesired racemization process (Table SI1). Furthermore, to gain insight on whether the racemization was caused by **3** reacting with metal salts present in the crude reaction mixture upon treatment with silica gel we conducted further experiments with the pure product (Scheme SI1).

Table SI1: Racemization studies during the purification of nitrile products (3**).**

 crude reaction mixture		 	
		<i>purification conditions</i>	
	entry	purification conditions	er
92:8 er (crude)	R=Ph (3b)	1 silica column chromatography	86:14 er
		2 silica column chromatography + 1% Et ₃ N	85:15 er
		3 basic alumina	92:8 er
		4 silica prep TLC	92:8 er
<hr/>			
96:4 er (crude)	R=SMe (3e)	5 silica column chromatography	88:12 er
		6 basic alumina	89:11 er
		7 silica prep TLC	96:4 er

Scheme SI1: Racemization studies on pure nitrile products (3**).**



6. References and Notes

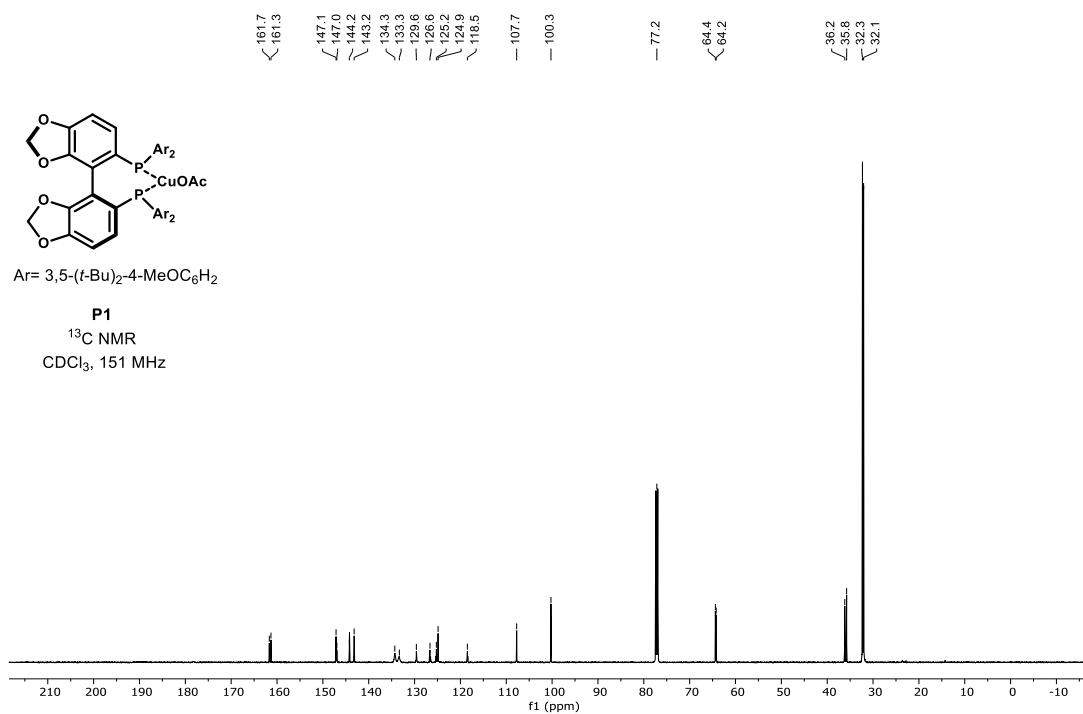
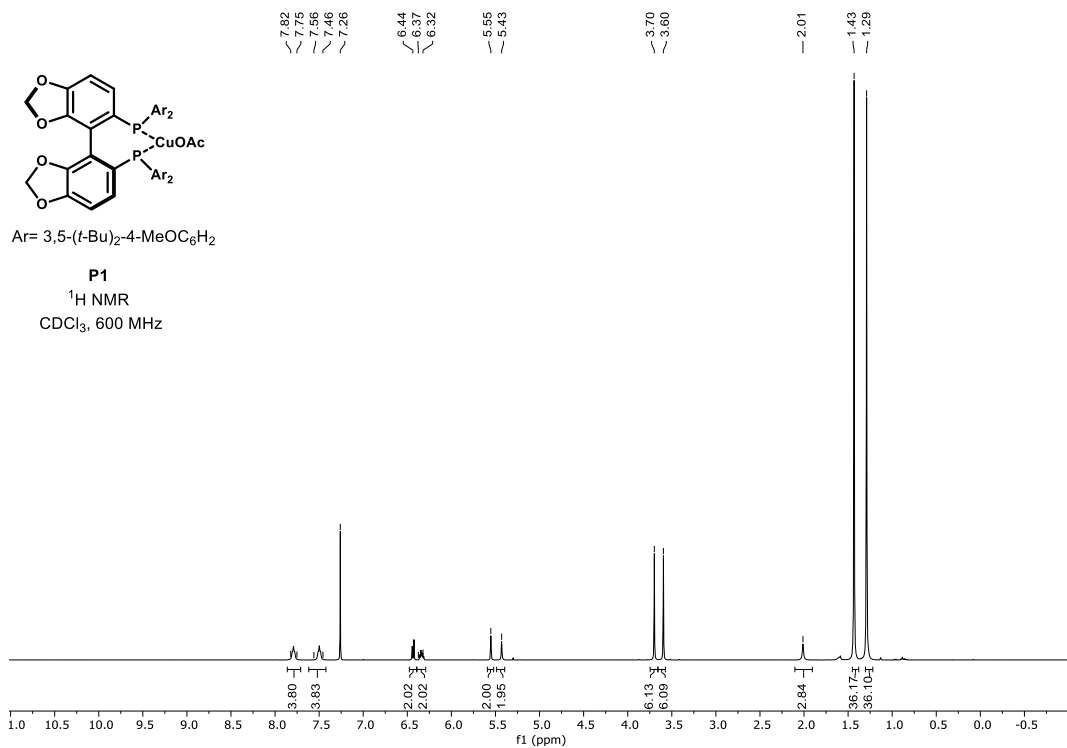
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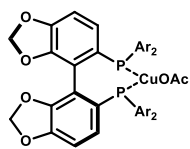
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7. Associated Analytical Data

7.1 NMR Spectra of Hydrocyanation Products and Starting Materials



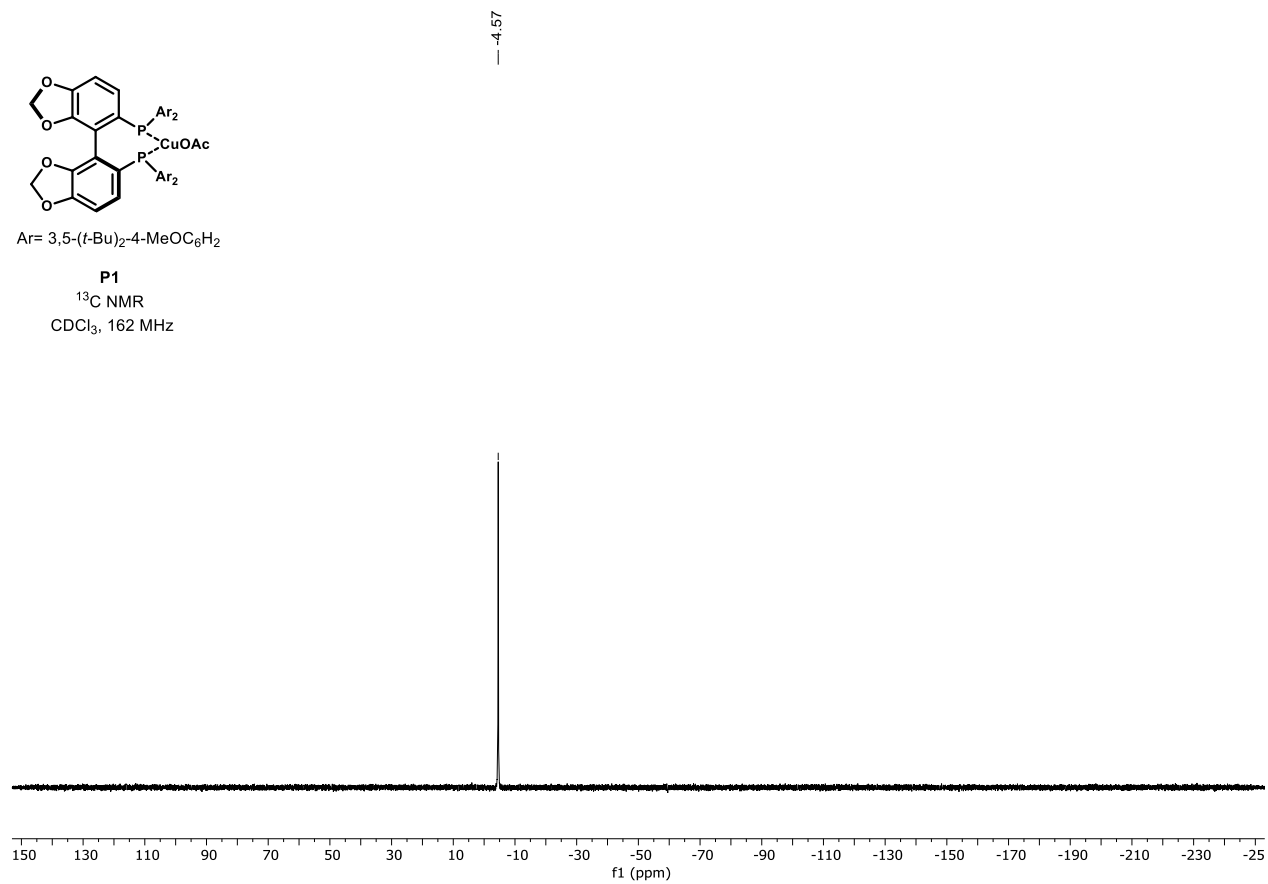


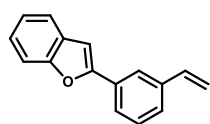
Ar= 3,5-(*t*-Bu)₂-4-MeOC₆H₂

P1

¹³C NMR

CDCl₃, 162 MHz

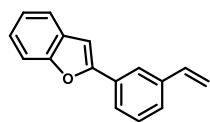
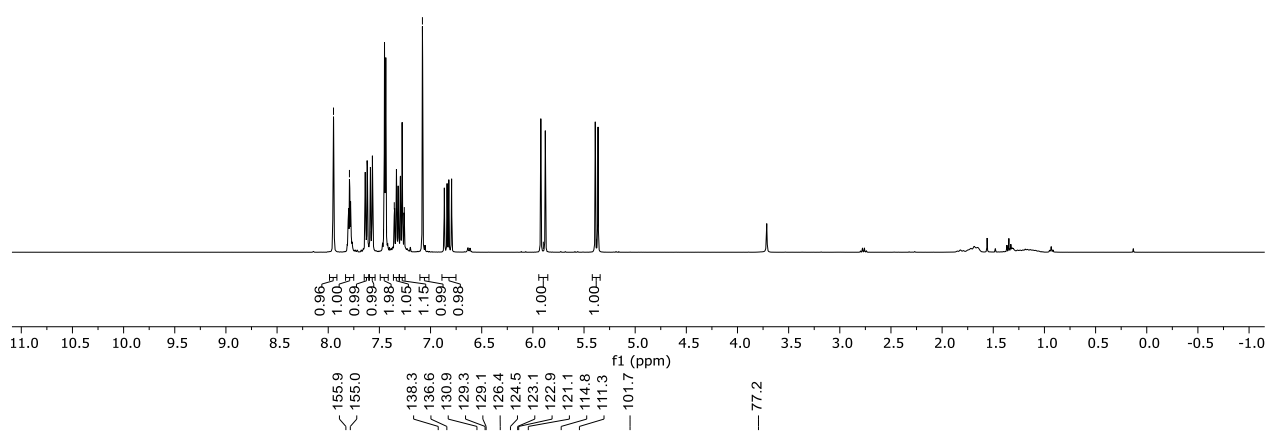




1f

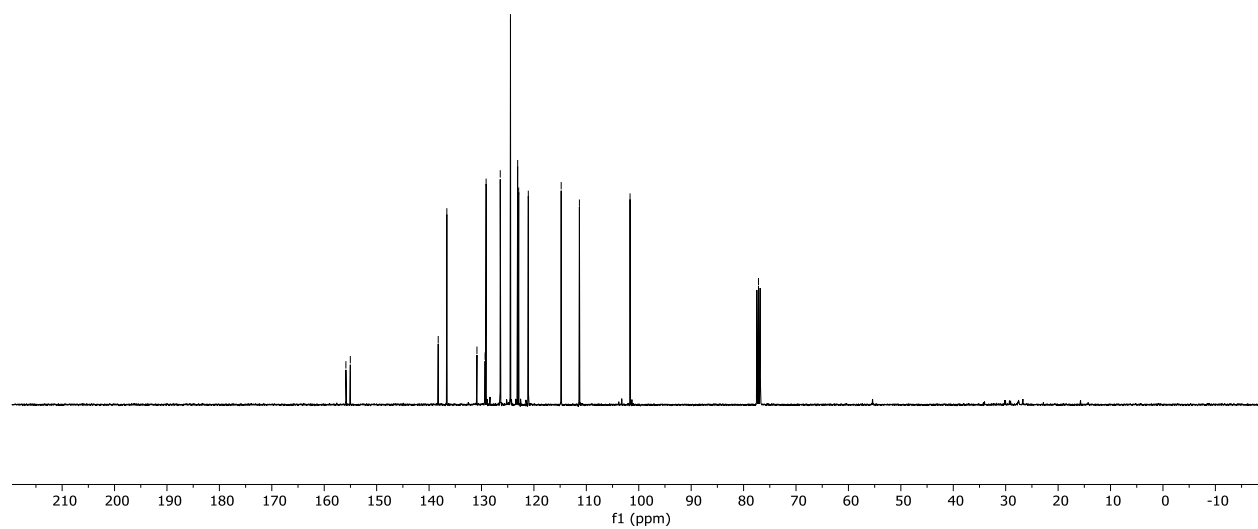
^1H NMR
CDCl₃, 400 MHz

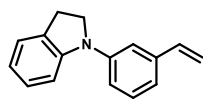
7.95
7.79
7.63
7.58
7.46
7.43
7.35
7.26
7.08
6.83
— 5.90
— 5.38



1f

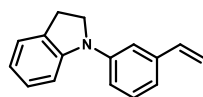
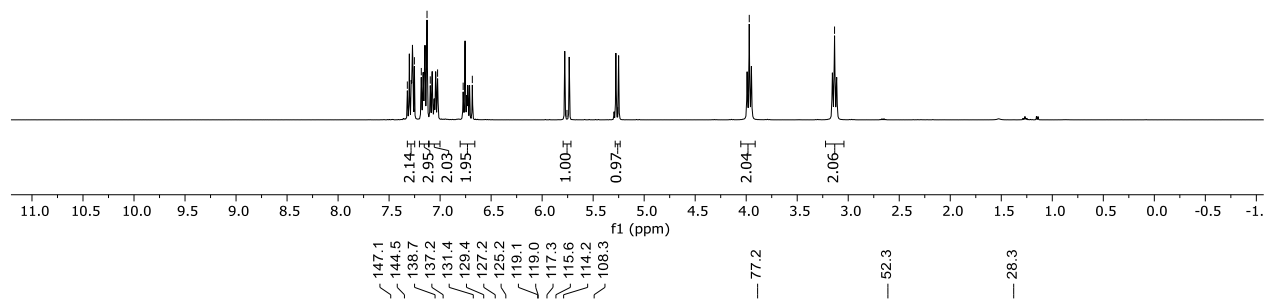
^{13}C NMR
CDCl₃, 101 MHz



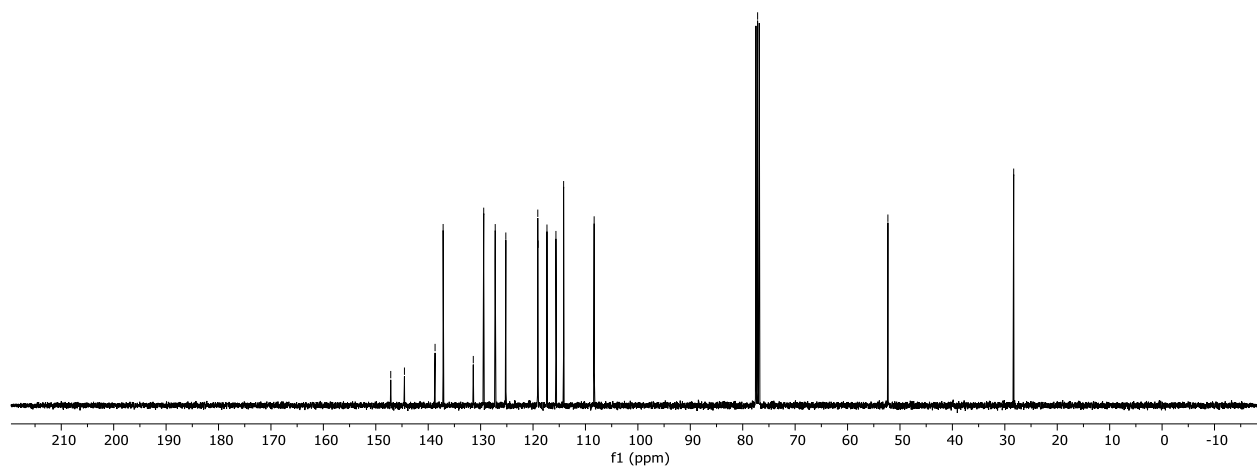


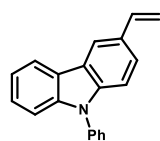
1h
¹H NMR
 CDCl₃, 400 MHz

7.32
 7.25
 7.18
 7.13
 7.10
 7.02
 6.77
 6.68
 — 5.76
 — 5.26
 — 3.97
 — 3.13

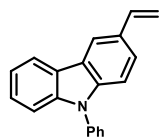
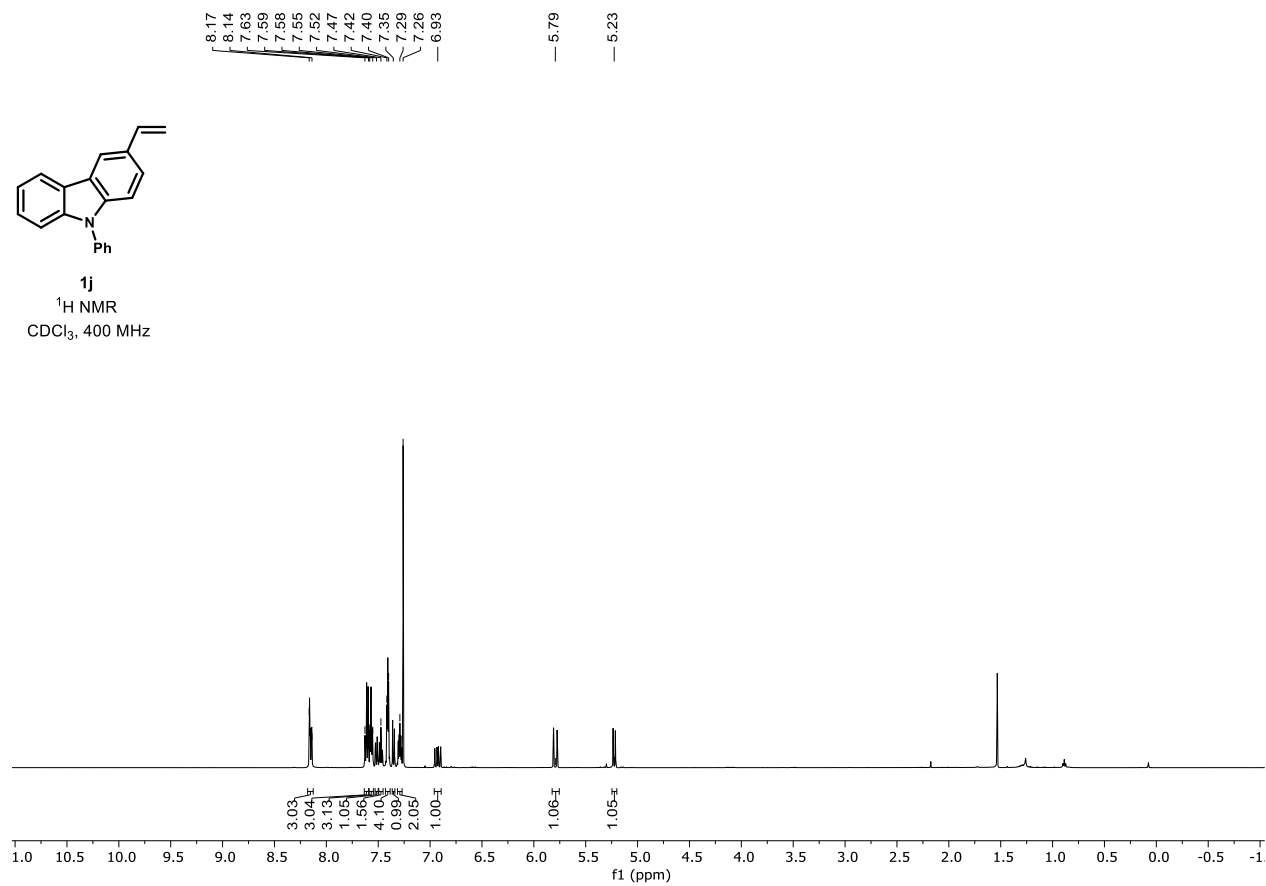


1h
¹³C NMR
 CDCl₃, 101 MHz

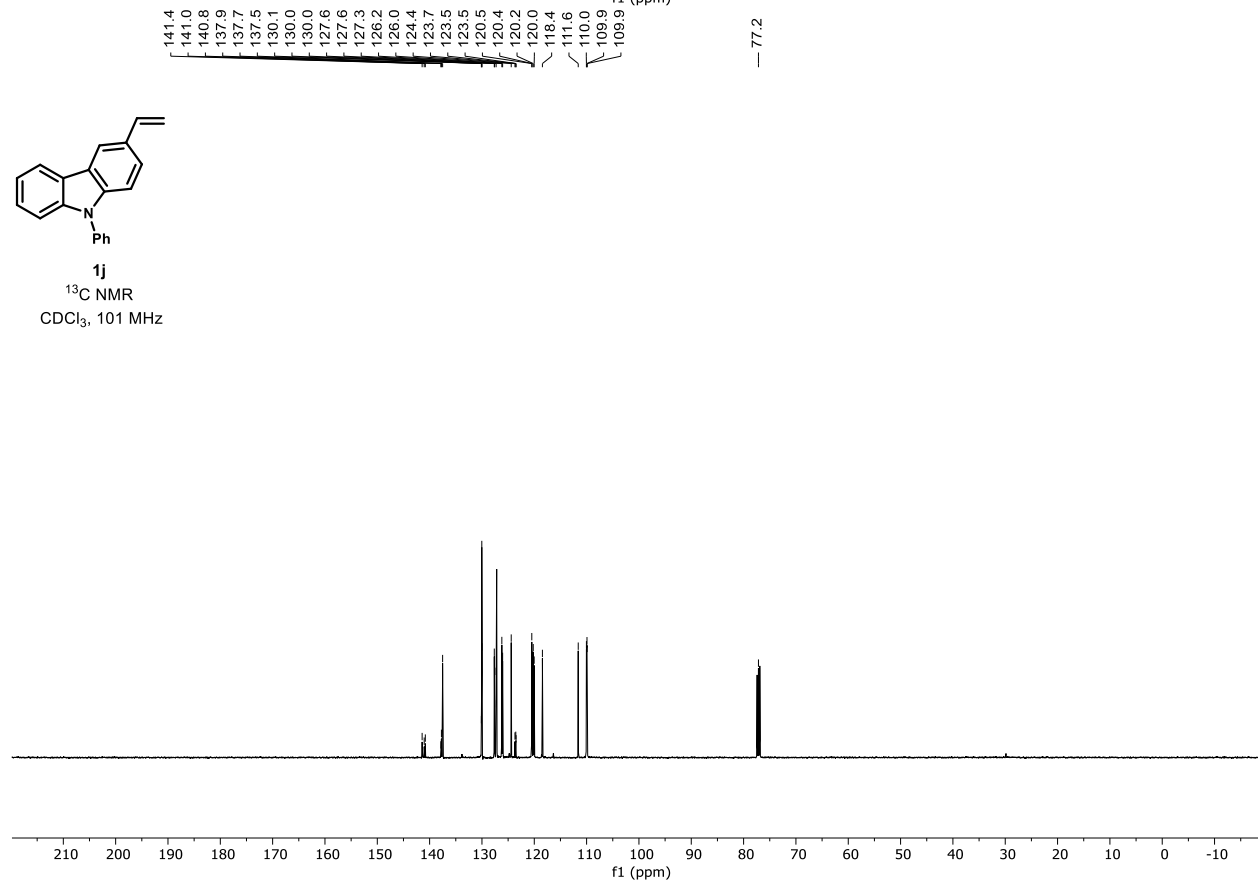


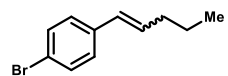


1j
¹H NMR
 CDCl₃, 400 MHz



1j
¹³C NMR
 CDCl₃, 101 MHz





1:2 Z:E mixture

SI-8

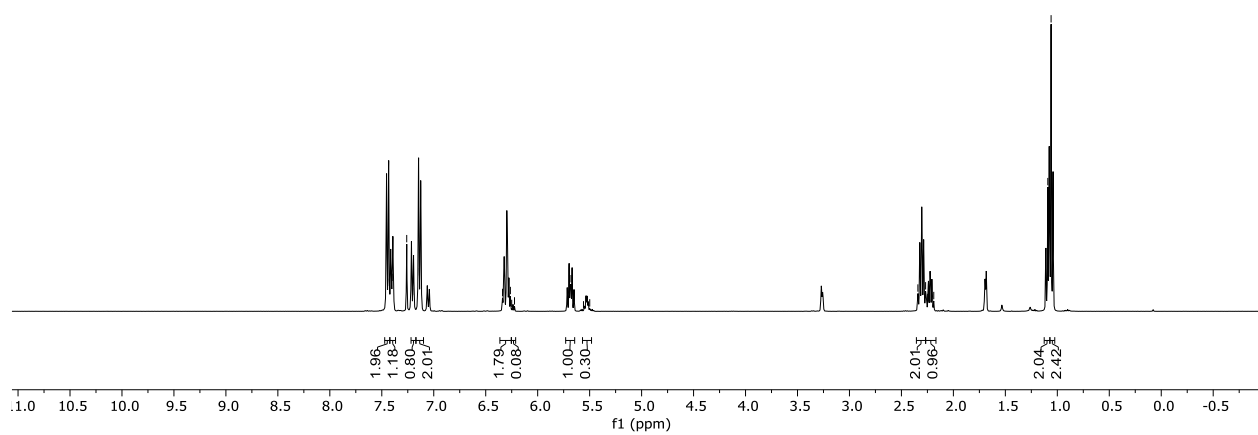
¹H NMR

CDCl₃, 400 MHz

7.44
7.40
7.26
7.20
7.14
6.34
6.26
6.25
6.22
5.88
5.56
5.50

2.34
2.27
2.25
2.19

1.09
1.06

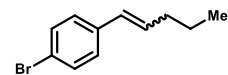


137.0
136.8
135.7
133.7
131.7
131.5
131.4
130.5
130.4
129.5
127.8
127.6
127.3
127.1
120.5
120.4

77.2

38.5

26.2
22.1
21.3
18.0
14.5
13.6

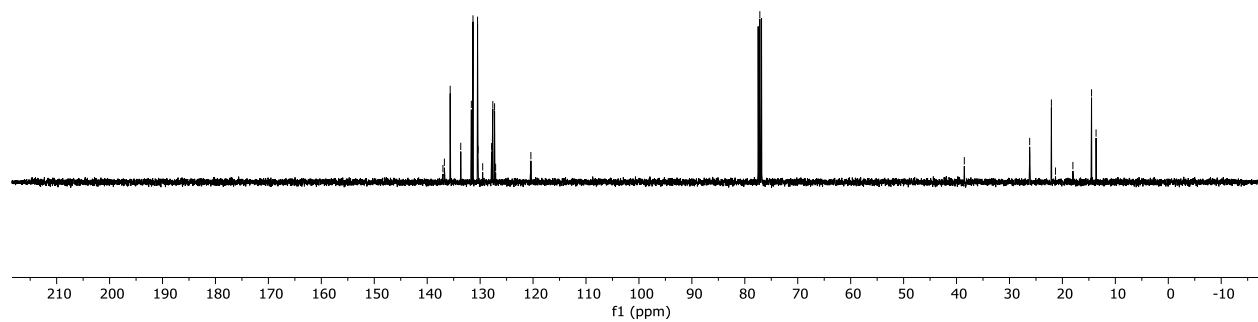


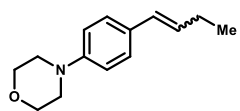
1:2 Z:E mixture

SI-8

¹³C NMR

CDCl₃, 100 MHz

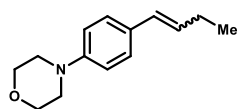
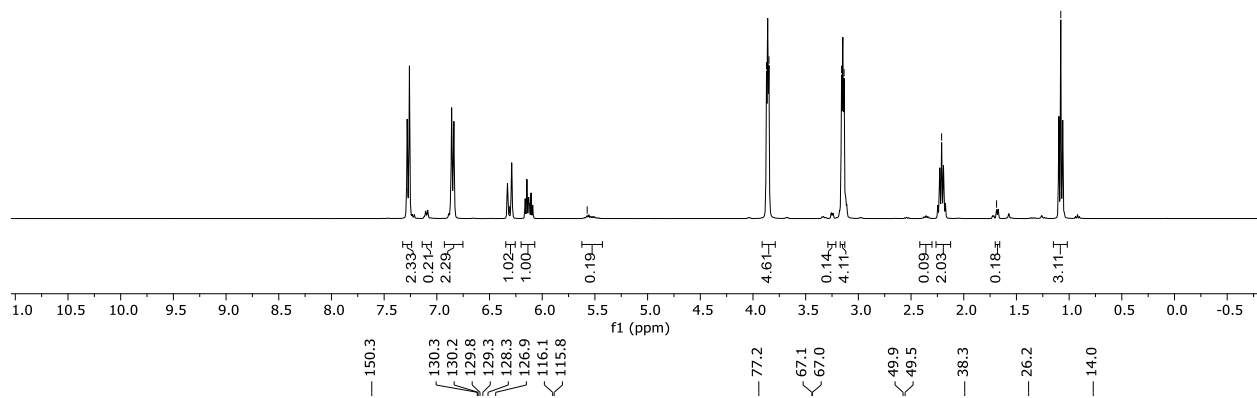




1:10 Z:E mixture

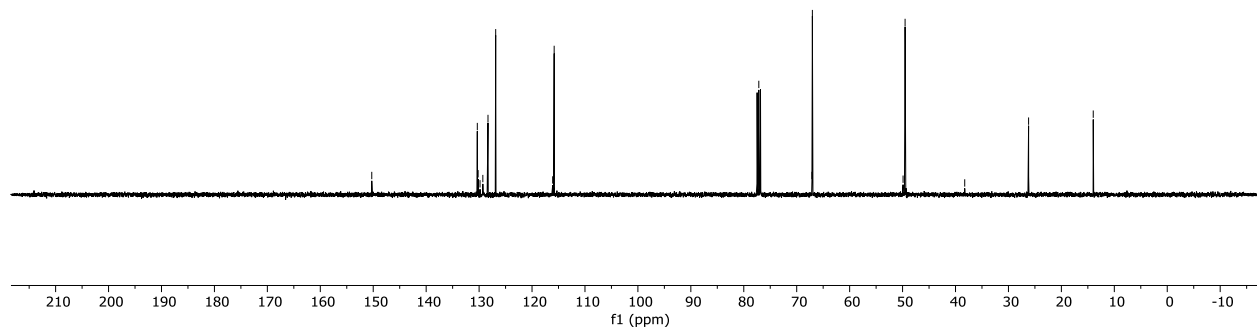
1m
¹H NMR
 CDCl₃, 400 MHz

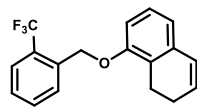
— 7.27
 — 6.85
 — 6.31
 — 6.13
 — 5.57
 — 3.87
 — 3.85
 — 3.16
 — 3.14
 — 2.21
 — 1.69
 — 1.08



1:10 Z:E mixture

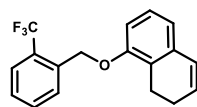
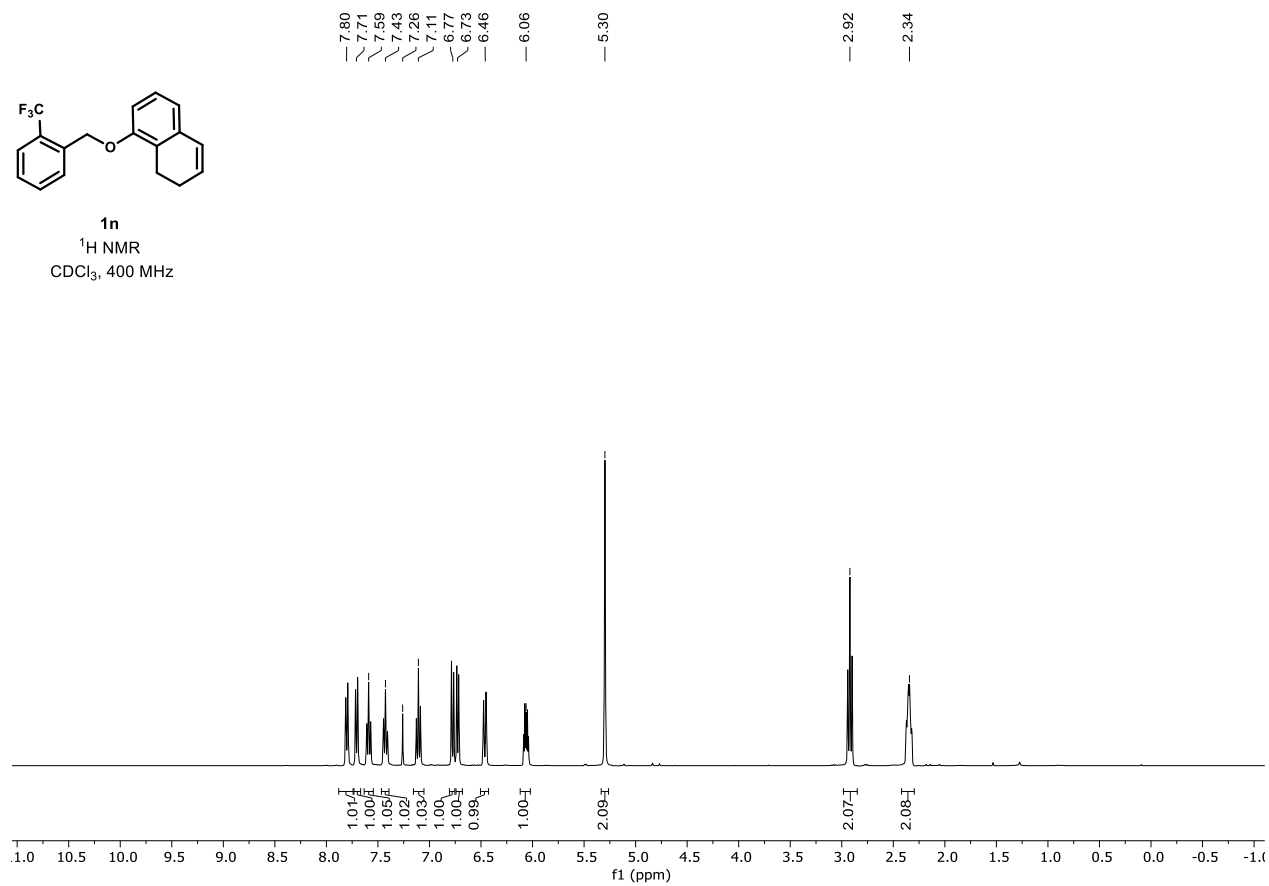
1m
¹³C NMR
 CDCl₃, 101 MHz





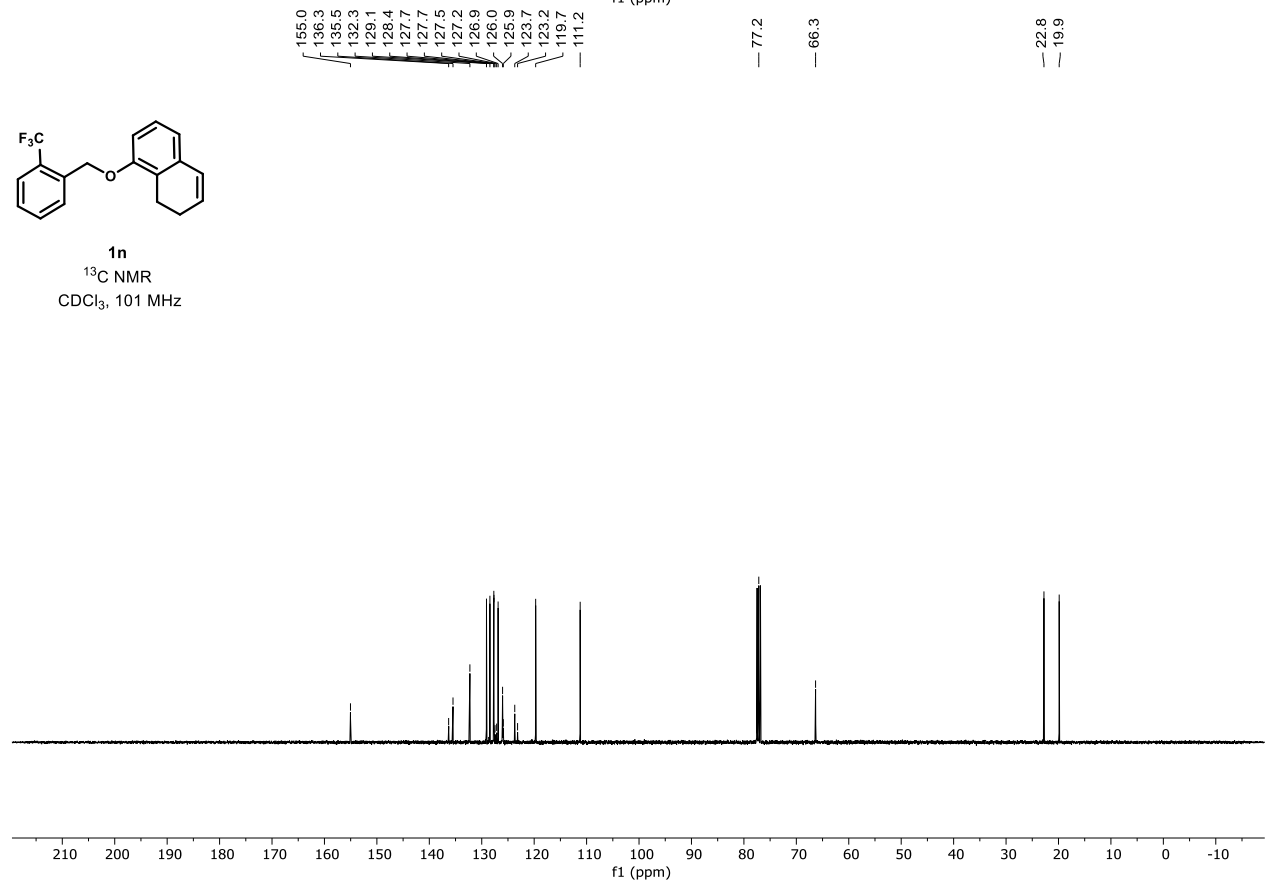
1n

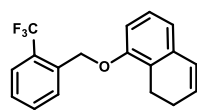
¹H NMR
CDCl₃, 400 MHz



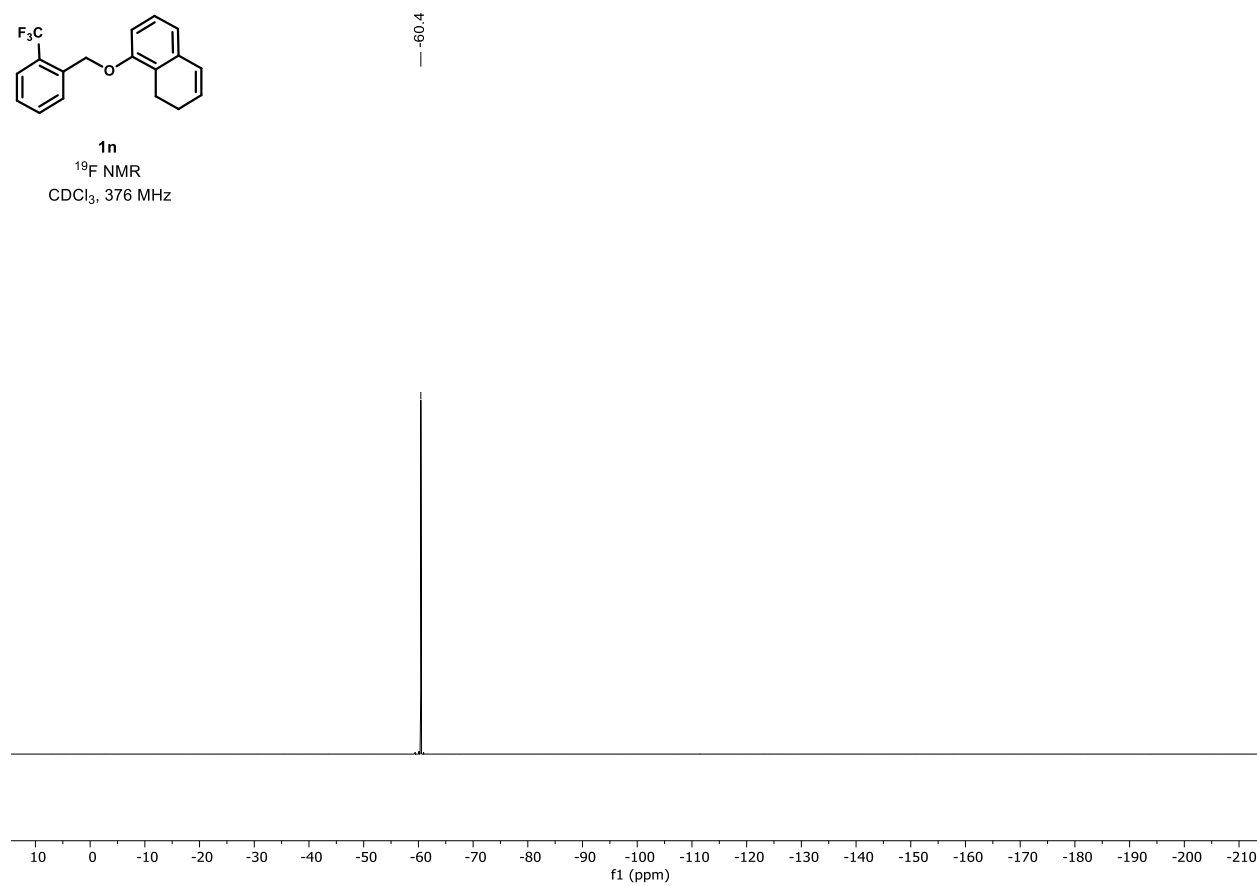
1n

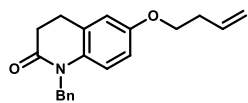
¹³C NMR
CDCl₃, 101 MHz



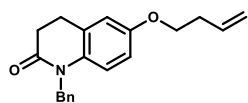
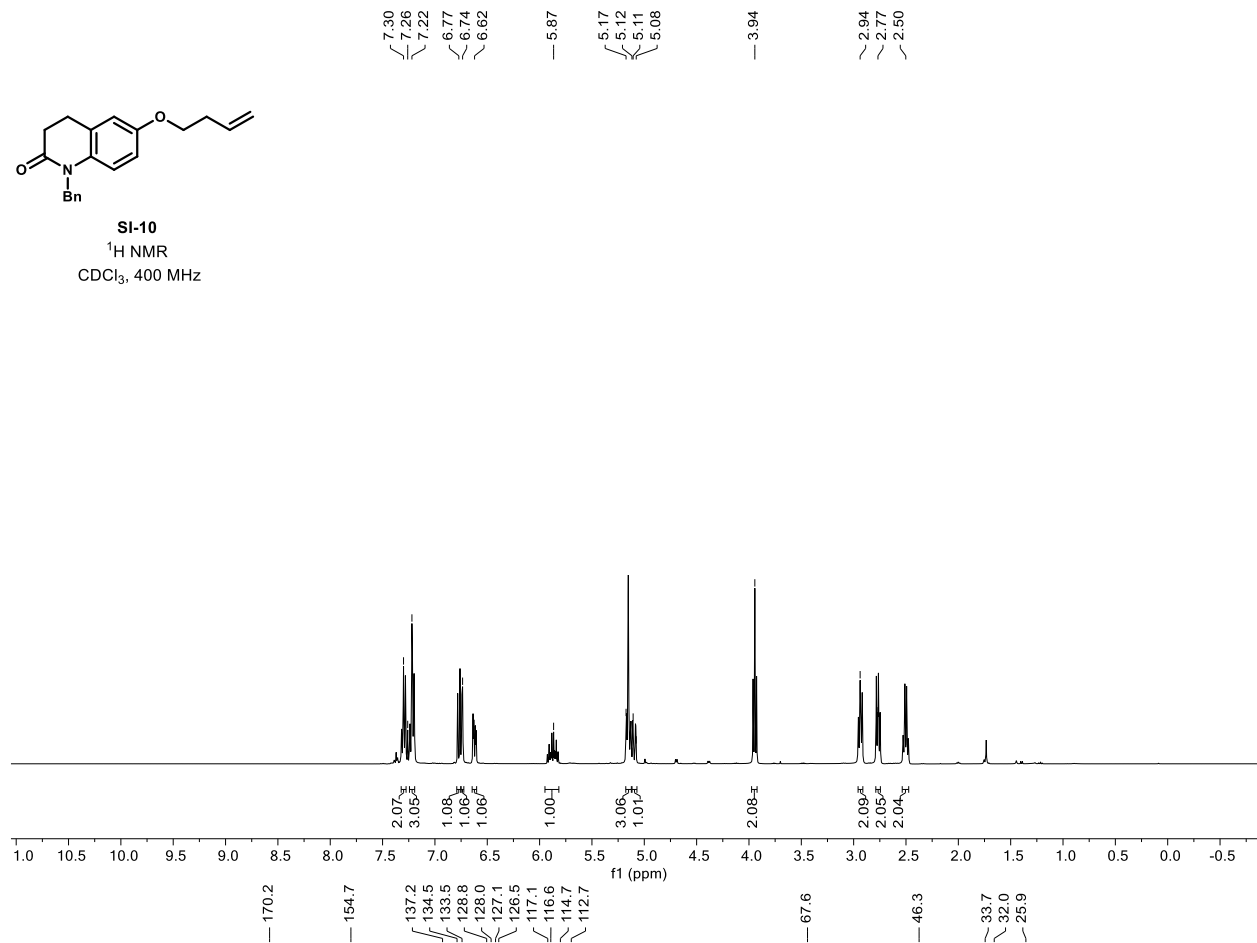


1n
¹⁹F NMR
CDCl₃, 376 MHz

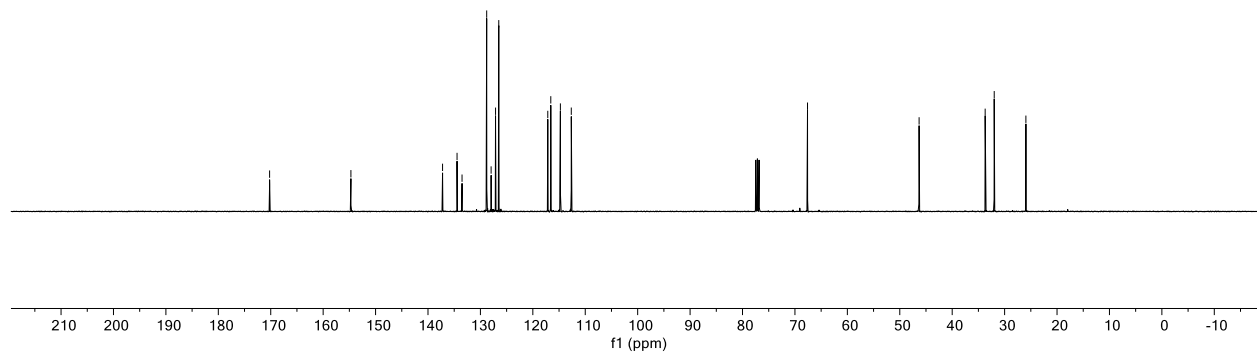


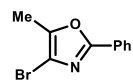


SI-10
¹H NMR
 CDCl₃, 400 MHz



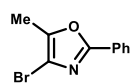
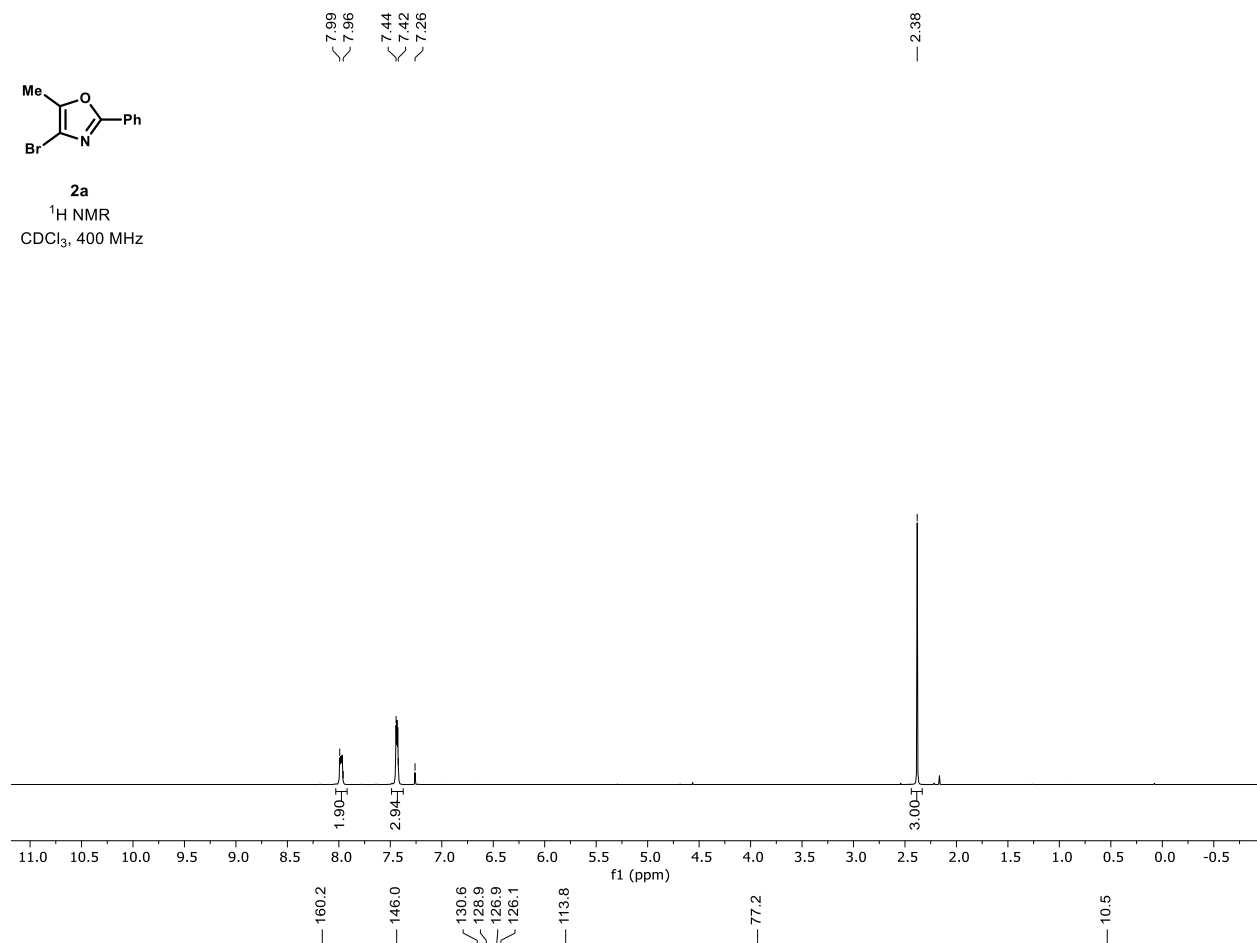
SI-10
¹³C NMR
 CDCl₃, 101 MHz





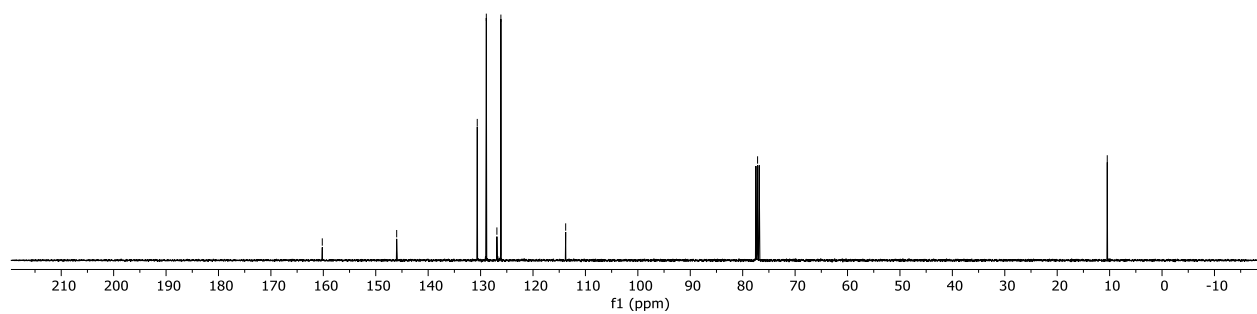
2a

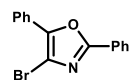
^1H NMR
CDCl₃, 400 MHz



2a

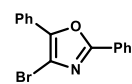
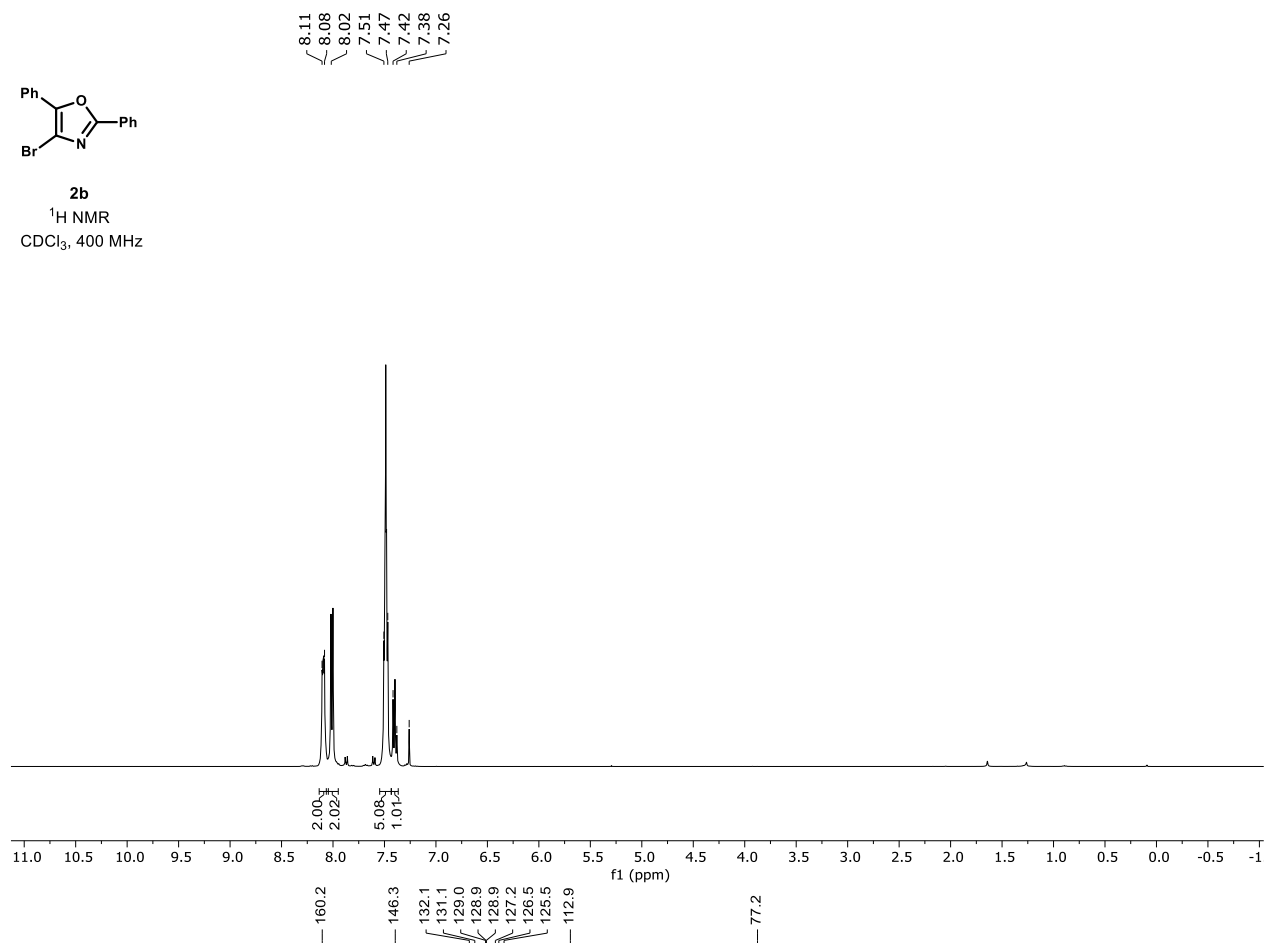
^{13}C NMR
CDCl₃, 101 MHz





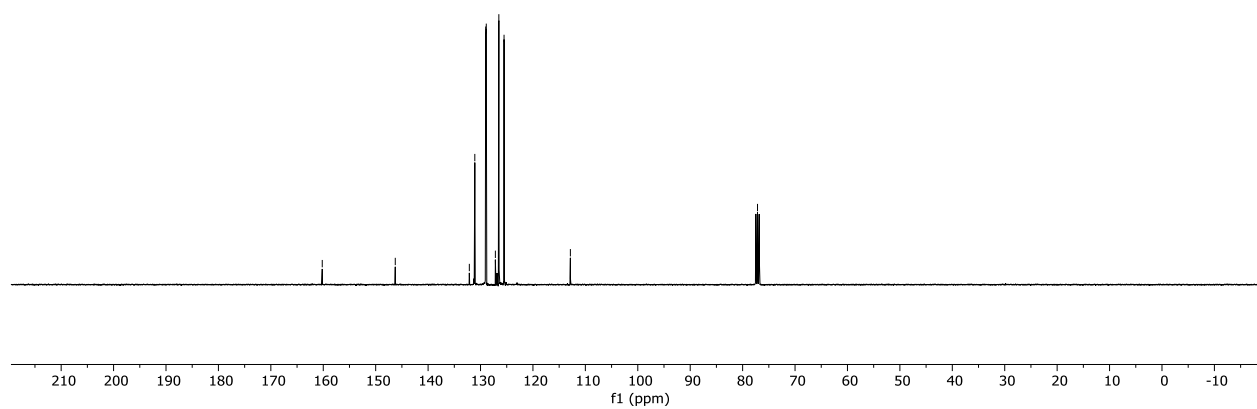
2b

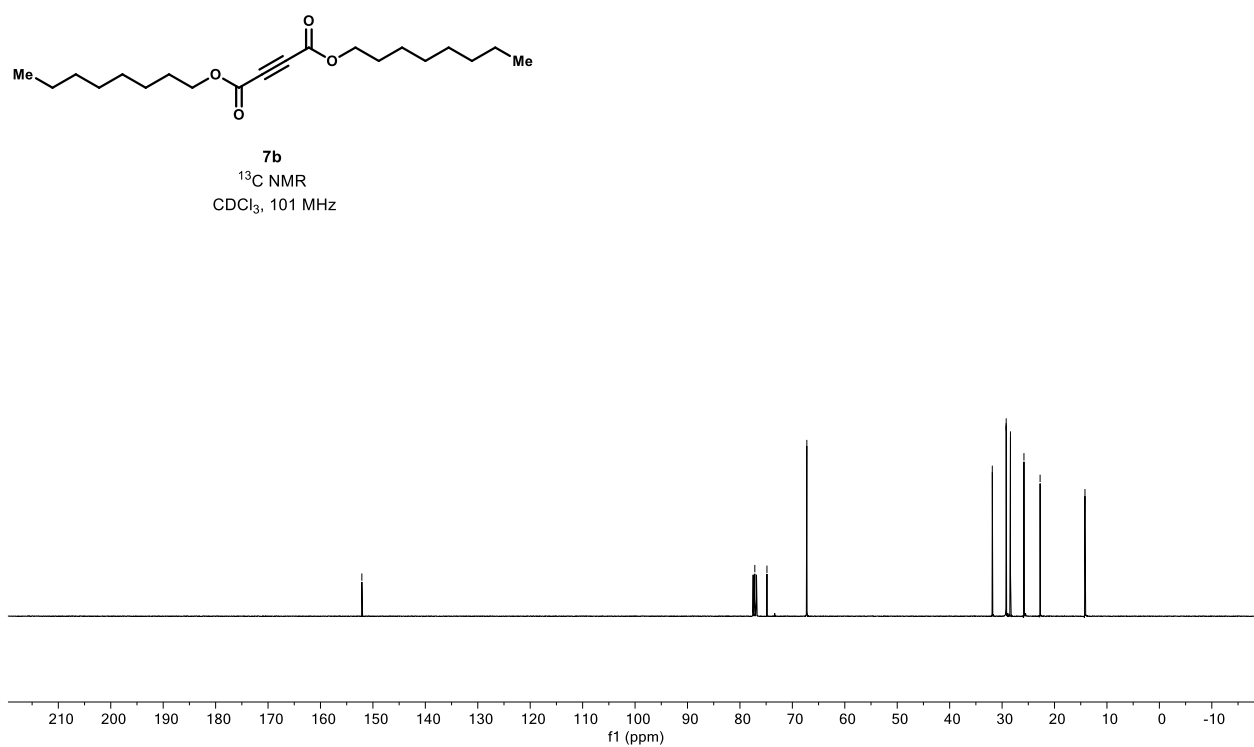
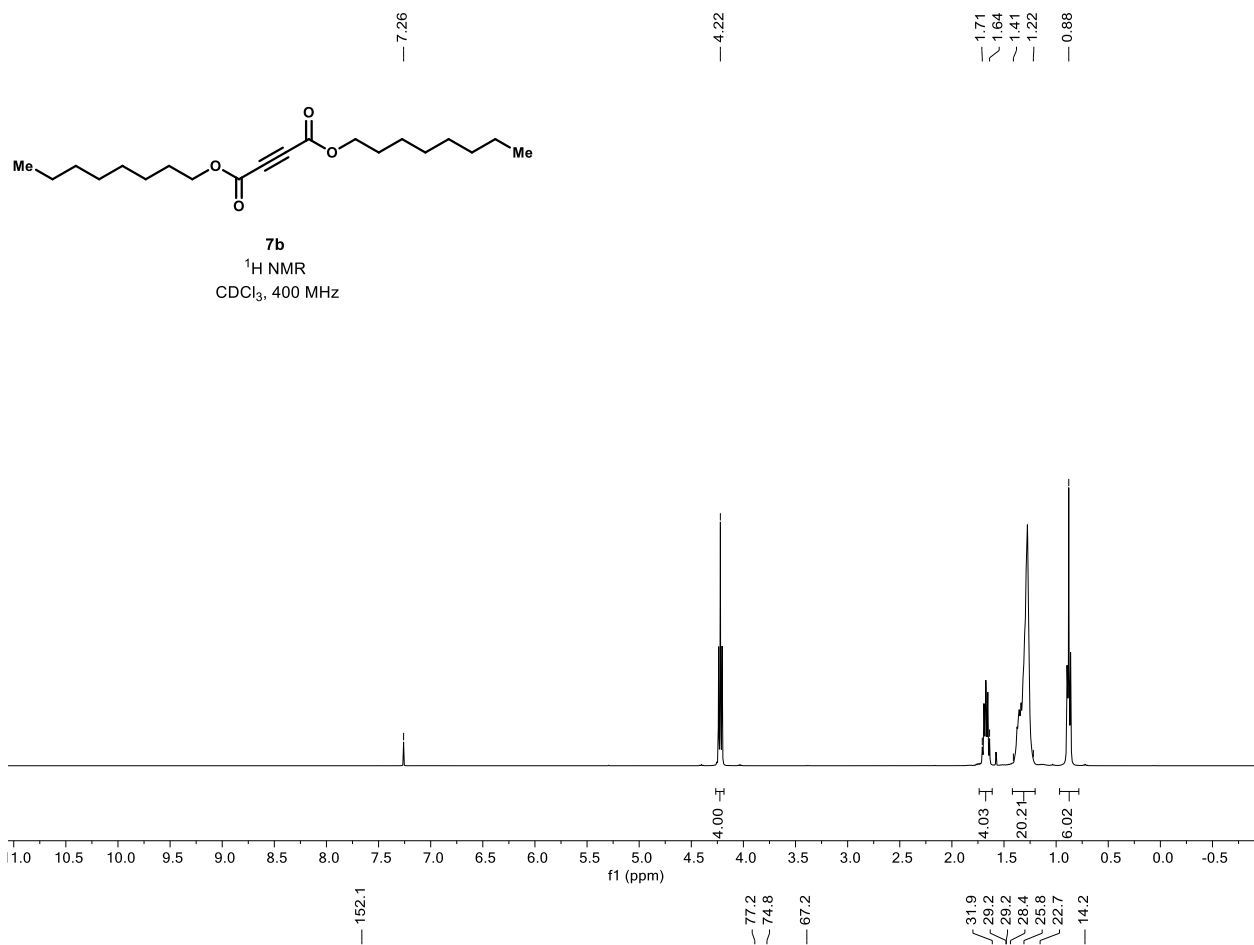
^1H NMR
 CDCl_3 , 400 MHz

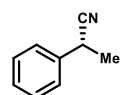


2b

^{13}C NMR
 CDCl_3 , 101 MHz

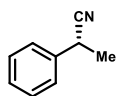
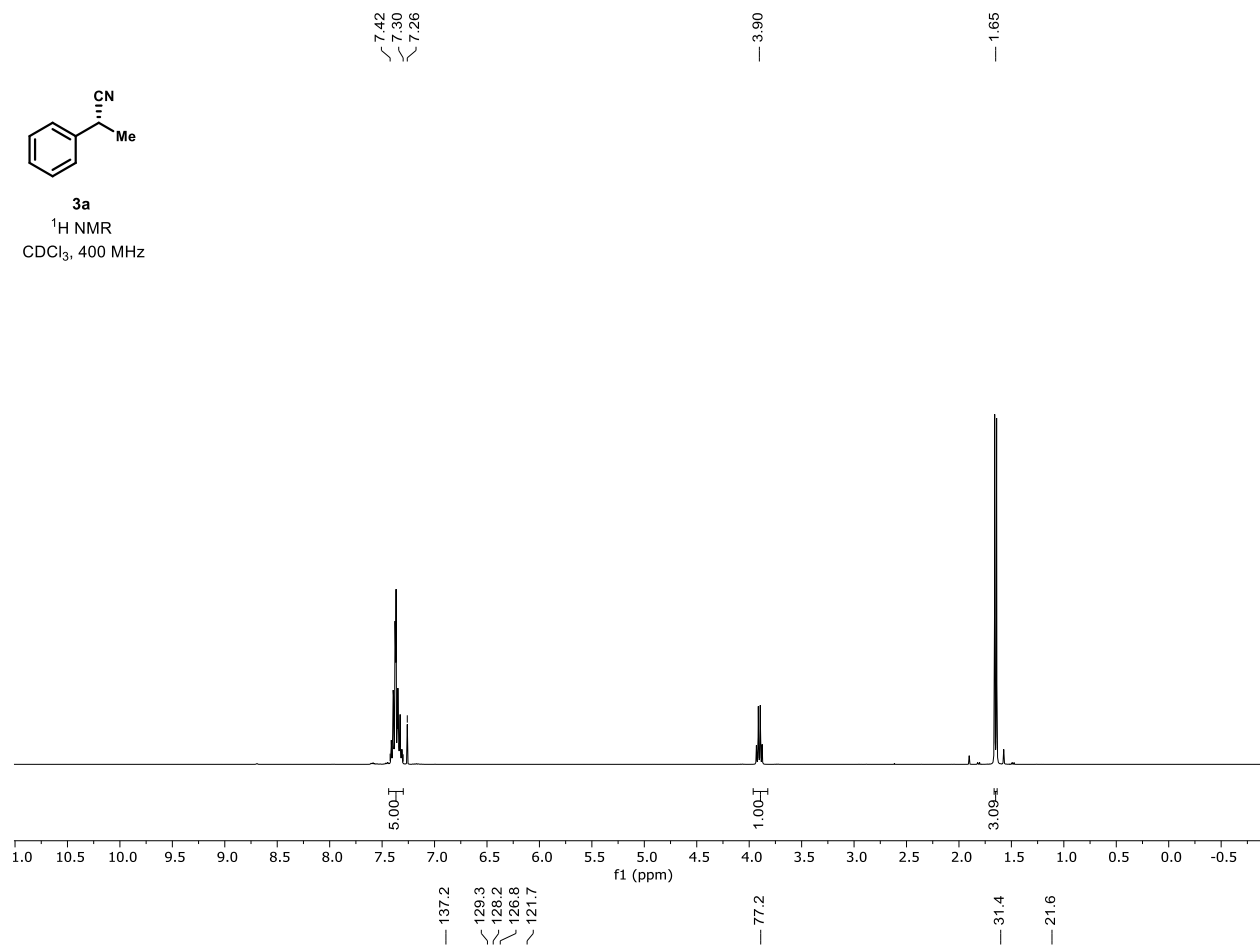






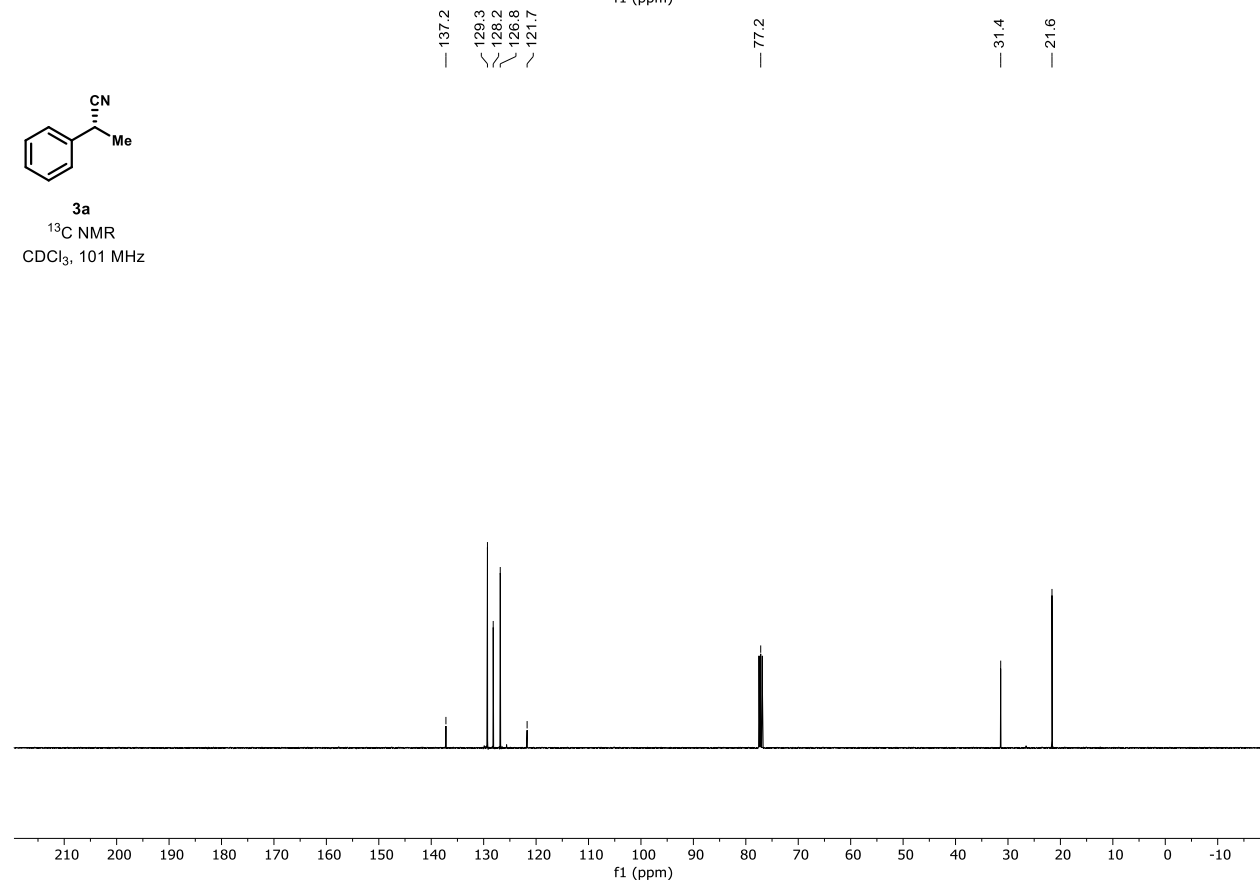
3a

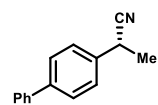
¹H NMR
CDCl₃, 400 MHz



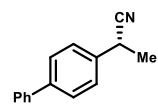
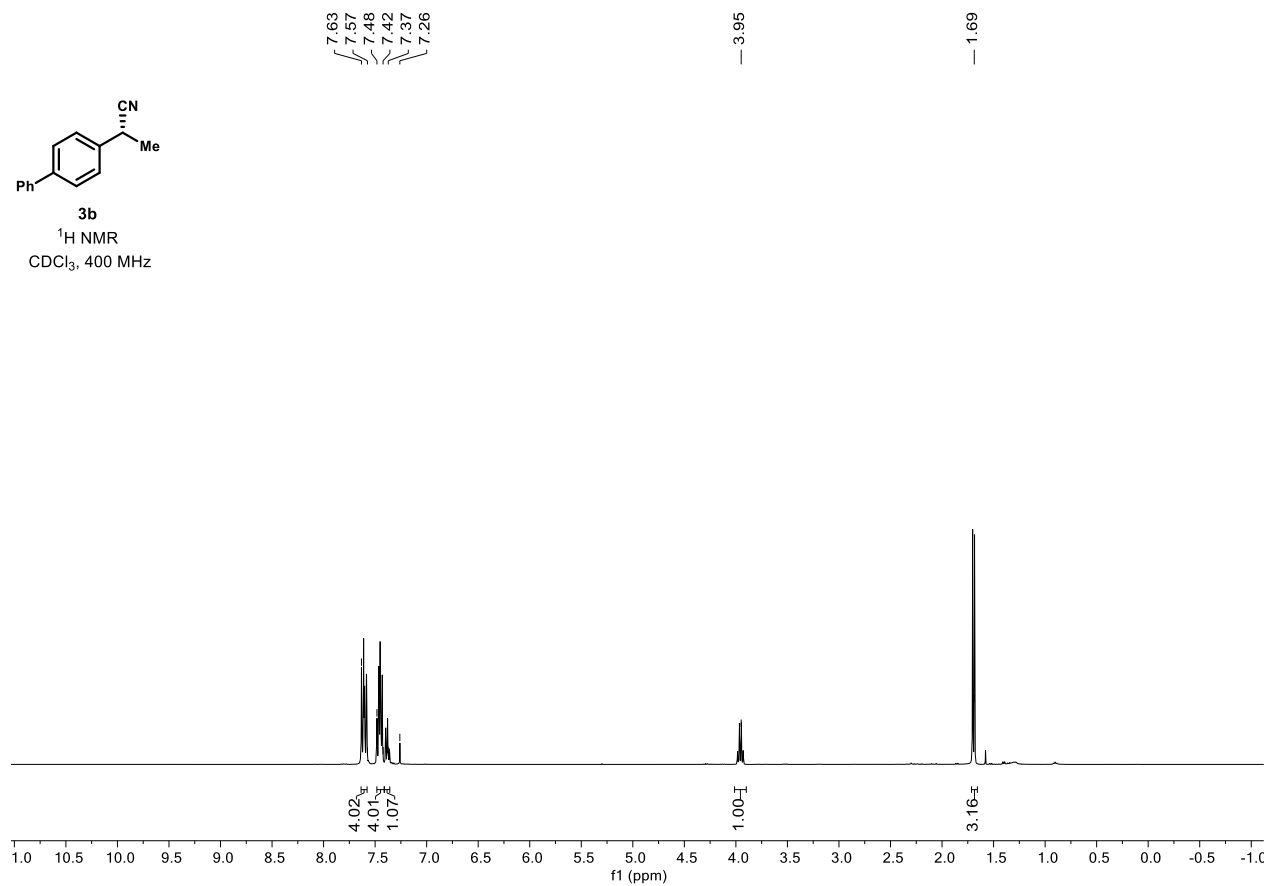
3a

¹³C NMR
CDCl₃, 101 MHz

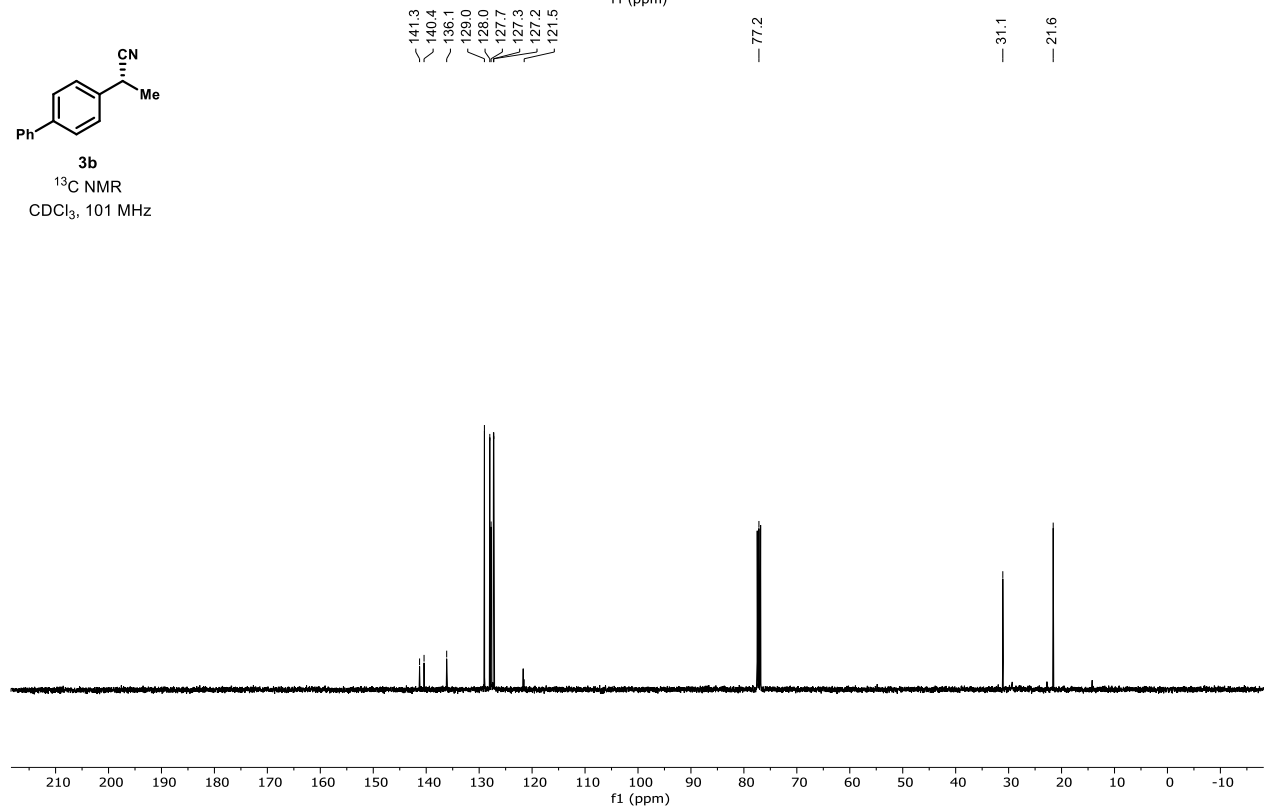


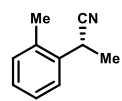


3b
¹H NMR
 CDCl₃, 400 MHz



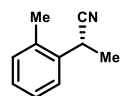
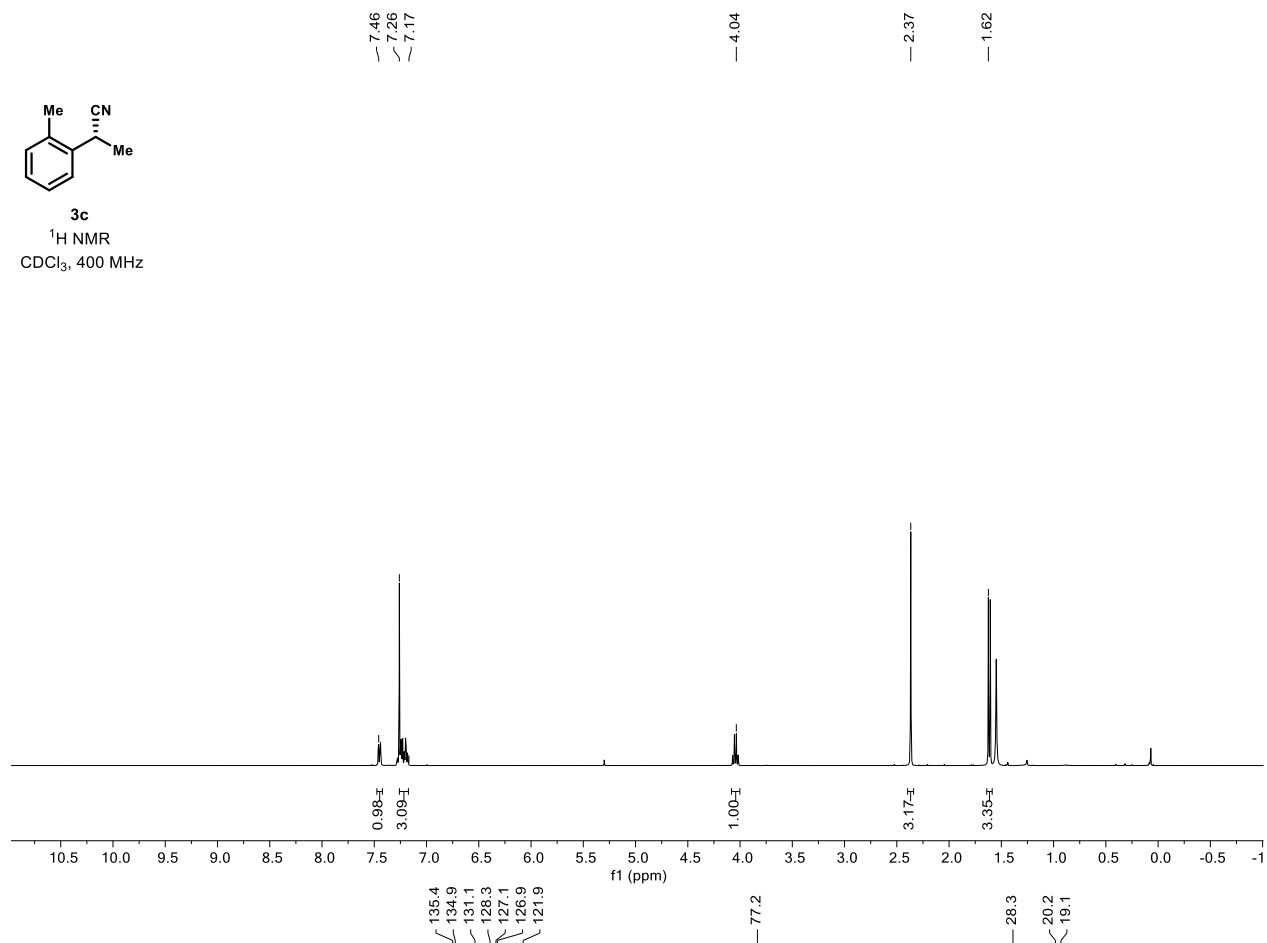
3b
¹³C NMR
 CDCl₃, 101 MHz





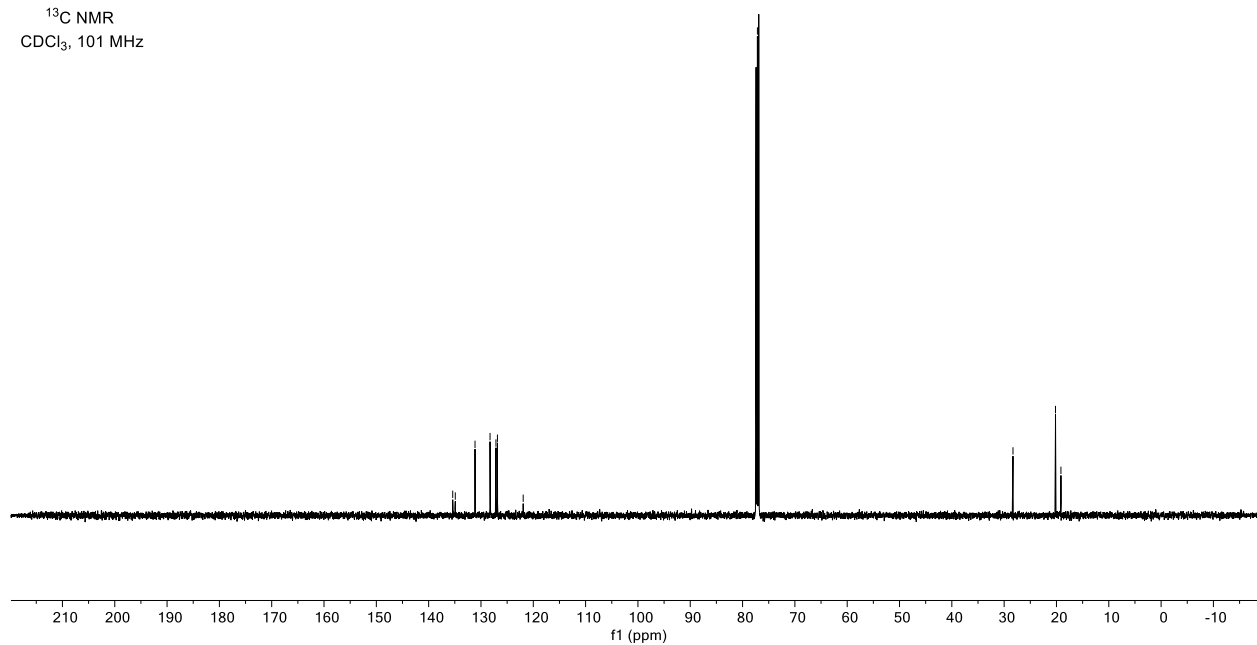
3c

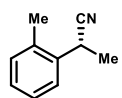
¹H NMR
CDCl₃, 400 MHz



3c

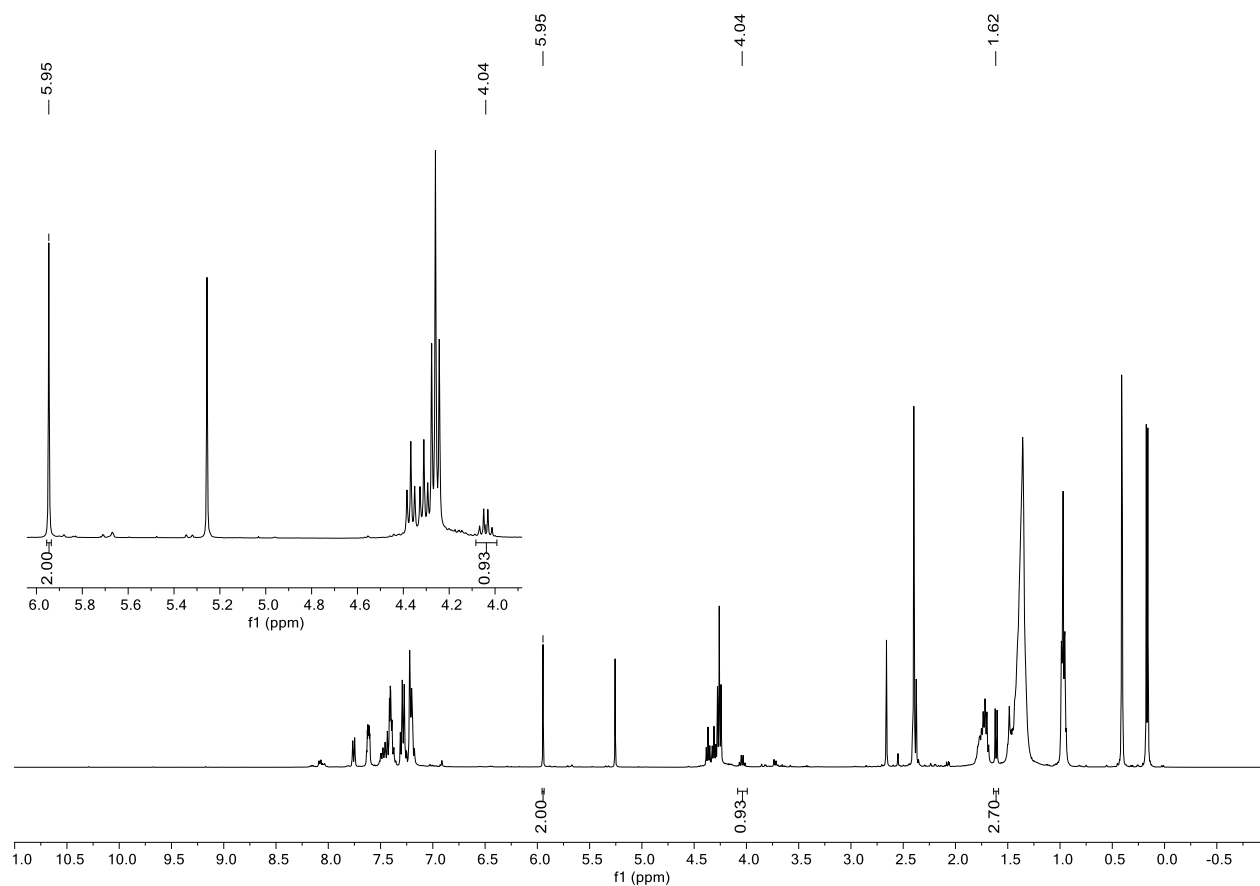
¹³C NMR
CDCl₃, 101 MHz

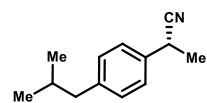




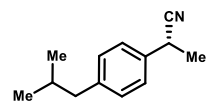
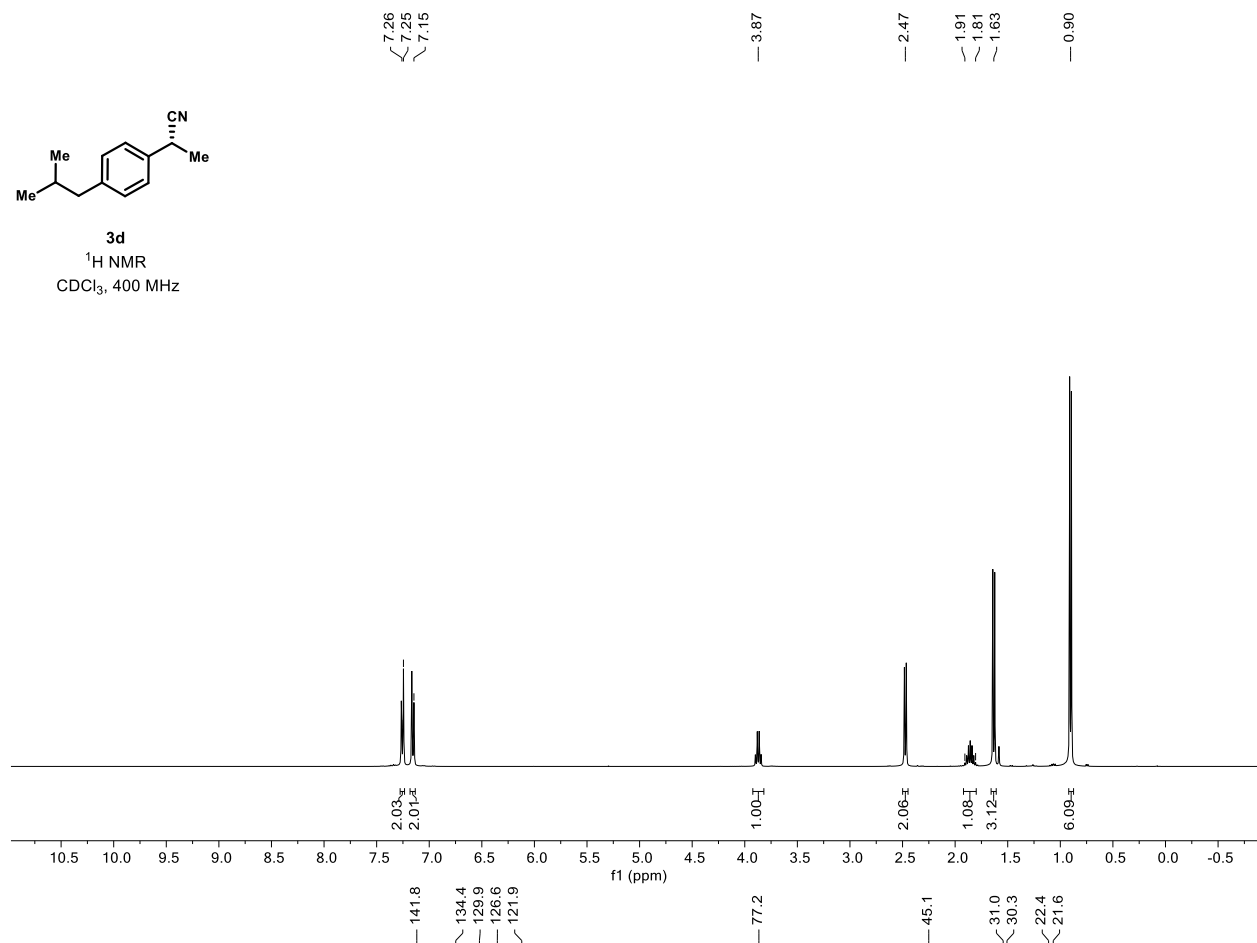
3c

^1H NMR (CDCl_3 , 400 MHz) of crude reaction mixture containing 0.5 mmol of 1,1,2,2-tetrachloroethane as internal standard

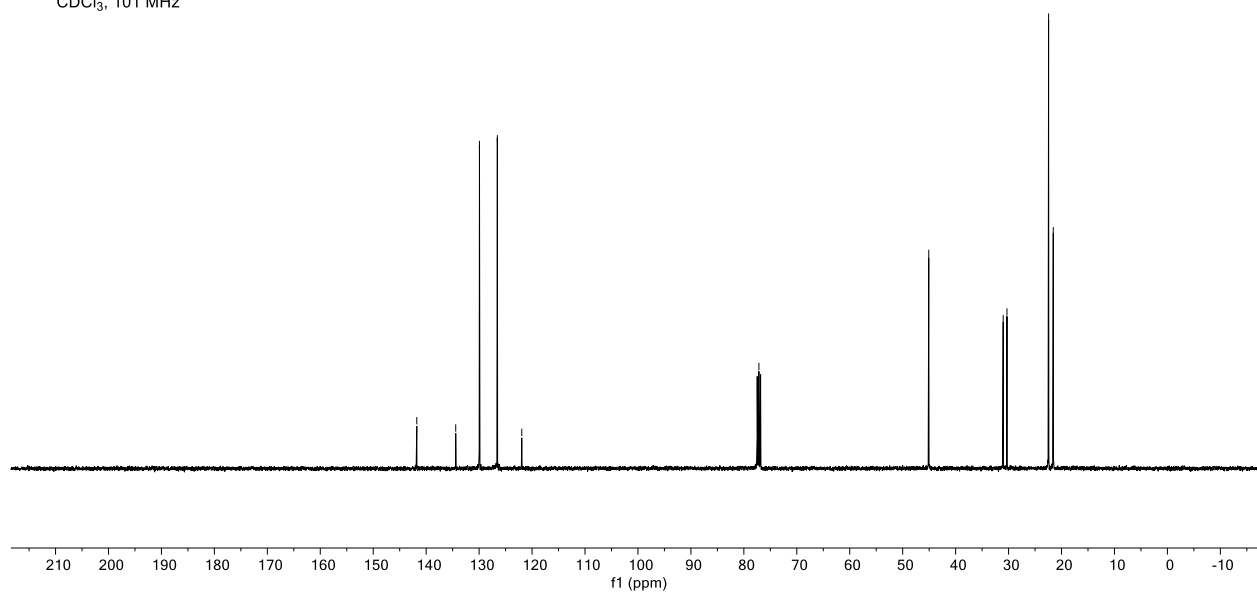


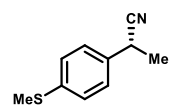


3d
¹H NMR
 CDCl₃, 400 MHz



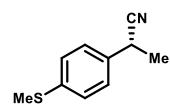
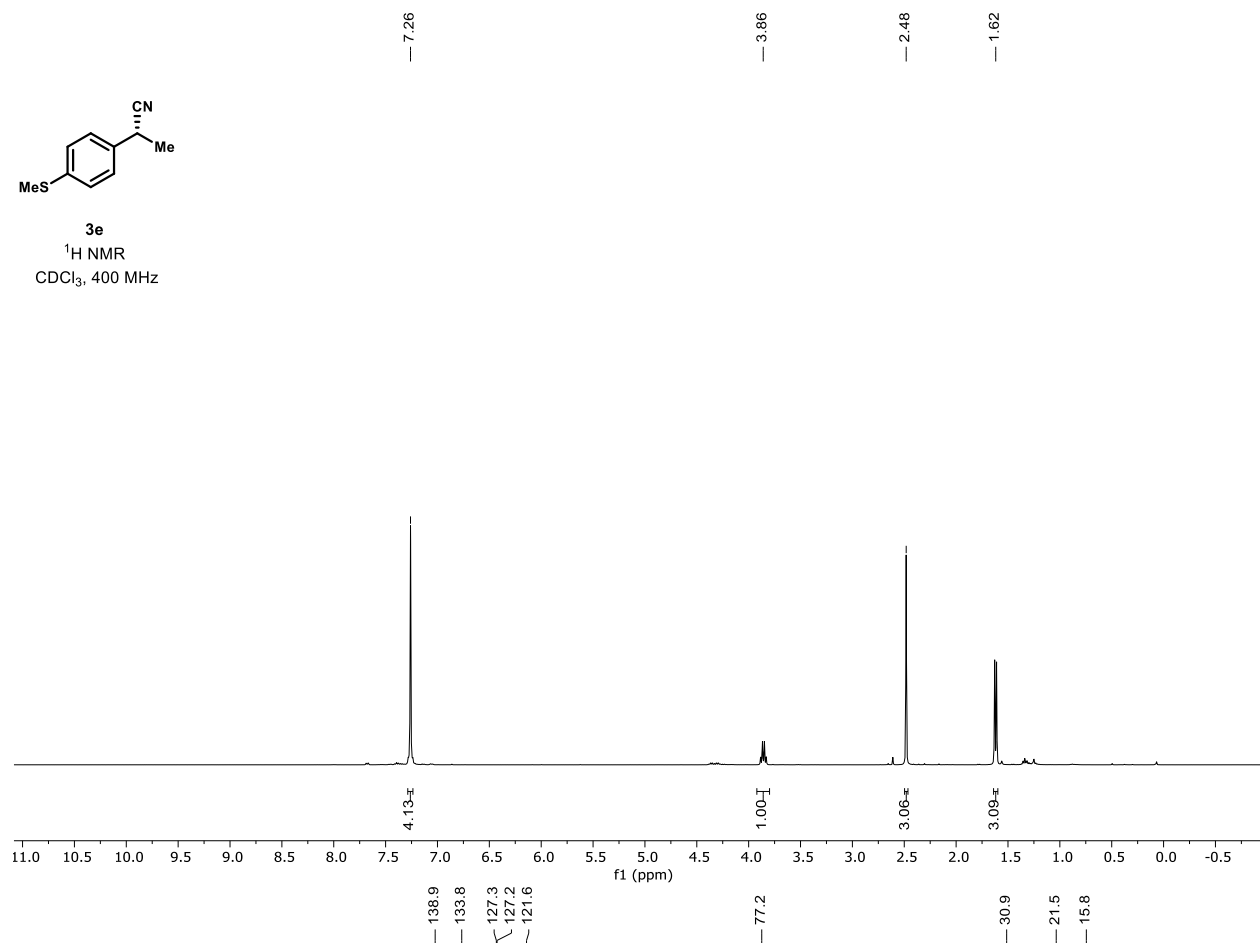
3d
¹³C NMR
 CDCl₃, 101 MHz





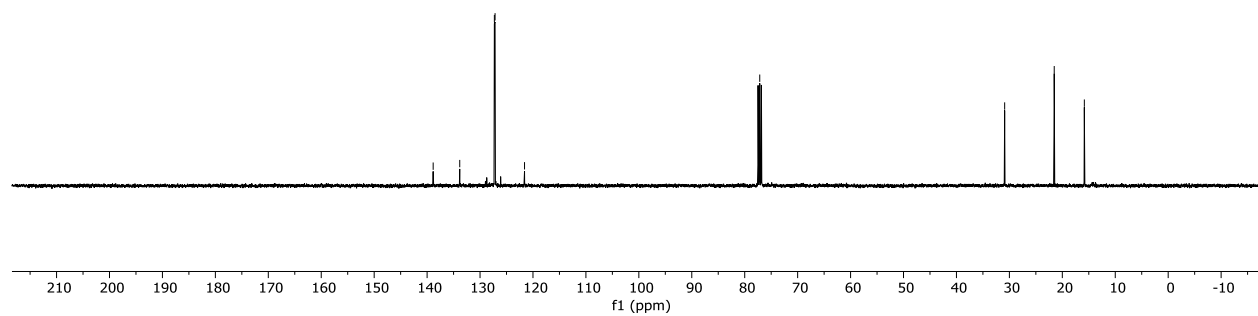
3e

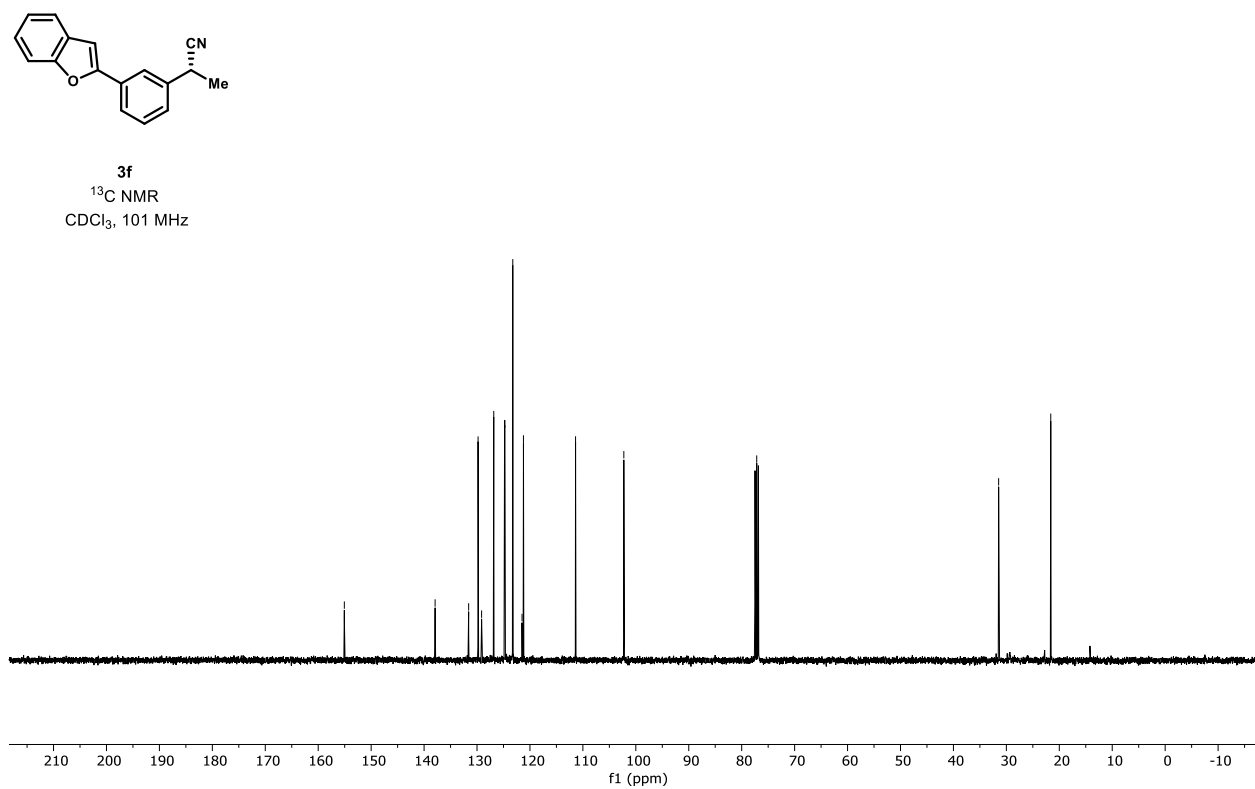
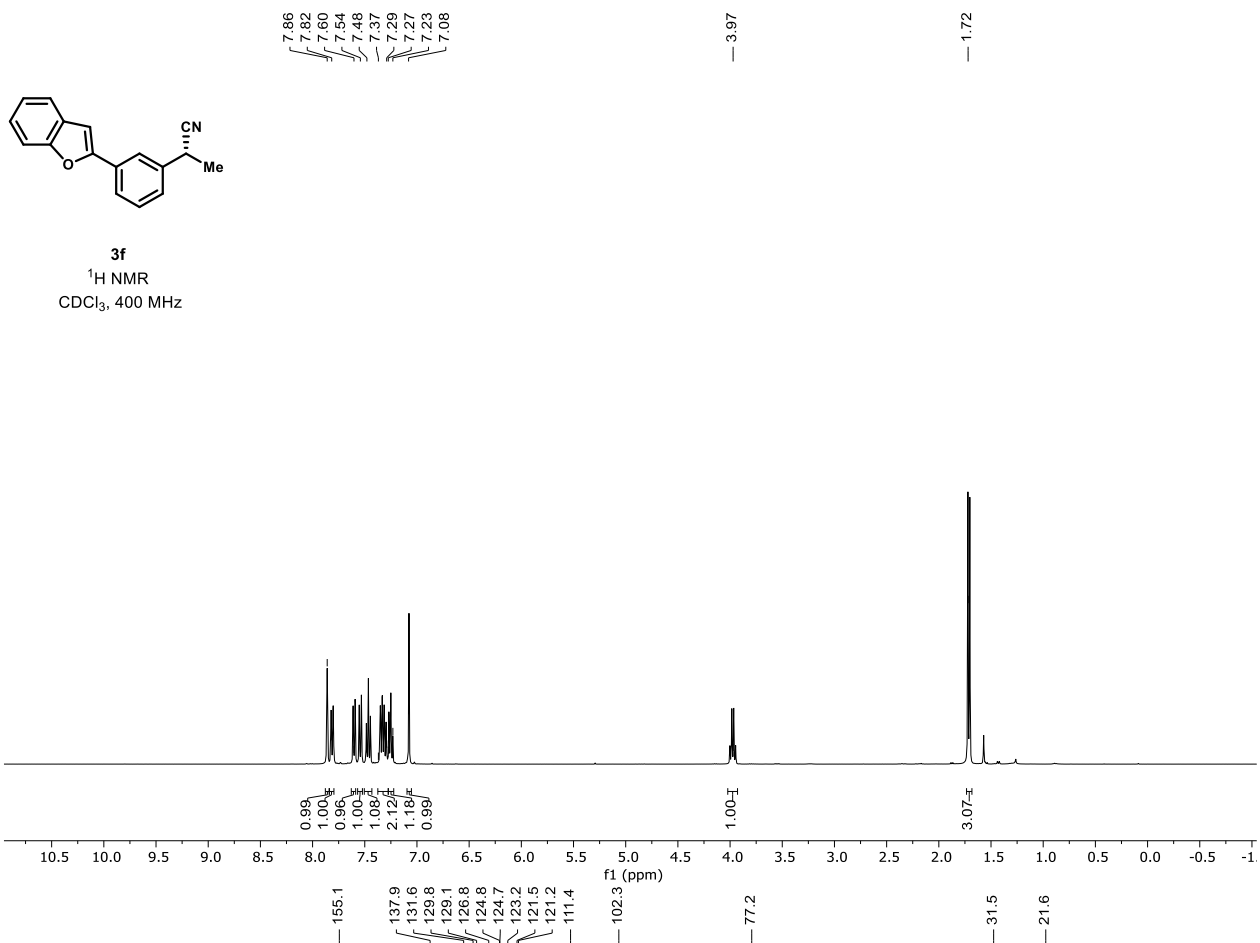
¹H NMR
CDCl₃, 400 MHz

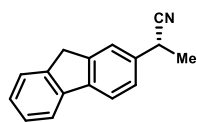


3e

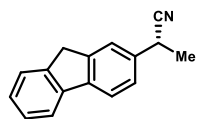
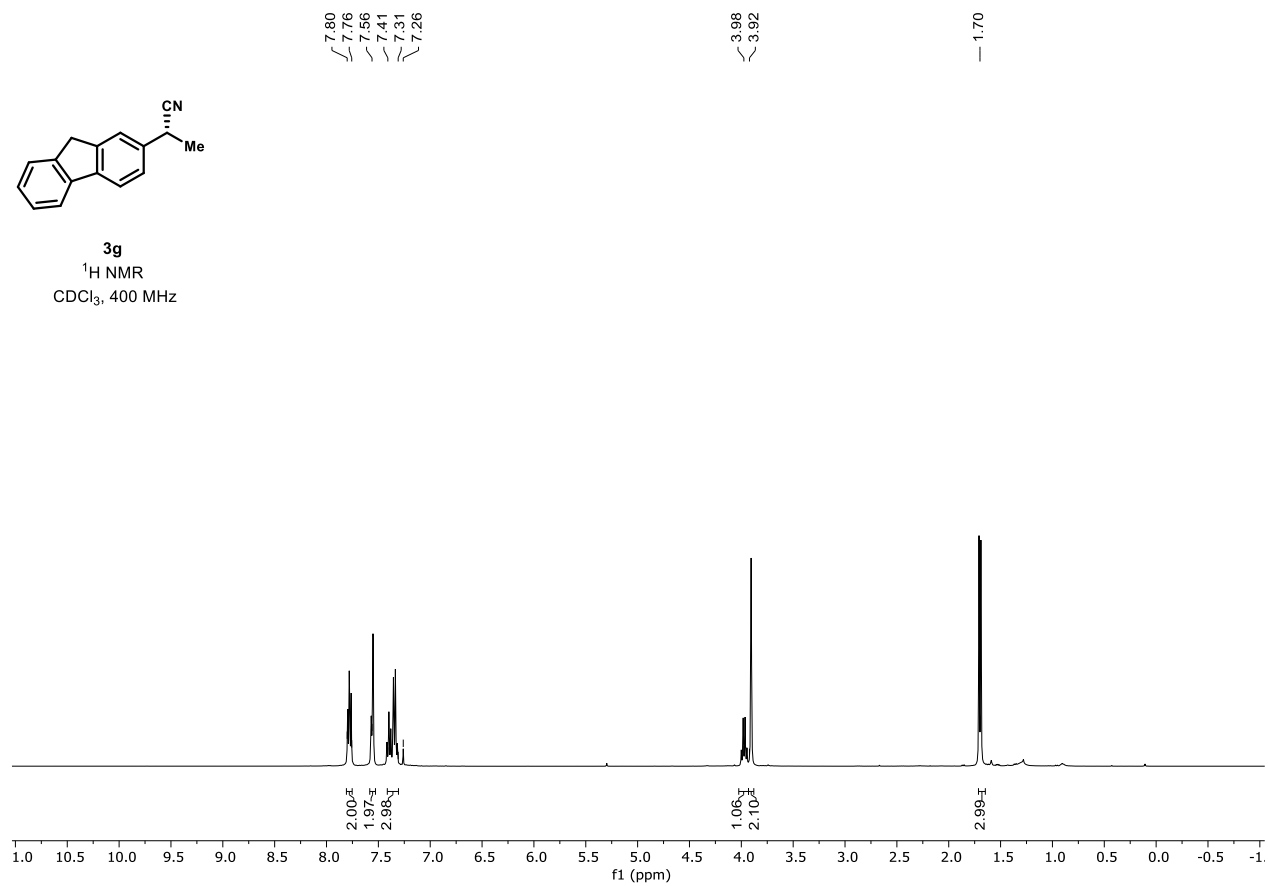
¹³C NMR
CDCl₃, 101 MHz



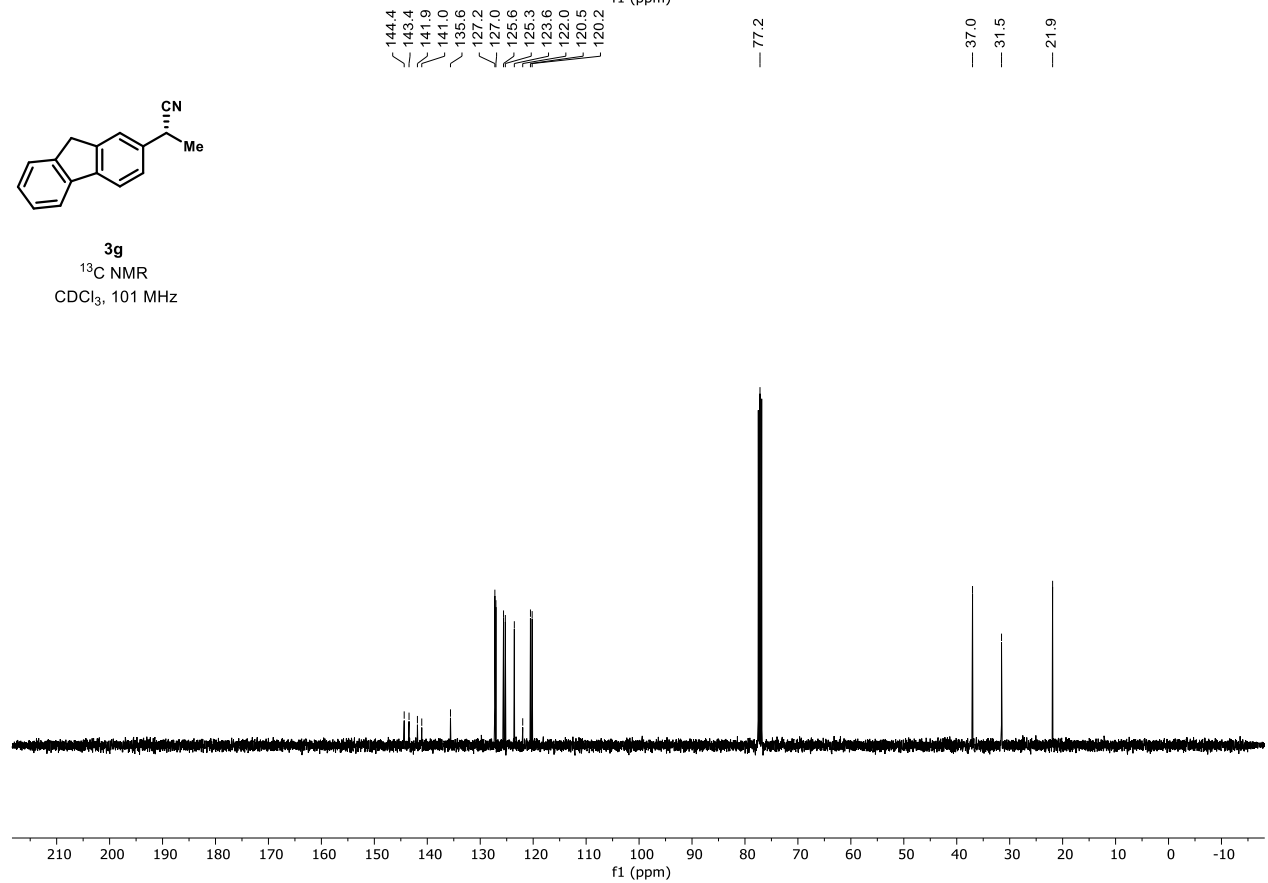


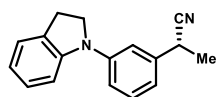


3g
¹H NMR
 CDCl₃, 400 MHz



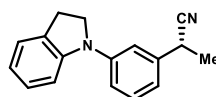
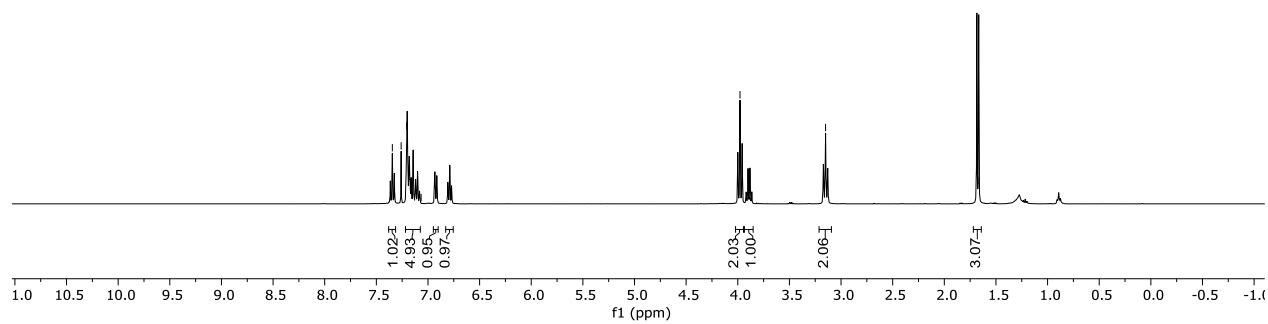
3g
¹³C NMR
 CDCl₃, 101 MHz





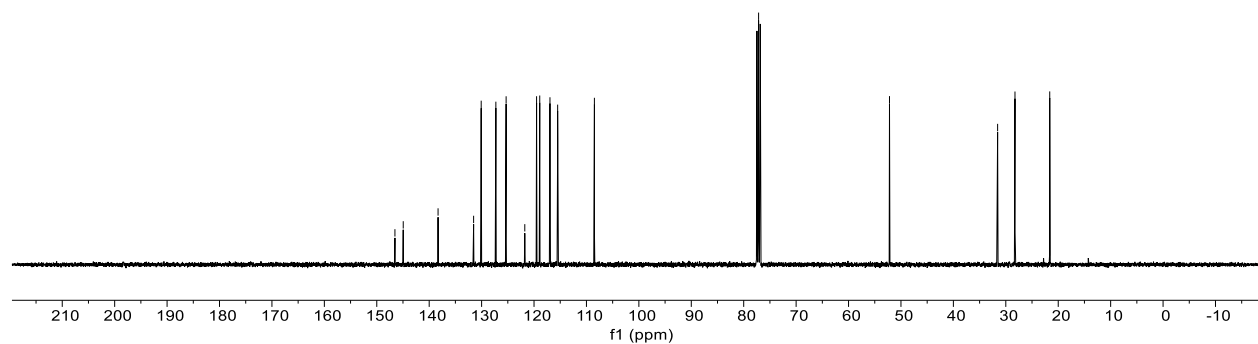
3h
¹H NMR
 CDCl₃, 400 MHz

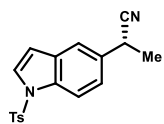
7.34
 7.26
 7.21
 7.07
 6.92
 6.76
 3.98
 3.89
 3.15
 1.67



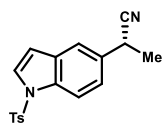
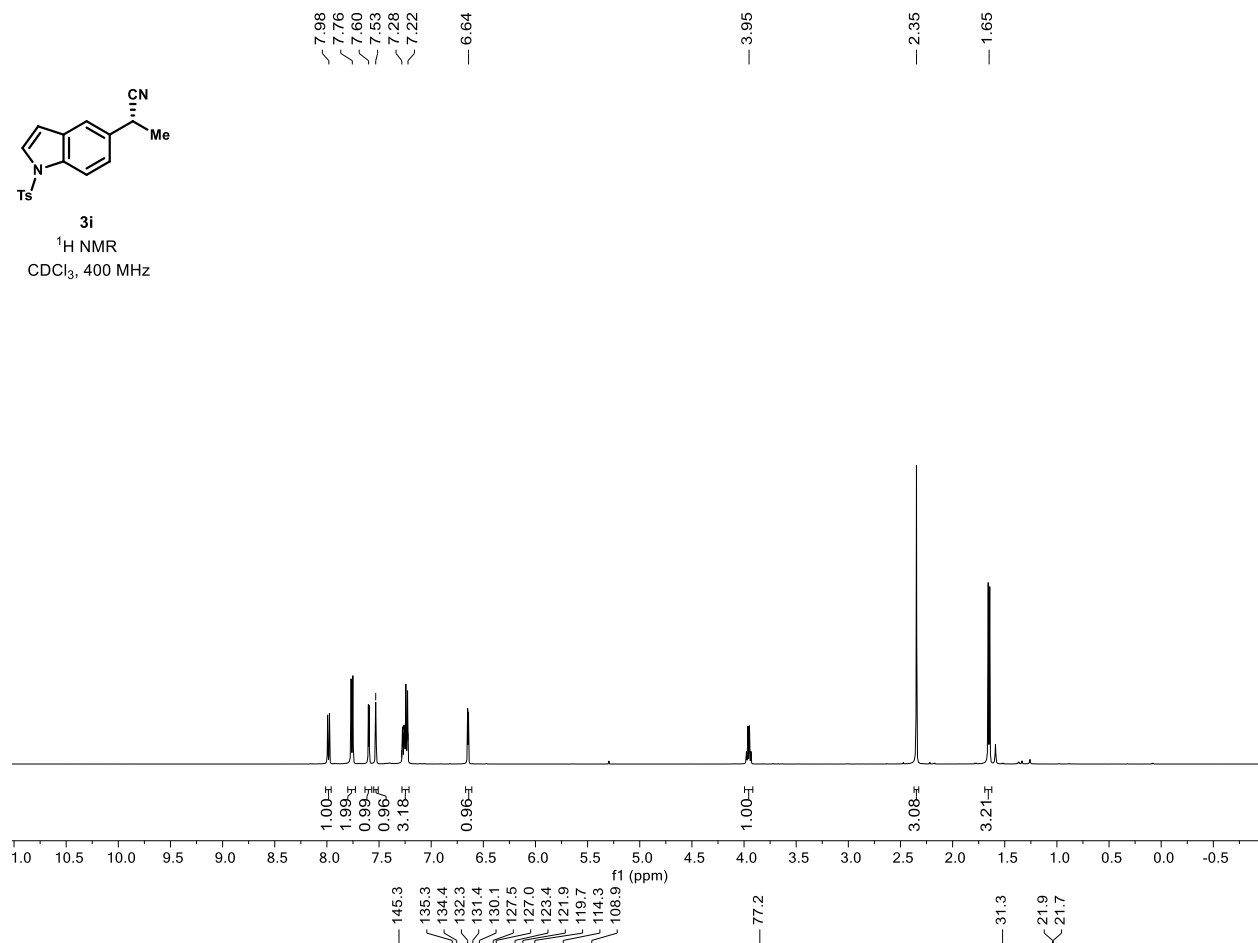
3h
¹³C NMR
 CDCl₃, 101 MHz

146.5
 145.0
 138.3
 131.5
 130.1
 127.3
 125.3
 121.8
 119.5
 118.9
 117.0
 115.5
 108.5
 77.2
 52.2
 31.6
 28.2
 21.6

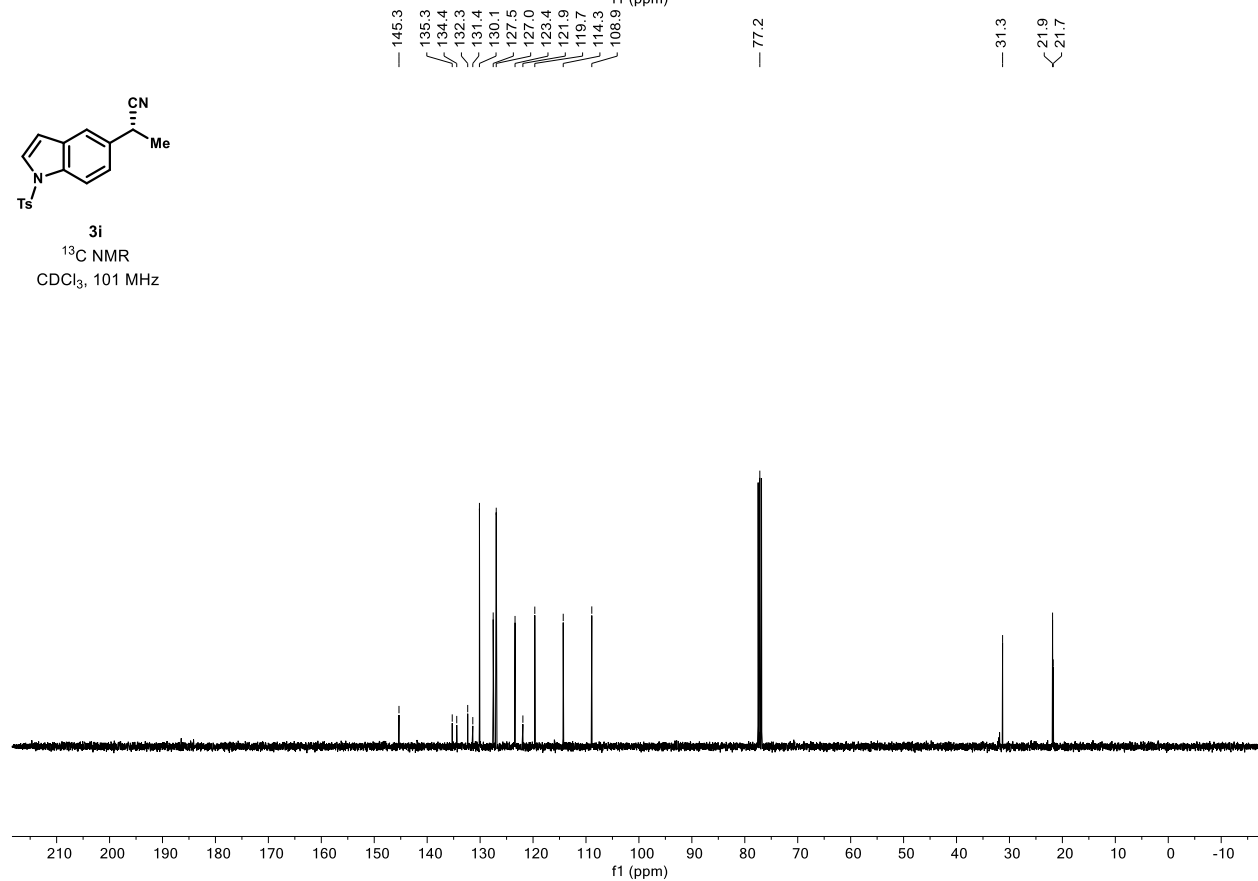


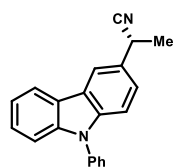


3i
¹H NMR
 CDCl₃, 400 MHz



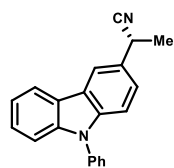
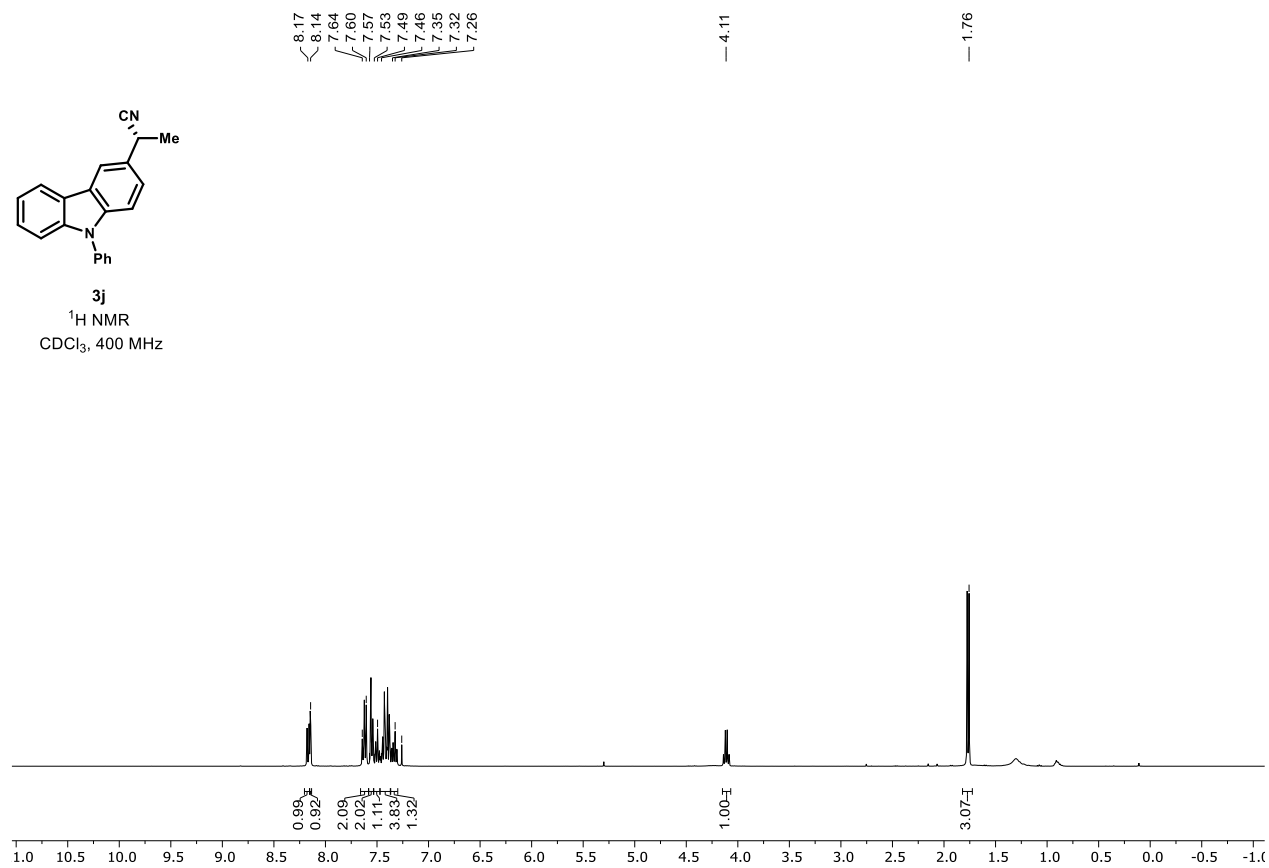
3i
¹³C NMR
 CDCl₃, 101 MHz





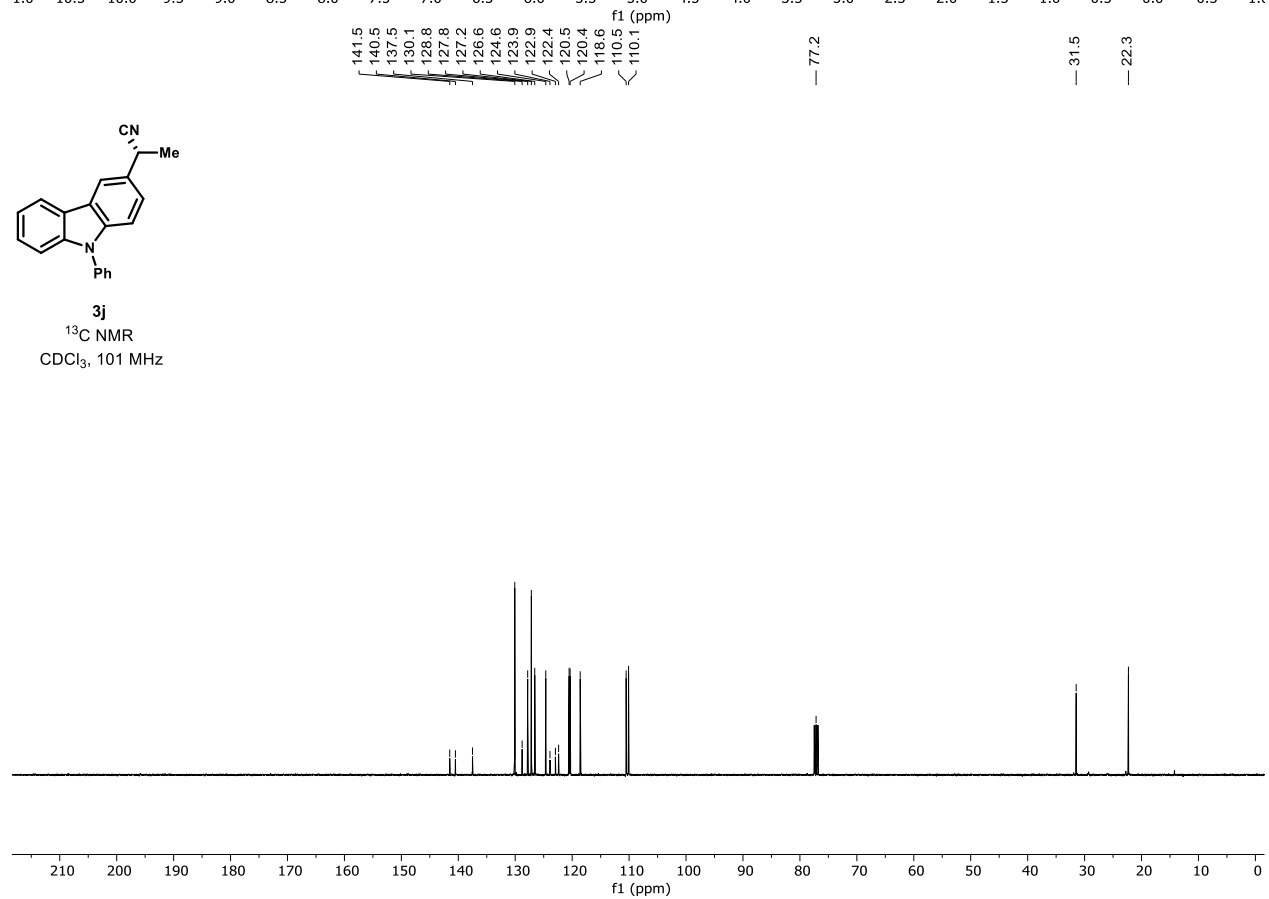
3j

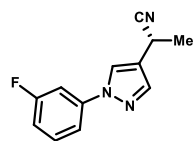
¹H NMR
CDCl₃, 400 MHz



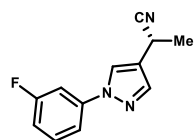
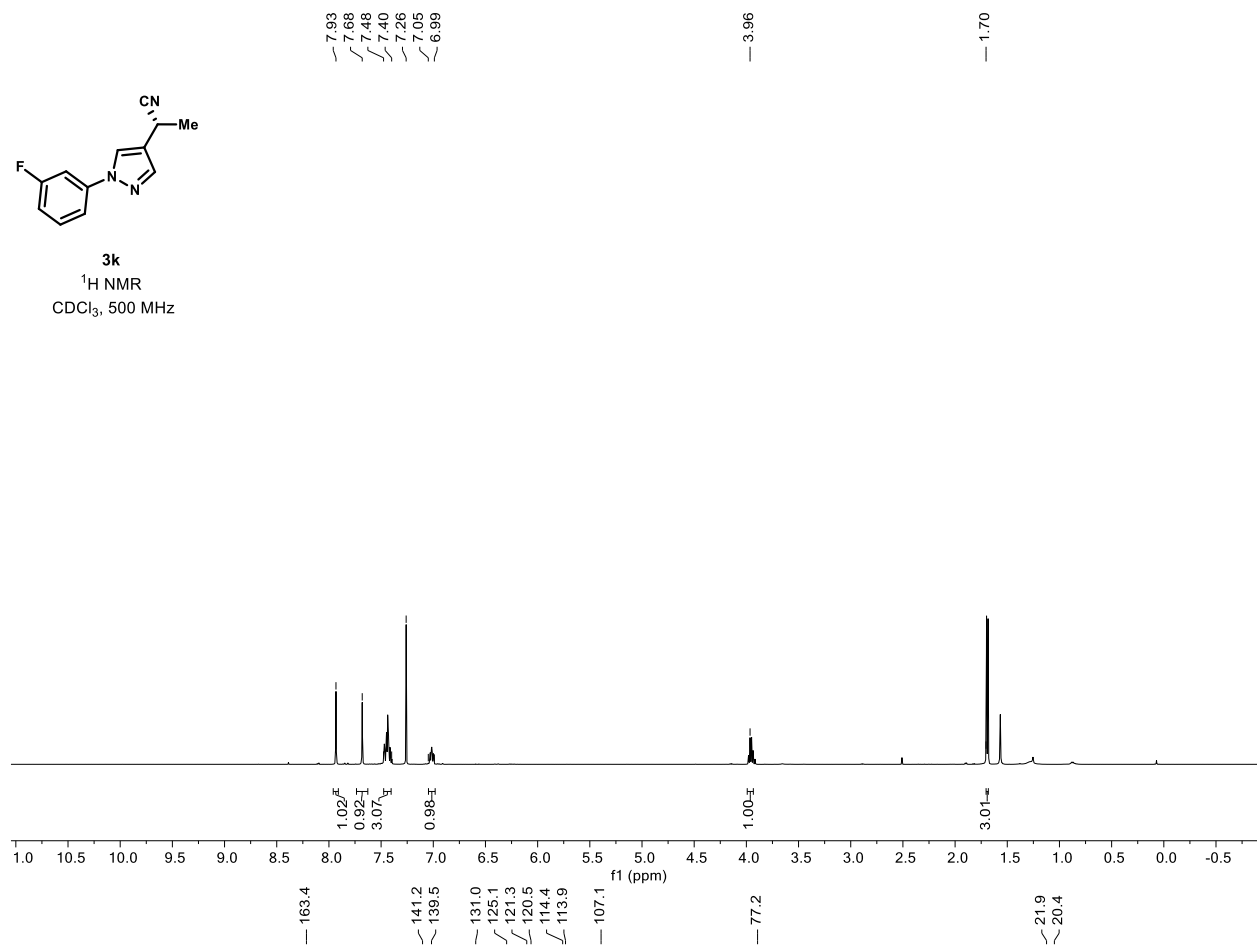
3j

¹³C NMR
CDCl₃, 101 MHz

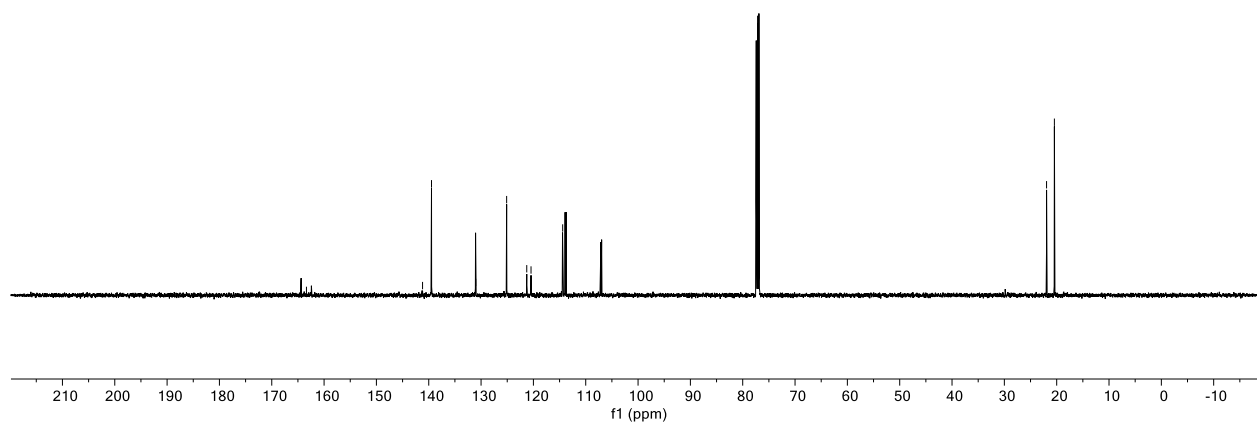


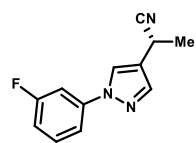


3k
¹H NMR
 CDCl₃, 500 MHz

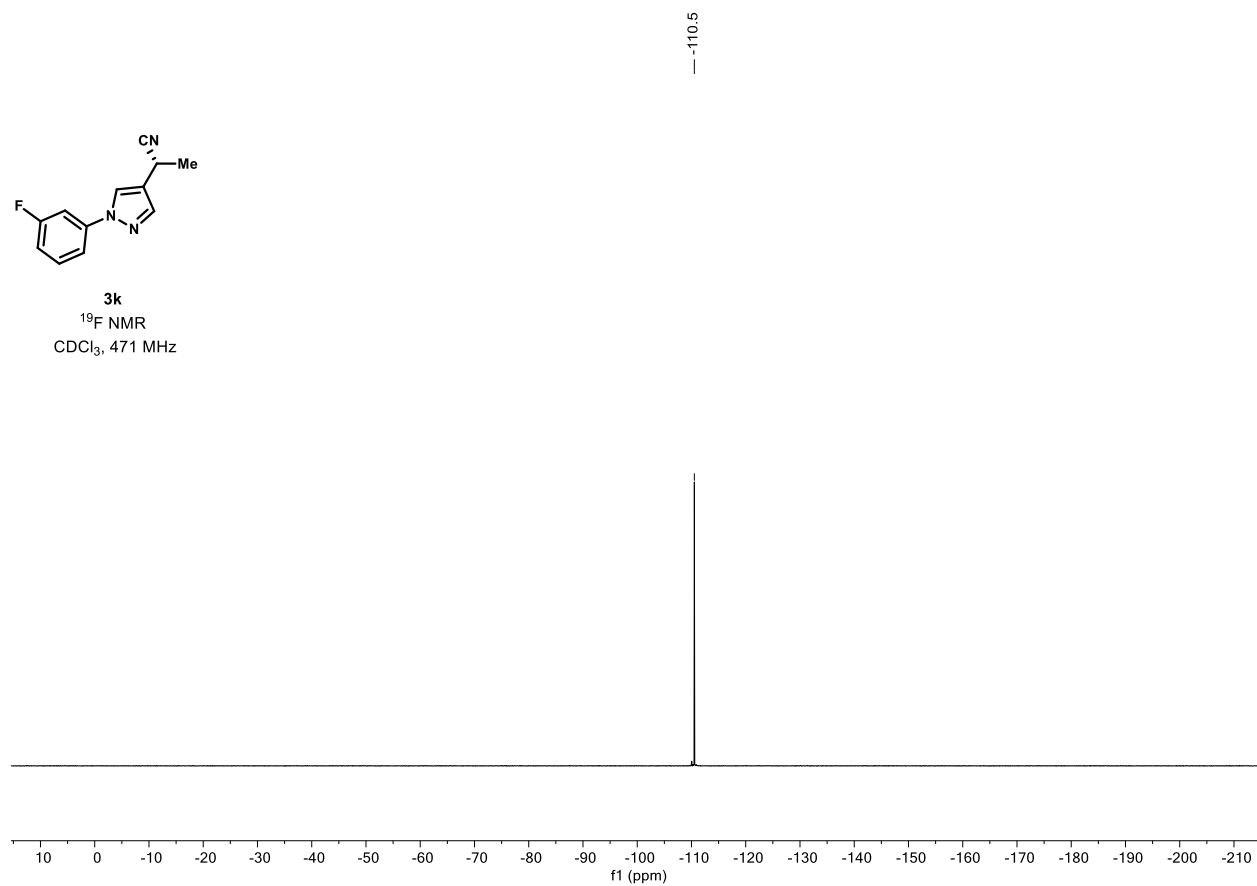


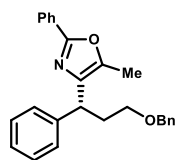
3k
¹³C NMR
 CDCl₃, 126 MHz





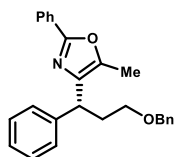
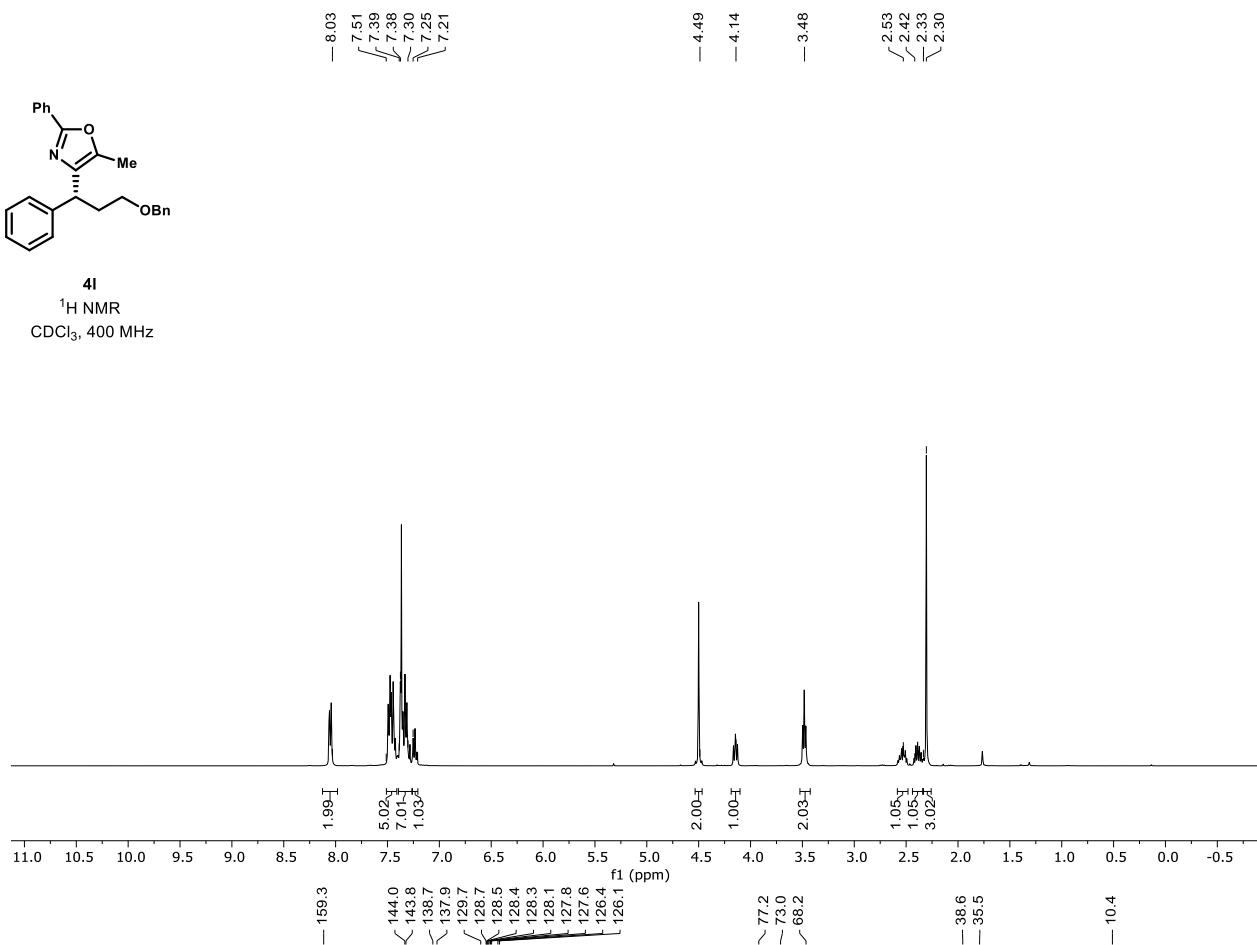
3k
¹⁹F NMR
CDCl₃, 471 MHz





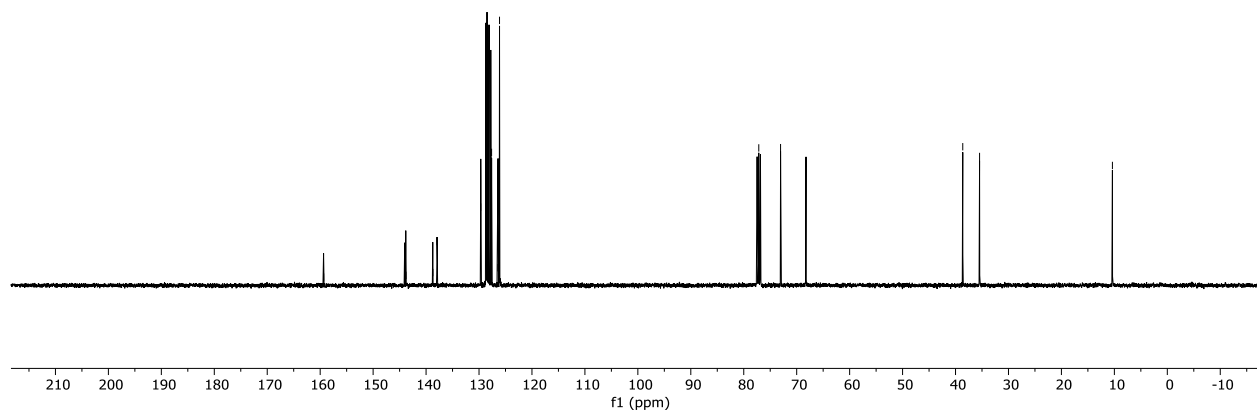
4l

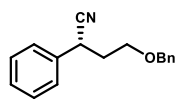
¹H NMR
CDCl₃, 400 MHz



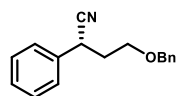
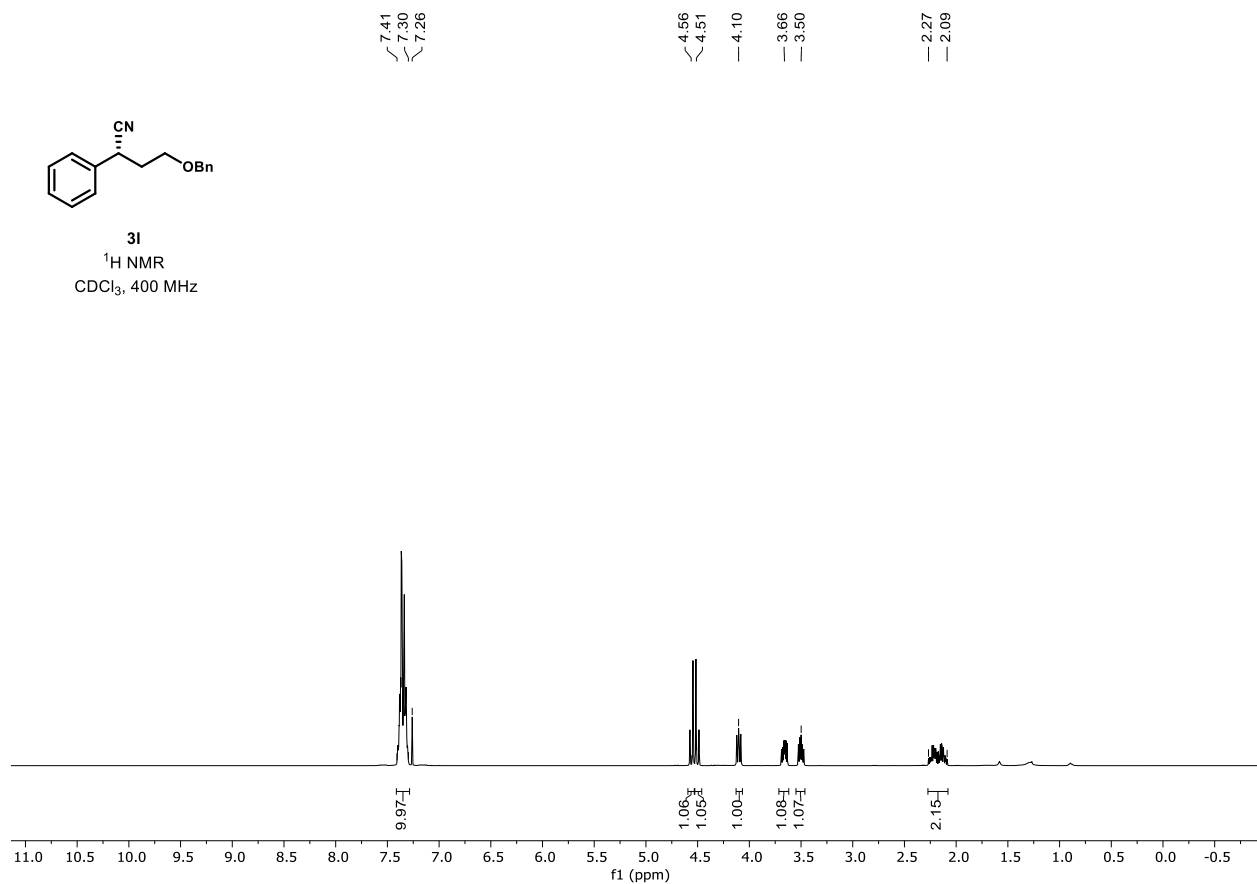
4l

¹³C NMR
CDCl₃, 101 MHz

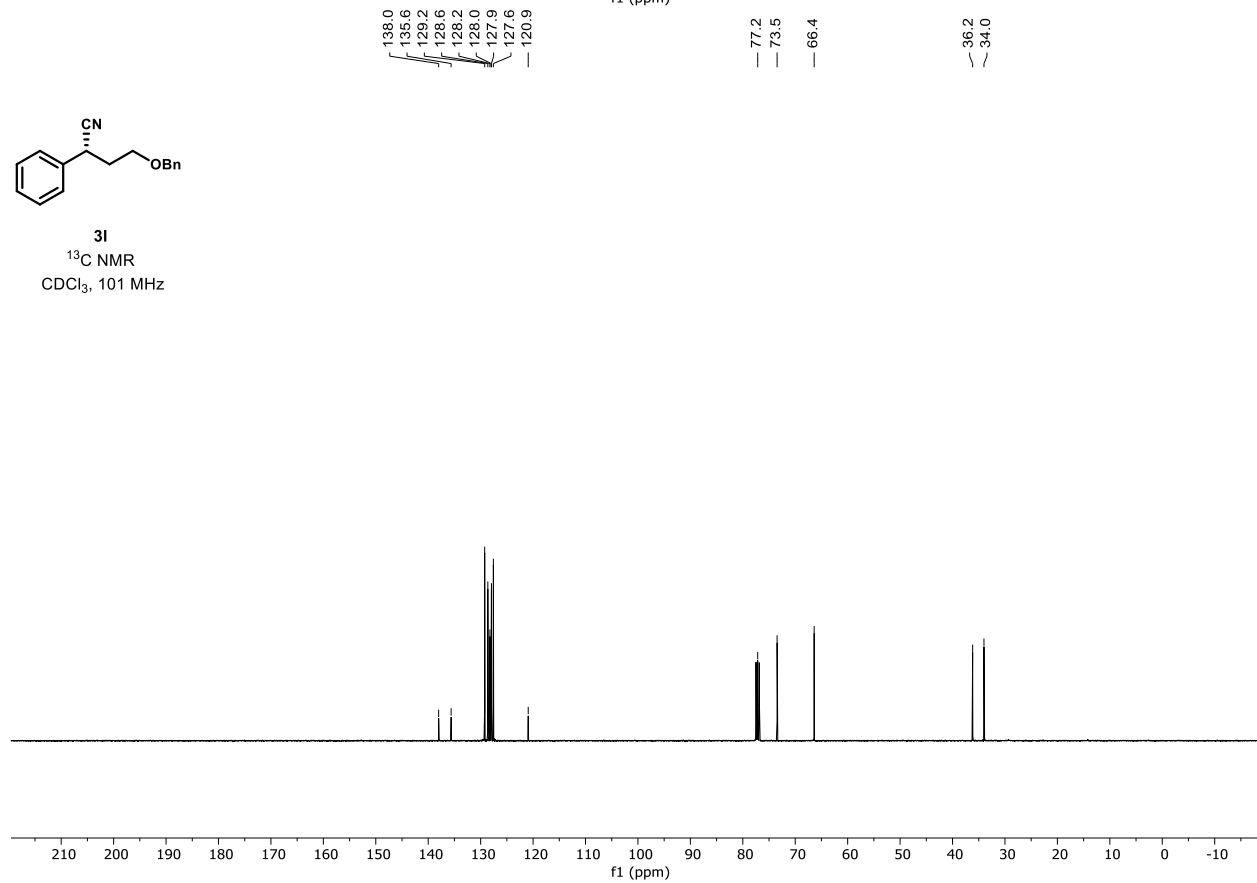


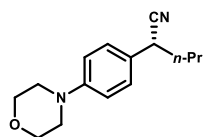


3l
¹H NMR
 CDCl₃, 400 MHz

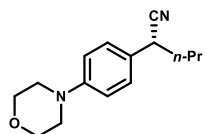
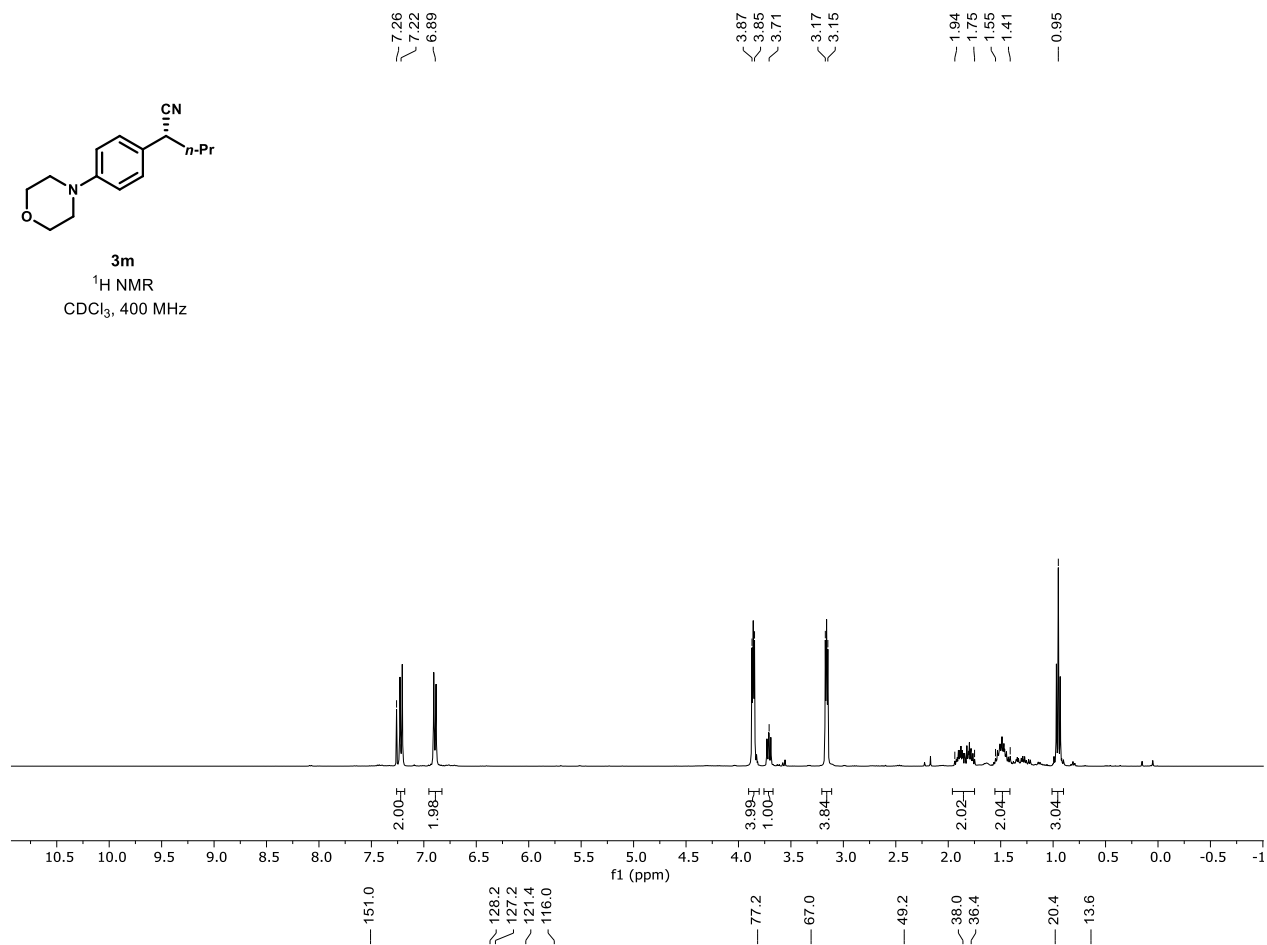


3l
¹³C NMR
 CDCl₃, 101 MHz

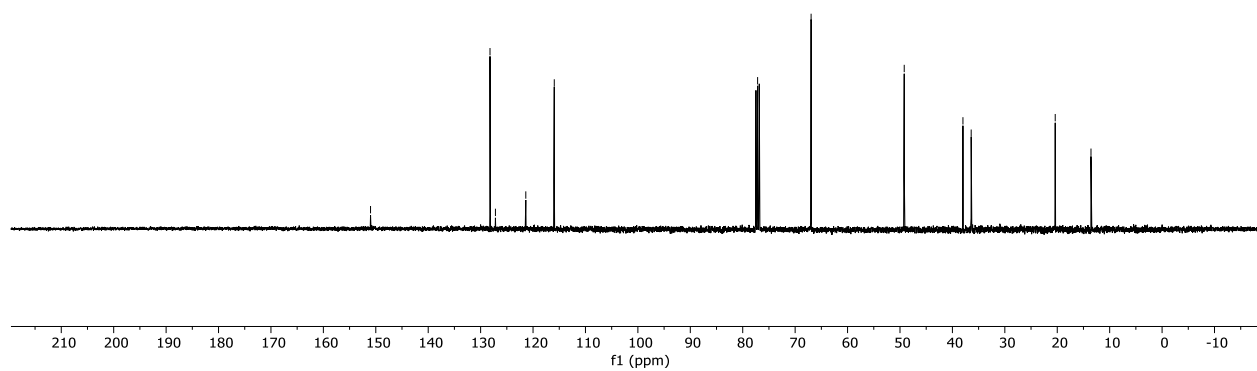


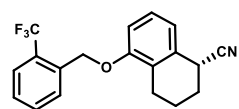


3m
¹H NMR
 CDCl₃, 400 MHz

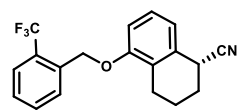
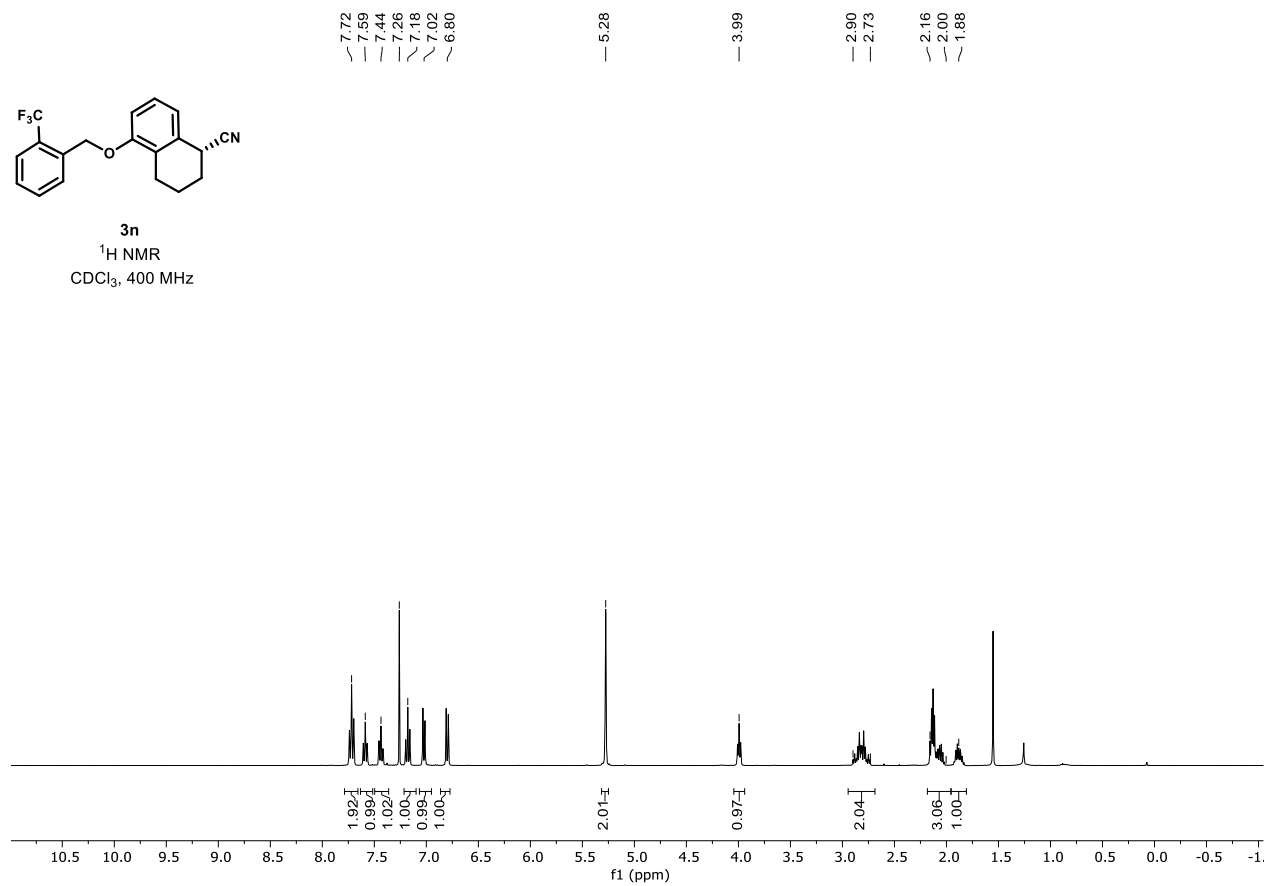


3m
¹³C NMR
 CDCl₃, 101 MHz

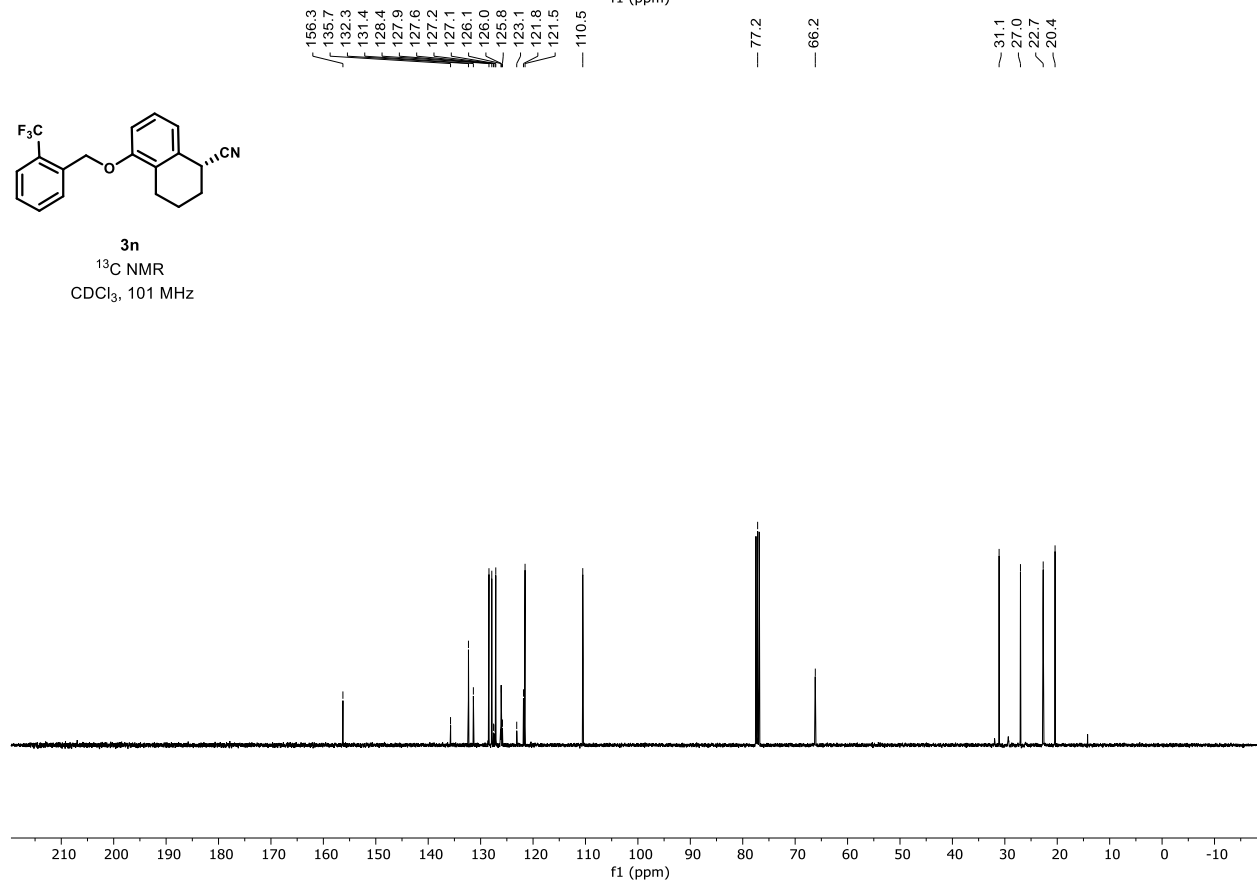


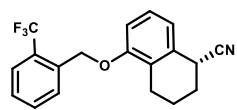


3n
¹H NMR
 CDCl₃, 400 MHz

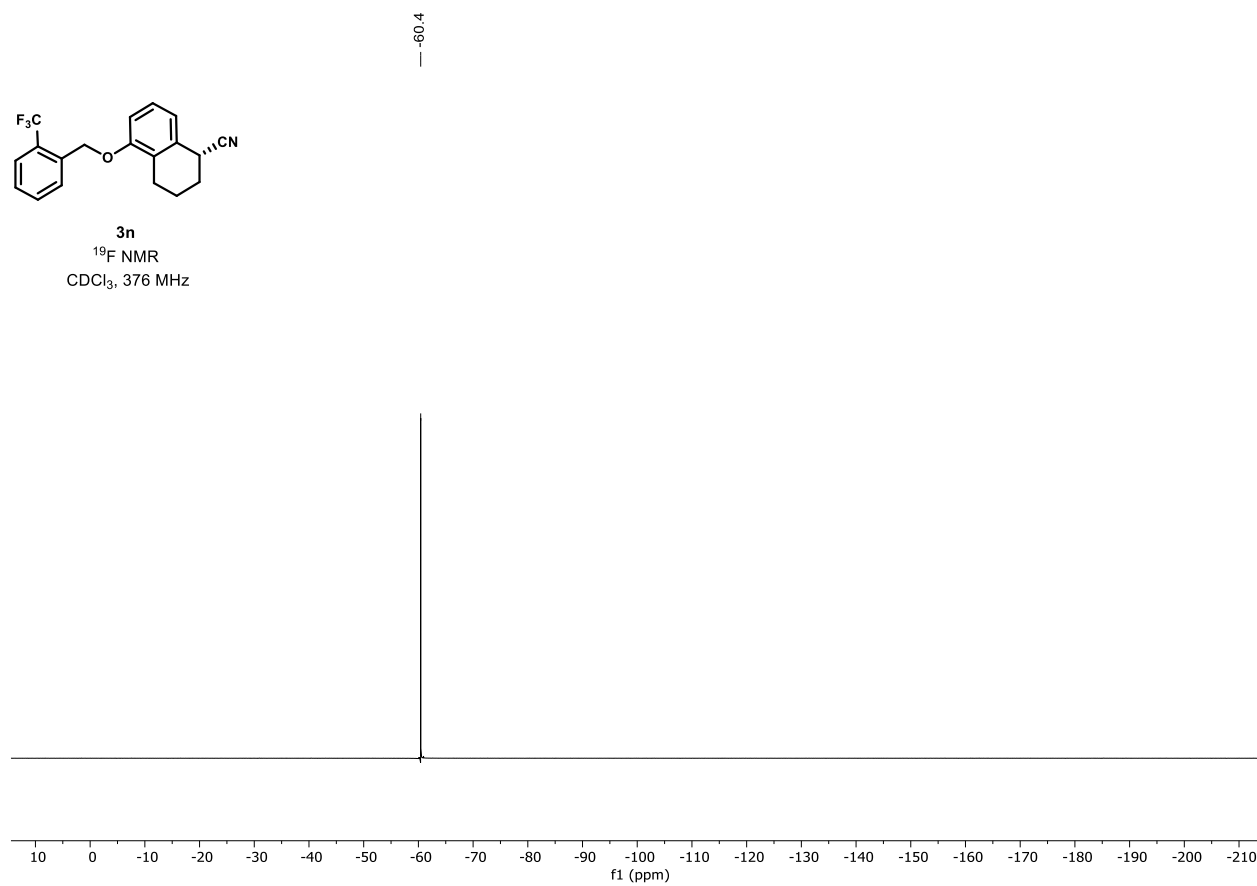


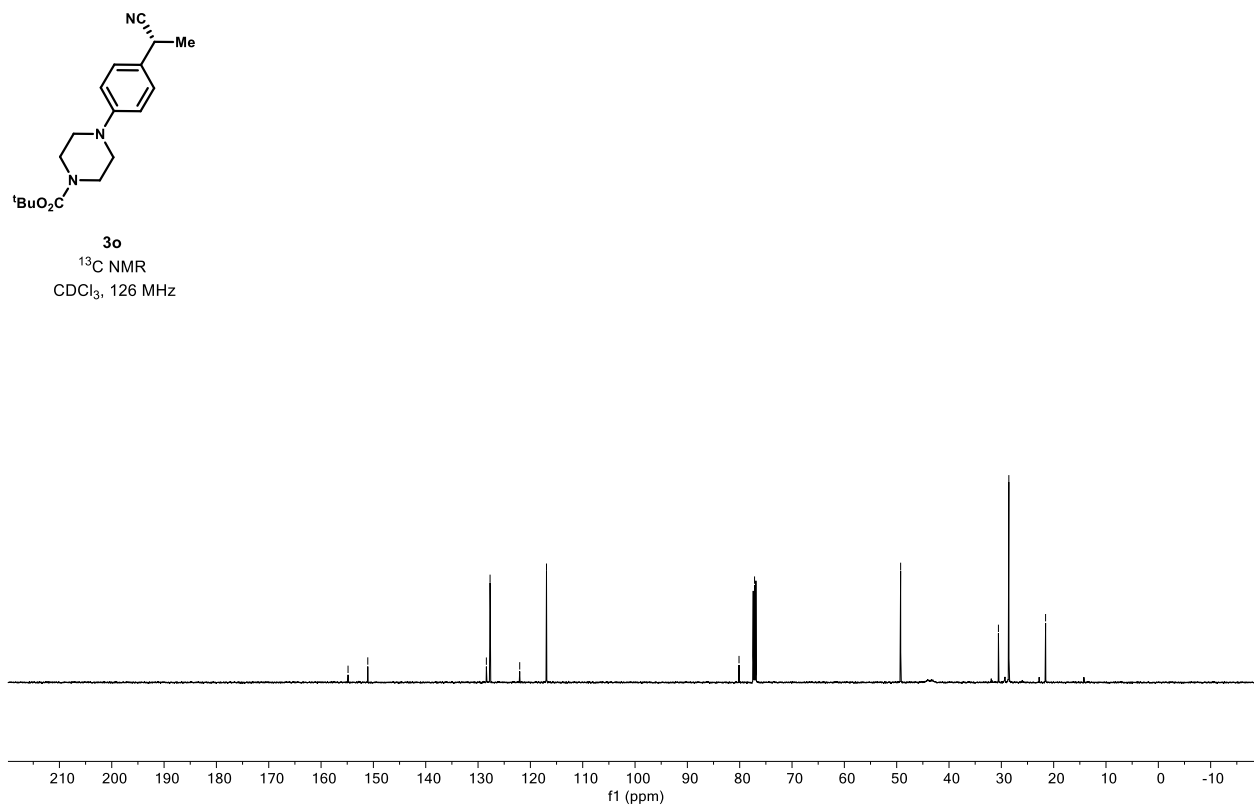
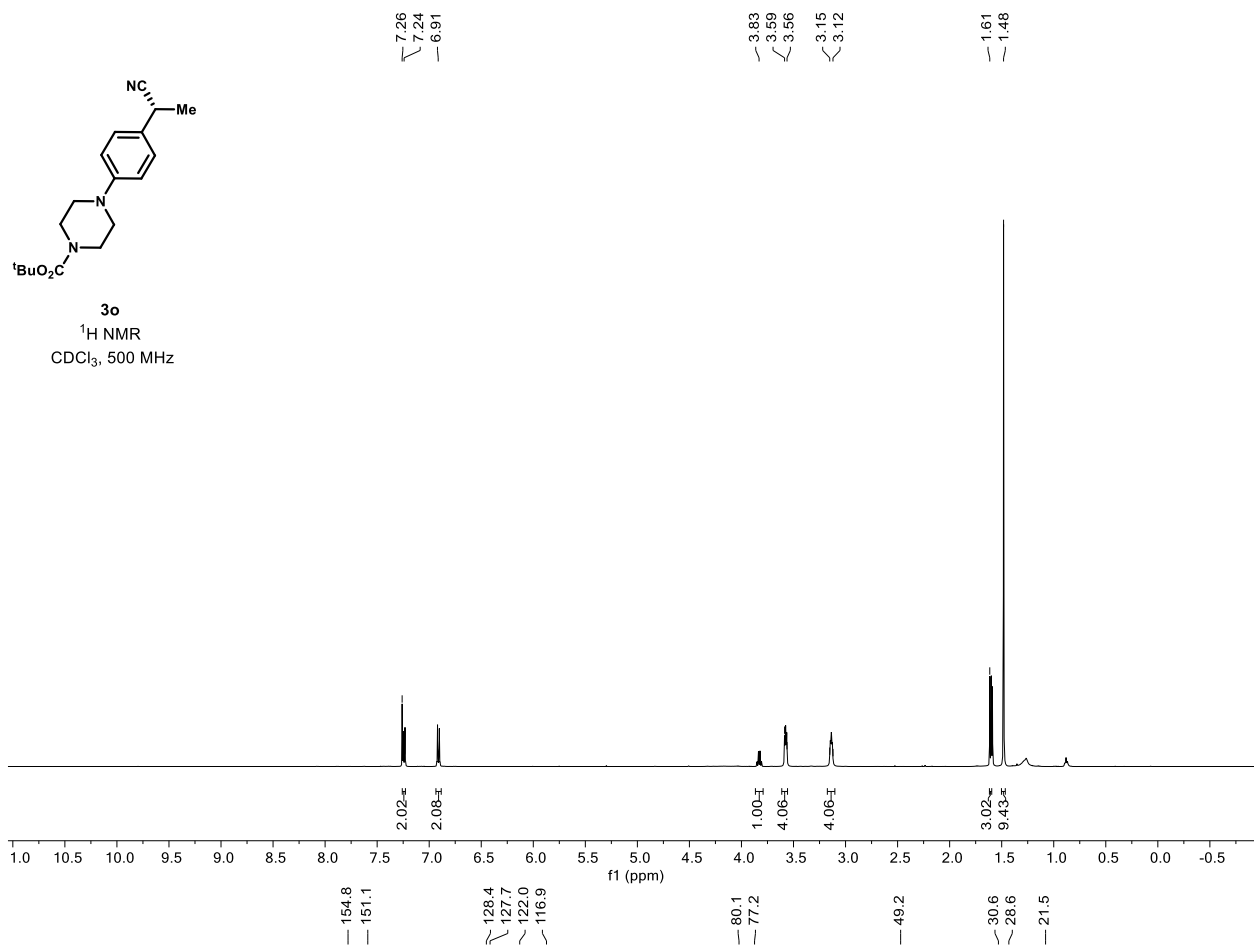
3n
¹³C NMR
 CDCl₃, 101 MHz

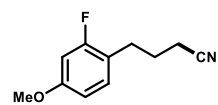




3n
¹⁹F NMR
 CDCl₃, 376 MHz



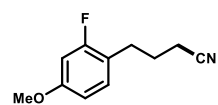
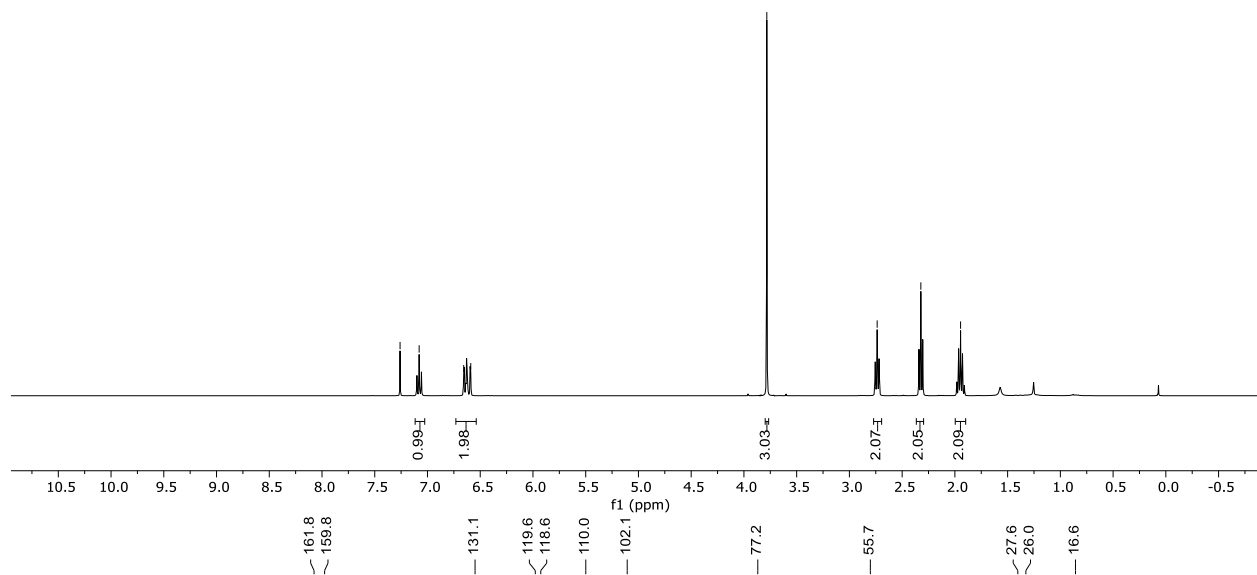




10a

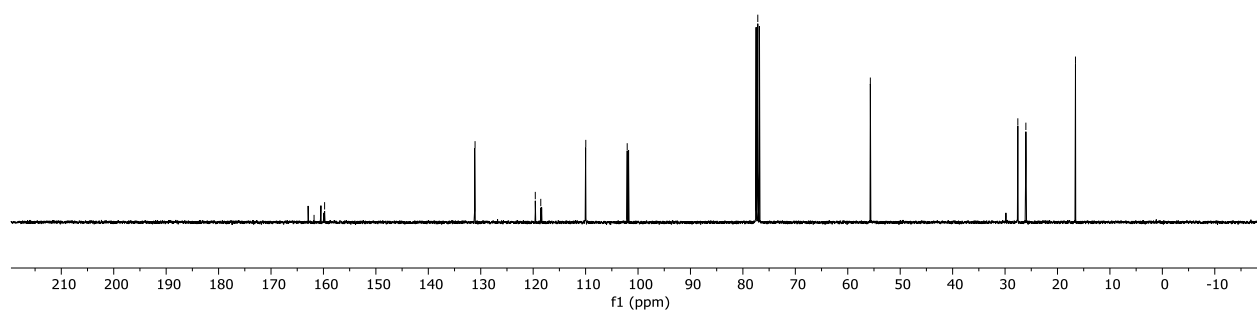
¹H NMR
CDCl₃, 400 MHz

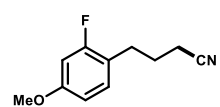
7.26
7.08
6.86
6.59
3.78
2.74
2.32
1.95



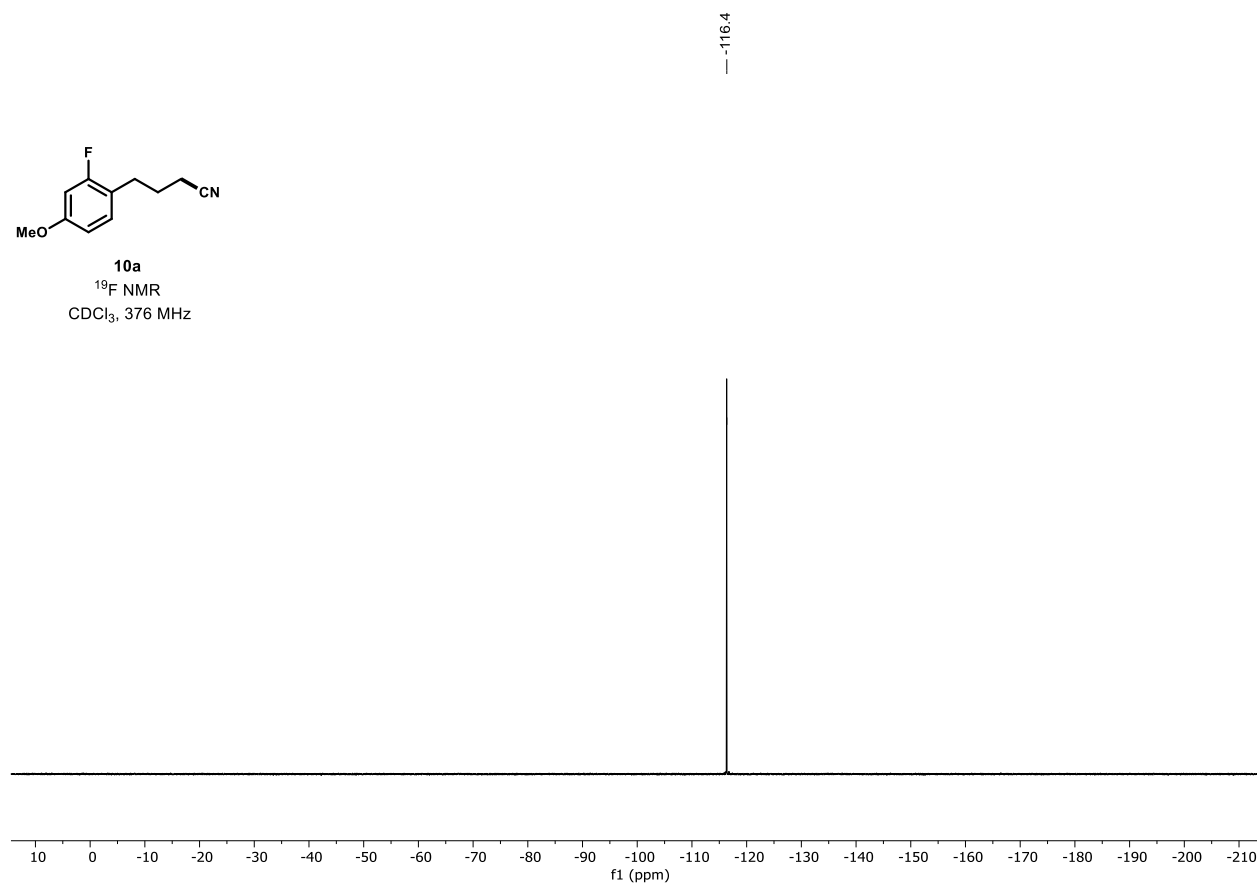
10a

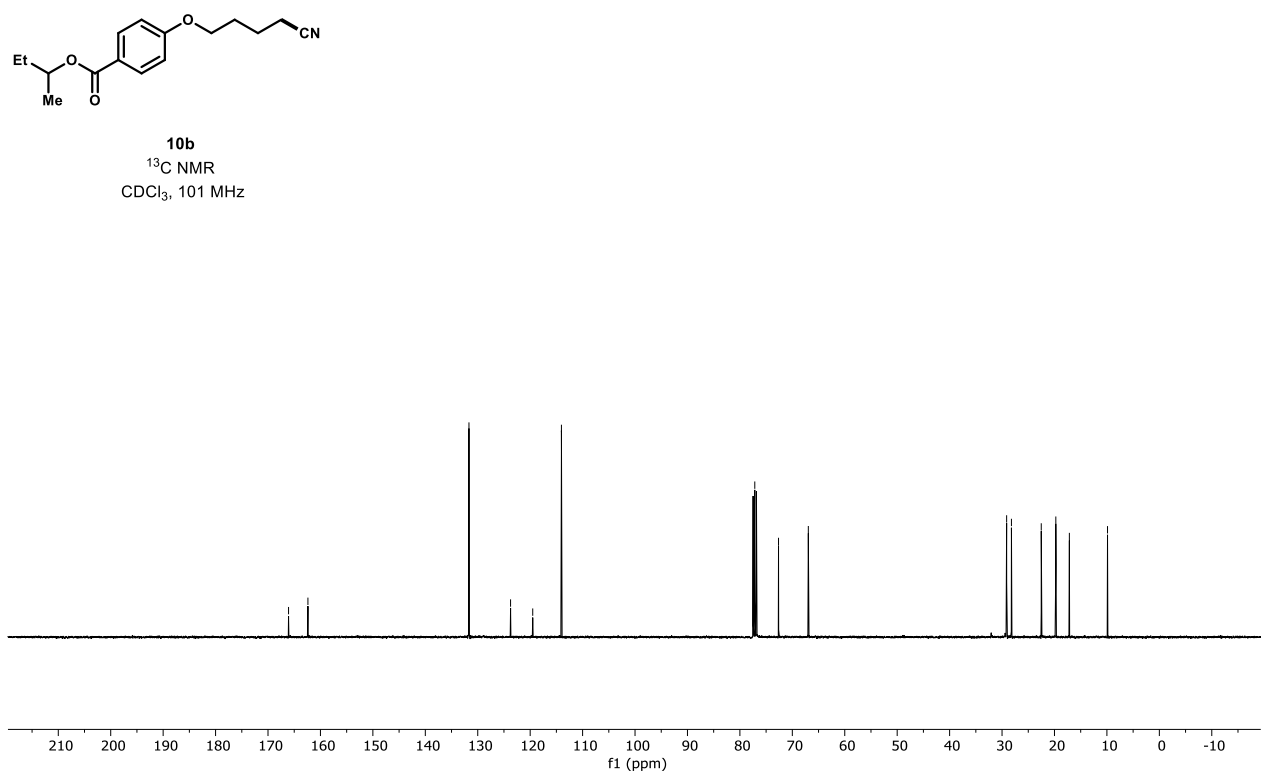
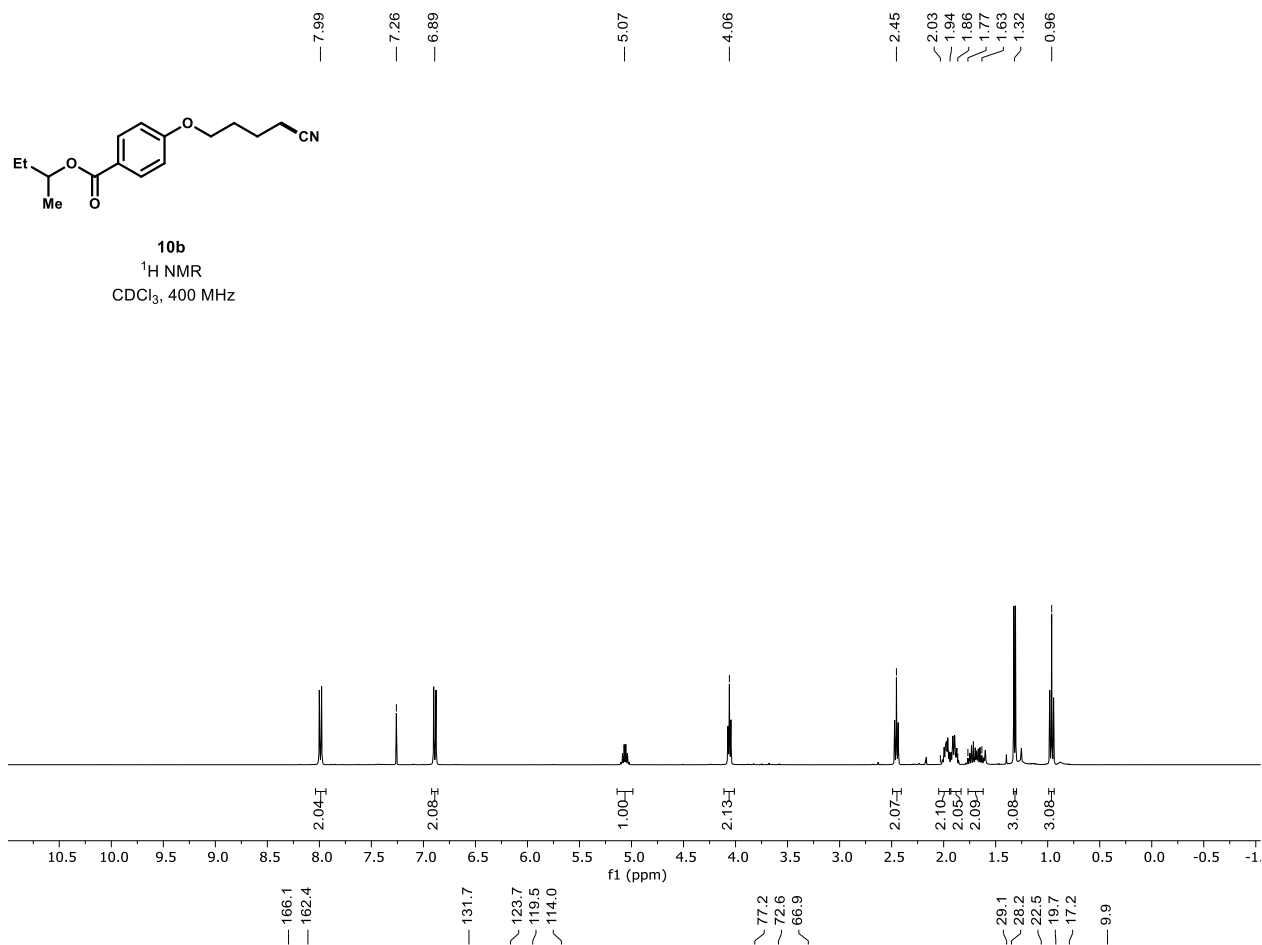
¹³C NMR
CDCl₃, 101 MHz

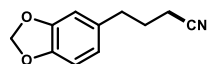




10a
¹⁹F NMR
CDCl₃, 376 MHz

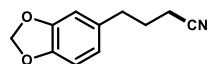
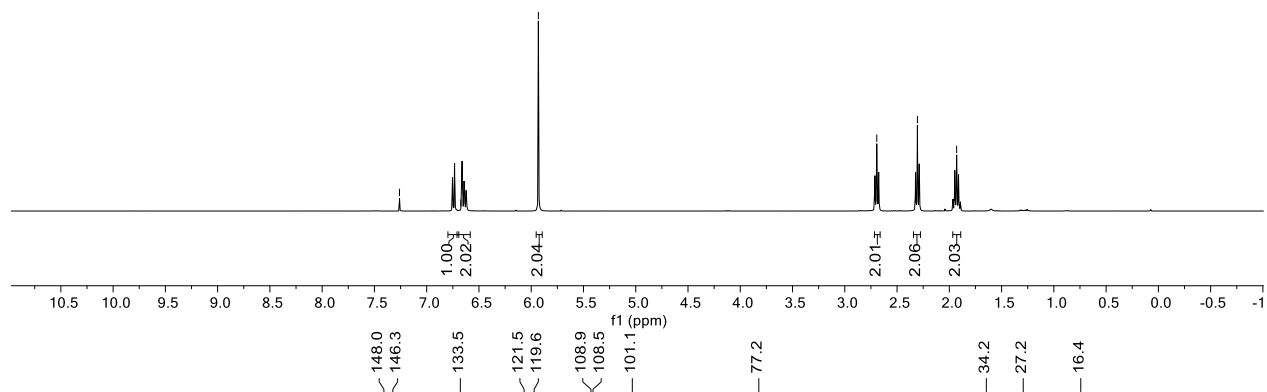




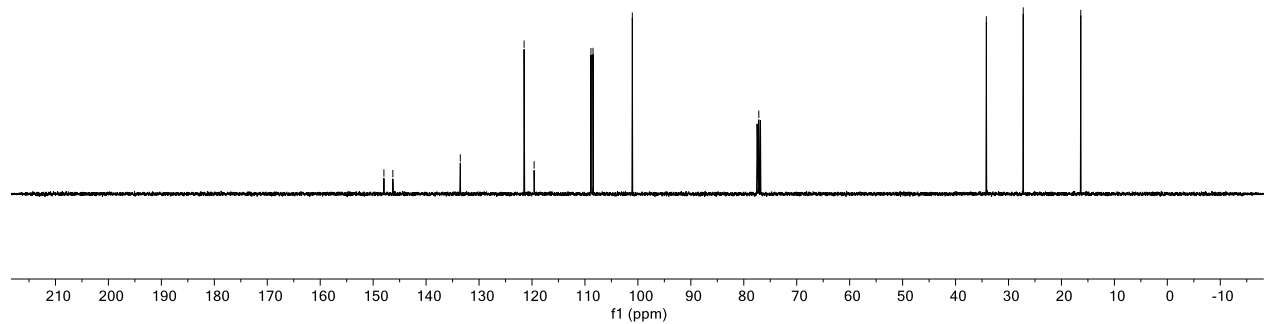


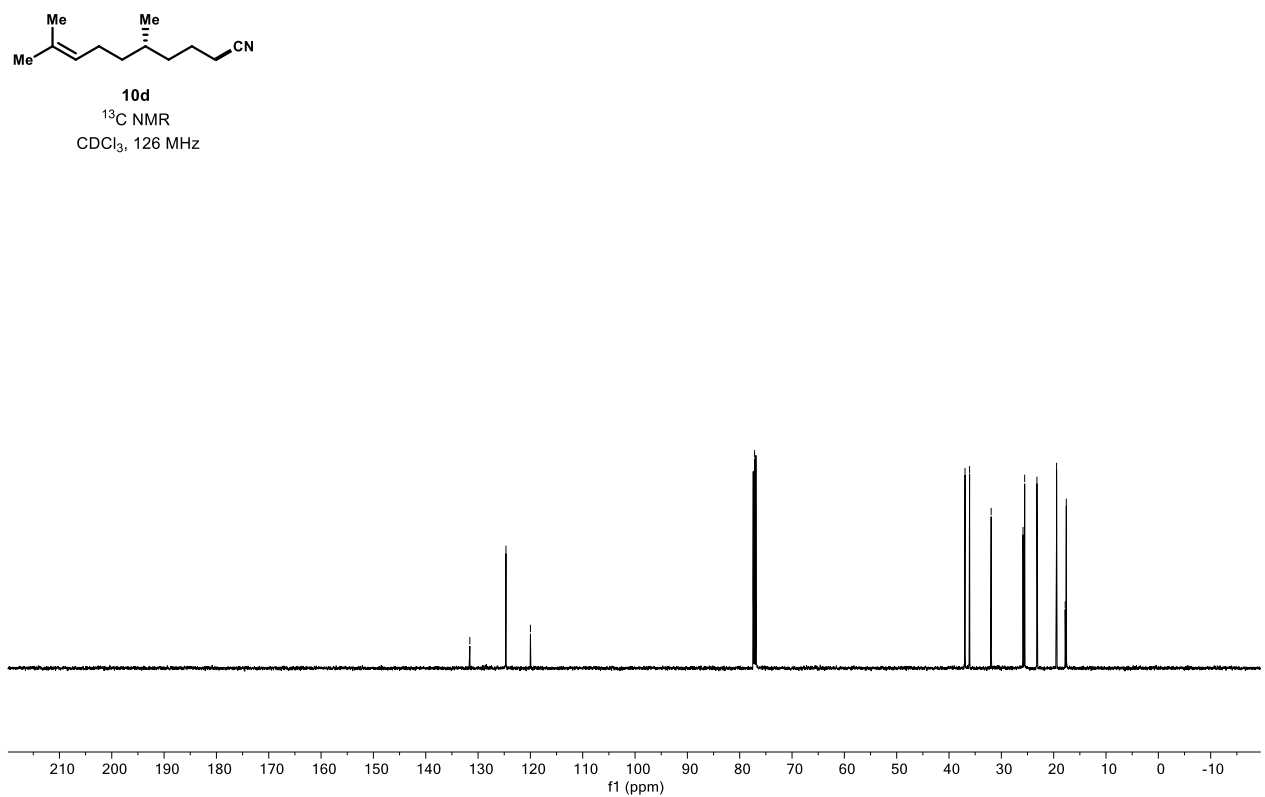
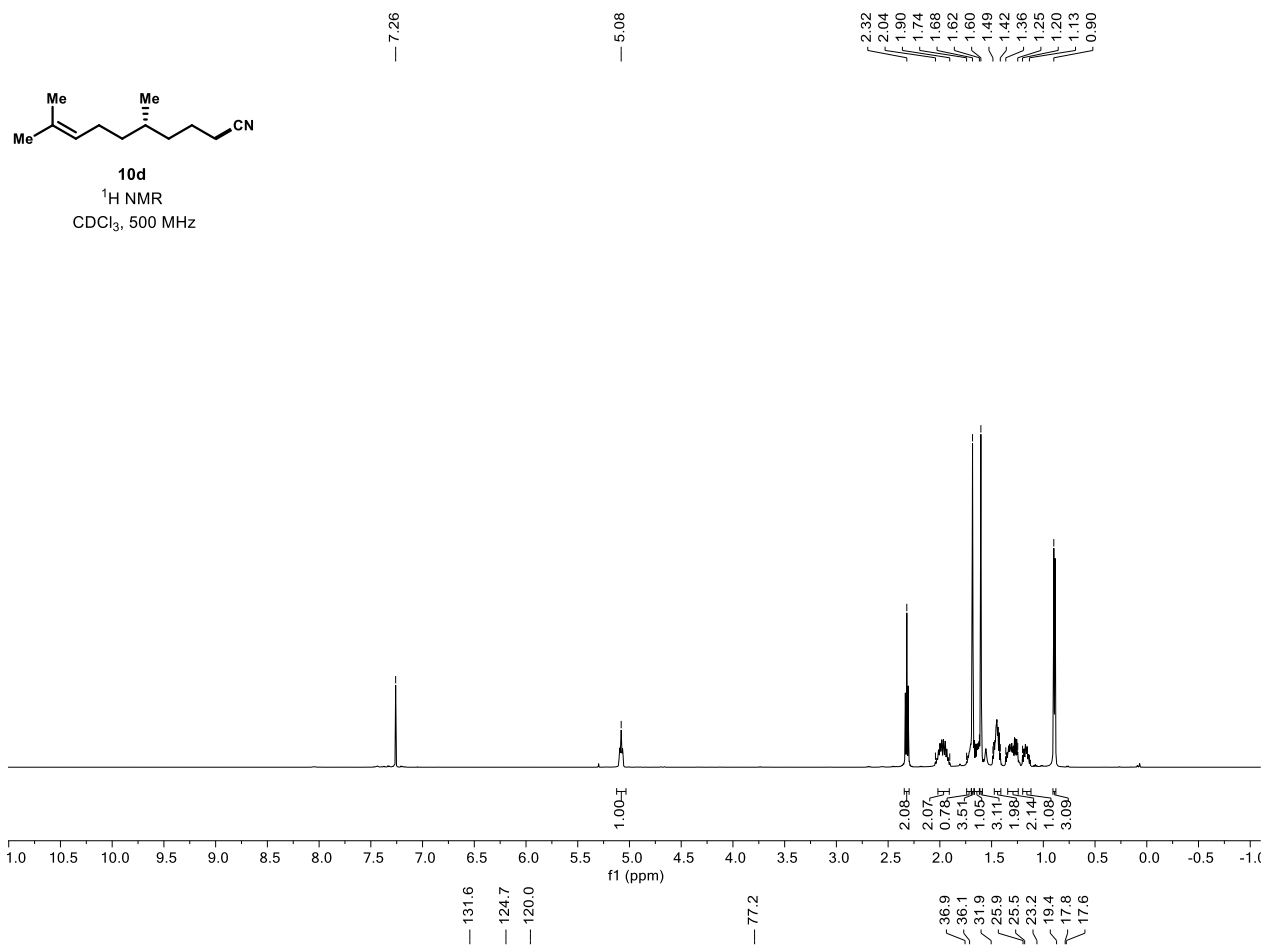
10c
¹H NMR
 CDCl₃, 400 MHz

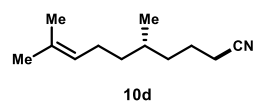
— 7.26
 — 6.74
 — 6.67
 — 6.63
 — 5.93
 — 2.69
 — 2.31
 — 1.93



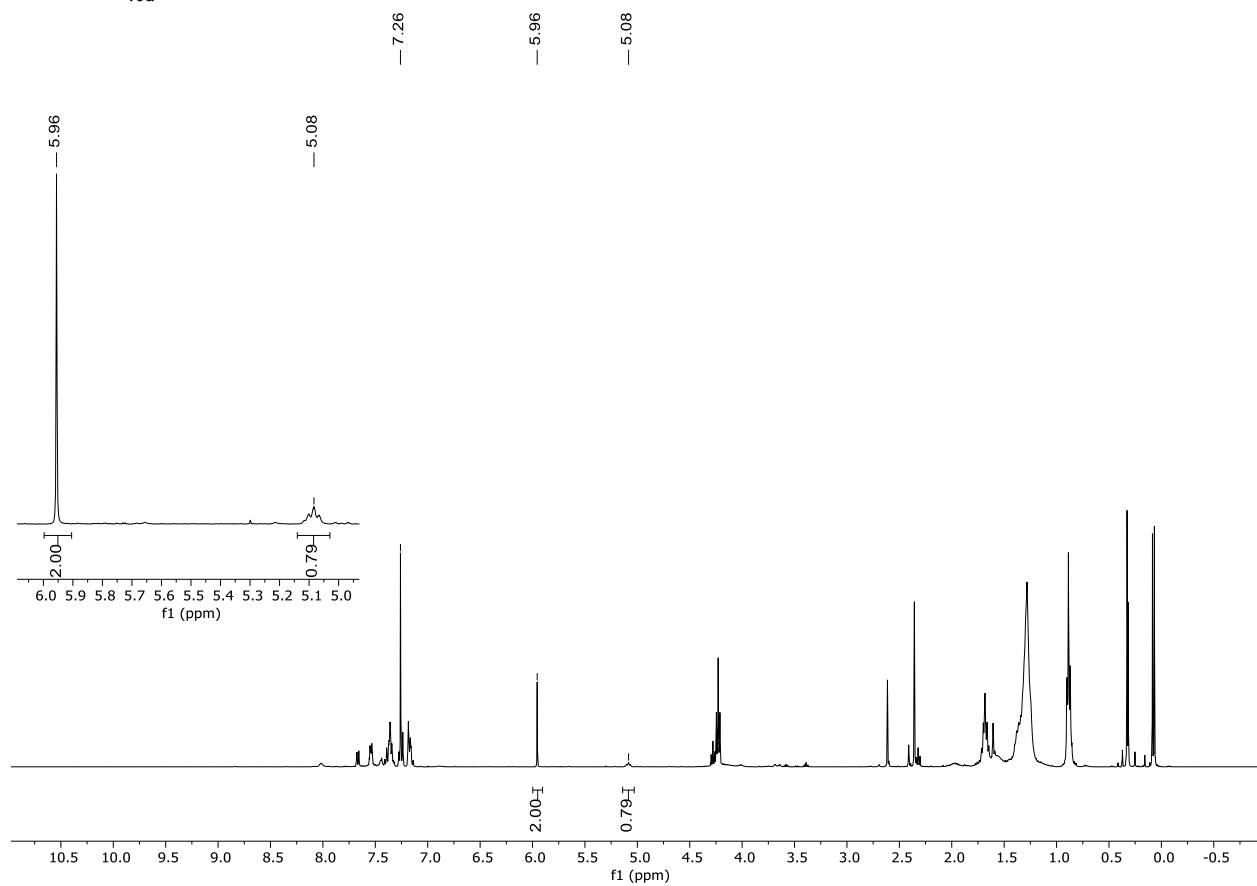
10c
¹³C NMR
 CDCl₃, 101 MHz

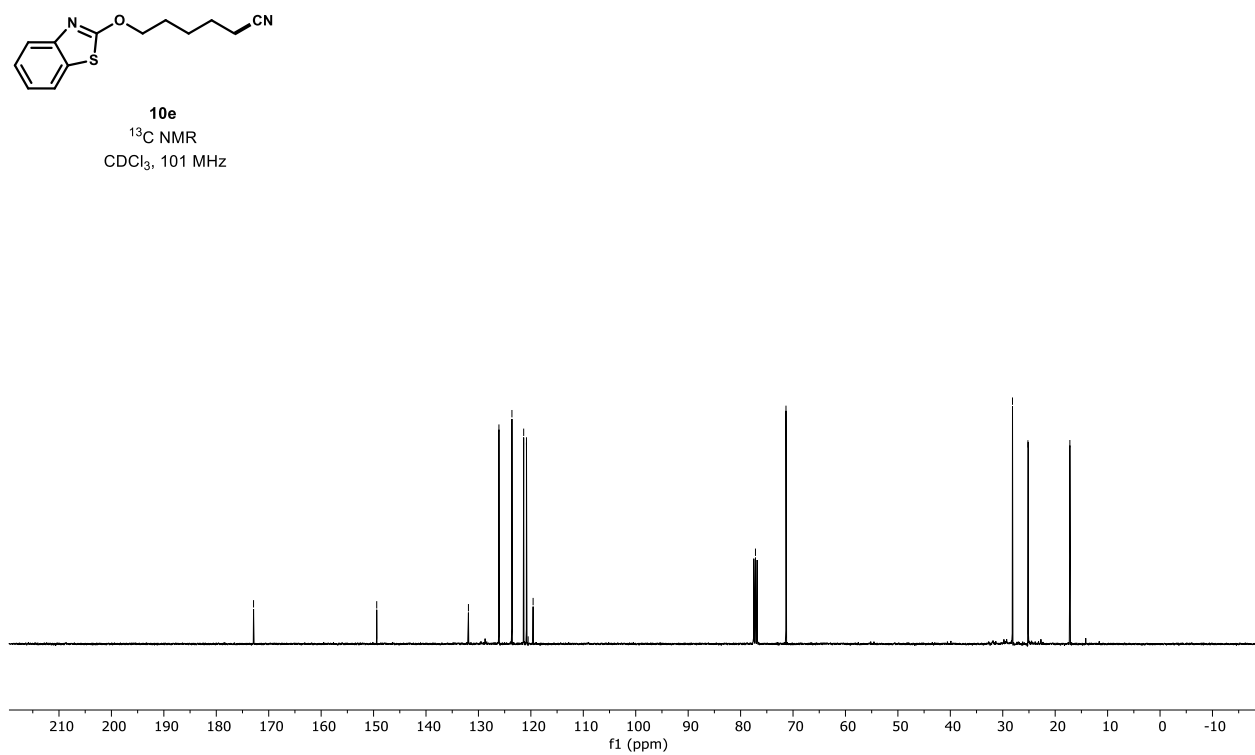
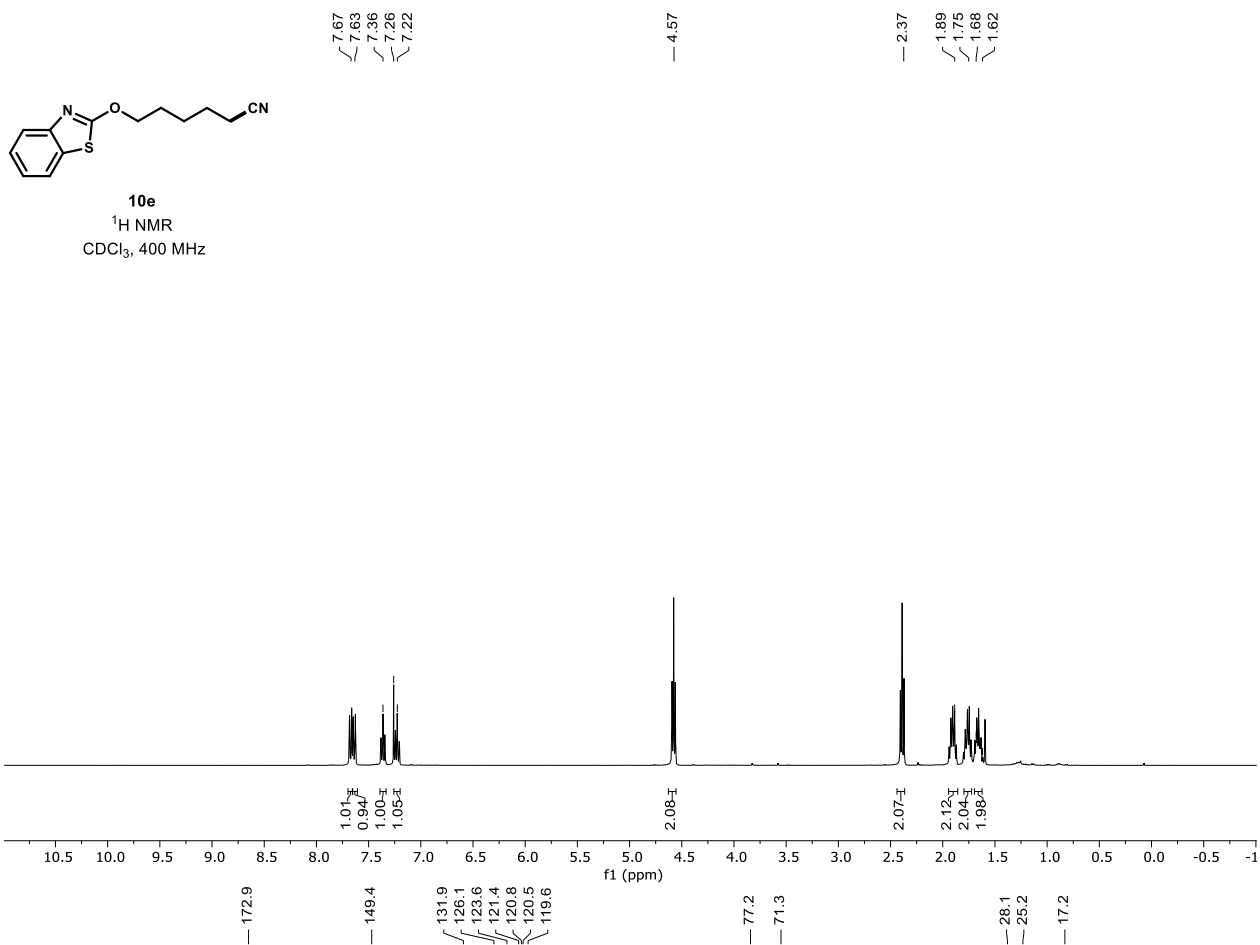


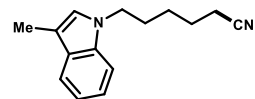




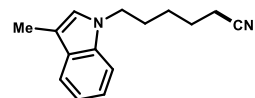
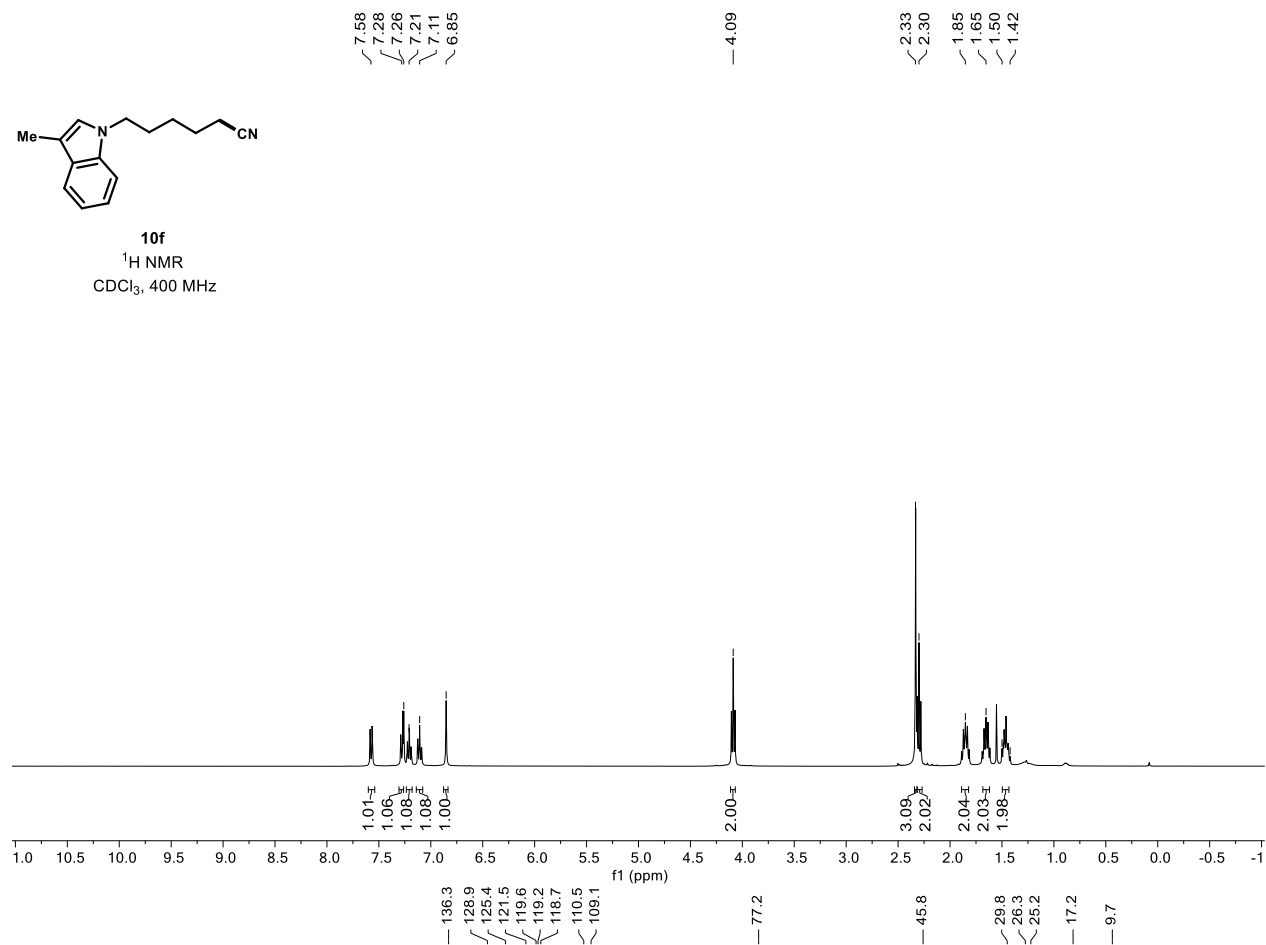
^1H NMR (CDCl_3 , 500 MHz) of crude reaction mixture containing 0.5 mmol of 1,1,2,2-tetrachloroethane as internal standard



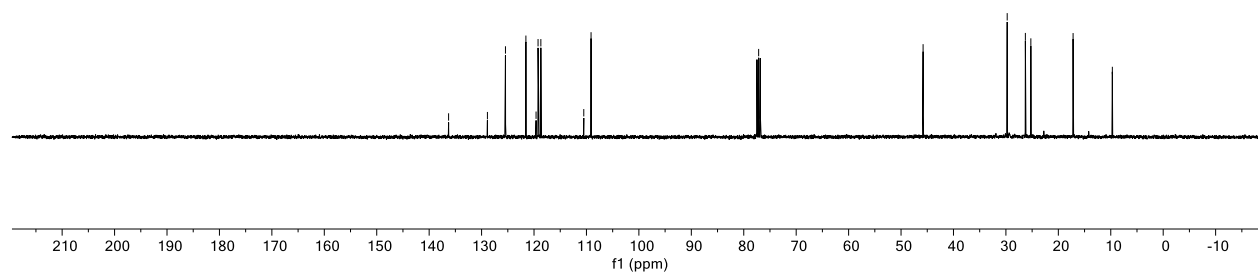


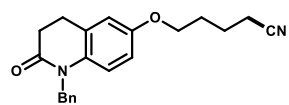


10f
¹H NMR
 CDCl₃, 400 MHz

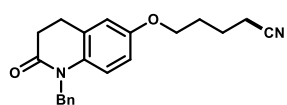
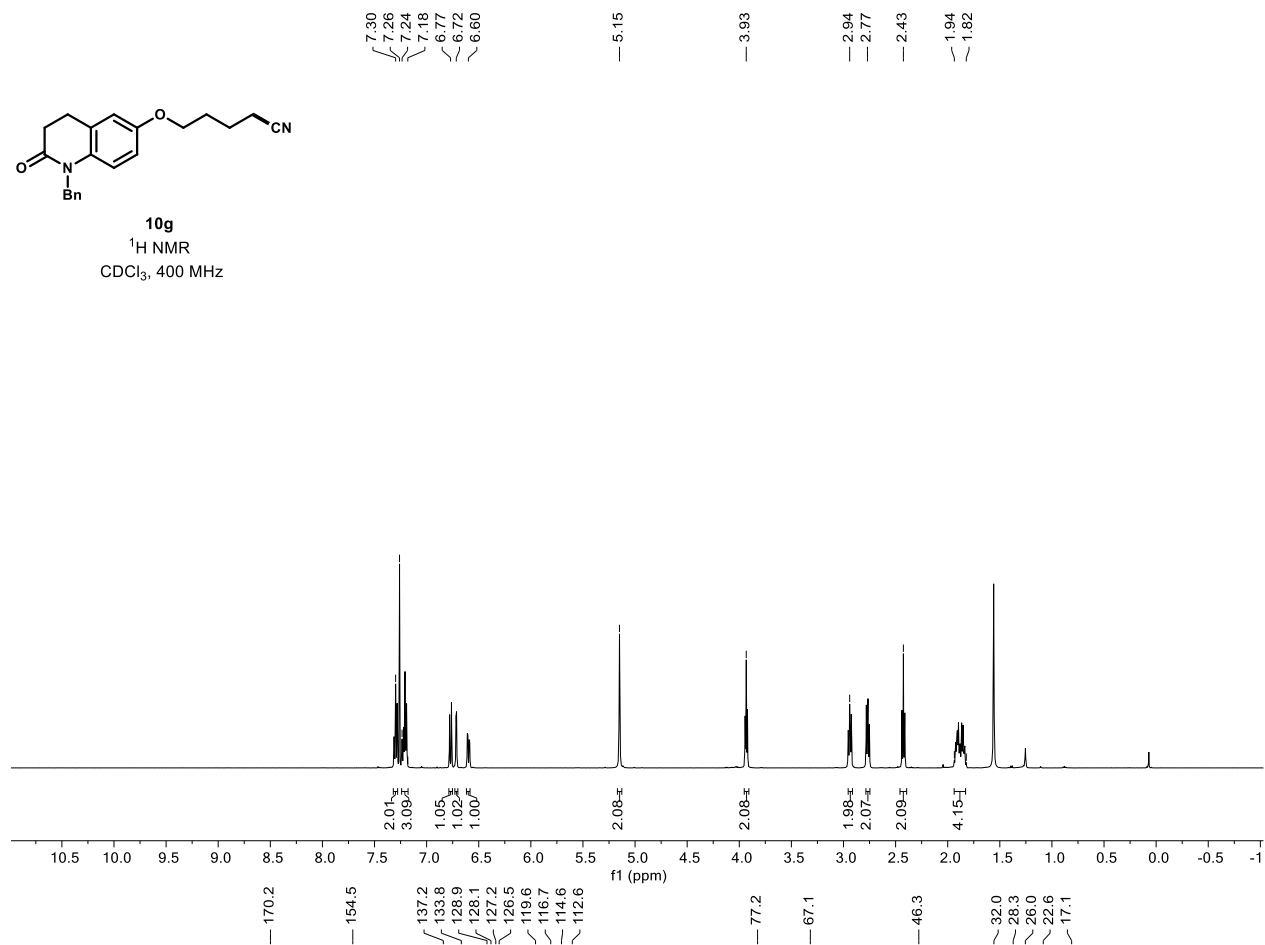


10f
¹³C NMR
 CDCl₃, 101 MHz

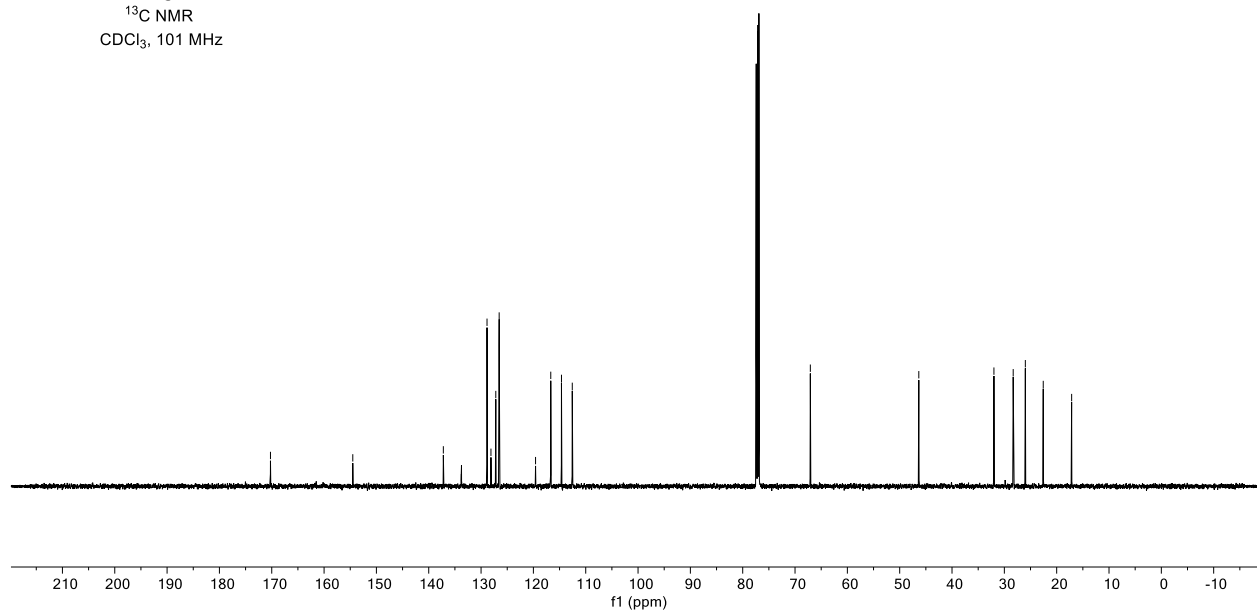


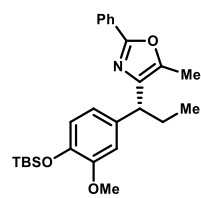


10g
¹H NMR
 CDCl₃, 400 MHz



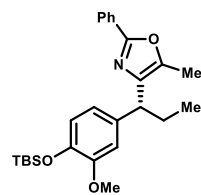
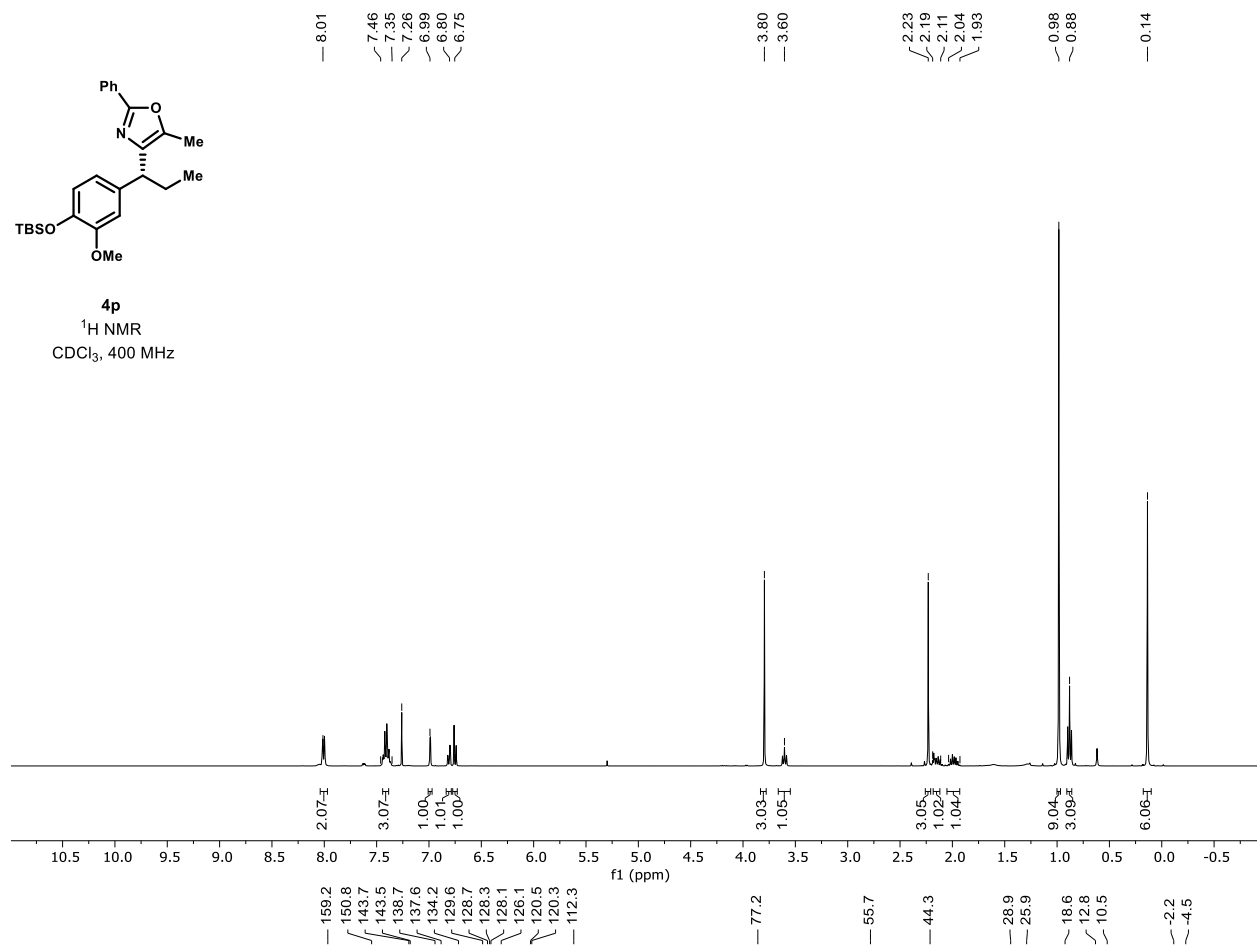
10g
¹³C NMR
 CDCl₃, 101 MHz





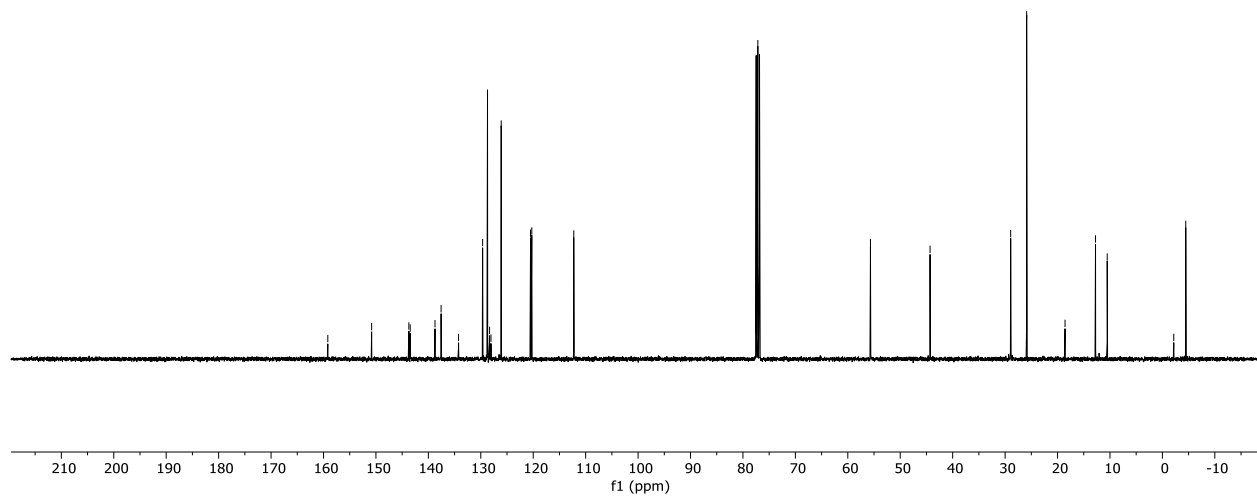
4p

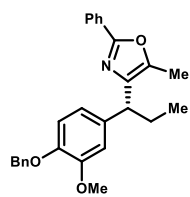
¹H NMR
CDCl₃, 400 MHz



4p

¹³C NMR
CDCl₃, 101 MHz

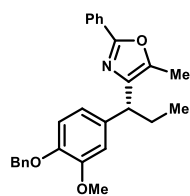
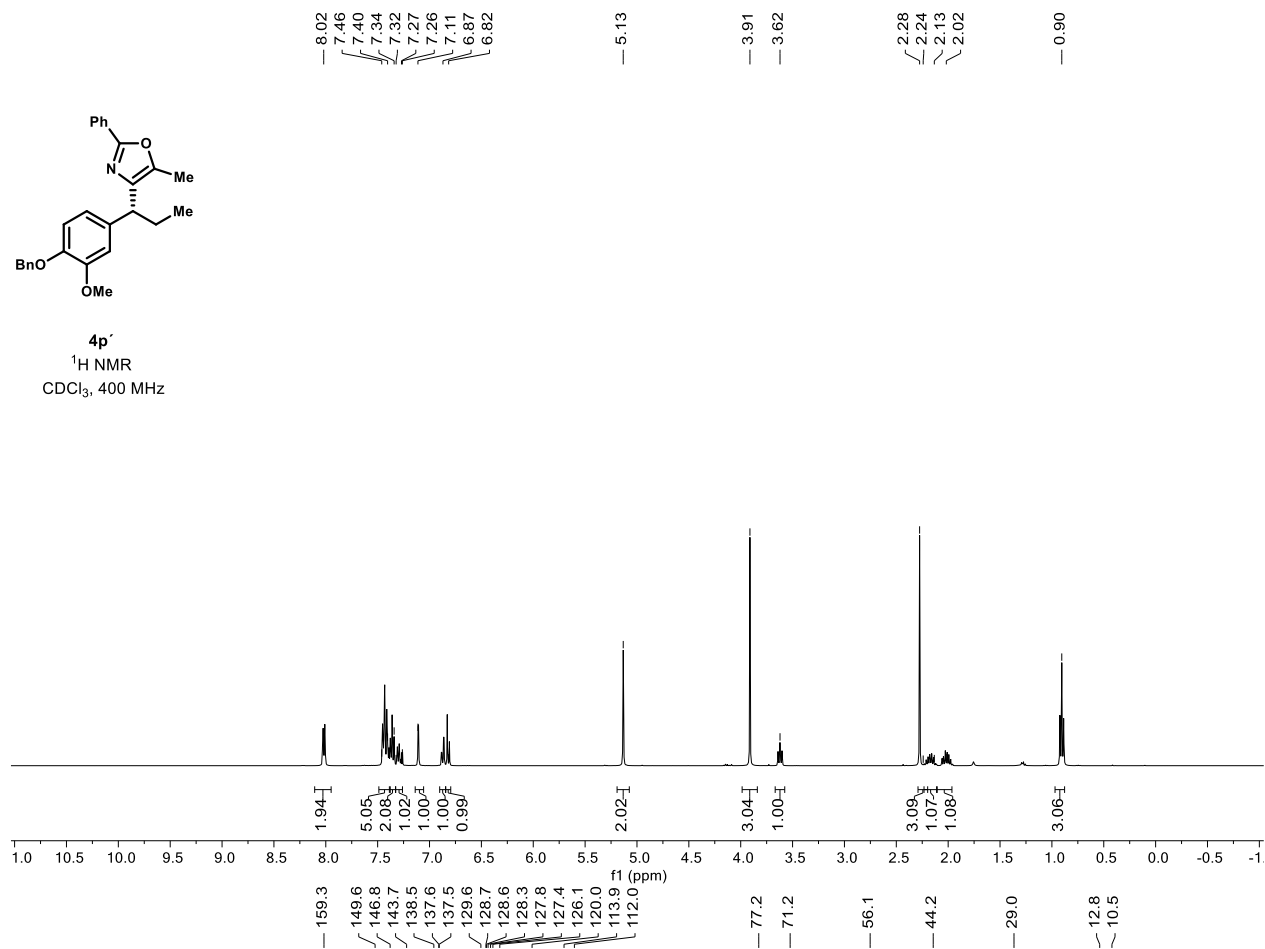




4p'

¹H NMR

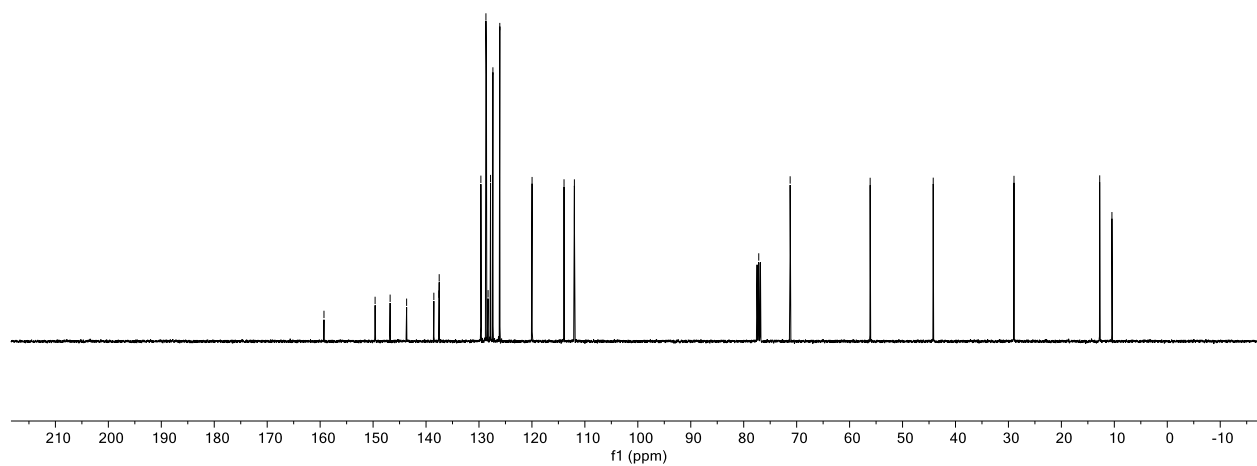
CDCl₃, 400 MHz

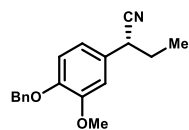


4p'

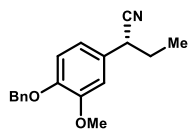
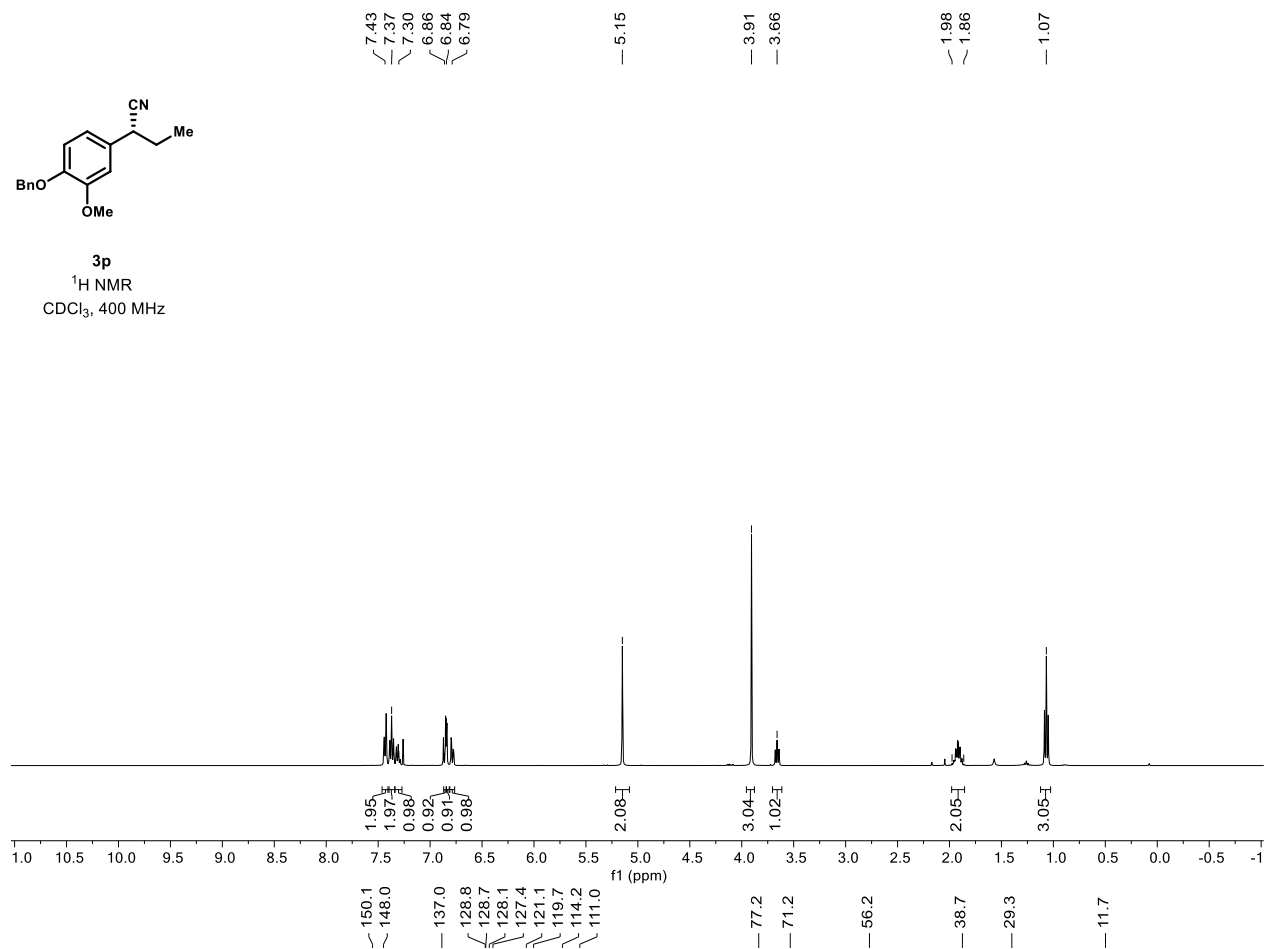
¹³C NMR

CDCl₃, 101 MHz

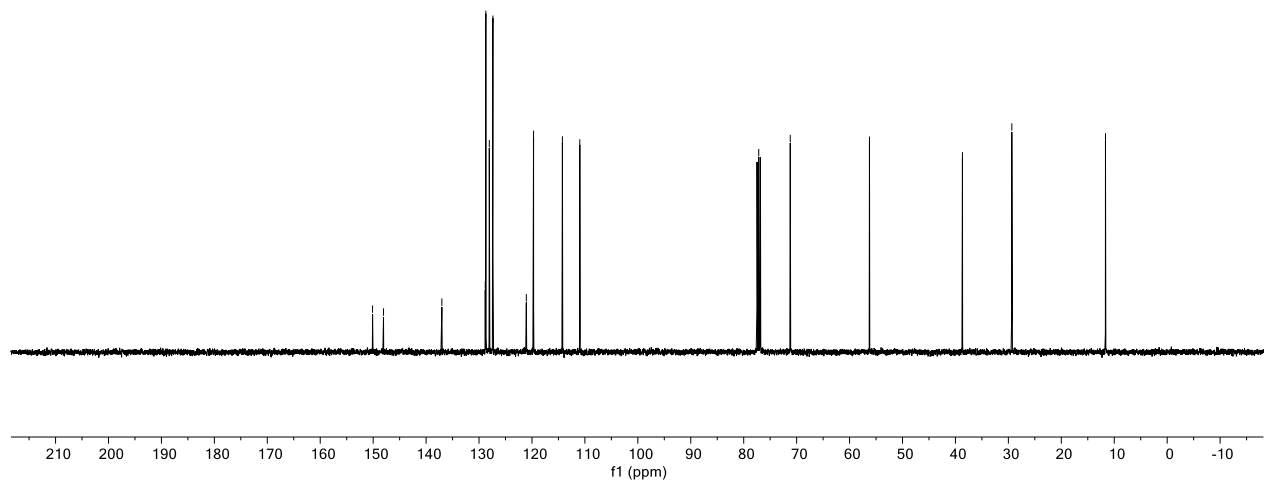




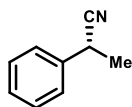
3p
¹H NMR
 CDCl₃, 400 MHz



3p
¹³C NMR
 CDCl₃, 101 MHz

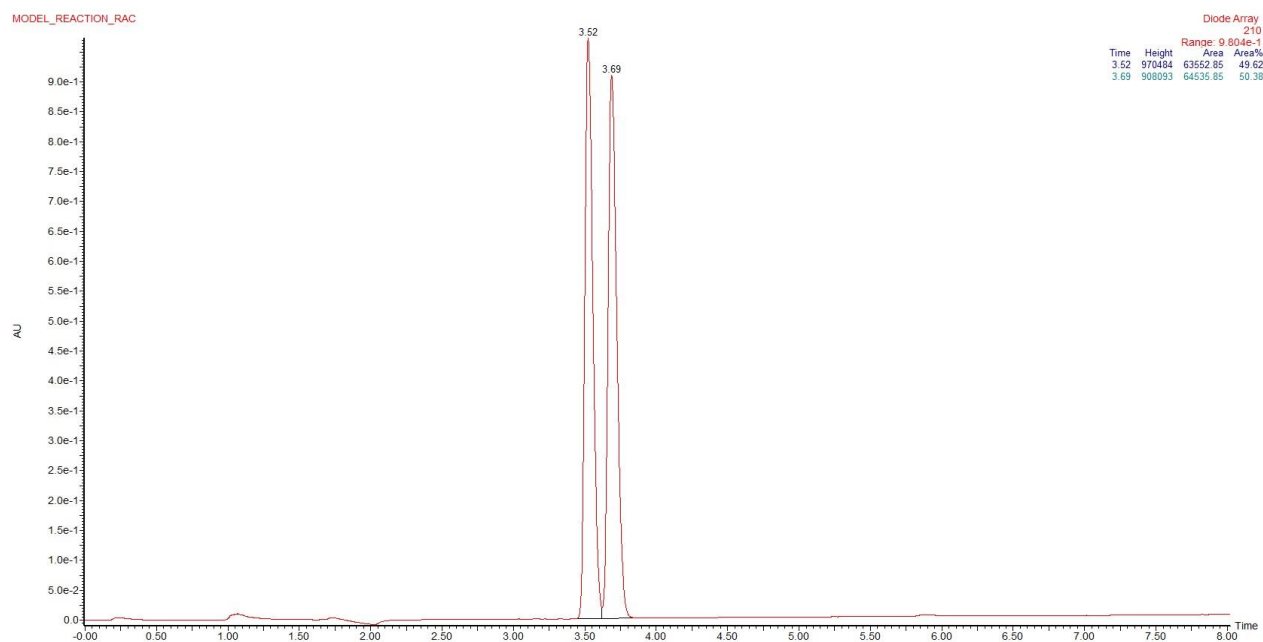
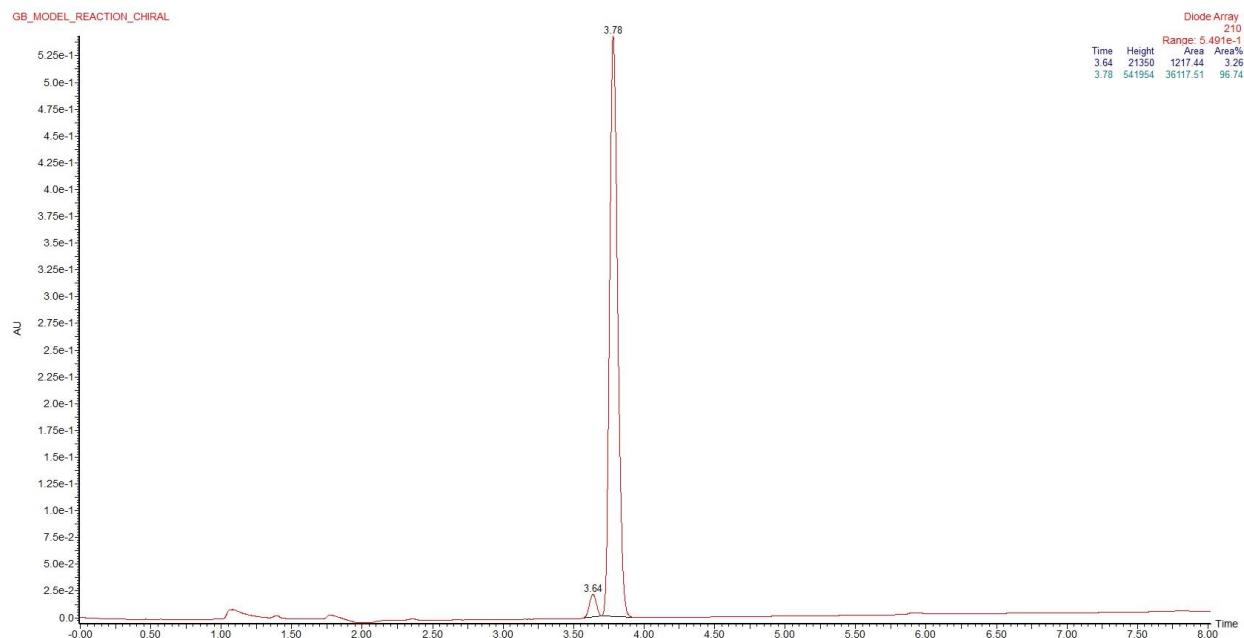


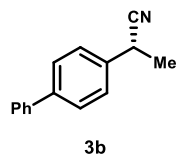
7.2 Chiral SFC and HPLC Traces of Hydrocyanation Products



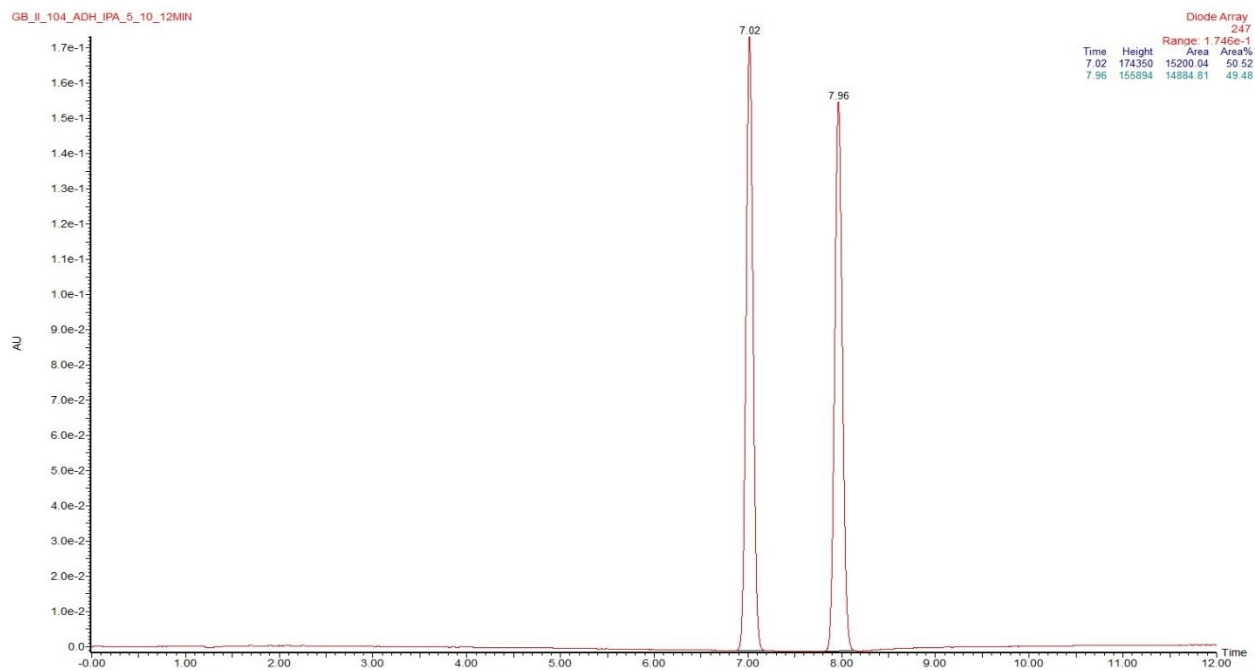
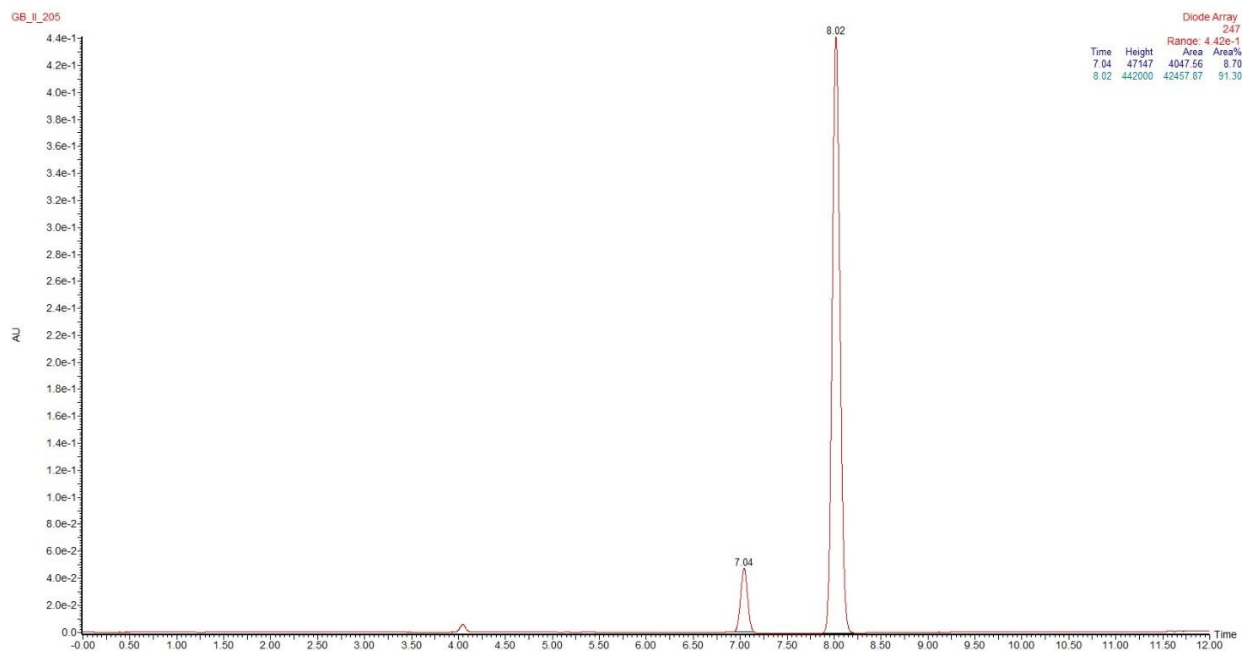
3a

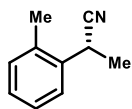
Chiral SFC analysis: Chiralcel OD-H (scCO₂/IPA = 99/1 to 98/2 over 16 minutes, 2.5 mL/min, 210-400 nm, 45 °C), 3.52 and 3.69 min.





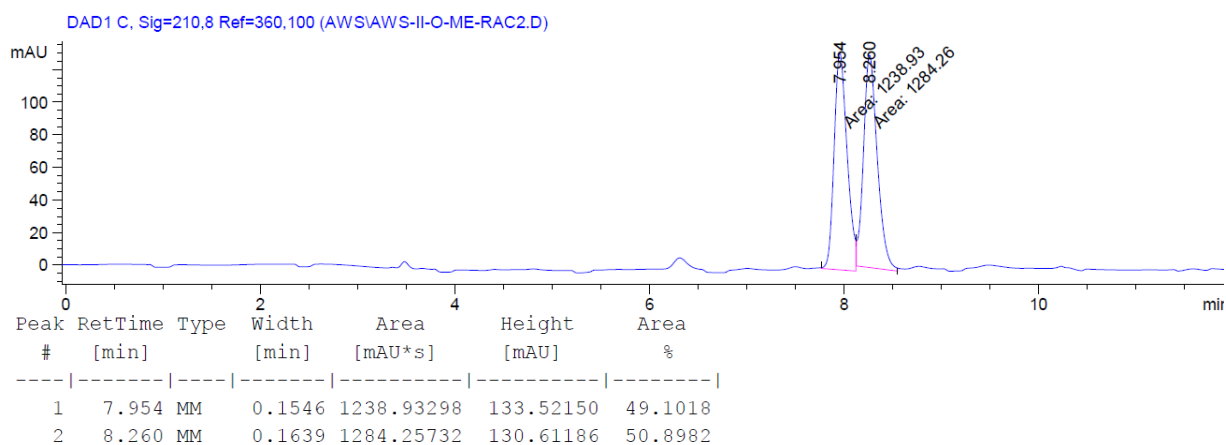
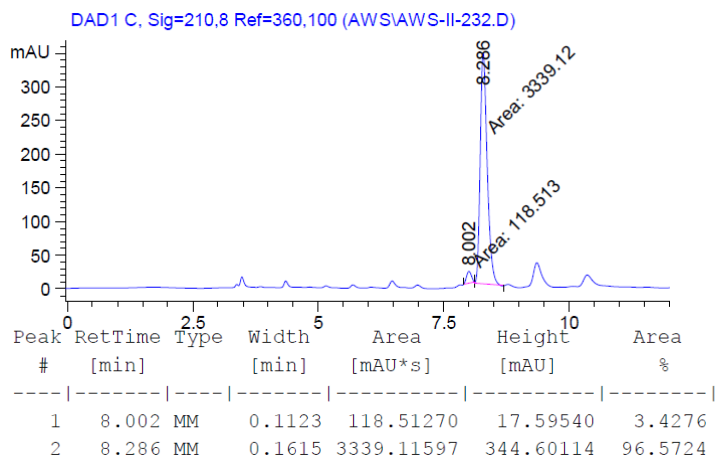
Chiral SFC analysis: Chiralcel AD-H (scCO₂/IPA = 95/5 to 90/10 over 12 minutes, 2.5 mL/min, 210-400 nm, 45 °C), 7.02 and 7.96 min.

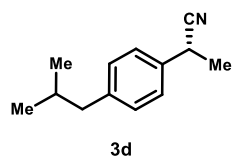




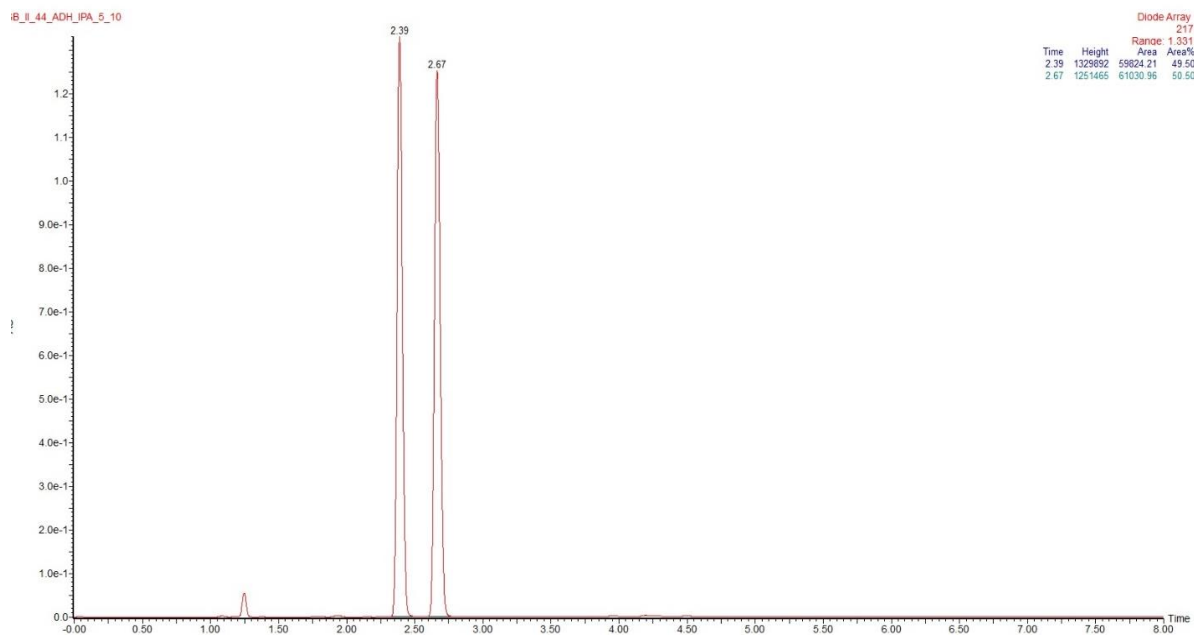
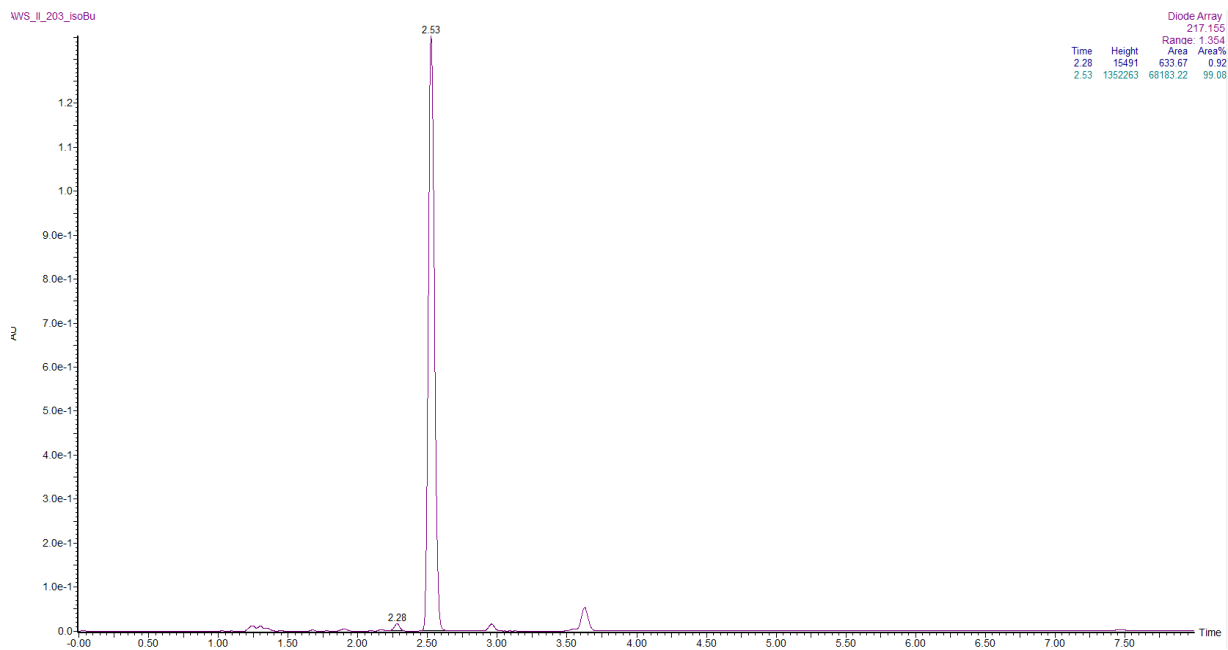
3c

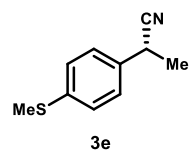
Chiral HPLC (AD-H, 210 nm, Hexane:IPA 99:1, 1 mL/min, 7.9 and 8.2 min).



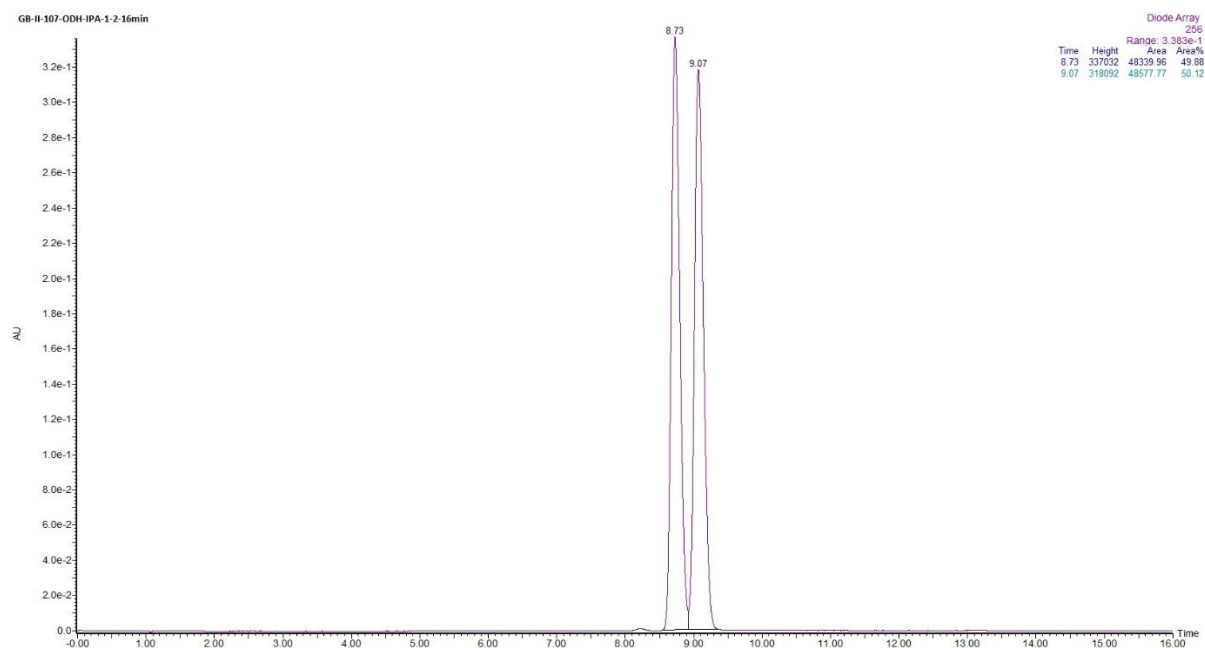
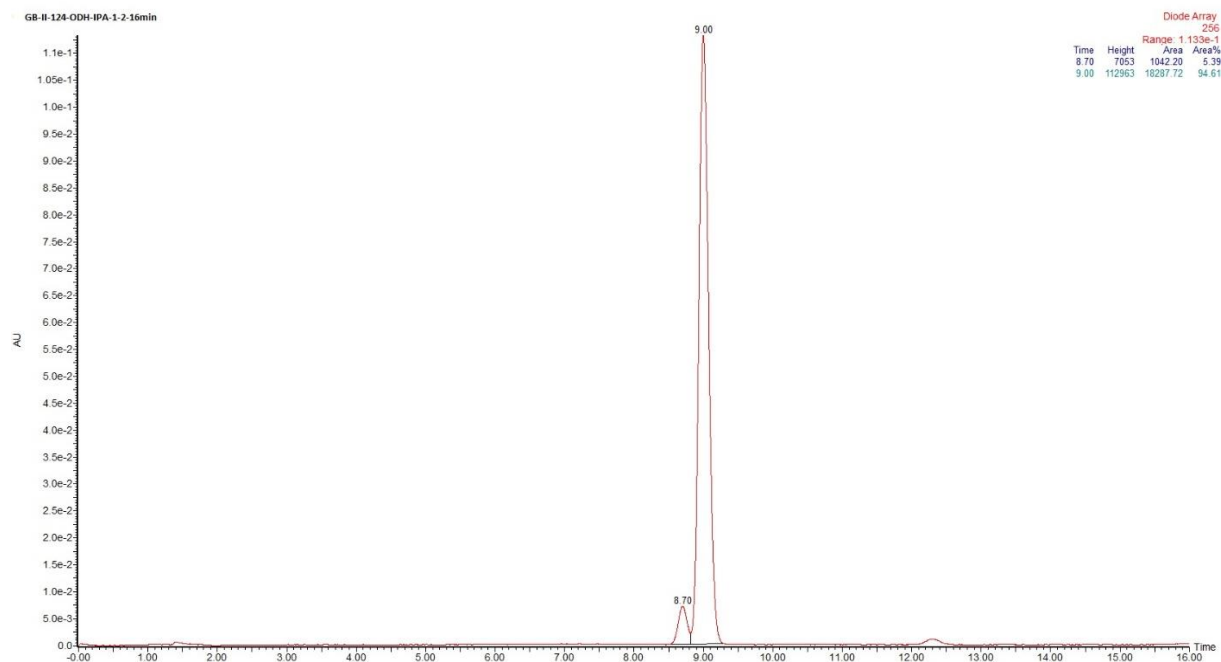


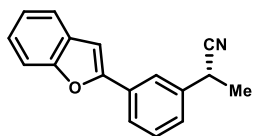
Chiral SFC analysis: Chiralcel AD-H (scCO₂/IPA = 95/5 to 90/10, 2.5 mL/min, 210-400 nm, 45 °C), 2.39 and 2.67 min.





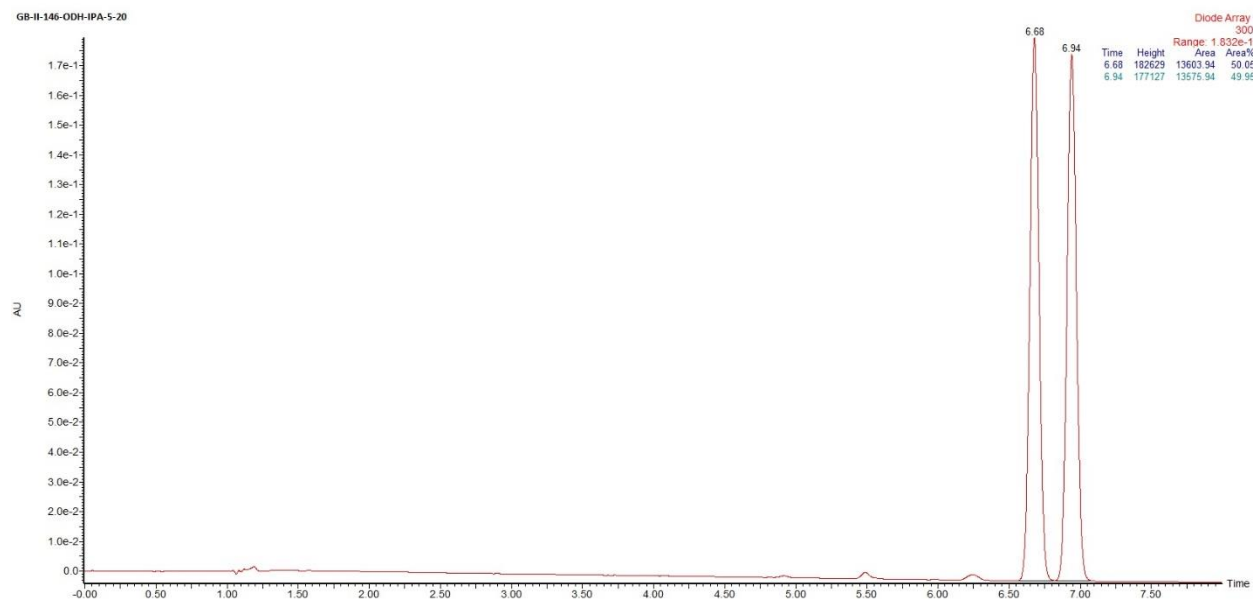
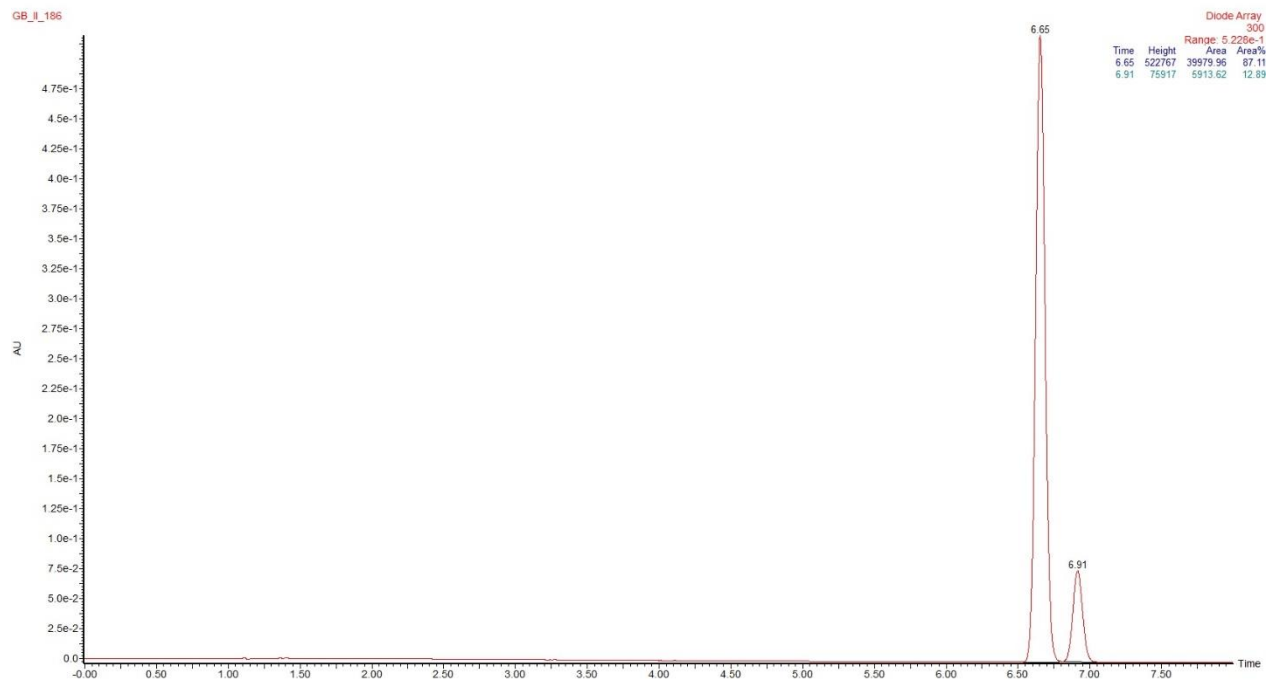
Chiral SFC analysis: Chiralcel OD-H (scCO₂/IPA = 99/1 to 98/2 over 16 minutes, 2.5 mL/min, 210-400 nm, 45 °C), 8.73 and 9.07 min.

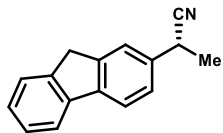




3f

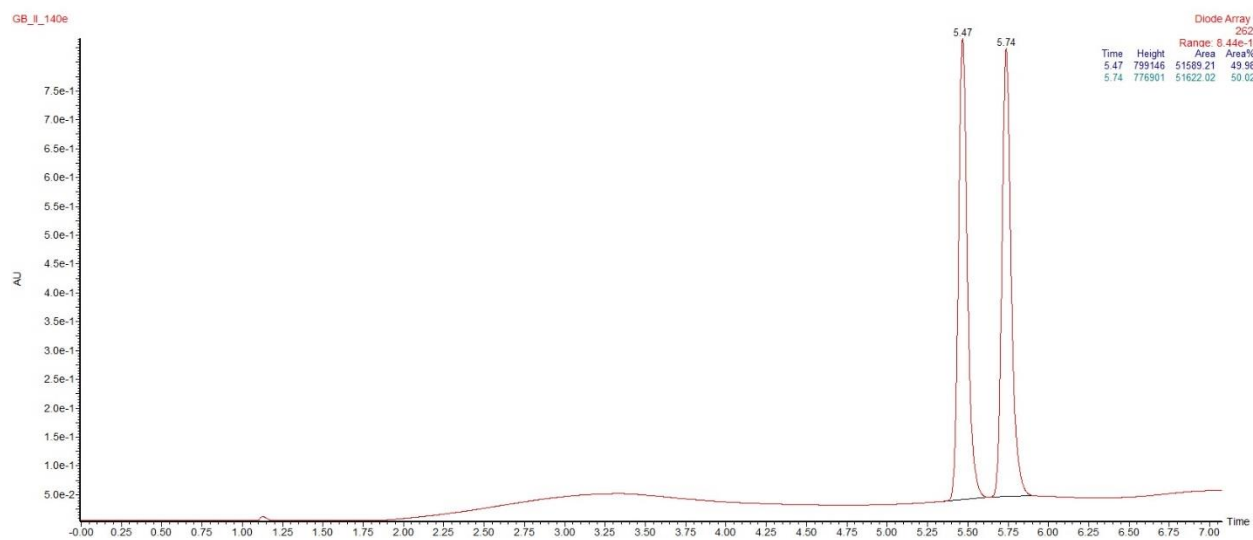
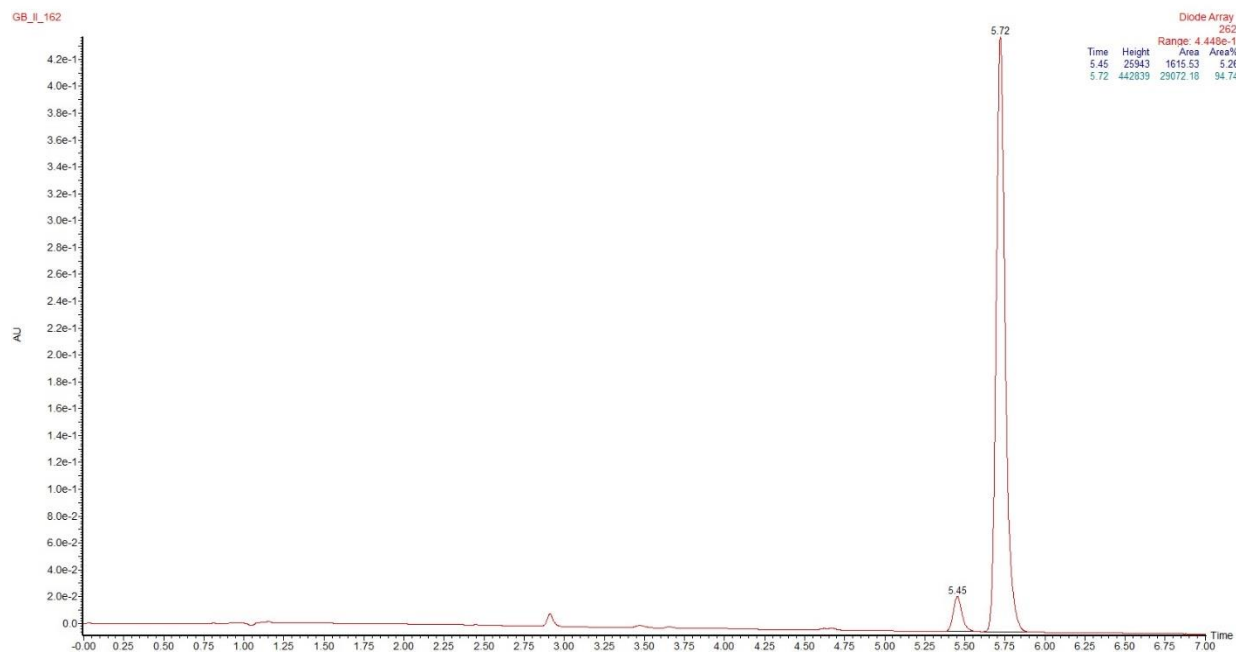
Chiral SFC analysis: Chiralcel OD-H (scCO₂/IPA = 95/5 to 80/20, 2.5 mL/min, 210-400 nm, 45 °C), 6.68 and 6.94 min.

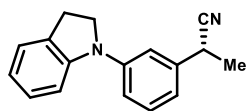




3g

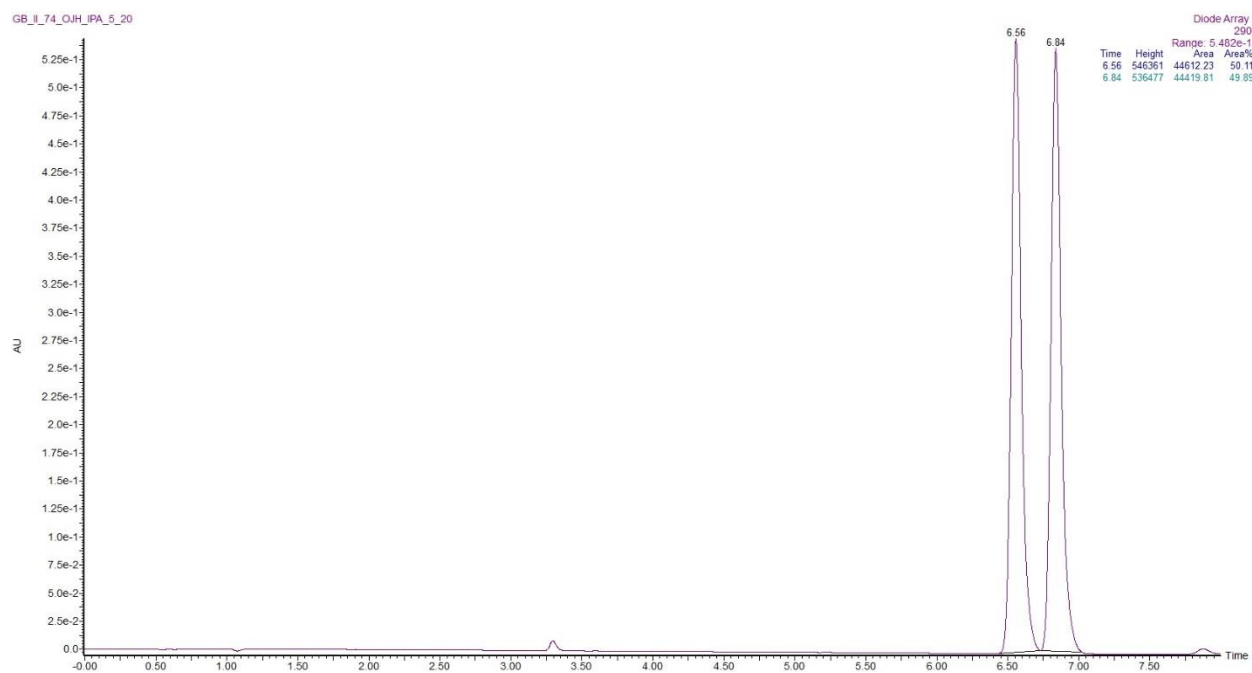
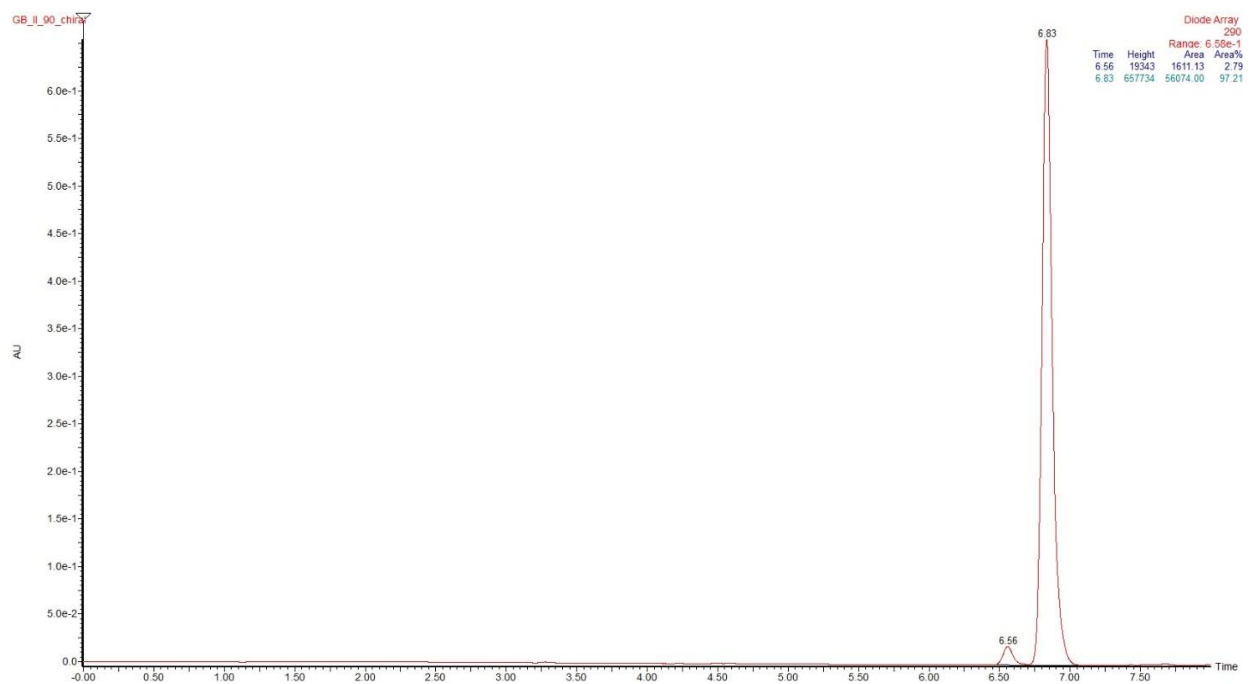
Chiral SFC analysis: Chiralcel OJ-H (scCO₂/IPA = 95/5 to 60/40, 2.5 mL/min, 210-400 nm, 45 °C), 5.47 and 5.74 min.

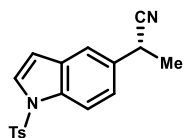




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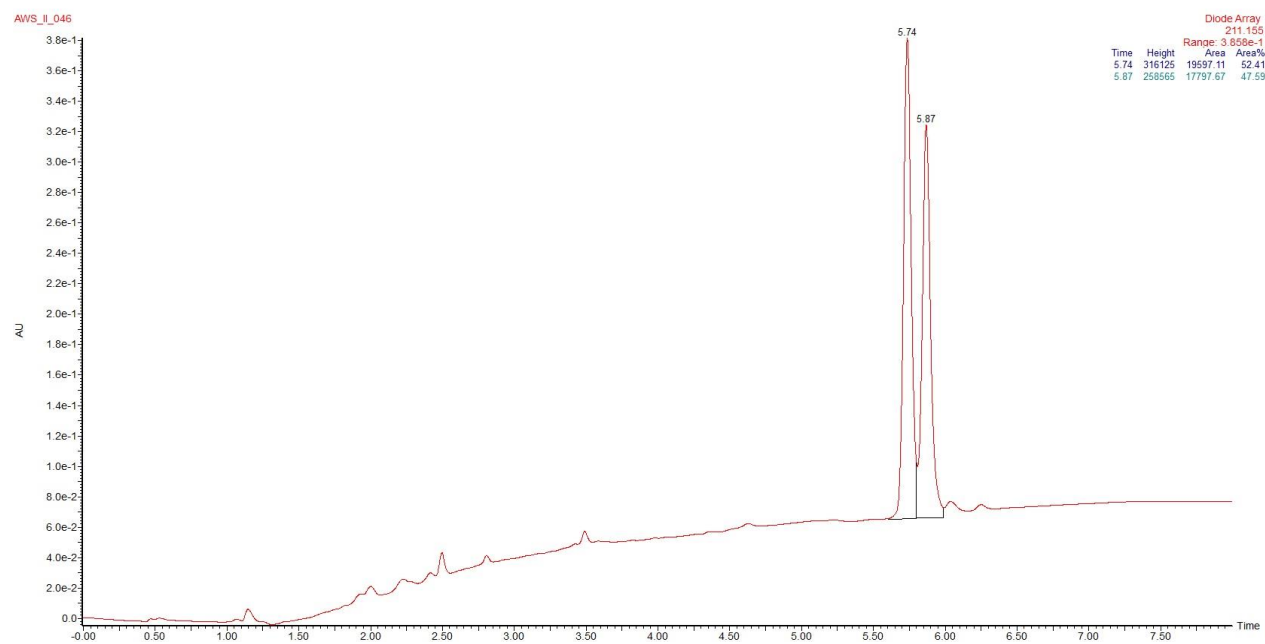
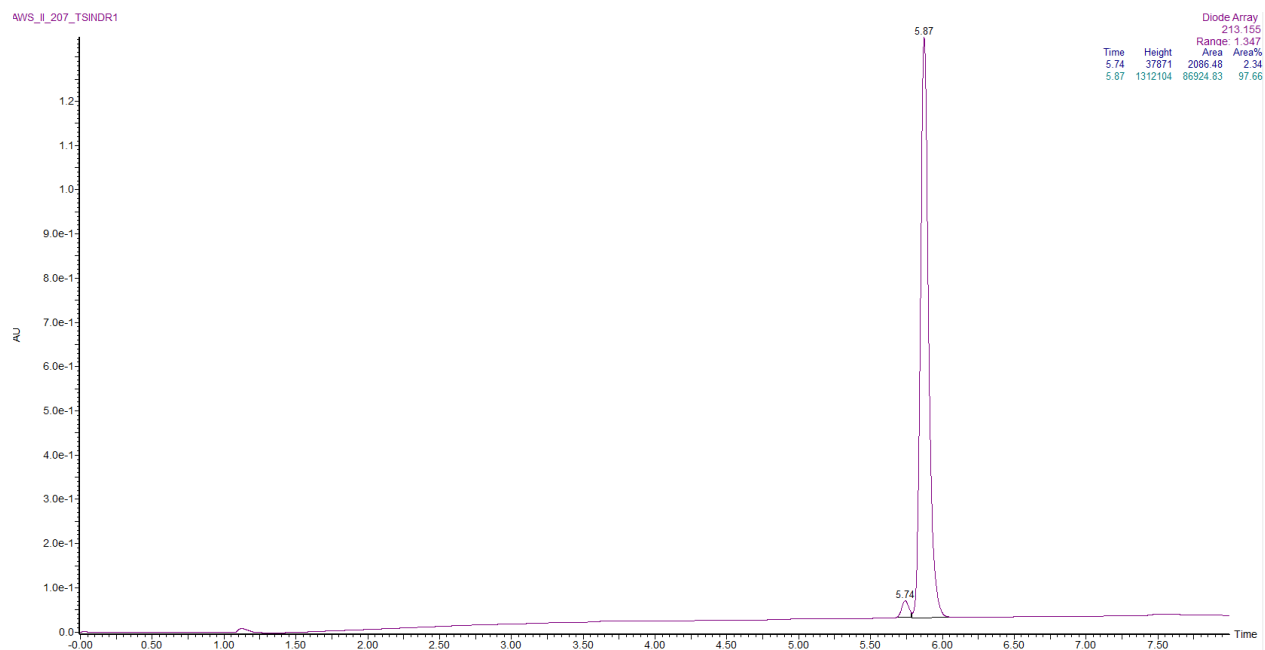
Chiral SFC analysis: Chiralcel OJ-H (scCO₂/IPA = 95/5 to 80/20, 2.5 mL/min, 210-400 nm, 45 °C), 6.56 and 6.84 min.

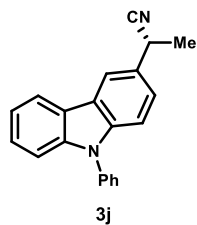




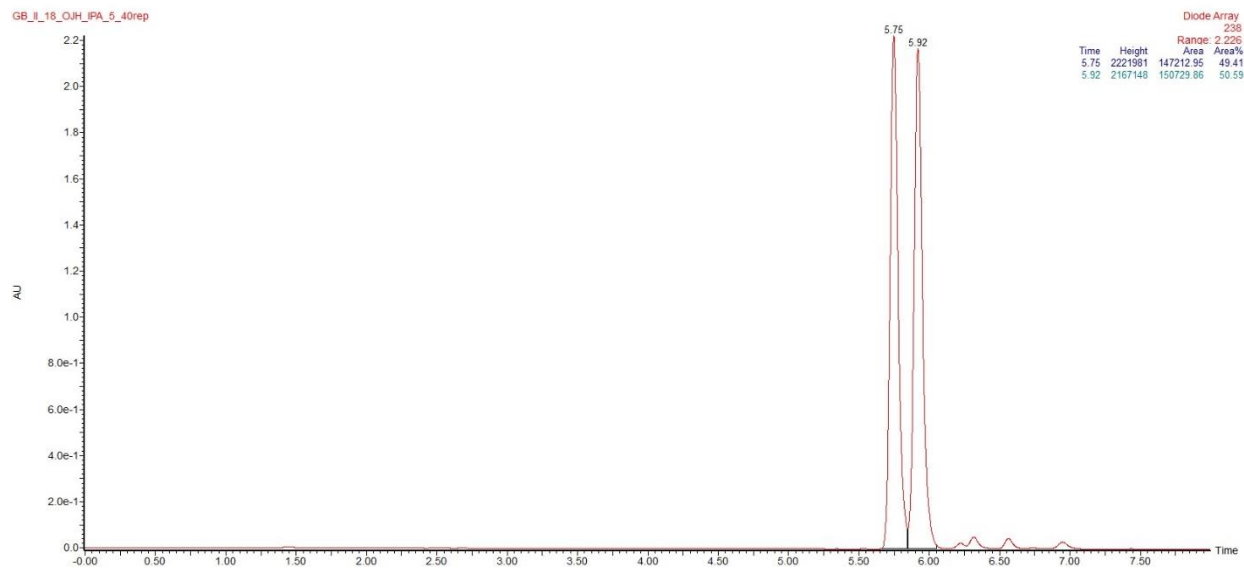
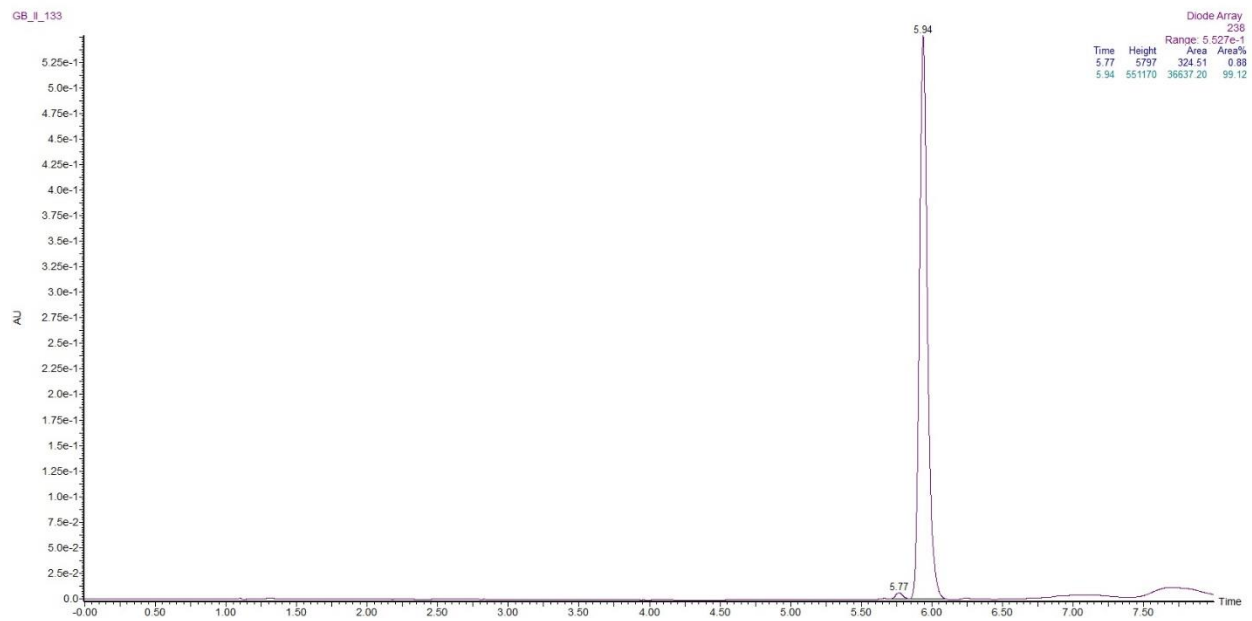
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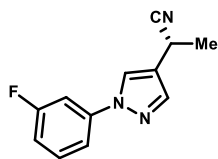
Chiral SFC analysis: Chiralcel OJ-H (scCO₂/IPA = 95/5 to 60/40, 2.5 mL/min, 210-400 nm, 45 °C), 5.74 and 5.87 min.





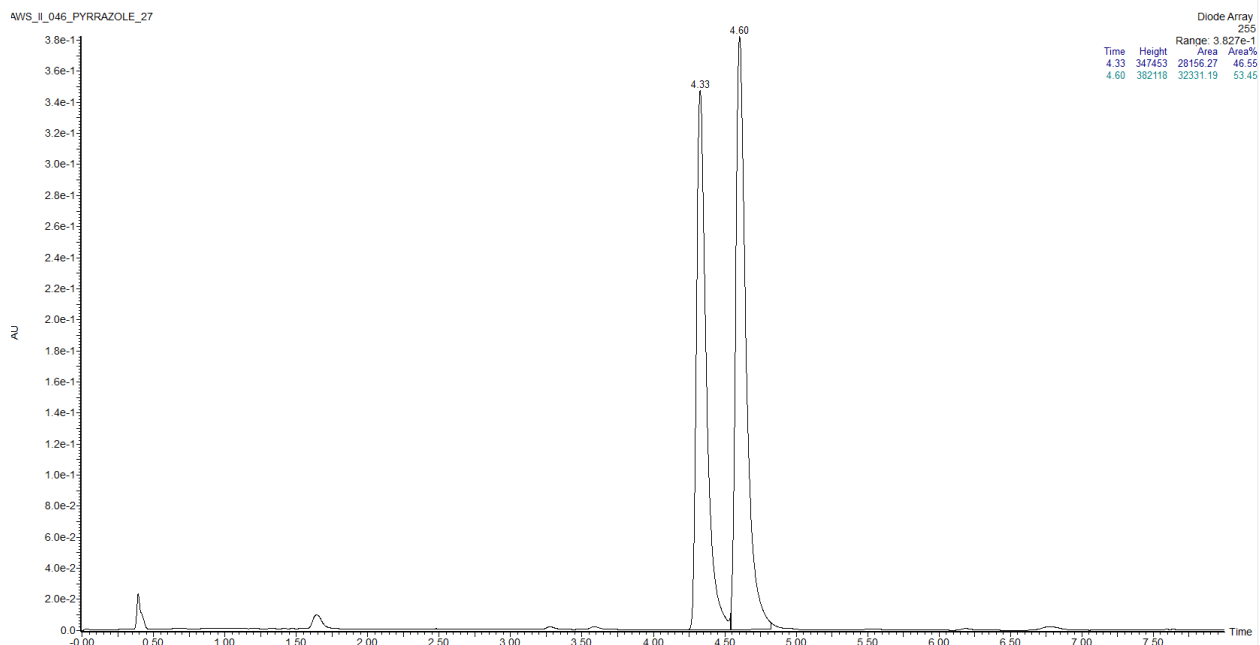
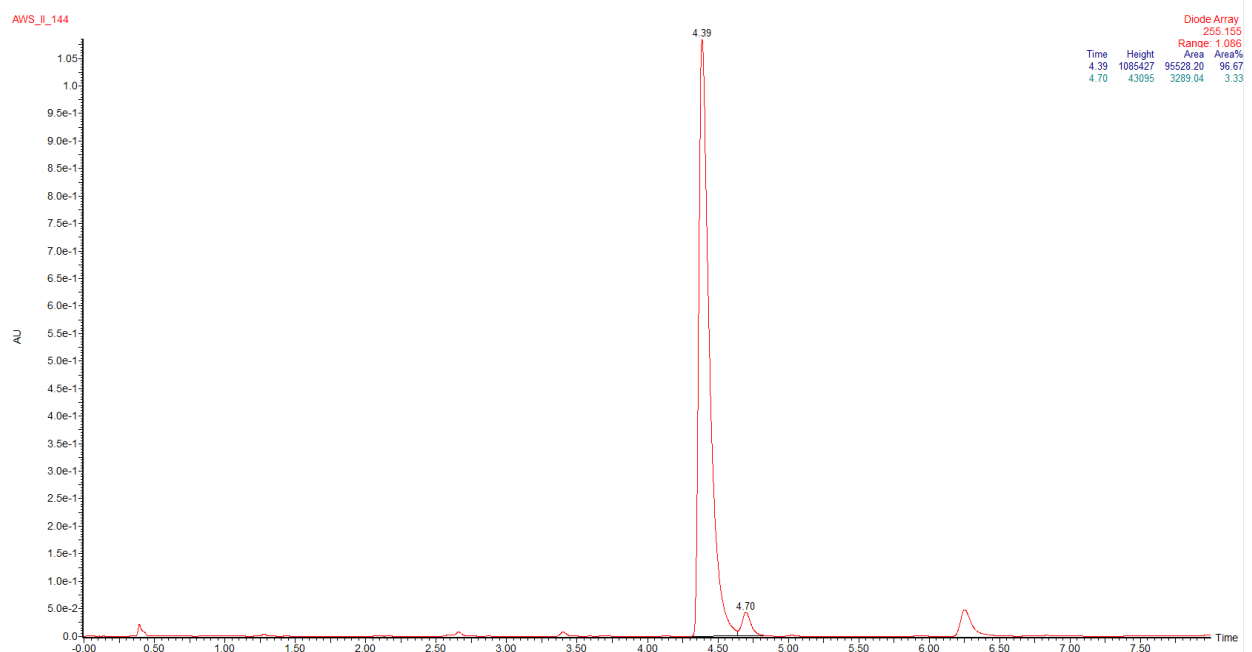
Chiral SFC analysis: Chiralcel OJ-H (scCO₂/IPA = 98/2 to 60/40, 2.5 mL/min, 210-400 nm, 45 °C), 5.75 and 5.92 min.

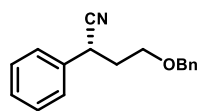




3k

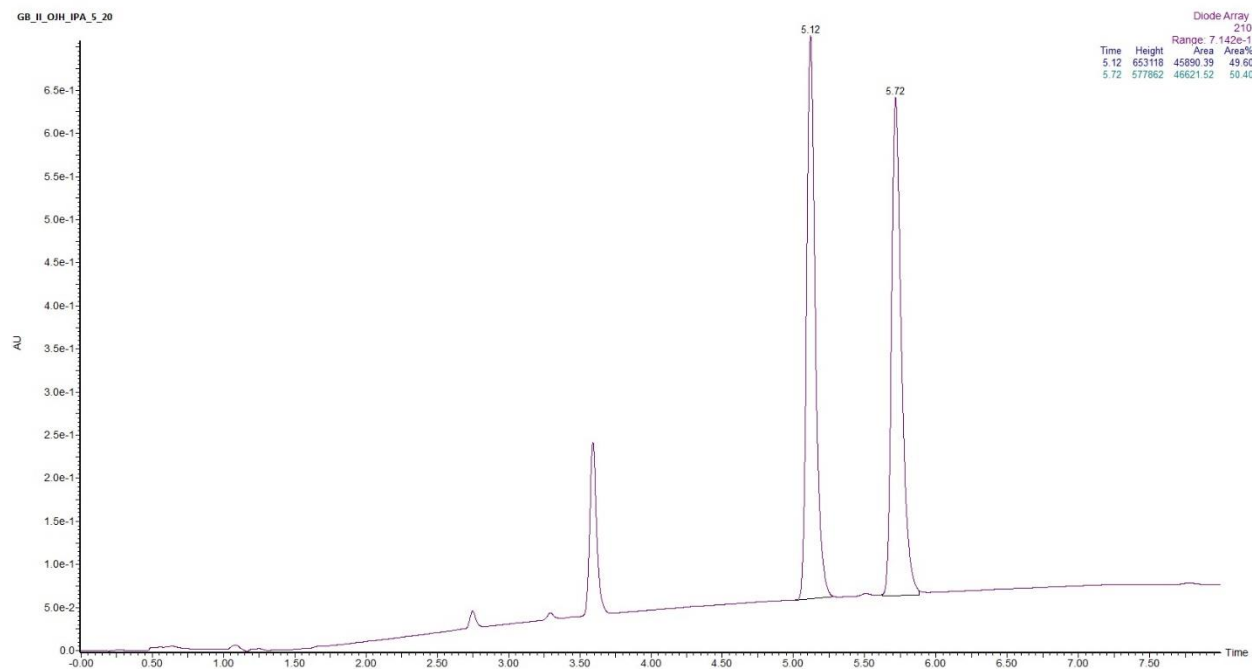
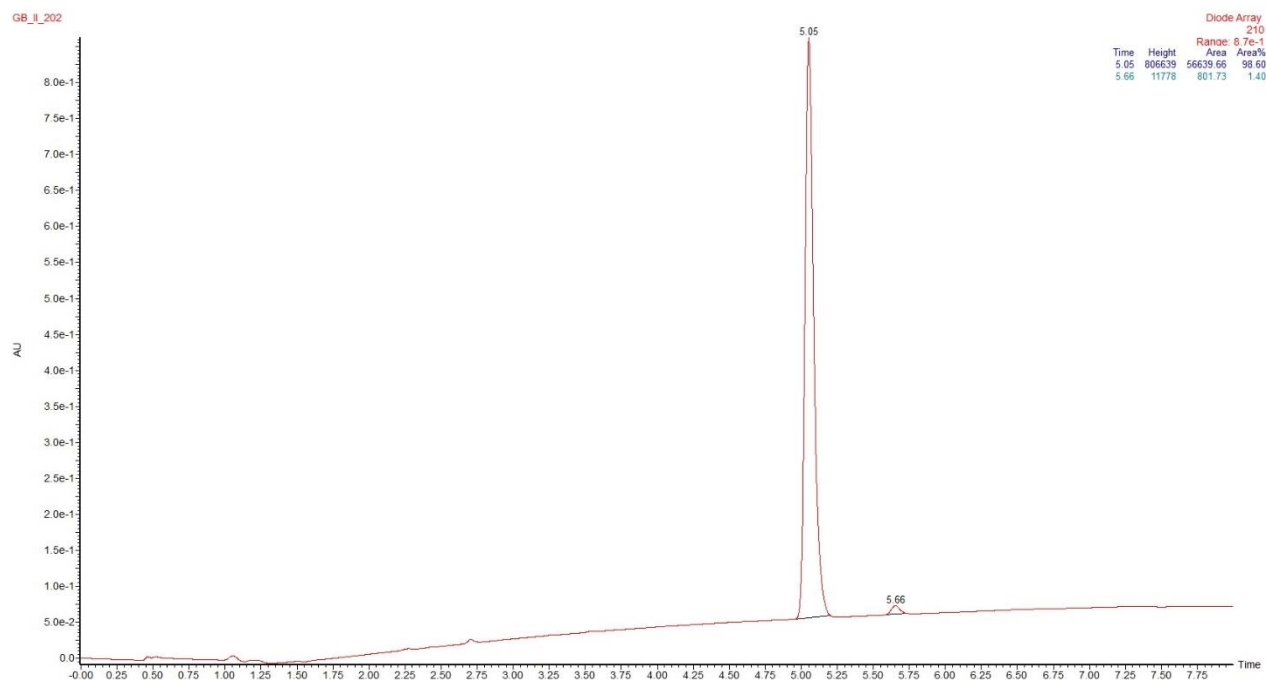
Chiral SFC analysis: CEL2 (scCO₂/IPA = 99/1 to 95/5, 2.5 mL/min, 210-400 nm, 45 °C), 4.33 and 4.60 min.

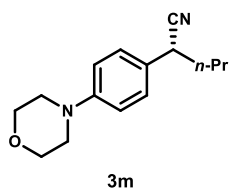




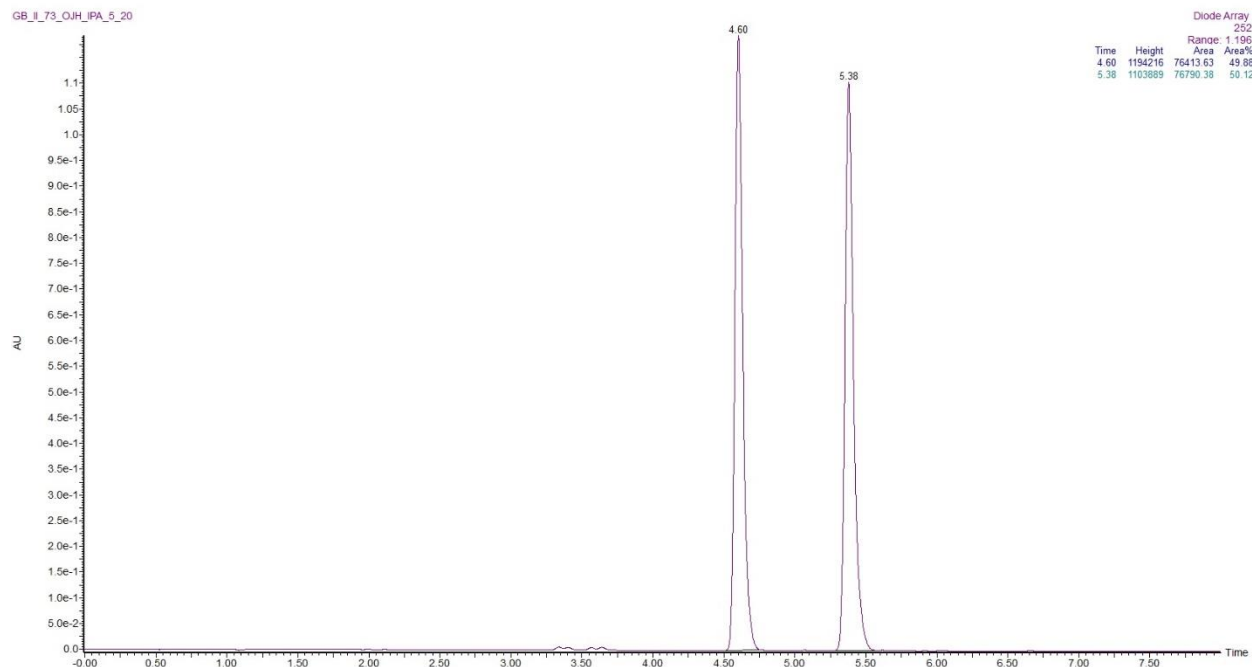
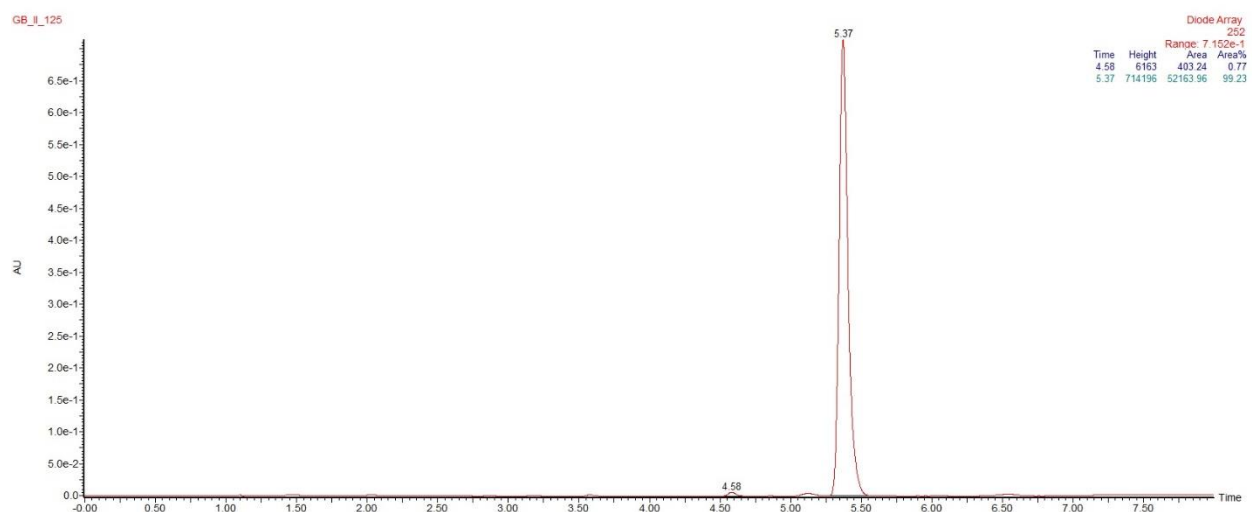
3I

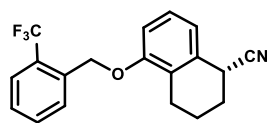
Chiral SFC analysis: Chiralcel OJ-H (scCO₂/IPA = 95/5 to 80/20, 2.5 mL/min, 210-400 nm, 45 °C), 5.12 and 5.72 min.





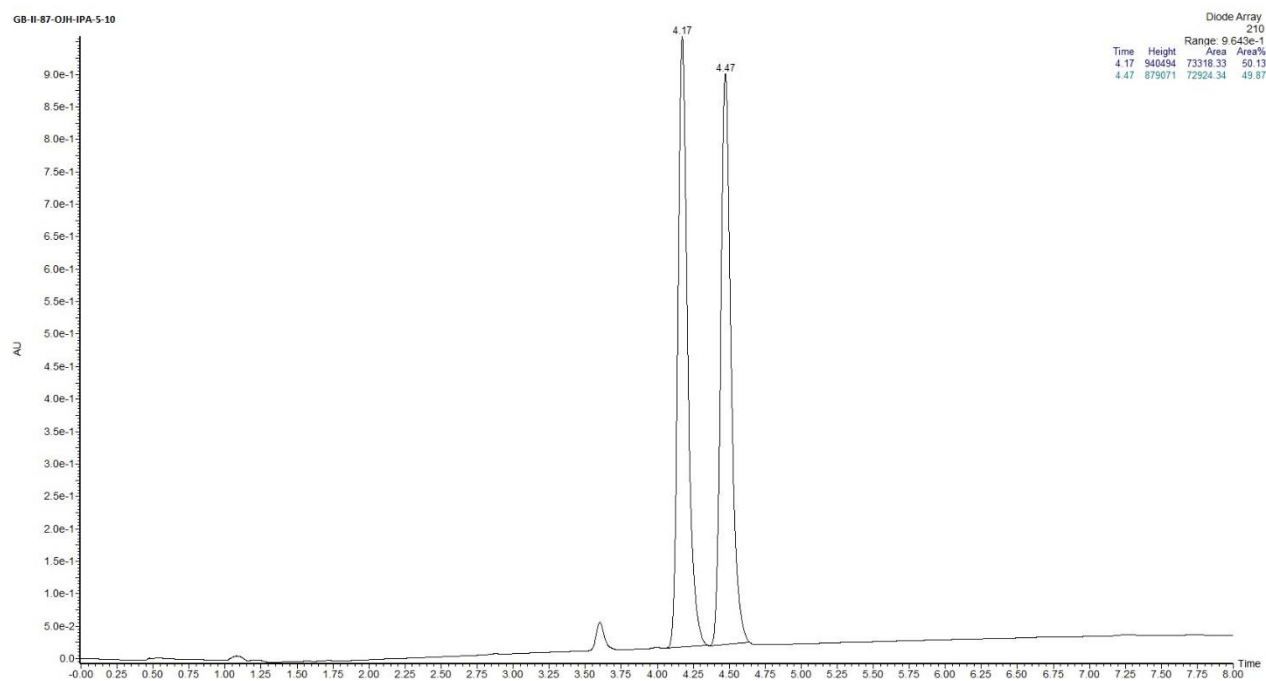
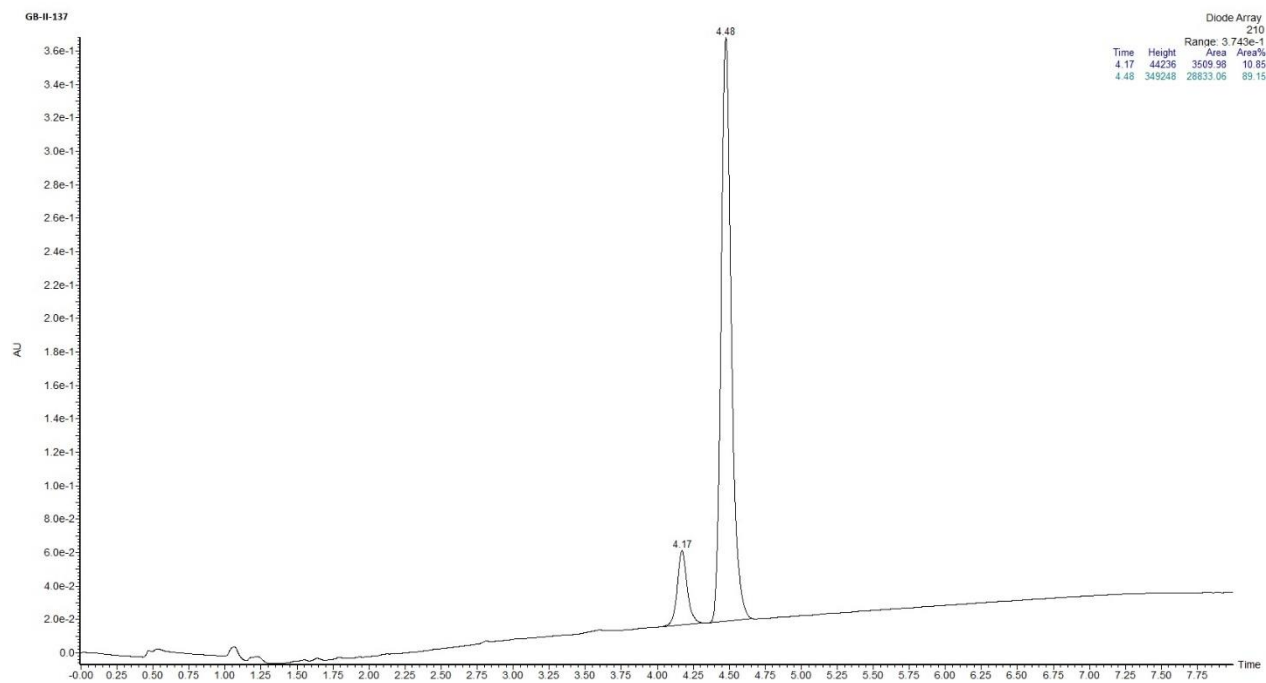
Chiral SFC analysis: Chiralcel OJ-H (scCO₂/IPA = 95/5 to 80/20, 2.5 mL/min, 210-400 nm, 45 °C), 4.60 and 5.38 min.

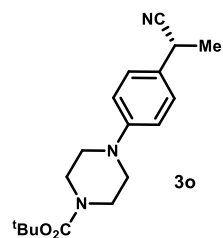




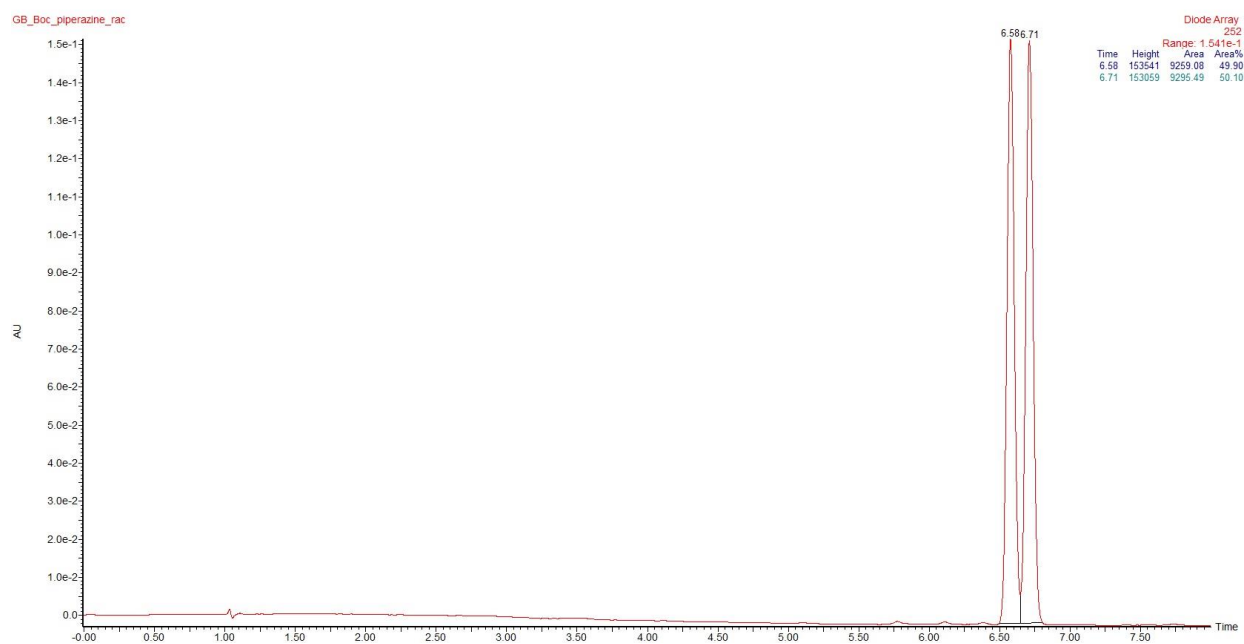
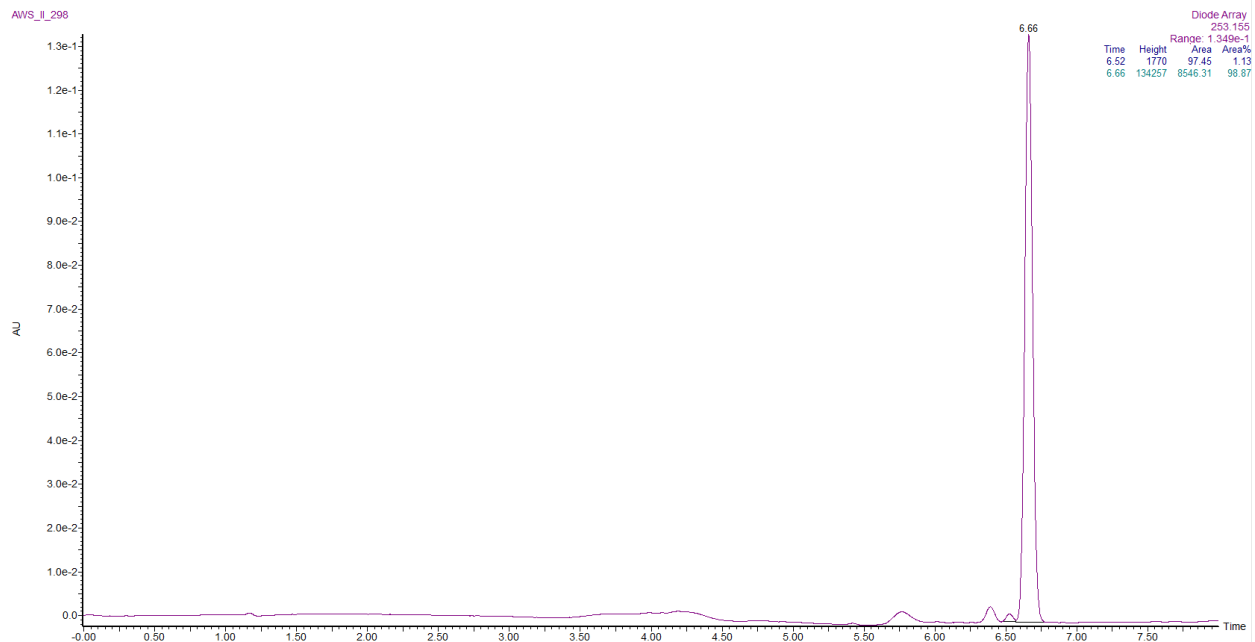
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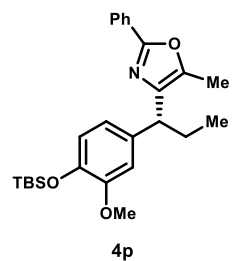
Chiral SFC analysis: Chiralcel OJ-H (scCO₂/IPA = 95/5 to 90/10, 2.5 mL/min, 210-400 nm, 45 °C), 4.17 and 4.47 min.



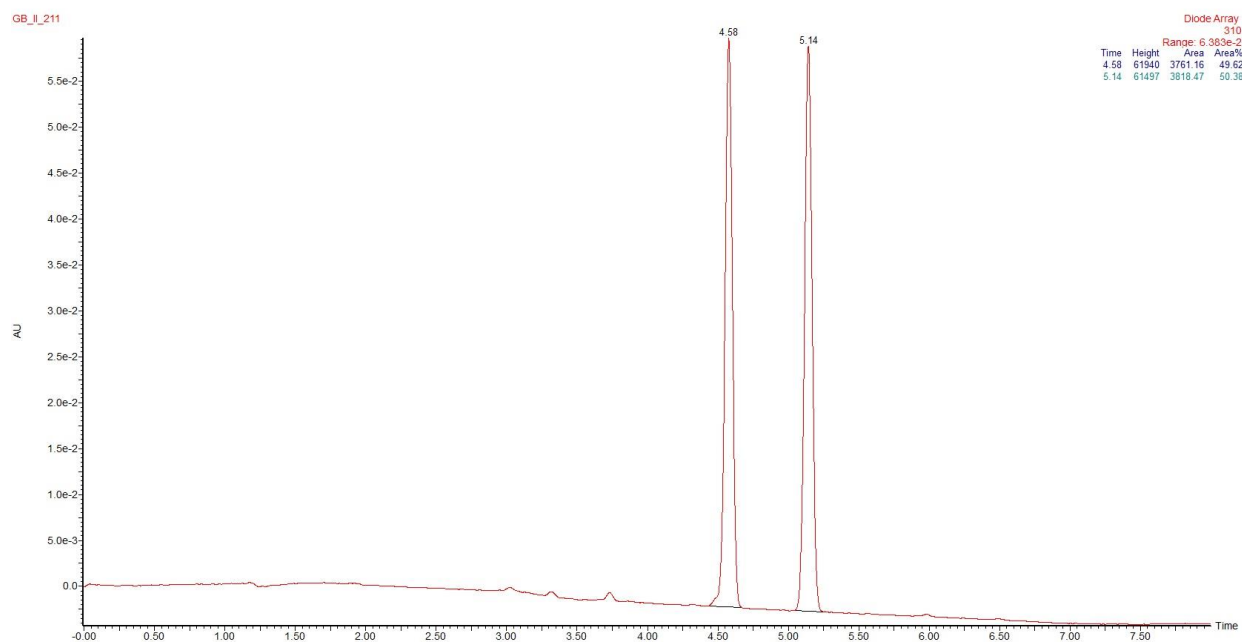
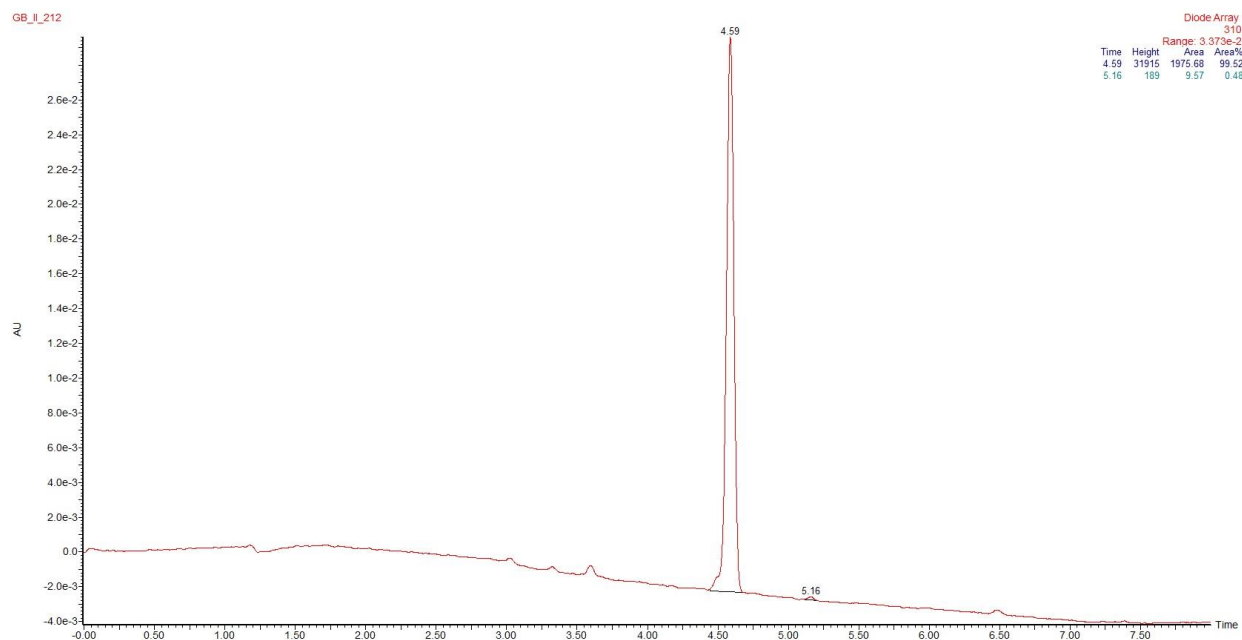


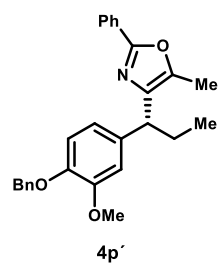
Chiral SFC analysis: Chiralpak AD-H (scCO₂/IPA = 95/5 to 80/20, 2.5 mL/min, 210-400 nm, 45 °C), 6.58 and 6.71 min.



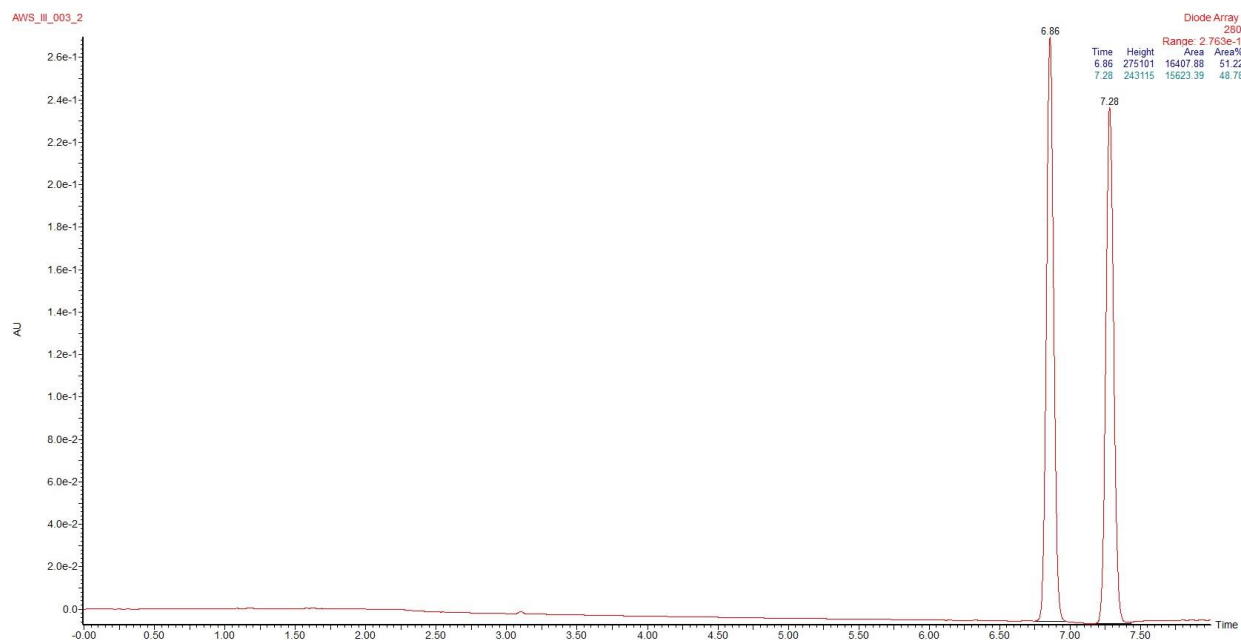


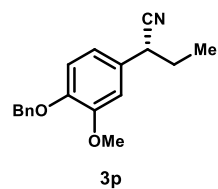
Chiral SFC analysis: Chiralpak AD-H (scCO₂/IPA = 95/5 to 80/20, 2.5 mL/min, 210-400 nm, 45 °C), 4.58 and 5.14 min.



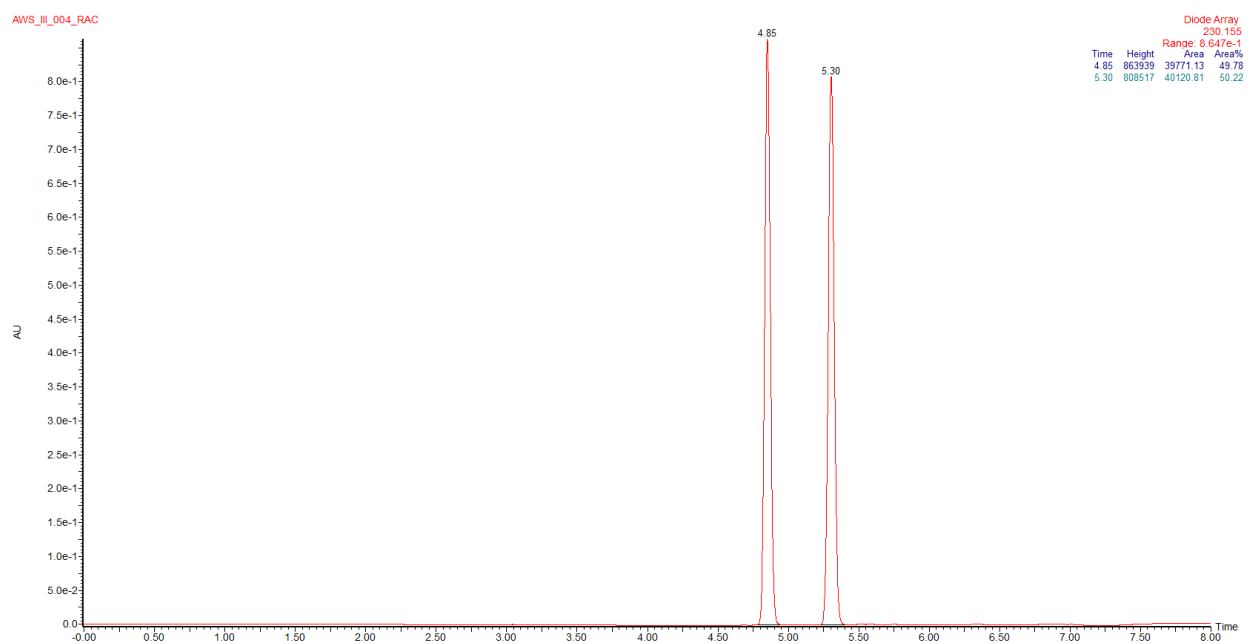
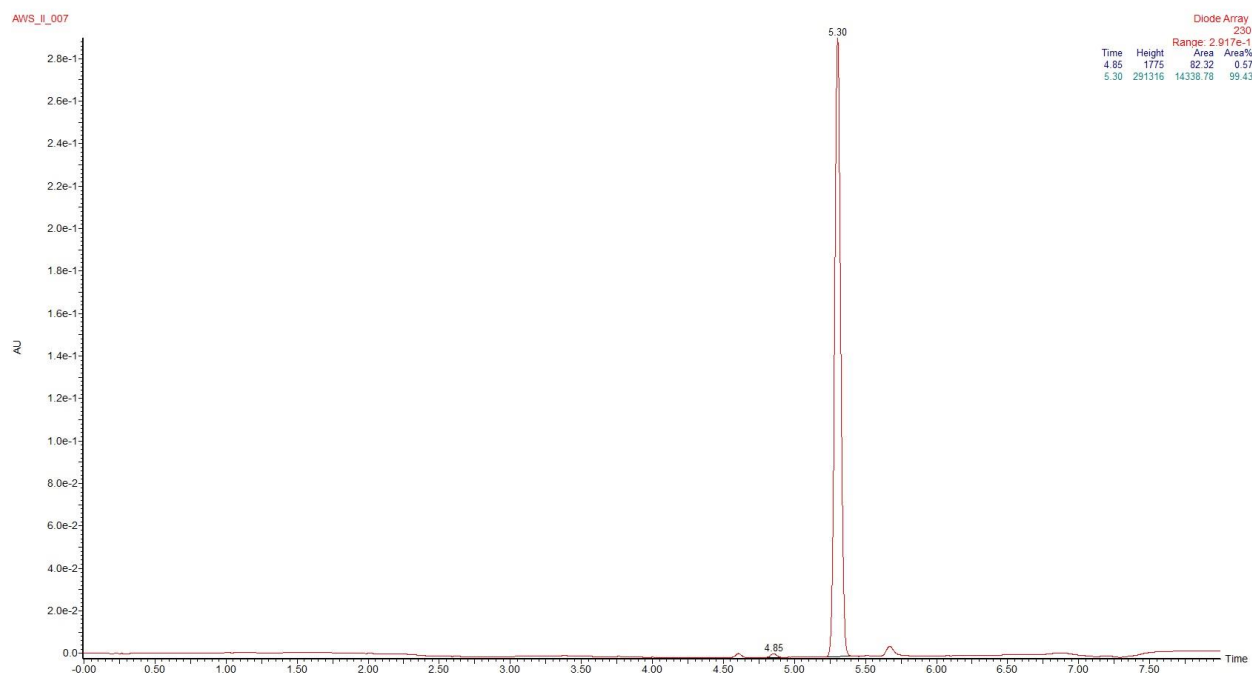


Chiral SFC analysis: Chiralpak AD-H (scCO₂/IPA = 95/5 to 60/40, 2.5 mL/min, 210-400 nm, 45 °C), 6.86 and 7.27 min.





Chiral SFC analysis: Chiralpak AD-H (scCO₂/IPA = 95/5 to 60/40, 2.5 mL/min, 210-400 nm, 45 °C), 4.85 and 5.30 min.



Supporting information.pdf (12.70 MiB)

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