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The hydroarylation of alkenes is an attractive approach to construct carbon–carbon (C–C) bonds from abundant and structurally diverse starting materials. Herein we report a palladium-catalyzed reductive Heck hydroarylation of unactivated and heteroatom-substituted terminal alkenes with an array of (hetero)aryl iodides. The reaction is anti-Markovnikov selective and tolerates a wide variety of functional groups on both the alkene and (hetero)aryl coupling partners. Additionally, applications of this method to complex molecule diversifications were demonstrated. Deuterium-labeling experiments are consistent with a mechanism in which the key alkylpalladium(II) intermediate is intercepted with formate and undergoes a decarboxylation/C–H reductive elimination cascade to afford the saturated product and turn over the cycle.

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Practical Intermolecular Hydroarylation of Terminal Alkenes via Reductive Heck Coupling

John A. Gurak, Jr.^[a] and Keary M. Engle^{*[a]}

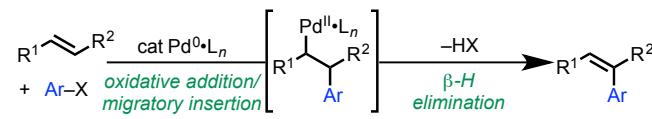
Abstract: The hydroarylation of alkenes is an attractive approach to construct carbon–carbon (C–C) bonds from abundant and structurally diverse starting materials. Herein we report a palladium-catalyzed reductive Heck hydroarylation of unactivated and heteroatom-substituted terminal alkenes with an array of (hetero)aryl iodides. The reaction is anti-Markovnikov selective and tolerates a wide variety of functional groups on both the alkene and (hetero)aryl coupling partners. Additionally, applications of this method to complex molecule diversifications were demonstrated. Deuterium-labeling experiments are consistent with a mechanism in which the key alkylpalladium(II) intermediate is intercepted with formate and undergoes a decarboxylation/C–H reductive elimination cascade to afford the saturated product and turn over the cycle.

The Mizoroki–Heck coupling of aryl halides and alkenes is an effective means of forging C–C bonds to enable preparation of densely functionalized alkenes.^[1] The broad functional group compatibility and vast scope of the Mizoroki–Heck reaction have allowed it to emerge as a staple transformation in complex-molecule synthesis. Mechanistically, the catalytic cycle involves oxidative addition of palladium(0) to an aryl halide followed by 1,2-migratory insertion to access a key alkylpalladium(II) intermediate. In the classical Mizoroki–Heck reaction, this intermediate succumbs to rapid β -hydride (β -H) elimination to deliver the functionalized alkene product, followed by HX reductive elimination to regenerate Pd(0), thereby closing the catalytic cycle. Alternatively, one could envision intercepting this intermediate with an additional reaction partner as a general strategy for programmed conversion of alkenes to various hydrofunctionalized or 1,2-difunctionalized products. Our laboratory has previously utilized chelation stabilization of organopalladium(II) intermediates to achieve hydroarylation of alkynes^[2] and alkenes^[3] via Heck-type nucleopalladation followed by protodepalladation. We thus became interested in exploring strategies for enabling similar modes of bond construction with organopalladium(II) intermediates in the absence of directing substituents. To this end, the goal of the present study was to develop a reductive Heck hydroarylation reaction of diverse terminal aliphatic and heteroatom-substituted alkenes.

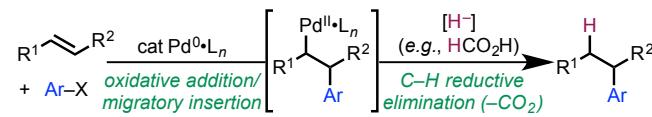
Reductive Heck hydroarylation involves intercepting the alkylpalladium(II) intermediate that is generated upon migratory insertion with a hydride source, most commonly formate. This transformation has been investigated since the early 1980s, and pioneering work by Cacchi^[4] and others during this period led to

effective protocols with several classes of C–C- π -bond-containing substrates that lack β -H atoms or that form stabilized π -allyl/ π -benzyl/enolate intermediates, including strained alkenes (e.g., norbornene),^[5] α,β -enones/enals,^[6] alkynes,^[7] tethered alkenes,^[8] and styrenes^[9] (Scheme 1).^[10] In contrast, application of this mode of reactivity to aliphatic terminal alkenes is comparatively undeveloped, likely due to the rapid nature of the aforementioned β -H elimination step with such substrates. To circumvent this issue, alternative strategies for hydroarylation of terminal aliphatic alkenes have been developed.^[11] In particular, Buchwald has described a CuH/Pd dual catalytic system for anti-Markovnikov hydroarylation of terminal alkenes with aryl bromides and electron-poor aryl chlorides.^[11c] To complement this approach, we became interested in developing a general monometallic reductive Heck protocol that would be operationally simple, employ readily available reaction components, and exhibit broad functional group compatibility, which motivated the present study. While this manuscript was in preparation, a related catalytic system for reductive Heck coupling of alkenes with aryl bromides was reported.^[12]

Classical Mizoroki–Heck Reaction



Reductive Heck Reaction



norbornenes	α,β-enones/enals	alkynes
(Catellani, 1980) (Cacchi, 1989)	(Cacchi, 1983) (Cacchi, 1984)	(Cacchi, 1984) (Endo, 1997)
tethered alkenes	styrenes	diverse terminal alkenes
(Larock, 1987)	(Torii, 1985)	this work
$R = \text{Alkyl, N, O, Si}$		

Scheme 1. Strategy and early precedents for the reductive Heck reaction.

To initiate our study, we elected to use 3-buten-1-ol and iodobenzene as model reaction partners for optimization (Table 1). At the outset we hypothesized that two key aspects would be vital for achieving successful reductive Heck coupling. First, the palladium catalyst would need to be coordinatively saturated throughout the catalytic cycle to suppress β -H elimination from

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the alkylpalladium(II) intermediate. Second, the rates of decarboxylation (to form Pd–H) and C–H reductive elimination would need to be sufficiently fast such that C–H bond formation could outcompete β -H elimination. With these considerations in mind, we began examining potential reaction conditions, deliberately using a high molar ratio of triphenyl phosphine relative to palladium (10:1). With potassium formate as the hydride source in the presence of water and a phase transfer reagent (TBABF_4) as additives, we were pleased to observe reductive Heck hydroarylation with several different inorganic bases (entries 1–8). Moderately strong bases provided higher yields than weaker bases, and, among those tested, K_3PO_4 offered the best yield. An approximately 4:1 ratio of anti-Markovnikov to Markovnikov addition products was observed, and the regioisomeric ratio was roughly constant across different conditions, reflecting earlier literature precedent of migratory insertion under a neutral Heck-type mechanism.^[13] Next, we investigated different formate sources (entries 9–12) and identified aqueous tetramethylammonium formate solution ($\text{TMA}\cdot\text{HCO}_2$) as a superior reductant that did not require additional water or tetraalkylammonium salts for high yield and selectivity. Lastly, we varied the palladium and phosphine loadings and found that 1% $\text{Pd}_2(\text{dba})_3$ with 20% PPh_3 performed similarly to higher loadings (entries 13–19). Increasing or decreasing the phosphine:palladium ratio from 10:1 led to lower yield. Extending the reaction time from 1 h to 4 h led to full consumption of starting material with a combined product yield of 92% and 4:1 r.r. (entry 10). Notably, the optimized protocol is operationally convenient, as it does not require rigorous exclusion of air or moisture and can be conveniently performed on the benchtop without specialized equipment or glassware.

Table 1. Optimization of reaction conditions.^[a]

Entry	$\text{Pd}_2(\text{dba})_3$ (%)	PPh_3 (%)	Base	Conditions	$1\mathbf{b}$		Yield $4\mathbf{b}$ + $4\mathbf{b}'$ (%) ^[b]	$4\mathbf{b}$: $4\mathbf{b}'$ ^[c]	SM (%)
					$4\mathbf{b}$	$4\mathbf{b}'$			
1	2.5	50	None	$\text{KHCO}_2\text{H}_2\text{O}/\text{TBABF}_4$	24	3.8	58		
2	2.5	50	$\text{KO}^\ddagger\text{Bu}$	$\text{KHCO}_2\text{H}_2\text{O}/\text{TBABF}_4$	44	3.9:1	31		
3	2.5	50	KOH	$\text{KHCO}_2\text{H}_2\text{O}/\text{TBABF}_4$	51	4:1	33		
4	2.5	50	K_2CO_3	$\text{KHCO}_2\text{H}_2\text{O}/\text{TBABF}_4$	43	3.8:1	39		
5	2.5	50	KHCO_3	$\text{KHCO}_2\text{H}_2\text{O}/\text{TBABF}_4$	18	3.5:1	67		
6	2.5	50	KH_2PO_4	$\text{KHCO}_2\text{H}_2\text{O}/\text{TBABF}_4$	1	ND	79		
7	2.5	50	K_2HPO_4	$\text{KHCO}_2\text{H}_2\text{O}/\text{TBABF}_4$	23	3.6:1	62		
8	2.5	50	K_3PO_4	$\text{KHCO}_2\text{H}_2\text{O}/\text{TBABF}_4$	61	4.1:1	23		
9	2.5	50	K_3PO_4	$\text{NaHCO}_2\text{H}_2\text{O}/\text{TBABF}_4$	40	4:1	41		
10	2.5	50	K_3PO_4	$\text{CsHCO}_2\text{H}_2\text{O}/\text{TBABF}_4$	47	4.2:1	28		
11	2.5	50	K_3PO_4	$\text{NH}_4\text{HCO}_2\text{H}_2\text{O}/\text{TBABF}_4$	19	3.8:1	63		
12	2.5	50	K_3PO_4	$\text{TMA}\cdot\text{HCO}_2$ (aq)/ TBABF_4	79	3.9:1	7		
13	2.5	50	K_3PO_4	$\text{TMA}\cdot\text{HCO}_2$ (aq)	89	3.5:1	6		
14	2.5	25	K_3PO_4	$\text{TMA}\cdot\text{HCO}_2$ (aq)	81	3.8:1	1		
15	2.5	10	K_3PO_4	$\text{TMA}\cdot\text{HCO}_2$ (aq)	67	4.1:1	ND		
16	2.5	5	K_3PO_4	$\text{TMA}\cdot\text{HCO}_2$ (aq)	5	ND	ND		
17	1	25	K_3PO_4	$\text{TMA}\cdot\text{HCO}_2$ (aq)	67	3.8:1	10		
18	1	20	K_3PO_4	$\text{TMA}\cdot\text{HCO}_2$ (aq)	80	4:1	3		
19	1	10	K_3PO_4	$\text{TMA}\cdot\text{HCO}_2$ (aq)	67	4.6:1	ND		
20 ^[d]	1	20	K_3PO_4	$\text{TMA}\cdot\text{HCO}_2$ (aq)	92	4:1	ND		

[a] $1\mathbf{b}$ (1 equiv), $\text{Pd}_2(\text{dba})_3$ (X%), PPh_3 (Y%), iodobenzene (2 equiv), base (2 equiv), H_2O (10 equiv), TBABF_4 (1 equiv), reductant (2 equiv), DMF (1.0 M), 80 C, 1 h. [b] Yields were determined by ^1H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. [c] The regioisomeric ratio was determined by ^1H NMR analysis of the crude reaction mixture (ND = not determined). [d] 4 h. TBABF_4 = tetrabutylammonium tetrafluoroborate, $\text{TMA}\cdot\text{HCO}_2$ (aq) = tetramethylammonium formate 30% w/w aqueous solution.

Having identified optimal conditions, we next explored the aryl iodide scope using allyl alcohol as the alkene partner (Table 2). This choice was motivated by the potential versatility of the alcohol moiety in downstream functionalization and because of

the high regioselectivity observed for this substrate (vide infra), which simplified purification and analysis in most cases. Both electron-deficient (**3a**–**3f**) and electron-rich (**3g**–**3i**) aryl iodides were competent coupling partners, affording the desired products in synthetically useful yields, even when multi-substituted (**3b**, **3c**, and **3i**) or sterically congested (**3k** and **3l**) aryl iodides were used. A variety of heteroaryl iodides were also suitable coupling partners for the reaction, including those containing pyridine (**3m**–**3o**), pyrazine (**3p**), quinoline (**3q**), or furan (**3r**) heterocycles. Additionally, the reaction was found to tolerate a range of functional groups that can serve as handles for further diversification, such as nitriles, ketones, halides, protected amines, and aldehydes. Notably, the regioselectivity of the insertion step appears to be influenced by the electronic nature of the aryl group, with electron-deficient aryl iodides giving lower regioisomeric ratios than electron-neutral or -rich aryl iodides.

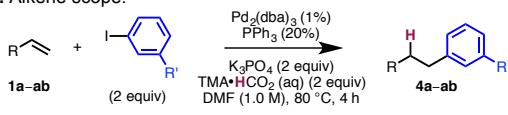
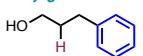
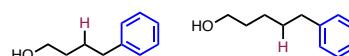
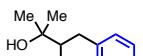
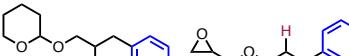
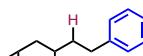
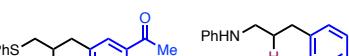
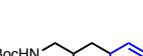
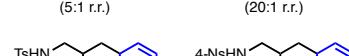
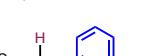
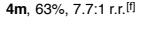
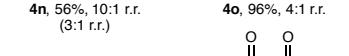
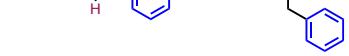
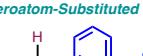
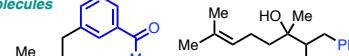
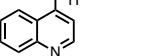
Table 2. Aryl iodide scope.^[a–c]

$1\mathbf{a}$	$\text{I}-\text{Ar}$ (2 equiv)	$\text{Pd}_2(\text{dba})_3$ (1%) PPh_3 (20%) K_3PO_4 (2 equiv) $\text{TMA}\cdot\text{HCO}_2$ (aq) (2 equiv) DMF (1.0 M), 80 °C, 4 h	$3\mathbf{a}$ – $3\mathbf{r}$

[a] $1\mathbf{a}$ (1 equiv), $\text{Pd}_2(\text{dba})_3$ (X%), PPh_3 (Y%), iodobenzene (2 equiv), base (2 equiv), H_2O (10 equiv), TBABF_4 (1 equiv), reductant (2 equiv), DMF (1.0 M), 80 C, 4–20 h. [b] Isolated yields. [c] The regioisomeric ratio of the isolated compound. The regioisomeric ratio of the crude reaction mixture as determined by ^1H NMR analysis is given in parenthesis if it differs from the ratio of the isolated material. $\text{TMA}\cdot\text{HCO}_2$ (aq) = tetramethylammonium formate 30% w/w aqueous solution.

Next, we probed the alkene coupling partner scope using iodobenzene and 3'-iodoacetophenone as representative aryl

Table 3. Alkene scope.^[a-c]


Non-Conjugated Terminal Alkenes
 4a, 66%, Single [15 mmol]: 60%, Single, 24 h
 4b, 88%, 5:1 r.r. (4:1 r.r.)
 4c, 84%, 4.5:1 r.r.
 4d, 74%, Single, 16 h[d]
 4e, 63%, Single
 4f, 30%, 3:1 r.r.
 4g, 89%, Single, 1:1 d.r.[e]
 4h, 43%, Single (5:1 r.r.)
 4i, 59%, Single (20:1 r.r.)
 4j, 96%, 3.5:1 r.r.
 4k, 57%, 12.5:1 r.r. (10:1 r.r.)
 4l, 41%, Single[d]
 4m, 63%, 7.7:1 r.r.[f]
 4n, 56%, 10:1 r.r. (3:1 r.r.)
 4o, 96%, 4:1 r.r.
 4p, 51%, 4:1 r.r. (3:1 r.r.)
 4q, 54%, 3:1 r.r.
 4r, 64%, 3.5:1 r.r. (3.8:1 r.r.)
 4s, 54%, 2.3:1 r.r. (3.8:1 r.r.)
 4t, 84%, 1.5:1 r.r., 24 h[d]
 4u, 30%, Single (4.2:1 r.r.)
Heteroatom-Substituted Terminal Alkenes
 4v, 71%, Single (5:1 r.r.)
 4w, 31%, 16.7:1 r.r.
 4x, 36%, 25:1 r.r. (2.5:1 r.r.)
Alkene-Containing Complex Molecules
 4y, 99%, Single from quinine
 4z, 71%, Single, 16 h[d] from sclareol
 4aa, 64%, Single, 16 h[d] from linalool
 4ab, 86%, Single, 16 h[d] from (+)-β-citronellene

[a] Alkene (1 equiv), Pd₂(dba)₃ (1%), PPh₃ (20%), aryl iodide (2 equiv), K₃PO₄ (2 equiv), TMA-HCO₂ (aq) (2 equiv), DMF (1.0 M), 80 °C, 4–24 h. [b] Isolated yields. [c] The regioisomeric ratio of the isolated compound. The regioisomeric ratio of the crude reaction mixture as determined by ¹H NMR analysis is given in parenthesis if it differs from the ratio isolated. [d] 2.5% Pd₂(dba)₃ and 50% PPh₃. [e] The alkene starting material 3g was a 1:1 mixture of diastereomers. [f] Contaminated with a constitutional isomer. TMA-HCO₂ = tetramethylammonium formate 30% w/w aqueous solution.

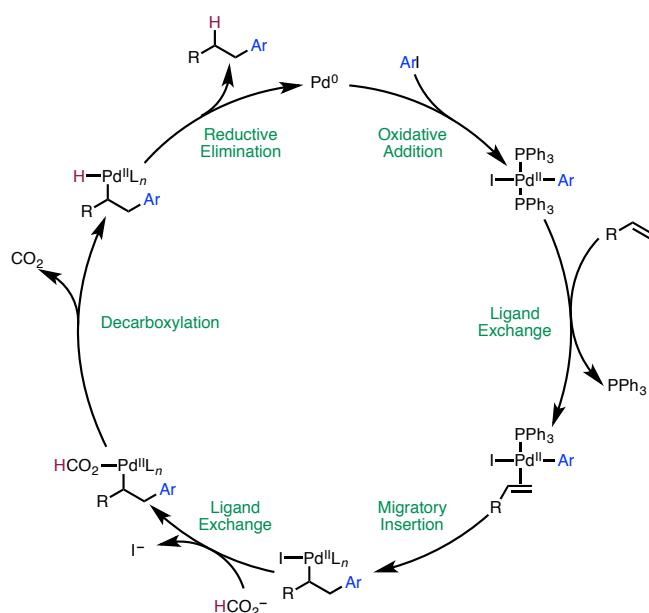
iodides, with the latter facilitating product isolation with non-polar alkenes (Table 3). High yields of the hydroarylated products were obtained for alcohol-containing substrates of various chain lengths (**4a–4c**), and the reaction was ≥4:1 selective across this series of alkenes. Steric hindrance adjacent to the alkene could be accommodated (**4d**), although higher palladium and phosphine loadings and a longer reaction time were required. The reaction was amenable to scale-up, providing **4a** in 60% yield on a 15 mmol scale; in this case, extended reaction time was required to achieve high conversion. The tetrahydropyran acetal protecting group (**4e**) was tolerated under the reaction conditions, as were epoxides (**4f** and **4g**), affording moderate to high yields of the desired products. Additionally, thioethers (**4h**), protected amines (**4i–4l**), and silanes (**4m**) were found to be compatible functional groups for this transformation. Non-activated aliphatic alkene hydrocarbons were also suitable substrates in this reaction (**4n–4p**), highlighting the broad scope of alkenes tolerated by this method. Esters (**4q** and **4r**) and lactams (**4s**), which are known to undergo hydrolysis under basic conditions at elevated temperatures, were well tolerated under the conditions. Moreover, alkenes containing Lewis basic functional groups with the capacity for metal binding, namely an imidazole (**4t**) and a urea (**4u**), were compatible.

In addition to non-conjugated terminal alkenes, we discovered that heteroatom-substituted terminal alkenes were also competent substrates in this reaction. Specifically, we found that a vinyl ether (**4v**), a vinyl silane (**4w**), and *N*-vinyl-pyrrolidinone (**4x**) reacted to give predominantly the anti-Markovnikov hydroarylated products, albeit in modest yield in the last two cases. Finally, to underscore the synthetic utility of this transformation, we explored a variety of alkene-containing natural products and derivatives thereof. Quinine reacted smoothly to provide the anti-Markovnikov hydroarylation product as a single regioisomer in quantitative yield (**4y**), emphasizing the power of this transformation to provide expedited access to cinchona alkaloid derivatives, which are useful chiral ligands and organocatalysts. A variety of terpene derivatives, including the bicyclic diterpene sclareol (**4z**) and the linear monoterpenes linalool (**4aa**) and (+)-β-citronellene (**4ab**), were also viable substrates, providing moderate to high yields of the anti-Markovnikov hydroarylation products as single regioisomers. Of note, the reaction is chemoselective for terminal alkenes, evidenced by **4aa** and **4ab** where the trisubstituted alkene underwent neither the hydroarylation reaction nor reduction to the alkane. Overall, this reductive Heck transformation is tolerant of a wide array of functional groups, including some that are potentially reductively labile, and it thus represents a powerful transformation to install aryl moieties over a diverse range of alkenes that complements existing methods.

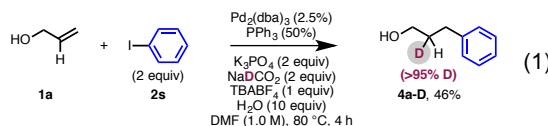
Regarding selectivity patterns, across the examples described above, the r.r. values ranged from 1.5:1 to >50:1, with the anti-Markovnikov product favored in all cases. Although many of the observed regioisomeric ratios are in accordance with literature precedents^[13] for a neutral Heck mechanism with these substrates, a detailed description of the origins of the observed trends remains outside of the scope of the present study. Generally speaking, it appears that the steric and electronic

properties of both the alkene and the migrating aryl group contribute to the activation energy of the product-determining step.

Based upon our results, we propose the catalytic cycle in Scheme 2. The initial sequence of events follows that of the Mizoroki-Heck reaction: oxidative addition of the aryl iodide, alkene coordination, and migratory insertion of the aryl group to give the alkylpalladium(II) intermediate. At this stage, rather than undergoing β -H elimination (as in the Mizoroki-Heck reaction), this intermediate exchanges iodide for formate, at which point decarboxylation generates a Pd-H species. Upon C-H reductive elimination, the reductive Heck product is formed and Pd(0) is regenerated to close the catalytic cycle. To validate that formate was indeed the source of hydrogen in the product, we performed the reaction using sodium formate-d. As expected, full deuterium incorporation in the product with no deuterium scrambling was observed, supporting our proposed mechanism (Equation 1).



Scheme 2. Proposed catalytic cycle.



In summary, we have developed a mild and operationally convenient palladium-catalyzed reductive Heck reaction of aliphatic and heteroatom-substituted terminal alkenes with (hetero)aryl iodides. Mechanistically, the catalytic cycle follows the same initial steps as the Mizoroki-Heck reaction to generate the alkylpalladium(II) intermediate, which then undergoes decarboxylation from a bound formate ligand followed by C-H reductive elimination to produce the hydroarylated product. The reaction provides predominantly the anti-Markovnikov product and is compatible with a wide variety of synthetically important functional groups, including many that are reductively labile. Notably, the transformation accommodates heterocycles,

including those containing basic sp^2 -hybridized nitrogen atoms, and can be used for complex molecule diversification. The procedure is scalable and requires only inexpensive, readily available components, highlighting its practicality as a synthetic tool. We anticipate that this method will find use in both target-oriented and divergent synthesis and that the mechanistic implications of this study will stimulate the development of additional alkene functionalization reactions in the future.

Experimental Details.

To a 1-Dram (4 mL) vial equipped with a magnetic stir bar were added $\text{Pd}_2(\text{dba})_3$ (1.8 mg, 0.002 mmol), triphenylphosphine (10.5 mg, 0.04 mmol), K_3PO_4 (84.9 mg, 0.4 mmol), alkene (0.2 mmol), aryl iodide (0.4 mmol), TMA-HCO₂ (30% w/w aqueous solution) (0.16 mL, 0.4 mmol), and DMF (0.2 mL). The vial was sealed with a solid screw cap and placed in a heating block that was pre-heated to 80 °C. After the designated reaction time, the reaction mixture was diluted with water (5 mL) and extracted with EtOAc (5 mL × 3). The combined organic layers were dried over Na_2SO_4 , concentrated *in vacuo*, and purified by column chromatography.

Acknowledgements

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Keywords: alkenes • Heck reaction • hydroarylation • palladium • regioselectivity

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Practical Intermolecular Hydroarylation of Terminal Alkenes via Reductive Heck Coupling

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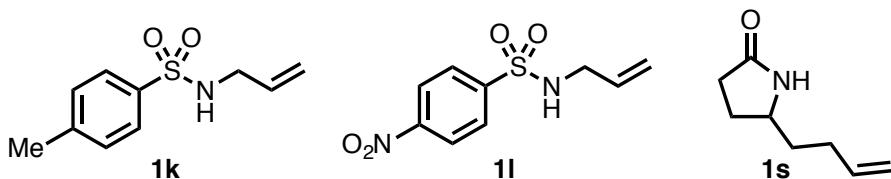
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General Information

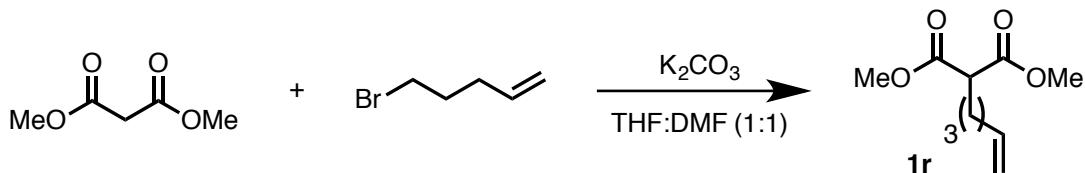
Unless stated otherwise, all materials were used as received from commercial sources without further purification. All glassware and stirring bars were dried in an oven at 100 °C overnight unless otherwise stated. DCM, EtOAc, Hexanes, MeOH, and DMF were purchased from Aldrich and used as received without additional drying. 1-Dram reaction vials were purchased from VWR (Cat#: 66011-041) and caps were purchased from ChemGlass (Cat#: CG-4911-10). Ambient temperature refers to 21–24 °C. Elevated temperatures were maintained by an Ika heating block for 1-Dram vials or a silicon oil bath for larger vessels. Thin-layer chromatography (TLC) was performed using EMD Millipore 250 mm silica gel F-254 plates (250 μ m) with F-254 fluorescent indicator and visualized by UV fluorescence quenching, iodine, Seebach's stain, or potassium permanganate stain. SiliCycle SiliaFlash P60 silica gel (particle size 40–63 μ m) was used for flash chromatography. 1 H and 13 C NMR spectra were recorded on a Bruker DRX equipped with a 5 mm DCH cryoprobe (600 MHz and 150 MHz, respectively). 19 F spectra were recorded on a Bruker DPX with a 5 mm QNP probe (376 MHz). 1 H spectra were reported relative to Me₄Si (δ 0.0) or residual solvent signals unless otherwise stated. 13 C NMR spectra were calibrated to residual solvent signals (CDCl₃ at 77.16 ppm and CD₃OD at 49.00). High-resolution mass spectra (HRMS) for **3c** and **3p** were recorded on an Agilent LC/MSD TOF mass spectrometer by electrospray ionization time of flight experiments. HRMS for **3i** and **3k** were recorded on an Agilent HR-ESI/APCI-MS TOF mass spectrometer by electrospray ionization time of flight experiments, while **4a-D** was recorded on the same instrument by atmospheric pressure chemical ionization time of flight experiments. All other HRMS were recorded on a Waters LC/MSD TOF mass spectrometer by electrospray ionization time of flight experiments. The calculated masses for were determined by ChemDraw for compounds analyzed by the Agilent systems and by the Waters software, which calibrates masses using an IUPAC reference,^[1] for compounds analyzed by the Waters instrument.

Substrate Synthesis

(Yields are unoptimized)



1k,^[2] **1l**,^[2] and **1s**^[3] were prepared according to literature procedures.

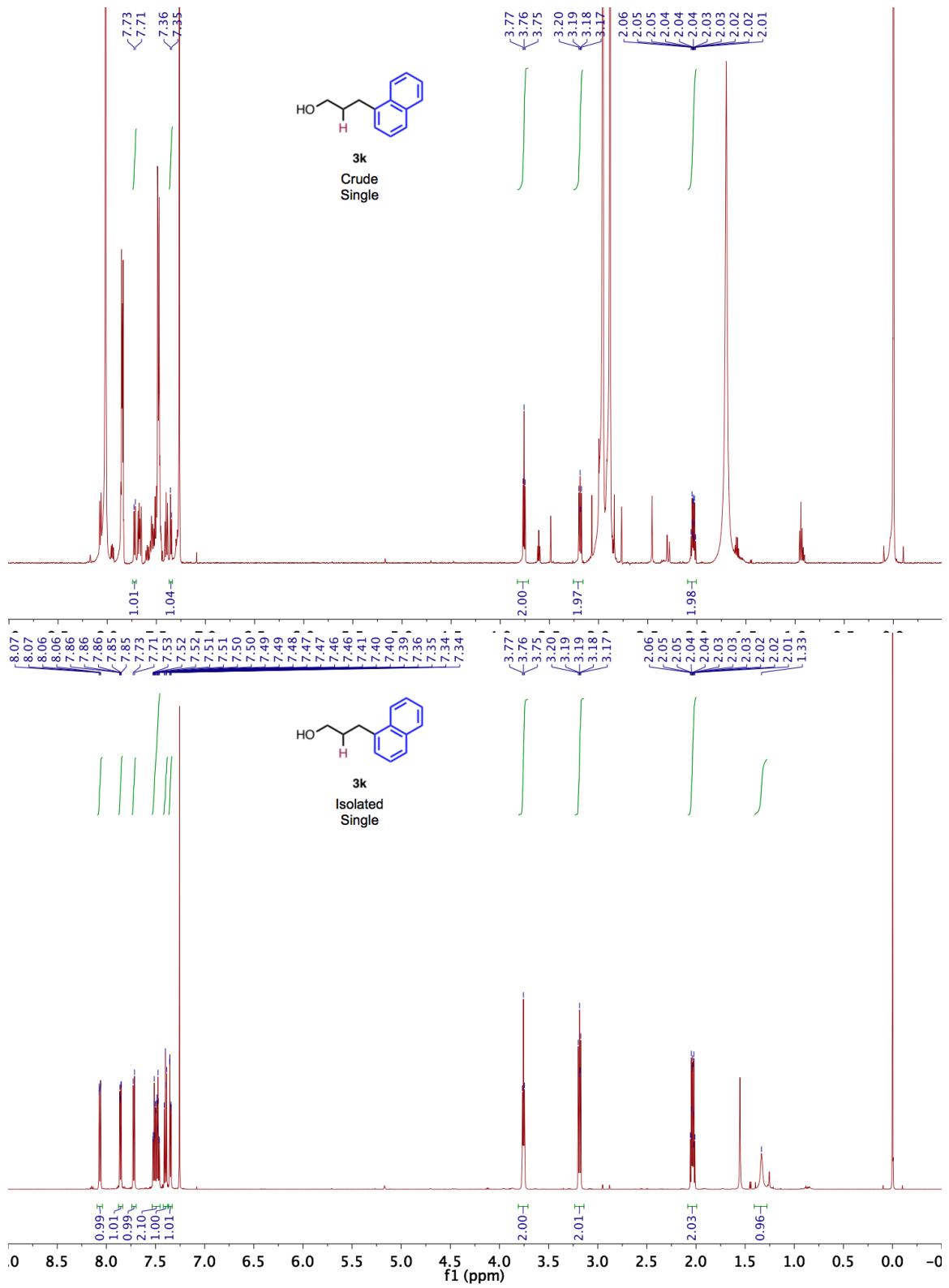


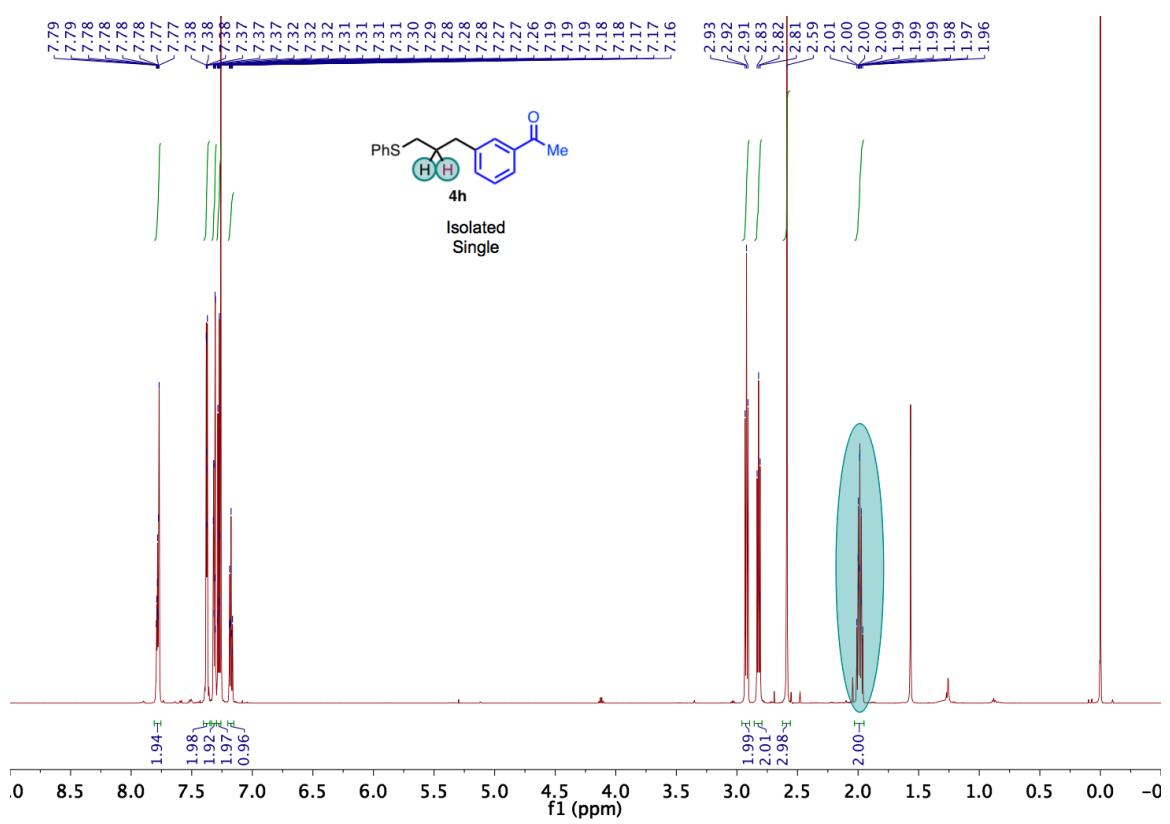
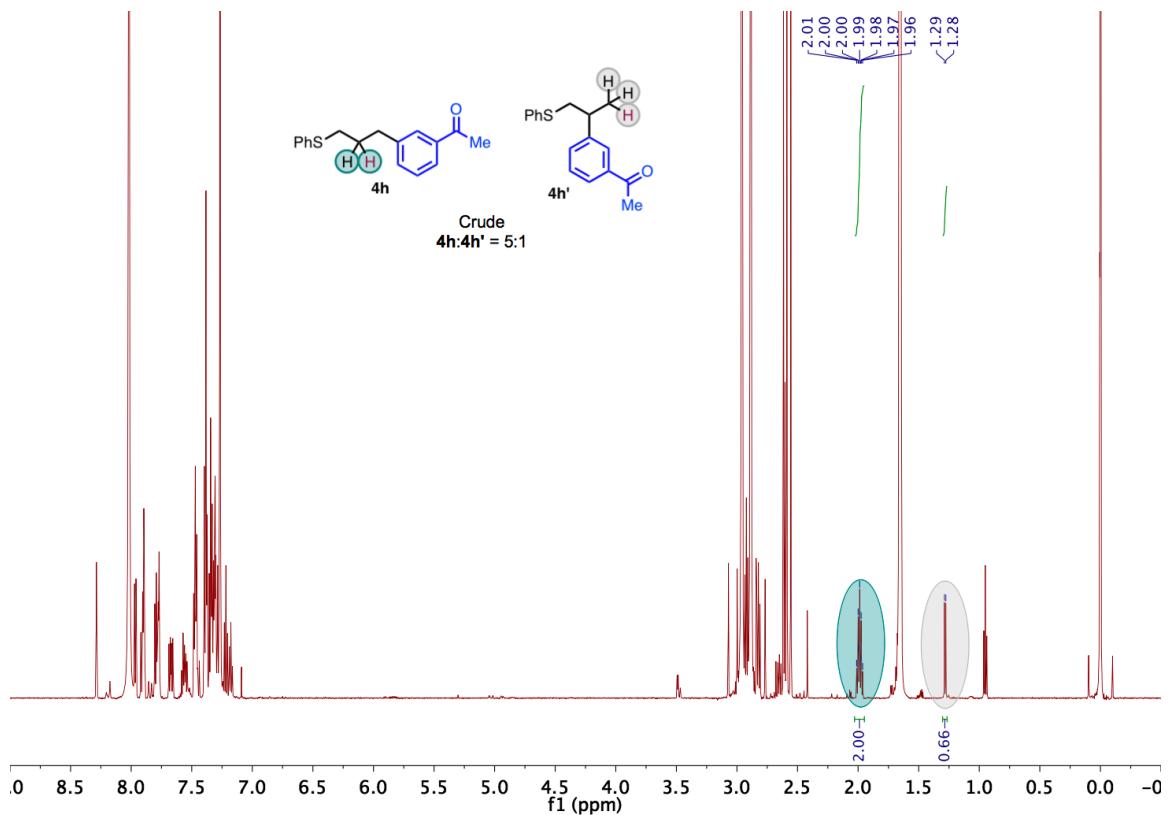
dimethyl 2-(pent-4-en-1-yl)malonate (1r): The title compound was prepared according to a procedure adapted from Deslongchamps.^[4] Dimethyl malonate (2.29 mL, 20.0 mmol), 1-bromo-5-pentene (0.47 mL, 4.00 mmol), and K₂CO₃ (2.76 g, 20.0 mmol) were charged into a 250-mL round bottom flask containing THF (7.5 mL) and DMF (7.5 mL), and the reaction was heated at 90 °C for 16 h. The reaction was allowed to cool to ambient temperature, and then hexanes (7.0 mL) was added. The solution was filtered over celite, concentrated *in vacuo*, and purified by column chromatography (15% EtOAc in Hexanes) to afford **1r** (582 mg, 73%) as a colorless oil. ¹H NMR (600 MHz, CDCl₃) δ 5.78 (ddt, *J* = 17.0, 10.2, 6.6 Hz, 1H), 5.08–4.93 (m, 2H), 3.74 (s, 6H), 3.37 (t, *J* = 7.5 Hz, 1H), 2.08 (q, *J* = 7.2 Hz, 2H), 1.95–1.88 (m, 2H), 1.47–1.38 (m, 2H). ¹³C NMR (150 MHz, CDCl₃) δ 169.99, 138.01, 115.22, 52.62, 51.71, 33.38, 28.43, 26.69. HRMS calcd. for C₁₀H₁₆NaO⁺ [M+Na]⁺: 223.0946, Found: 223.0949.

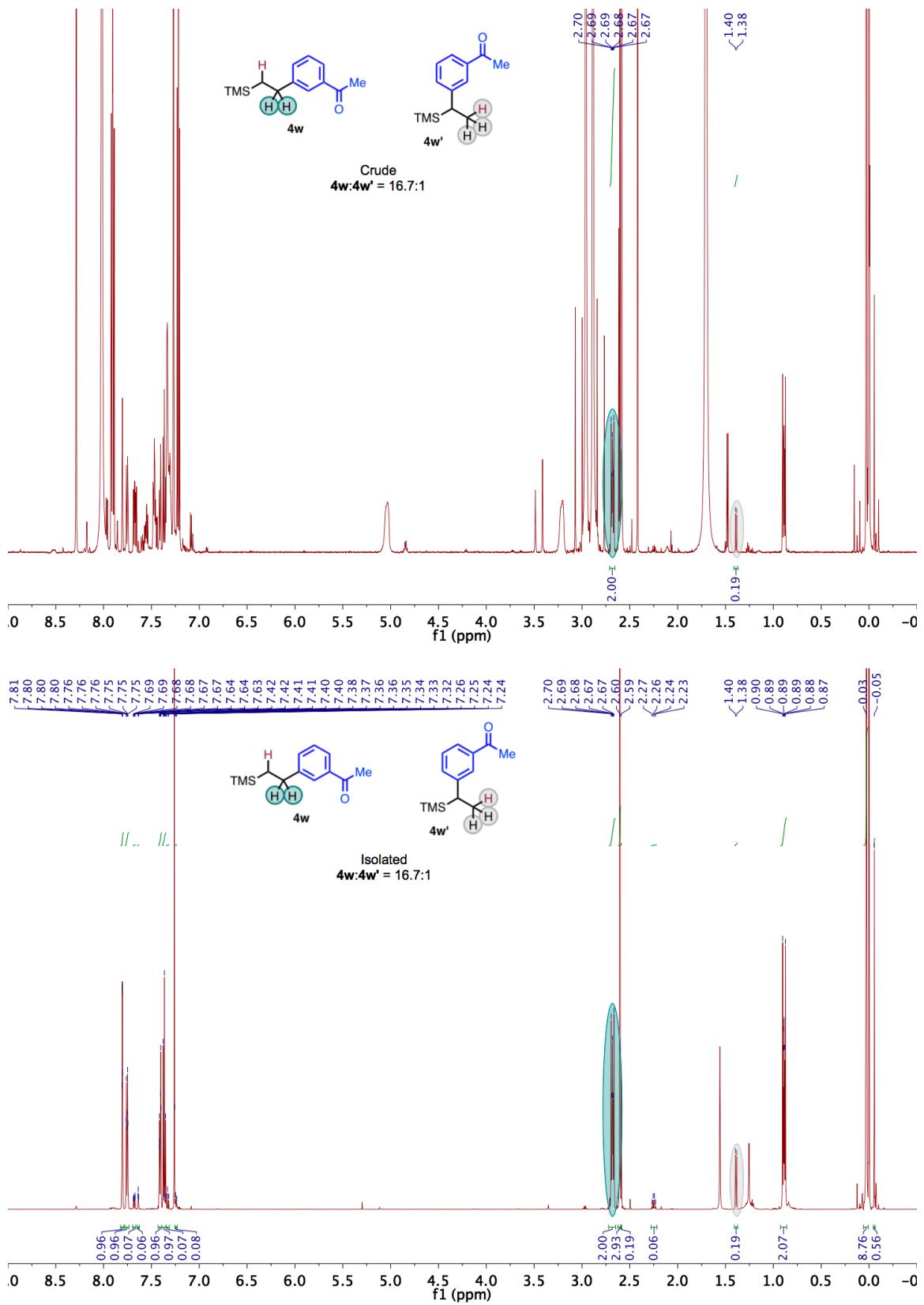
Determination of Regioisomeric Ratios

The regioisomeric ratios of the products prepared in this study were determined directly from ^1H NMR spectra of the crude reaction mixtures and from samples of subsequently isolated products. In cases with only a single regioisomer, trace impurities were sometimes detected in the ^1H NMR spectra of the crude reaction mixture, but the peaks of these minor byproducts did not appear to correspond to the other potential regioisomer. In these cases, except for the major product, no other compounds were formed in sufficient quantity to be isolated and characterized.

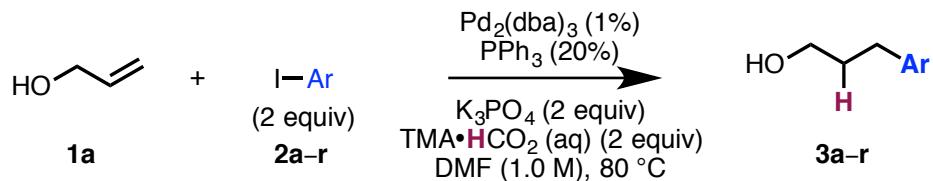
Below, three representative examples of ^1H NMR spectra of crude reaction mixtures and purified samples are included to illustrate how regioisomeric ratios were determined through integration of diagnostic ^1H resonances.







General Procedure for Evaluating Aryl Iodide Scope



Unless otherwise stated, the procedure was as follows. To a 1-Dram (4 mL) vial equipped with a magnetic stir bar were added $\text{Pd}_2(\text{dba})_3$ (1.8 mg, 0.002 mmol), triphenylphosphine (10.5 mg, 0.04 mmol), K_3PO_4 (84.9 mg, 0.4 mmol), allyl alcohol (11.6 mg, 0.2 mmol), aryl iodide (0.4 mmol), $\text{TMA}\cdot\text{HCO}_2$ (30% w/w aqueous solution) (0.16 mL, 0.4 mmol), and DMF (0.2 mL). The vial was sealed with a solid screw cap and placed in a heating block that was pre-heated to 80°C . After the designated reaction time, the reaction mixture was diluted with water (5 mL) and extracted with EtOAc (5 mL \times 3). The combined organic layers were dried over Na_2SO_4 , concentrated *in vacuo*, and purified by column chromatography to produce $3a-r$.

3-(4-(trifluoromethyl)phenyl)propan-1-ol (3a): The reaction was carried out according to the general procedure using aryl iodide **2a**. The reaction was run for 4 h, and the product was purified by flash column chromatography (20–33% EtOAc in Hexanes) to afford **3a** (27.4 mg, 67% yield) as a yellow oil. This product was isolated as a single regioisomer as determined by ¹H NMR analysis; the crude reaction mixture also contained only a single regioisomer by ¹H NMR analysis. Characterization data matched that of commercial sources.

4-(3-hydroxypropyl)-2-(trifluoromethyl)benzonitrile (3b): The reaction was carried out according to the general procedure using aryl iodide **2b**. The reaction was run for 16 h, and the product was purified by flash column chromatography (5–10% EtOAc in DCM) to afford **3b** (21.2 mg, 46% yield) as a white solid. This product was isolated as a single regioisomer as determined by ¹H NMR analysis. The isolated r.r. differed from that of the crude reaction mixture (10:1 r.r.). ¹**H NMR** (600 MHz, CDCl₃) δ 7.76 (d, *J* = 7.9 Hz, 1H), 7.63 (s, 1H), 7.52 (d, *J* = 7.9 Hz, 1H), 3.70 (t, *J* = 6.2 Hz, 2H), 2.92–2.84 (m, 2H), 1.97–1.88 (m, 2H), 1.41 (s, 1H). ¹³**C NMR** (150 MHz, CDCl₃) δ 148.49, 134.92, 133.01 (*q*, *J*_{C-F} = 32.5 Hz), 132.34, 127.00 (*q*, *J*_{C-F} = 4.5 Hz), 122.56 (*q*, *J*_{C-F} = 273.8 Hz), 115.81, 107.62 (*q*, *J*_{C-F} = 2.2 Hz), 61.59, 33.46, 32.30. ¹⁹**F NMR** (376 MHz, CDCl₃) δ -62.18. **HRMS** calcd. for C₁₁H₁₁F₃NO⁺ [M+H]⁺: 230.0793, Found: 230.0786.

3-(4-nitro-3-(trifluoromethyl)phenyl)propan-1-ol (3c): The reaction was carried out according to the general procedure using aryl iodide **2c**. The reaction was run for 4 h, and the product was purified by flash column chromatography (5–10% EtOAc in DCM) to afford **3c** (19.8 mg, 40% yield) as a yellow solid. This product was isolated as a single regioisomer as determined by ¹H NMR analysis. The isolated r.r. differed from that of the crude reaction mixture (6.3:1 r.r.). ¹**H NMR** (600 MHz, CDCl₃) δ 7.85 (d, *J* = 8.2 Hz, 1H), 7.66 (d, *J* = 1.8 Hz, 1H), 7.55 (dd, *J* = 8.3, 1.8 Hz, 1H), 3.71 (t, *J* = 6.3 Hz, 2H), 2.94–2.84 (m, 2H), 1.98–1.89 (m, 2H), 1.38 (s, 1H). ¹³**C NMR** (150 MHz, CDCl₃) δ 148.22, 146.35, 132.87, 128.06 (*q*, *J*_{C-F} = 5.3 Hz), 125.53, 124.01 (*q*, *J*_{C-F} = 33.8 Hz), 122.16 (*q*, *J*_{C-F} = 273.0 Hz), 61.57, 33.54, 31.96. ¹⁹**F NMR** (376 MHz, CDCl₃) δ -60.22. **HRMS** calcd. for C₁₀H₁₀ClF₃NO₃⁻ [M+Cl]⁻: 284.0307, Found: 284.0305.

1-(3-(3-hydroxypropyl)phenyl)ethan-1-one (3d): The reaction was carried out according to the general procedure using aryl iodide **2d**. The reaction was run for 4 h, and the product was purified by flash column chromatography (10–20% EtOAc in Hexanes) to afford **3d** (21.2 mg, 60% yield) as a yellow oil. This product was isolated as a single regioisomer as determined by ¹H NMR analysis; the crude reaction mixture also contained only a single regioisomer by ¹H NMR analysis. ¹**H NMR** (600 MHz, CDCl₃) δ 7.84–7.77 (m, 2H), 7.45–7.36 (m, 2H), 3.69 (t, *J* = 6.4 Hz, 2H), 2.84–2.75 (m, 2H), 2.60 (s, 3H), 1.97–1.89 (m, 2H), 1.33 (s, 1H). ¹³**C NMR** (150 MHz, CDCl₃) δ 198.54, 142.55, 137.45, 133.45, 128.77, 128.27, 126.28, 62.15, 34.22, 32.05, 26.84. **HRMS** calcd. for C₁₁H₁₅O₂⁺ [M+H]⁺: 179.1072, Found: 179.1073.

1-(4-(3-hydroxypropyl)phenyl)ethan-1-one (3e): The reaction was carried out according to the general procedure using aryl iodide **2e**. The reaction was run for 4 h, and the product was purified by flash column chromatography (10–20% EtOAc in DCM) to afford **3e** (26.7 mg, 75% yield) as a yellow oil. This product was isolated as an inseparable 8.3:1 mixture of regioisomers as determined by ¹H NMR analysis; the crude reaction mixture also contained the same ratio of regioisomers by ¹H NMR analysis. The peaks for both the major and minor regioisomer were dispersed enough to unambiguously assign the two regioisomers separately.

Characterization data for the major regioisomer (3e): ¹H NMR (600 MHz, CDCl₃) ¹H NMR (600 MHz, CDCl₃) δ 7.92–7.86 (m, 2H), 7.32–7.28 (m, 2H), 3.72–3.65 (m, 2H), 2.78 (dd, *J* = 8.6, 6.8 Hz, 2H), 2.59 (s, 3H), 1.97–1.86 (m, 2H). ¹³C NMR (150 MHz, CDCl₃) δ 198.54, 142.55, 137.45, 133.45, 128.77, 128.27, 126.28, 62.15, 34.22, 32.05, 26.84. HRMS calcd. for C₁₁H₁₅O₂⁺ [M+H]⁺: 179.1072. Found: 179.1075.

Characterization data for the minor regioisomer (3e'): 1H NMR (600 MHz, CDCl₃) 7.96–7.92 (m, 2H), 7.37–7.33 (m, 2H), 3.75 (t, *J* = 5.9 Hz, 2H), 3.04 (h, *J* = 6.9 Hz, 1H), 2.59 (s, 3H), 1.35–1.27 (m, 3H). ¹³C NMR (150 MHz, CDCl₃) 149.94, 123.14, 67.90, 42.04, 17.04 (Note: One aromatic carbon peak could not be assigned.)

3-(4-bromophenyl)propan-1-ol (3f): The reaction was carried out according to the general procedure using aryl iodide **2f**. The reaction was run for 4 h, and the product was purified by flash column chromatography (20–33% EtOAc in Hexanes) to afford **3f** (26.2 mg, 61% yield) as a yellow oil. This product was isolated as a single regioisomer as determined by ¹H NMR analysis; the crude reaction mixture also contained only a single regioisomer by ¹H NMR analysis. Characterization data matched that of commercial sources.

tert-butyl (4-(3-hydroxypropyl)phenyl)carbamate (3g): The reaction was carried out according to the general procedure using aryl iodide **2g**. The reaction was run for 4 h, and the product was purified by flash column chromatography (30–40% EtOAc in Hexanes) to afford **3g** (29.6 mg, 59% yield) as a yellow oil. This product was isolated as a single regioisomer as determined by ¹H NMR analysis; the crude reaction mixture also contained only a single regioisomer by ¹H NMR analysis. Characterization data were consistent with previously reported data.^[5]

3-(4-methoxyphenyl)propan-1-ol (3h): The reaction was carried out according to the general procedure using aryl iodide **2g**. The reaction was run for 4 h, and the product was purified by flash column chromatography (20–33% EtOAc in Hexanes) to afford **3h** (20.6 mg, 62% yield) as a colorless oil. This product was isolated as a single regioisomer as determined by ¹H NMR analysis; the crude reaction mixture also contained only a single regioisomer by ¹H NMR analysis. Characterization data matched that of commercial sources.

3-(benzo[d][1,3]dioxol-5-yl)propan-1-ol (3i): The reaction was carried out according to the general procedure using aryl iodide **2i**. The reaction was run for 4 h, and the product was purified by flash column chromatography (25% EtOAc in Hexanes) to afford **3i** (23.3 mg, 65% yield) as a yellow oil. This product was isolated as a single regioisomer as determined by ¹H NMR analysis; the crude reaction mixture also contained only a single regioisomer by ¹H NMR analysis.

1H NMR (600 MHz, CDCl₃) δ 6.73 (d, *J* = 7.9 Hz, 1H), 6.70 (d, *J* = 1.7 Hz, 1H), 6.65 (dd, *J* = 7.9, 1.6 Hz, 1H), 5.92 (s, 2H), 3.67 (t, *J* = 6.4 Hz, 2H), 2.67–2.60 (m, 2H), 1.90–1.81 (m, 2H), 1.25 (s, 1H). **13C NMR** (150 MHz, CDCl₃) δ 147.73, 145.77, 135.76, 121.25, 109.01, 108.30, 100.90, 62.29, 34.57, 31.94. **HRMS** calcd. for C₁₀H₁₁O₃⁺ [M–H][–]: 179.0714, Found: 179.0713.

3-(naphthalen-2-yl)propan-1-ol (3j): The reaction was carried out according to the general procedure using aryl iodide **2j**. The reaction was run for 4 h, and the product was purified by flash column chromatography (20–33% EtOAc in Hexanes) to afford **3j** (26.4 mg, 71% yield) as a yellow oil. This product was isolated as a single regioisomer as determined by ¹H NMR analysis; the crude reaction mixture also contained a single regioisomer by ¹H NMR analysis. Characterization data were consistent with previously reported data.^[6]

3-(naphthalen-1-yl)propan-1-ol (3k): The reaction was carried out according to the general procedure using aryl iodide **2k**. The reaction was run for 20 h, and the product was purified by flash column chromatography (20–33% EtOAc in Hexanes) to afford **3k** (23.6 mg, 63% yield) as a yellow oil. This product was isolated as a single regioisomer as determined by ¹H NMR analysis; the crude reaction mixture also contained only a single regioisomer by ¹H NMR analysis. **1H NMR** (600 MHz, CDCl₃) δ 8.07 (dd, *J* = 8.4, 1.3 Hz, 1H), 7.86 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.72 (d, *J* = 8.1 Hz, 1H), 7.49 (dd, *J* = 22.6, 8.0, 6.7, 1.4 Hz, 2H), 7.40 (dd, *J* = 8.1, 7.0 Hz, 1H), 7.35 (dd, *J* = 7.0, 1.2 Hz, 1H), 3.76 (t, *J* = 6.3 Hz, 2H), 3.22–3.15 (m, 2H), 2.09–2.00 (m, 2H), 1.33 (s, 1H). **13C NMR** (150 MHz, CDCl₃) δ 138.06, 134.04, 131.97, 128.92, 126.84, 126.14, 125.94, 125.67, 125.62, 123.90, 62.66, 33.67, 29.32. **HRMS** calcd. for C₁₃H₁₃O[–] [M–H][–]: 185.0972, Found: 185.0967.

3-(o-tolyl)propan-1-ol (3l): The reaction was carried out according to the general procedure using aryl iodide **2l**. The reaction was run for 16 h, and the product was purified by flash column chromatography (20–33% EtOAc in Hexanes) to afford **3l** (14.0 mg, 47% yield) as a yellow oil. This product was isolated as a single regioisomer as determined by ¹H NMR analysis; the crude reaction mixture also contained only a single regioisomer by ¹H NMR analysis. Characterization data matched that of commercial sources.

3-(pyridin-2-yl)propan-1-ol (3m): The reaction was carried out according to the general procedure using aryl iodide **2m**. The reaction was run for 16 h, and the product was purified by flash column chromatography (5% MeOH in DCM) to afford **3m** (11.7 mg, 43% yield) as a yellow oil. This product was isolated as an inseparable 20:1 mixture of regioisomers as determined by ¹H NMR analysis. The isolated r.r. differed from that of the crude reaction mixture (5.5:1 r.r.). Characterization data matched that of commercial sources.

3-(4-methoxyphenyl)propan-1-ol (3n): The reaction was carried out according to the general procedure using aryl iodide **2n**. The reaction was run for 4 h, and the product was purified by flash column chromatography (5% MeOH in DCM) to afford **3n** (13.5 mg, 49% yield) as a yellow oil. This product was isolated as a single regioisomer as determined by ¹H NMR analysis; the crude reaction mixture also contained only a single regioisomer by ¹H NMR analysis. Characterization data matched that of commercial sources.

3-(4-methoxyphenyl)propan-1-ol (3o): The reaction was carried out according to the general procedure using aryl iodide **2o**. The reaction was run for 16 h, and the product was purified by flash column chromatography (5% MeOH in DCM) to afford **3o** (10.3 mg, 38% yield) as a yellow oil. This product was isolated as an inseparable 6.4:1 mixture of regioisomers as determined by ¹H NMR analysis; the crude reaction mixture also contained the same ratio of regioisomers by ¹H NMR analysis. The peaks for both the major and minor regioisomer were dispersed enough to unambiguously assign the two regioisomers separately.

Characterization data for the major regioisomer (3o) matched that of commercial sources.

Characterization data for the minor regioisomer (3o'): ¹H NMR (600 MHz, CDCl₃) δ 8.52 (d, *J* = 4.8 Hz, 2H), 7.21–7.17 (m, 2H), 3.75 (d, *J* = 6.6 Hz, 2H), 2.95 (h, *J* = 6.9 Hz, 1H), 1.30 (d, *J* = 7.0 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) 149.94, 123.14, 67.90, 42.04, 17.04.

3-(pyrazin-2-yl)propan-1-ol (3p): The reaction was carried out according to the general procedure using aryl iodide **2p**. The reaction was run for 4 h, and the product was purified by flash column chromatography (5% MeOH in DCM) to afford **3p** (10.8 mg, 39% yield) as a yellow oil. This product was isolated as an inseparable 25:1 mixture of regioisomers as determined by ¹H NMR analysis. The isolated r.r. differed from that of the crude reaction mixture (3.4:1 r.r.). ¹H NMR (600 MHz, CDCl₃) δ 8.51 (d, *J* = 1.5 Hz, 1H), 8.49 (dd, *J* = 2.6, 1.6 Hz, 1H), 8.43 (d, *J* = 2.6 Hz, 1H), 3.73 (t, *J* = 6.0 Hz, 2H), 2.98 (t, *J* = 7.2 Hz, 2H), 2.52 (s, 1H), 2.03 (tt, *J* = 7.2, 6.0 Hz, 2H). ¹³C NMR (150 MHz, CDCl₃) δ 157.23, 144.98, 143.81, 142.50, 62.06, 32.10, 31.58. HRMS calcd. for C₇H₁₁N₂O⁺ [M+H]⁺: 139.08659, Found: 139.0866.

3-(7-chloroquinolin-4-yl)propan-1-ol (3q): The reaction was carried out according to the general procedure using aryl iodide **2q**. The reaction was run for 16 h, and the product was purified by flash column chromatography (2–5% MeOH in DCM) and preparative TLC (5% MeOH in DCM) to afford **3q** (24.2 mg, 55% yield) as a yellow oil. This product was isolated as an inseparable 50:1 mixture of regioisomers as determined by ¹H NMR analysis. The isolated r.r. differed from that of the crude reaction mixture (33.3:1 r.r.). ¹H NMR (600 MHz, CDCl₃) δ 8.80 (d, *J* = 4.5 Hz, 1H), 8.11 (d, *J* = 2.1 Hz, 1H), 8.02 (d, *J* = 8.9 Hz, 1H), 7.51 (dd, *J* = 9.0, 2.2 Hz, 1H), 7.28–7.26 (m, 1H), 3.77 (t, *J* = 6.2 Hz, 2H), 3.23–3.15 (m, 2H), 2.08–1.98 (m, 2H), 1.56 (s, 1H). (Note: The proton signal at 7.28 ppm is partially masked by CDCl₃.) ¹³C NMR (150 MHz, CDCl₃) δ 151.32, 148.92, 148.38, 135.13, 129.17, 127.52, 126.14, 125.17, 121.20, 61.96, 32.87, 28.43. HRMS calcd. for C₁₂H₁₃ClNO⁺ [M+H]⁺: 222.0686, Found: 222.0685

5-(3-hydroxypropyl)furan-2-carbaldehyde (3r): The reaction was carried out according to the general procedure using aryl iodide **2r**. The reaction was run for 4 h, and the product was purified by flash column chromatography (40% EtOAc in DCM) to afford **3r** (21.9 mg, 71% yield) as a yellow oil. This product was isolated as a single regioisomer as determined by ¹H NMR analysis; the crude reaction mixture also contained only a single

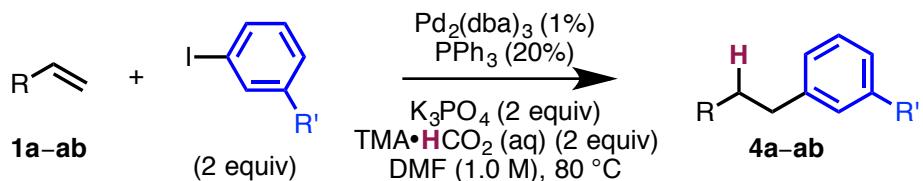
regioisomer by ¹H NMR analysis. The peaks for both the major and minor regioisomer were dispersed enough to unambiguously assign the two regioisomers separately.

Characterization data for the major regioisomer (3r): ¹H NMR (600 MHz, CDCl₃) δ 9.53 (s, 1H), 7.18 (d, *J* = 3.5 Hz, 1H), 6.28 (dt, *J* = 3.5, 0.8 Hz, 1H), 3.72 (t, *J* = 6.2 Hz, 2H), 2.86 (t, *J* = 7.6 Hz, 2H), 1.98 (tt, *J* = 7.5, 6.2 Hz, 2H), 1.46 (s, 1H). ¹³C NMR (150 MHz, CDCl₃) δ 177.12, 163.31, 152.09, 109.10, 108.95, 61.82, 30.55, 24.93. HRMS calcd. for C₂₃H₂₄N₃O⁺ [M+H]⁺: 155.0708, Found: 155.0705.

Characterization data for the minor regioisomer (3r'): 1H NMR (600 MHz, CDCl₃) δ 9.55 (s, 1H), 7.20 (d, *J* = 3.6 Hz, 1H), 6.36 (dd, *J* = 3.6, 0.7 Hz, 1H), 3.84 (qd, *J* = 10.2, 9.8, 6.8 Hz, 2H), 3.15 (h, *J* = 6.8 Hz, 1H), 1.35 (d, *J* = 7.1 Hz, 3H). (Note: Not all of the carbons could be accounted for in the ¹³C NMR; therefore, ¹³C NMR data is not reported.)

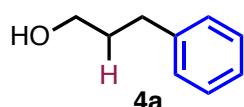


General Procedure for Evaluating Alkene Scope



Unless otherwise stated, the procedure was as follows. To a 1-Dram (4 mL) vial equipped with a magnetic stir bar were added $\text{Pd}_2(\text{dba})_3$ (1.8 mg, 0.002 mmol), triphenylphosphine (10.5 mg, 0.04 mmol), K_3PO_4 (84.9 mg, 0.4 mmol), alkene (0.2 mmol), iodobenzene (81.6 mg, 0.4 mmol) or 3-iodoacetophenone (98.4 mg, 0.4 mmol), $\text{TMA}\cdot\text{HCO}_2$ (30% w/w aqueous solution) (0.16 mL, 0.4 mmol), and DMF (0.2 mL). The vial was sealed with a solid screw cap and placed in a heating block that was pre-heated to 80 °C. After the designated reaction time, the reaction mixture was diluted with water (5 mL) and extracted with EtOAc (5 mL × 3). The combined organic layers were dried over Na_2SO_4 , concentrated *in vacuo*, and purified by column chromatography to produce **4a-ab**.

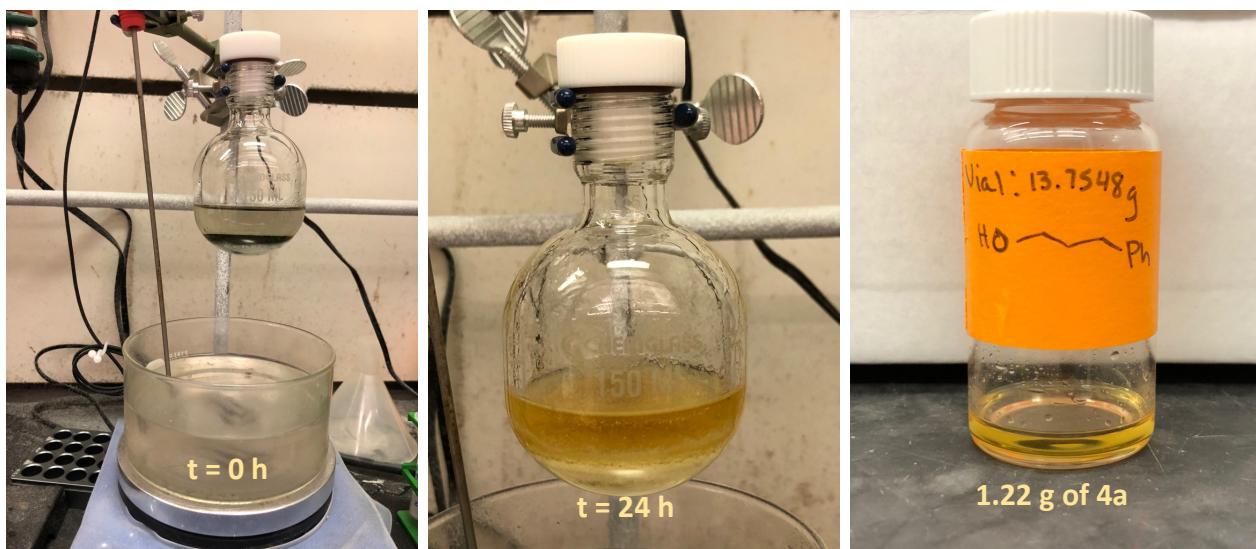
3-phenylpropan-1-ol (4a): The reaction was carried out according to the general procedure using iodobenzene and alkene **1a**.



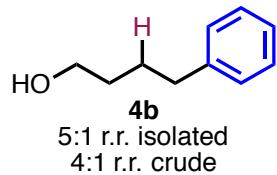
The reaction was run for 4 h, and the product was purified by flash column chromatography (15–25% EtOAc in Hexanes) to afford **4a** (18.0 mg, 66% yield) as a yellow oil. This product was isolated as a single regioisomer as determined by ¹H NMR analysis; the crude reaction mixture also contained only a single regioisomer by ¹H NMR analysis. Characterization data matched that of commercial sources.

Scale-up:

Alkene **1a** (1.02 mL, 15.0 mmol), iodobenzene (3.36 mL, 30.0 mmol), K₃PO₄ (6.37 g, 30.0 mmol), Pd₂(dba)₃ (137.4 mg, 0.15 mmol), triphenylphosphine (787 mg, 3.0 mmol), TMA•HCO₂ (30% w/w aqueous solution) (11.9 mL, 30.0 mmol), and DMF (15.0 mL) were added to a 150 mL sealed tube. The reaction was submerged into a pre-heated 80 °C silicon oil bath, and was run for 24 h. After cooling to ambient temperature, the reaction mixture was diluted with water (100 mL) and extracted with EtOAc (100 mL × 3). The combined organic layers were washed with brine (100 mL × 5), dried over Na₂SO₄, concentrated *in vacuo*, and purified by flash column chromatography (10–25% EtOAc in Hexanes) to afford **4a** (1.22 g, 60% yield) as a yellow oil. This product was isolated as a single regioisomer as determined by ¹H NMR analysis; the crude reaction mixture also contained only a single regioisomer by ¹H NMR analysis. Characterization data matched that of commercial sources.

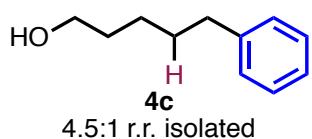


4-phenylbutan-1-ol (4b): The reaction was carried out according to the general procedure using iodobenzene and alkene **1b**.



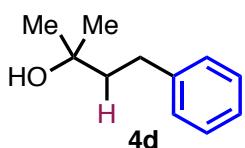
The reaction was run for 4 h, and the product was purified by flash column chromatography (15–25% EtOAc in Hexanes) to afford **4b** (26.4 mg, 88% yield) as a yellow oil. This product was isolated as an inseparable 5:1 mixture of regioisomers as determined by ¹H NMR analysis. The isolated r.r. differed from that of the crude reaction mixture (4:1 r.r.). Characterization data matched that of commercial sources.

5-phenylpentan-1-ol (4c): The reaction was carried out according to the general procedure using iodobenzene and alkene **1c**.



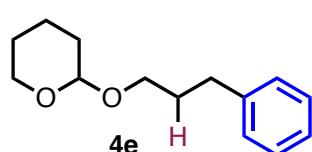
The reaction was run for 4 h, and the product was purified by flash column chromatography (25% EtOAc in Hexanes) to afford **4c** (27.6 mg, 84% yield) as a yellow oil. This product was isolated as an inseparable 4.5:1 mixture of regioisomers as determined by ¹H NMR analysis; the crude reaction mixture also contained the same ratio of regioisomers by ¹H NMR analysis. Characterization data matched that of commercial sources for the major regioisomer and that of previously reported data^[7] for the minor regioisomer.

2-methyl-4-phenylbutan-2-ol (4d): The reaction was carried out according to a slightly modified procedure using iodobenzene and alkene **1d** and higher loadings of Pd₂(dba)₃ (4.6 mg, 0.005 mmol) and triphenylphosphine (26.2 mg, 0.1 mmol).



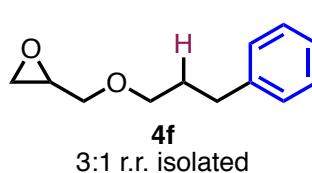
The reaction was run for 16 h, and the product was purified by flash column chromatography (15% EtOAc in Hexanes) to afford **4d** (24.5 mg, 74% yield) as a yellow oil. This product was isolated as a single regioisomer as determined by ¹H NMR analysis; the crude reaction mixture also contained only a single regioisomer by ¹H NMR analysis. Characterization data matched that of commercial sources.

2-(3-phenylpropoxy)tetrahydro-2H-pyran (4e): The reaction was carried out according to the general procedure using iodobenzene and alkene **1e**.



The reaction was run for 4 h, and the product was purified by flash column chromatography (0-5% EtOAc in Hexanes) and preparative TLC (2% EtOAc in Hexanes) to afford **4e** (28.0 mg, 63% yield) as a yellow oil. This product was isolated as a single regioisomer as determined by ¹H NMR analysis; the crude reaction mixture also contained only a single regioisomer by ¹H NMR analysis. ¹H NMR (600 MHz, CDCl₃) δ 7.28 (t, *J* = 7.7 Hz, 2H), 7.23-7.12 (m, 3H), 4.58 (dd, *J* = 4.6, 3.0 Hz, 1H), 3.87 (ddd, *J* = 11.0, 7.7, 3.2 Hz, 1H), 3.78 (dt, *J* = 9.7, 6.6 Hz, 1H), 3.53-3.47 (m, 1H), 3.41 (dt, *J* = 9.7, 6.5 Hz, 1H), 2.77-2.65 (m, 2H), 1.93 (tt, *J* = 7.8, 6.6 Hz, 2H), 1.84 (dtt, *J* = 13.1, 5.3, 3.1 Hz, 1H), 1.72 (ddt, *J* = 12.6, 9.1, 3.0 Hz, 1H), 1.64-1.48 (m, 4H). ¹³C NMR (150 MHz, CDCl₃) δ 142.20, 128.58, 128.44, 125.88, 99.07, 67.02, 62.52, 32.64, 31.50, 30.93, 25.65, 19.83. HRMS calcd. for C₁₄H₂₀NaO₂⁺ [M+Na]⁺: 243.1361, Found: 243.1356.

2-((3-phenylpropoxy)methyl)oxirane (4f): The reaction was carried out according to the general procedure using iodobenzene and alkene **1f**.



The reaction was run for 4 h, and the product was purified by flash column chromatography (5-10% EtOAc in Hexanes) to afford **4f** (11.4 mg, 30% yield) as a yellow oil. This product was isolated as an inseparable 3:1 mixture of regioisomers as determined by ¹H NMR analysis; the crude reaction mixture also contained only a single regioisomer by ¹H NMR analysis.

The following characterization data corresponds to the mixture of the two regioisomers and a mixture of 1:1 diastereomers for the minor regioisomer. ¹H NMR (600 MHz, CDCl₃) δ 7.29 (ddt, *J* = 13.4, 7.1, 2.1 Hz, 2.65H), 7.25-7.16 (m, 3.82H), 3.71 (dd, *J* = 11.5, 3.1 Hz, 1.30H), 3.65 (dd, *J* = 9.4, 6.3 Hz, 0.17H), 3.63-3.55 (m, 0.31H), 3.55-3.46 (m, 2.20H), 3.42-3.36 (m, 1.32H), 3.16 (ddt, *J* = 5.8, 4.1, 2.9 Hz, 1H), 3.11 (dddt, *J* = 7.3, 5.5, 4.4, 2.8 Hz, 0.29H), 3.04 (h, *J* = 7.0 Hz, 0.30H), 2.80 (dd, *J* = 5.0, 4.1 Hz, 1H), 2.76 (ddd, *J* = 5.0, 4.1, 0.7 Hz, 0.31H), 2.73-2.67 (m, 2H), 2.61 (dd, *J* = 5.1, 2.7 Hz, 1H), 2.56 (ddd, *J* = 6.9, 5.0, 2.7 Hz, 0.30H), 1.95-1.89 (m, 2H), 1.30 (d, *J* = 7.0 Hz, 1.01H). ¹³C NMR (150 MHz, CDCl₃) δ 144.37, 142.00, 128.60, 128.51, 128.47, 127.46, 126.51, 125.94, 71.69, 71.65, 70.81, 51.05, 51.03, 44.48, 44.36, 40.17, 40.15, 32.39, 31.40, 18.42. HRMS calcd. for C₁₂H₁₆NaO₂⁺ [M+Na]⁺: 215.1048, Found: 215.1051.

3-phenethyl-7-oxabicyclo[4.1.0]heptane (4g): The reaction was carried out according to the general procedure using iodobenzene and alkene **1g** (used as a 1:1 mixture of diastereomers). The reaction was run for 4 h, and the product was purified by flash column chromatography (5% EtOAc in Hexanes) to afford **4g** (36.1 mg, 89% yield) as a yellow oil. This product was isolated as a single regioisomer and an inseparable 1:1 mixture of diastereomers as determined by ¹H NMR analysis; the crude reaction mixture also contained

only a single regioisomer and a 1:1 mixture of diastereomers by ¹H NMR analysis. The following characterization data corresponds to the mixture of diastereomers. ¹H NMR (600 MHz, CDCl₃) δ 7.27 (td, *J* = 7.5, 3.3 Hz, 2H), 7.20–7.14 (m, 3H), 3.18 (dt, *J* = 4.2, 2.1 Hz, 0.5H), 3.16–3.11 (m, 1.5H), 2.59 (t, *J* = 8.0 Hz, 2H), 2.22 (ddt, *J* = 14.7, 3.9, 1.9 Hz, 0.5H), 2.15 (dp, *J* = 15.1, 1.9 Hz, 0.5H), 2.09 (dtd, *J* = 15.5, 5.7, 2.0 Hz, 0.5H), 2.01 (dddd, *J* = 15.7, 6.6, 4.9, 2.7 Hz, 0.5H), 1.84 (ddd, *J* = 15.6, 11.4, 6.4 Hz, 0.5H), 1.70 (dddd, *J* = 14.9, 12.2, 5.1, 1.3 Hz, 0.5H), 1.60–1.44 (m, 3.5H), 1.39 (ddt, *J* = 14.6, 6.8, 2.1 Hz, 1H), 1.31–1.11 (m, 1H), 0.96 (dtd, *J* = 13.4, 10.9, 6.2 Hz, 0.5H). ¹³C NMR (150 MHz, CDCl₃) δ 142.78, 142.64, 128.47, 128.46, 128.44, 128.41, 125.83, 125.82, 53.23, 52.79, 52.08, 51.98, 38.70, 38.40, 33.41, 33.09, 32.21, 31.95, 30.78, 29.48, 27.19, 25.38, 24.51, 23.62. HRMS calcd. for C₁₄H₁₉O⁺ [M+H]⁺: 203.1436, Found: 203.1441.

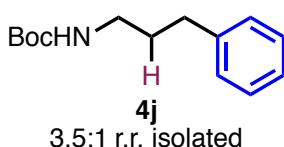
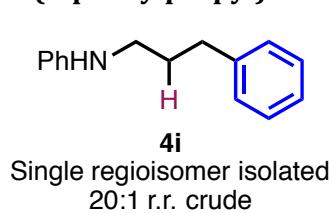
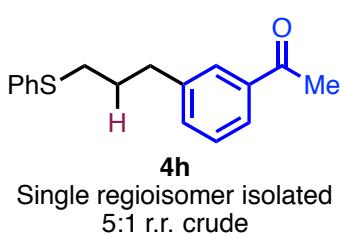
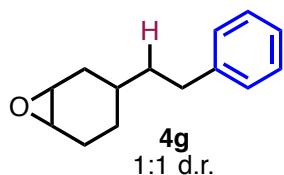
1-(3-(3-(phenylthio)propyl)phenyl)ethan-1-one (4h): The reaction was carried out according

to the general procedure using 3'-iodoacetophenone and alkene **1h**. The reaction was run for 4 h, and the product was purified by flash column chromatography (5% EtOAc in Hexanes) and preparative TLC (5% EtOAc in Hexanes) to afford **4h** (23.4 mg, 43% yield) as a yellow oil. This product was isolated as a single regioisomer as determined by ¹H NMR analysis. The isolated r.r. differed from that of the crude reaction mixture (5:1 r.r.). ¹H NMR (600 MHz, CDCl₃) δ 7.81–7.75 (m, 2H), 7.40–7.35 (m, 2H), 7.33–7.29 (m, 2H), 7.29–7.26 (m, 2H), 7.20–7.15 (m, 1H), 2.92 (t, *J* = 7.2 Hz, 2H), 2.86–2.79 (m, 2H), 2.59 (s, 3H), 2.03–1.95 (m, 2H). ¹³C NMR (150 MHz, CDCl₃) δ 198.42, 142.00, 137.48, 136.44, 133.46, 129.42, 129.05, 128.79, 128.33, 126.39, 126.14, 34.59, 33.05, 30.63, 26.84. HRMS calcd. for C₂₁H₁₉OS⁺ [M+H]⁺: 271.1157, Found: 271.1158.

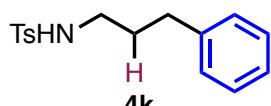
N-(3-phenylpropyl)aniline (4i): The reaction was carried out according to the general procedure using iodobenzene and alkene **1i**. The reaction was run for 4 h, and the product was purified by flash column chromatography (2.5% DCM/2.5% Et₂O/95% Hexanes) to afford **4i** (25.1 mg, 59% yield) as a yellow oil. This product was isolated as a single regioisomer as determined by ¹H NMR analysis. The isolated r.r. differed from that of the crude reaction mixture (20:1 r.r.). Characterization data matched previously reported data.^[8]

tert-butyl (3-phenylpropyl)carbamate (4j): The reaction was carried out according to the general procedure using iodobenzene and alkene **1j**. The reaction was run for 4 h, and the product was purified by flash column chromatography (15% EtOAc in Hexanes) to afford **4j** (45.2 mg, 96% yield) as a yellow oil.

This product was isolated as an inseparable 3.5:1 mixture of regioisomers as determined by ¹H NMR analysis; the crude reaction mixture also contained the same ratio of regioisomers by ¹H NMR analysis. Characterization data matched previously reported data for both the major^[9] and minor^[10] regioisomers.



4-methyl-N-(3-phenylpropyl)benzenesulfonamide (4k): The reaction was carried out according

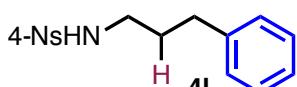


12.5:1 r.r. isolated
10:1 r.r. crude

to the general procedure using iodobenzene and alkene **1k**. The reaction was run for 4 h, and the product was purified by flash column chromatography (25% EtOAc in Hexanes) and preparative TLC (25% EtOAc in Hexanes) to afford **4k** (33.0 mg, 57% yield) as a colorless oil. This product was isolated as an inseparable 12.5:1 mixture of regioisomers as determined by ¹H NMR analysis. The isolated r.r. differed from that of the

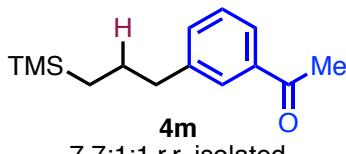
crude reaction mixture (10:1 r.r.). Characterization data matched previously reported data for both the major^[11] and minor^[12] regioisomers.

4-nitro-N-(3-phenylpropyl)benzenesulfonamide (4l): The reaction was carried out according



to a slightly modified procedure using iodobenzene and alkene **1l** and higher loadings of Pd₂(dba)₃ (4.6 mg, 0.005 mmol) and triphenylphosphine (26.2 mg, 0.1 mmol). The reaction was run for 16 h, and the product was purified by flash column chromatography (20–33% EtOAc in Hexanes) and preparative TLC (20% EtOAc in Hexanes) to afford **4l** (26.2 mg, 41% yield) as a yellow oil. This product was isolated as a single regioisomer as determined by ¹H NMR analysis, the crude reaction mixture also contained only a single regioisomer by ¹H NMR analysis. ¹H NMR (600 MHz, CDCl₃) δ 8.37–8.32 (m, 2H), 8.03–7.97 (m, 2H), 7.29–7.25 (m, 4H), 7.23–7.17 (m, 1H), 7.12–7.07 (m, 2H), 4.57–4.41 (m, 1H), 3.04 (q, *J* = 6.8 Hz, 2H), 2.63 (t, *J* = 7.5 Hz, 2H), 1.87–1.80 (m, 2H). ¹³C NMR (150 MHz, CDCl₃) δ 150.20, 146.03, 140.49, 128.76, 128.43, 128.41, 126.49, 124.55, 42.92, 32.77, 31.29. HRMS calcd. for C₁₅H₁₅N₂O₄S[−] [M-H][−]: 319.0753, Found: 319.0751.

1-(3-(3-(trimethylsilyl)propyl)phenyl)ethan-1-one (4m): The reaction was carried out



7.7:1:1 r.r. isolated

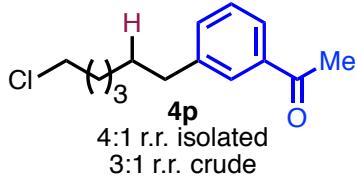
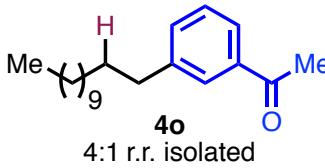
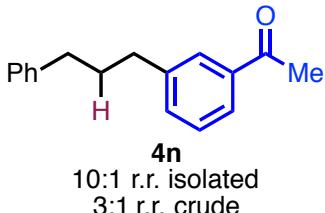
according to the general procedure using 3'-iodoacetophenone and alkene **1m**. The reaction was run for 4 h, and the product was purified by flash column chromatography (2% EtOAc in Hexanes) to afford **4m** (29.4 mg, 63% yield) as a colorless oil. This product was isolated as an inseparable 7.7:1:1 mixture of the two regioisomers and a third constitutional isomer as determined by ¹H NMR analysis;

the crude reaction mixture also contained the same product ratio by ¹H NMR analysis. The following characterization data corresponds to the mixture of the three isomers. ¹H NMR (600 MHz, CDCl₃) δ 7.82 (t, *J* = 1.9 Hz, 0.13H), 7.80–7.74 (m, 2H), 7.68 (dt, *J* = 7.7, 1.4 Hz, 0.13H), 7.62 (t, *J* = 1.9 Hz, 0.13H), 7.44–7.41 (m, 0.13H), 7.40–7.35 (m, 2H), 7.33 (t, *J* = 7.7 Hz, 0.14H), 7.22 (dt, *J* = 7.6, 1.5 Hz, 0.15H), 2.95 (h, *J* = 7.1 Hz, 0.13H), 2.68 (t, *J* = 7.7 Hz, 2H), 2.61 (s, 3.3H), 2.59 (s, 0.45H), 2.00 (dd, *J* = 10.3, 5.3 Hz, 0.14H), 1.87–1.79 (m, 0.27H), 1.67–1.60 (m, 2H), 1.29 (d, *J* = 6.9 Hz, 0.42H), 1.00 (dd, *J* = 14.7, 7.7 Hz, 0.13H), 0.93 (dd, *J* = 14.7, 7.4 Hz, 0.14H), 0.85 (t, *J* = 7.2 Hz, 0.43H), 0.57–0.50 (m, 2H), -0.02 (s, 9H), -0.07 (s, 1.25H), -0.11 (s, 1.18H). ¹³C NMR (150 MHz, CDCl₃) δ 198.76, 198.63, 150.61, 144.66, 143.41, 137.36, 137.33, 137.12, 133.50, 132.60, 131.75, 128.66, 128.58, 128.36, 128.35, 127.51, 126.50, 126.24, 126.06, 124.80, 39.88, 39.48, 36.56, 26.96, 26.86, 26.83, 26.36, 26.22, 22.53, 16.69, 14.43, -0.81, -1.55, -2.84. HRMS calcd. for C₁₄H₂₀OSi⁺ [M+H]⁺: 235.1518, Found: 235.1518.

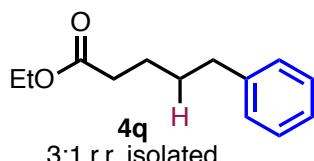
1-(3-(3-phenylpropyl)phenyl)ethan-1-one (4n): The reaction was carried out according to the general procedure using 3'-iodoacetophenone and alkene **1n**. The reaction was run for 4 h, and the product was purified by flash column chromatography (5% EtOAc in Hexanes) and preparative TLC (2% EtOAc in Hexanes) to afford **4n** (26.5 mg, 56% yield) as a colorless oil. This product was isolated as an inseparable 10:1 mixture of regioisomers as determined by ¹H NMR analysis. The isolated r.r. differed from that of the crude reaction mixture (3:1 r.r.). The following characterization data corresponds to the mixture of the two regioisomers. ¹H NMR (600 MHz, CDCl₃) δ 7.83–7.74 (m, 2.2H), 7.42–7.34 (m, 2.2H), 7.29 (dd, *J* = 8.6, 6.6 Hz, 2H), 7.25–7.14 (m, 3.3H), 7.08–7.04 (m, 0.21H), 3.08 (h, *J* = 7.0 Hz, 0.10H), 2.92 (dd, *J* = 13.4, 6.9 Hz, 0.10H), 2.82 (dd, *J* = 13.5, 8.0 Hz, 0.11H), 2.74–2.69 (m, 2H), 2.66 (t, *J* = 7.7 Hz, 2H), 2.60 (s, 3H), 2.57 (s, 0.28H), 2.03–1.95 (m, 2H), 1.28 (d, *J* = 6.9 Hz, 0.34H). ¹³C NMR (150 MHz, CDCl₃) δ 198.53, 147.51, 142.96, 142.08, 140.42, 137.39, 137.30, 133.43, 129.28, 128.67, 128.65, 128.63, 128.57, 128.50, 128.29, 127.01, 126.45, 126.18, 126.13, 126.00, 45.03, 41.96, 35.53, 35.40, 33.00, 26.85, 26.84, 21.24. HRMS calcd. for C₁₇H₁₉O⁺ [M+H]⁺: 239.1436, Found: 239.1440.

1-(3-dodecylphenyl)ethan-1-one (4o): The reaction was carried out according to the general procedure using 3'-iodoacetophenone and alkene **1o**. The reaction was run for 4 h, and the product was purified by flash column chromatography (2% EtOAc in Hexanes) to afford **4o** (55.3 mg, 96% yield) as a colorless oil. This product was isolated as an inseparable 4:1 mixture of regioisomers as determined by ¹H NMR analysis; the crude reaction mixture also contained the same product ratio by ¹H NMR analysis. The following characterization data correspond to the mixture of the two regioisomers. ¹H NMR (600 MHz, CDCl₃) δ 7.77 (dt, *J* = 8.9, 1.7 Hz, 2.5H), 7.42–7.33 (m, 2.5H), 2.74 (h, *J* = 7.1 Hz, 0.26H), 2.69–2.63 (m, 2H), 2.61 (s, 0.75H), 2.60 (s, 3H), 1.61 (tdd, *J* = 15.8, 9.2, 6.6 Hz, 2.5H), 1.39–1.09 (m, 23.22H), 0.88 (td, *J* = 7.0, 4.2 Hz, 3.71H). ¹³C NMR (150 MHz, CDCl₃) δ 198.64, 198.61, 148.70, 143.62, 137.37, 137.33, 133.42, 132.04, 128.63, 128.57, 128.27, 126.89, 126.26, 126.00, 40.08, 38.45, 35.99, 32.07, 32.05, 31.58, 29.82, 29.80, 29.79, 29.75, 29.72, 29.70, 29.63, 29.50, 29.47, 29.42, 27.82, 26.86, 26.85, 22.84, 22.83, 22.37, 14.27. HRMS calcd. for C₂₀H₃₃O⁺ [M+H]⁺: 289.2531, Found: 289.2536.

1-(3-(6-chlorohexyl)phenyl)ethan-1-one (4p): The reaction was carried out according to the general procedure using 3'-iodoacetophenone and alkene **1p**. The reaction was run for 4 h, and the product was purified by flash column chromatography (5% EtOAc in Hexanes) and preparative TLC (2% EtOAc in Hexanes) to afford **4p** (24.5 mg, 51% yield) as a colorless oil. This product was isolated as an inseparable 4:1 mixture of regioisomers as determined by ¹H NMR analysis. The isolated r.r. differed from that of the crude reaction mixture (3:1 r.r.). The following characterization data correspond to the mixture of the two regioisomers. ¹H NMR (600 MHz, CDCl₃) δ 7.78 (td, *J* = 5.0, 4.5, 2.4 Hz, 2.5H), 7.42–7.34 (m, 2.5H), 3.53 (t, *J* = 6.7 Hz, 2H), 3.48 (td, *J* = 6.7, 2.4 Hz, 0.5H), 2.77 (h, *J* = 7.0 Hz, 0.24H), 2.70–2.65 (m, 2H), 2.61 (s, 0.75H), 2.60 (s, 3H), 1.81–1.70 (m, 2.5H), 1.70–1.59 (m, 2.5H), 1.47 (td, *J* = 9.3, 7.4, 5.5 Hz, 2H), 1.44–1.33 (m, 2.25H), 1.32–1.24 (m, 1.12H). ¹³C NMR (150 MHz, CDCl₃) δ 198.56, 148.10, 143.24, 137.46, 137.38, 133.39, 131.99, 128.75, 128.64, 128.21, 126.76, 126.48, 126.14, 45.21, 45.03, 39.99, 37.58, 35.81, 32.73, 32.64, 31.33, 28.59, 26.87, 26.85, 26.83, 25.12, 22.34. HRMS calcd. for C₁₄H₂₀ClO⁺ [M+H]⁺: 239.1203, Found: 239.1208.

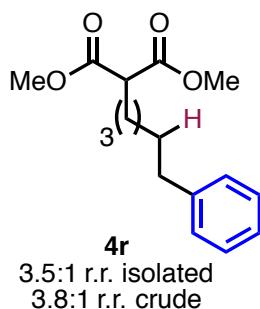


ethyl 5-phenylpentanoate (4q): The reaction was carried out according to the general procedure



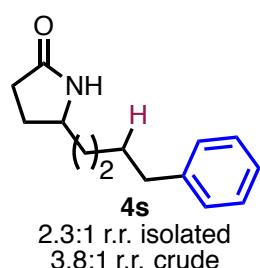
using iodobenzene and alkene **1q**. The reaction was run for 4 h, and the product was purified by flash column chromatography (5% EtOAc in Hexanes) to afford **4q** (22.2 mg, 54% yield) as a yellow oil. This product was isolated as an inseparable 3:1 mixture of regioisomers as determined by ¹H NMR analysis; the crude reaction mixture also contained the same product ratio by ¹H NMR analysis. Characterization data matched previously reported data for both the major^[13] and minor^[14] regioisomers.

dimethyl 2-(5-phenylpentyl)malonate (4r): The reaction was carried out according to the



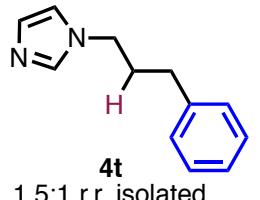
general procedure using iodobenzene and alkene **1r**. The reaction was run for 4 h, and the product was purified by flash column chromatography (10% EtOAc in Hexanes) to afford **4r** (35.9 mg, 64% yield) as a colorless oil. This product was isolated as an inseparable 3.5:1 mixture of regioisomers as determined by ¹H NMR analysis. The isolated r.r. differed from that of the crude reaction mixture (3.8:1 r.r.). The following characterization data corresponds to the mixture of the two regioisomers. ¹H NMR (600 MHz, CDCl₃) δ 7.27 (td, *J* = 7.6, 5.8 Hz, 2.6H), 7.20–7.14 (m, 4H), 3.73 (s, 6H), 3.70 (s, 0.9H), 3.69 (s, 0.9H), 3.35 (t, *J* = 7.6 Hz, 1H), 3.31 (t, *J* = 7.6 Hz, 0.3H), 2.67 (dt, *J* = 14.2, 7.1 Hz, 0.3H), 2.62–2.56 (m, 2H), 1.94–1.82 (m, 2.6H), 1.66–1.56 (m, 3H), 1.40–1.30 (m, 4.3H), 1.23 (d, *J* = 6.9 Hz, .9H). ¹³C NMR (150 MHz, CDCl₃) δ 170.07, 170.03, 170.01, 147.38, 142.67, 128.63, 128.52, 128.47, 128.40, 127.80, 127.08, 126.06, 125.79, 52.60, 52.58, 52.56, 51.84, 51.73, 39.73, 37.91, 35.92, 31.25, 28.97, 28.96, 28.92, 27.35, 25.53, 22.44. HRMS calcd. for C₁₆H₂₃O₄⁺ [M+H]⁺: 279.1596, Found: 279.1594.

5-(4-phenylbutyl)pyrrolidin-2-one (4s): The reaction was carried out according to the general



procedure using iodobenzene and alkene **1s**. The reaction was run for 4 h, and the product was purified by flash column chromatography (50–75% EtOAc in Hexanes) and preparative TLC (20% EtOAc in DCM) to afford **4s** (23.4 mg, 54% yield) as a colorless oil. This product was isolated as an inseparable 2.3:1 mixture of regioisomers as determined by ¹H NMR analysis. The isolated r.r. differed from that of the crude reaction mixture (3.8:1 r.r.). The following characterization data corresponds to the mixture of the two regioisomers and a mixture of 1:1 diastereomers for the minor regioisomer. ¹H NMR (600 MHz, CDCl₃) δ 7.33–7.26 (m, 3H), 7.23–7.14 (m, 4.3H), 5.71 (s, 1H), 5.64 (m, 0.44H), 3.61 (p, *J* = 6.6 Hz, 1H), 3.56 (ddq, *J* = 9.5, 6.6, 3.3, 2.8 Hz, 0.45H), 2.68 (dq, *J* = 13.5, 7.0 Hz, 0.46H), 2.62 (t, *J* = 7.7 Hz, 2H), 2.38–2.17 (m, 4.4H), 1.74–1.62 (m, 3.6H), 1.60–1.45 (m, 3.2H), 1.44–1.28 (m, 3H), 1.26 (dd, *J* = 7.0, 0.8 Hz, 1.5H). ¹³C NMR (150 MHz, CDCl₃) δ 178.29, 178.23, 178.21, 146.92, 146.84, 142.30, 128.61, 128.46, 127.01, 126.28, 125.92, 54.63, 54.60, 54.58, 40.13, 40.04, 36.74, 35.85, 35.01, 34.92, 34.51, 34.43, 31.37, 30.27, 30.23, 30.20, 27.44, 27.32, 27.30, 25.59, 22.57, 22.50. HRMS calcd. for C₁₄H₂₀NO⁺ [M+H]⁺: 218.1545, Found: 218.1545.

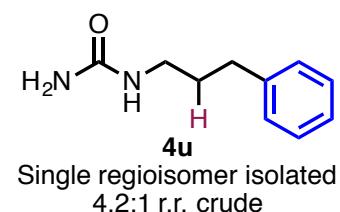
1-(3-phenylpropyl)-1*H*-imidazole (4t): The reaction was carried out according to a slightly



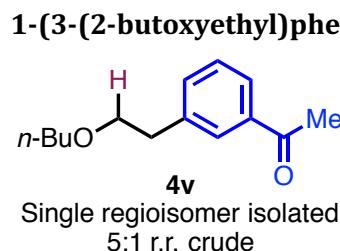
modified procedure using iodobenzene and alkene **1t** and higher loadings of Pd₂(dba)₃ (4.6 mg, 0.005 mmol) and triphenylphosphine (26.2 mg, 0.1 mmol). The reaction was run for 24 h, and the product was purified by flash column chromatography (100% EtOAc) to afford **4t** (31.3 mg, 84% yield) as a yellow oil. This product was isolated as an inseparable 1.5:1 mixture of regioisomers as determined by ¹H NMR analysis; the crude reaction mixture also contained the same product ratio by ¹H NMR analysis. The following characterization

data corresponds to the mixture of the two regioisomers. **1H NMR** (600 MHz, CDCl_3) δ 7.47 (s, 1H), 7.30 (td, J = 7.6, 1.6 Hz, 3.2H), 7.26–7.19 (m, 2H), 7.18–7.13 (m, 2H), 7.13–7.10 (m, 1.3H), 7.08 (s, 1H), 6.98 (s, 0.6H), 6.92 (s, 1H), 6.73 (s, 0.6H), 4.10–4.01 (m, 1.3H), 3.93 (t, J = 7.0 Hz, 2H), 3.13 (h, J = 7.1 Hz, 0.6H), 2.62 (t, J = 7.6 Hz, 2H), 2.13 (p, J = 7.3 Hz, 2H), 1.29 (d, J = 7.0 Hz, 2H). **13C NMR** (150 MHz, CDCl_3) δ 142.79, 140.38, 137.51, 137.25, 129.63, 129.23, 128.88, 128.74, 128.48, 127.25, 127.08, 126.45, 119.28, 118.83, 54.48, 46.27, 41.83, 32.58, 32.40, 18.70. **HRMS** calcd. for $\text{C}_{12}\text{H}_{15}\text{N}_2^+$ $[\text{M}+\text{H}]^+$: 187.1235, Found: 187.1237.

1-(3-phenylpropyl)urea (4u): The reaction was carried out according to the general procedure using iodobenzene and alkene **1u**. The reaction was run for 4 h, and the product was crystallized from DCM and Et_2O to afford **4u** (10.7 mg, 30% yield) as a white solid. This product was isolated as a single diastereomer as determined by **1H NMR** analysis. The isolated r.r. differed from that of the crude reaction mixture (4.2:1 r.r.). **1H NMR** (600 MHz, CDCl_3) δ 7.29 (dd, J = 8.2, 6.9 Hz, 2H), 7.23–7.15 (m, 3H), 4.40 (s, 1H), 4.23 (s, 2H), 3.20 (q, J = 6.7 Hz, 2H), 2.72–2.63 (m, 2H), 1.85 (p, J = 7.3 Hz, 2H). **13C NMR** (150 MHz, CDCl_3) δ 158.56, 141.54, 128.62, 128.51, 126.16, 40.56, 33.28, 31.77. **HRMS** calcd. for $\text{C}_{10}\text{H}_{15}\text{N}_2\text{O}^+$ $[\text{M}+\text{H}]^+$: 179.1184, Found: 179.1181.



1-(3-(2-butoxyethyl)phenyl)ethan-1-one (4v): The reaction was carried out according to the general procedure using 3'-iodoacetophenone and alkene **1v**. The reaction was run for 4 h, and the product was purified by flash column chromatography (5% EtOAc in Hexanes) to afford **4v** (31.2 mg, 71% yield) as a yellow oil. This product was isolated as a single regioisomer as determined by **1H NMR** analysis. The isolated r.r. differed from that of the crude reaction mixture (5:1 r.r.). **1H NMR** (600 MHz, CDCl_3) δ 7.85–7.82 (m, 1H), 7.80 (dt, J = 7.6, 1.5 Hz, 1H), 7.44 (dt, J = 7.7, 1.5 Hz, 1H), 7.38 (t, J = 7.6 Hz, 1H), 3.65 (t, J = 7.0 Hz, 2H), 3.43 (t, J = 6.6 Hz, 2H), 2.94 (t, J = 7.0 Hz, 2H), 2.60 (s, 3H), 1.58–1.51 (m, 2H), 1.38–1.31 (m, 2H), 0.90 (t, J = 7.4 Hz, 3H). **13C NMR** (150 MHz, CDCl_3) δ 198.46, 140.01, 137.35, 133.93, 128.85, 128.64, 126.45, 71.47, 70.98, 36.33, 31.91, 26.82, 19.48, 14.04. **HRMS** calcd. for $\text{C}_{14}\text{H}_{21}\text{O}_2^+$ $[\text{M}+\text{H}]^+$: 221.1542, Found: 221.1534.



1-(3-(2-(trimethylsilyl)ethyl)phenyl)ethan-1-one (4w): The reaction was carried out according to the general procedure using 3'-idoacetophenone and alkene **1w**. The reaction was run for 4 h, and the product was purified by flash column chromatography (2% EtOAc in Hexanes) to afford **4w** (13.5 mg, 31% yield) as a yellow oil. This product was isolated as an inseparable 16.7:1 mixture of regioisomers as determined by **1H NMR** analysis; the crude reaction mixture also contained the same product ratio by **1H**

NMR analysis. The peaks for both the major and minor regioisomer were dispersed enough to unambiguously assign the two regioisomers separately.

Characterization data for the major regioisomer (4w): **1H NMR** (600 MHz, CDCl_3) δ 7.82–7.79 (m, 1H), 7.76 (dt, J = 7.5, 1.5 Hz, 1H), 7.41 (dt, J = 7.8, 1.4 Hz, 1H), 7.36 (t, J = 7.6 Hz, 1H), 2.71–2.65 (m, 2H), 2.60 (s, 3H), 0.91–0.86 (m, 2H), 0.03 (s, 9H). **13C NMR** (150 MHz, CDCl_3) δ 198.63, 146.02, 137.36, 132.86, 128.62, 127.63, 125.93, 30.14, 26.86, 18.86, -1.60. **HRMS** calcd. for $\text{C}_{13}\text{H}_{21}\text{OSi}^+$ $[\text{M}+\text{H}]^+$: 221.1362, Found: 221.1363.

Characterization data for the minor regioisomer (4w'): 1H NMR (600 MHz, CDCl_3) δ 7.68 (dt, J = 7.7, 1.5 Hz, 1H), 7.64 (t, J = 1.8 Hz, 1H), 7.33 (t, J = 7.7 Hz, 1H), 7.24 (d, J = 7.8 Hz, 1H), 2.59 (s, 3H), 2.25 (q, J = 7.5 Hz, 1H), 1.39 (d, J = 7.5 Hz, 3H), -0.05 (s, 9H). **13C NMR** (150 MHz, CDCl_3) δ

198.72, 146.80, 131.90, 128.30, 126.70, 124.72, 30.00, 29.86, 14.89, -3.24. (Note: One aromatic carbon peak could not be assigned.)

1-phenethylpyrrolidin-2-one (4x): The reaction was carried out according to the general procedure using iodobenzene and alkene **1x**. The reaction was run for 4 h, and the product was purified by flash column chromatography (20–30% EtOAc in DCM) and preparative TLC (20% EtOAc in DCM) to afford **4x** (13.7 mg, 36% yield) as a yellow oil. This product was isolated as an inseparable 25:1 mixture of regioisomers as determined by ¹H NMR analysis. The isolated r.r. differed from that of the crude reaction mixture (2.5:1 r.r.). **¹H NMR** (600 MHz, CDCl₃) δ 7.32–7.27 (m, 2H), 7.22 (ddq, *J* = 7.1, 3.6, 1.7, 1.3 Hz, 3H), 3.57–3.49 (m, 2H), 3.25 (t, *J* = 7.0 Hz, 2H), 2.88–2.81 (m, 2H), 2.35 (t, *J* = 8.1 Hz, 2H), 1.99–1.91 (m, 2H). **¹³C NMR** (150 MHz, CDCl₃) ¹³C NMR (151 MHz, CDCl₃) δ 174.40, 138.40, 128.21, 128.06, 125.97, 47.22, 43.61, 33.41, 30.56, 17.57. **HRMS** calcd. for C₁₂H₁₆NO⁺ [M+H]⁺: 190.1232, Found: 190.1234.

(R)-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-phenethylquinuclidin-2-yl)methanol (4y):

The reaction was carried out according to the general procedure using iodobenzene and alkene **1y**. The reaction was run for 4 h, and the product was purified by flash column chromatography (5–15% MeOH in DCM) to afford **4y** (80.1 mg, 99% yield) as an off-white solid. This product was isolated as a single regioisomer as determined by ¹H NMR analysis; the crude reaction mixture also contained only a single regioisomer by ¹H NMR analysis. **¹H NMR** (600 MHz, CD₃OD) δ 8.70 (d, *J* = 4.6 Hz, 1H), 7.96 (dd, *J* = 9.2, 1.4 Hz, 1H), 7.77 (d, *J* = 4.6 Hz, 1H), 7.47 (d, *J* = 2.7 Hz, 1H), 7.46–7.41 (m, 1H), 7.21–7.16 (m, 2H), 7.13–7.07 (m, 3H), 6.01 (s, 1H), 4.13–4.06 (m, 1H), 4.03 (s, 3H), 3.54 (t, *J* = 9.0 Hz, 1H), 3.43 (dd, *J* = 12.9, 10.5 Hz, 1H), 3.09 (td, *J* = 11.6, 5.4 Hz, 1H), 2.93–2.80 (m, 1H), 2.54 (t, *J* = 7.7 Hz, 2H), 2.17 (dd, *J* = 13.4, 7.0 Hz, 1H), 2.11 (tt, *J* = 11.4, 3.1 Hz, 1H), 2.01 (d, *J* = 4.4 Hz, 1H), 1.95 (p, *J* = 8.0 Hz, 1H), 1.80–1.70 (m, 1H), 1.67–1.52 (m, 3H). **¹³C NMR** (150 MHz, CD₃OD) δ 160.13, 148.13, 147.98, 144.79, 142.81, 131.57, 129.39, 129.35, 127.68, 126.92, 123.66, 120.45, 102.32, 69.15, 61.30, 57.85, 57.12, 44.95, 36.63, 34.64, 34.18, 26.50, 26.41, 19.72. **HRMS** calcd. for C₂₆H₃₁N₂O₂⁺ [M+H]⁺: 403.2386, Found: 403.2383.

1-(3-((3*R*)-3-hydroxy-5-((1*R*,2*R*,8*aS*)-2-hydroxy-2,5,5,8*a*-tetramethyldecahydronaphthalen-1-yl)-3-methylpentyl)phenyl)ethan-1-one (4z):** The reaction was carried out according to a

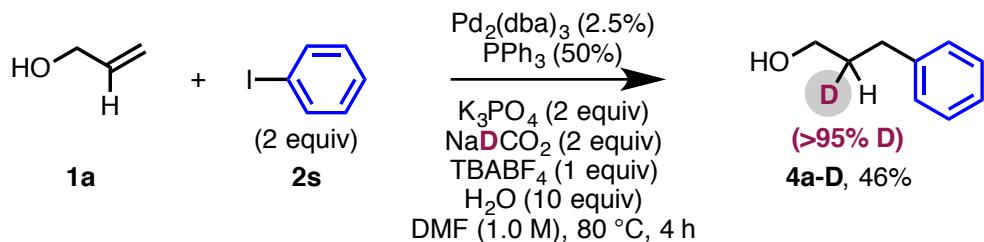
slightly modified procedure using 3'-iodoacetophenone and alkene **1z** and higher loadings of Pd₂(dba)₃ (4.6 mg, 0.005 mmol) and triphenylphosphine (26.2 mg, 0.1 mmol). The reaction was run for 16 h, and the product was purified by flash column chromatography (33–40% EtOAc in Hexanes) to afford **4z** (60.6 mg, 71% yield) as an off-white solid. This product was isolated as a single regioisomer as determined by ¹H NMR analysis; the crude reaction mixture also contained only a single regioisomer by ¹H NMR analysis. **¹H NMR** (600 MHz, CDCl₃) δ 7.83–7.79 (m, 1H), 7.79–7.74 (m, 1H), 7.40 (dt, *J* = 7.4, 1.5 Hz, 1H), 7.36 (td, *J* = 7.6, 1.4 Hz, 1H), 2.82–2.71 (m, 2H), 2.59 (d, *J* = 1.0 Hz, 3H), 1.93–1.51 (m, 11H), 1.44 (ddd, *J* = 14.3, 11.8, 3.9 Hz, 2H), 1.37 (ddd, *J* = 13.7, 9.7, 5.6 Hz, 2H), 1.26 (d, *J* = 1.3 Hz, 4H), 1.21–1.11 (m, 5H), 1.03–0.92 (m, 2H), 0.87 (s, 3H), 0.79 (d, *J* = 6.4 Hz, 6H). **¹³C NMR** (150 MHz, CDCl₃) δ 198.57, 143.65, 137.42, 133.43, 128.72, 128.29, 126.04, 75.04, 73.11, 61.99, 56.20, 45.13, 44.78, 44.55, 42.12, 39.88, 39.39,

33.53, 33.38, 30.47, 26.86, 26.30, 24.57, 21.63, 20.69, 19.07, 18.57, 15.54. **HRMS** calcd. for $C_{28}H_{44}NaO_3^+ [M+Na]^+$: 451.3188, Found: 451.3187.

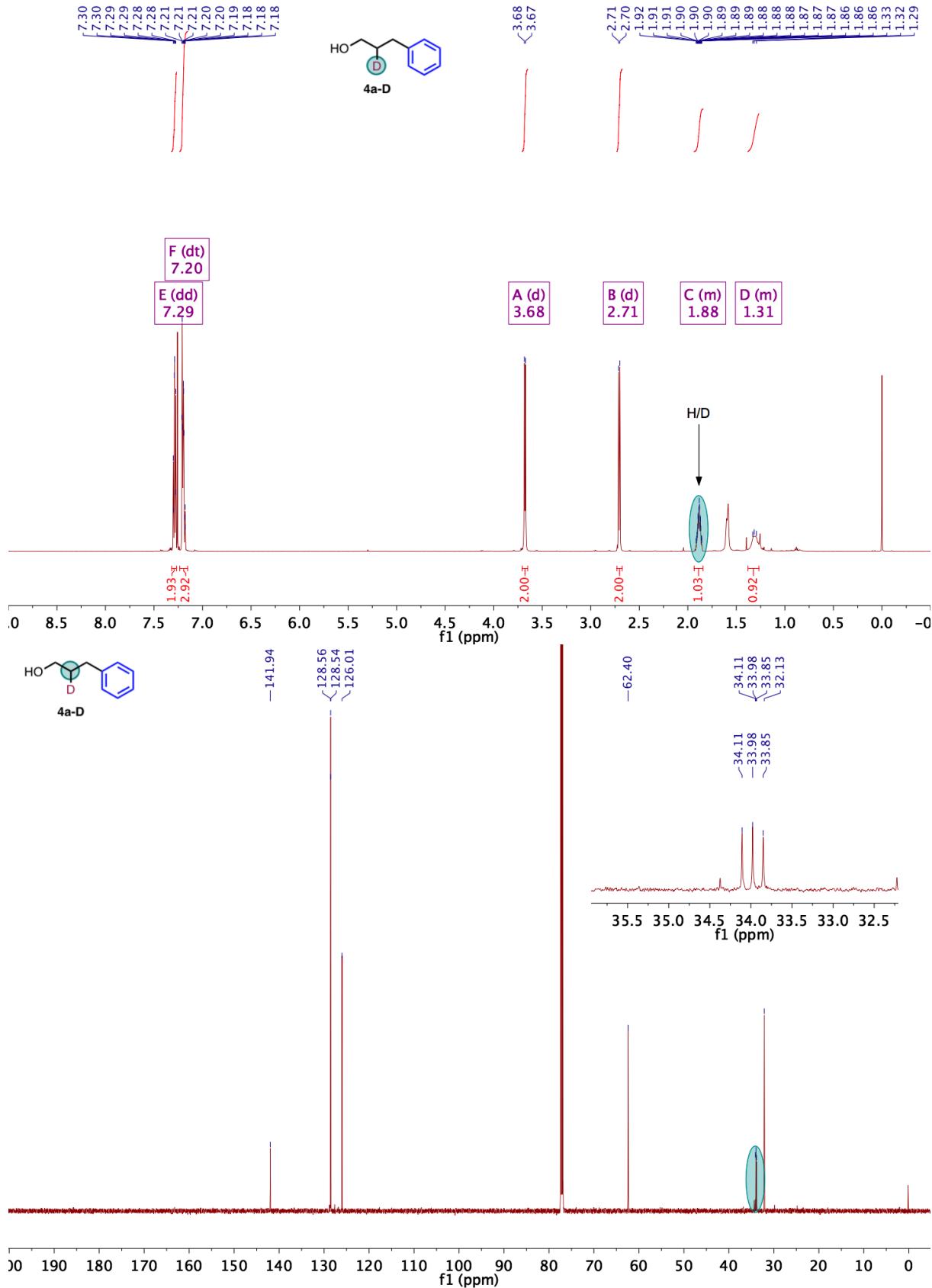
3,7-dimethyl-1-phenyloct-6-en-3-ol (4aa): The reaction was carried out according to a slightly modified procedure using 3'-iodoacetophenone and alkene **1aa** and higher loadings of $Pd_2(dbu)_3$ (4.6 mg, 0.005 mmol) and triphenylphosphine (26.2 mg, 0.1 mmol). The reaction was run for 16 h, and the product was purified by flash column chromatography (5% EtOAc in Hexanes) to afford **4aa** (29.8 mg, 64% yield) as a yellow oil. This product was isolated as a single regioisomer as determined by 1H NMR analysis; the crude reaction mixture also contained only a single regioisomer by 1H NMR analysis. Characterization data matched previously reported data.^[15]

(S)-1-(3-(3,7-dimethyloct-6-en-1-yl)phenyl)ethan-1-one (4ab): The reaction was carried out according to a slightly modified procedure using 3'-iodoacetophenone and alkene **1ab** and higher loadings of $Pd_2(dbu)_3$ (4.6 mg, 0.005 mmol) and triphenylphosphine (26.2 mg, 0.1 mmol). The reaction was run for 16 h, and the product was purified by flash column chromatography (2% EtOAc in Hexanes) to afford **4ab** (44.5 mg, 86% yield) as a colorless oil. This product was isolated as a single regioisomer as determined by 1H NMR analysis; the crude reaction mixture also contained only a single regioisomer by 1H NMR analysis. **1H NMR** (600 MHz, $CDCl_3$) δ 7.81–7.73 (m, 2H), 7.41–7.33 (m, 2H), 5.09 (tp, J = 7.0, 1.4 Hz, 1H), 2.71 (ddd, J = 13.3, 10.7, 5.2 Hz, 1H), 2.66–2.61 (m, 1H), 2.60 (s, 3H), 2.06–1.91 (m, 2H), 1.70–1.61 (m, 4H), 1.60 (s, 3H), 1.52–1.43 (m, 2H), 1.39 (dddd, J = 14.7, 9.6, 7.2, 4.1 Hz, 1H), 1.20 (dddd, J = 13.3, 9.5, 7.6, 6.2 Hz, 1H), 0.95 (d, J = 6.3 Hz, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 198.58, 143.83, 137.36, 133.37, 131.36, 128.61, 128.20, 125.99, 124.91, 38.98, 37.06, 33.50, 32.30, 26.84, 25.86, 25.61, 19.64, 17.79. **HRMS** calcd. for $C_{18}H_{27}O^+ [M+H]^+$: 259.2062, Found: 259.2064.

Deuterium Incorporation Experiment



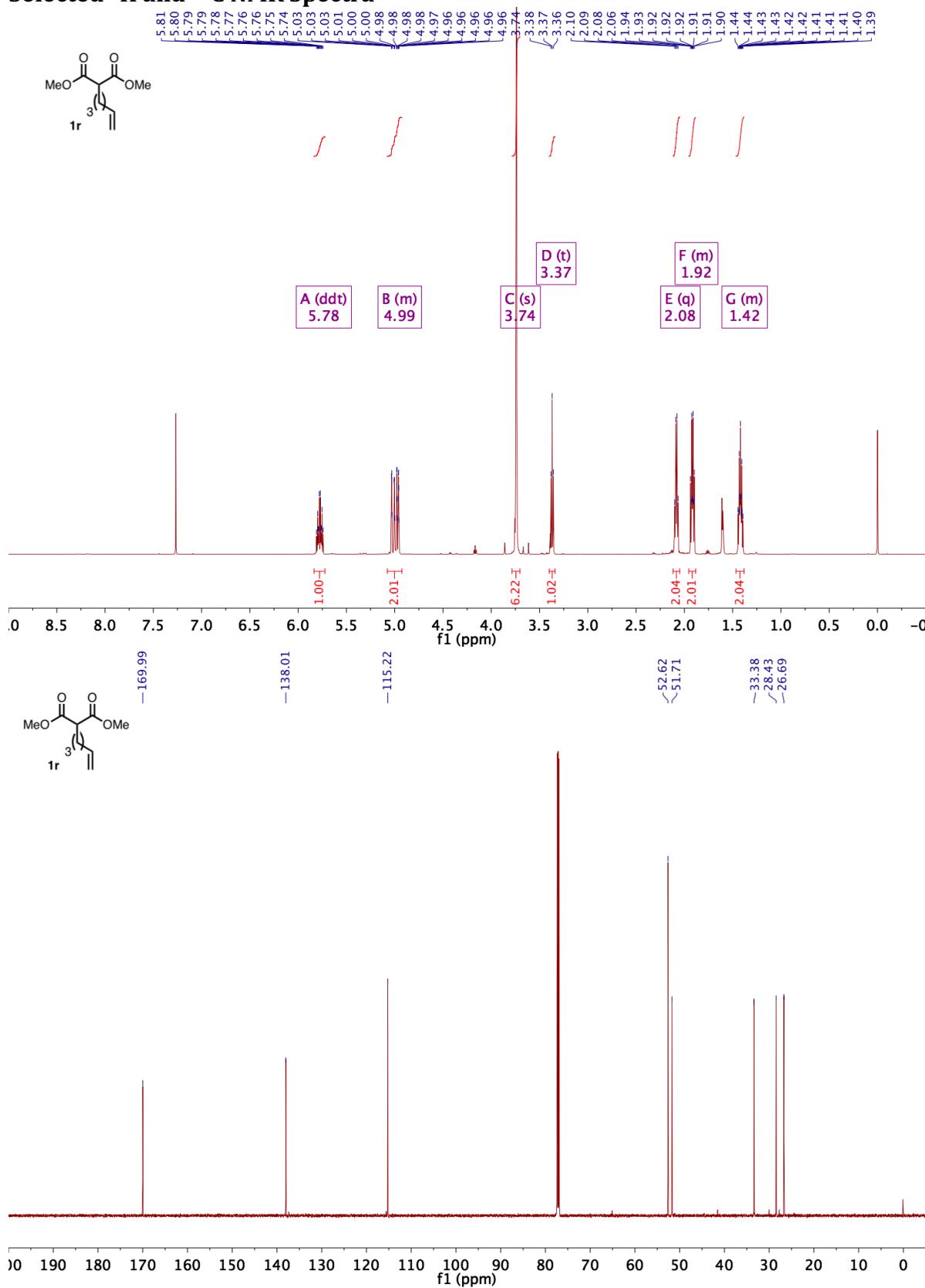
To a 1-Dram (4 mL) vial equipped with a magnetic stir bar were added $\text{Pd}_2(\text{dba})_3$ (4.6 mg, 0.005 mmol), triphenylphosphine (26.2 mg, 0.1 mmol), K_3PO_4 (84.9 mg, 0.4 mmol), allyl alcohol (11.6 mg, 0.2 mmol), iodobenzene (81.6 mg, 0.4 mmol), NaDCO_2 (27.6 mg, 0.4 mmol), tetrabutylammonium tetrafluoroborate (65.9 mg, 0.2 mmol), water (36 μL , 2 mmol), and DMF (0.2 mL). The vial was sealed with a solid screw cap and placed in a heating block that was pre-heated to 80 $^\circ\text{C}$. After 4 h, the reaction mixture was diluted with water (5 mL) and extracted with EtOAc (5 mL \times 3). The combined organic layers were dried over Na_2SO_4 , concentrated *in vacuo*, and purified by column chromatography to (10–25% EtOAc in Hexanes) to afford **4a-D** (12.5 mg, 46% yield) as a yellow oil. This product was isolated as a single regioisomer as determined by ^1H NMR analysis; the crude reaction mixture also contained only a single regioisomer by ^1H NMR analysis. **$^1\text{H NMR}$** (600 MHz, CDCl_3) δ 7.29 (dd, J = 8.2, 7.0 Hz, 2H), 7.20 (dt, J = 8.2, 1.9 Hz, 3H), 3.68 (d, J = 6.4 Hz, 2H), 2.71 (d, J = 7.8 Hz, 2H), 1.93–1.84 (m, 1H), 1.38–1.27 (m, 1H). **$^{13}\text{C NMR}$** (150 MHz, CDCl_3) δ 141.94, 128.56, 128.54, 126.01, 62.40, 33.98 (t, J = 19.7 Hz), 32.13. **HRMS** calcd. for $\text{C}_9\text{H}_{10}\text{D}^+$ $[\text{M} - \text{H}_2\text{O} + \text{H}]^+$: 120.0918, Found: 120.0918.

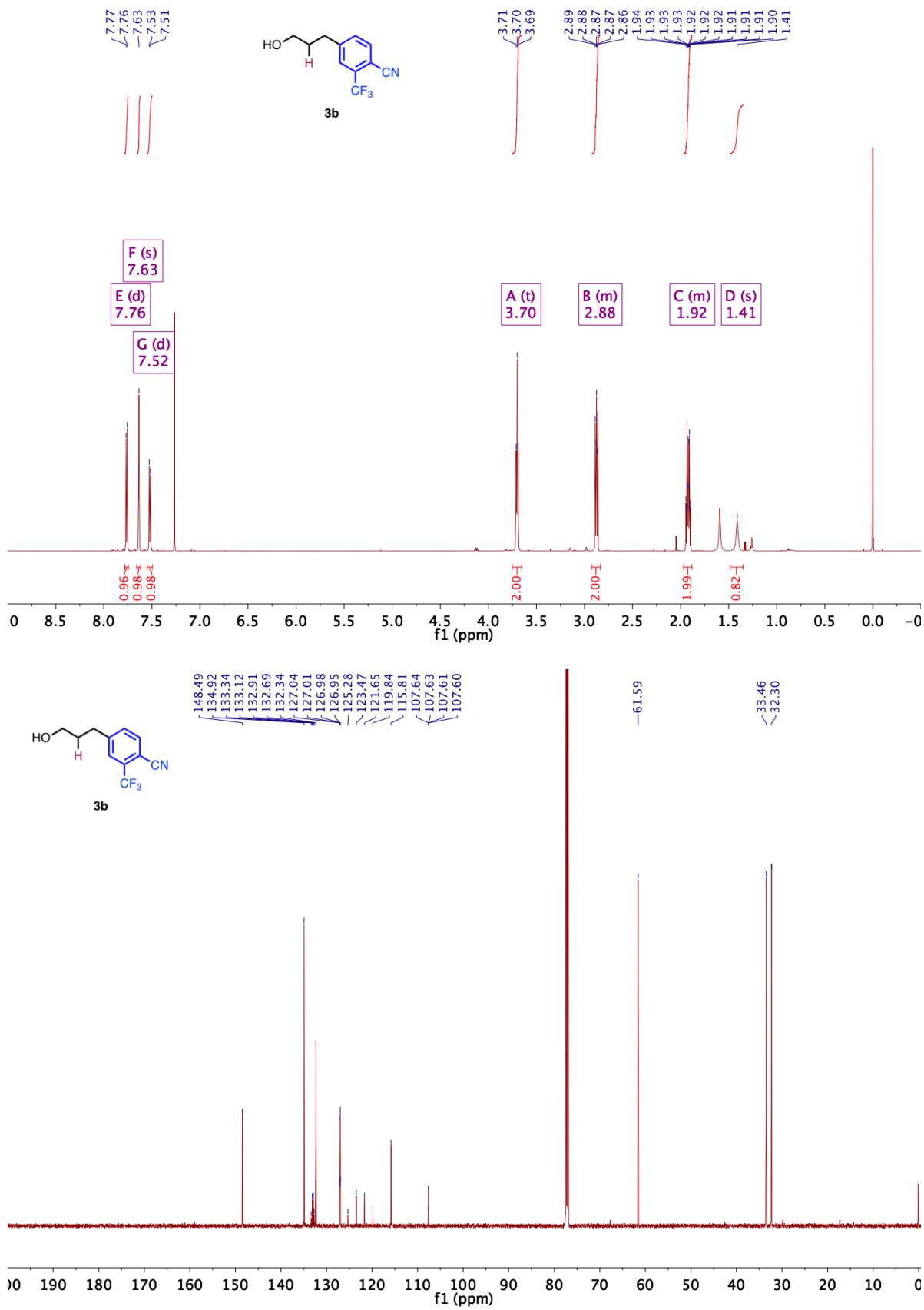


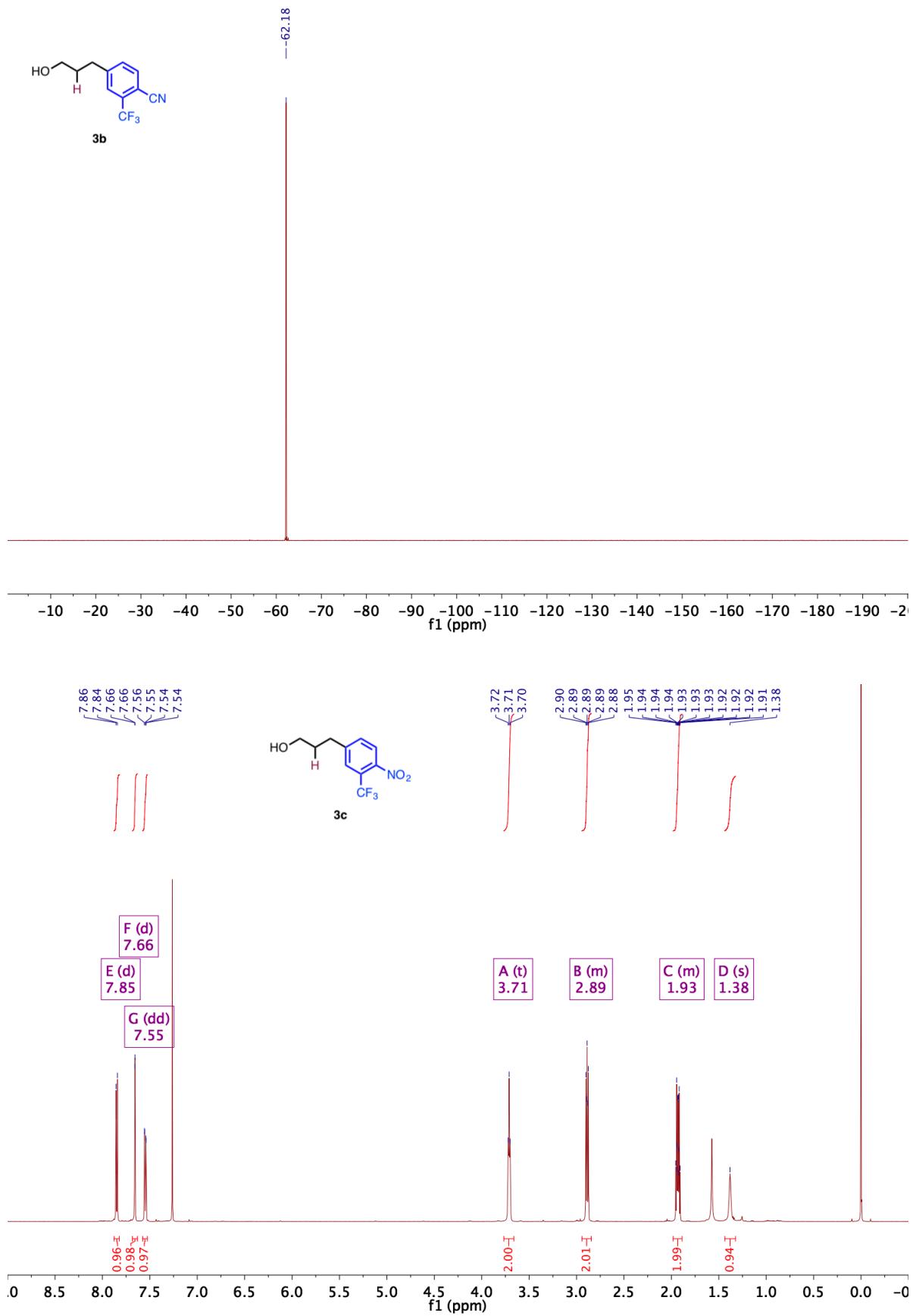
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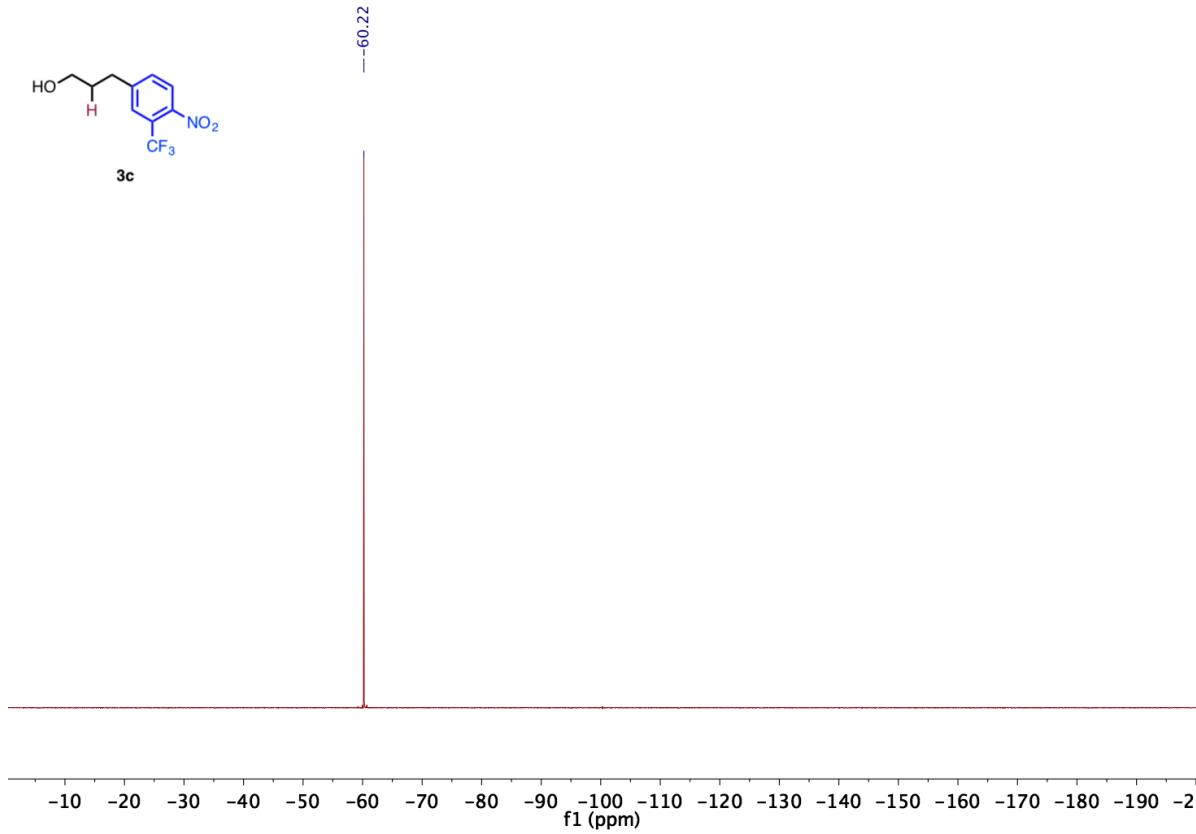
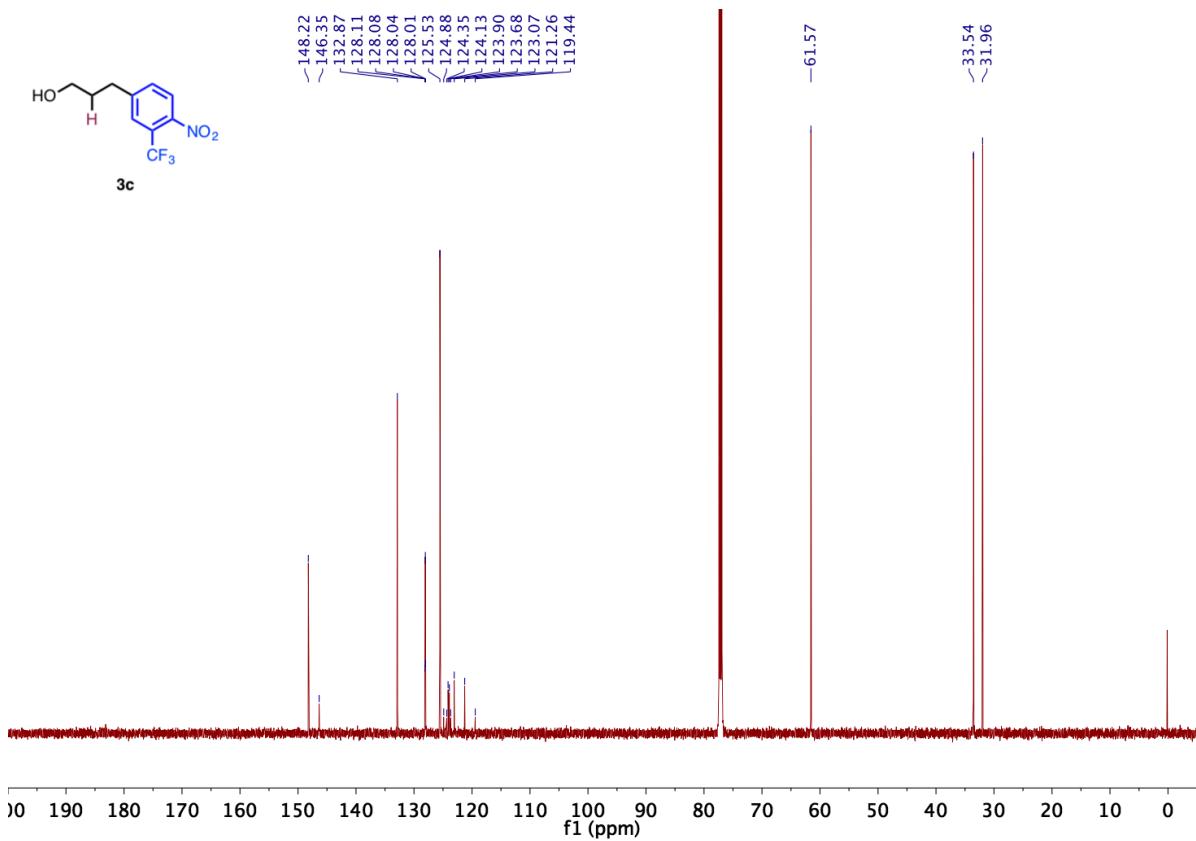
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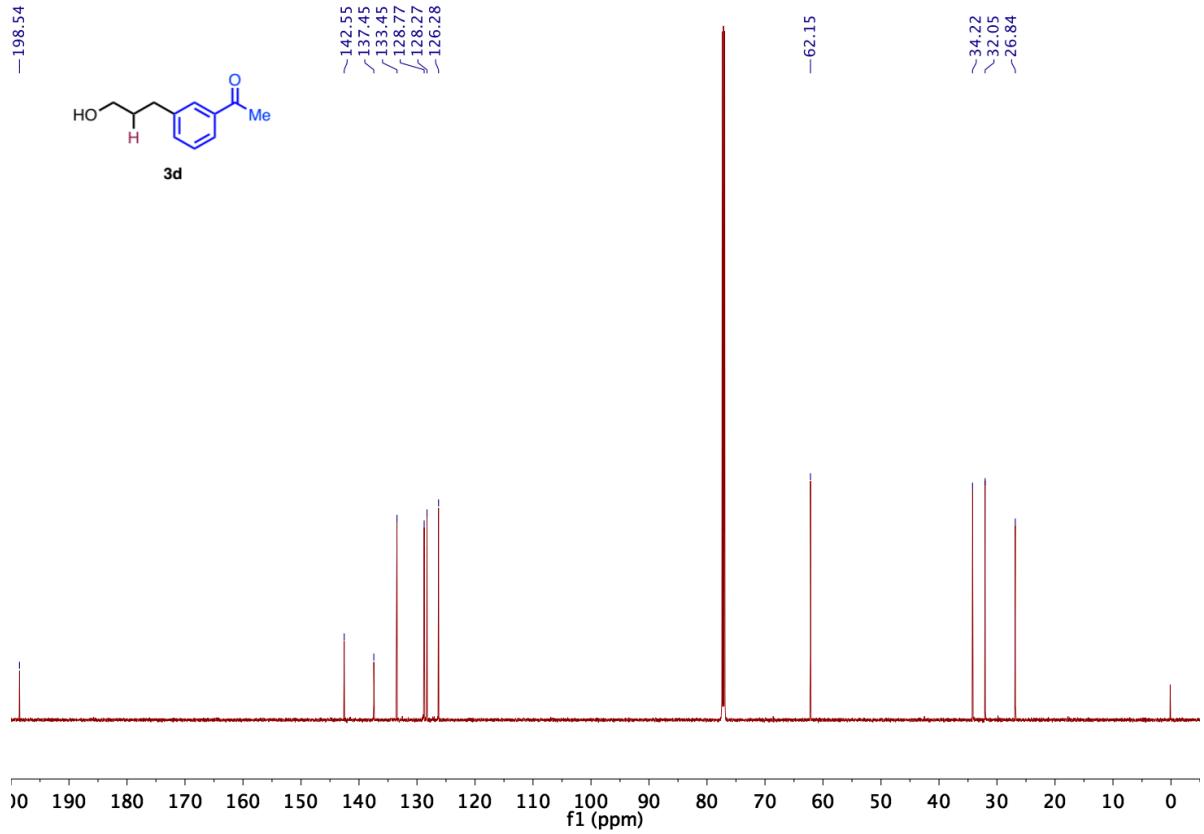
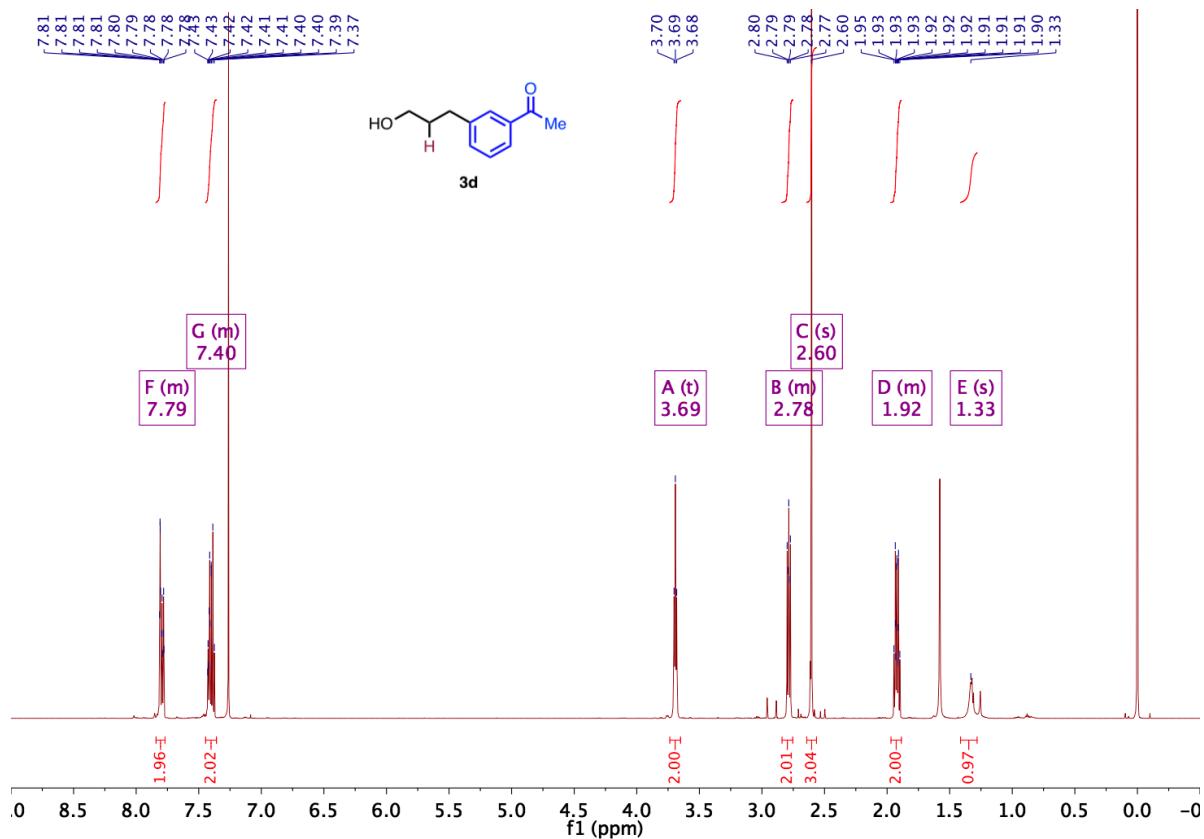
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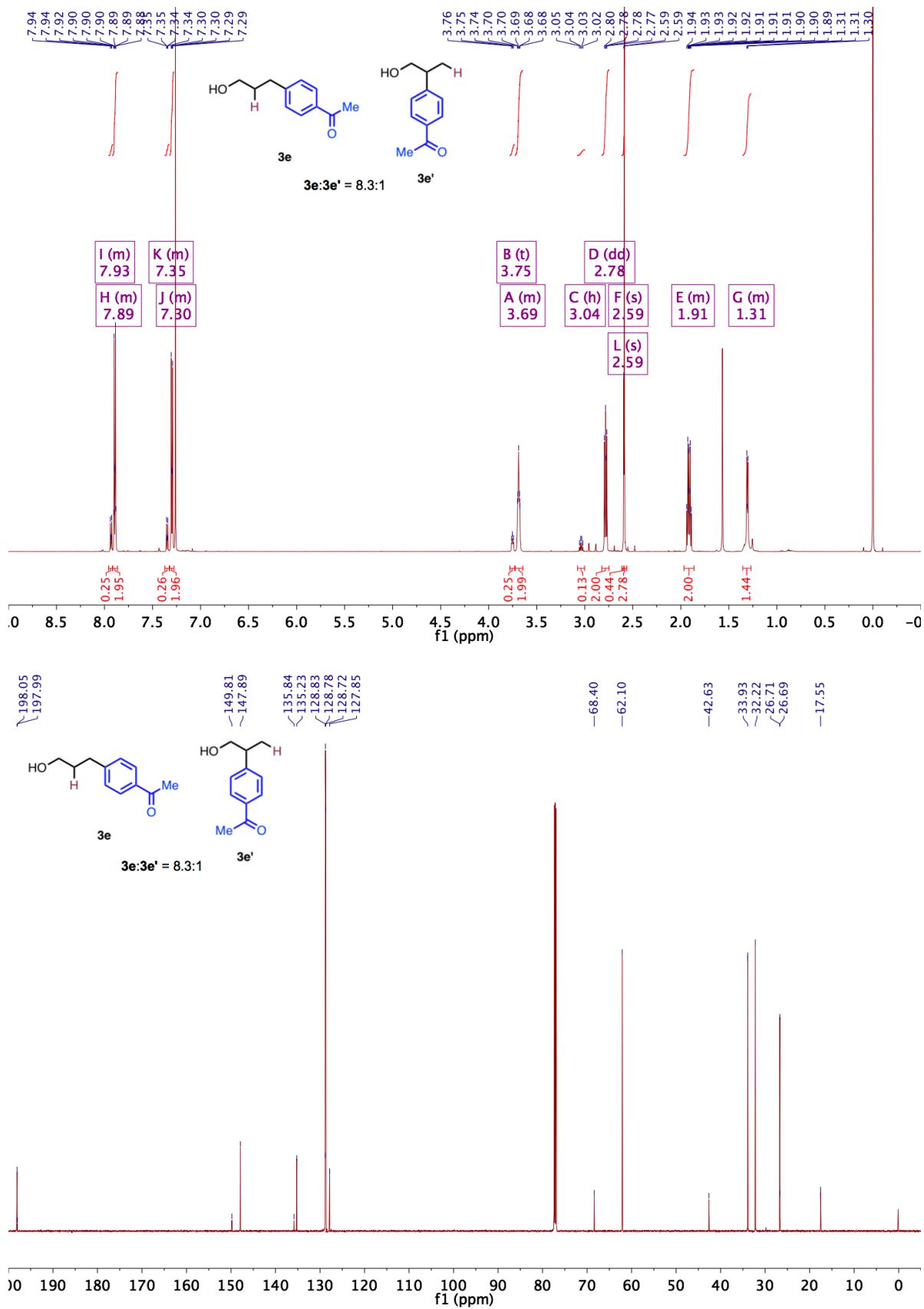


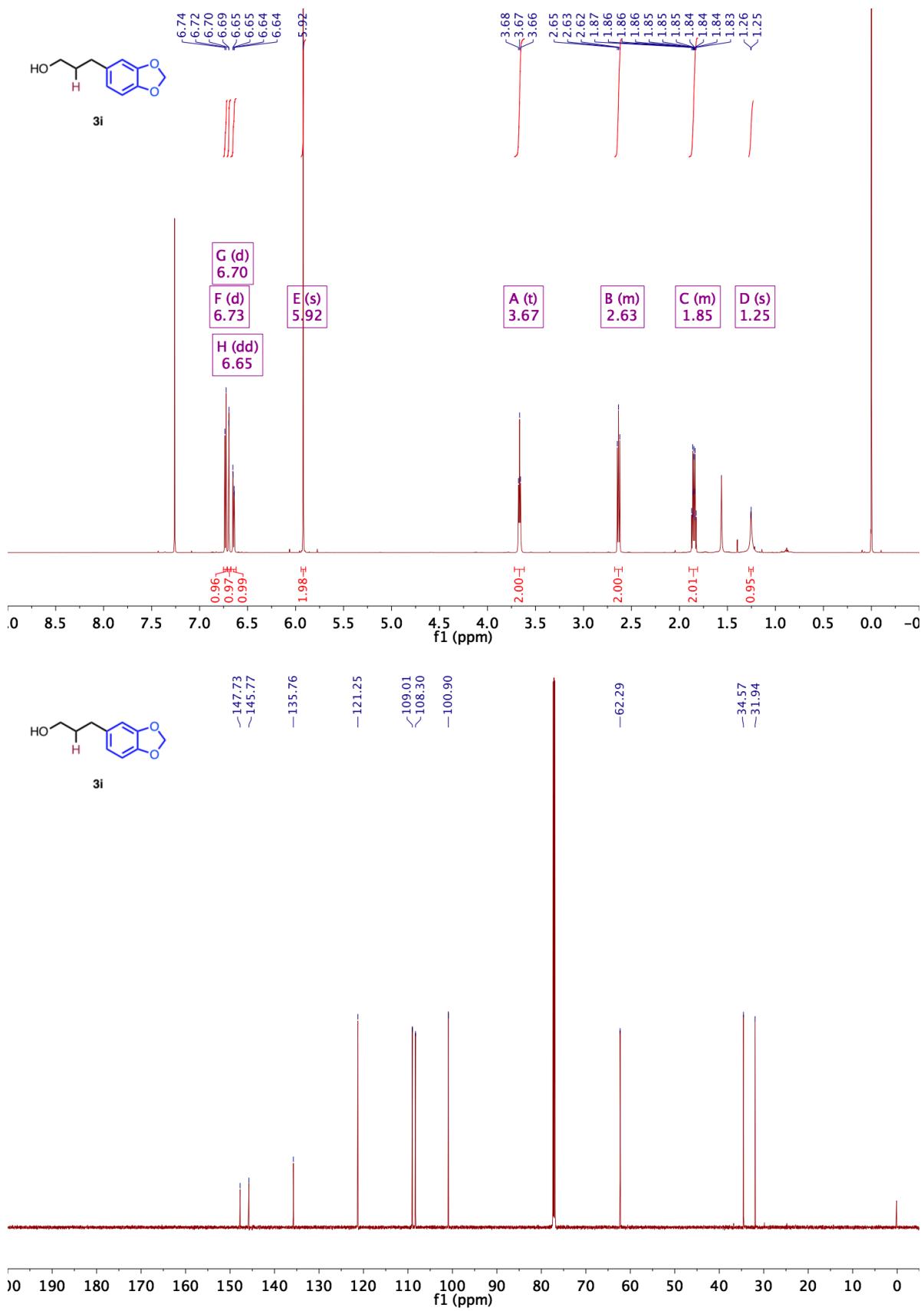


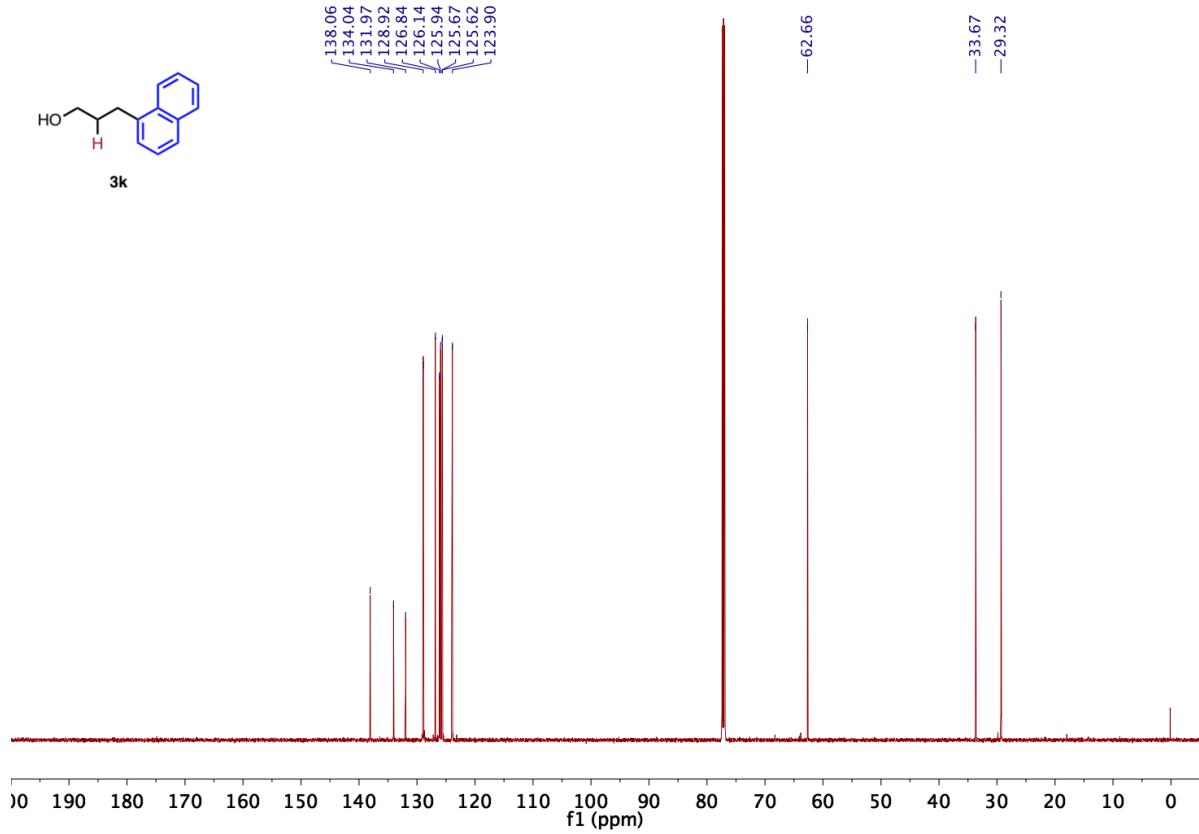
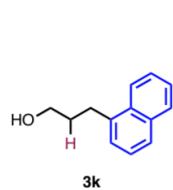
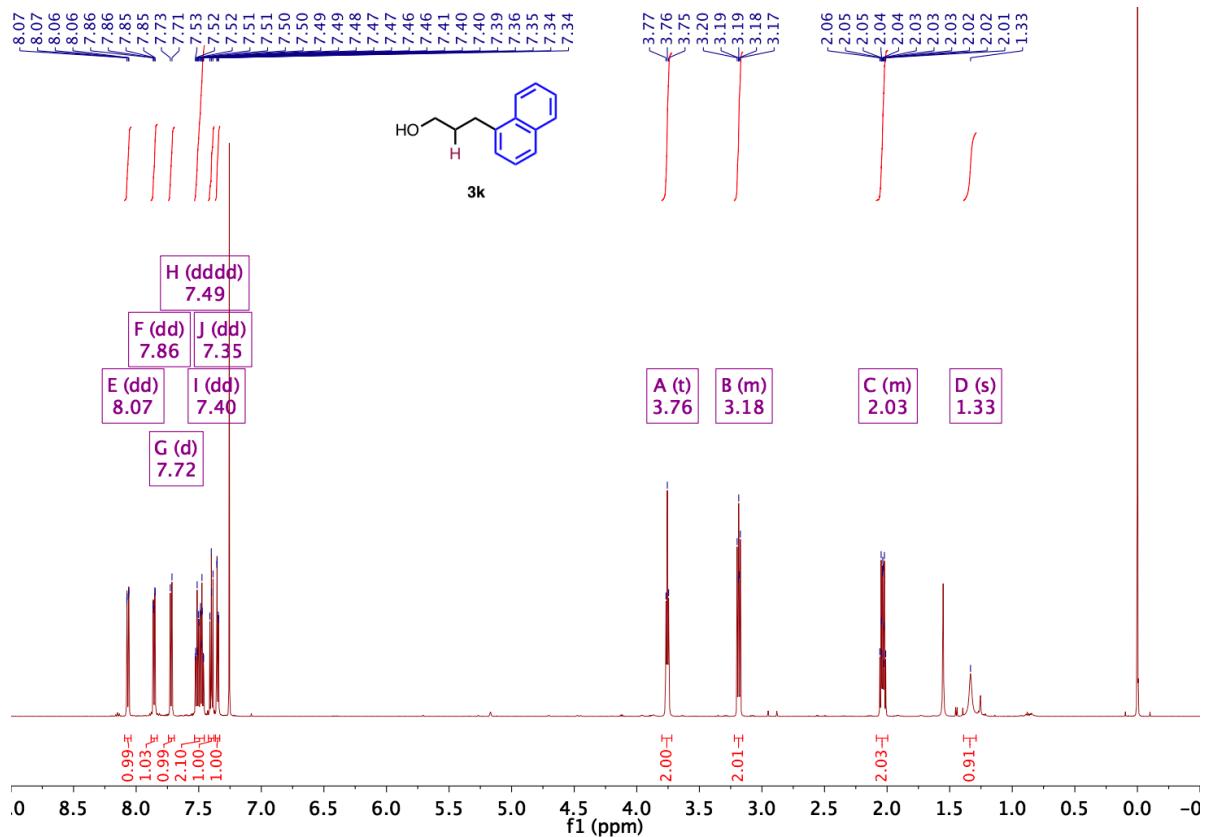


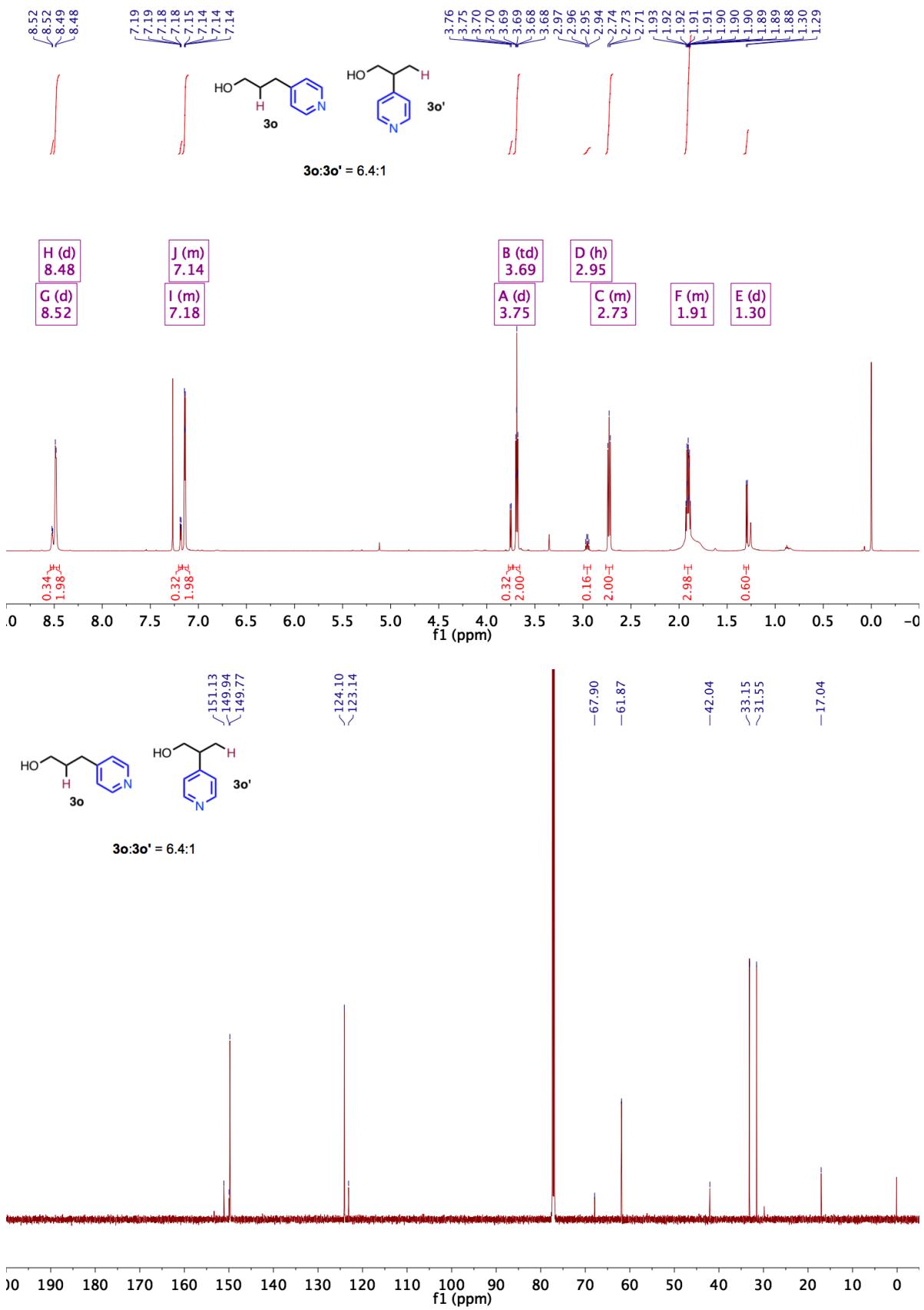


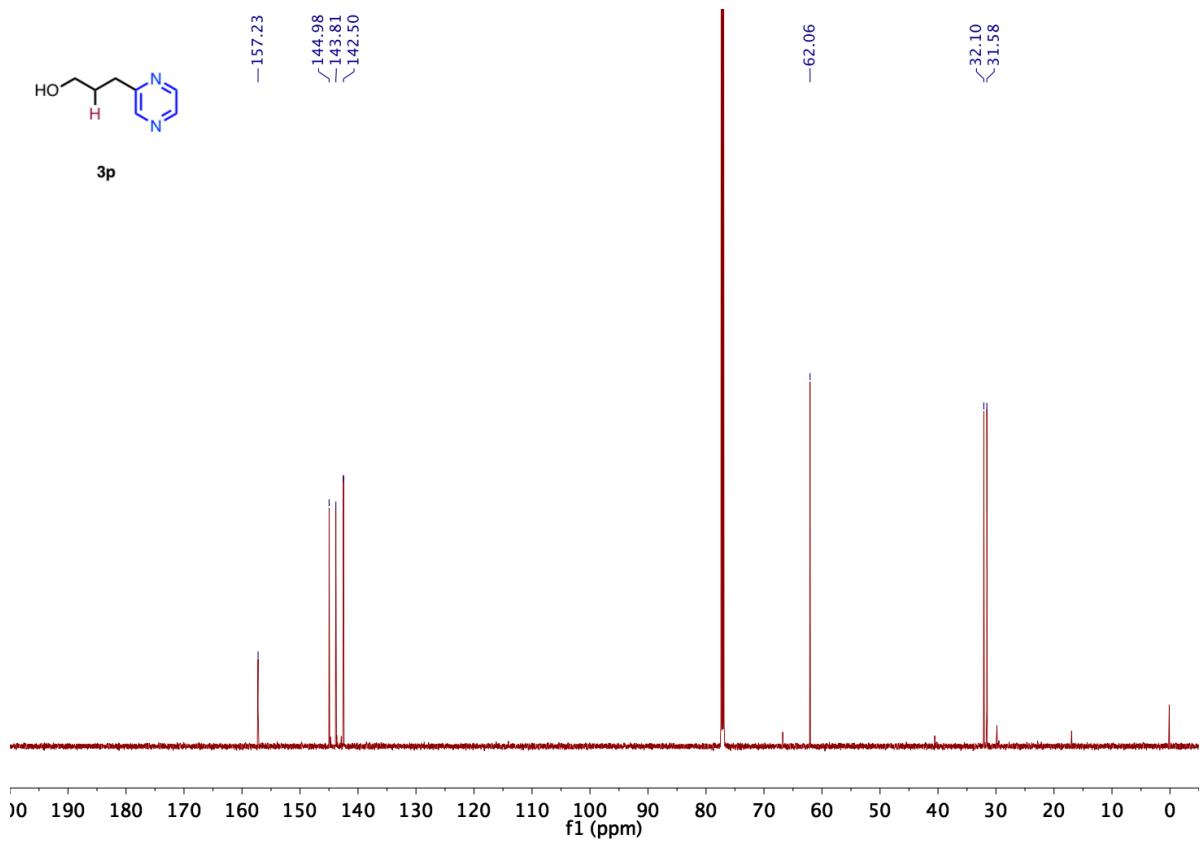
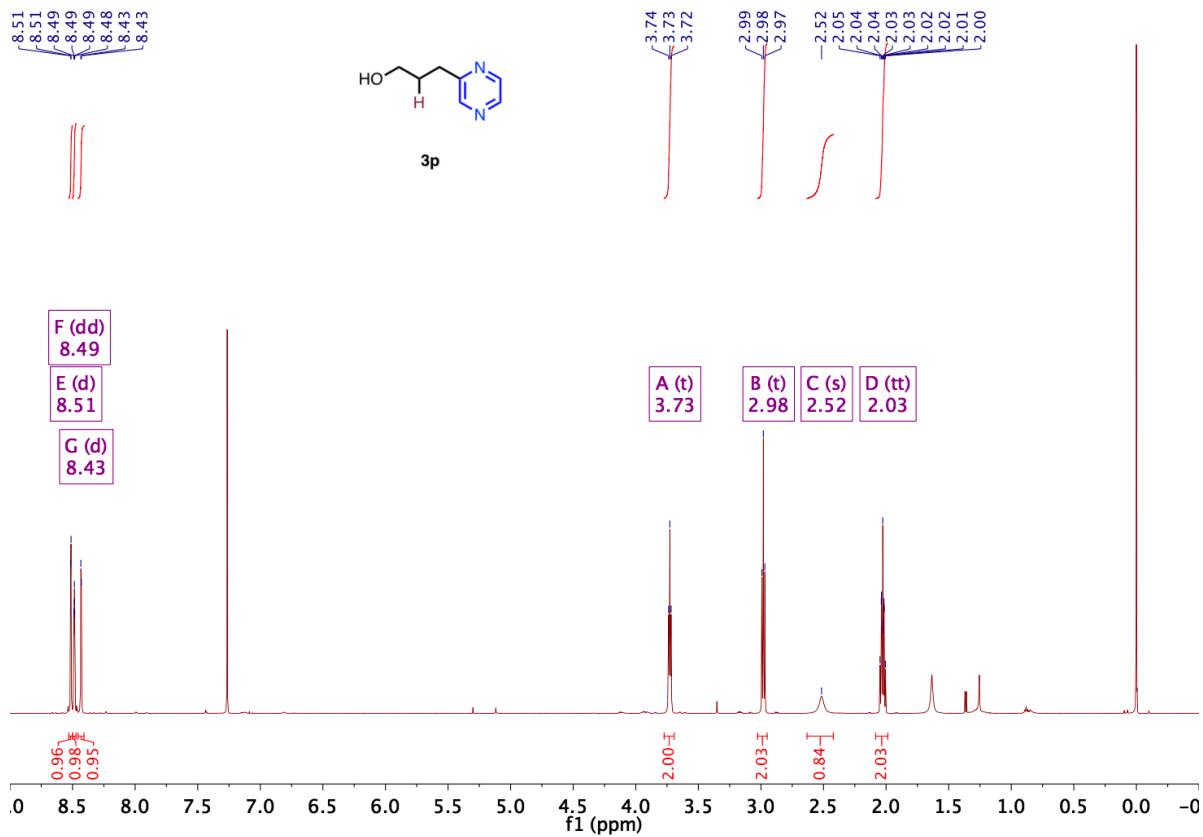


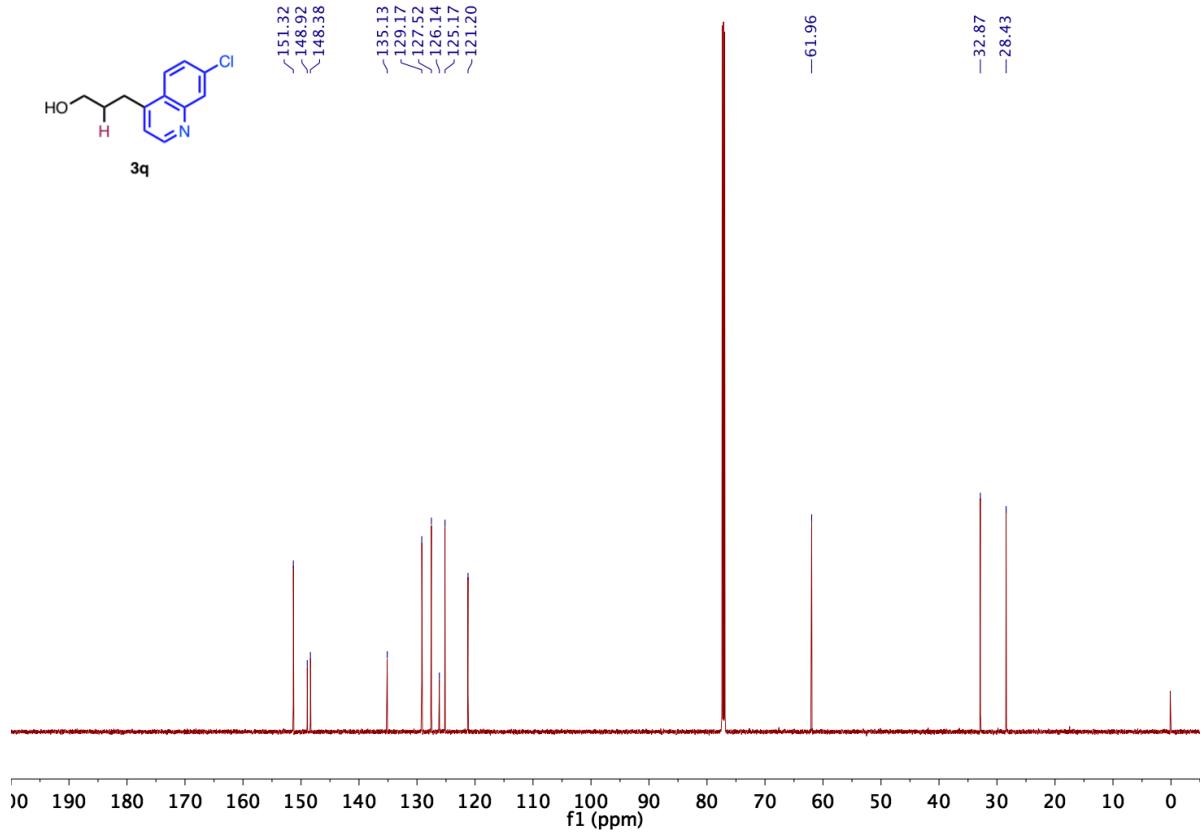
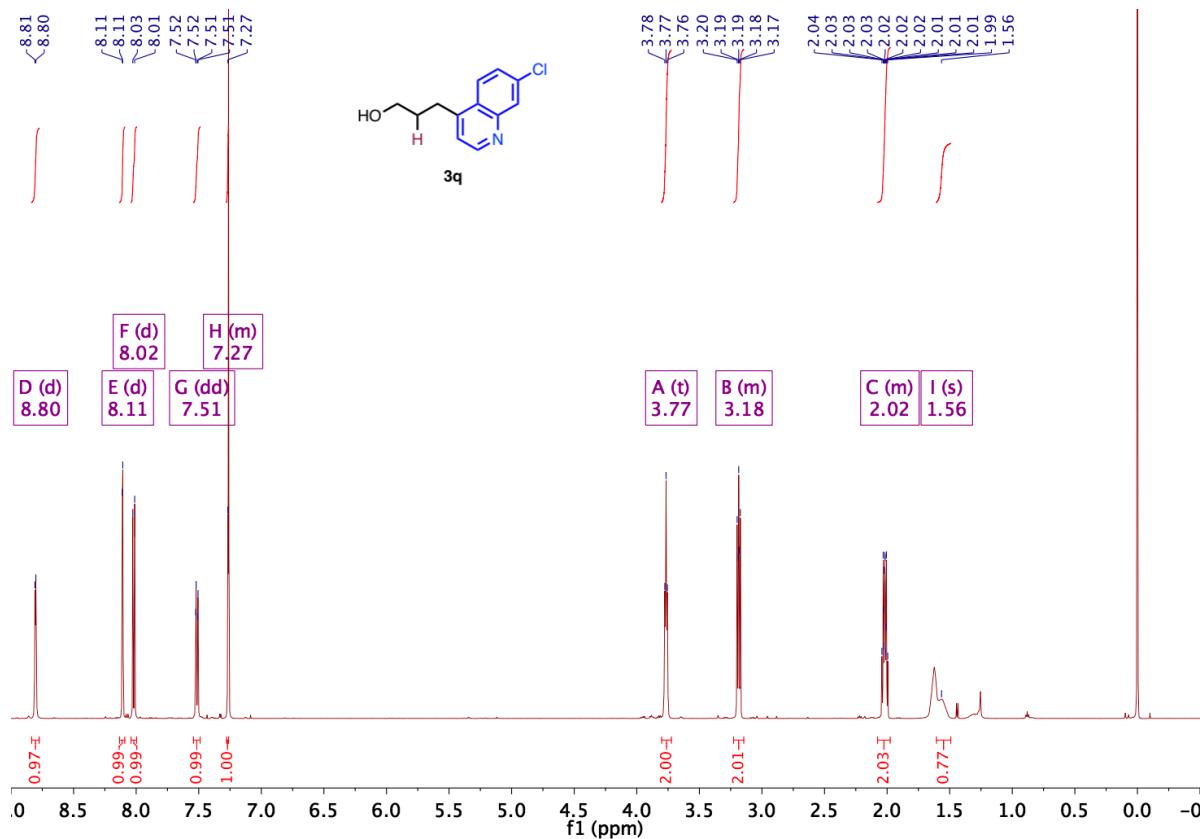


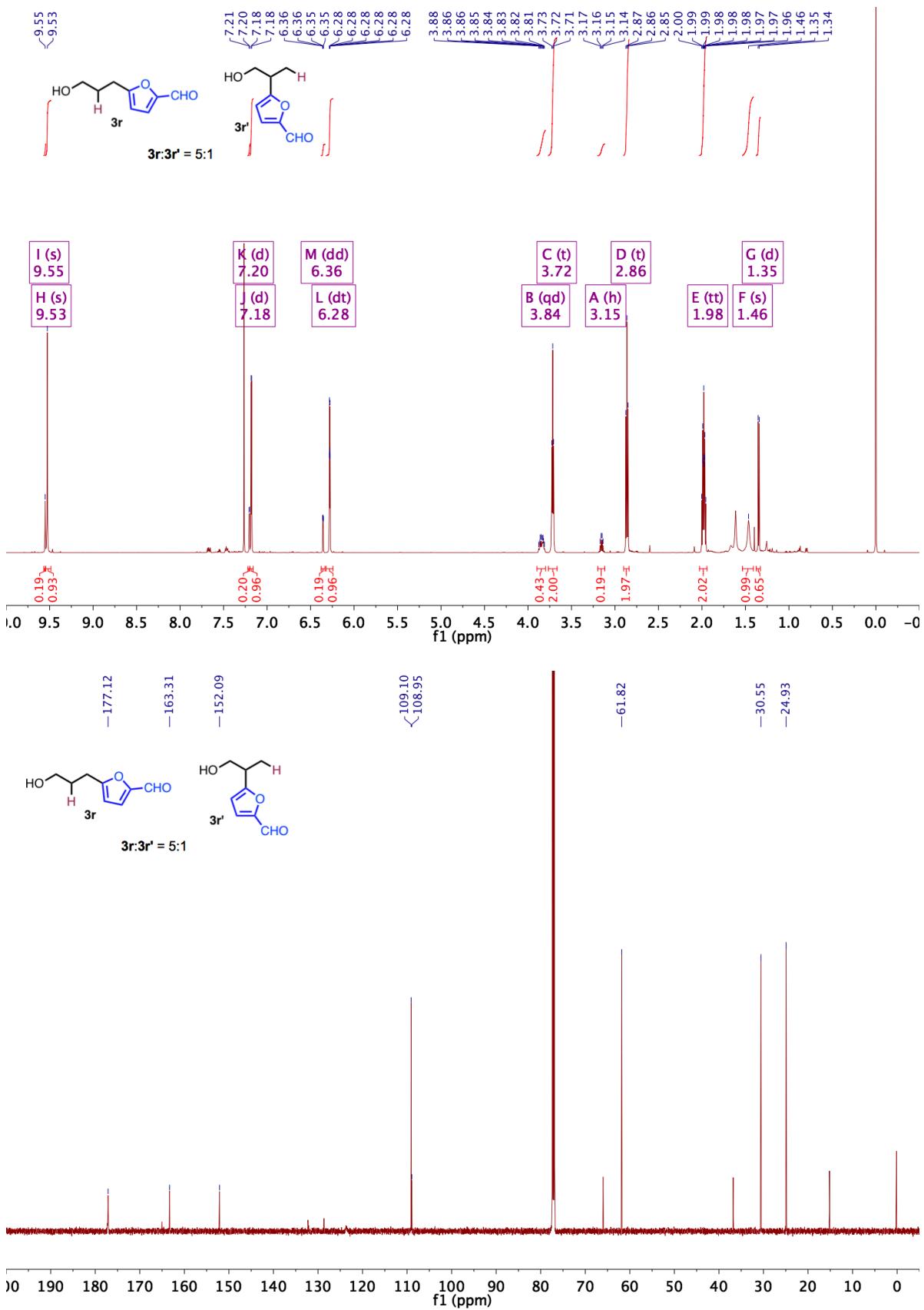


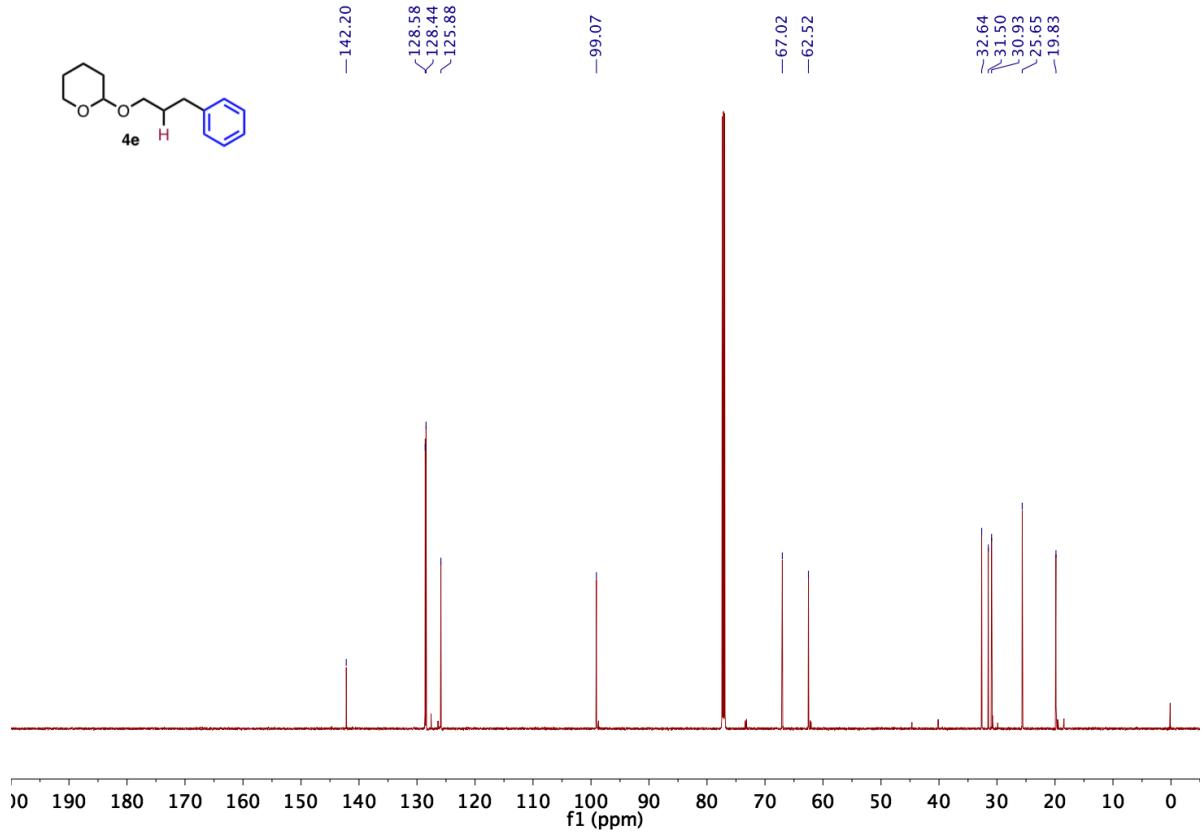
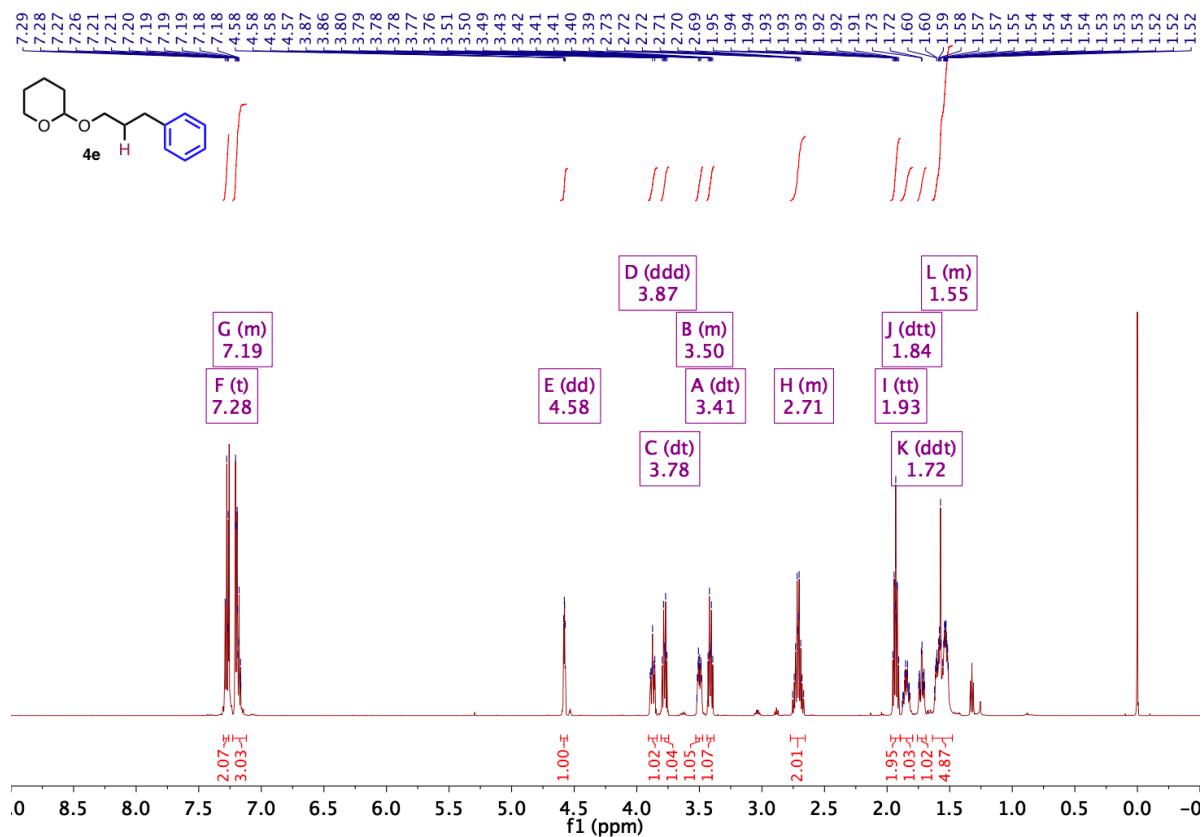


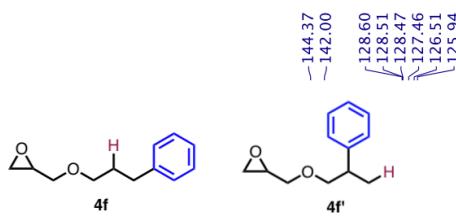
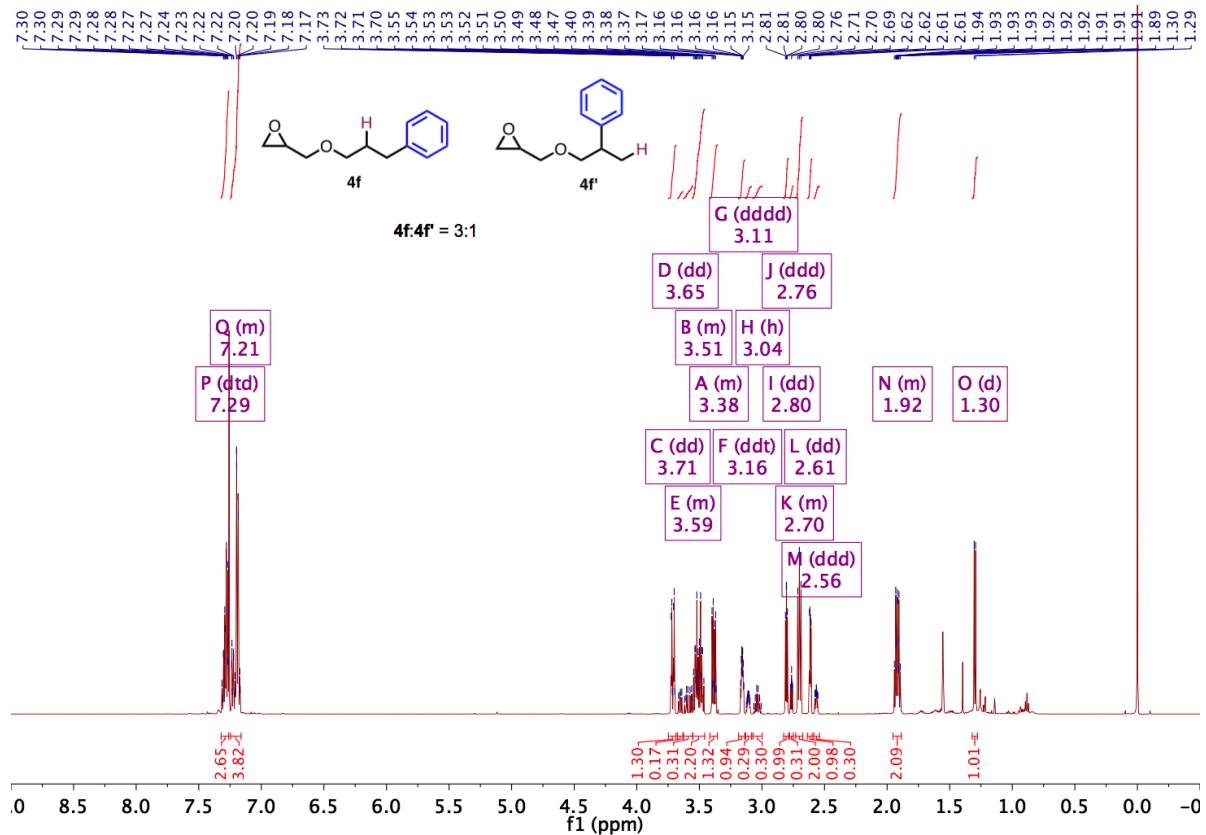




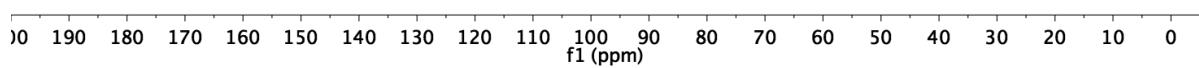


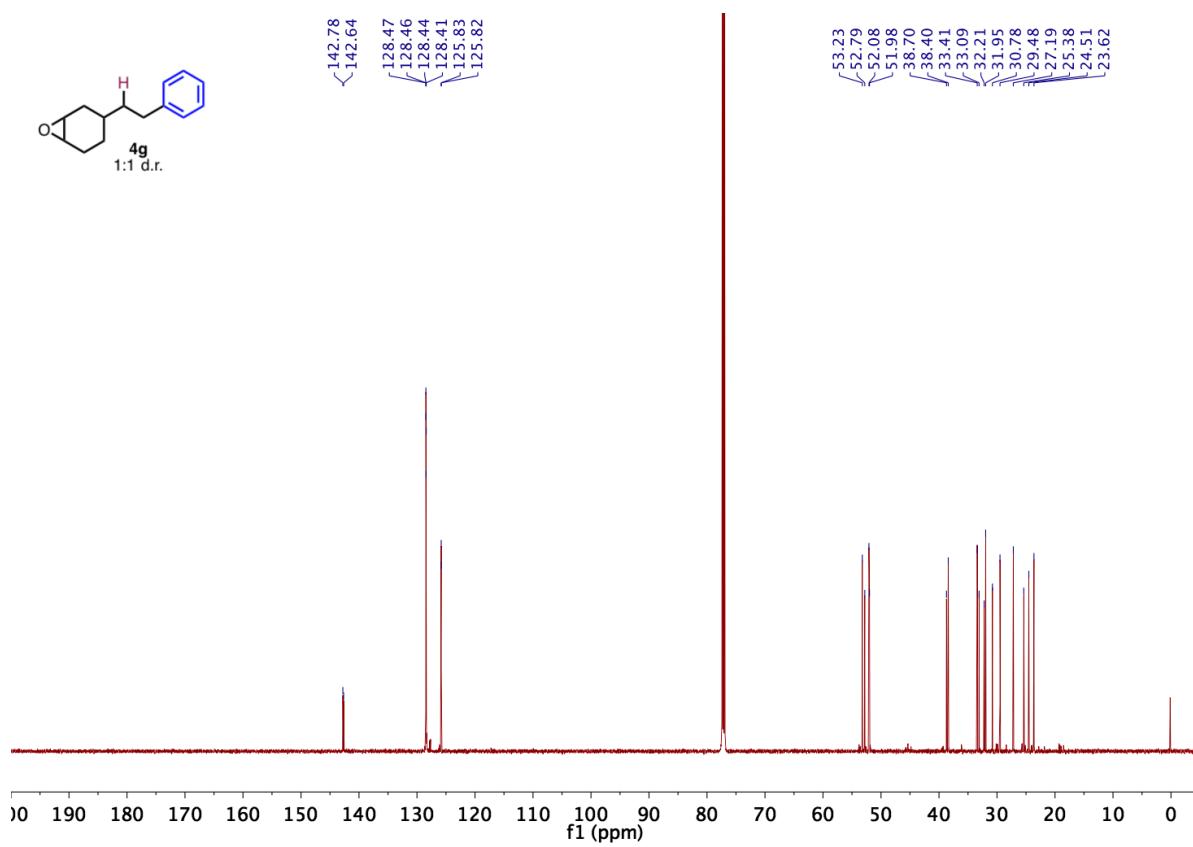
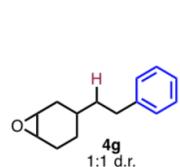
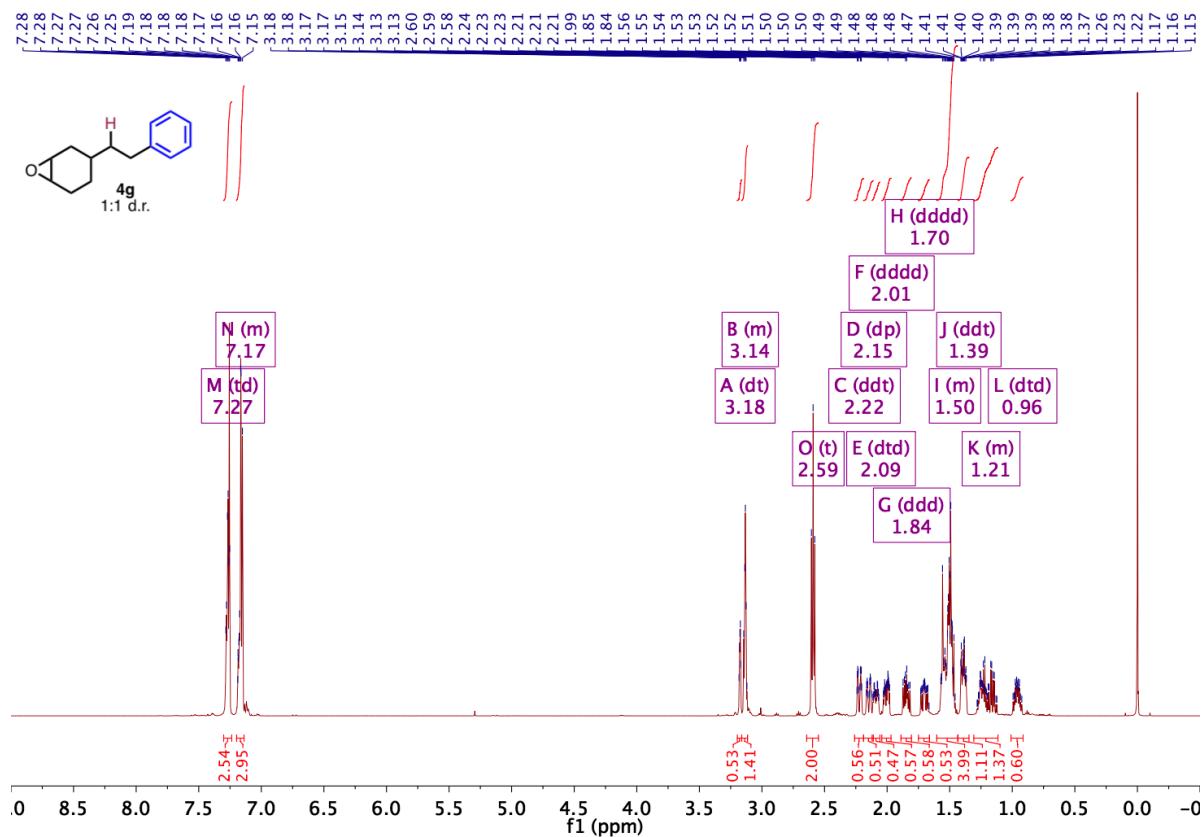


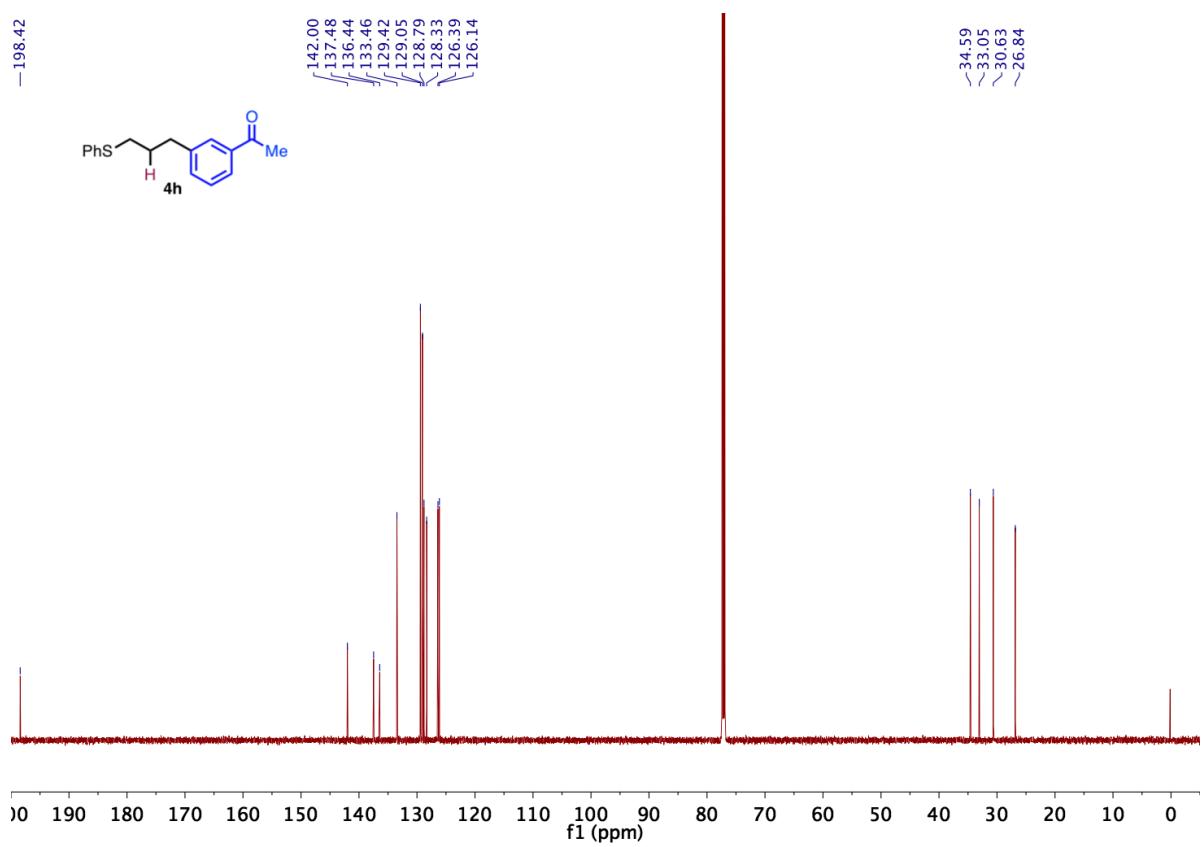
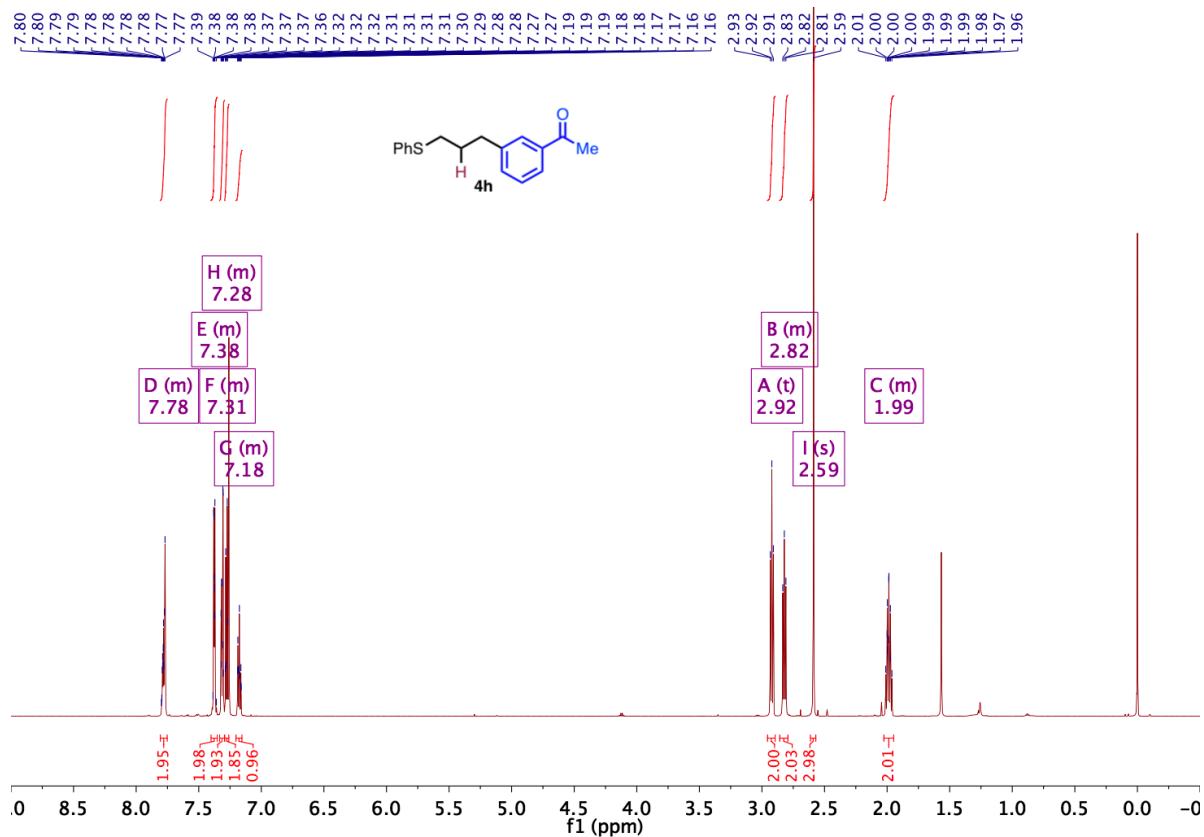


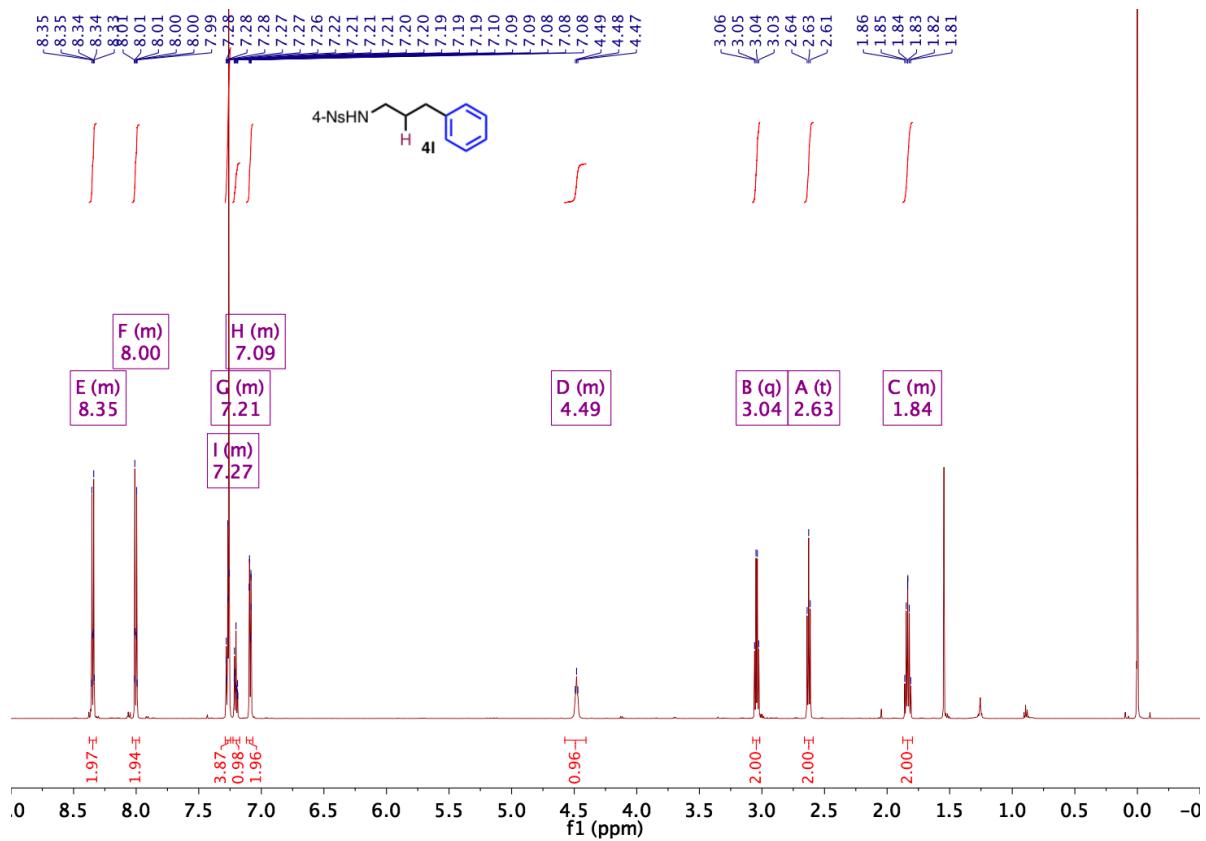


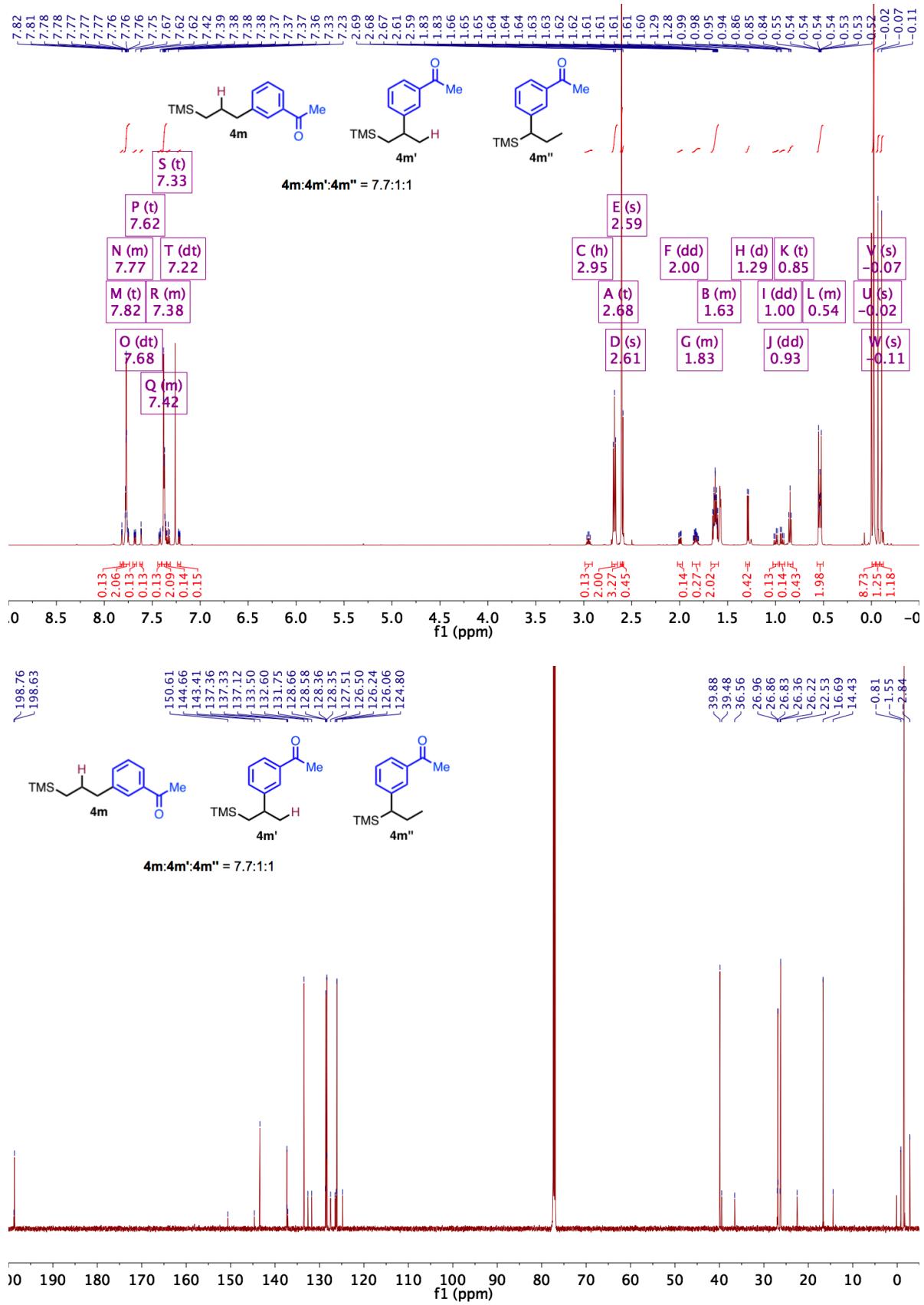
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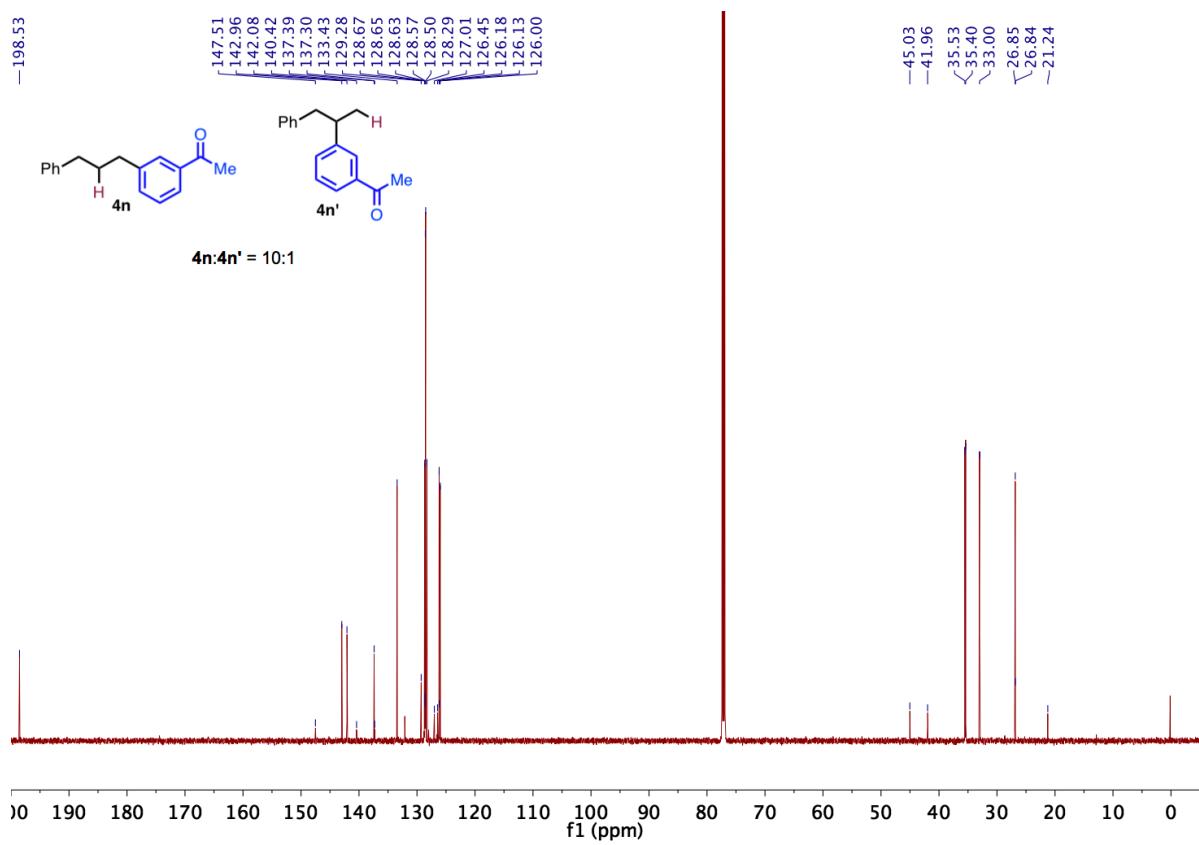
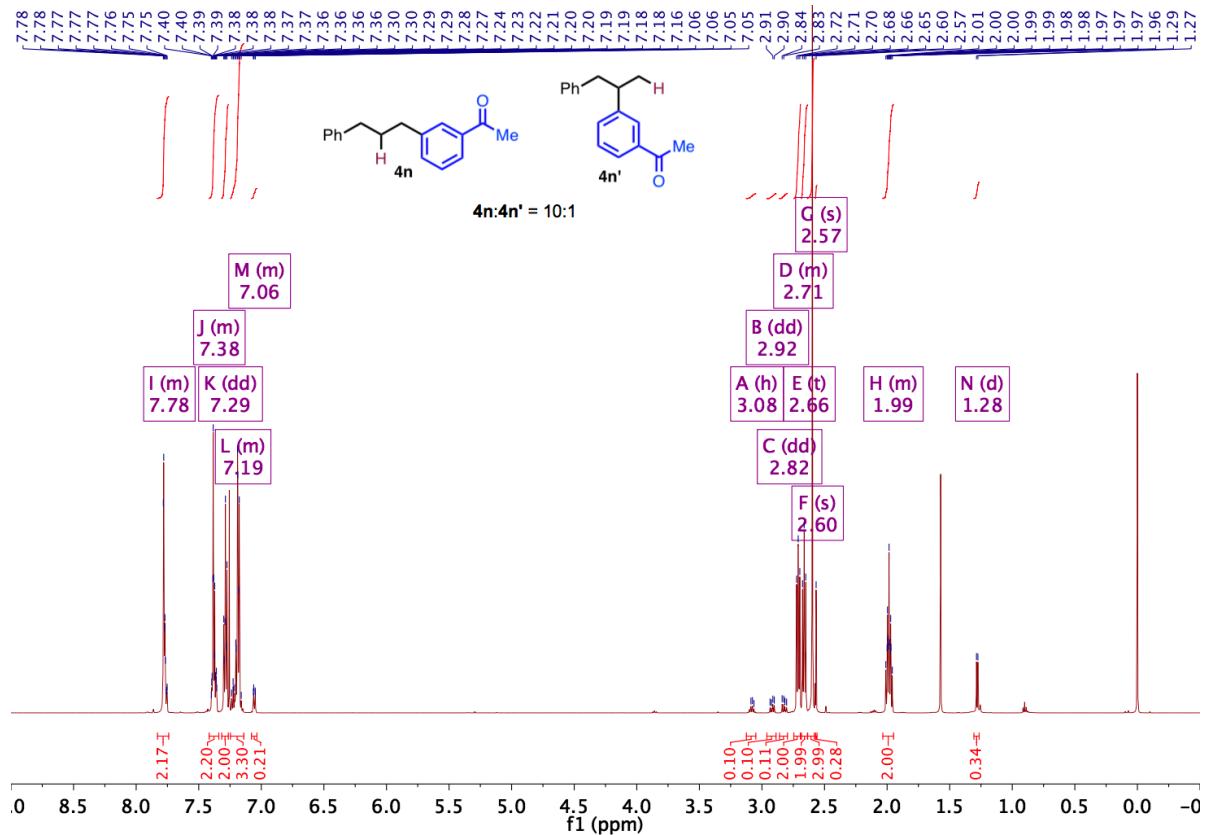


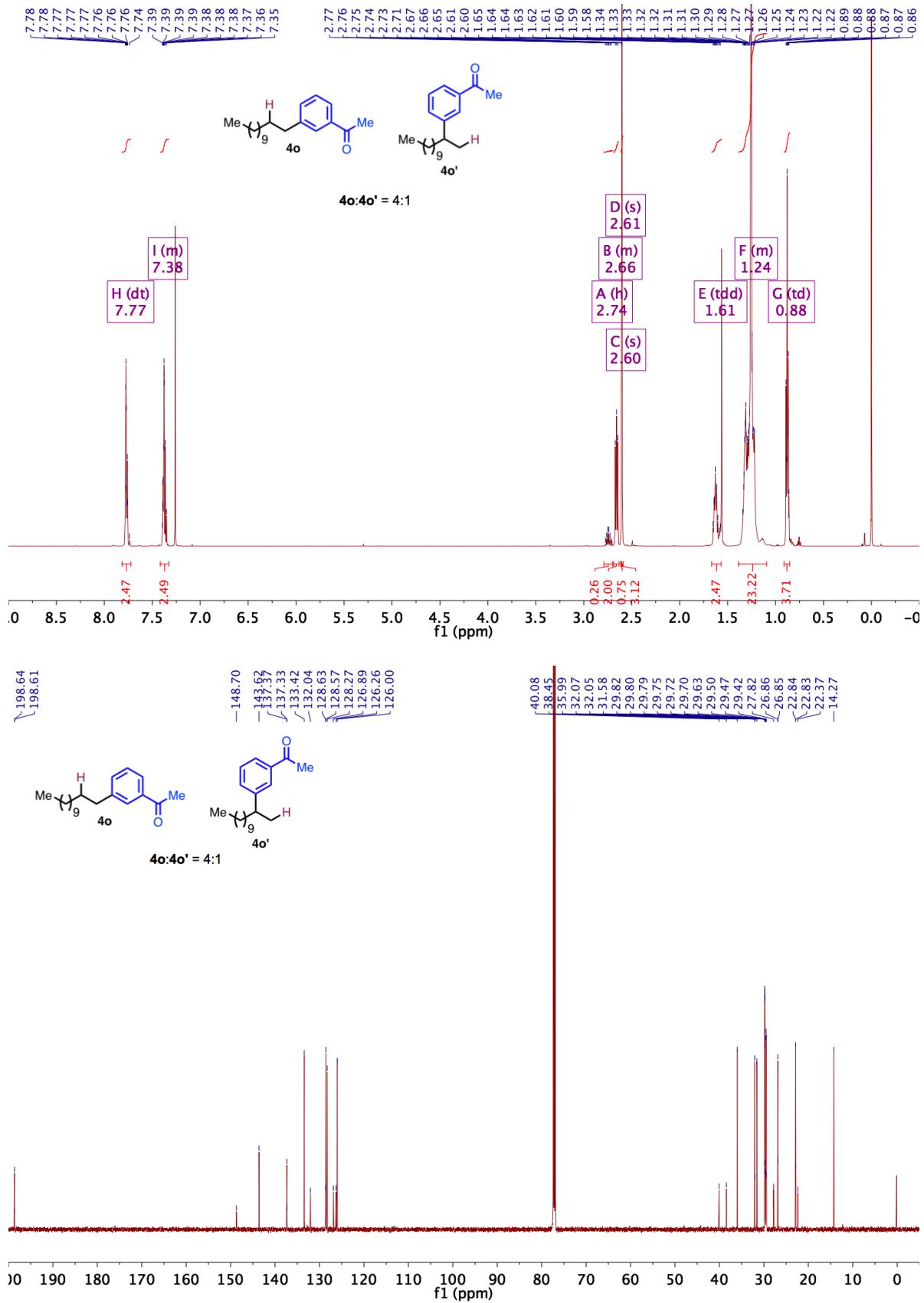


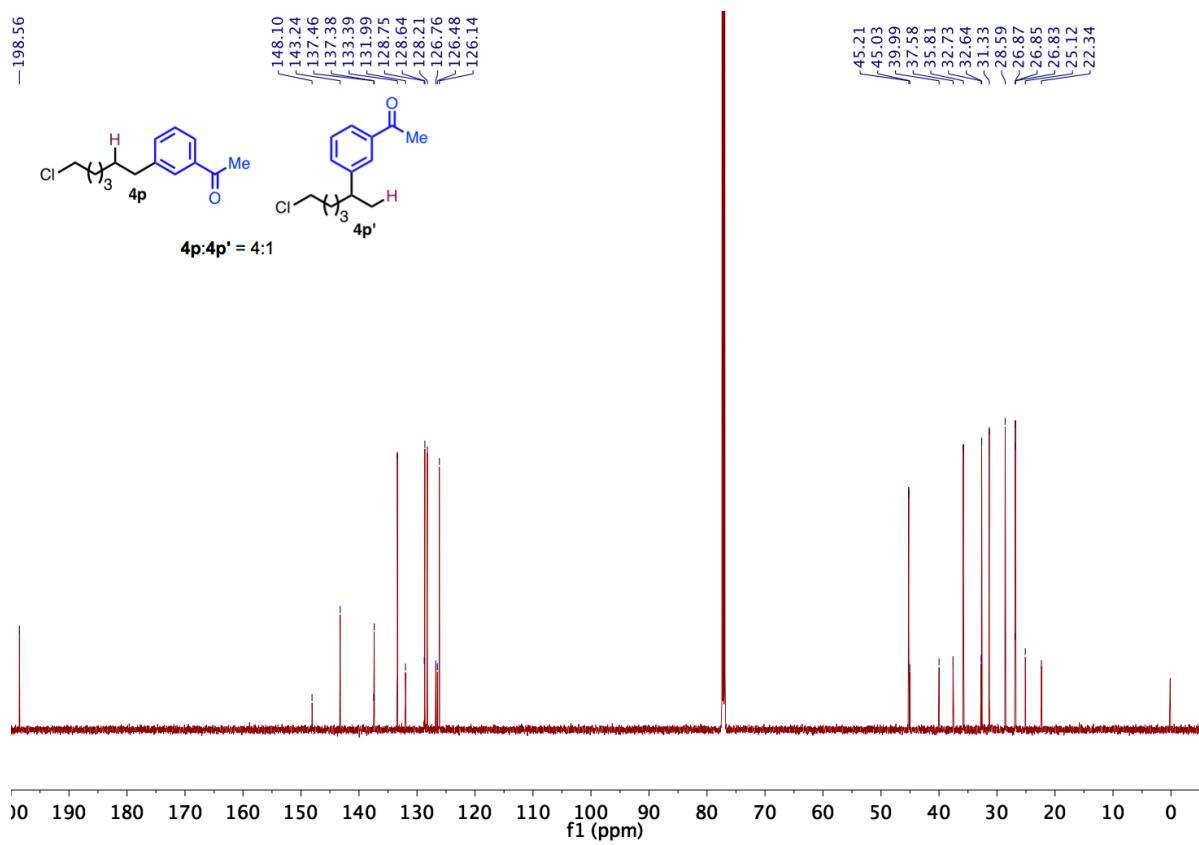
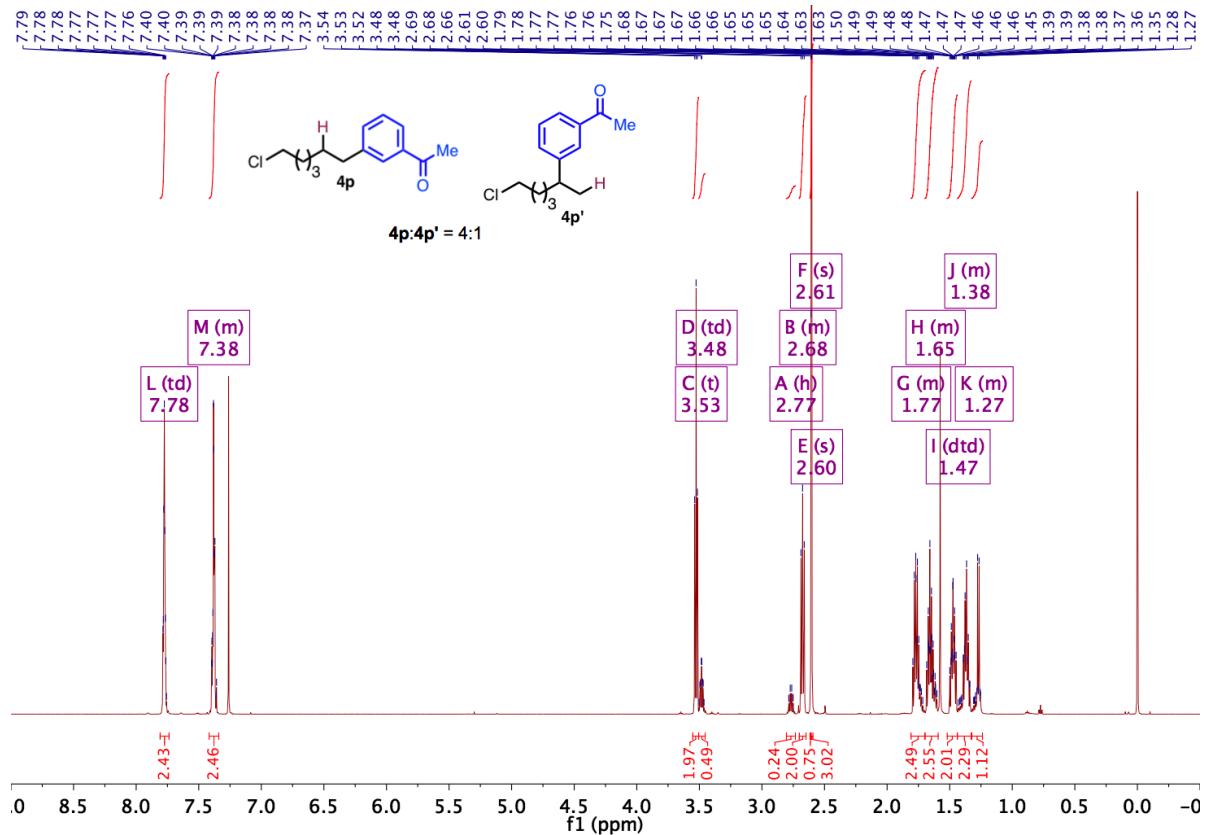


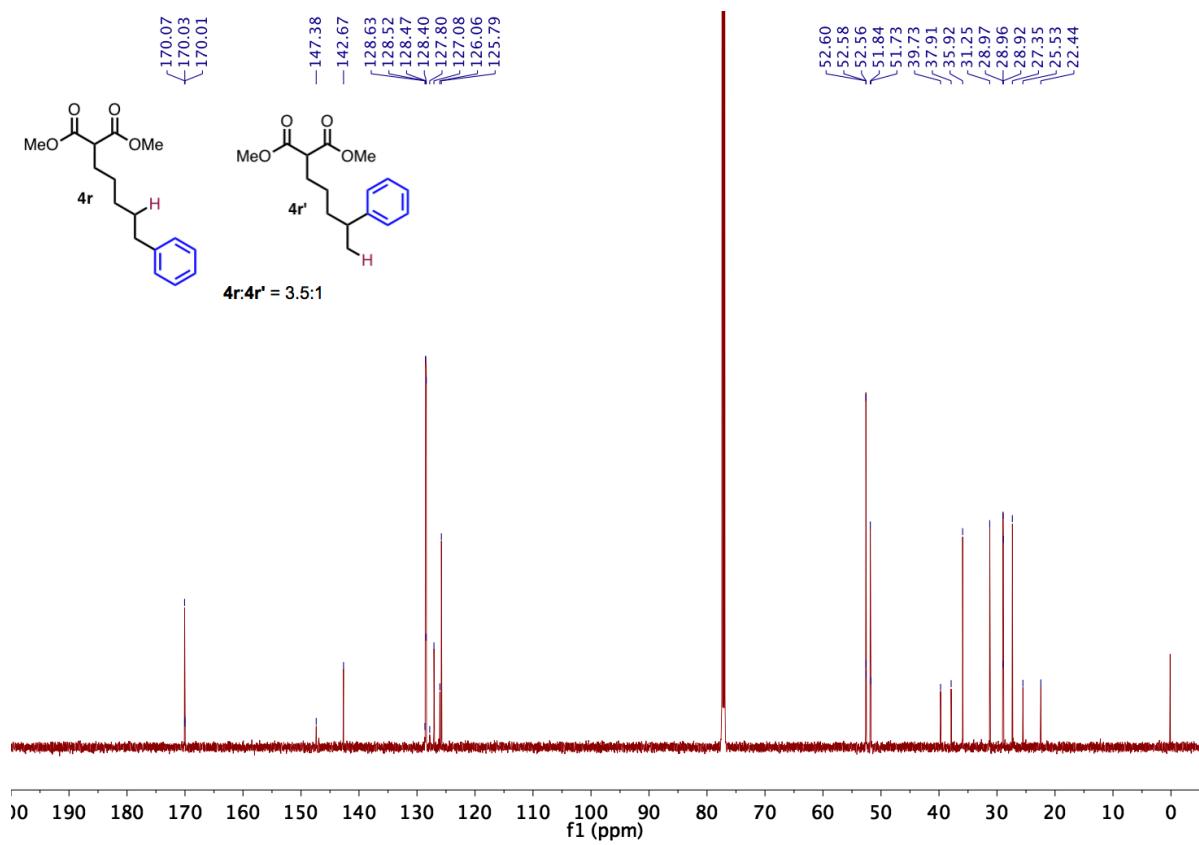
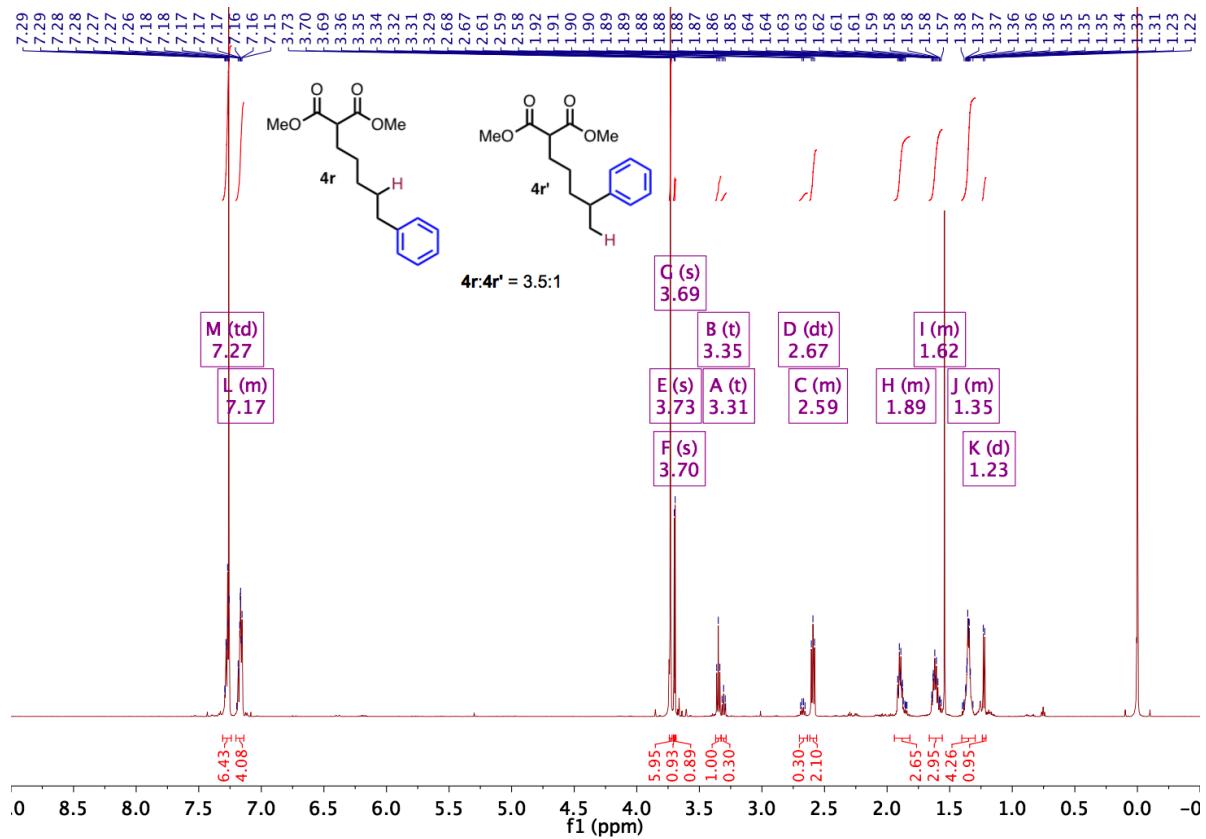


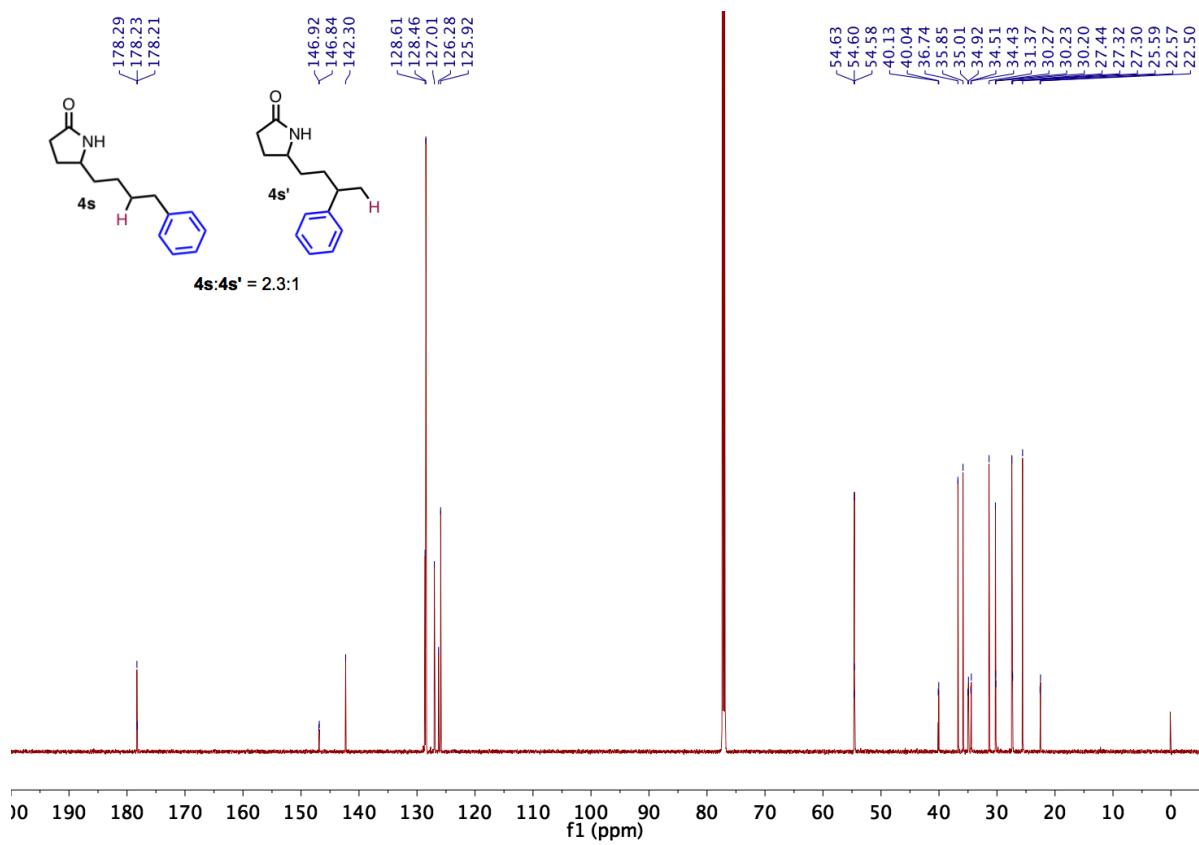
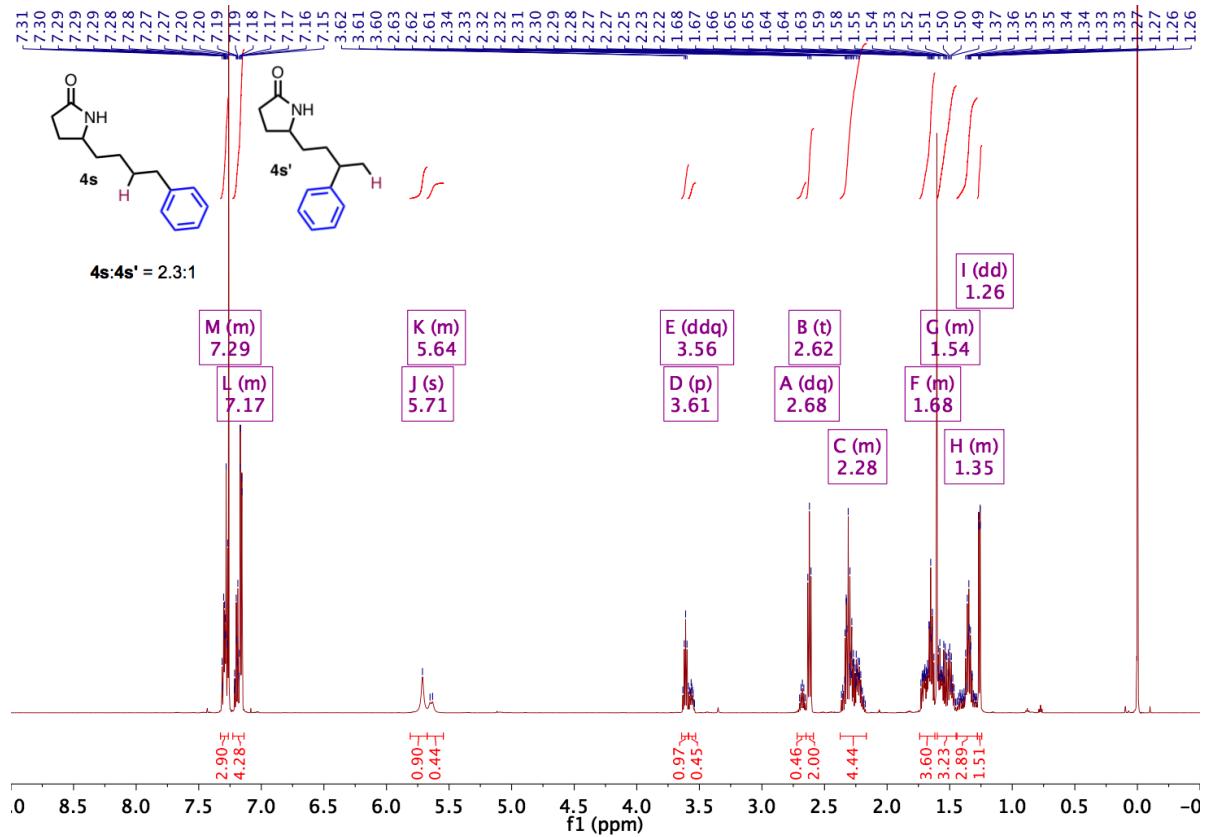


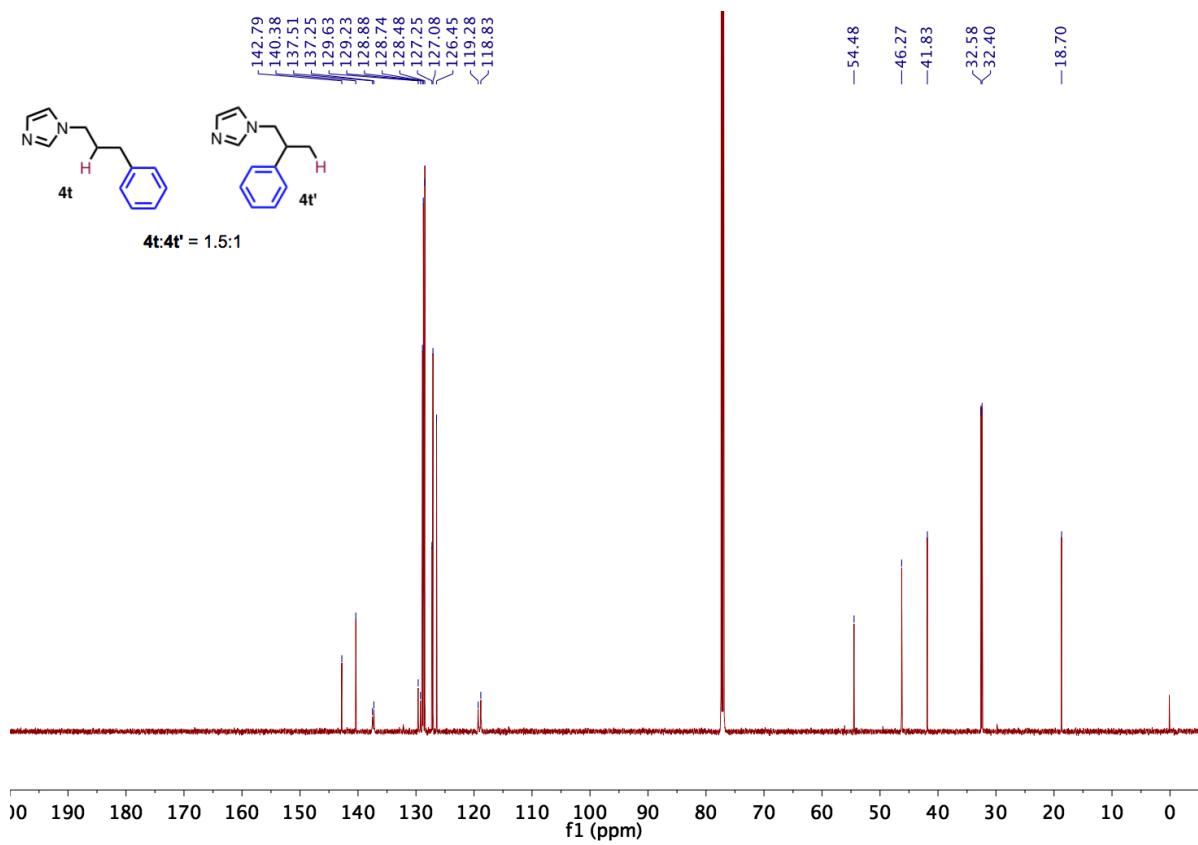
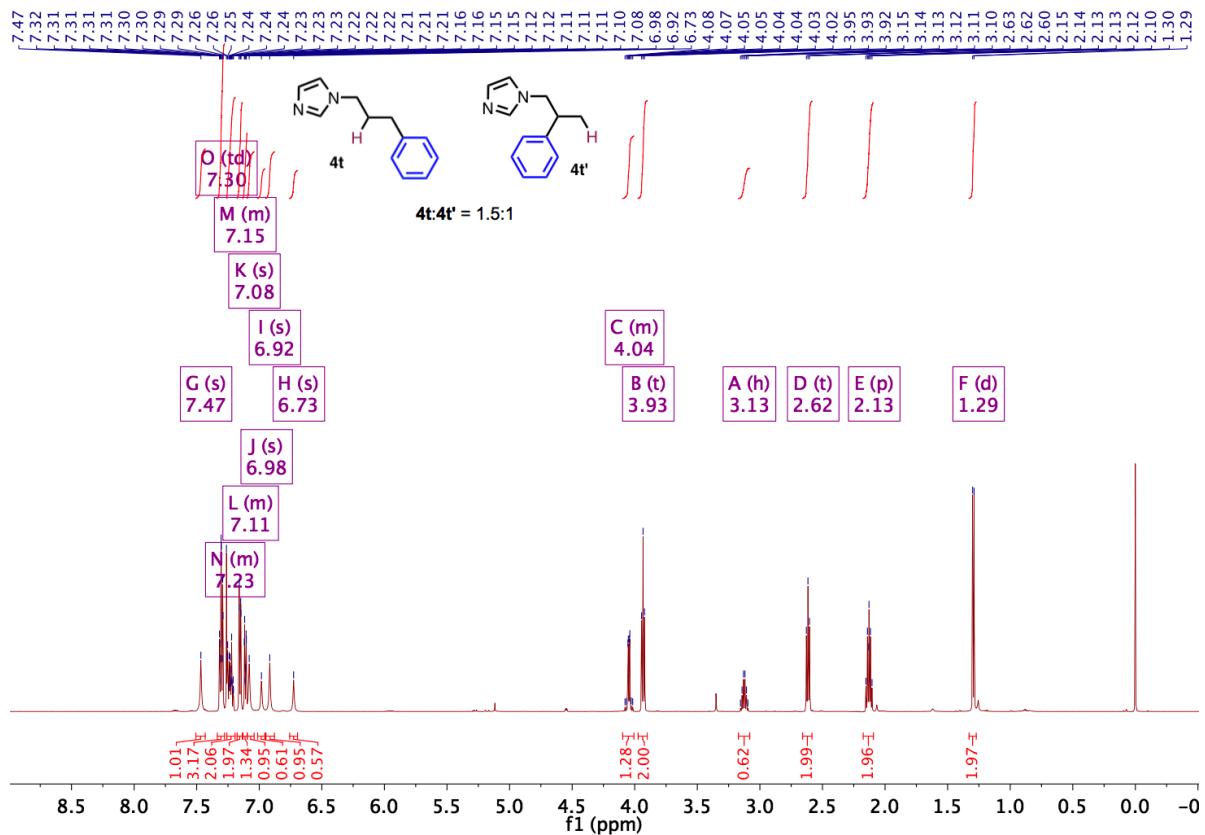


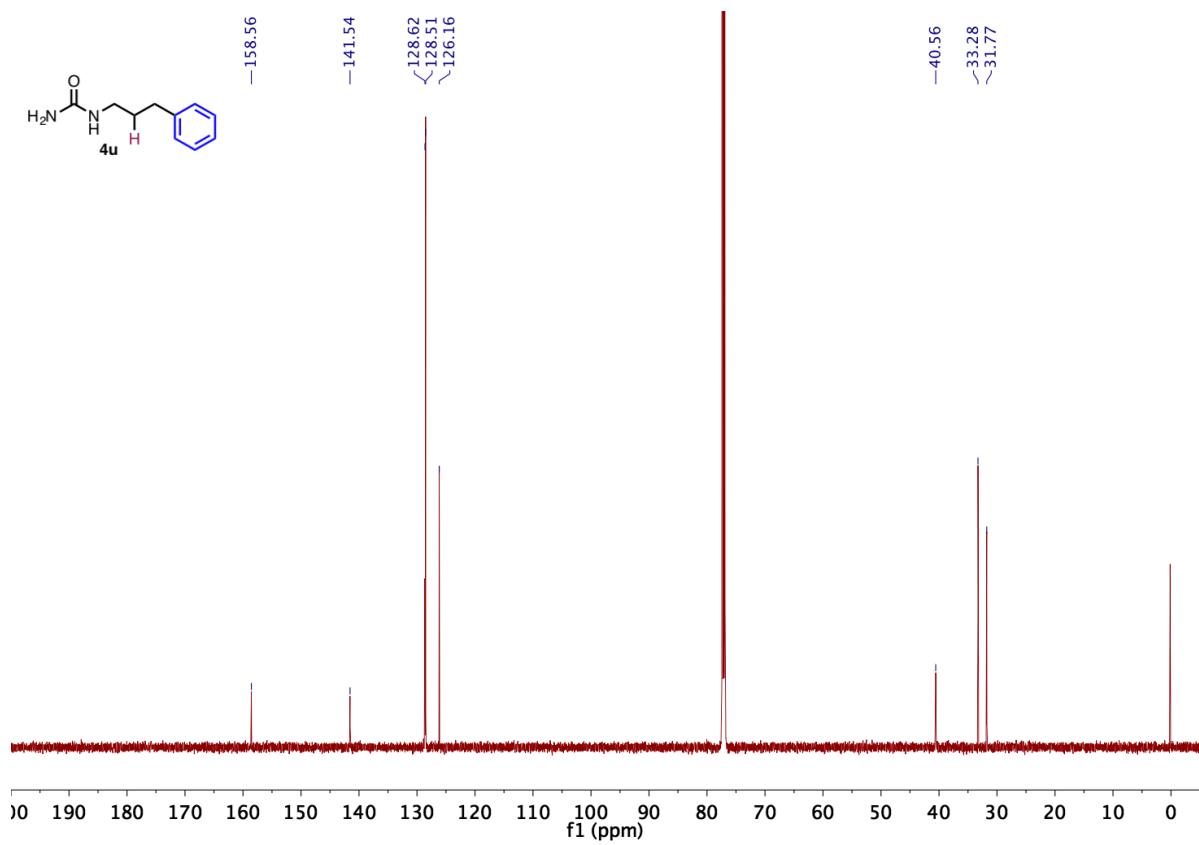
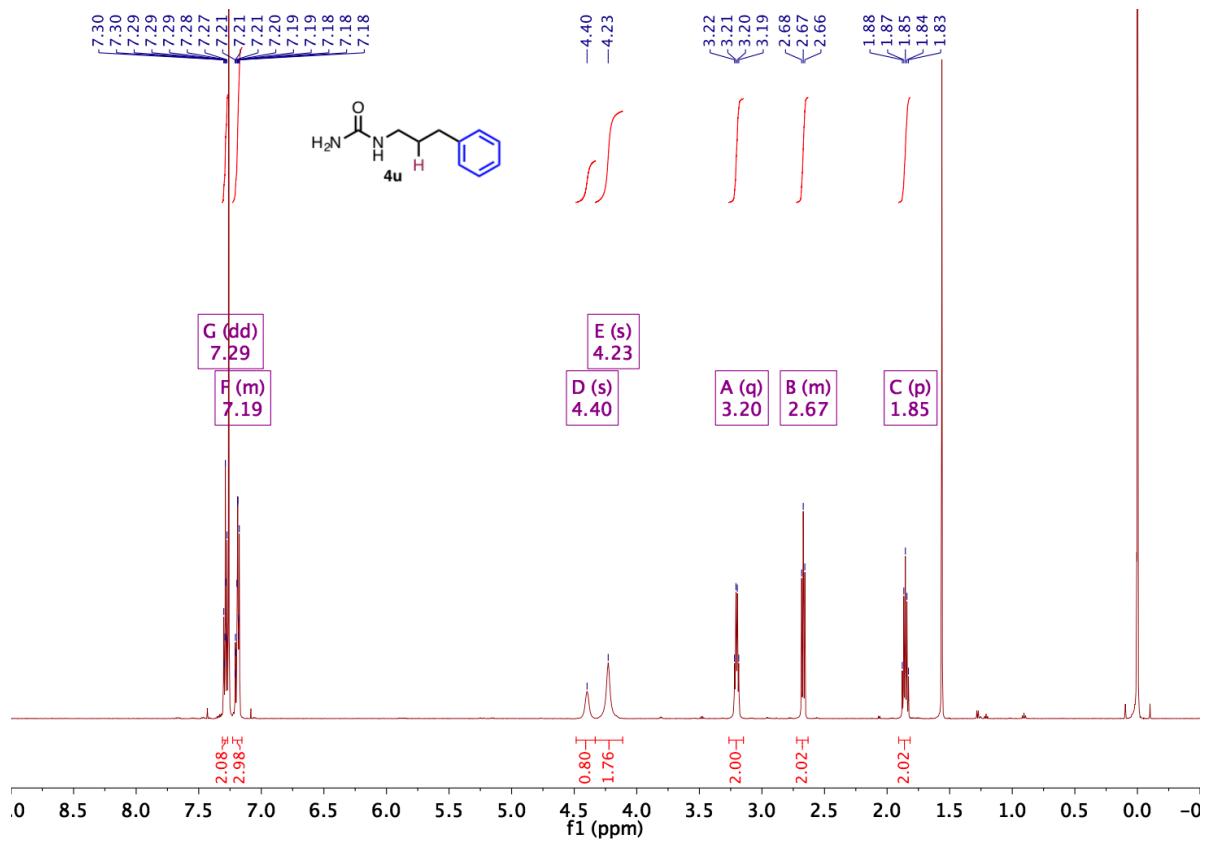


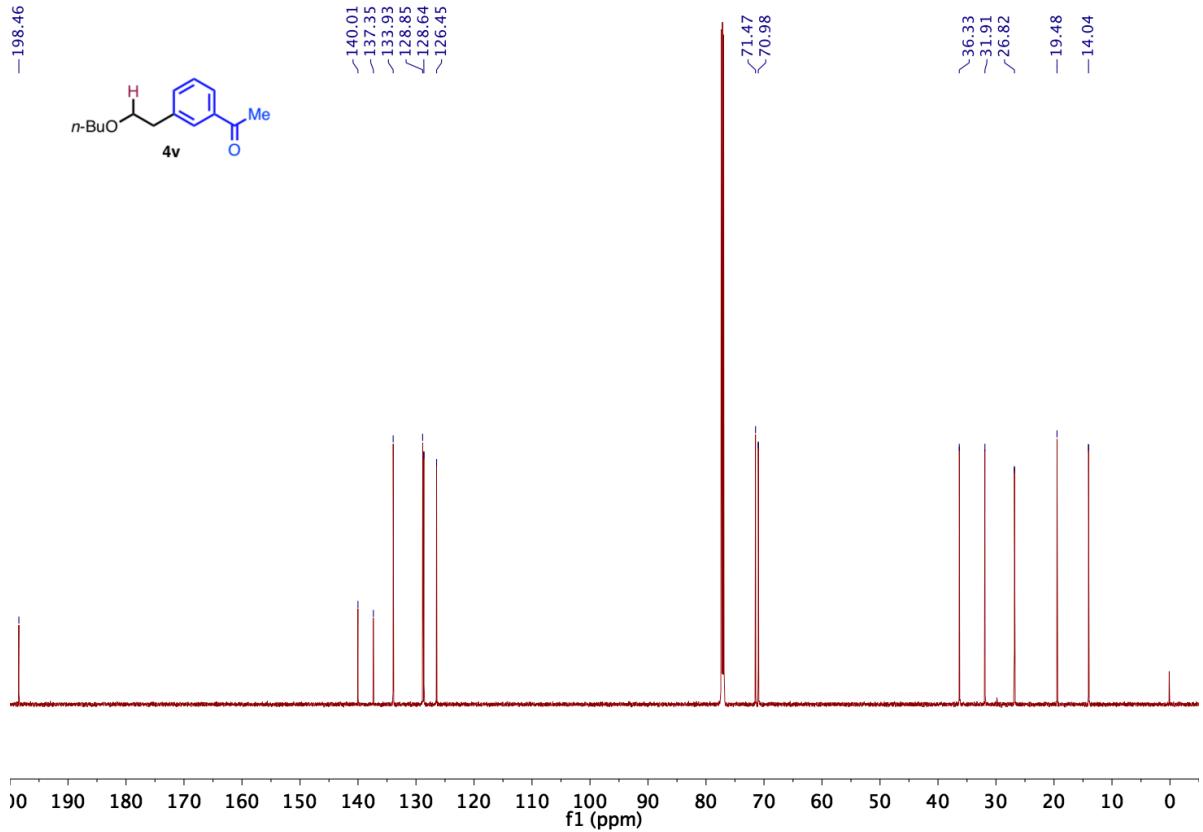
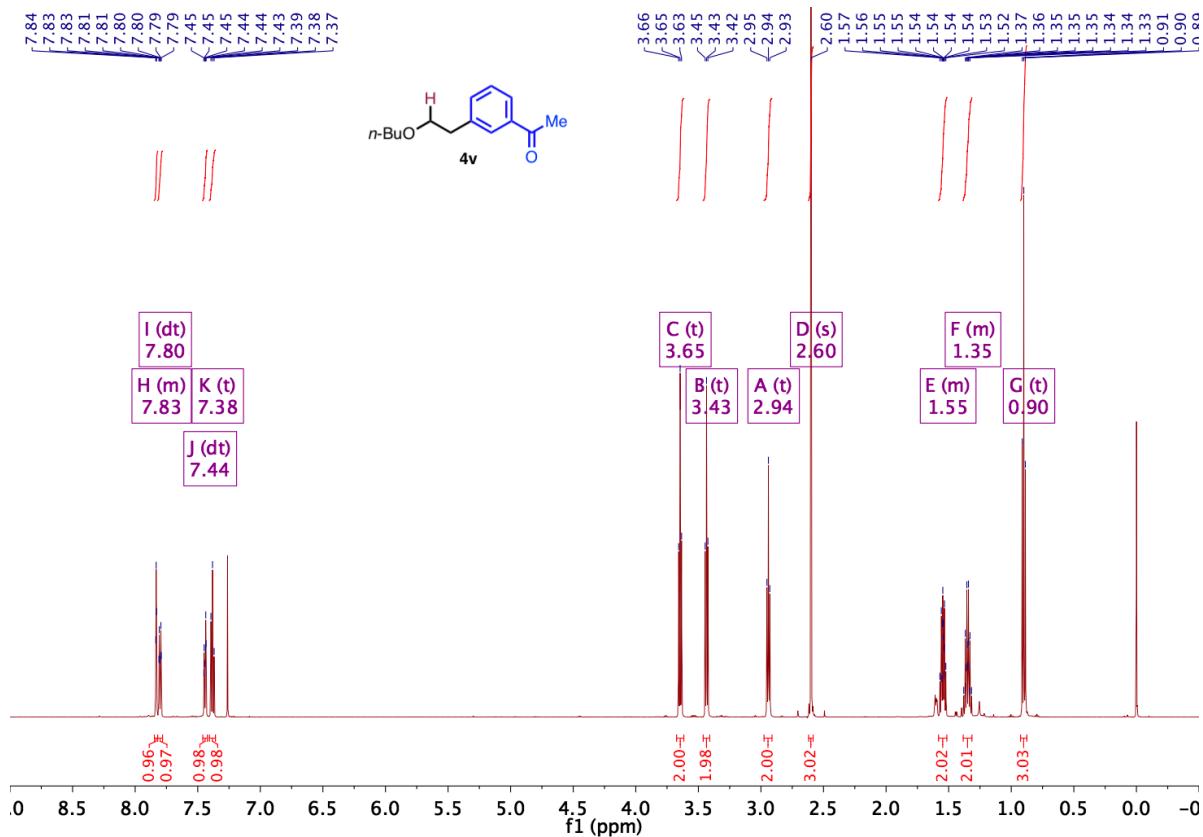


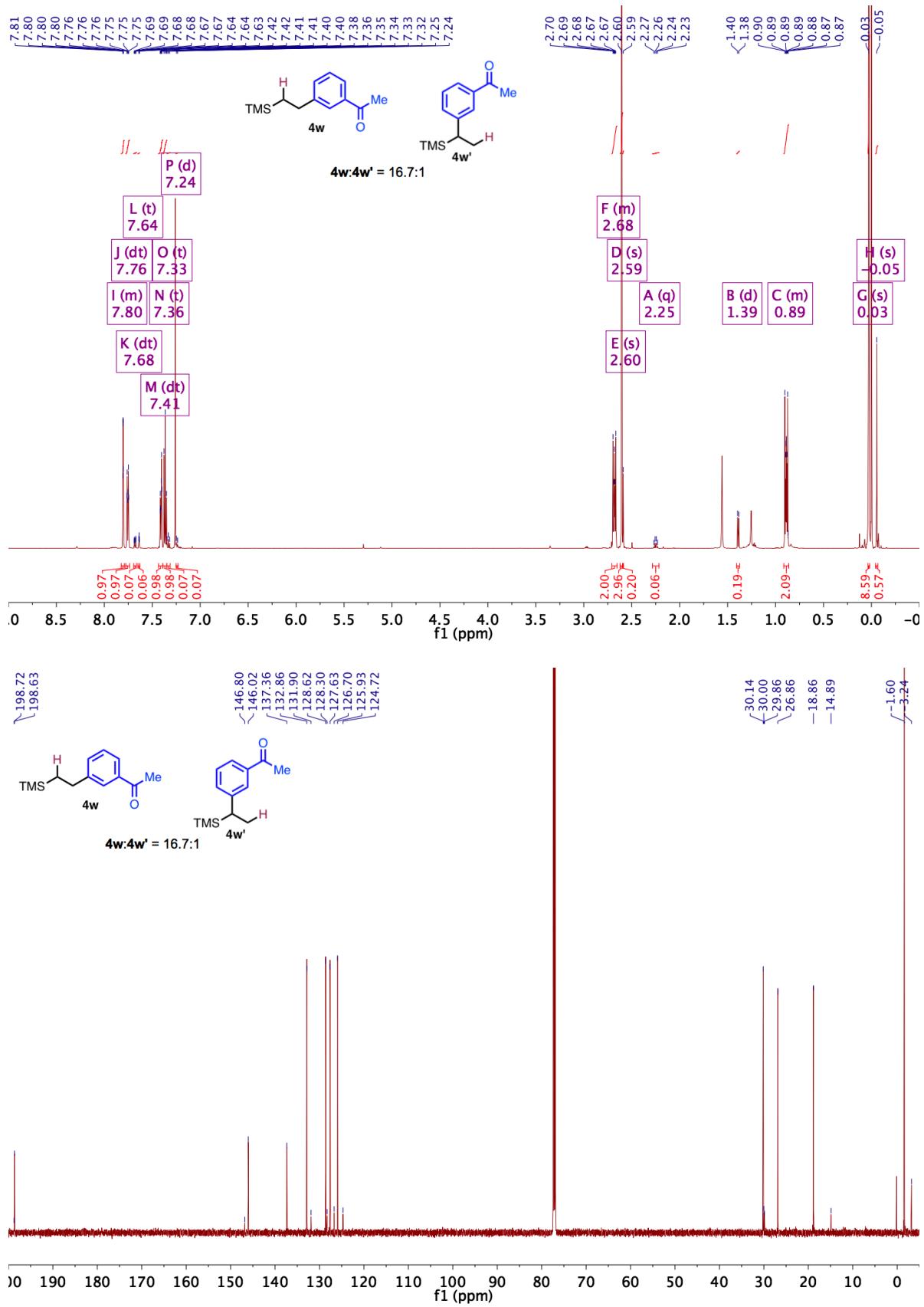


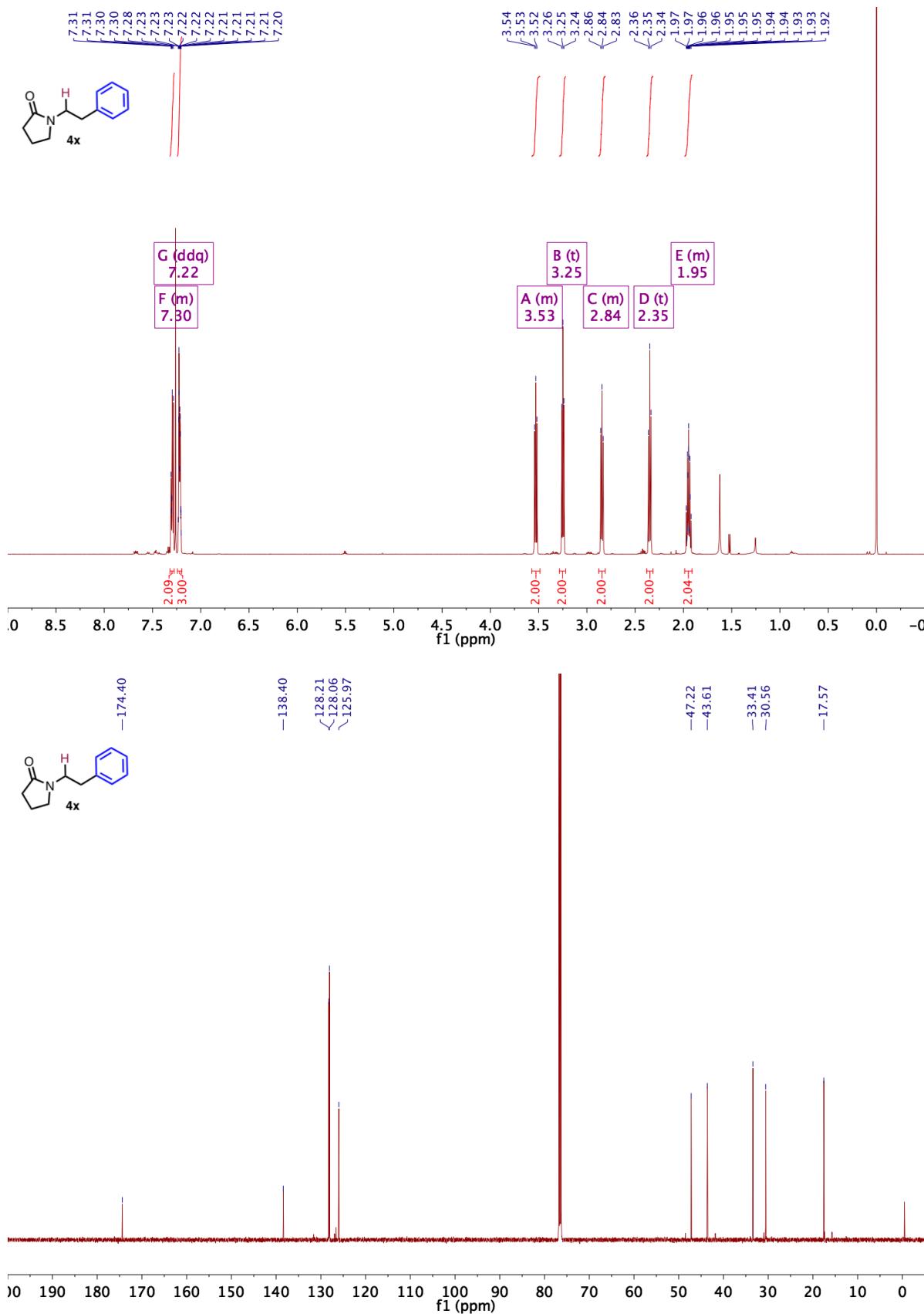


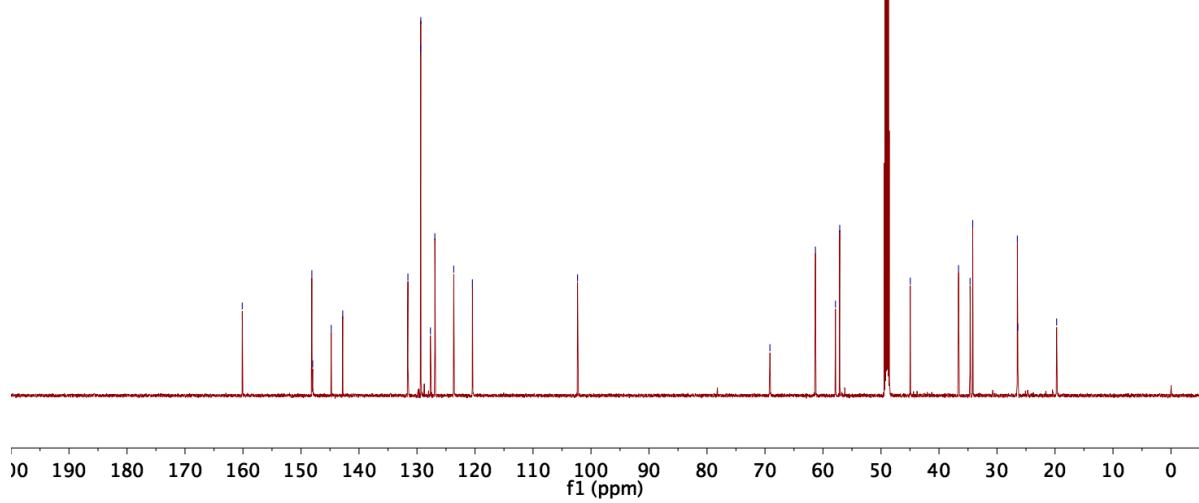
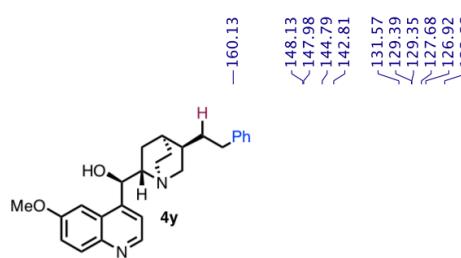
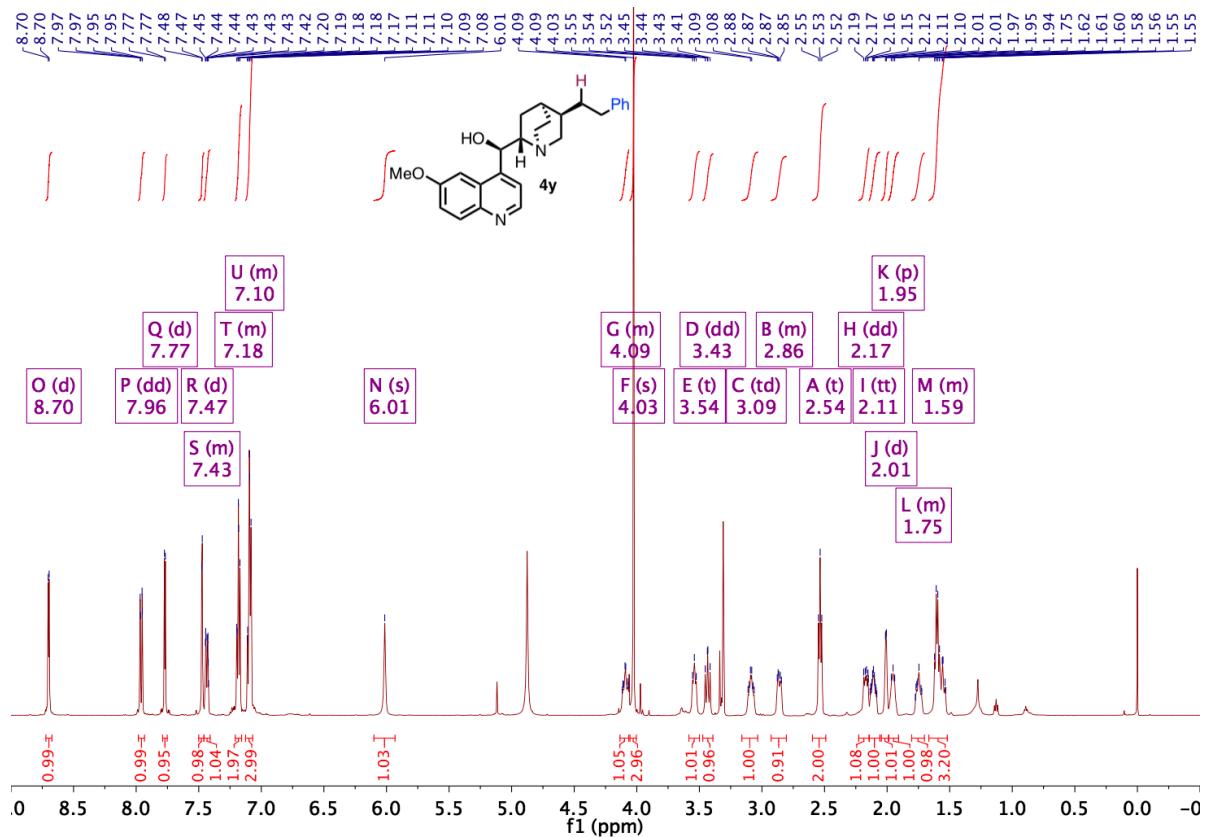


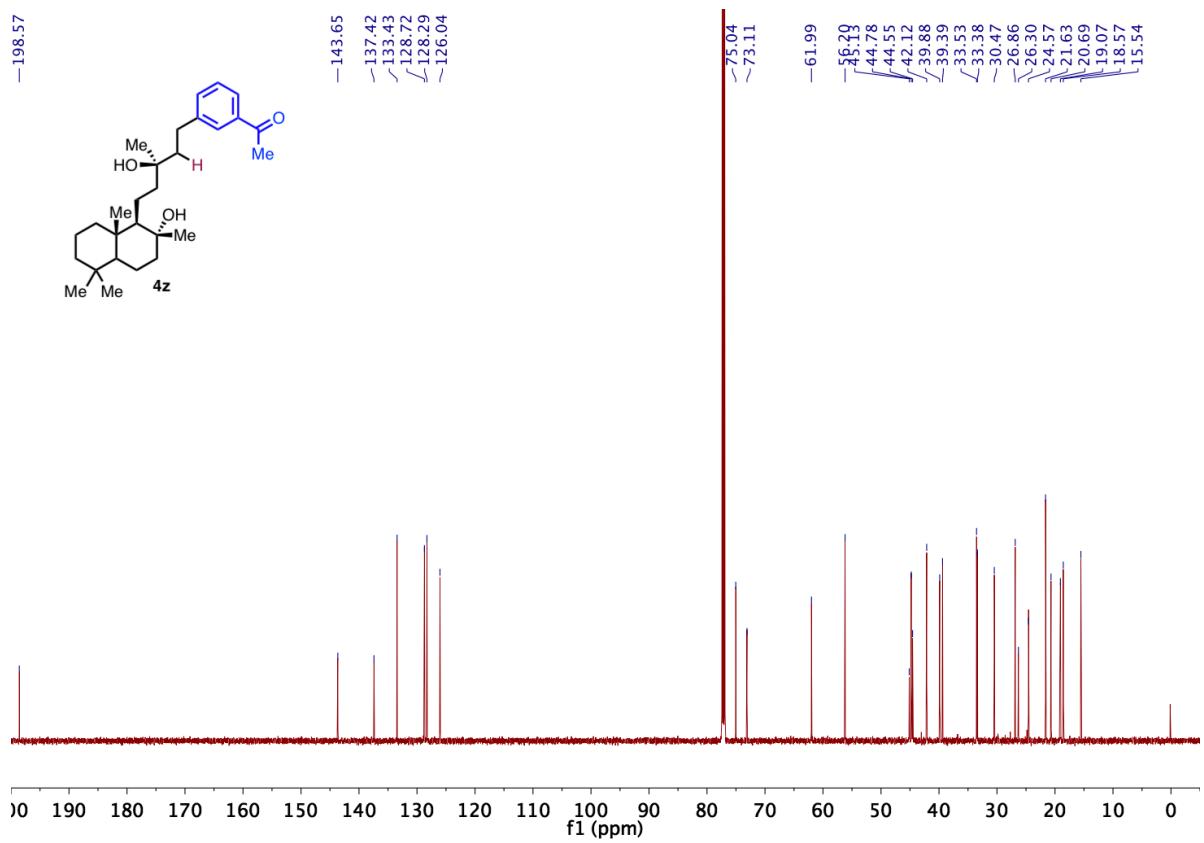
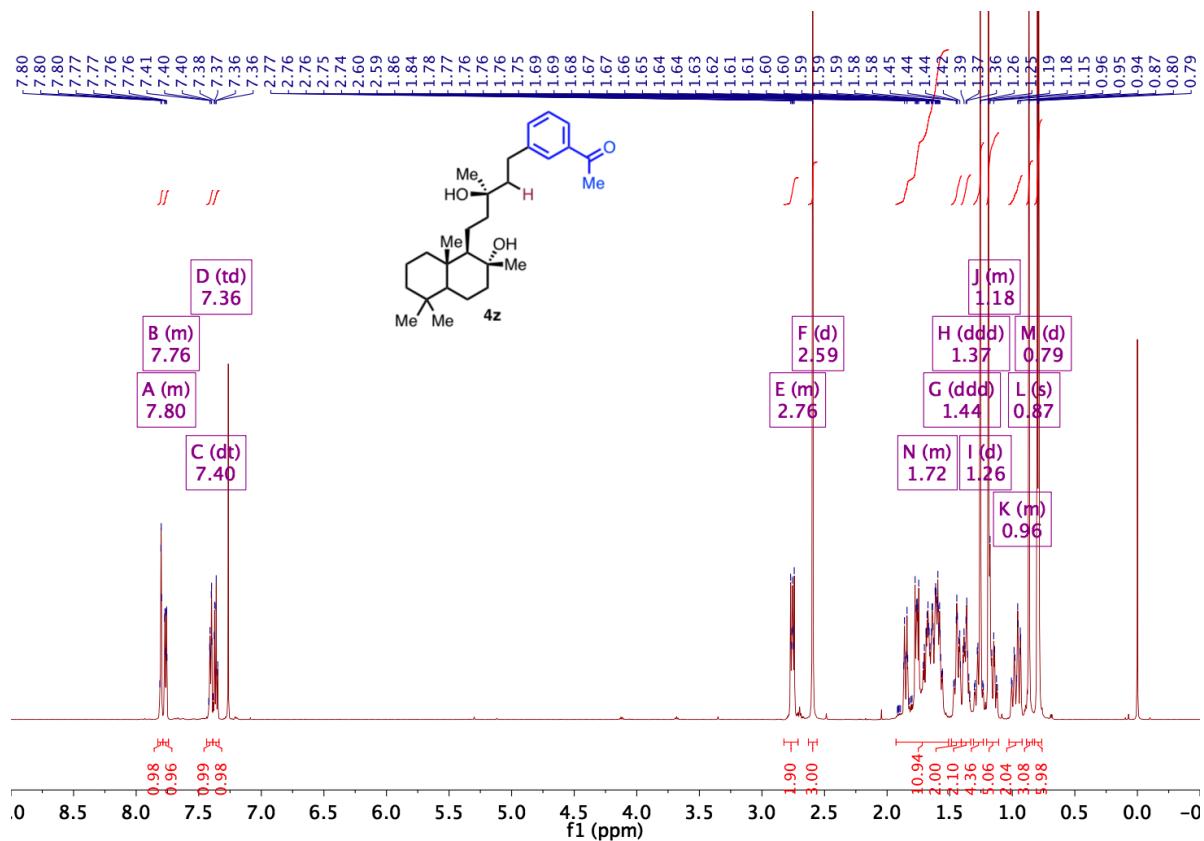


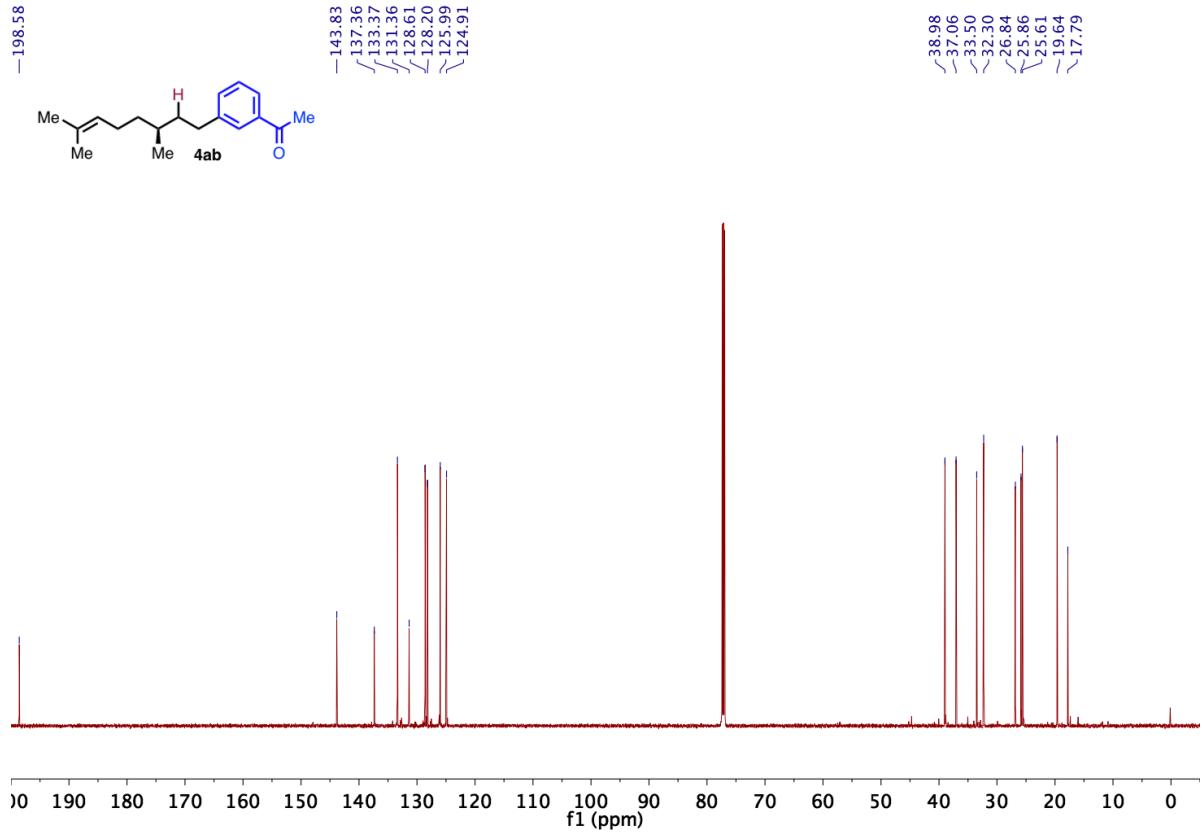
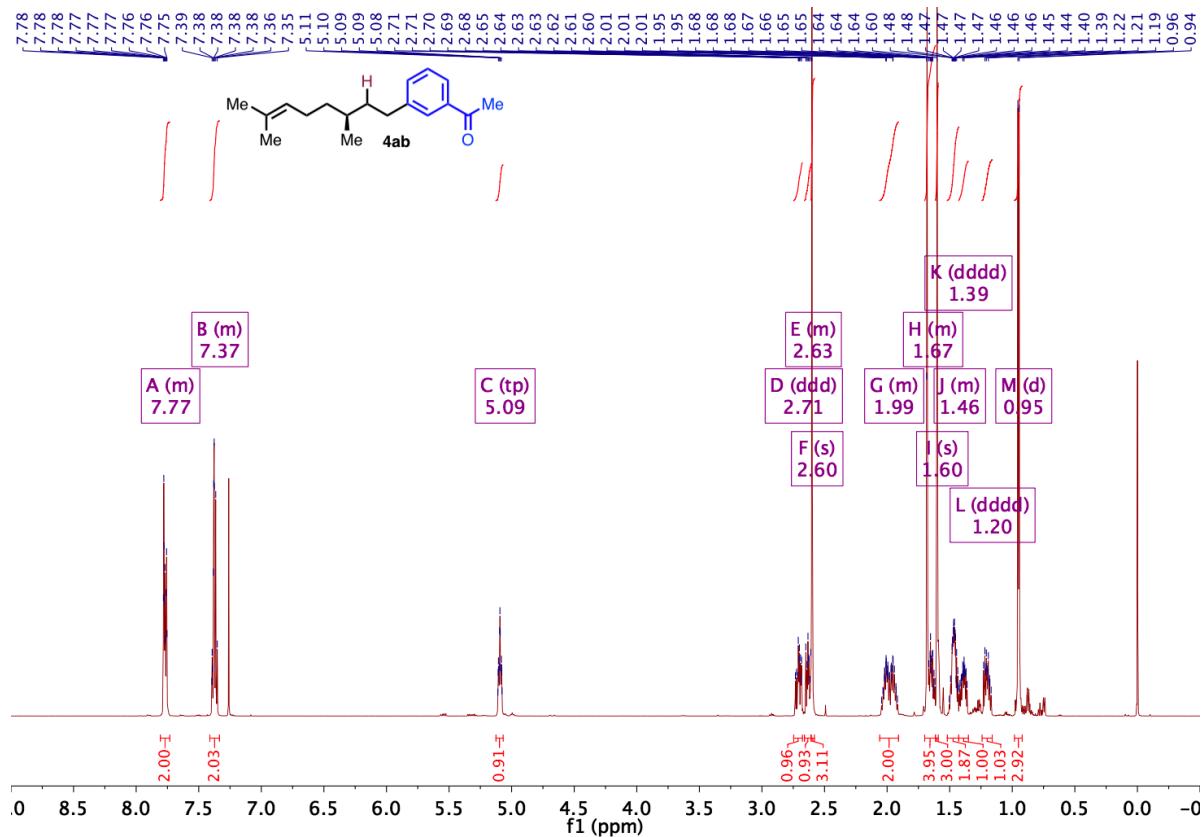


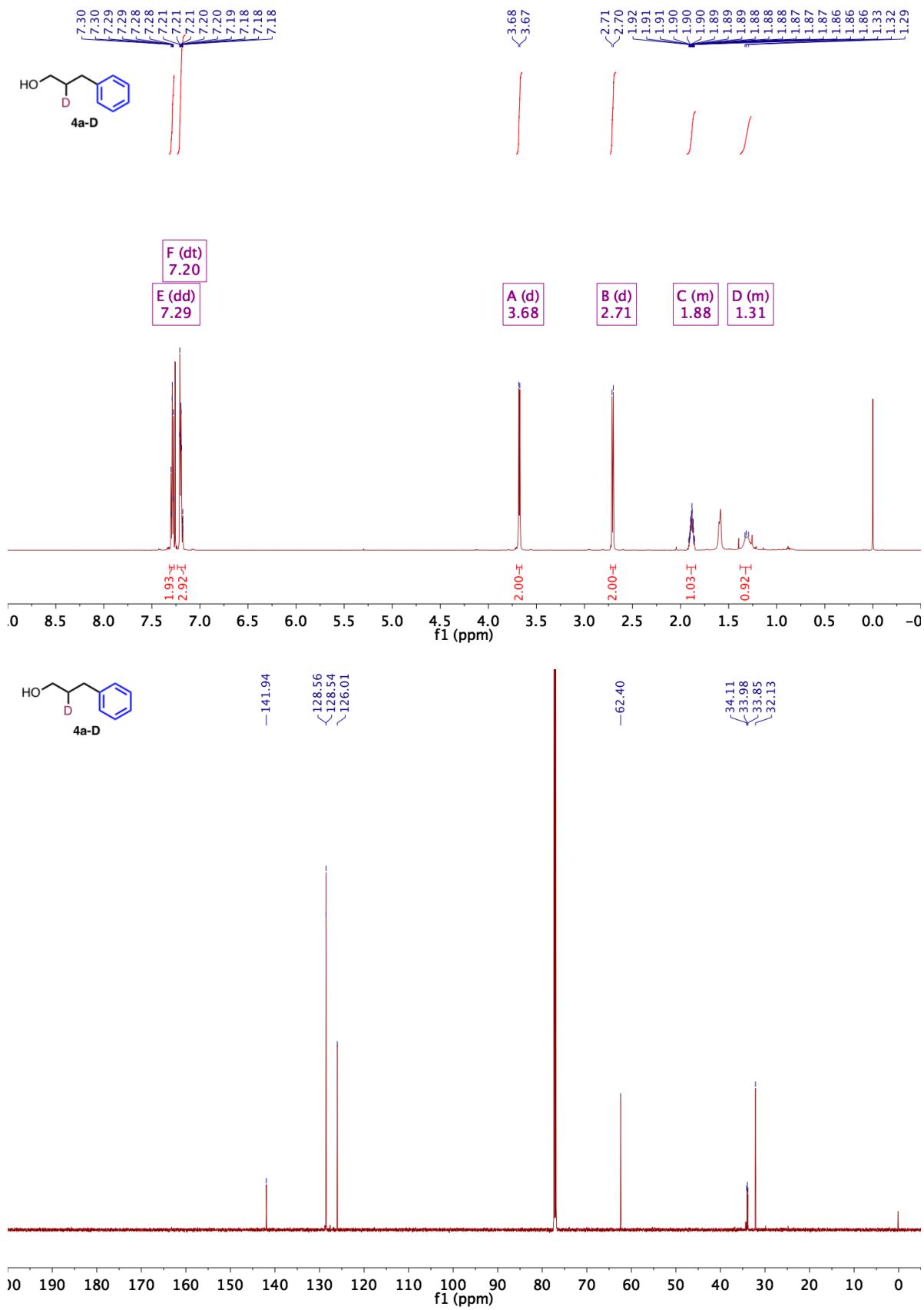












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