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# Studies on vinamidinium salt amine exchange reactions, borohydride reductions, and subsequent transformations

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# HONORS PROGRAM
## Senior Honors Project

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**Studies on vinamidinium salt amine exchange reactions, borohydride reductions, and subsequent transformations**

*by*

*Xin Jia*

*Honors Thesis*

*in*

*Department of Chemistry*
*University of Richmond*
*Richmond, VA*

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*Advisor: Dr. John Gupton*

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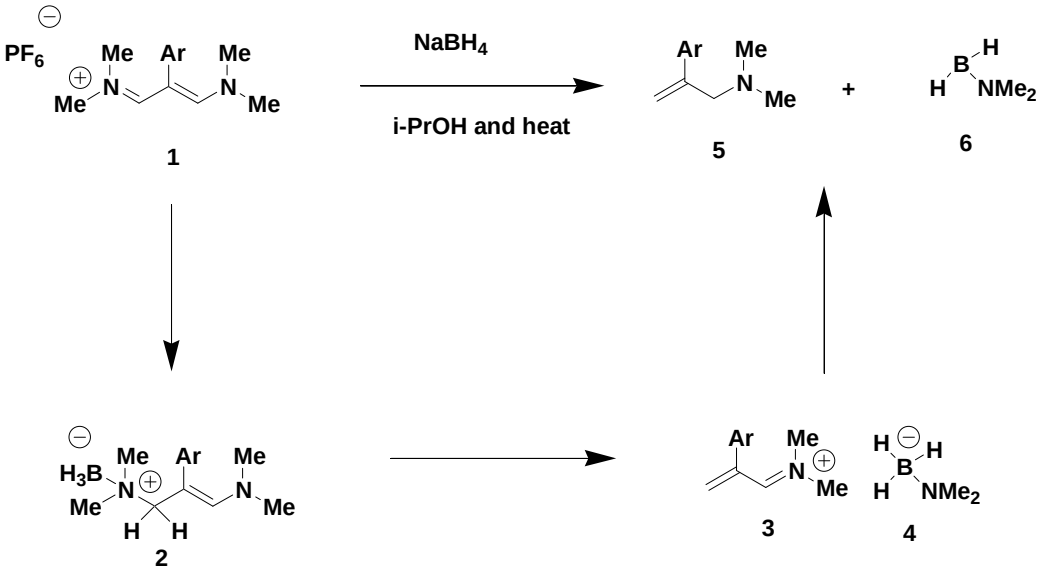
**I. Abstract**

Allylic amines are fundamental building blocks in organic chemistry, and the syntheses of allylic amines are important for industrial and synthetic goals. Gupton and coworkers have previously reported the synthesis of various analogs of vinamidinium salts from arylacetic acids via reaction with phosphorous oxychloride/DMF in excellent yield and purity. Previous studies indicate that vinamidinium salts undergo sodium borohydride reduction to give tertiary allylic amines in good yield. In this research project, the goal is to expand and to utilize the conversion of vinamidinium salts and their derivatives to a variety of functionalized allylic amines. More specifically, amine exchange reactions of vinamidinium salts were accomplished with different amines followed by sodium borohydride reduction to yield secondary and tertiary allylic amines. The tertiary allylic amines were then alkylated and subjected to base mediated rearrangement to yield a variety of highly functionalized tertiary homoallylic amines.

## II. Introduction

Allylic amines are key structural elements in a variety of important naturally occurring molecules as well as industrial and pharmaceutical compounds. They are also among the most versatile intermediates in the synthesis of other important molecules. Allylic amines are fragments that are encountered in natural products and often transformed to a range of products by reduction or oxidation of the double bond.[1] Consequently, allylic amines are used as starting materials for the synthesis of numerous compounds such as $\alpha$- and $\beta$-amino acids,[2] alkaloids[3,4] and carbohydrate derivatives.[5] They are also important building blocks for the cross-linking of proteins[6], rhodium catalyzed ylide formation[7], directed metalation reactions[8] and the preparation of GABA uptake inhibitors[9].

Gupton and coworkers have previously reported[10] the sodium borohydride reduction of 2-aryl-N,N,N,N-teramethylvinamidium salts to give 2-aryl-3-N,N-dimethylaminopropenes (**5**) in good yield. Scheme 1 depicts a suggested mechanism for how this reaction occurs.




**Scheme 1. Sodium Borohydride Reduction of Vinamidinium Salts**

The reaction depicted in Scheme 1 gives extremely pure 2-aryl-N,N-dimethylallylic amines (**5**) from the vinamidinium salts (**1**). It has been reported in the literature[11] that the vinamidinium salts have

the potential of serving as three-carbon building blocks for a wide array of carbocycles and heterocycles. Positions 1 and 3 of the vinamidinium system are electrophilic, and position 2 is slightly nucleophilic. Furthermore, vinamidinium salts can also regioselectively incorporate an appended substituent onto a new ring system, making them attractive starting materials for the synthesis of new medicinal and agriculture agents.[12]

Vinamidinium salts can be easily prepared by reaction of arylacetic acids with phosphorous oxychloride and DMF when heated.[13] This easy and efficient synthetic method has facilitated expansion of the synthetic utility of vinamidinium salts by creating new vinamidinium salts with novel substituents.

It is worth noting several factors when synthesizing new substituents to expand the vinamidinium salt skeleton.[13] First, the necessary substituted arylacetic acid should be commercially accessible and easily obtained. Second, a substituent on the arylacetic acid should be chosen that will impart interesting properties to the carbocycles and heterocycles that will be formed from the vinamidinium salt.

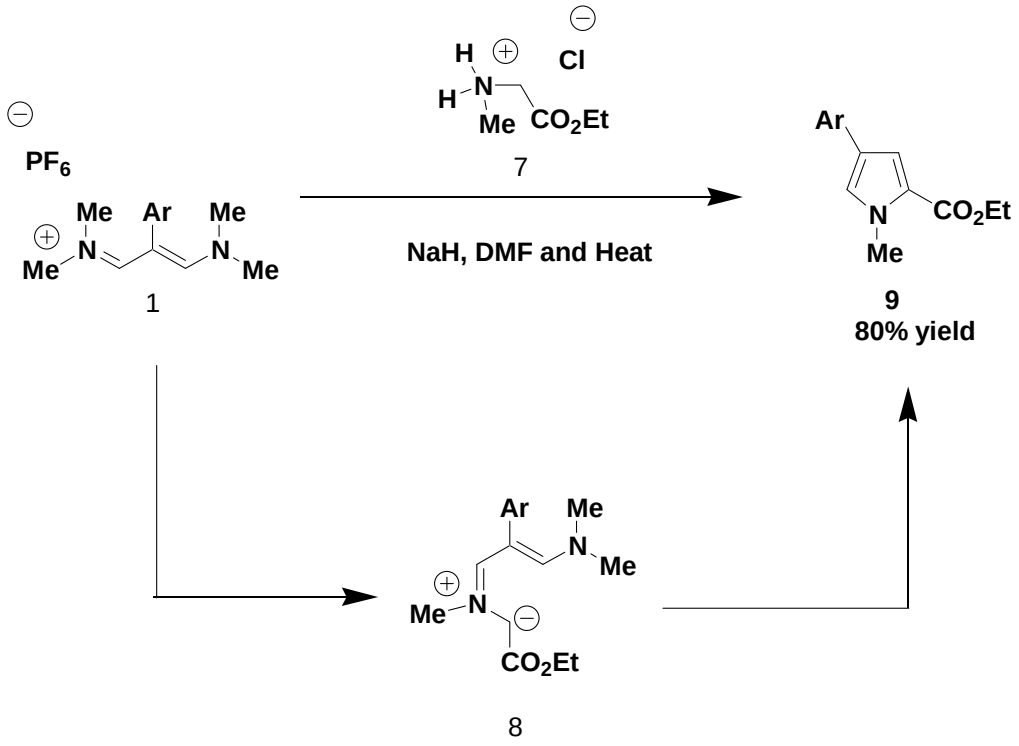
The nature of the substitutent group attached to the acetic acid appears to be a crucial factor in determining whether the $POCl_3$/DMF conditions are successful. The reports in the literature[14] for preparing 2-substituted vinamidinium salts from an $\alpha$-substituted acetic acid, suggest successful C-2 substituents are aryl groups or electron-withdrawing groups (CN, $NO_2$, Cl, Br, $CO_2R$).[12] This trend may be due to a ketene being generated from an $\alpha$-substituted acetyl chloride intermediate. Previous studies[12] also observed that the aryl group at the 2-position of the vinamidinium salt has a pronounced effect on the reaction pathway. Therefore, we have synthesized 2-aryl-N,N,N,N-tetramethyl-vinamidinium salts from arylacetic acids via reaction with phosphorous oxycloride/DMF in excellent yield and excellent purity.

Quaternary salts derived from properly functionalized tertiary allylic amines can be used as substrates[15] to undergo base mediated [2,3]-sigmatropic rearrangement reactions[16]. The high efficiency

and high levels of stereocontrol associated with the rearrangement reactions will allow homoallylic amines to be produced. This ultimately extends the generality of tertiary allylic amines.

**III. Results and Discussion**

In order to utilize the conversion of vinamidinium salts to allylic amines, it is necessary to synthesize vinamidinium salts (**1**) with diverse amine functionality. Amine exchange reactions of vinamidinium salts have been previously used for the preparation of highly functionalized pyrroles as depicted in Scheme 2.

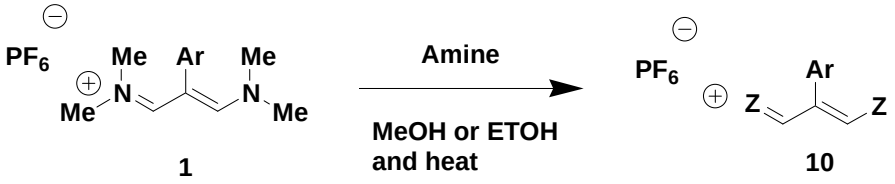



**Scheme 2. Preparation of 2,4-Disubstitutedpyrroles from Vinamidinium Salts**

Subsequently, we carried out amine exchange reactions with a variety of amines as presented in Table 1. We carried out the reactions by heating excess primary or secondary amines with the vinamidinium salt in methanol or ethanol for four hours. In both cases, the driving force of the reaction is the release of dimethylamine gas. Both cyclic secondary amines and acyclic secondary amines behaved very well in the exchange reactions with the majority of the products being produced in higher

than 90% yield. Primary amines also react with vinamidinium salts with the yield of the amine exchange salts as high as 97%. In addition, we have also examined several different aromatic substituents on the vinamidinium salt (**10j-10m** in Table 1). The high yield and excellent purity of the amine-exchanged products show the generality of the synthetic scheme and demonstrate that such functional group changes do not impact the yield or purity of the amine exchange products.

**Table 1. Amine Exchange Reactions of Vinamidinium Salts**




**1** **10**

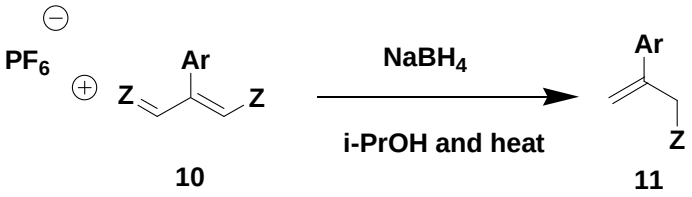
| Compound | Amine group (Z) | Ar group | %Yield of Exchanged Salt |
|---|---|---|---|
| 10a | pyrrolidinyl | 4-methoxyphenyl | 99 |
| 10b | morpholinyl | 4-methoxyphenyl | 99 |
| 10c | piperidinyl[12] | 4-methoxyphenyl | 89 |
| 10d | diethylamino | 4-methoxyphenyl | 96 |
| 10e | dipropylamino | 4-methoxyphenyl | 93 |
| **10f** | **butylamino** | **4-methoxyphenyl** | **71** |
| **10g** | **hexylamino** | **4-methoxyphenyl** | **97** |
| **10h** | **s-butylamino** | **4-methoxyphenyl** | **50** |
| **10i** | **2,4-dimethoxybenzylamino** | **4-methoxyphenyl** | **50** |
| 10j | butylamino | 4-chlorophenyl | 98 |
| 10k | butylamino | 3,4-dimethoxyphenyl | 97 |
| 10l | butylamino | 4-methylphenyl | 97 |
| 10m | butylamino | 1-naphthyl | 97 |

(Note: The reactions not in bold were carried out by coworkers)

The various amine exchanged vinamidinium salts underwent reduction by refluxing the exchanged salts with sodium borohydride in isopropanol for 24 hours (Table 2). The resulting allylic amines (**11**) were produced in very good yield with excellent purity. The primary amine exchanged vinamidinium salts (**11f-11m**, Table 2) underwent reduction reactions very efficiently with yields as high as 99%. The secondary amine exchange salts (**11a-11e**, Table 2) also underwent this reduction reaction

to yield corresponding allylic amines in very high yield. The crude products were nearly analytically pure and often utilized in subsequent reactions without additional purification. All of the results suggest the efficiency and generality of this synthetic strategy.

**Table 2. Sodium Borohydride Reduction of Amine Exchanged Vinamidinium Salts**

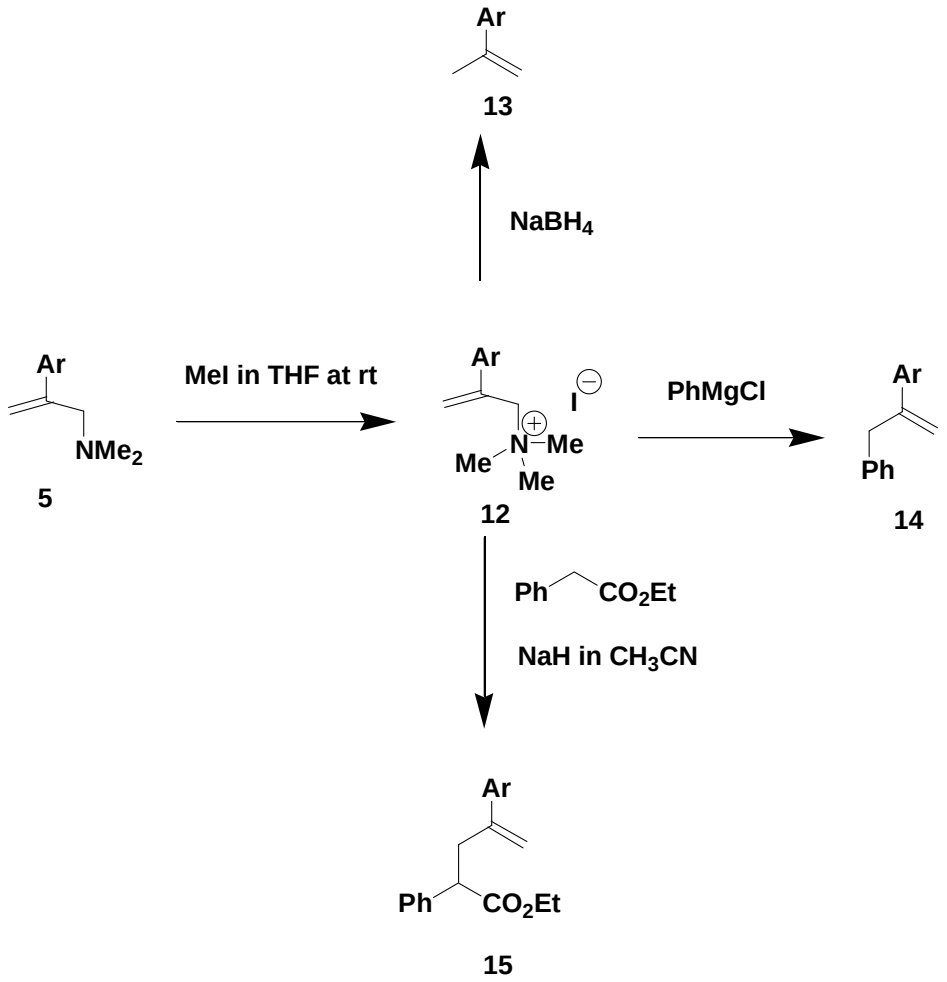



10 11

| Compound | Amine group (Z) | Ar group | %Yield of Allylic amine |
|---|---|---|---|
| 11a | pyrrolidinyl | 4-methoxyphenyl | 89 |
| 11b | morpholinyl[7] | 4-methoxyphenyl | 97 |
| 11c | piperidinyl | 4-methoxyphenyl | 97 |
| 11d | diethylamino | 4-methoxyphenyl | 96 |
| 11e | dipropylamino | 4-methoxyphenyl | 99 |
| **11f** | **butylamino** | **4-methoxyphenyl** | **62** |
| **11g** | **hexylamino** | **4-methoxyphenyl** | **99** |
| **11h** | **s-butylamino** | **4-methoxyphenyl** | **62** |
| **11i** | **2,4-dimethoxybenzylamino** | **4-methoxyphenyl** | **60** |
| 11j | butylamino | 4-chlorophenyl | 99 |
| 11k | butylamino | 3,4-dimethoxyphenyl | 99 |
| 11l | butylamino | 4-methylphenyl | 94 |
| 11m | butylamino | 1-naphthyl | 98 |

(Note: The reactions not in bold were carried out by coworkers)

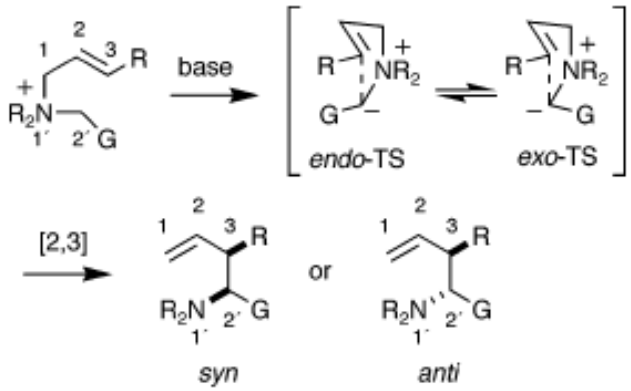
As mentioned earlier, one of the very significant reactions of tertiary allylic amines is conversion to quaternary ammonium salts, which can further undergo a variety of useful reactions. Scheme 3 has depicted the previous reports of such reactions of 2-aryl-N,N-dimethylallylic amines (**5**). In Scheme 3, reactions performed with the quaternary salts (**12**) from previous studies include reduction to styrenes[15] (**13**), Grignard alkylation to yield highly functionalized styrenes (**14**) and enolate alkylations to provide highly functionalized allylic systems (**15**).




**Scheme 3. Reaction of Quaternary Salts with Nucleophiles and Reducing Agents**

Furthermore, in order to examine some of the tertiary allylic amines in such an application described in Scheme 3, other types of allylic ammonium salts, which undergo base mediated [2,3]-sigmatropic rearrangements have been studied. The [2,3]-sigmatropic rearrangement of allylic ammonium ylides has become a powerful strategy for the synthesis of nitrogen heterocycles.[16] [2,3]-Sigmatropic rearrangement reactions are widely recognized as a facile bond reorganization process, particularly for allylic nitrogen and sulfur ylides.[17] As shown in Scheme 4, the rearrangement reactions can be rationalized as to proceed via an envelope-like five-membered transition state, creating a C-C bond and at least one new stereogenic center (Scheme 4).[16] Also, the relative stereochemical outcome of being “syn” versus “anti” products is determined by steric and electronic interactions between the

allyl moiety and the anion-stabilizing group (G) in the *endo* and *exo* transition states. In addition, the nitrogen atom of the ylides is required to be quaternary to allow the rearrangement reaction to occur.

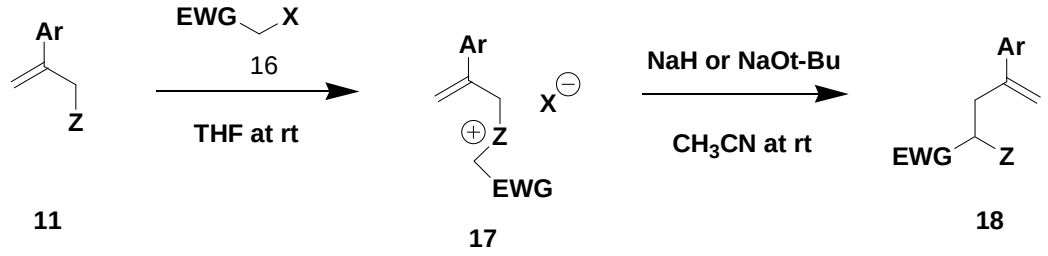



**Scheme 4. The [2,3]-sigmatropic rearrangement of ammonium ylides (R=alkyl, G-anion stabilizing group)**

Consequently, a pyrrolidine allylic amine (**11a**) was alkylated with ethyl $\alpha$-bromoacetate in THF to yield the corresponding quaternary salt (**17a**) in good yield with high purity. It is worth noting that the crude salt (**17a**) resulting from alkylation reaction was nearly analytically pure, so that the product was immediately used in the rearrangement step. All the quaternary salts (**17a- 17l**) resulting from alkylation reactions were treated with sodium hydride or sodium t-butoxide in acetonitrile at room temperature. The resulting homoallylic products represent uniquely functionalized $\alpha$-substituted amino acid esters (**18**) and were obtained (Table 3) in very high purity. By varying the aryl group on the quaternary salts, different analogs of uniquely functionalized $\alpha$-substituted amino acid esters (**18a -18g**) were synthesized. The percentage yield of the reactions was generally good, ranging from 62% to 90%.

We have further expanded the application of this synthetic scheme by reacting the allylic amines with other alkyllating agents with electron withdrawing groups as presented in Table 3. As a result, a variety of uniquely functionalized $\alpha$-aminoketones (**18h-18j**) were prepared in reasonable yield.

**Table 3. Alkylation and Rearrangement of Tertiary Allylic Amines**




11 17 18

| Compound | Amine group (Z) | Ar group | EWG | %Yield of Rearranged Amine |
|---|---|---|---|---|
| 18a | pyrrolidinyl | 4-methoxyphenyl | $CO_2Et$ | 83 |
| 18b | dimethylamino | 4-chlorophenyl | $CO_2Et$ | 90 |
| 18c | dimethylamino | 4-methoxyphenyl | $CO_2Et$ | 54 |
| 18d | dimethylamino | 4-bromophenyl | $CO_2Et$ | 70 |
| 18e | dimethylamino | phenyl | $CO_2Et$ | 67 |
| 18f | dimethylamino | 3,4-dimethoxy-phenyl | $CO_2Et$ | 62 |
| 18g | dimethylamino | naphthyl | $CO_2Et$ | 72 |
| 18h | dimethylamino | 4-methoxyphenyl | 4-bromo-benzoyl | 49 |
| 18i | dimethylamino | 4-methoxyphenyl | benzoyl | 76 |
| 18j | dimethylamino | 4-methoxyphenyl | 4-nitrobenzoyl | 82 |
| 18k | dimethylamino | 4-methoxyphenyl | 2-nitrophenyl | 21 |
| 18l | dimethylamino | 4-methoxyphenyl | 4-nitrophenyl | 53 |

(Note: These reactions were carried out by coworkers)

**IV. Conclusion:**

In this research project, we have established a very practical and efficient preparation of different analogs of amine exchanged vinamidinium salts (**10**) along with their reduction to the corresponding allylic amines (**11**). Both primary and secondary amine exchanged salts containing various aromatic substitutents also undergo reduction reactions in an efficient manner. In order to further

expand the application of allylic amine chemistry, some of the tertiary allylic amines were treated with a variety of electron deficient haloalkane derivatives and under basic conditions the quaternary salts underwent [2,3]-sigmatropic rearrangement to yield uniquely functionalized homoallylic systems (**18**). Such transformations demonstrate the general synthetic utility of vinamidinium salts and their derivatives. More importantly, they have offered an efficient alternative to the traditional preparation of highly functionalized allylic amines.

## V. Experimental[18]

### General

All chemicals were used as received from the manufacturer (Aldrich Chemicals and Fisher Scientific). All solvents were dried over 4 angstrom molecular sieves prior to their use. NMR spectra were obtained on either a Bruker 300 MHz spectrometer, a Bruker 500 MHz spectrometer or a Varian Gemini 200 MHz spectrometer in either $CDCl_3$, $d_6$-DMSO or $d_6$-acetone solutions. IR spectra were recorded on a Nicolet Avatar 320 FT-IR spectrometer with an HATR attachment. High resolution mass spectra were provided on a Biotof Q electrospray mass spectrometer at the University of Richmond or by the Midwest Center for Mass Spectrometry at the University of Nebraska at Lincoln. Low resolution GC-MS spectra were obtained on a Shimadzu QP 5050 instrument. Melting points and boiling points are uncorrected. Chromatographic separations were carried out on a Harrison Chromatotron (equipped with a silica plate) or Biotage SP-1 instrument (equipped with a silica cartridge) and ethyl acetate/hexane was used as the eluant in both instances. The reaction products were eluted within the range of 6-8 column volumes of eluant with a mix of 60-80% ethyl acetate: 20-40% hexane. TLC analyses were conducted on silica plates with hexane/ethyl acetate as the eluant. Vinamidinium salts utilized for the described studies were prepared according to standard procedures**.** All purified reaction products gave TLC results, GC-MS spectra, and $^{13}C$ NMR spectra consistent with a sample purity of >95%. When the preparation of an analytical sample is reported, the crude reaction product was of sufficient purity to be used in subsequent steps without further purification.

**1-(2-(4-Methoxyphenyl)-3-pyrrolidin-1-yl-allylidene)pyrrolidinium Hexafluorophosphate (10a).** To a 100 mL round bottom flask equipped with a magnetic stirring bar and reflux condenser, was added 4-methoxyphenyl vinamidinium salt (**1**, 1.00 g, 2.64 mmol), pyrrolidine (1.12 g, 15.9 mmol) and 40 mL of anhydrous ethanol. The resulting reaction mixture was refluxed for 24 h and then cooled to room temperature at which point a solid precipitated. The solid was vacuum filtered with a Buchner funnel and was washed with 2 x 20 mL of cold ethanol. The resulting material was dried using a Kugelrohr apparatus to give a light yellow solid (1.12 g, 99.1 % yield). The resulting solid exhibited the following physical properties: mp 158 - 159°C; $^1H$ NMR ($CDCl_3$) $\delta$1.84 (m, 8H), 2.71 (t, *J* = 6.0 Hz, 4H), 3.82 (t, *J* = 6.0 Hz, 4H), 3.87 (s, 3H), 6.89 (d, *J* = 8.5 Hz, 2H), 7.18 (d, *J* = 8.5 Hz, 2H), 7.79 (s, 2H); $^{13}C$ NMR ($CDCl_3$) $\delta$160.1, 133.8, 124.4, 113.8, 113.3,

106.3, 56.5, 55.3, 49.3, 26.0, 23.7; IR (neat) 1572 $cm^{-1}$; HRMS (ES) *m/z* calcd for $C_{18}H_{25}N_2O$ 285.1961, found 285.1967. (Note: This reaction was carried out by coworkers)

**N-(3-(Butylamino)-2-(4-methoxyphenyl)allylidene)butan-1-aminium Hexafluorophosphate (10f).** This compound was prepared by the above procedure with the exception that butylamine was used in place of pyrrolidine in which case a 71% yield of a solid was obtained. This material exhibited the following physical properties: mp 163 – 165 °C, $^1$H NMR ($CDCl_3$) $\delta$0.94 (t, *J* = 7.5 Hz, 6H), 1.34 (m, 4H), 1.58 (m, 4H), 3.49 (q, *J* = 7.0 Hz, 4H), 3.89 (s, 3H), 6.11 (broad s, 2H), 7.13 (d, *J* = 5.5 Hz, 2H), 7.14 (d, *J* = 5.5 Hz, 2H), 7.96 (d, *J* = 15.0 Hz, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$162.9, 160.7, 131.2, 119.4, 116.6, 107.1, 55.5, 49.6, 32.0, 19.4 and 13.5; IR (neat) 1584 $cm^{-1}$; HRMS (ES) *m/z* calcd for $C_{18}H_{29}N_2O$ 289.2274, found 289.2301.

**N-(3-(Hexylamino)-2-(4-methoxyphenyl)allylidene)hexan-1-aminium Hexafluorophosphate (10g).** This compound was prepared from by the above procedure with the exception that hexylamine was used in place of pyrrolidine in which case a 97% yield of a solid was obtained. This material exhibited the following physical properties: mp 173 – 176 °C, $^1$H NMR ($CDCl_3$) $\delta$0.86 (t, *J* = 6.6 Hz, 6H), 1.26 (broad s, 12 H), 1.58 (t, *J* = 7.2 Hz, 4H), 3.44 (t, *J* = 7.2 Hz, 4H), 3.83 (s, 3H), 6.40 (broad s, 2H), 7.07 (d, *J* = 9.0 Hz, 2H), 7.13 (d, *J* = 9.0 Hz, 2H) and 7.80 (broad s, 2H); $^{13}$C NMR ($CDCl_3$) *d* 162.6, 160.6, 131.1, 119.3, 116.5, 107.2, 55.4, 49.9, 31.1, 30.0, 25.8, 22.4 and 13.8; IR (neat) 1602 $cm^{-1}$; HRMS (ES) *m/z* calcd for $C_{22}H_{37}N_2O$ 345.2900, found 345.2935.

**N-(3-(sec-Butylamino)-2-(4-methoxyphenyl)allylidene)butan-2-aminium Hexafluorophosphate (10h).** This compound was prepared by the above procedure with the exception that sec-butylamine was used in place of pyrrolidine in which case a 50% yield of a solid was obtained after flash chromatography. This material exhibited the following physical properties: mp 142 – 144 °C, $^1$H NMR ($CDCl_3$) $\delta$0.93 (t, *J* = 7.5 Hz, 6H), 1.28 (d, *J* = 5.5 Hz, 6H), 1.54 (m, 4H), 3.64 (m, 2H), 3.90 (s, 3H), 5.86 (broad s, 2H), 7.13 (s, 4H) and 8.07 (d, *J* = 15.5 Hz, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 161.3, 160.4, 131.0, 119.6, 116.5, 106.9, 57.8, 55.3, 29.6, 20.3 and 10.1; IR (neat) 1585 $cm^{-1}$; HRMS (ES) *m/z* calcd for $C_{18}H_{29}N_2O$ 289.2274, found 289.2258.

**N-(3-(2,4-Dimethoxybenzyl)amino)-2-(4-methoxyphenyl)allylidene)-1-(2,4-dimethoxy-phenyl)methanaminium Hexafluorophosphate (10i).** This compound was prepared by the above procedure with the exception that 2,4-dimethoxybenzylamine was used in place of pyrrolidine in which case a 50% yield of a solid was obtained after flash chromatography. This material exhibited the following physical properties: mp 70 – 72 °C, $^1$H NMR ($CDCl_3$) $\delta$3.76 (s, 6H), 3.82 (s, 6H), 3.86 (s, 3H), 4.53 (s, 4H), 6.44 (broad s, 2H), 6.47 (dd, *J* = 2.0 Hz, *J* = 8.5 Hz, 2H), 7.19 (d, *J* = 8.5 Hz, 2H), 8.05 (broad s, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$162.1, 161.6, 160.4, 158.5, 131.1, 130.8, 119.9, 116.1, 115.8, 106.7, 104.6, 98.7, 60.4, 55.4, 53.5, 49.7; IR (neat) 1584 $cm^{-1}$; HRMS (ES) *m/z* calcd for $C_{28}H_{33}N_2O_5$ 477.2384, found 477.2341.

**1-(2-(4-Methoxyphenyl)allyl)pyrrolidine (11a).** To a 100 mL round bottom flask equipped with a magnetic stir bar and condenser was added the amine exchanged vinamidinium salt **(10a)** (1.00 g, 2.64 mmol), sodium borohydride (0.300 g, 7.93 mmol) and 50 mL of anhydrous isopropanol. The resulting reaction mixture was refluxed for 24 hours, allowed to cool to room temperature and was concentrated *in vacuo*. The crude residue was diluted with 100 mL of ethyl acetate and the organic layer was washed with water (3 x 50 mL) and brine (2 x 50 mL). The organic phase was

dried using anhydrous $Na_2SO_4$ and was filtered and concentrated *in vacuo* to give a viscous oil. This material was subjected to flash chromatographic purification on a silica column using a Biotage SP-1 instrument and a hexane/ethyl acetate gradient in which case 0.510 g (89% yield) of an oil was obtained. This material exhibited the following physical properties: bp 148 – 150 °C at 1.6 Torr, $^1$H NMR ($CDCl_3$) $\delta$1.78 (broad s, 4H), 2.55 (broad s, 4H), 3.46 (broad s, 2H), 3.83 (s, 3H), 5.19 (s, 1H), 5.36 (s, 1H), 6.88 (d, *J* = 8.5 Hz, 2H) and 7.49 (d, *J* = 8.5 Hz, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 159.0, 145.1, 133.1, 127.3, 113.6, 112.7, 61.0, 55.2, 54.2 and 23.6; HRMS (ES) *m/z* calcd for $C_{14}H_{20}NO$ 218.1539, found 218.1550. (Note: This reaction was carried out by coworkers)

**n-Butyl-[2-(4-methoxyphenyl)-allyl]amine (11f).** This compound was prepared according to the previous procedure with the exception that amine exchanged vinamidinium salt **10f** was used. Chromatographic purification of the crude reaction product resulted in a 62% yield of a solid, which exhibited the following physical properties: mp 140 – 145 °C; $^1$H NMR ($CDCl_3$) $\delta$ 0.89 (t, *J* = 7.5 Hz, 3H), 1.28 (m, 2H), 1.63 (quintet, *J* = 7.5 Hz, 2H), 2.98 (t, *J* = 7.5 Hz, 2H), 3.85 (s, 3H), 4.20 (s, 2H), 5.47 (s, 1H), 5.64 (s, 1H), 6.98 (d, *J* = 8.4 Hz, 2H) and 7.37 (d, *J* = 8.4 Hz, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 162.6, 160.5, 131.5, 119.5, 116.4, 107.1, 55.4, 49.6, 32.0, 19.4 and 13.4; IR (neat) 3258 cm$^{-1}$; HRMS (ES) *m/z* calcd for $C_{14}H_{22}NO$ 220.1696, found 220.1714.

**n-Hexyl-[2-(4-methoxyphenyl)-allyl]amine (11g).**This compound was prepared according to the previous procedure with the exception that amine exchanged vinamidinium salt **10g** was used. Chromatographic purification of the crude reaction product resulted in a 99% yield of a viscous oil, which exhibited the following physical properties: bp 68 – 69 °C at 0.83 Torr; $^1$H NMR ($CDCl_3$) $\delta$0.87 (t, *J* = 6.9 Hz, 3H), 1.25 (broad s, 6H), 1.49 (m, 2H), 2.71 (t, *J* = 7.5 Hz, 2H), 3.79 (s, 2H), 3.81 (s, 3H), 5.25 (s, 1H), 5.43 (s, 1H), 6.89 (d, *J* = 9.0 Hz, 2H) and 7.35 (d, *J* = 9.0 Hz, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$159.8, 142.5, 130.7, 127.3, 114.8, 114.3, 55.3, 52.4, 48.4, 31.4, 28.2, 26.5, 24.4 and 13.9; IR (neat) 3200 cm$^{-1}$; HRMS (ES) *m/z* calcd for $C_{16}H_{26}NO$ 248.2014, found 248.2080.

**s-Butyl-[2-(4-methoxyphenyl)-allyl]amine (11h).** This compound was prepared according to the previous procedure with the exception that amine exchanged vinamidinium salt **10h** was used. Chromatographic purification of the crude reaction product resulted in a 62% yield of a viscous oil, which exhibited the following physical properties: bp 78 – 79 °C at 0.23 Torr; $^1$H NMR ($CDCl_3$) $\delta$ 0.84 (t, *J* = 4.5 Hz, 3H), 1.29 (d, *J* = 3.9 Hz, 3H), 1.56 (m, 1H), 1.68 (m, 1H), 3.00 (m, 1H), 3.86 (s, 3H), 4.04 (d, *J* = 14.4 Hz, 1H), 4.18 (d, *J* = 14.4 Hz, 1H), 5.43 (s, 1H), 5.58 (s, 1H), 6.97 (d, *J* = 8.7 Hz, 2H) and 7.38 (d, *J* = 8.7 Hz, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$160.4, 138.2, 128.4, 127.5, 119.2, 114.9, 56.0, 55.4, 49.0, 26.2, 15.7 and 9.4; IR (neat) 3227 cm$^{-1}$; HRMS (ES) *m/z* calcd for $C_{14}H_{22}NO$ 220.1696, found 220.1730.

**(2,4-Dimethoxybenzyl)-[2-(4-methoxyphenyl)-allyl]amine (11i)**. This compound was prepared according to the previous procedure with the exception that amine exchanged vinamidinium salt **10i** was used. Chromatographic purification of the crude reaction product resulted in a 60% yield of a viscous oil, which exhibited the following physical properties: bp 128 – 129 °C at 0.81 Torr; $^1$H NMR ($CDCl_3$) $\delta$3.59 (s, 3H), 3.81 (s, 3H), 3.84 (s, 2H), 3.86 (s, 3H), 4.10 (s, 2H), 6.41 (d, *J* = 2.5 Hz, 1H), 6.47 (dd, *J* = 2.5 Hz, *J* = 8.0 Hz, 1H), 6.96 (d, *J* = 8.5 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 1H) and 7.32 (d, *J* = 8.0 Hz, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$162.4, 160.3, 158.6, 138.1, 132.2, 128.3, 127.4, 119.1, 114.6, 110.5, 105.1, 98.4, 60.5, 55.4, 55.2, 50.5 and 47.8; IR (neat) 3228 cm$^{-1}$; HRMS (ES) *m/z* calcd for $C_{19}H_{24}NO_3$ 314.1751, found 314.1747.

**4-(4-Methoxyphenyl)-2-pyrrolidin-1-yl-pent-4-enoic acid ethyl ester (18a).** To a 100 mL round bottom flask equipped with a magnetic stir bar and condensor was added 0.029 g (1.18 mmol) of sodium hydride, and 30 mL of anhydrous acetonitrile. t-Butanol (0.197 g 2.34 mmol) was added to the flask and the resulting mixture was allowed to react until gas evolution was no longer observed. Quaternary salt **17a** (0.351 g, 0.913 mmol) was added to the reaction mixture and the resulting solution was allowed to stir overnight. The reaction mixture was quenched with several mL of ethanol and the solvent was removed from the reaction mixture *in vacuo.* The resulting residue was dissolved in ethyl acetate (30 mL) and the ethyl acetate phase was then extracted with water (2 x 30 mL) and brine (2 x 30 mL) and dried over anhydrous sodium sulfate. After the ethyl acetate phase was filtered and concentrated *in vacuo*, the resulting residue was subjected to flash chromatographic purification on a silica column using a Biotage SP-1 instrument and a hexane:ethyl acetate gradient in which case 0.270 g (98% yield) of an oil was obtained. This material exhibited the following physical properties: bp 95 – 96 °C at 0.63 Torr; $^{1}$H NMR ($CDCl_3$) $\delta$ 1.23 (t, *J* = 7.0 Hz, 3H), 1.79 (broad s, 4H), 2.63 (m, 2H), 2.80 (m, 2H), 2.93 (dd, *J* = 10.0 Hz, J = 13.5 Hz, 1H), 3.00 (dd, *J* = 5.0 Hz, *J* = 13.5 Hz, 1H), 3.30 (dd, *J* = 5.0 Hz, J = 10.0 Hz, 1H), 3.83 (s, 3H), 4.09 (q, *J* = 7.0 Hz, 2H), 5.06 (s, 1H), 5.27 (s, 1H), 6.87 (d, *J* = 7.0 Hz, 2H) and 7.35 (d, *J* = 7.0 Hz, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 172.0, 159.2, 144.0, 132.9, 127.4, 113.9, 113.7, 65.7, 60.3, 55.3, 50.7, 37.7, 23.4 and 14.3; ; IR (neat) 1720 $cm^{-1}$; HRMS (ES) *m/z* calcd for $C_{18}H_{26}NO_3$ 304.1907, found 304.1911. ((Note: This reaction was carried out by coworkers)

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