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The aromatic Claisen rearrangement is a powerful sigmatropic reaction which unfortunately lacks regioselectivity. In this work, various tetralone-based imine derivative substrates featuring an intramolecular base were investigated to better understand the potential role of the tautomerization step in aromatic Claisen rearrangement regioselectivity. High regioselectivity (> 85%) for the more sterically hindered *versus* the less sterically hindered position was observed for a methyl oxime and for aliphatic imines. Despite steric hindrance, the allyl aryl ether's *meta* substituent was found to have a significant electronic effect towards regioselectivity. As selectivity is one of the greatest challenges in organic synthesis, our research findings aim to tackle this challenge in the context of *ortho*-alkylation. Continued experiments which investigate the aromatic Claisen rearrangement regioselectivity of imine derivatives such as hydrazones are currently in progress.

INTERNAL BASE-DIRECTED REGIOSELECTIVE AROMATIC CLAISEN REARRANGEMENTS OF IMINE DERIVATIVES

by

Runzi Li

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Approved by

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APPROVAL PAGE

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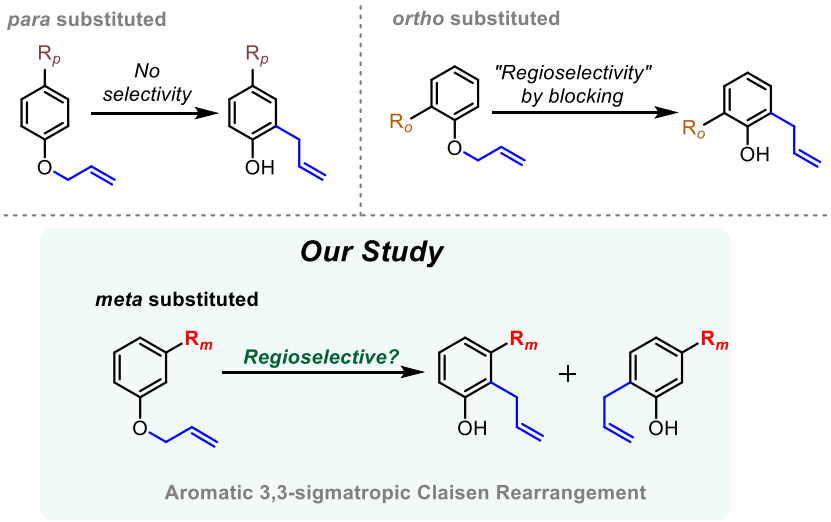
CHAPTER I: INTRODUCTION

Carbon-carbon bond formations are essential for synthetic organic chemistry. One such example, the aromatic Claisen rearrangement, is a classic 3,3-sigmatropic rearrangement which was discovered in 1912 in which an allyl aryl ether converts to an *ortho*-allyl phenol (**Figure 1**).[1] Unfortunately, despite its utility in organic synthesis, including the syntheses of natural products, the aromatic Claisen rearrangement typically lacks regioselectivity for *nonsymmetrical* allyl aryl ether systems.[2-5] Reports of the aromatic Claisen rearrangement in literature, therefore, typically utilize *symmetrical* systems with no substitution or only *para* substitution (**Figure 1**, top left panel), eliminating the concern for *ortho*-regioselectivity.[6-8] Alternatively, literature reports may use *ortho* substituents to block off one of the available sites, forcing "regioselective" allyl migration to the open site (**Figure 1**, top right panel).[9]

Figure 1. Project overview: Regioselective aromatic Claisen rearrangement directed by an internal base meta to the allyl aryl ether starting material's allyloxy substituent.

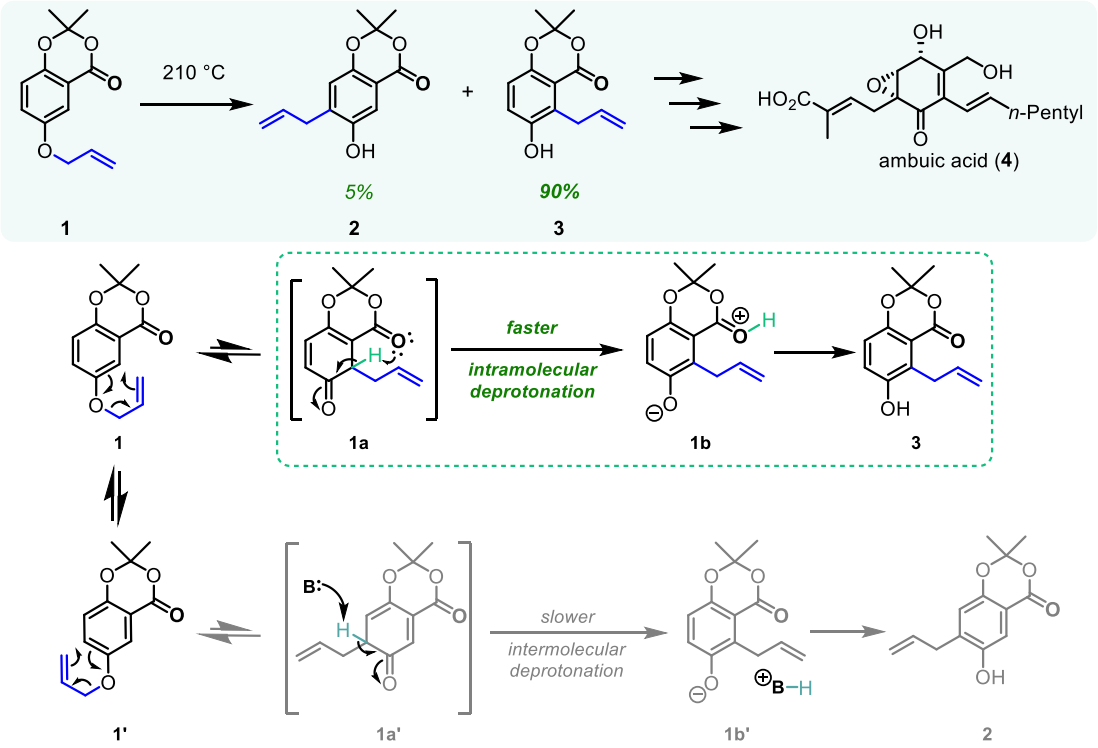


Meta substituents are generally avoided when selecting aromatic Claisen rearrangement substrates due to their introduction of asymmetry, and thought to only affect regioselectivity by

steric effects (presumably directing allyl migration to the less sterically hindered site, *i.e.*, the site farther away from the steric bulk of the *meta* substituent). For example, in a recent report studying Claisen rearrangement regioselectivity in ionic liquids, Han *et al*. reported regioselectivities of up to 2.4:1 ratios favoring the less sterically congested aromatic Claisen product.[10]

Surprisingly, the opposite regioselectivity was observed during the Croatt group's efforts to synthesize ambuic acid (**Figure 2**) – the aromatic Claisen rearrangement of lactone **1** selectively yielded the more sterically congested product (**3**) at a 20:1 ratio, in high yield.[11]

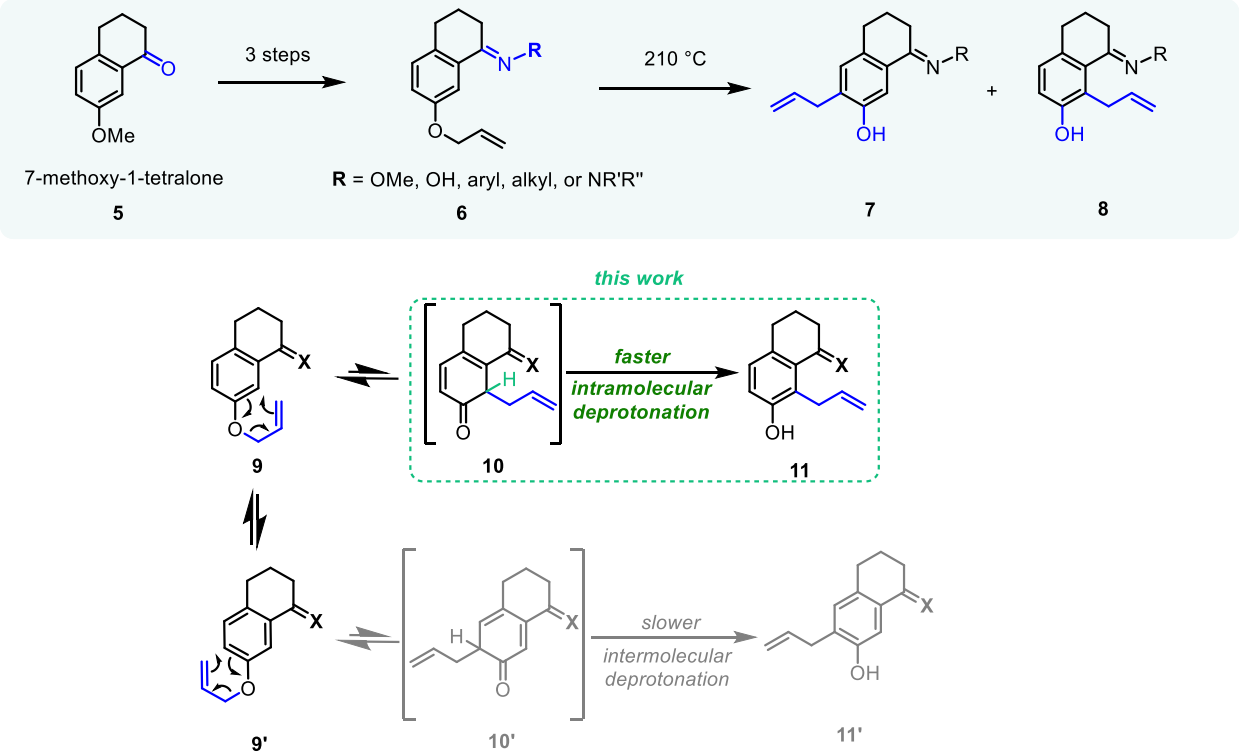
Figure 2. Proposed mechanism for the aromatic Claisen rearrangement of lactone 1 towards the total synthesis of ambuic acid (4).[11]



Our rationalization for the observed selectivity focuses on the tautomerization step of the reaction mechanism and is the basis for this work (**Figure 2**). We hypothesize that despite steric hindrance, an internal base at the *meta* position (*e.g.*, "**X**" in **Figure 3**, or the lactone carbonyl of

1 in **Figure 2**) could aid in the keto-enol tautomerization step from **10** to **11**. Because the tautomerization from **10** to **11** (or **10'** to **11'**) can be approximated as "irreversible" processes due to strong aromatic preference for the phenol product, the faster tautomerization of **10** to **11** (*vs.* **10'** to **11'**) would effectively remove one of the two γ,δ-unsaturated ketone intermediates (**10**) from the equilibrium and direct the regioselectivity of the aromatic Claisen rearrangement.

Figure 3. (*Top*) Overview: internal base-directed regioselective aromatic Claisen rearrangements of imine derivatives. (*Bottom*) Aromatic Claisen rearrangement intermediates. Note that the top route is proposed to involve a faster keto-enol tautomerization step due to the presence of an internal base X.



To tackle the regioselectivity challenges of nonsymmetrical Claisen systems, this work investigated aromatic Claisen rearrangement regioselectivity which is proposed to be directed by an intramolecular base at the *meta* position (**Figures 1** and **3**). Based on preliminary data collected

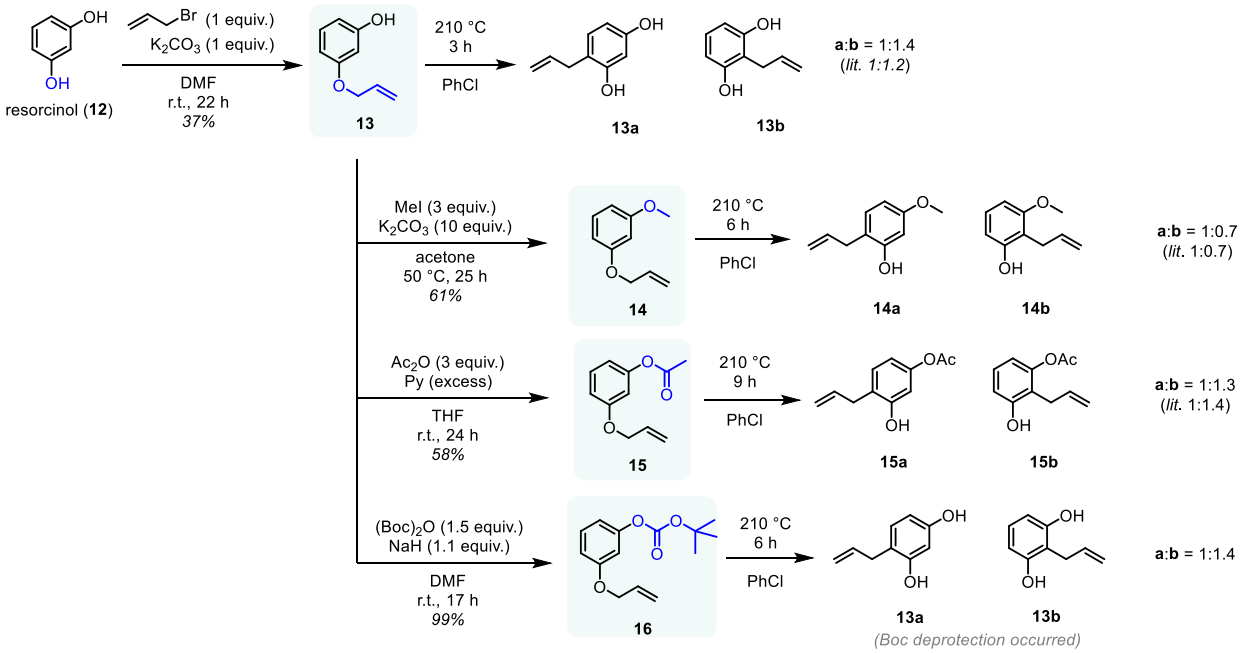
by our group which suggests correlation between a *meta*-internal base and high (> 90%) aromatic Claisen rearrangement regioselectivity (**Figure 2**),[11] this work tested the central hypothesis that an intramolecular base at the *meta* position could influence the keto-enol tautomerization step of the aromatic Claisen rearrangement reaction mechanism, thus removing one of the two γ,δ-unsaturated ketone intermediates from the equilibrium and directing the regioselectivity of the aromatic Claisen rearrangement. Specifically, the syntheses and regioselectivity investigations of various aromatic Claisen rearrangement substrates featuring an imine-derived internal base were conducted (see **Figure 3**).

CHAPTER II: RESULTS AND DISCUSSION

Method Validation: Resorcinol Derivatives.

To verify the method validity, various aromatic Claisen rearrangement substrates featuring an internal base at the *meta* position that have previously been reported in the literature were prepared and tested, then compared with their literature regioselectivity values. As shown in **Figure 4**, commercially available resorcinol (**12**) was used to prepare various substrates featuring an oxygen-based intramolecular base in one to two steps. The observed aromatic Claisen rearrangement regioselectivity for substrates **13-15** agreed well with the reported literature values (**Figure 4**).[12] Notably, substrate **16**, the *tert*-butyloxycarbonyl ("Boc") protected analog of phenol **13**, underwent Boc-deprotection under the Claisen reaction conditions and displayed Claisen rearrangement regioselectivity like that of phenol **13**.

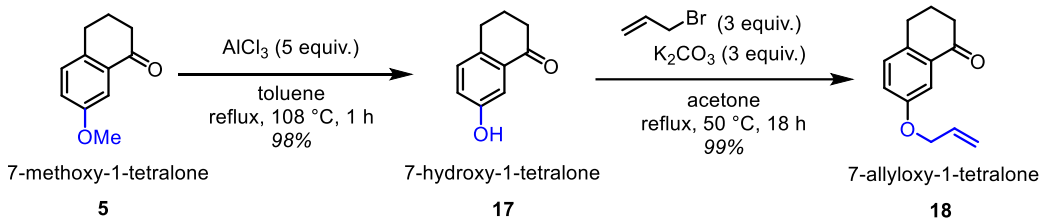
Figure 4. Method validation: Syntheses and aromatic Claisen rearrangement regioselectivity studies of resorcinol derivatives. Literature values taken from Ref. 12.



Tetralone Derivatives.

All target imine derivative substrates presented herein share the common starting material 7-allyloxy-1-tetralone (**18**). As outlined in **Figure 5**, commercially available bicycle **5** was first demethylated to produce phenol **17**, then cleanly allylated using allyl bromide and potassium carbonate to yield ketone **18**.

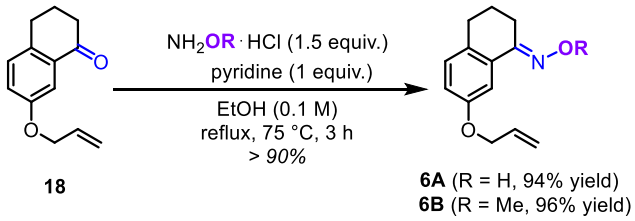
Figure 5. Synthesis of 7-allyloxy-1-tetralone (18).



Although the demethylation of **5** is reasonably straightforward and 90% yields were consistently obtained at the 2-5 g scale (an improvement from previously reported[13] ~80% yields at the 1 g scale), flash column purification initially proved difficult and time-consuming. The purification protocol was later modified to the current acid/base extraction method (see **Experimental** section), and up to a 98% yield was obtained (**Figure 5**). The new acid/base extraction purification protocol is less time intensive and produces less solvent waste, making it a greener and more scalable method for producing phenol **17** at high yield. The allylation of phenol **17** also utilizes an extraction-based purification method and consistently produces 95-99% yield at the 0.5 g scale (**Figure 5**), generating enough ketone **18** to proceed to the next step.

Oxime **6B** was prepared from the addition of methoxylamine to ketone **18** at 96% yield (**Figure 6**), an improvement from the previously reported 79% yield for this reaction.[13] Following a similar synthetic procedure, oxime **6A** was prepared from the addition of hydroxylamine to ketone **18** at 94% yield (**Figure 6**). Oxime **6A** was significantly more unstable and prone to hydrolysis than protected oxime **6B**, even when stored below room temperature.

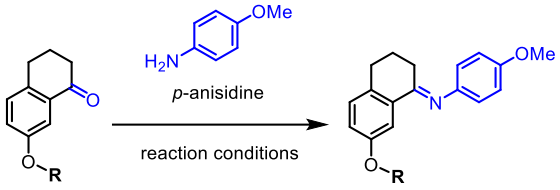
Figure 6. Synthesis of oximes.



Due to the water-sensitive nature of imines[14] (the ketone/aldehyde *vs*. imine equilibrium favors the ketone/aldehyde, especially at acidic pH), imine synthesis initially proved challenging. Imines **5A** and **6C** (**Table 1**) were selected as model substrates for developing a modular synthetic procedure for the target imine substrates, in part because the required amine starting material, *p*-anisidine (*i.e*., 4-methoxyaniline), is a colorimetric indicator for aldehydes and ketones in foods and oils due to its readiness to form imines. Despite over 20 attempts to prepare imines from *p*-anisidine (and either ketone **18** or test substrate **5** as the ketone starting material), the most successful attempt between entries 1-20 only generated the desired imine product **6C** in less than 30% yield (**Table 1**).

Parameters such as stoichiometry, reaction temperature (room temperature to 108 °C), solvent (toluene, trimethyl orthoformate,[15] or a combination of the two), acid catalyst (no catalyst, acetic acid, concentrated hydrochloric acid, or concentrated sulfuric acid), the presence or absence of 4 Å molecular sieves, as well as reaction time (from 15 minutes to 3 days) were adjusted, with entry 19 describing the most successful attempt until attempting the synthesis with 5 Å molecular sieves (**Table 1**). Because ^{1}H NMR spectra of the purified product fractions suggested significant side reaction products (presumably from product decomposition), the reaction temperature and/or reaction time were adjusted to increase yield, to no avail.

Table 1. Attempted Syntheses of Imines 5A and 6C.*



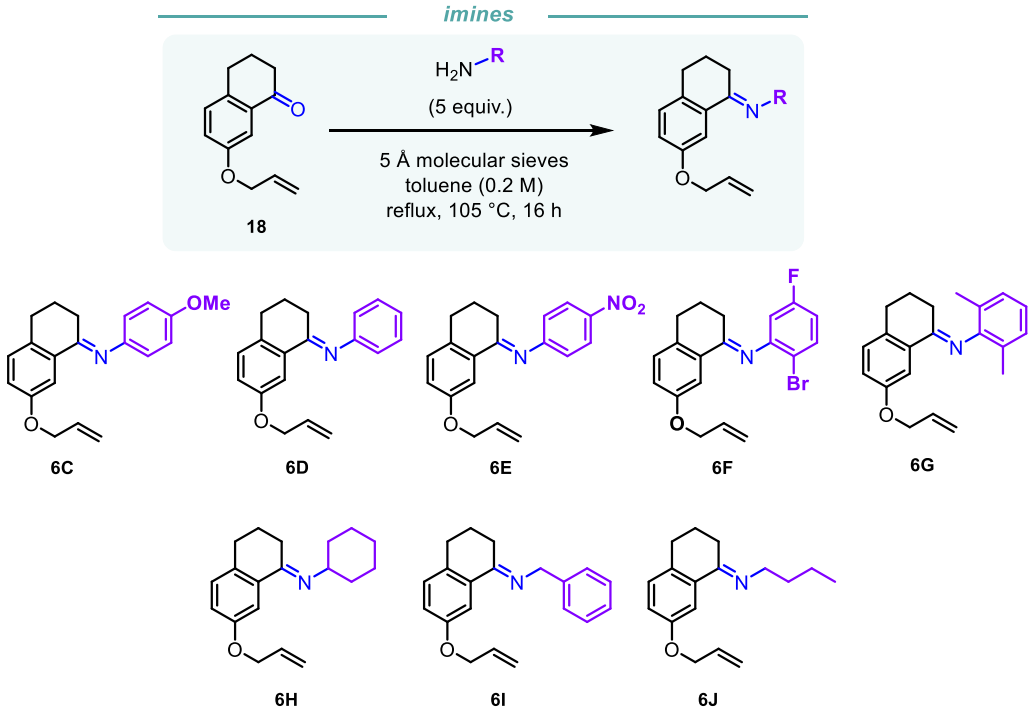
entry	R group	*p*-anisidine (equiv.)	cat. (equiv.)	drying agent(s)	solvent (conc.)	time (h)	temp. (°C)	% yield
1	allyl	1.0	-	4 Å molecular sieves	toluene (0.1 M)	20	108	n.d.
2	allyl	1.1	-	4 Å molecular sieves, trimethylorthoformate (5 equiv.)	toluene (0.2 M)	19	108	n.d.
3	allyl	1.1	-	trimethylorthoformate (10 equiv.)	toluene (0.2 M)	23	108	n.d.
4	Me	2.0	AcOH (0.05)	trimethylorthoformate (10 equiv.)	ethanol (1 M)	18	75	n.d.
5	Me	1.2	-	4 Å molecular sieves	toluene (0.2 M)	20	108	trace
6	Me	1.2	-	solvent	trimethylorthoformate (0.5 M)	20	r.t.	n.d.
7	Me	1.5	-	anhydrous Na_2SO_4	toluene (0.5 M)	90	17	n.d.
8	Me	1.5	-	solvent	trimethylorthoformate (0.5 M)	90	17	n.d.
9	Me	1.2	HCl (0.5)	trimethylorthoformate (10 equiv.)	toluene (0.5 M)	108	19	n.d.
10	Me	1.2	-	solvent	trimethylorthoformate (0.5 M)	> 24	98	n.d.
11	Me	1.2	H_2SO_4 (1.0)	solvent	trimethylorthoformate (0.5 M)	> 24	98	n.d.
12	allyl	1.2	H_2SO_4 (1.0)	solvent	trimethylorthoformate (0.5 M)	21	98	n.d.
13	allyl	1.2	H_2SO_4 (1.0)	solvent	trimethylorthoformate (0.5 M)	0.25	98	n.d.
14	allyl	1.2	AcOH (1.0)	solvent	trimethylorthoformate (0.2 M)	24	98	n.d.
15	allyl	1.2	-	solvent	trimethylorthoformate (0.25 M)	> 24	98	n.d.
16	Me	1.2	-	4 Å molecular sieves	toluene (0.5 M)	20	105	60%
17	Me	1.2	H_2SO_4 (1.0)	4 Å molecular sieves	toluene (0.5 M)	20	105	n.d.
18	Me	2.0	-	4 Å molecular sieves	toluene (0.5 M)	> 24	105	n.d.
19	allyl	1.5	-	4 Å molecular sieves	toluene (0.5 M)	17	105	trace
20	allyl	1.5	H_2SO_4 (1.0)	4 Å molecular sieves	toluene (0.25 M)	24	80	n.d.
21	allyl	5.0	-	5 Å molecular sieves	toluene (0.2 M)	16	105	62%
22	allyl	5.0	-	4 Å molecular sieves	toluene (0.2 M)	16	105	19%

* **Note:** "-" indicates no catalyst used; "n.d." indicates desired product not detected.

The synthesis of imine **6C** was only successful (54-62% yield) when the ketone and amine starting materials were refluxed overnight in the presence of 5 Å molecular sieves (entry 21). Under the same reaction conditions, except using 4 Å instead of 5 Å molecular sieves, the imine yield decreased dramatically to 19% (compare entries 21 and 22 in **Table 1**). This observation that the type of molecular sieve used (*e.g.*, 4 Å *vs.* 5 Å) can have a significant effect on the yield of molecular sieve-mediated ketimine syntheses is consistent with a recent literature report by Yasukawa *et al.*[16]

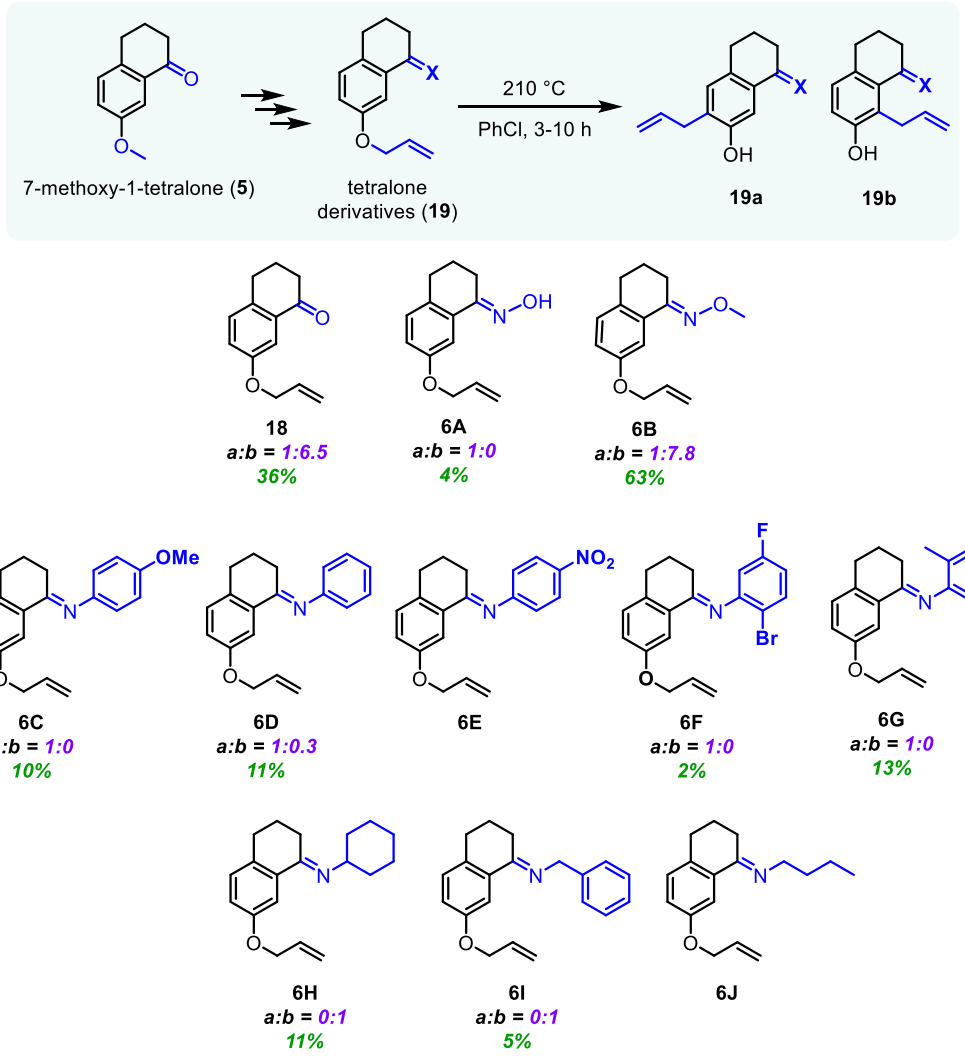
Following the most successful attempt in **Table 1** (entry 21) as a general synthetic procedure, imine substrates **6C**-**6J** were prepared (**Figure 7**). Due to challenges with sample hydrolysis in the NMR solvent, imines **6E**, **6I**, and **6J** are currently being remade.

Figure 7. Synthesis of imines.



Ketone **18** and imine derivatives **6A**-**6J** (**Figure 8**) were then subjected to the aromatic Claisen rearrangement conditions for regioselectivity studies (**Figure 8**).

Figure 8. Aromatic Claisen rearrangement regioselectivity of tetralone derivatives. The product ratio (a:b) and the overall yield of both products for each substrate is listed under the corresponding substrate structure.



Note. Note that a product ratio of a:b = 1:0, for example, indicates that only product "a" was detected. The aromatic Claisen regioselectivity studies for imines 6E and 6J are currently in progress. After the aromatic Claisen rearrangement, the X group remained intact only for ketone 18 and oxime 6B. For all other substrates (6A and 6C-6J), only the hydrolyzed ketone products (*i.e.*, 18a and 18b) were observed and used for regioselectivity ratio determination.

Excitingly, ketone **18** and oxime **6B** displayed high (> 85%) product regioselectivity ratios of **a**:**b** equal to 1:6.5 and 1:7.8, respectively (**Figure 8**). As ketone **18** can be seen as a simplified model of lactone **1**, the original substrate for which we observed high aromatic Claisen rearrangement regioselectivity, the regioselectivity for ketone **18** (**a**:**b** = 1:6.5) was lower than that for lactone **1** (**a**:**b** = 1:20) but still significantly higher than the approximate 1:1 regioproduct ratios which are typically reported for nonsymmetrical aromatic Claisen rearrangement substrates in the literature (*e.g.*, the most highly regioselective resorcinol derivative substrate in **Figure 4** only has **a**:**b** = 1:1.4).

For the moisture-sensitive substrates oxime **6A** and imines **6C**, **6D**, and **6F**-**6I**, only the hydrolyzed ketone products (*i.e.*, **18a** and **18b**) were detected as aromatic Claisen rearrangement products (**Figure 8**). For oxime **6A** and aromatic imines **6C**, **6D**, **6F**, and **6G**, reactivity at the less sterically hindered position (**a**) was the major or only product observed. For aliphatic imines **6H** and **6I**, only the more sterically congested product (**b**) was detected. Due to reproducibility challenges caused by sample hydrolysis during purification, the aromatic Claisen rearrangement regioselectivity of imines **6E**, **6I**, and **6J** are currently being reinvestigated.

CHAPTER III: EXPERIMENTAL

General Methods.

All chemicals were of commercially available grade and used without further purification, unless noted otherwise. Commercial ACS grade solvents such as ethyl acetate (EtOAc), tetrahydrofuran (THF), dimethylformamide (DMF), toluene (PhMe), and chlorobenzene (PhCl) were used for reactions, extractions, and chromatography. For moisture-sensitive reactions, solvents were purified by an Innovative Technologies solvent purification system, then stored over 4 Å activated molecular sieves under positive N_2 atmosphere for at least 72 h prior to use. Unless noted otherwise, all reactions were carried out under positive N_2 atmosphere using oven-dried glassware equipped with rubber septa. Reactions were monitored using analytical thin-layer chromatography (TLC) on silica gel- and/or basic alumina gel-coated plates. TLC visualization was assisted by 254 nm ultraviolet (UV) light irradiation. For the flash column purification of moisture-sensitive imines, the silica gel column was basified by adding 1-5% v/v triethylamine to all eluents, including during column packing.

Nuclear magnetic resonance (NMR) spectra were recorded either on a JEOL 400 or 500 MHz spectrometer, either in commercially purchased chloroform-*d*, acetone-d_6, or DMSO-d_6. NMR data are described as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, and m = multiplet and/or multiple resonances), coupling constant (*J*) in Hertz (Hz), and integration. Chemical shifts (δ) are given in parts per million (ppm) and referenced against NMR solvent residual protium shifts (*e.g.*, chloroform-*d* at δ = 7.26 ppm) for ^{1}H NMR, or referenced against NMR solvent carbon shifts (*e.g.*, chloroform-*d* at δ = 77.16 ppm) for ^{13}C NMR. High-resolution mass spectrometry (HRMS) spectra were performed on a Thermo Fisher Scientific UPLC/LTQ Orbitrap XL system with an electrospray

ionization source. To minimize sample hydrolysis, a direct infusion method was used for moisture-sensitive compounds. Single-crystal X-ray diffraction was performed on a Bruker Venture D8 equipped with dual Mo/Cu sealed sources, Oxford Cryosystems cold stream, and APEX shutterless pixel array detector.

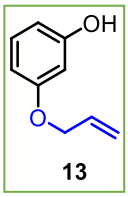
General Procedure for the Aromatic Claisen Rearrangement of Allyl Aryl Ethers.

In an oven-dried 10-mL Pyrex glass microwave vial equipped with a magnetic stir bar, 0.2 to 0.5 mmol of the allyl aryl ether substrate was dissolved in 2 to 5 mL of dry chlorobenzene. The vial was sealed using a plastic cap, then heated at 210 °C for 3 to 10 h using a microwave reactor. The reaction progression was monitored at one- or three-hour intervals using TLC (silica gel and/or basic alumina gel) and ^{1}H NMR. Samples for ^{1}H NMR reaction monitoring were prepared by directly taking a 100-μL aliquot of the reaction mixture at the appropriate time point, evaporating under reduced pressure, then redissolving in chloroform-*d*.

To quantify the aromatic Claisen rearrangement product ratios (**a**:**b**), the crude reaction mixture was evaporated under reduced pressure immediately after reaction completion, then analyzed by ^{1}H NMR (chloroform-*d*). The products were purified by silica gel flash column purification for characterization.

Resorcinol Derivatives.

Allyl aryl ether 13.



Commercial resorcinol (1.50 g, 13.6 mmol) and K_2CO_3 (1.88 g, 13.6 mmol) were stirred in 65 mL of dry acetone. Allyl bromide (1.2 mL, 14 mmol) was added dropwise, and the reaction mixture was heated at 50 °C for 22 h. The reaction mixture was evaporated under reduced pressure, redissolved in EtOAc, then extracted using water and EtOAc (× 3). The combined EtOAc extracts were washed with brine, dried over Na_2SO_4, then

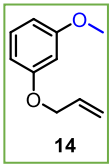
evaporated under reduced pressure. Purification was performed on a silica column (10% EtOAc:hexanes, isocratic) to yield allyl aryl ether **13** as a pale-yellow oil. ^{1}H NMR data agrees with previously reported literature values.[17]

Yield: 732 mg, 37%.

R_f = 0.17 (silica TLC, 10% EtOAc:hexanes).

^{1}H NMR (chloroform-*d*, 400 MHz): δ 7.17 – 7.08 (m, 1H), 6.55 – 6.48 (m, 1H), 6.46 – 6.39 (m, 2H), 6.05 (ddt, *J* = 17.1, 10.5, 5.3 Hz, 1H), 5.46 – 5.36 (m, 1H), 5.29 (dd, *J* = 10.5, 1.7 Hz, 1H), 4.83 (broad s, 1H), 4.51 (dt, *J* = 5.4, 1.6 Hz, 2H).

Allyl aryl ether 14.



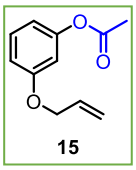
Allyl aryl ether **13** (150 mg, 0.999 mmol), K_2CO_3 (1.380 g, 9.99 mmol), and methyl iodide (0.19 mL, 430 mg, 3.0 mmol) were stirred in 5 mL of dry acetone at 50 °C for 25 h. The reaction mixture was evaporated under reduced pressure, redissolved in EtOAc, then extracted using water and EtOAc (× 3). The combined EtOAc extracts were washed with brine, dried over Na_2SO_4, then evaporated under reduced pressure. Purification was performed on a silica column (10% EtOAc:hexanes, isocratic) to yield allyl aryl ether **14** as a clear, pale-yellow oil. ^{1}H NMR data agrees with previously reported literature values.[12]

Yield: 99.6 mg, 61%.

R_f = 0.61 (silica TLC, 10% EtOAc:hexanes).

^{1}H NMR (chloroform-*d*, 400 MHz): δ 7.18 (t, *J* = 8.2 Hz, 1H), 6.56 – 6.46 (m, 3H), 6.06 (ddt, *J* = 17.3, 10.5, 5.4 Hz, 1H), 5.42 (dt, *J* = 17.4, 1.6 Hz, 1H), 5.29 (d, *J* = 10.3 Hz, 1H), 4.56 – 4.49 (m, 2H), 3.79 (s, 3H).

Allyl aryl ether 15.



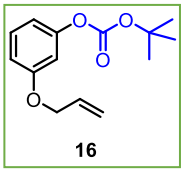
Allyl aryl ether **13** (140 mg, 0.932 mmol) was dissolved in pyridine (2.0 mL, 2.0 g, 25 mmol, excess) and THF (4 mL). After adding the acetic anhydride (265 μL, 2.80 mmol), the reaction mixture was stirred at room temperature for 24 h, quenched using saturated $NaHCO_3$ (aq.) solution, then extracted using water and EtOAc (× 3). (**Caution**: For workup procedures involving $NaHCO_3$, pressure buildup inside the separatory funnel can become dangerous. Remember to release pressure in the separatory funnel often.) The combined EtOAc extracts were washed with brine, dried over Na_2SO_4, then evaporated under reduced pressure. Purification was performed on a silica column (10% EtOAc:hexanes, isocratic) to yield allyl aryl ether **15** as a clear, pale-yellow oil. ^{1}H NMR data agrees with previously reported literature values.[12]

Yield: 112 mg, 58%.

$\boldsymbol{R}_f$ = 0.40 (silica TLC, 10% EtOAc:hexanes).

^{1}H NMR (chloroform-*d*, 400 MHz): δ 7.31 – 7.22 (m, 1H), 6.79 (dd, *J* = 8.3, 2.5 Hz, 1H), 6.72 – 6.63 (m, 2H), 6.04 (ddt, *J* = 17.3, 10.5, 5.3 Hz, 1H), 5.41 (dd, *J* = 17.3, 1.7 Hz, 1H), 5.29 (d, *J* = 10.5 Hz, 1H), 4.52 (d, *J* = 5.4 Hz, 2H), 2.29 (s, 3H).

Allyl aryl ether 16.



Adapted from the synthetic procedure for a similar Boc-protected alcohol.[18] Allyl aryl ether **13** (140 mg, 0.932 mmol), NaH (41 mg, 1.026 mmol), and di-*tert*-butyl dicarbonate (306 mg, 1.400 mmol) were mixed in 5 mL of DMF at room temperature for 17 h. The reaction mixture was stirred at room temperature for 24 h, quenched using cold water, then extracted using water and EtOAc (× 3). The combined EtOAc extracts were washed with brine, dried over Na_2SO_4, then evaporated under reduced pressure. Purification was

performed on a silica column (10% EtOAc:hexanes, isocratic) to yield allyl aryl ether **16** as a clear, pale-yellow oil.

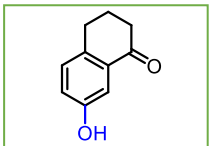
Yield: 233 mg, 99%.

R_f = 0.41 (silica TLC, 10% EtOAc:hexanes).

^{1}H NMR (chloroform-*d*, 400 MHz): δ 7.30 – 7.21 (m, 1H), 6.82 – 6.71 (m, 3H), 6.04 (ddt, *J* = 17.3, 10.5, 5.3 Hz, 1H), 5.41 (dd, *J* = 17.1, 1.8 Hz, 1H), 4.55 – 4.49 (m, 2H), 1.56 (s, 9H).

Tetralone Derivatives.

Phenol 17.



7-hydroxy-1-tetralone
17

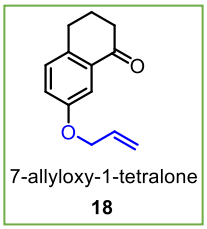
Very slowly and carefully, commercial 7-methoxy-1-tetralone (**5**; 2.0 g, 11 mmol) was added to a suspension of $AlCl_3$ (7.6 g, 57 mmol) in toluene (20 mL) over the course of 1 minute. The reaction mixture was heated at 108 °C for 1 h, then allowed to cool to room temperature. Very slowly and carefully, the reaction mixture was quenched using cool water (20 mL). (**Caution**: $AlCl_3$ is corrosive and reacts violently and exothermically with water to produce HCl gas. Wear a face mask when handling $AlCl_3$, and quench any residual $AlCl_3$ very slowly and carefully using water that is at room temperature or cooler.) The reaction mixture was extracted using water and EtOAc (× 3). The combined EtOAc extracts were extracted using 20% w/v NaOH (aq.) solution (× 3), and the combined aqueous extracts were then acidified to pH ~2 using 6 M HCl (aq.) solution, causing large amounts of the phenol product to precipitate. The acidified aqueous mixture was extracted using EtOAc (× 3), and the combined organic extracts were washed with brine, dried over Na_2SO_4, evaporated under reduced pressure, washed using hexanes (× 3), then further dried under vacuum to yield phenol **17** as a pale-brown, semicrystalline solid powder. ^{1}H NMR data agrees with previously reported values.[13]

Yield: 1.8 g, 98%.

R_f = 0.20 (silica TLC, 25% EtOAc:hexanes).

^{1}H NMR (acetone-d_6, 400 MHz): δ 8.47 (s, 1H), 7.39 (d, *J* = 2.6 Hz, 1H), 7.17 (d, *J* = 8.2 Hz, 1H), 7.02 (dd, *J* = 8.3, 2.7 Hz, 1H), 2.88 (t, *J* = 6.1 Hz, 2H), 2.55 (t, *J* = 6.5 Hz, 2H), 2.07 (quint, *J* = 6.5 Hz, 2H).

Ketone 18.



7-allyloxy-1-tetralone
18

Phenol **17** (400 mg, 2.466 mmol) and K_2CO_3 (1.023 g, 7.399 mmol) were stirred in 12.5 mL of dry acetone. Allyl bromide (0.9 mL, 9.865 mmol) was added dropwise, and the reaction mixture was heated at 50 °C for 14 h. The reaction mixture was evaporated under reduced pressure, redissolved in EtOAc, then extracted using water and EtOAc (× 3). The combined EtOAc extracts were washed with brine, dried over Na_2SO_4, then evaporated under reduced pressure, yielding ketone **18** as a pale-red solid. ^{1}H NMR data agrees with previously reported values.[13]

To obtain crystals for single-crystal X-ray diffraction (XRD), a solution of ketone **18** in 10% EtOAc:hexanes was allowed to slowly evaporate at room temperature in a small glass vial to produce clear, colorless crystals suitable for XRD.

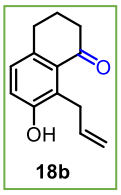
Yield: 499 mg, 99%.

R_f = 0.68 (silica TLC, 25% EtOAc:hexanes).

^{1}H NMR (chloroform-*d*, 400 MHz): δ 7.52 (d, *J* = 2.7 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 1H), 7.08 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.05 (ddt, *J* = 17.4, 10.6, 5.4 Hz, 1H), 5.42 (d, *J* = 17.4 Hz, 1H), 5.29 (d, *J* = 10.5 Hz, 1H), 4.57 (d, *J* = 5.2 Hz, 2H), 2.90 (t, *J* = 6.1 Hz, 2H), 2.63 (t, *J* = 6.5 Hz, 2H), 2.12 (quint, *J* = 6.2 Hz, 2H).

HRMS: m/z calculated for $[C_{13}H_{15}O_2]^+$ ($[M + H]^+$) 203.1067, found 203.1065.

Ketone 18b.

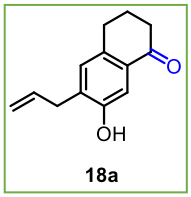


18b

Yield (from the aromatic Claisen rearrangement of ketone **18**): 24.4 mg, 31% (off-white solid). ^{1}H NMR data agrees with previously reported literature values.[13]

^{1}H NMR (chloroform-*d*, 400 MHz): δ 7.02 (m, 2H), 6.07 (ddt, *J* = 16.5, 11.4, 6.0 Hz, 1H), 5.69 (s, 1H), 5.14 – 5.04 (m, 2H), 3.90 (d, *J* = 5.9 Hz, 2H), 2.88 (t, *J* = 6.2 Hz, 2H), 2.64 (t, *J* = 6.6 Hz, 2H), 2.05 (p, *J* = 6.4 Hz, 2H).

Ketone 18a.

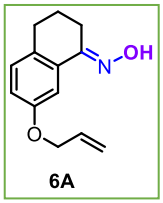


18a

Yield (from the aromatic Claisen rearrangement of ketone **18**): 3.8 mg, 5% (light-yellow solid). ^{1}H NMR data agrees with previously reported literature values.[13]

^{1}H NMR (chloroform-*d*, 400 MHz): δ 7.59 (s, 1H), 7.02 (s, 1H), 6.09 – 5.94 (m, 2H), 5.18 – 5.10 (m, 2H), 3.44 (d, *J* = 6.5 Hz, 2H), 2.87 (t, *J* = 6.1 Hz, 2H), 2.62 (t, *J* = 6.5 Hz, 2H), 2.10 (quint, *J* = 6.3 Hz, 2H).

Oxime 6A.



6A

Adapted from the reported synthetic procedure for a similar oxime.[19] Ketone **18** (130 mg, 0.643 mmol) and hydroxylamine hydrochloride (67 mg, 0.964 mmol) were mixed in 5 mL of dry ethanol. Pyridine (52 µL, 0.643 mmol) was added, and the reaction mixture was heated at 75 °C for 3 h. The reaction mixture was evaporated under reduced pressure, redissolved in EtOAc, then extracted using water and EtOAc (× 3). The combined EtOAc extracts were washed with brine, dried over Na_2SO_4, then evaporated under reduced pressure. Purification was performed on a silica column (10% EtOAc:hexanes, isocratic) to yield oxime **6A** as a pale-yellow oil.

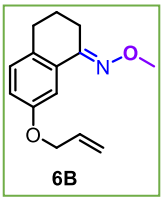
Yield: 131 mg, 94%.

***R*f** = 0.16 (silica TLC, 10% EtOAc:hexanes).

^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.10 (s, 1H), 7.36 (d, *J* = 2.7 Hz, 1H), 7.09 (d, *J* = 8.4 Hz, 1H), 6.87 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.02 (ddt, *J* = 17.3, 10.2, 5.0 Hz, 1H), 5.36 (d, *J* = 18.1 Hz, 1H), 5.24 (d, *J* = 10.5 Hz, 1H), 4.53 (d, *J* = 5.0 Hz, 2H), 2.62 (q, *J* = 6.9 Hz, 4H), 1.72 (p, *J* = 6.4 Hz, 2H).

^{13}C NMR (chloroform-*d*, 101 MHz): δ 157.2, 156.0, 133.4, 132.8, 130.9, 129.9, 118.0, 117.8, 108.5, 69.0, 29.1, 23.9, 21.6.

Oxime 6B.



Adapted from a previously reported synthetic procedure.[13] Ketone **18** (150 mg, 0.74 mmol) and methoxylamine hydrochloride (93 mg, 1.11 mmol) were mixed in 7.4 mL of dry ethanol. Pyridine (60 μL, 0.74 mmol) was added, and the reaction mixture was heated at 75 °C for 3 h. The reaction mixture was evaporated under reduced pressure, redissolved in EtOAc, washed using 1 M HCl (aq.) solution, then extracted using water and EtOAc (× 3). The combined EtOAc extracts were washed with saturated $NaHCO_3$ (aq.) solution, washed with brine, dried over Na_2SO_4, then evaporated under reduced pressure. Purification was performed on a silica gel column (10% EtOAc:hexanes, isocratic) to yield oxime **6B** as a clear, pale-orange oil. ^{1}H NMR data agrees with previously reported values.[13]

Yield: 164 mg, 96%.

***R*f** = 0.49 (silica TLC, 10% EtOAc:hexanes).

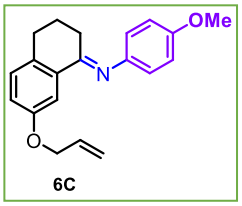
^{1}H NMR (chloroform-*d*, 400 MHz): δ 7.51 (d, *J* = 2.7 Hz, 1H), 7.04 (d, *J* = 8.5 Hz, 1H), 6.86 (dd, *J* = 8.3, 2.7 Hz, 1H), 6.07 (ddt, *J* = 17.4, 10.6, 5.4 Hz, 1H), 5.43 (dd, *J* = 17.2, 1.7 Hz, 1H), 5.32 – 5.25 (m, 1H), 4.56 (d, *J* = 5.2 Hz, 2H), 3.99 (s, 2H), 2.68 (m, 4H), 1.81 (p, *J* = 6.4 Hz, 2H).

^{13}C NMR (chloroform-*d*, 101 MHz): δ 157.11, 154.10, 133.51, 132.43, 131.53, 129.70, 117.79, 117.29, 108.58, 69.02, 62.14, 29.06, 24.20, 21.77.

General Procedure for the Synthesis of Imines.

In an oven-dried round-bottomed flask equipped with a magnetic stir bar, 0.4 to 2.0 mmol of ketone **18** (1 equiv.) and the appropriate amine starting material (5 equiv.) were dissolved in 2 to 10 mL of dry PhMe. Activated 5 Å molecular sieves (60% w/v with respect to the PhMe solvent) were then added, and the flask was sealed with a rubber septum and heated at 105 °C for approximately 16 h under positive N_2 atmosphere. Reaction progression was monitored using basic alumina gel TLC. The reaction mixture was quantitatively transferred using 1% v/v triethylamine:EtOAc and filtered through a thick pad of celite and sand over a coarse glass frit, then evaporated under reduced pressure. Purification was performed on a silica column pretreated using 1%-5% v/v triethylamine solution (eluent: 1%-5% v/v triethylamine in 0%-10% EtOAc:hexanes, isocratic or gradient) to yield the imine as a red, orange, or yellow oil.

Imine 6C.



Yield: 114 mg, 62% (red oil).

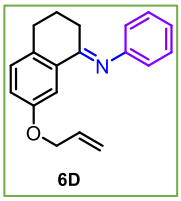
R_f = 0.34 (silica TLC, 1% triethylamine in 10% EtOAc:hexanes); 0.60 (basic alumina TLC, 10% EtOAc:hexanes).

^{1}H NMR (chloroform-*d*, 400 MHz): δ 7.85 (d, *J* = 2.6 Hz, 1H), 7.10 (d, *J* = 8.4 Hz, 1H), 6.98 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.75 (d, *J* = 8.7 Hz, 2H), 6.07 (ddt, *J* = 17.4, 10.5, 5.3 Hz, 1H), 5.43 (dd, *J* = 17.4, 1.8 Hz, 1H), 5.34 – 5.23 (m, 1H), 4.60 (d, *J* = 5.3 Hz, 2H), 3.82 (s, 2H), 2.83 (t, *J* = 6.1 Hz, 2H), 2.61 – 2.43 (m, 2H), 1.88 (quint, *J* = 6.3 Hz, 2H).

^{13}C NMR (chloroform-*d*, 101 MHz): δ 166.0, 157.3, 156.0, 144.8, 135.0, 134.1, 133.4, 130.0, 121.0, 119.5, 117.7, 114.4, 109.6, 69.1, 55.6, 29.9, 29.3, 23.4.

HRMS: m/z calculated for $[C_{20}H_{22}O_2N]^+$ ($[M + H]^+$) 308.1651, found 308.1647.

Imine 6D.



Yield: 128 mg, 80% (orange-red oil).

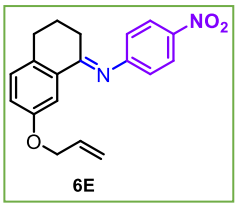
R_f = 0.62 (silica TLC, 10% EtOAc:hexanes).

^{1}H NMR (chloroform-*d*, 400 MHz): δ 7.85 (d, *J* = 2.7 Hz, 1H), 7.34 (t, *J* = 7.7 Hz, 2H), 7.11 (d, *J* = 8.5 Hz, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 7.00 (dd, *J* = 8.4, 2.8 Hz, 1H), 6.80 (d, *J* = 7.7 Hz, 2H), 6.08 (ddt, *J* = 17.4, 10.6, 5.4 Hz, 1H), 5.43 (d, *J* = 17.4 Hz, 1H), 5.28 (d, *J* = 10.6 Hz, 1H), 4.60 (d, *J* = 5.4 Hz, 2H), 2.83 (t, *J* = 6.0 Hz, 2H), 2.57 – 2.38 (m, 2H), 1.89 (p, *J* = 6.2 Hz, 2H).

^{13}C NMR (chloroform-*d*, 101 MHz): δ 165.7, 157.3, 151.8, 134.8, 134.3, 133.4, 130.0, 129.1, 123.2, 119.7, 119.6, 117.8, 109.7, 69.1, 29.9, 29.3, 23.3.

HRMS: m/z calculated for $[C_{19}H_{20}ON]^+$ ($[M + H]^+$) 278.1545, found 278.1543.

Imine 6E.

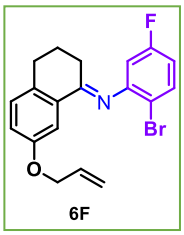


Yield: 103 mg, 46% (red oil).

R_f = 0.66 (silica TLC, 20% EtOAc:hexanes); 0.46 (basic alumina TLC, 10% EtOAc:hexanes).

Note that the imine NMR sample was significantly (~50%) hydrolyzed. Experiments are currently in progress to cleanly isolate the imine from its hydrolysis products.

Imine 6F.



Yield: 123 mg, 55% (red oil).

R_f = 0.60 (silica TLC, 10% EtOAc:hexanes).

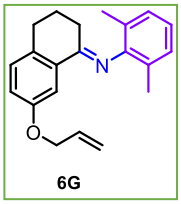
^{1}H NMR (chloroform-*d*, 400 MHz): δ 7.86 (d, *J* = 2.4 Hz, 1H), 7.52 (dd, *J* = 8.8, 5.7 Hz, 1H), 7.14 (d, *J* = 8.4 Hz, 1H), 7.03 (dd, *J* = 8.3, 2.7 Hz, 1H), 6.68 (td, *J* = 8.5, 2.8 Hz,

1H), 6.55 (dd, *J* = 9.3, 2.9 Hz, 1H), 6.07 (ddt, *J* = 16.2, 10.4, 5.3 Hz, 1H), 5.44 (d, *J* = 17.2 Hz, 1H), 5.29 (d, *J* = 10.5 Hz, 1H), 4.60 (d, *J* = 5.4 Hz, 2H), 2.85 (t, *J* = 6.1 Hz, 2H), 2.40 (t, *J* = 6.4 Hz, 2H), 1.94 (p, *J* = 6.3 Hz, 2H).

^{19}F NMR (chloroform-*d*, 376 MHz): δ -114.05.

^{13}C NMR (chloroform-*d*, 101 MHz): δ 167.9, 163.7, 161.3, 157.3, 151.6, 134.8, 133.8, 133.8, 133.3, 130.1, 120.3, 117.9, 111.2, 110.1, 107.6, 69.1, 30.6, 29.2, 23.0.

Imine 6G.



Yield: 37 mg, 20% (clear, yellow-orange oil). Note that due to low yield, this synthesis was repeated multiple times and at higher scales to obtain sufficient imine material for aromatic Claisen rearrangement regioselectivity studies.

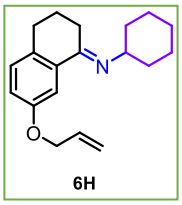
***R*$_f$** = 0.54 (silica TLC, 10% EtOAc:hexanes); 0.92 (basic alumina TLC, 10% EtOAc:hexanes).

^{1}H NMR (chloroform-*d*, 400 MHz): δ 8.00 (d, *J* = 2.7 Hz, 1H), 7.15 (d, *J* = 8.5 Hz, 1H), 7.09 – 6.99 (m, 3H), 6.96 – 6.89 (m, 1H), 6.09 (ddt, *J* = 17.4, 10.6, 5.3 Hz, 1H), 5.46 (d, *J* = 17.4 Hz, 1H), 5.30 (d, *J* = 10.4 Hz, 1H), 4.63 (d, *J* = 5.3 Hz, 2H), 2.86 (t, *J* = 6.1 Hz, 2H), 2.25 (t, *J* = 6.4 Hz, 2H), 2.04 (s, 6H), 1.90 (quint, *J* = 6.2 Hz, 2H).

^{13}C NMR (chloroform-*d*, 101 MHz): δ 165.0, 157.2, 149.1, 134.5, 134.0, 133.4, 130.0, 127.9, 125.8, 122.7, 119.4, 117.8, 110.0, 69.1, 30.0, 29.3, 23.1, 18.2.

HRMS: m/z calculated for $[C_{21}H_{24}ON]^+$ ($[M + H]^+$) 306.1858, found 306.1853.

Imine 6H.



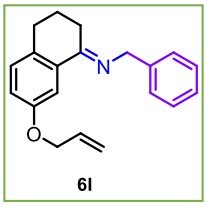
Yield: 154 mg, 78% (red oil).

***R*$_f$** = 0.53 (silica TLC, 1% triethylamine in 10% EtOAc:hexanes); 0.92 (basic alumina TLC, 10% EtOAc:hexanes).

^{1}H NMR (chloroform-*d*, 400 MHz): δ 7.78 (d, *J* = 2.7 Hz, 1H), 7.03 (d, *J* = 8.2 Hz, 1H), 6.87 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.07 (ddt, *J* = 17.4, 10.7, 5.4 Hz, 1H), 5.44 (d, *J* = 17.3 Hz, 1H), 5.28 (d, *J* = 10.4 Hz, 1H), 4.57 (d, *J* = 5.4 Hz, 2H), 3.53 (tt, *J* = 9.6, 4.1 Hz, 1H), 2.75 (t, *J* = 6.1 Hz, 2H), 2.58 (t, *J* = 6.4 Hz, 2H), 1.91 (quint, *J* = 6.4 Hz, 2H), 1.83 (dt, *J* = 11.7, 3.3 Hz, 2H), 1.74 – 1.63 (m, 2H), 1.60 – 1.46 (m, 2H), 1.46 – 1.18 (m, 4H).

^{13}C NMR (chloroform-*d*, 101 MHz): δ 161.3, 157.2, 136.4, 133.7, 133.1, 129.5, 117.7, 117.6, 117.5, 110.2, 69.0, 58.5, 33.8, 29.2, 27.2, 26.0, 25.0, 23.3.

Imine 6I.



Yield: 78 mg, 38% (yellow oil).

***R*$_{f}$** = 0.46 (silica TLC, 10% EtOAc:hexanes); 0.52 (basic alumina TLC, 10% EtOAc:hexanes).

Note that the imine NMR sample was significantly (~50%) hydrolyzed. Experiments are currently in progress to cleanly isolate the imine from its hydrolysis products.

CHAPTER IV: CONCLUSIONS

The regioselectivity of aromatic Claisen rearrangements for *meta*-substituted allyl aryl ethers is affected by the electronic and steric effects of the *meta* substituent. For the investigated tetralone-based imine derivatives, high (> 85%) regioselectivity for the more sterically hindered (**b**) versus the less sterically hindered product (**a**) was observed for protected oxime **6B** (**a**:**b** = 1:6.5), and for aliphatic imines **6H** and **6I** (only **b** detected). Tetralone-based ketone **18** also displayed a high product regioselectivity of **a**:**b** equal to 1:6.5. These findings suggest a significant electronic or neighboring group participation effect of the allyl aryl ether *meta*-substituent on regioselectivity, since a sterics perspective would predict the opposite (*i.e.*, that sterically hindered **b** is the minor product). Further experimentation and computational studies regarding the reaction pathway are needed to better understand the regioselectivity influence of the *meta*-substituent electronics, *viz.*, if there is an intramolecular acid/base interaction which influences the keto-enol tautomerization kinetics, or if there is an electronic effect on the relative energy of the favored substrate conformer. The aromatic Claisen rearrangement regioselectivity of imines **6E**, **6I**, and **6J** as well as several hydrazone substrates are currently being reinvestigated.

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Figure A9. ^{1}H NMR (chloroform-*d*, 400 MHz) of allyl aryl ether 13.

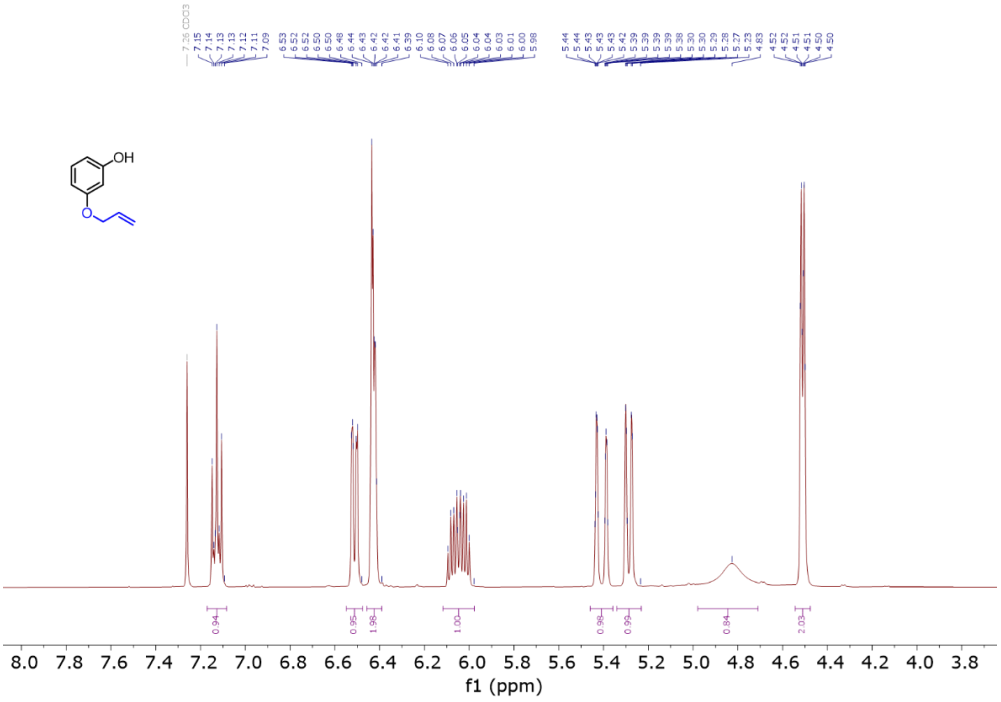

Figure A10. ^{1}H NMR (chloroform-*d*, 400 MHz) of allyl aryl ether 14.

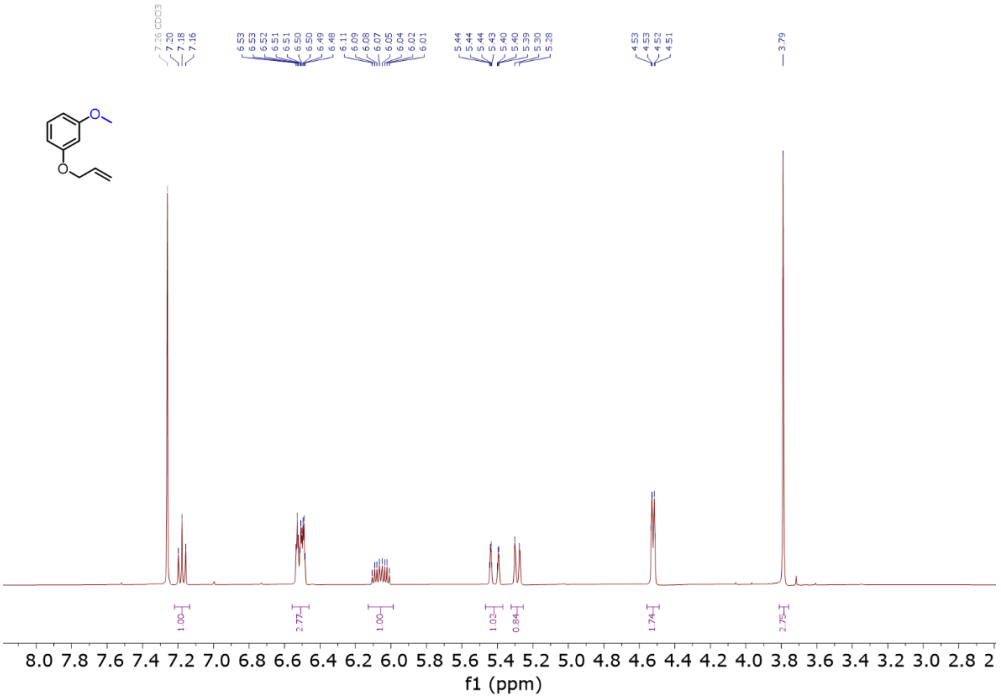

Figure A11. ^{1}H NMR (chloroform-*d*, 400 MHz) of allyl aryl ether 15.

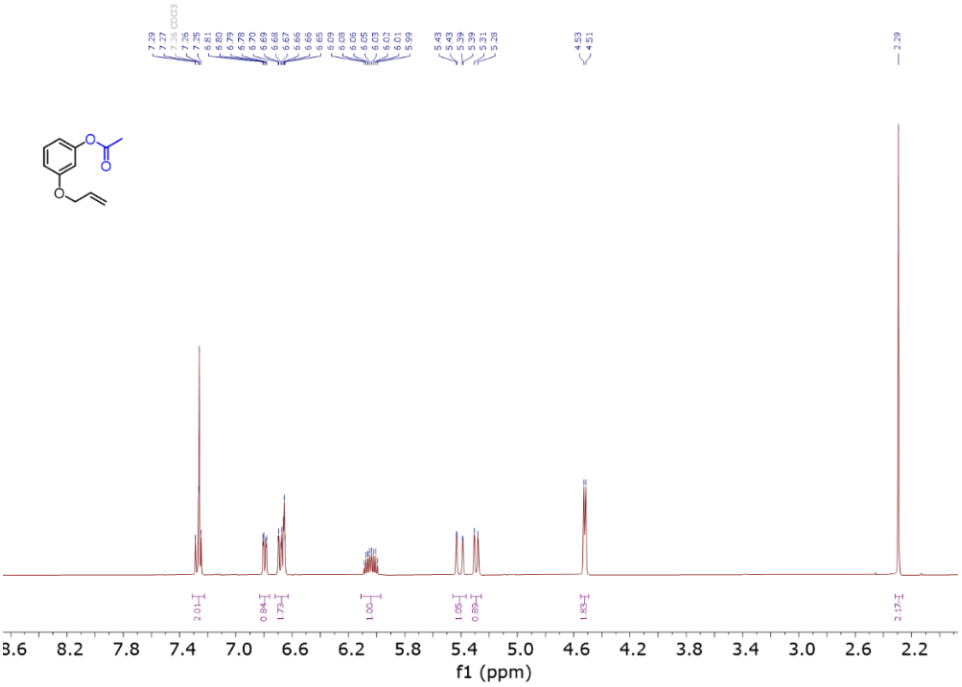

Figure A12. ^{1}H NMR (chloroform-*d*, 400 MHz) of allyl aryl ether 16.

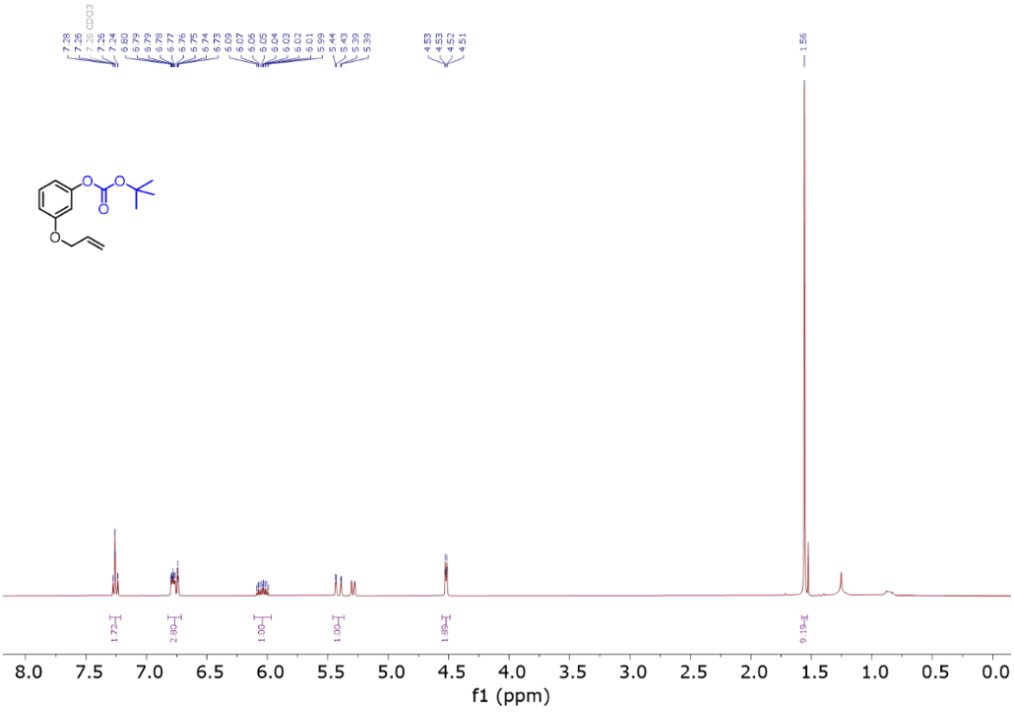

Figure A13. ^{1}H NMR (acetone-d_6, 400 MHz) of phenol 17.

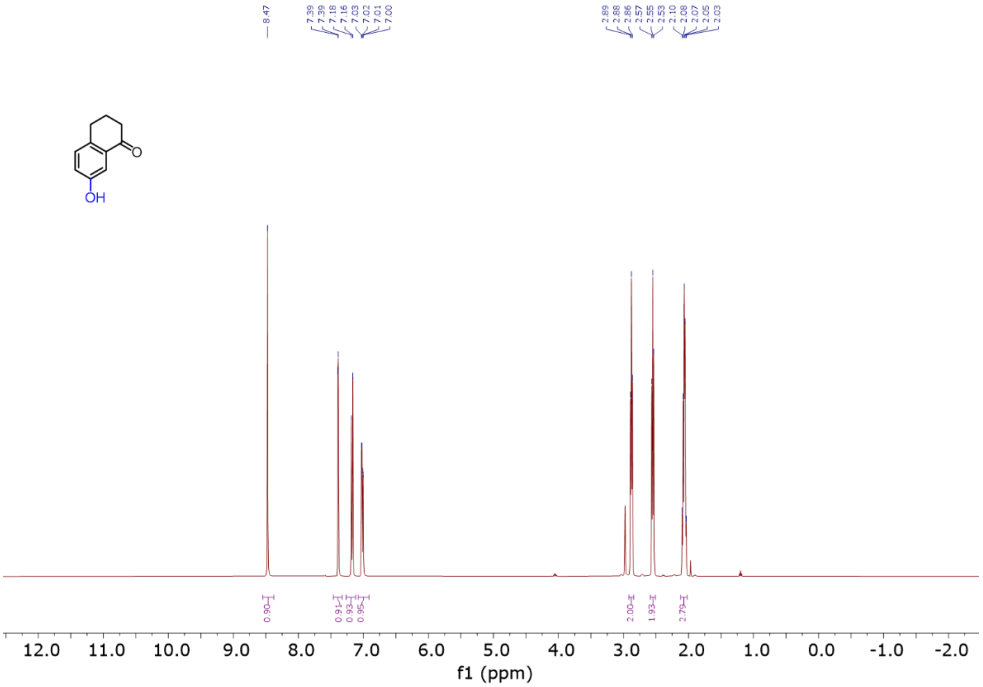

Figure A14. ^{1}H NMR (chloroform-*d*, 400 MHz) of ketone 18.

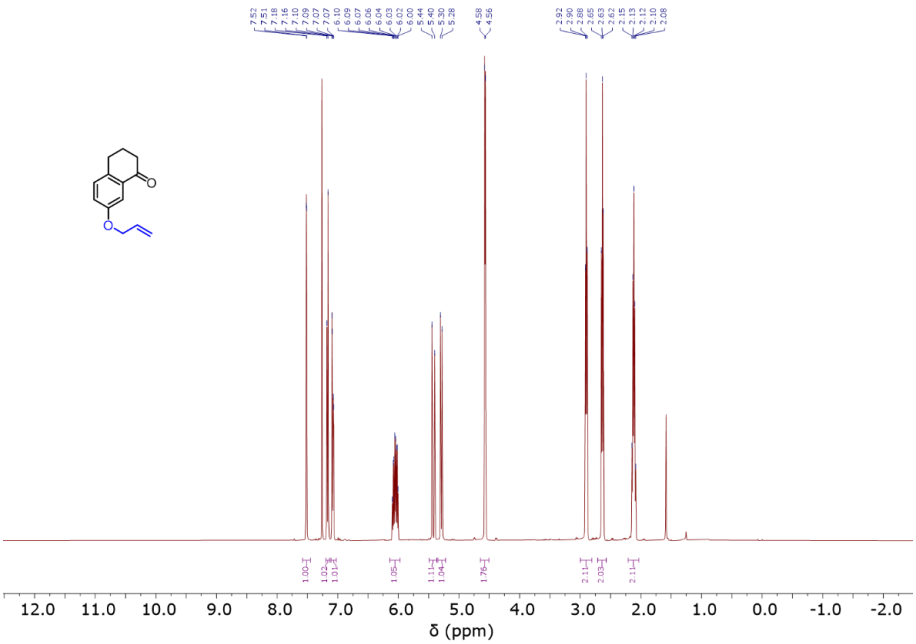

Figure A15. ^{1}H NMR (DMSO-d_6, 400 MHz) of oxime 6A.

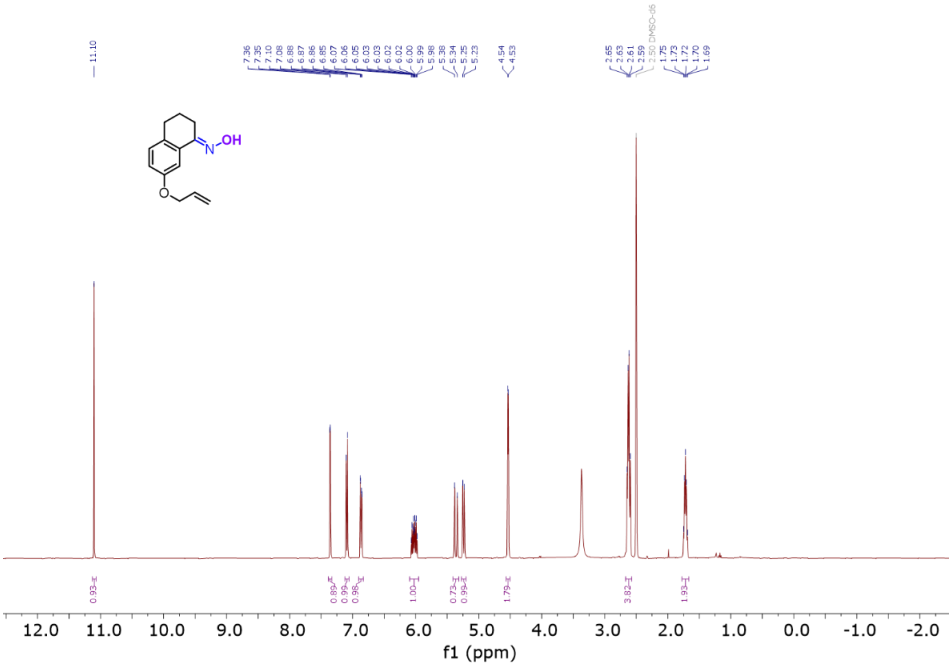

Figure A16. ^{13}C NMR (chloroform-*d*, 101 MHz) of oxime 6A.

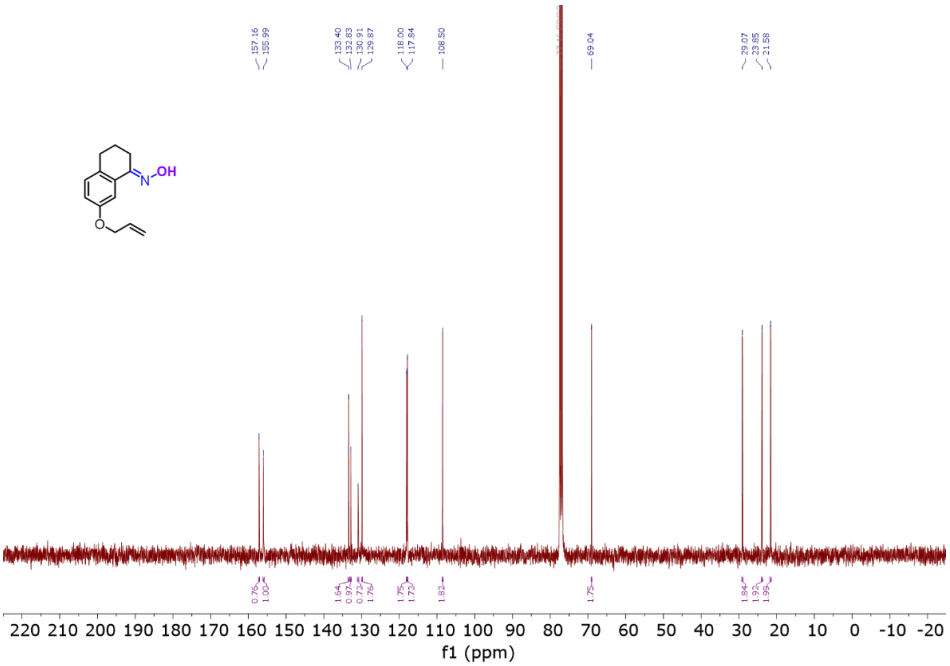

Figure A17. ^{1}H NMR (chloroform-*d*, 400 MHz) of oxime 6B.

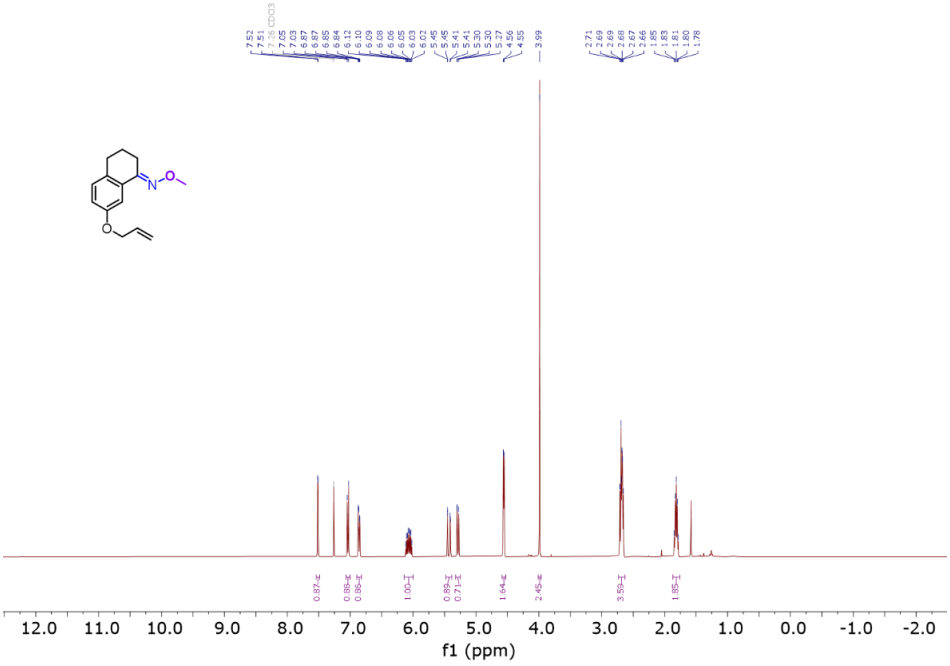

Figure A18. ^{13}C NMR (chloroform-*d*, 101 MHz) of oxime 6B.

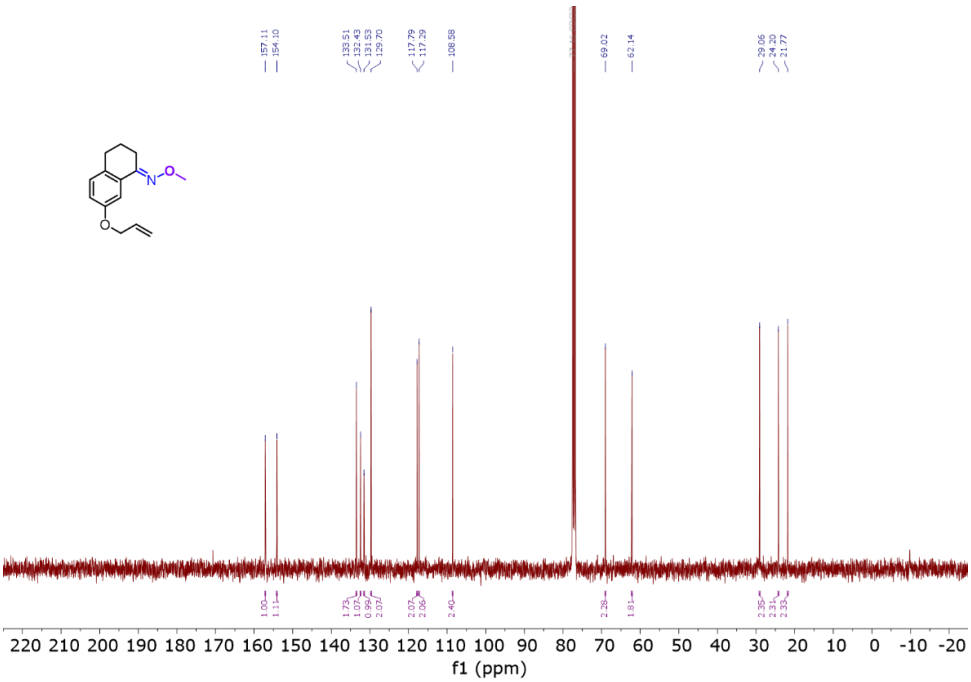

Figure A19. ^{1}H NMR (chloroform-*d*, 400 MHz) of imine 6C.

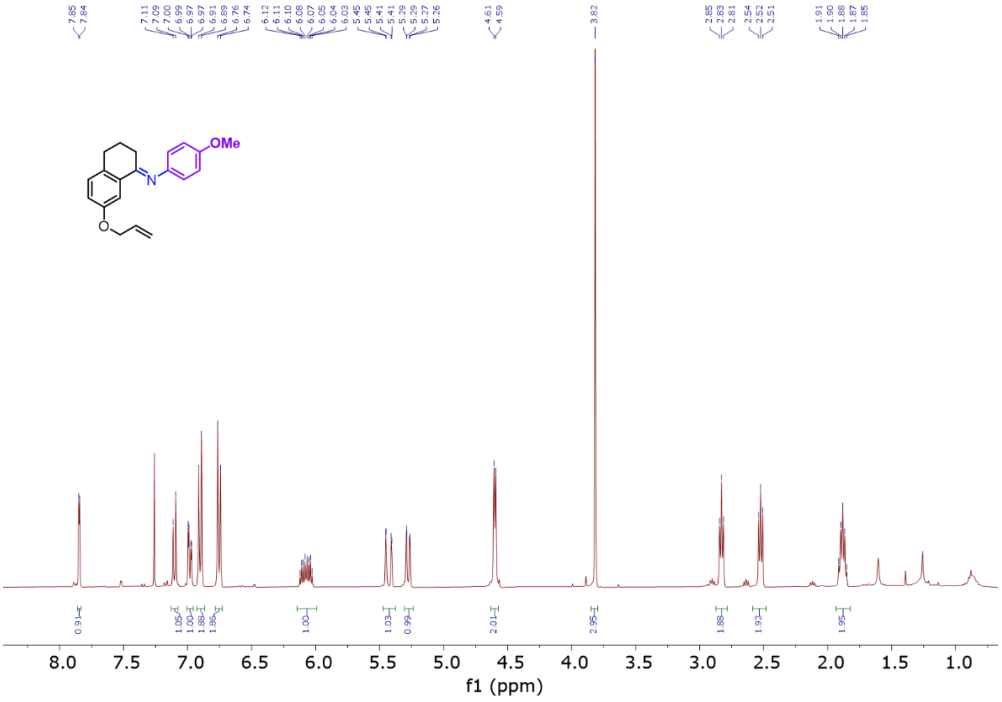

Figure A20. ^{13}C NMR (chloroform-*d*, 101 MHz) of imine 6C.

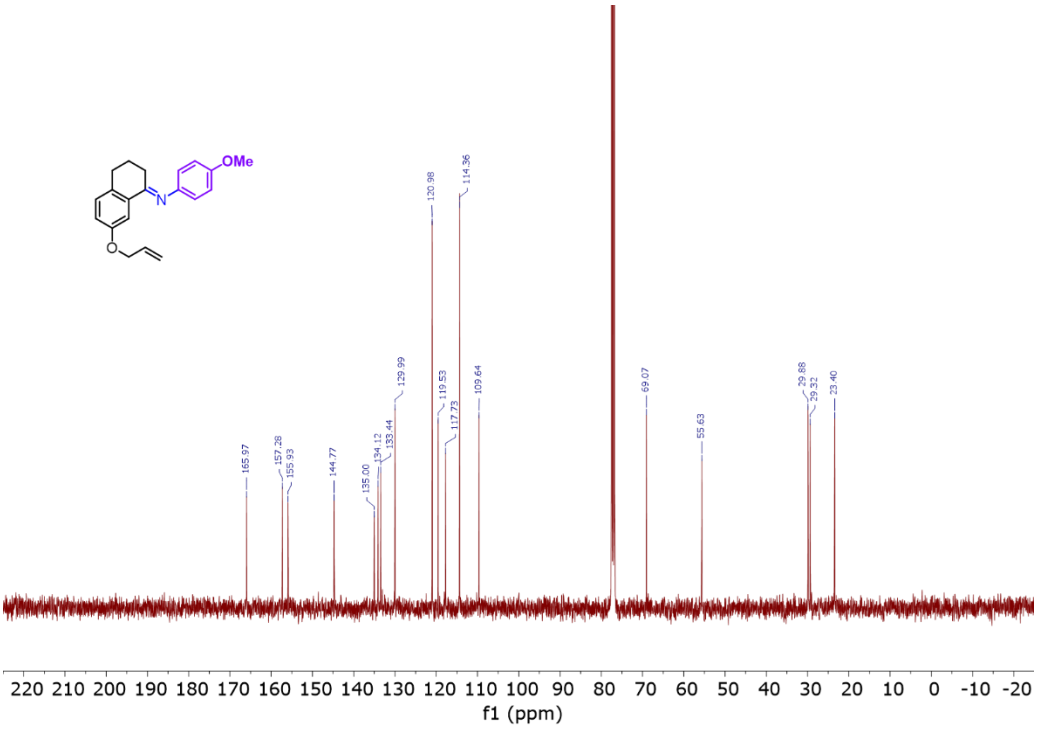

Figure A21. ^{1}H NMR (chloroform-*d*, 400 MHz) of imine 6D.

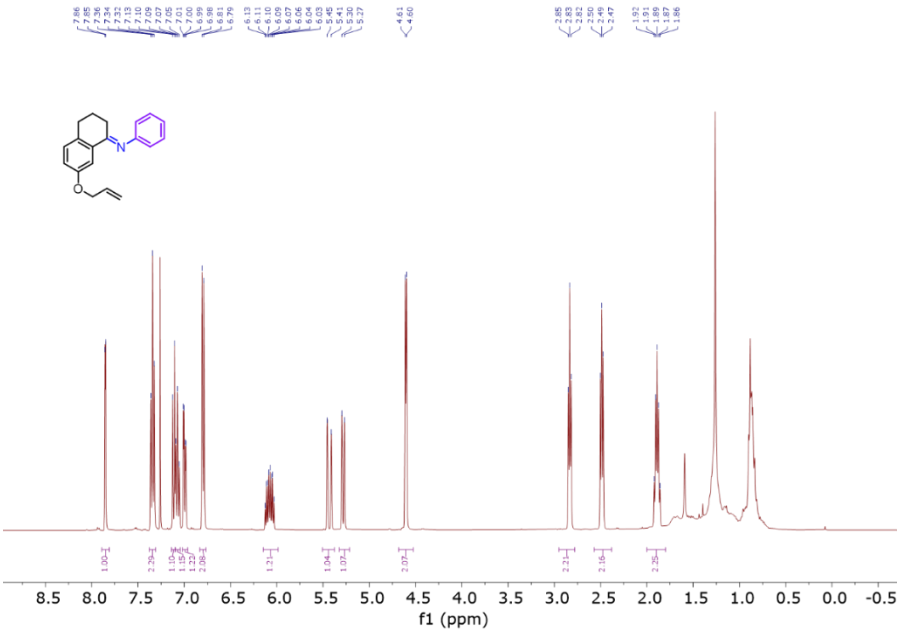

Figure A22. ^{13}C NMR (chloroform-*d*, 101 MHz) of imine 6D.

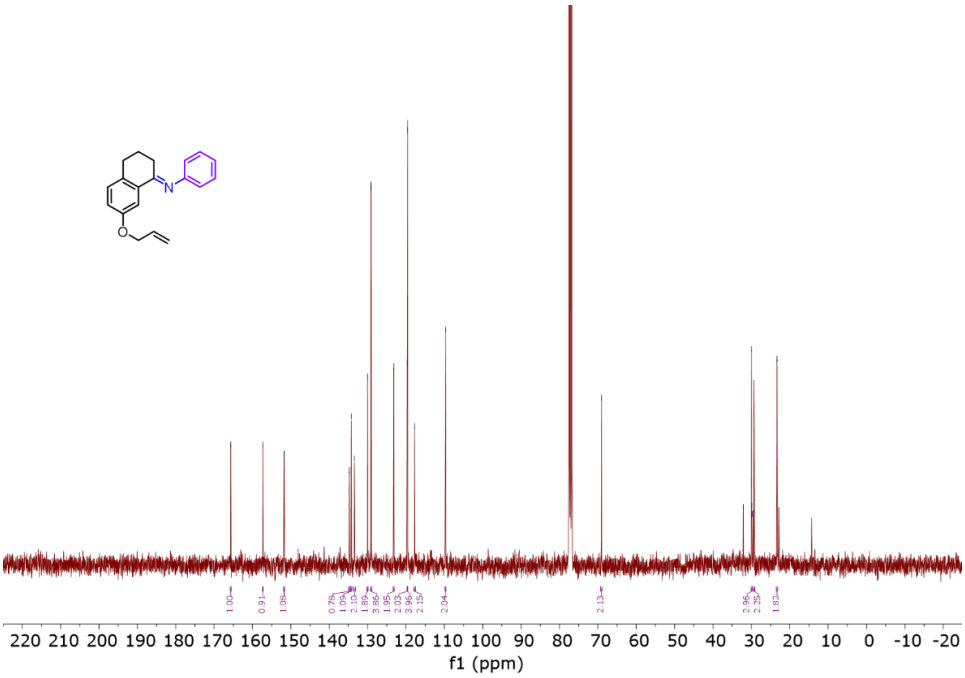

Figure A23. ^{1}H NMR (chloroform-*d*, 400 MHz) of imine 6F.

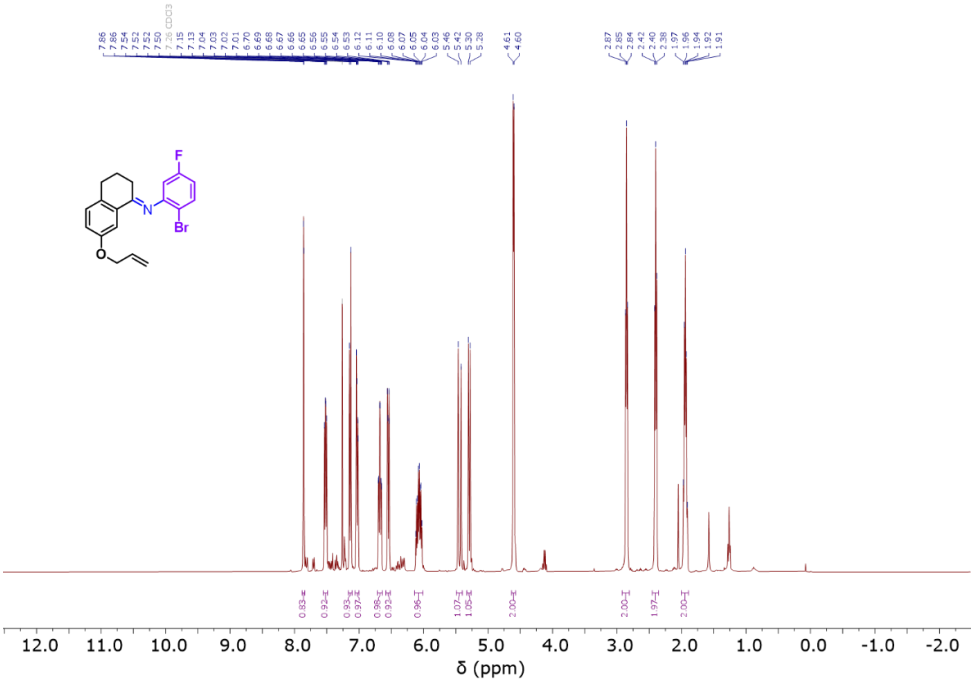

Figure A24. ^{19}F NMR (chloroform-*d*, 376 MHz) of imine 6F.

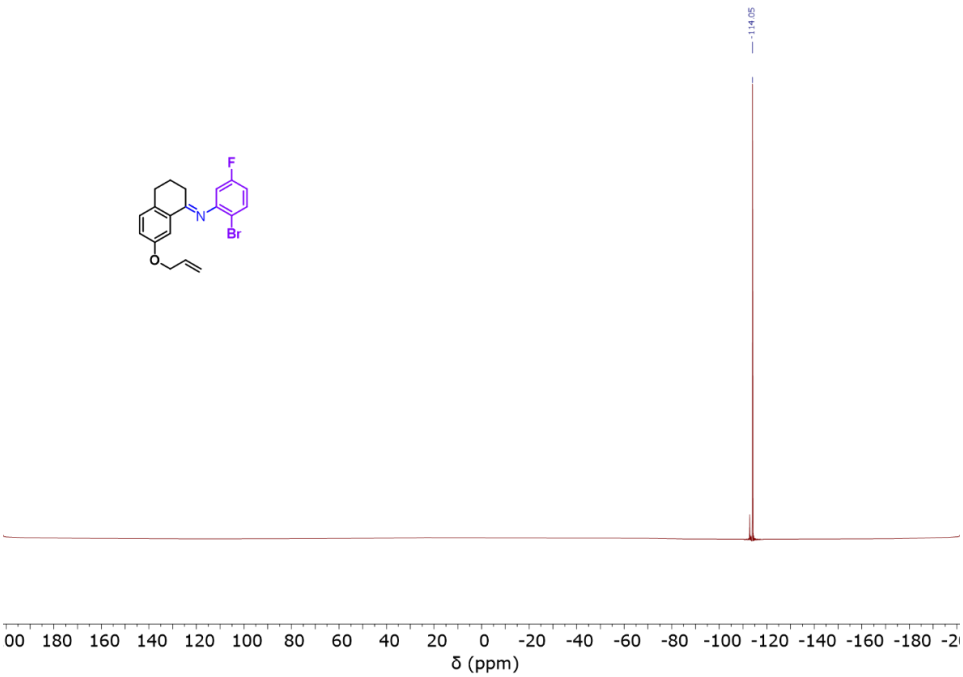

Figure A25. ^{13}C NMR (chloroform-*d*, 101 MHz) of imine 6F.

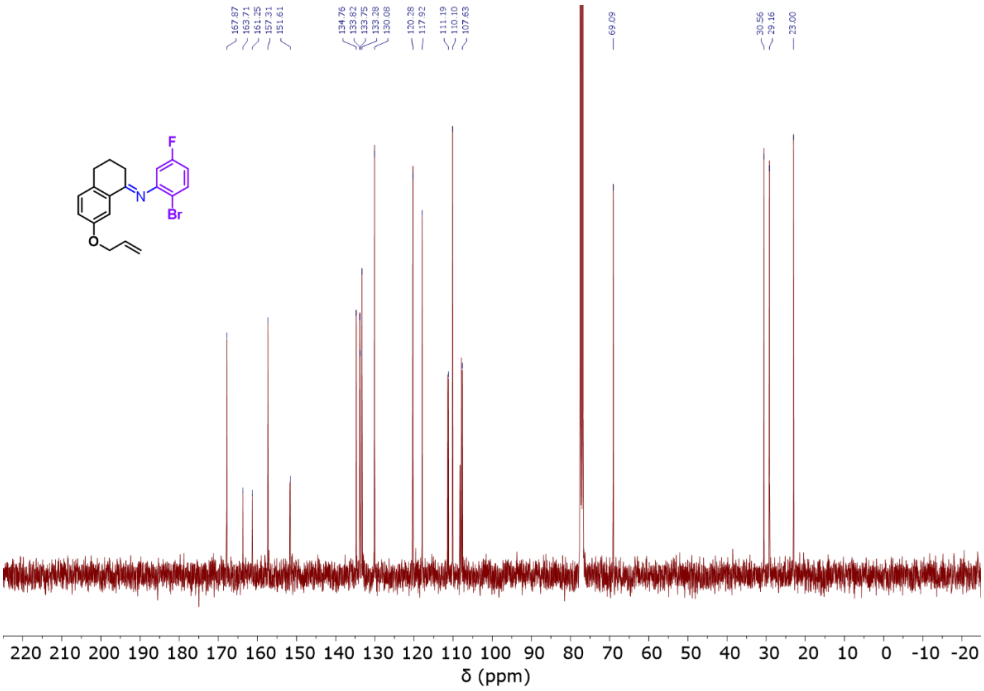

Figure A26. ^{1}H NMR (chloroform-*d*, 400 MHz) of imine 6G.

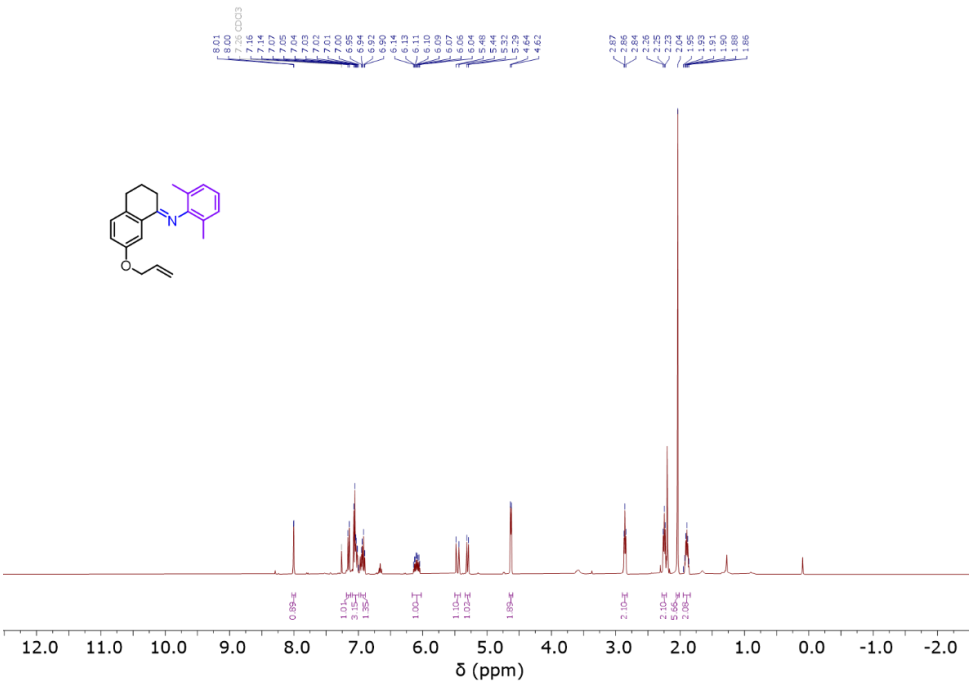

Figure A27. ^{13}C NMR (chloroform-*d*, 101 MHz) of imine 6G.

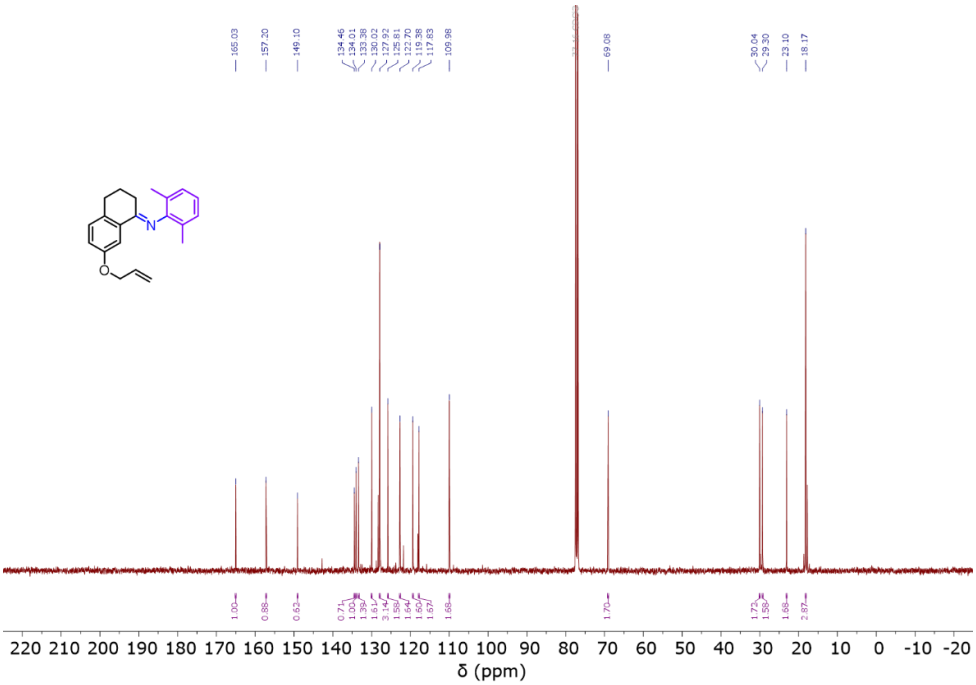

Figure A28. ^{1}H NMR (chloroform-*d*, 400 MHz) of imine 6H.

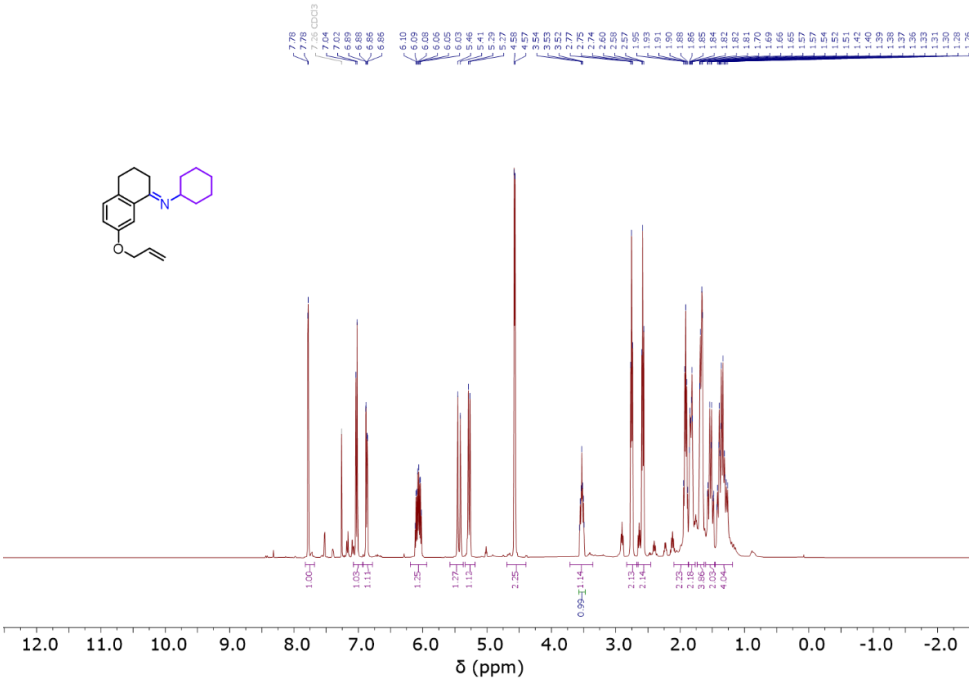

Figure A29. ^{13}C NMR (chloroform-*d*, 101 MHz) of imine 6H.

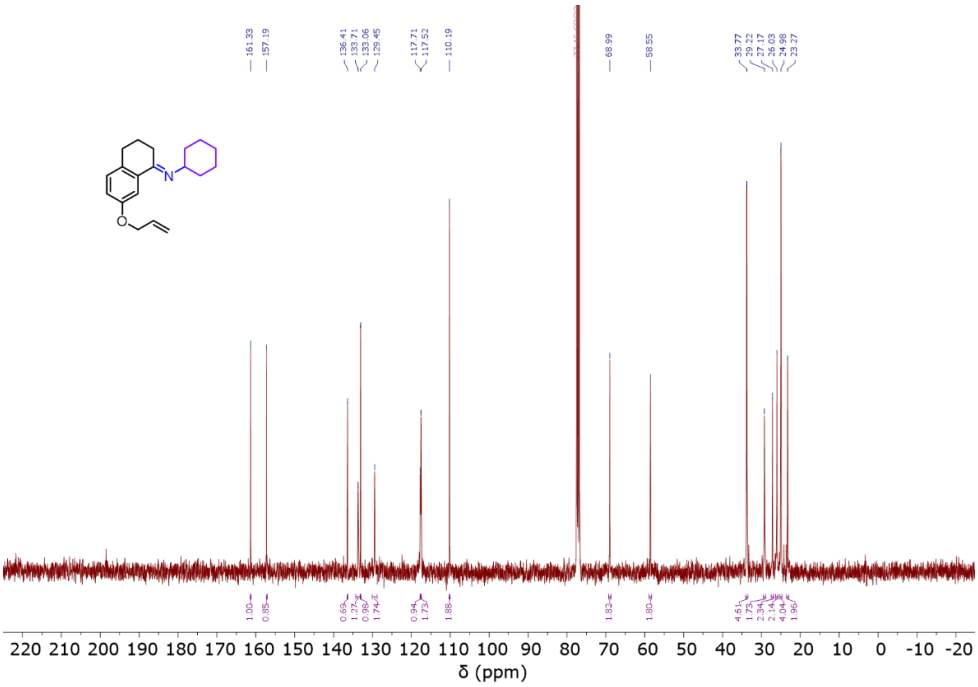

Figure A30. ^{1}H NMR (chloroform-*d*, 400 MHz) of ketone 18b.

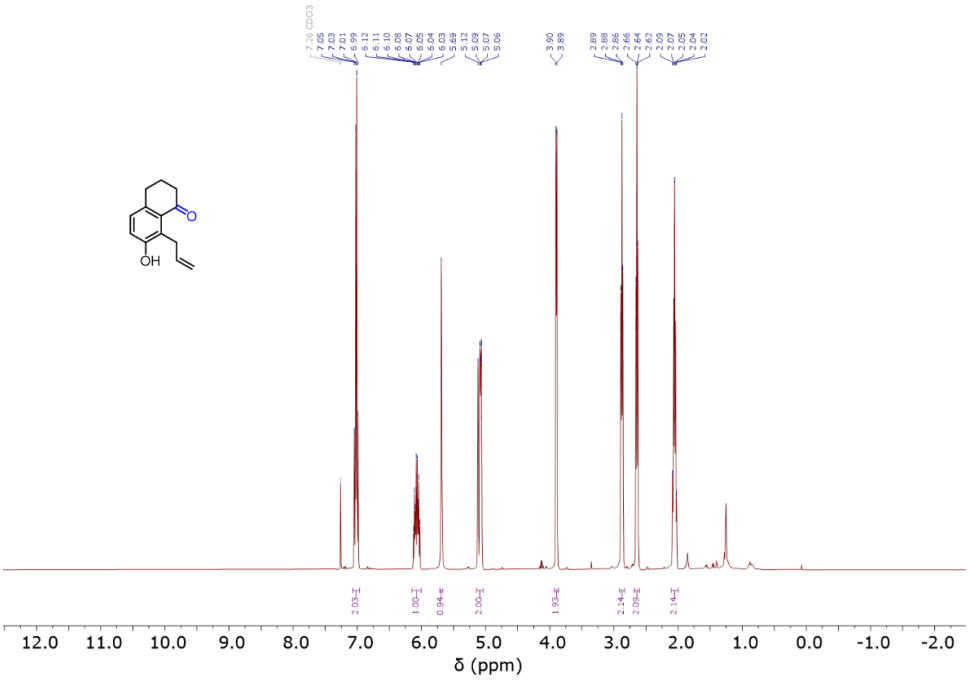

Figure A31. ^{1}H NMR (chloroform-*d*, 400 MHz) of ketone 18a.