# PALLADIUM-CATALYZED AND THERMAL REARRANGEMENTS OF *N*-ALLYL YNAMIDES

by

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# PALLADIUM-CATALYZED AND THERMAL REARRANGEMENTS OF *N*-ALLYL YNAMIDES

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Under the Supervision of Professor Richard P. Hsung

At the University of Wisconsin-Madison

Ynamides have emerged as a highly useful functional group over the last ten years due in large part to their unique balance between reactivity and stability. They have been widely employed by exploiting three modes of reactivity: (1) inherent nucleophilicity, (2) activation by π-Lewis and Brönsted acids, and (3) isomerization to ketenimines *via* metal-catalyzed or thermal rearrangements. This thesis will showcase our studies on the generation and fate of ketenimines prepared by Pd-catalyzed *N*-to-*C* allyl transfers and thermal *aza*-Claisen rearrangements of *N*-allyl ynamides.

We were initially interested in trapping *in situ* generated ketenimines and ketenimino–Pd-π-allyl complexes with external nucleophiles for the *de novo* synthesis of α-allyl amidines, vinylogous amidines, and imidates. We later discovered that silyl-ketenimines were isolable, allowing us to demonstrate that the isomerization between ynamido– and ketenimino–Pd-π-allyl complexes occurred intramolecularly through tightly coordinated ion pairs.

By careful scrutiny of reaction byproducts, we characterized a rare *N*-to-*C* 1,3-sulfonyl shift leading to quaternary nitrile formation through the ketenimine intermediates.

Though the 1,3-sulfonyl shift was fascinating, it prevented us from fully utilizing the *in situ* generated ketenimines. Therefore, we developed a new class of *N*-phosphoryl derived ynamides and found that because 1,3-phosphoryl shifts were not operational, they could be employed in tandem *aza*-Claisen–[2 + 2] cycloadditions with imines to give azetidine-2-imines. In addition, we disclosed a series of tandem *aza*-Claisen–carbocyclizations using *N*-sulfonyl and *N*-phosphoryl ynamides for the synthesis of α,β-unsaturated cyclopentenimines and complex bi-and tricyclic scaffolds.

Finally, we demonstrated the feasibility of intercepting the ketenimino-Pd-π-allyl intermediates with tethered alkenes *via* highly diastereoselective intramolecular [2 + 2] cycloadditions. The alkene substitution pattern played an imminent role in favoring either a fused or crossed cycloaddition pathway, leading to fused or bridged cycloadducts.

# Acknowledgments

First, I thank the Lord, for I can do all things through Him who gives me strength. To my loving wife, Brittland, I owe more than mere words can express. You are my rock, my foundation, and my strength. You held me together when I thought I would surely fall apart; I would be lost without you. I thank you with all my heart for your patience, understanding, and utmost support. You are amazing. To my son, Markis, I love you so very much. You're a gift from God and you brightened the darkest of days with your smiles and laughter. Thank you.

I thank my parents, Chris and Judi, for teaching me to love to learn and to pursue my dreams without fear. Thank you, as well, to my brothers and sisters for your love and encouragement. I am so blessed to have Jeff and Linda, my father- and mother-in-law, in my life. Thanks for all you do for Brittland, Markis, and me. I am so fortunate to have such a big, supportive family.

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THIS DISSERTATION IS DEDICATED

TO MY WIFE, BRITTLAND, AND SON, MARKIS,

WITH ALL MY LOVE AND AFFECTION…

# Table of Contents

## List of Abbreviations

| | |
|---|---|
| [α] | specific rotation |
| Å | angstrom(s) |
| Ac | acetyl |
| $Ac_2O$ | acetic anhydride |
| anhyd | anhydrous |
| APCI | atmospheric pressure chemical ionization |
| aq | aqueous |
| Ar | aryl |
| Bn | benzyl |
| Boc | *tert*-butyoxycarbonyl |
| $Boc_2O$ | di-*tert*-butyl dicarbonate |
| br d | broad doublet |
| br s | broad singlet |
| br t | broad triplet |
| *n*-Bu | *normal*-butyl |
| C | celsius |
| calcd | calculated |
| Cbz | carboxybenzyl |
| concn | concentration |
| COSY | correlation spectroscopy |
| Cy | cyclohexyl |
| δ | chemical shift in ppm |

| | |
|---|---|
| d | doublet |
| dd | doublet of doublets |
| ddd | doublet of doublets of doublets |
| dddd | doublet of doublets of doublets of doublets |
| DCE | 1,2-dichloroethane |
| DCM | dichloromethane |
| DIPEA | *N,N'*-di*iso*propylethylamine |
| DMAP | 4-dimethylamino pyridine |
| DMF | *N,N*-dimethylformamide |
| DME | 1,2-dimethoxyethane |
| DMSO | dimethyl sulfoxide |
| *dr* | diastereomeric ratio |
| dt | doublet of triplets |
| *ee* | enantiomeric excess |
| ESI | electrospray ionization |
| equiv | equivalent |
| Et | ethyl |
| $Et_2O$ | diethyl ether |
| EtOAc | ethyl acetate |
| EtOH | ethanol |
| g | gram |
| h | hour |
| HMPA | hexamethylphosphoric triamide |

| | |
|---|---|
| HRMS | high resolution mass spectrometry |
| Hz | hertz |
| imid | imidazole |
| IPA | *iso*-propyl alcohol |
| IR | infared absorption spectroscopy |
| *J* | spin-spin coupling constant in hertz |
| kcal | kilocalorie |
| KHMDS | potassium hexamethyldisilazide |
| LAH | lithium aluminum hydride |
| LCMS | liquid chromatography/mass spectroscopy |
| LDA | lithium di*iso*propyl amide |
| m | multiplet |
| *M* | molar |
| MBS | *para*-methoxybenzenesulfonyl |
| *m/e* | mass to charge ratio |
| Me | methyl |
| mg | milligram |
| MHz | megahertz |
| mmHg | millimeters of mercury |
| min | minute |
| mL | milliliter |
| mM | millimolar |
| mmol | millimole |

| | |
|---|---|
| mol | moles |
| mp | melting point |
| Ms | methanesulfonyl |
| M.S. | molecular sieves |
| MTBE | methyl *tert*-butyl ether |
| *N* | normal |
| NBS | *N*-bromosuccinimide |
| NMR | nuclear magnetic resonance spectrometry |
| nOe | nuclear Overhauser enhancement |
| OAc | acetate |
| OMe | methoxy |
| Ph | phenyl |
| pipH | piperidine |
| $PPh_3$ | triphenylphosphine |
| ppm | parts per million |
| *p*-Ns | *para*-nitrobenzenesulfonyl |
| *p*-TsOH | *para*-toluenesulfonic acid |
| PPTS | pyridinium *para*-toluene sulfonate |
| *n*-Pr | *normal*-propyl |
| pyr | pyridine |
| q | quartet |
| quint | quintet |
| RCM | ring closing metathesis |

| | |
|---|---|
| *R* | Rectus (configurational) |
| $R_f$ | retention factor |
| rt | room temperature |
| *S* | Sinister (configurational) |
| s | singlet |
| SM | starting material |
| TBAF | tetra-*n*-butylammonium fluoride |
| TBDPS | *tert*-butyldiphenylsilyl |
| TBS | *tert*-butyldimethylsilyl |
| td | triplet of doublets |
| TES | triethylsilyl |
| Tf | trifluoromethanesulfonate |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| TIPS | triisopropylsilyl |
| TLC | thin layer chromatography |
| TMS | trimethylsilyl |
| Tol | toluene |
| Ts | *p*-toluenesulfonyl |
| tt | triplet of triplets |
| X | halogen (or group otherwise indicated) |

# List of Figures, Schemes, and Tables

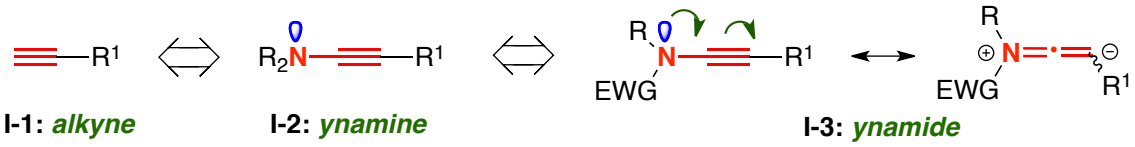
# Chapter 1. Introduction to Ynamides

# Chapter 1. Introduction to Ynamides

## 1.1 Reactivity and Stability of Ynamides

Ynamines[1] **I-2** and ynamides[2] **I-3** fall into a unique subclass of hetero-alkynes, where a nitrogen atom has been directly attached to the alkyne such that the nitrogen [*N*]-lone pair of electrons is delocalized into the π-system. This generates very electron-rich, polarized alkynes [**Figure I-1**].

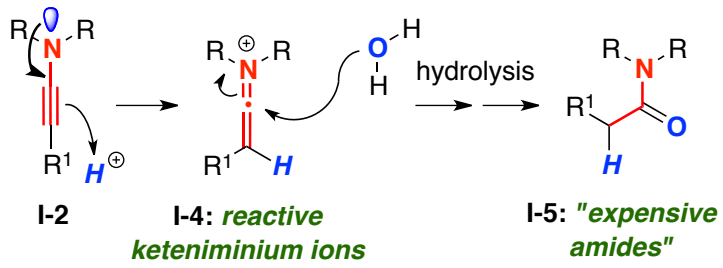
**Figure I-1. Structure of Ynamines and Ynamides**




**I-1:** ***alkyne*** **I-2:** ***ynamine*** **I-3:** ***ynamide***

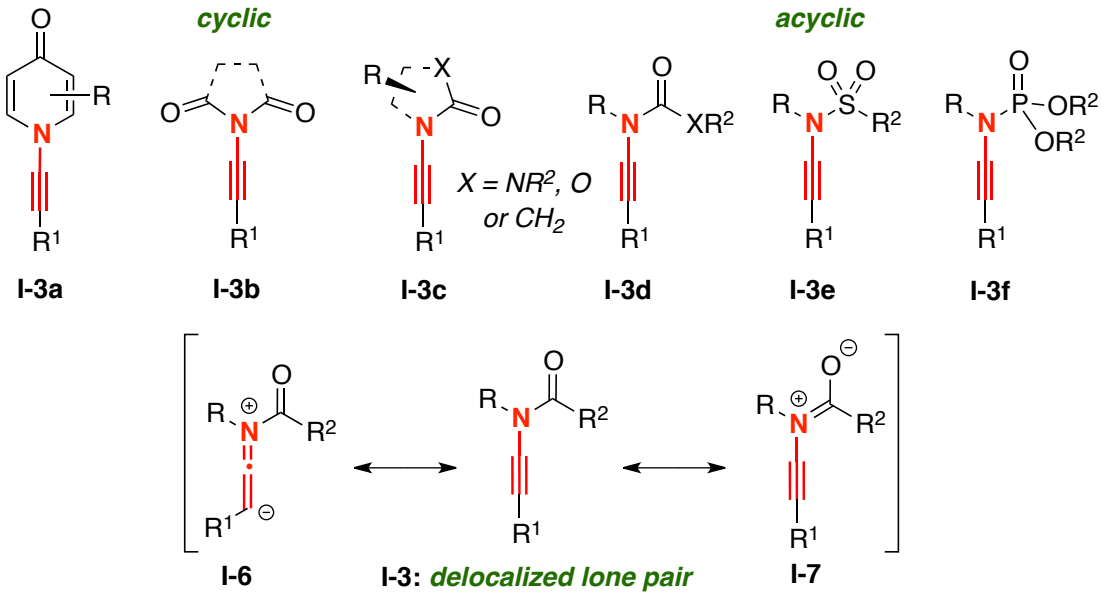
Ynamines are highly nucleophilic due to the nitrogen lone pair delocalization and therefore highly reactive. This allowed for the development of some exceptional chemistry in the 1960's through 1980's.[1] Unfortunately, reactions had to be kept scrupulously dry to prevent protonation of the ynamine leading to hydrolysis through keteniminium ion **I-4** resulting in a lengthy synthesis of simple amides **I-5** [**Scheme I-1**]. Not surprisingly, this severely limited the synthetic utility of ynamines and ultimately resulted in their decline from prominence.

**Scheme I-1. Problematic Ynamine Hydrolysis**




By introducing an electron-withdrawing group [EWG] to the nitrogen atom, thereby creating ynamides **I-3**, delocalization of the nitrogen-lone pair of electrons into the alkyne π-system could be mitigated to more effectively balance reactivity and hydrolytic stability [**Scheme I-2**]. A variety of cyclic and acyclic ynamides have been reported to date, most notably those derived from oxazolidinones **I-3c**, carbamates **I-3d** [X = O], and arylsulfonamides **I-3e** [$R_2$ = Ar].[2]

**Scheme I-2. Classes of Ynamides**



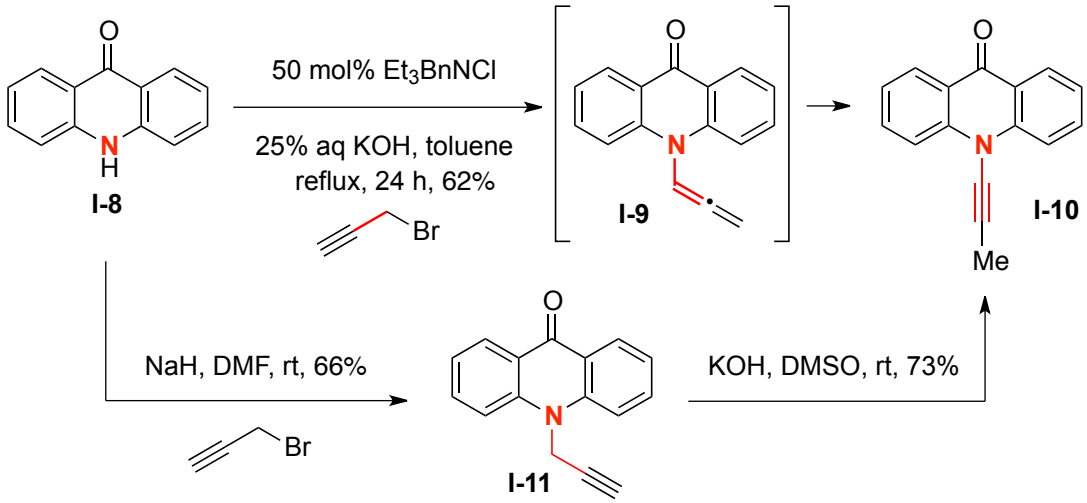
## 1.2 Ynamide Synthesis

Though there have been a vast number of methods for preparing ynamides reported over the last fifty years, almost all fall into four main categories: (1) isomerization from allenamides, (2) elimination from vinyl halides, (3) coupling of iodonium salts, and (4) amidative cross-coupling reactions. A few notable examples from each class will be discussed.

### 1.2.1 Isomerization from Allenamides

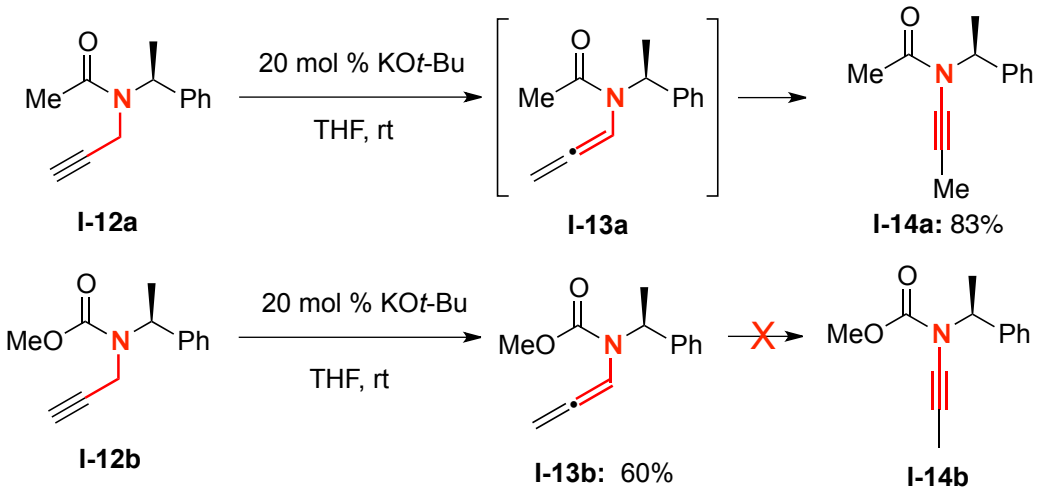
Galy[3] initially demonstrated the preparation of acridone-derived ynamide **I-10** by isomerization from *in situ* generated proparyl amide **I-11** using phase transfer conditions **[Scheme I-3]**. Interestingly, when 12 mol % KOH was used and the reaction was stopped at 4 h, allenamide **I-10** was isolated in 90% yield, representing the foundation for some of our later work on allenamide synthesis. Katritzky[4] later showed that isolation of propargyl amide **I-11** and subsequent isomerization using KOH in DMSO gave more reproducible results for ynamide formation without isolation of the intermediate allenamide **I-9**.

**Scheme I-3. Base-Induced Isomerization of Acridone Derived Ynamides**




Our group expanded on this isomerization protocol to prepare chiral amide-derived ynamides such as **I-14a** from propargyl amide **I-12a** [**Scheme I-4**].[5] Notably, this method was not suitable for the preparation of carbamate-derived ynamide **I-14b**. Instead, the reaction stopped at allenamide **I-13b** with no isomerization to ynamide **I-14b** found.

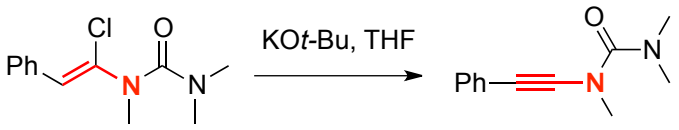
**Scheme I-4. Base-Induced Isomerization of Amide-Derived Ynamides**



### 1.2.2 Elimination from Vinyl Halides

Viehe[6] reported the first elimination protocol for preparing ynamides in 1972. They found that ynamide **I-16** could be synthesized via a base induced elimination of H–Cl from α-chloroenamide **I-15** [**Scheme I-5**].

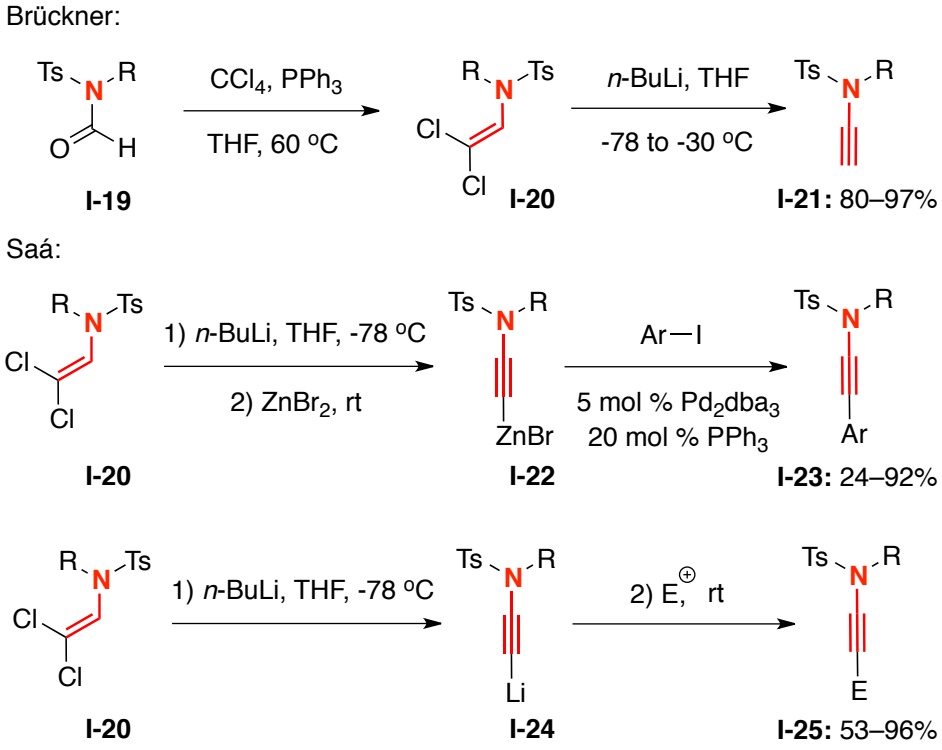
**Scheme I-5. Viehe's Ynamide Synthesis by Elimination**




**I-15** **I-16**: 64%

Brückner[7] and Saa[8] later reported a more general elimination procedure from β,β-dichloroenamides [**Scheme I-6**]. Brückner first showed that β,β-dichloroenamides **I-20**, which was easily prepared by an intercepted Corey-Fuchs reaction, could be subjected to *n*-BuLi to first eliminate H–Cl and then undergo lithium halogen exchange and protonation to afford terminal ynamides **I-21**. Saá found that transmetallatation of the lithiated ynamide with $ZnBr_2$ allowed for a subsequent Negishi coupling to prepare aryl-terminated ynamides **I-23** [**Scheme I-6**]. Alternatively, direct addition of an electrophile to **I-24** led to a variety of terminally-substituted ynamides **I-25**.[9]

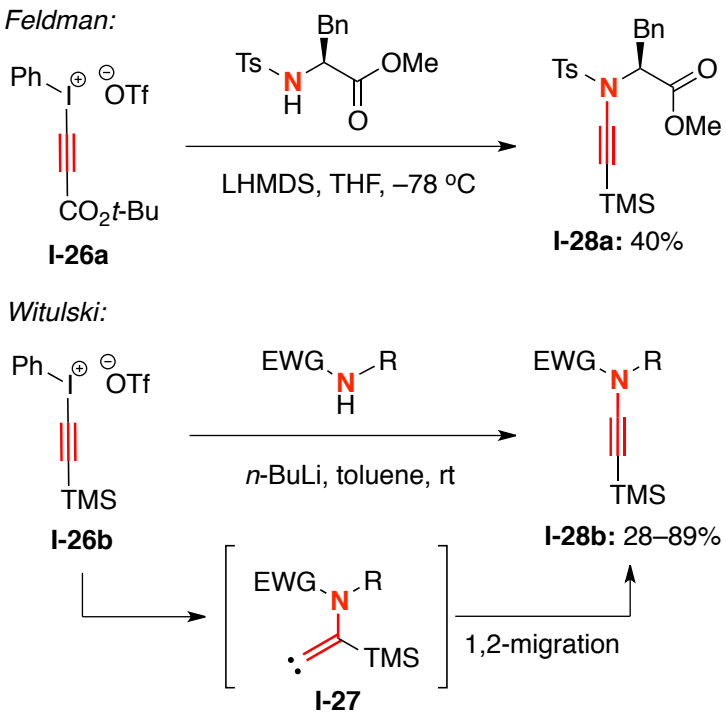
**Scheme I-6. Elimination of β,β-Dichloroenamides**




### 1.2.3 From Alkynyliodonium Salts

Feldman[10] first described a method to synthesize chiral ynamide **I-28a** from alkynyliodonium triflate salt **I-26a**. Witulski[11] later reported a more detailed discussion of the mechanism for this transformation, showing that a 1,2 migration was involved through **I-27**. They were also able to expand the substrate scope to prepare a variety of terminally-silylated ynamides **I-28b**. The silyl group could be readily cleaved using TBAF to prepare terminally unsubstituted ynamides, as well [**Scheme I-7**].

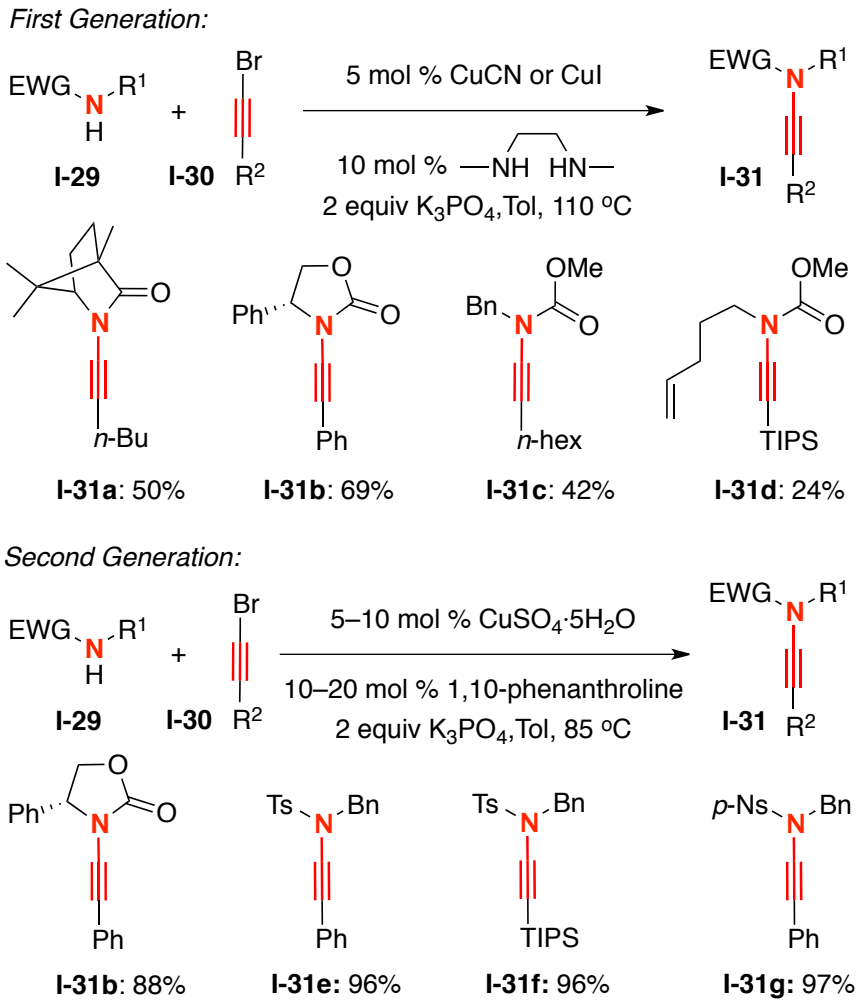
**Scheme I-7. Ynamides From Alkynyliodonium Triflates**




### 1.2.4 Amidative Cross-Coupling

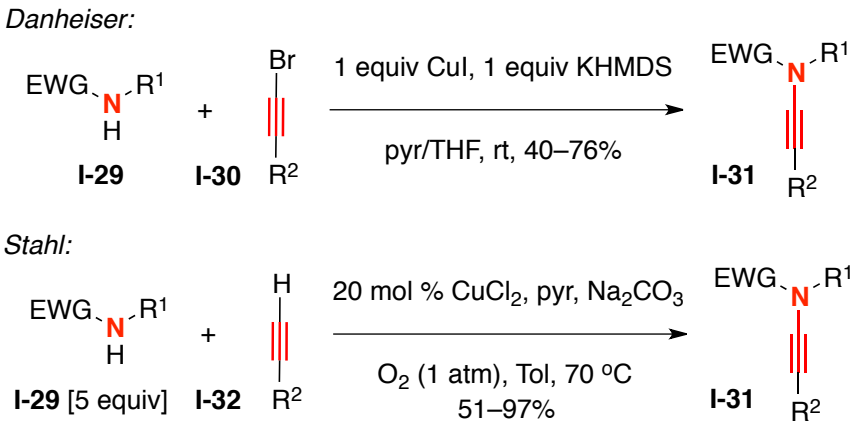
The most widely used method for preparing ynamides, a catalytic amidative cross-coupling, was developed in our labs. Our first-generation[12] cross-coupling employed Cu(I) salts with DMEDA [*N*,*N*'-dimethylethylenediamine] as the ligand and worked well for amides and carbamates, but failed with sulfonamides [**Scheme I-8**]. Also, the reactions required temperatures of 110 °C for optimal yields. Our second-generation[13] protocol using $CuSO_4 \cdot 5H_2O$ and 1,10-phenanthroline could be used to efficiently prepare *N*-sulfonyl ynamides, as well as amide and carbamate-derived ynamides while also proceeding at more mild reaction temperatures.

**Scheme I-8. Hsung's First and Second Generation Amidative Cross-Coupling**




A complementary method was described by Danheiser[14] using stoichiometric CuI and KHMDS [potassium hexamethyldisilazide] for the preparation of a variety of ynamides **I-31** [**Scheme I-9**]. One noteworthy feature was that the reaction could be carried out at rt. Stahl[15] also described an aerobic oxidative cross-coupling of amides and terminal-alkynes **I-32**. This eliminated the need for preparing relatively unstable alkynyl bromides, but also required the use of 5 equiv of amide to minimize dimerization of the alkyne.

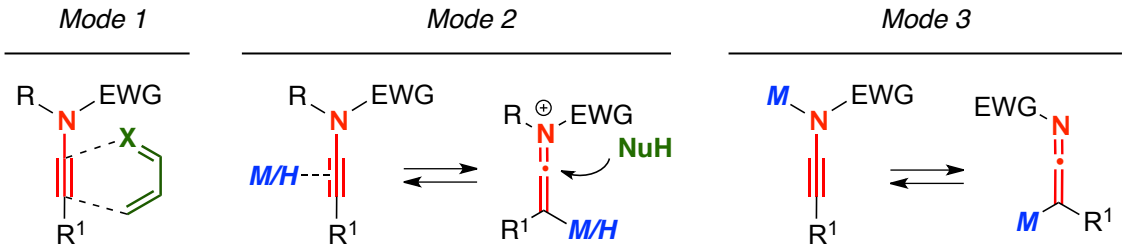
**Scheme 1-9. Danheiser and Stahl's Cross-Coupling Protocols**




## 1.3 Reactivity of Ynamides

Ynamides have attracted so much interest from the synthetic community because of their unique balance between reactivity and stability. Ynamides have largely been exploited through three modes of reactivity: (1) inherent nucleophilicity, (2) activation through the π-system using π-Lewis and Brönsted acids, and (3) isomerization to ketenimines *via* metal-catalyzed and thermal rearrangements [**Figure I-2]**.

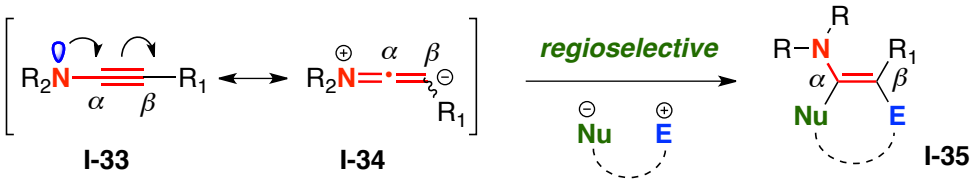
**Figure I-2. Modes of Ynamide Reactivity**



### 1.3.1 Inherent Nucleophilicity of Ynamides

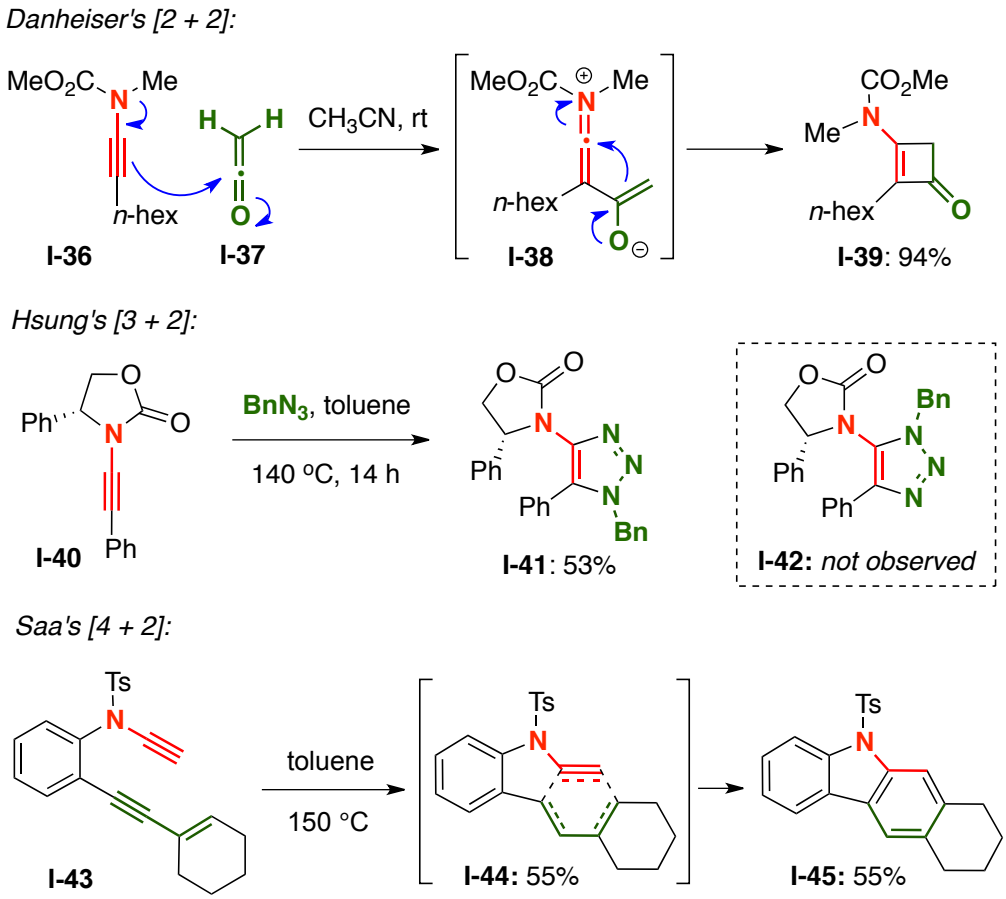
The inherent nucleophilicity at the β-carbon and electrophilicity at the α-carbon of ynamides affords exceptional regiochemical control during a variety of reactions with other polarized species [**Scheme I-10**]. This innate regiochemical bias is most clearly demonstrated in cycloaddition reactions.

**Scheme I-10. Bond-Polarization of Ynamides**




Ynamides have been employed in a vast array of cycloaddition reactions, though most are Lewis or Bronsted-acid catalyzed. However, to clearly illustrate the *inherent* reactivity of ynamides, one example each of a thermal, non-catalyzed [2 + 2], [3 + 2], and [4 + 2] cycloaddition is described in **Scheme I-11**. Danheiser[16] demonstrated that carbamate-derived ynamide **I-36** could participate in a stepwise-[2 + 2] cycloaddition with ketene **I-37** at rt to afford **I-39** in 94% yield as a single regiochemical isomer. In a similar manner, our group[17] reported the thermal [3 + 2] cycloaddition of chiral ynamide **I-40** with *N*-benzyl azide at 140 $^{o}$C to yield **I-41** in 53%. The other possible regioisomer **I-42** was not observed, owing to the unique bond polarization of ynamides. The intramolecular [4 + 2] cycloaddition of ynamide **I-43** was shown by Saa[18] to proceed at 150 $^{o}$C to give carbazoles **I-45**.

**Scheme I-11. Thermal Ynamide Cycloadditions**

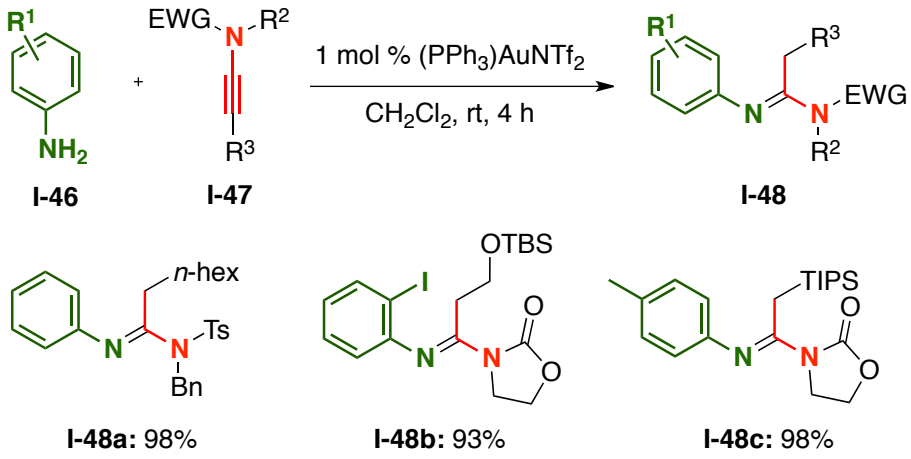



### 1.3.2 Lewis and Brönsted Acid Activation Through π-System

#### 1.3.2.1 Nucleophilic Additions

Both Lewis and Brönsted acids have been extensively used to activate ynamides, allowing nucleophiles to selectively add to the alkyne. In one recent example, Skrydstrup[19] reported the addition of amines to ynamides **I-47** for the preparation of primary amidines **I-48** using Gagosz's electrophilic gold catalyst [**Scheme I-12**]. The reaction conditions tolerated a variety of *N*-EWGs and aromatic amine nucleophiles, but one limitation was that only primary amidines could be prepared [see **Chapter 2**].

**Scheme I-12. Skrydstrup's Amidine Preparation**

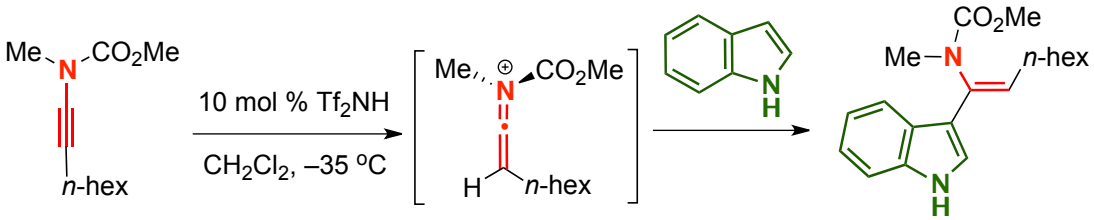



**I-46** **I-47** **I-48**

**I-48a:** 98% **I-48b:** 93% **I-48c:** 98%

Brönsted acids have also been used to carry out similar nucleophilic additions. One relevant example is Zhang's[20] intermolecular hydroarylation of ynamide **I-36** using catalytic trifluoromethanesulfonimide [$Tf_2NH$] to afford α-aryl enamide **I-50** through keteniminium ion **I-49** [**Scheme I-13**]. Our group[21] disclosed an intramolecular Pictet-Spengler version of this transformation as well.

**Scheme I-13. Zhang's Hydroarylation**

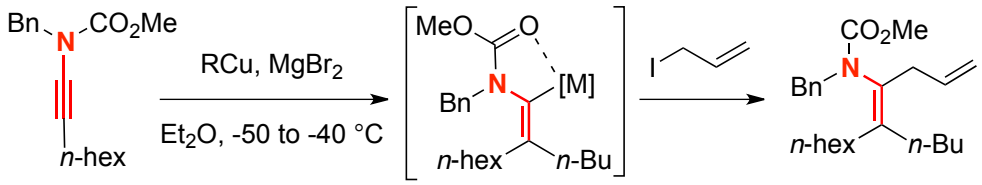



**I-36** **I-49** **I-50:** 74%, *Z*/*E* = >20:1

### 1.3.2.2 Umpolung-Type Additions

Interestingly, the regioselectivity can be completely switched so that the nucleophile adds to the ynamide β-carbon by invoking chelation between the *N*-EWG and Lewis acid. Marek[22] first demonstrated this phenomenon in the three-component coupling of ynamides like **I-51** with various organocuprates and electrophiles [**Scheme I-14**]. Chelation of the organometal reagent to the *N*-EWG allowed the nucleophile to add selectively to the β-carbon to give metallo-intermediate **I-52**. Trapping of **I-52** with allyl iodide then afforded tetrasubstituted enamide **I-53**. Other oxophilic metals, especially zinc, have been used in similar Umpolung-type additions.

**Scheme I-14. Chelation Controlled Addition**



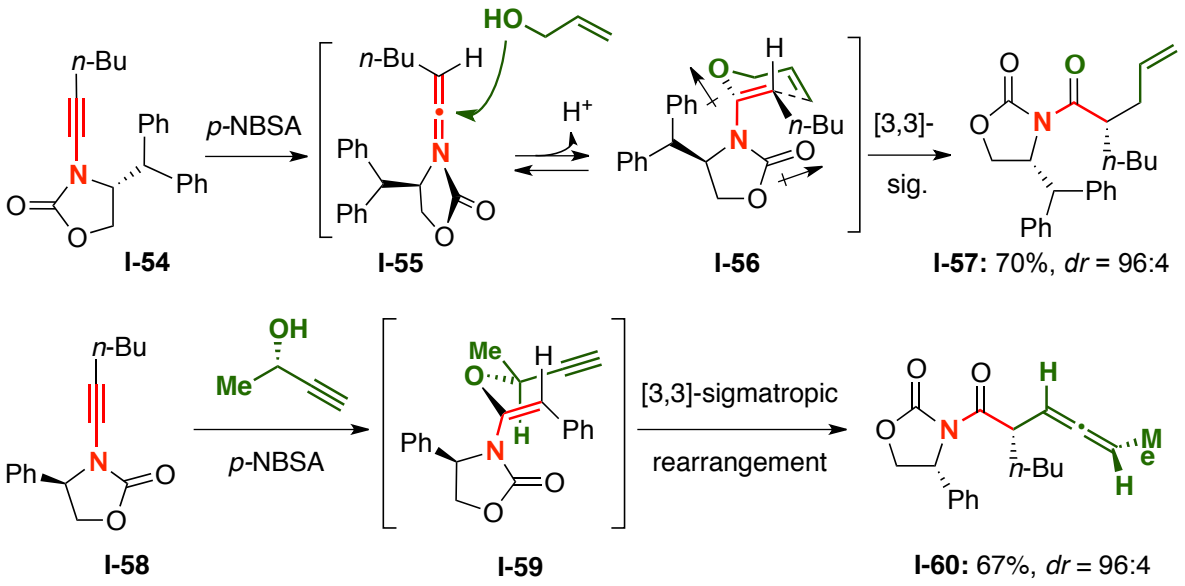

**I-51** **I-52** **I-53:** 55%

### 1.3.2.3 Tandem Addition–Rearrangements

In recent literature, there have been several examples of using the addition of nucleophiles to trigger pericyclic rearrangements. For example, we described a diastereoselective tandem hydroetherification–Ficini-Claisen[23] rearrangement for the synthesis of imide **I-57** [**Scheme I-15**]. Initially, ynamide **I-54** was activated by *p*-nitrobenzenesulfonic acid [*p*-NBSA] to give keteniminium ion **I-55**. Addition of allyl alcohol triggered the diastereoselective [3,3]-sigmatrophic rearrangement through dipole

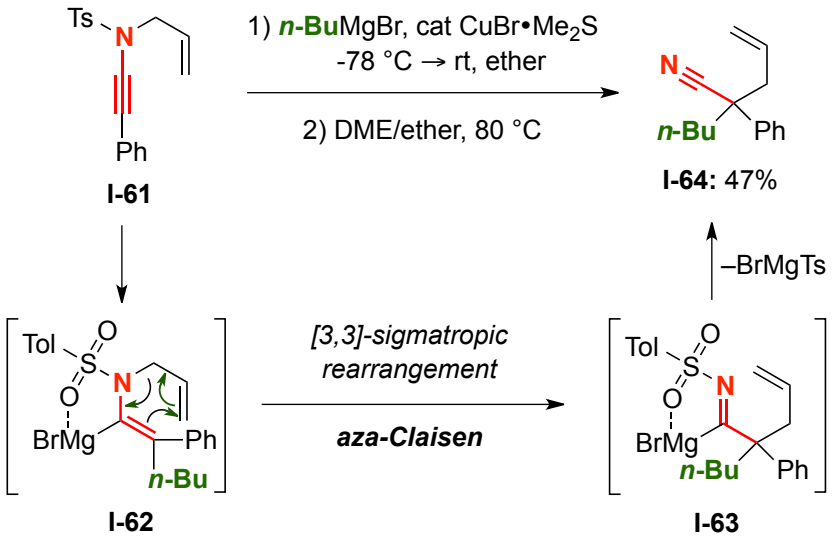
minimized **I-56** to give **I-57**. In addition, we disclosed highly diastereoselective Saucy-Marbet[24] rearrangements initiated by addition of propargyl alcohols to ynamides such as **I-58** to afford chiral allene **I-60**.

**Scheme I-15. Hsung's Ynamide Finici-Claisen and Saucy-Marbet Rearrangements**




Oshima and Yorimitsu[25] found that after umpolung addition of an alkyl grignard to ynamide **I-61**, the intermediate metallo-enamide **I-62** underwent a subsequent *aza*-Claisen rearrangement and detosylation to afford nitrile **I-64** [**Scheme I-16**].

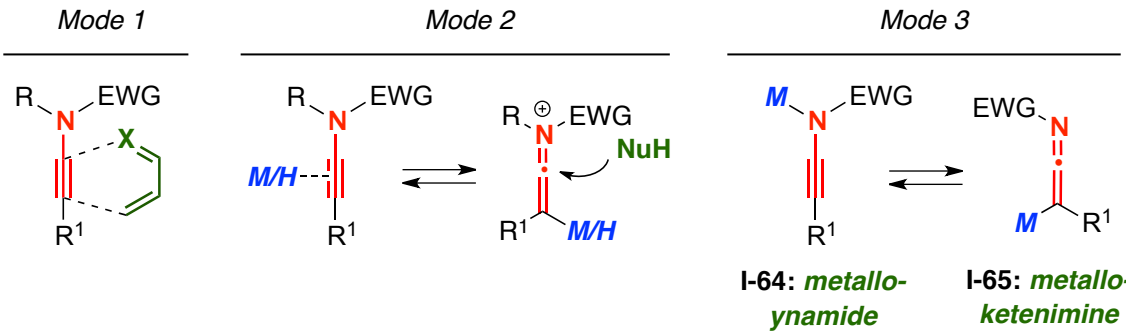
**Scheme I-16. Oshima and Yorimitsu's *Aza*-Claisen Rearrangement**




### 1.3.3 *In Situ* Metallo-Ynamides and Ketenimines

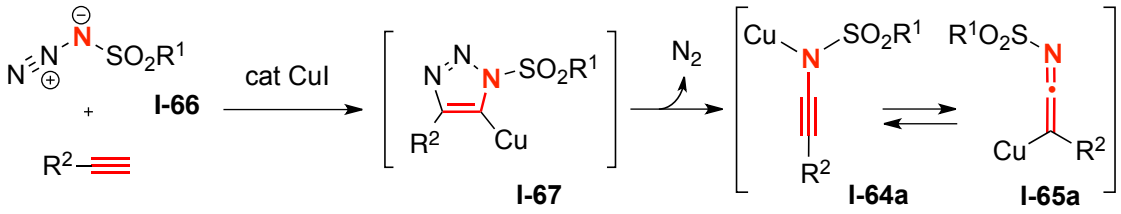
The first mode of ynamide reactivity deals with exploiting their inherent nucleophilicity and the second involves activation by π-Lewis and Brönsted acids to allow ensuing nucleophilic additions or cycloadditions to occur [**Figure I-3**]. The third mode of reactivity focuses on their rearrangement to ketenimines and metallo-ketenimines.

**Figure I-3. Modes of Ynamide Reactivity**



In 2005, Chang[26] first reported the propensity of *N*-sulfonyl triazoles generated from Huisgen alkyne–azide–[3 + 2] cycloadditions to extrude nitrogen gas, thereby forming Cu-ynamides **I-64a** *in situ* [**Scheme I-17**]. Furthermore, it was found that **I-64a** readily tautomerized to electrophilic Cu-ketenimines **I-65a**, which could be trapped with a variety of heteronucleophiles. Since Chang's initial work, the chemistry of *in situ* generated metallo ynamides and ketenimines has grown immensely [see **Chapter 2**].

**Scheme I-17. Metallo-Ynamides from Huisgen Azide–[3 + 2] Cycloadditions**




## 1.4 Conclusions

Because of the unique balance between reactivity and stability, the chemistry of ynamides has exploded in the last twenty years. Much of this has exploited the inherent nucleophilicity of ynamides or keteniminium generation by π-Lewis and Brönsted acids, however there has recently been a surge of interest in exploring the reactivity of *in situ* generated σ-activated metallo-ynamides. This third mode of reactivity will be the main focus of this thesis.

# Chapter 2. Nucleophilic Additions to *N*-Allyl Ynamides

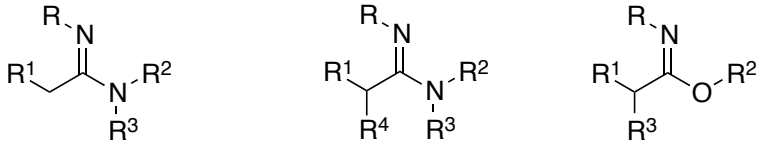
# Chapter 2. Nucleophilic Additions to *N*-Allyl Ynamides

## 2.1 Introduction to Amidines and Imidates

### 2.1.1 Amidines, Imidates, and Their General Preparation

Amidines[27,28] are a widely used functional group in medicinal chemistry[29] and an important pharmacophore in drug discovery.[30] They can be highly diversified depending on the substituents on nitrogen and the amidinyl $sp^2$-carbon, with the degree of branching distinguishing between primary **II-1** and secondary **II-2** amidines [**Figure II-1**]. Imidates **II-3**[31] are an oxy-analog and can similarly be fully functionalized at nitrogen, oxygen, and carbon.

**Figure II-1. Structure of Amidines and Imidates**

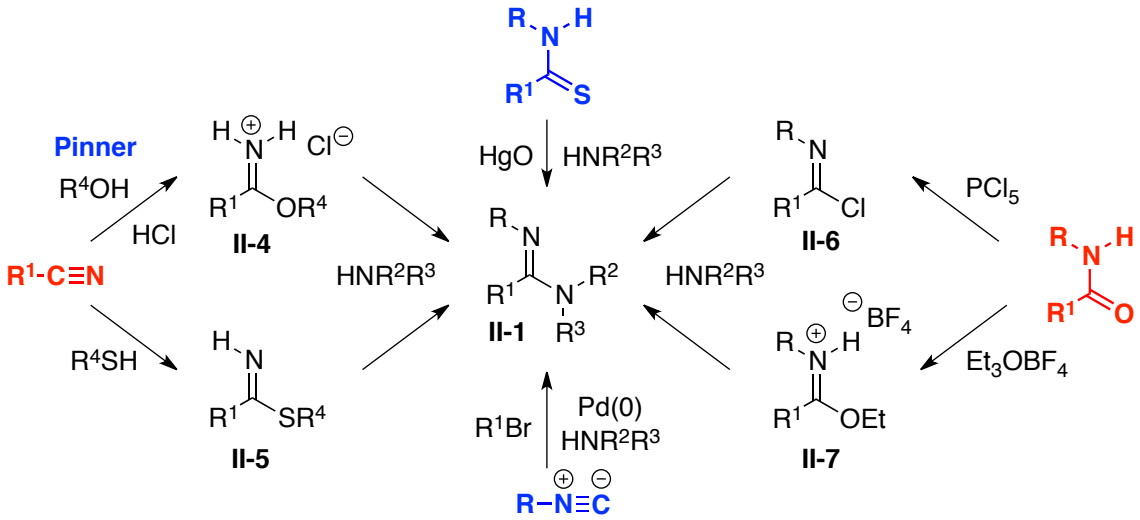



**II-1:** primary amidines **II-2:** secondary amidines **II-3:** imidates

There are several methods for preparing aliphatic and aromatic amidines, typically from nitriles, amides, thioamides, and isonitriles. The most widely used methods are the Pinner[32] and modified Pinner[33] reactions of nitriles with alcohols and thiols to give imidates **I-4** and thioimidates **I-5**, which afford amidines upon exposure to amine nucleophiles. However, these two methods don't work well for preparing secondary amidines and cannot be used for tertiary amidines. Alternatively, amides and thioamides are often used.[27,28] Amides may be activated by chlorinating or alkylating agents to give **II-6** or **II-7**,

respectively, which may be subsequently transformed to amidines by addition of amine nucleophiles. Thioamides may be used to directly prepare amidines by exposure to amines in the presence of mercury salts. Recently, Whitby[34] described an alternative preparation of amidines via Pd(0) catalyzed additions of aryl or alkyl halides and amines to isonitriles. The most recent advances in amidine preparation revolve around the interception of metallo-ynamide intermediates with amine nucleophiles [see **Scheme II-2**].

**Scheme II-1. General Preparation of Amidines**

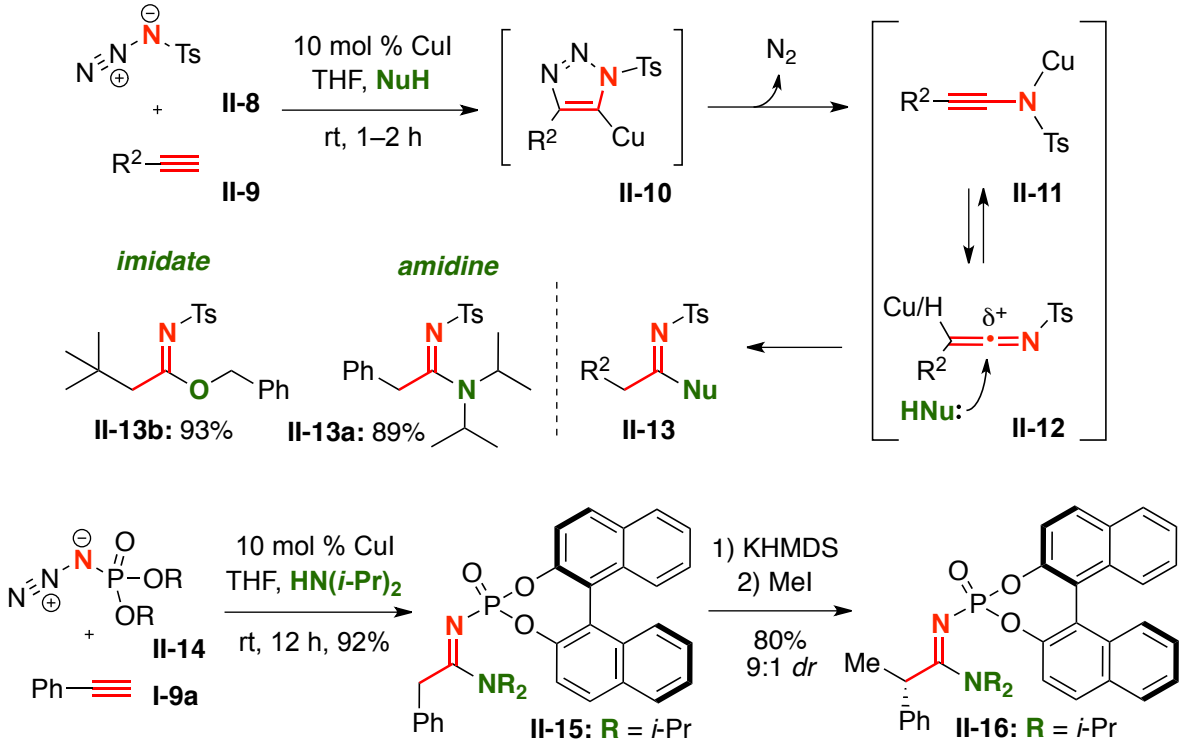



### 2.1.2 Generation and Trapping of Cu-Ketenimines

In 2005, Chang[26] reported the first examples of nucleophilic trappings of metallo-ketenimines generated *in situ* via Cu(I)-catalyzed Huisgen–[3 + 2] cycloadditions of *N*-sulfonyl azides with terminal alkynes. As shown in **Scheme II-2**, when a sulfonyl was used as the azide nitrogen's electron-withdrawing group [EWG], the intermediate Cu-triazoles **II-10** underwent extrusion of $N_2$ to generate metallo-ynamides **II-11** and their tautomeric form,

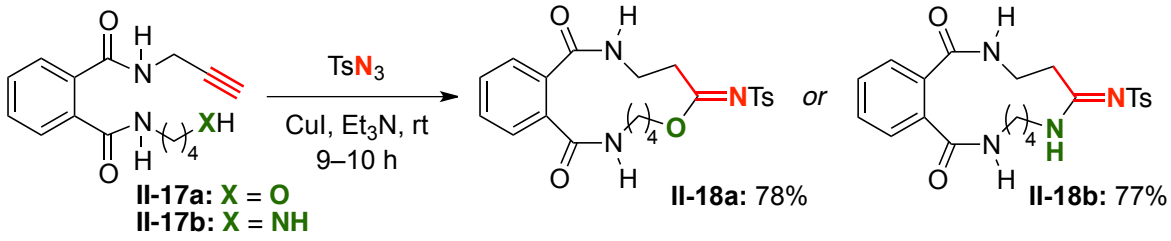
metallo-ketenimines **II-12**. In the presence of amine nucleophiles, the electrophilic ketenimines **II-12** could be trapped to yield primary amidines such as **II-13a**, representing a successful three-component coupling. In 2006, Chang[35] expanded this methodology to include nucleophilic trappings with alcohols, giving rise to *N*-sulfonyl imidates like **II-13b**. They later showed that *N*-phosphoryl azides[36] **I-14** could similarly be employed to give *N*-phosphoryl amidines **II-15**. Notably, when a chiral binol-derived phosphoryl-protecting group was used as in **II-15**, the amidine could be diastereoselectively alkylated to prepare chiral secondary amidines.

**Scheme II-2. Chang's 3-Component Coupling for Amidines and Imidates**



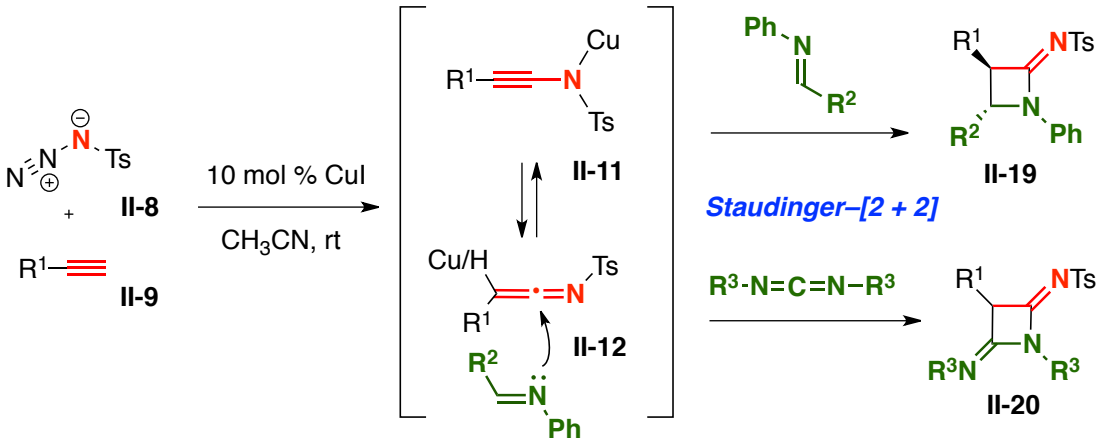
Fu[37] later used this methodology to synthesize a variety of macrocyclic imidates **II-18a** and amidines **II-18b** *via* intramolecular addition of primary amines and alcohols to *in situ* generated Cu-ketenimines [**Scheme II-3**].

**Scheme II-3. Intramolecular Addition for Macrocyclic Amidines and Imidates**




Fokin[38] and Xu[39] elegantly demonstrated the synthesis of azetidine imines **II-19** and 2,4-diiminoazetidine imines **II-20** by reacting imines and carbodiimides with *in situ* generated Cu-ketenimines **II-12**, respectively, in Staudinger-type [2 + 2] cycloadditions [**Scheme II-4**]. For **II-19**, the predominant isomers were *trans*, however the *cis* isomers could be favored by using electron-deficient imines, owing to the well-studied diastereoselective 4π-electron electrocyclic ring closure after initial attack of the *N*-lone pair onto the electrophilic ketenimine.

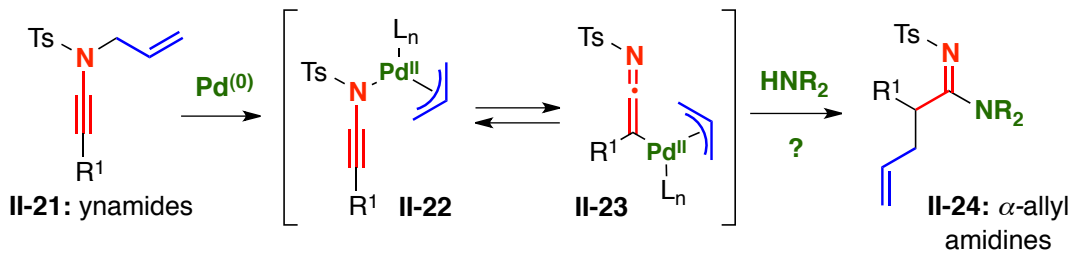
**Scheme II-4. Fokin and Xu's Intermolecular [2 + 2] for Azetadine Imines**




## 2.2 Pd-Catalyzed Amidine Synthesis from *N*-Allyl Ynamides

Inspired by the beautiful work on amidine and imidate synthesis through the interception of Cu-ynamides and Cu-ketenimines,[26,35–39] we postulated that analogous ynamido-Pd-π-allyl complexes **II-22** could be accessed from Pd(0)-catalyzed reactions of *N*-allyl ynamides **II-21** [**Scheme II-5**].[40–42] We envisioned that trapping of the tautomeric ketenimino-Pd-π-allyl complexes **II-23** with external amine nucleophiles[40,42] would then allow for the synthesis of secondary α-allyl amidines **II-24** through a unique *N*-to-*C* allyl transfer.

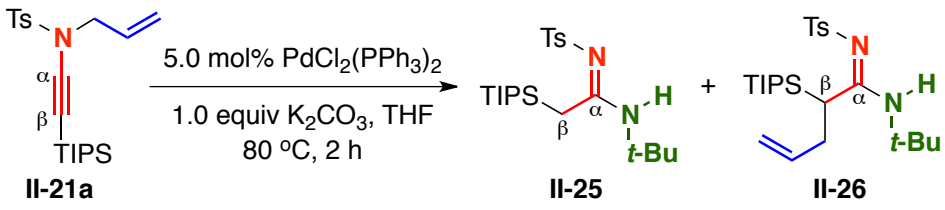
**Scheme II-5. α-Allyl Amidines from *N*-Allyl Ynamides**



### 2.2.1 Deallylative Primary Amidine Formation

Our initial discovery in the synthesis of amidines came while exploring the hydroamination of *N*-allyl ynamide **II-21a** with 5.0 mol % $Pd(PPh)_3Cl_2$ and *t*-butyl amine [**Scheme II-6**]. To our surprise, the major product when using 10 equiv of *t*-butyl amine was amidine **II-25**, where the allyl group had been cleaved. Significantly, by decreasing the amount of amine used, α-allyl amidine **II-26** became a competing product, signifying that a deallylative hydroamination-type pathway was at least not the only one in operation.

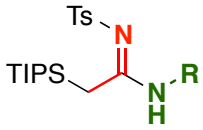
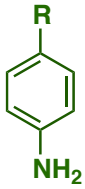
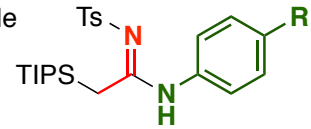
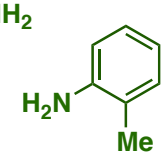
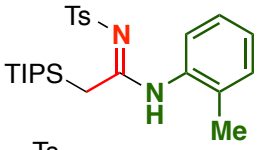
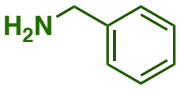
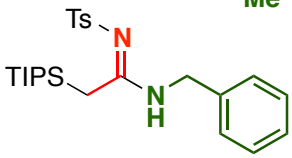
**Scheme II-6. Discovery of Divergent Amidine Synthesis from *N*-Allyl Ynamides**




| $H_2N$-*t*-Bu [equiv]: | yield [%]: | | |
|---|---|---|---|
| 10.0 | | 94 | ≤2 |
| 5.0 | | 94 | 5 |
| 3.0 | | 42 | 37 |

We first decided to focus our attention on the preparation of des-allyl amidines by using 5 equiv of primary amine nucleophile, thereby avoiding the complication of the migrating allyl group [**Table II-1**]. Using 5.0 mol % $PdCl_2(PPh_3)_2$ at 80 °C, the reaction progressed smoothly with primary aliphatic and aromatic amines yielding primary des-allyl amidines **II-27–II-33** in moderate to excellent yields from ynamide **II-21a**. Not surprisingly, the yields were lower when electron-deficient and sterically hindered nucleophiles were used [entries 5 and 6].

**Table II-1. Deallylative Primary Amidine Formation**

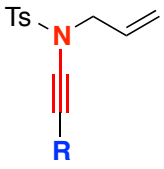
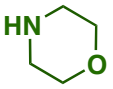
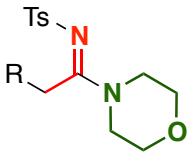
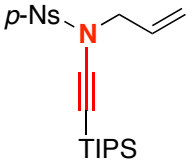
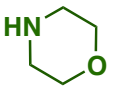
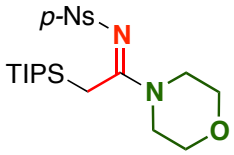
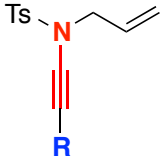
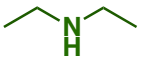
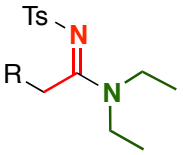
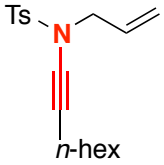
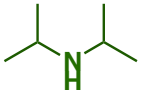
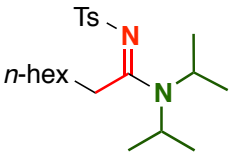
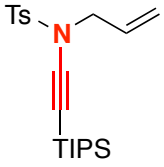
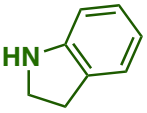
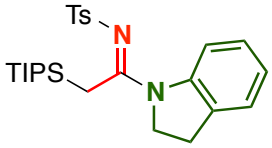
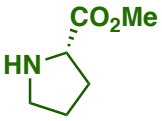
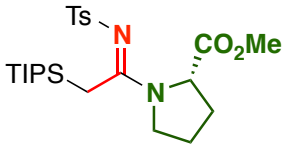
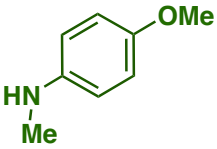
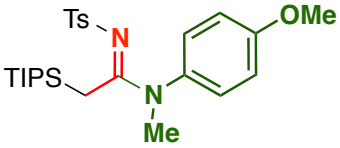
| entry | amines [5.0 equiv][a] | amidine products | | yield [%][b] |
|---|---|---|---|---|
| 1 | $H_2N-R$, R = *n*-Bu |  | R = *n*-Bu | **II-27** 87 |
| 2 | $H_2N-R$, R = *c*-hex | | R = *c*-hex | **II-28** 92 |
| 3 |  R = OMe |  | R = OMe | **II-29** 50 |
| 4 | R = H | | R = H | **II-30** 71 |
| 5 | R = Cl | | R = Cl | **II-31** 22 |
| 6 |  |  | | **II-32** 30 |
| 7 |  |  | | **II-33** ≥95 |

[a] Reaction conditions: Ynamide **II-21a**, 5.0 mol % $PdCl_2(PPh_3)_2$, 1.0 equiv $K_2CO_3$, THF [conc = 0.05 *M*], 80 °C, 5-8 h. [b] Isolated yields.

### 2.2.2 Deallylative Secondary Amidine Formation

We continued our investigation of des-allyl amidine synthesis using a variety of secondary amine nucleophiles [**Table II-2**]. The substrate scope was exceptional, tolerating a wide variety of terminally-functionalized ynamides as well as cyclic [entries 1–5, 11], acyclic [entries 6–9], sterically hindered [entry 9], and aromatic [entries 10 and 12] secondary amines in moderate to excellent yields.

**Table II-2. Selected Examples of Deallylative Secondary Amidine Formation**

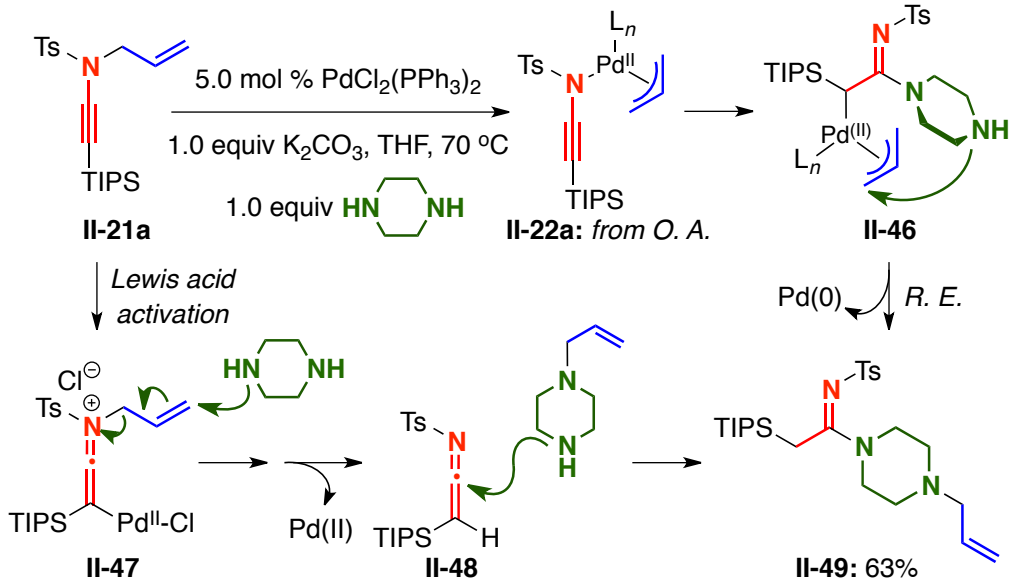
| entry | ynamides | amines[a] | amidine products | | yield [%][b] |
|---|---|---|---|---|---|
| 1 |  **II-21a** |  |  | **R** = TIPS | **II-34** ≥95 |
| 2 | **II-21b** | | | **R** = *t*-Bu | **II-35** ≥95 |
| 3 | **II-21c** | | | **R** = $(CH_2)_3OTBS$ | **II-36** 92 |
| 4 | **II-21d** | | | **R** = 2-MeO-Ph | **II-37** 37 |
| 5 |  **II-21e** |  |  | | **II-38** 39 |
| 6 |  **II-21a** |  |  | **R** = TIPS | **II-39** ≥95 |
| 7 | **II-21f** | | | **R** = Ph | **II-40** ≥95 |
| 8 | **II-21g** | | | **R** = *n*-hex | **II-41** ≥95 |
| 9 |  **II-21g** |  |  | | **II-42** 70 |
| 10 |  **II-21a** |  |  | | **II-43** ≥95 |
| 11 | **II-21a** |  |  | | **II-44** ≥95 |
| 12 | **II-21a** |  |  | | **II-45** 82 |

[a] Reaction conditions: 5.0 mol % $PdCl_2(PPh_3)_2$, 1.0 equiv $K_2CO_3$, THF [conc = 0.05 *M*], 80 °C, 5-8 h. [b] Isolated yields.

Interestingly, when piperizine was used as the nucleophile, *N*-allylated amidine **II-49** was isolated in 63%, lending some information as to the mechanism of deallylation [**Scheme**

**II-7**]. One possible mechanistic pathway could involve ynamido-Pd-π-allyl complex **II-22a**, resulting from oxidative addition of Pd(0) to ynamide **II-21a**. Tautomerization and nucleophilic attack by piperizine would give **II-46**, which followed by an intramolecular Tsuji-Trost[43] type deallylation could afford **II-49**. Alternatively, the reaction could proceed through Lewis acid activation of **II-21a** by Pd(II) to give Pd-keteniminium complex **II-47**, followed by intermolecular deallylation and subsequent nucleophilic attack by *N*-allyl piperizine on ketenimine **II-48**.

**Scheme II-7. Possible Deallylation Pathways**



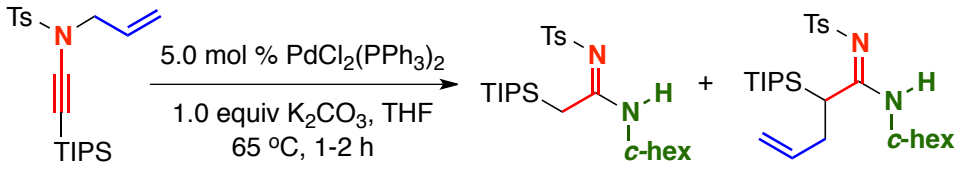

### 2.2.3 *N*-to-*C* Allyl Transfer Amidine Formation

#### 2.2.3.1 Optimization of Allyl Transfer

While exploring des-allyl amidine synthesis, we thought it should be possible to alter the reaction pathway to favor the more mechanistically intriguing allyl transfer that we

observed in our initial experimentation. We had shown that the distribution of allylated to non-allylated amidines depended strongly on the amount of nucleophile used, with more nucleophile favoring the deallylation pathway. Conversely, by slow introduction of 1 equiv of amine *via* syringe pump addition, α-allyl amidine **II-51** could be isolated in 73% yield [**Table II-3**].

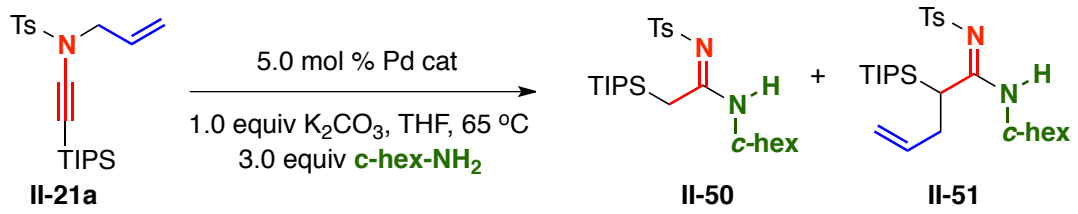
**Table II-3. Effect of Equivalents of Amine on Allyl Transfer**




| | | | |
|---|---|---|---|
| ***c*-hex-NH$_2$** [equiv]: | 5.0 | yield [%]: 92 | 5 |
| | 3.0 | 63 | 24 |
| | 1.0 | 44 | 45 |
| *syringe pump add'n:* | 1.0 | 11 | 73 |

The slow addition of amine was cumbersome and still resulted in some des-allyl amidine formation. So, next we screened a small library of Pd(II) and Pd(0) sources to investigate the dependence of deallylation on the catalyst used [**Table II-4**]. With Pd(II) catalysts [entries 1-5], the deallylation pathway was dominant, however the Pd(0) source $Pd(PPh_3)_4$ [entry 6] gave exclusively the allyl transfer amidine **II-51** even adding *excess* amine in one portion [i.e. not slow addition].

**Table II-4. Impact of Pd Source on Allyl Transfer**

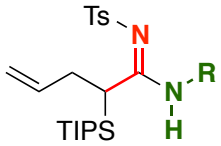
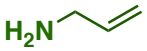
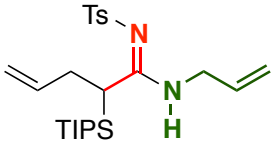
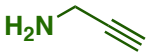
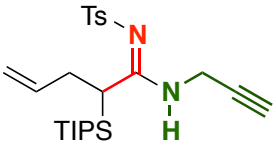
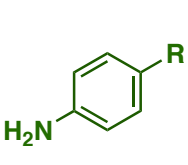
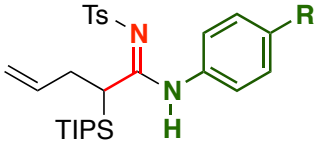
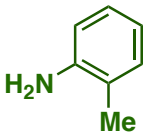
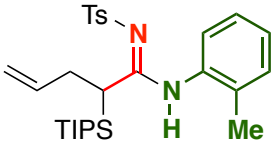



| entry | Pd source | time [h] | isolated yield [%] | |
|---|---|---|---|---|
| 1 | $Pd(PPh_3)_2Cl_2$ | 2 | 63 | 24 |
| 2 | $Pd(dppe)Cl_2$ | 48 | 30 | <5 |
| 3 | $Pd(dppf)Cl_2$ | 24 | 95 | 0 |
| 4 | $PdCl_2$ | 20 | 66 | 16 |
| 5 | $Pd(OAc)_2$ | 20 | 65 | 8 |
| **6** | **$Pd(PPh_3)_4$** | **3** | **0** | **≥95** |

### 2.2.3.2 Allyl Transfer with Primary Amines

Having optimized the conditions to achieve the *N*-to-*C* allyl transfer by using a Pd(0) catalyst, we constructed a library of α-allyl amidines from primary amine nucleophiles. As shown in **Table II-5**, a variety of alkyl amines could be employed [entries 1–4], resulting in amidines **II-52–II-55** in good to excellent yields. Also, electron-rich, electron-deficient, and sterically-hindered aniline-based nucleophiles [entries 5–9] were tolerated in moderate to good yields to give **II-56–II-60**.

**Table II-5. Synthesis of α-Allyl Amidines From Primary Amines**

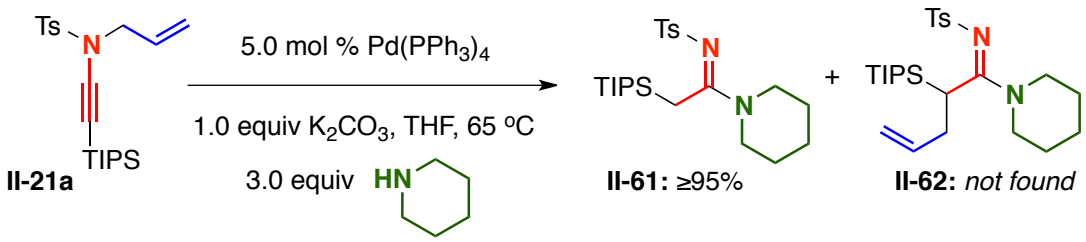
| entry | primary amines[a] | α–allyl amidine | | yield [%][b] | |
|---|---|---|---|---|---|
| 1 | $H_2N$–R, R = *n*-Bu |  | R = *n*-Bu | **II-52** | ≥95 |
| 2 | $H_2N$–R, R = *t*-Bu | | R = *t*-Bu | **II-53** | 90 |
| 3 |  |  | | **II-54** | 73 |
| 4 |  |  | | **II-55** | 76 |
| 5 |  R = OMe |  | R = OMe | **II-56** | 67 |
| 6 | R = H | | R = H | **II-57** | 85[c] |
| 7 | R = Cl | | R = Cl | **II-58** | 78[d] |
| 8 | R = $CF_3$ | | R = $CF_3$ | **II-59** | 54 |
| 9 |  |  | | **II-60** | 52 |

[a] Reaction conditions: Ynamide **II-21a**, 5.0 mol % $Pd(PPh_3)_4$, 1.0 equiv $K_2CO_3$, 3.0 equiv amine, THF [conc = 0.05 *M*], 65 °C, 5–8 h. [b] Isolated yields. [c] 1.0 equiv of amine used. [d] Reaction time was 24 h.

### 2.2.3.3 Mechanism for Ally Transfer Versus Deallylation

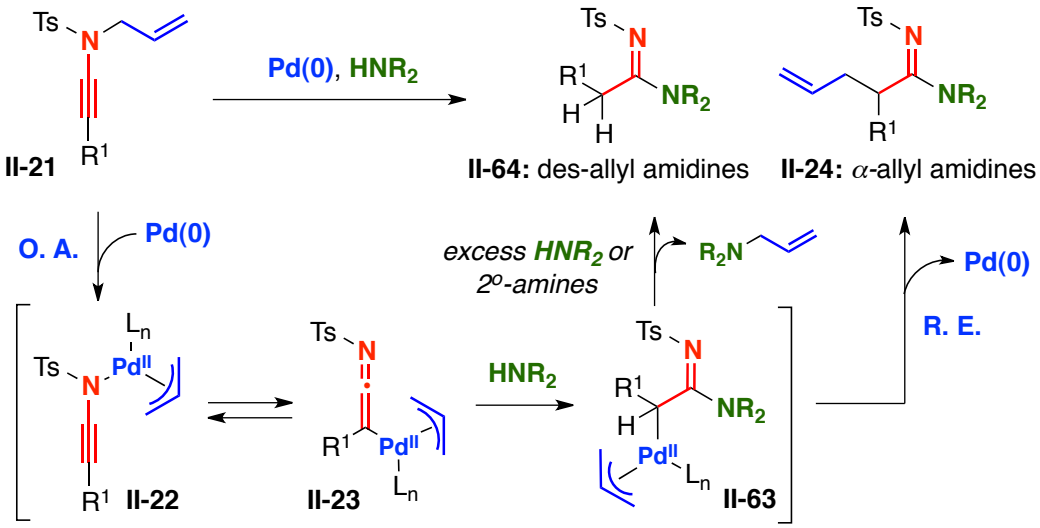
Unfortunately, when we began to assess the substrate tolerance with respect to secondary amine nucleophiles, we again discovered that the deallylation pathway was dominant, if not exclusive. As a revealing example, the addition of piperidine to ynamide **II-21a** in the presence of 5.0 mol % $Pd(PPh_3)_4$ gave des-allyl amidine **II-61** as the sole product [**Scheme II-8**].

**Scheme II-8. Problematic Allyl Transfer With Secondary Amines**



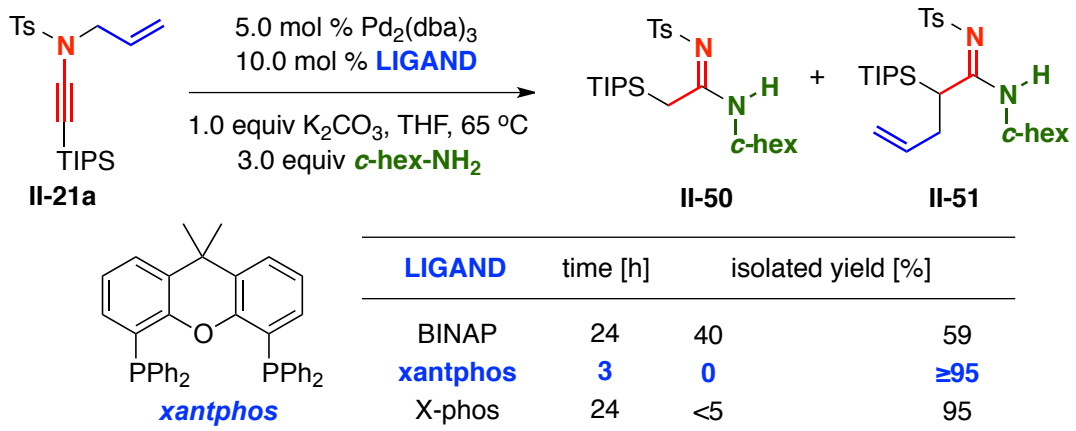

At this time, we were quite discouraged by our inability to favor allyl transfer amidine synthesis with secondary amines, but still persistent. All of our previous experimentation had allowed us to develop a mechanistic model for the divergence between allyl transfer and deallylation [**Scheme II-9**]. After the initial oxidative addition of Pd(0) to ynamide **II-21**, ynamido-Pd-π-allyl complex **II-22** and it's tautomeric form **II-23** should result. The nucleophilic amine may then add to **II-23** to give the amidine-Pd-π-allyl complex **II-63**. We learned previously that by using excess of amine or more nucleophilic secondary amines,[44] des-allyl amidine **II-64** resulted, likely through a Tsuji-Trost[43] type addition of the amine to the Pd-π-allyl. Alternatively, when less nucleophilic primary amines were used or added slowly, reductive elimination could be favored resulting in α-allyl amidines **II-24**. So, it became clear that to favor allyl transfer, we had to favor reductive elimination.

**Scheme II-9. Mechanistic Interpretation of Reaction Divergence**




Reductive elimination is known to be facilitated by bulky and/or electron-rich phosphine ligands.[45-47] So, we carefully chose a small group of ligands to study and quickly discovered that xantphos[45,46] and X-phos[47] were excellent at promoting allyl transfer with primary amine nucleophiles, though X-phos required a far longer reaction time to go to completion [**Table II-6**]. It is noteworthy that $Pd_2(dba)_3$ alone [with *n*-Bu amine as nucleophile] was not suitable, resulting in a mixture of starting material and both allyl and des-allyl amidine products, clearly demonstrating the ligand effect.

**Table II-6. Effect of Phosphine Ligand on Allyl Transfer**

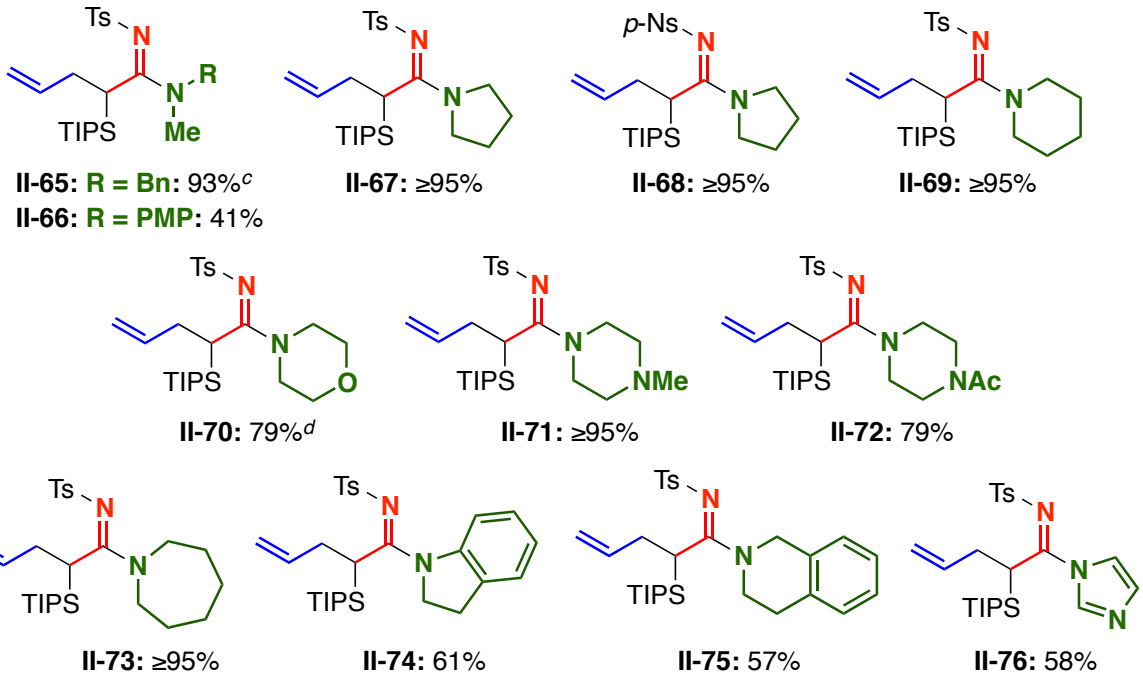



| LIGAND | time [h] | | isolated yield [%] |
|---|---|---|---|
| BINAP | 24 | 40 | 59 |
| **xantphos** | **3** | **0** | **≥95** |
| X-phos | 24 | <5 | 95 |

### 2.2.3.4 Allyl Trnasfer with Secondary Amines

The real discovery came when using our new catalytic system [5.0 mol % $Pd_2(dba)_3$ and 10.0 mol % xantphos] in amidine synthesis employing *secondary* amine nucleophiles.[40] Gratifyingly, the amine scope was excellent, tolerating a wide range of secondary amines in moderate to excellent yields with little to no deallylation observed even by crude $^1H$ NMR [**Figure II-2**]. In many cases, especially for **II-65** and **II-66**, the NMR spectra was convoluted by rotameric issues, but nOe analysis revealed that the amidines adopted an *E* geometry with respect to the C=N bond [see **Appendix II**].

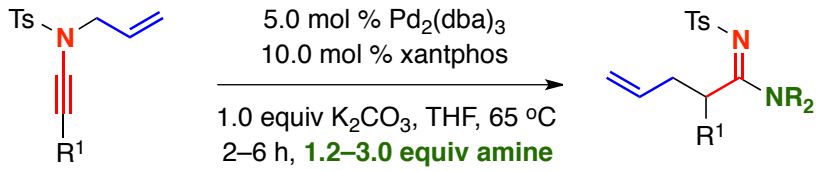
**Figure II-2. Secondary Amines in α-Allyl Amidine Synthesis**[a,b]




[a] Reaction conditions: Ynamide **II-21a**, 5.0 mol % $Pd_2(dba)_3$, 10.0 mol % xantphos, 1.0 equiv $K_2CO_3$, 3.0 equiv amine, THF [conc = 0.05 *M*], 65 °C, 1.5–6 h. [b] Isolated yields. [c] 10.0 mol % $Pd_2(dba)_3$, 20.0 mol % xantphos, and 5.0 equiv amine were used. [d] The only successful example using 5.0 mol % $Pd(PPh_3)_4$.

With an established catalytic system for allyl transfer in hand, we looked at how non-TIPS terminated ynamides would behave. A variety of silyl-terminated ynamides **II-21h**–**II-21j** gave the respective α-allyl amidines in excellent yields using pyrrolidine as the nucleophile [**Table II-7**, entries 1–3]. Also, alkyl-terminated ynamides **II-21c** and **II-21k** were tolerated, though the yields were slightly diminished [entries 4–6].

**Table II-7. Tolerance for Ynamide Functionality**



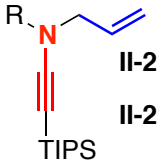
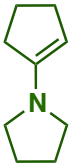
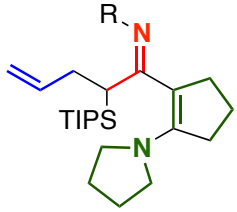
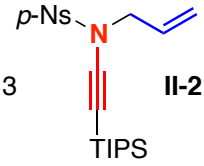
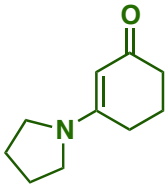
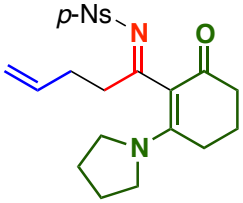
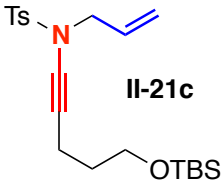
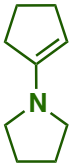
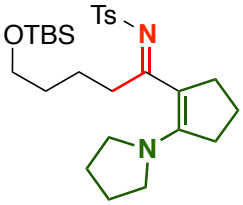
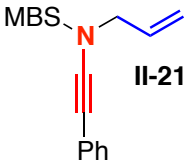
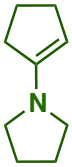
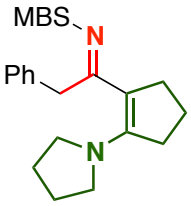
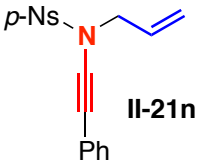
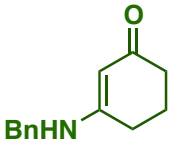
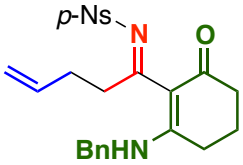
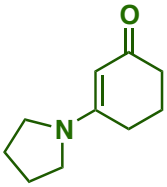
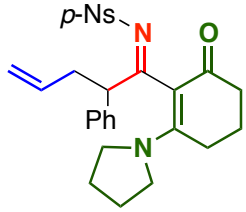

| entry | ynamides | $R^1$ = | amidines | $NR_2$ = | yield [%][a] |
|---|---|---|---|---|---|
| 1 | **II-21h** | TBDPS | **II-77** | pyrrolidinyl | 95 |
| 2 | **II-21i** | TBS | **II-78** | pyrrolidinyl | 94 |
| 3 | **II-21j** | TES | **II-79** | pyrrolidinyl | 87 |
| 4 | **II-21c** | $(CH_2)_3OTBS$ | **II-80** | *c*-hex-NH | 41 |
| 5 | **II-21k** | *c*-hex | **II-81** | pyrrolidinyl | 54 |
| 6 | **II-21k** | *c*-hex | **II-82** | *c*-hex-NH | 69 |

[a] Isolated yields.

### 2.2.4 Addition of Enamines for Vinylogous Amidine Synthesis

Thus far, we had developed a catalytic system that favored reductive elimination over amine-promoted deallylation for the synthesis of α-allyl amidines. We wondered how far we could push the boundaries of reactivity and, therefore, decided to investigate the use of *carbon*-nucleophiles in vinylogous amidine synthesis.[42] Enamines and vinylogous amides seemed to be ideal choices and turned out to work quite well [**Table II-8**], though the allyl transfer vs. deallylation again became problematic in some cases and no clear trend was evident. One major problem with using enamine **II-83** was enamine hydrolysis as amidines resulting from pyrrolidine addition were also seen [see **Scheme II-10**]. Unfortunately, the use of more stable, and less nucleophilic, enamides did not result in the desired amidine formation [See **Chapter 3**]. Also, vinyologous amide **II-85** bearing a free amine resulted in no discernable formation of **II-91**, instead largely decomposing.

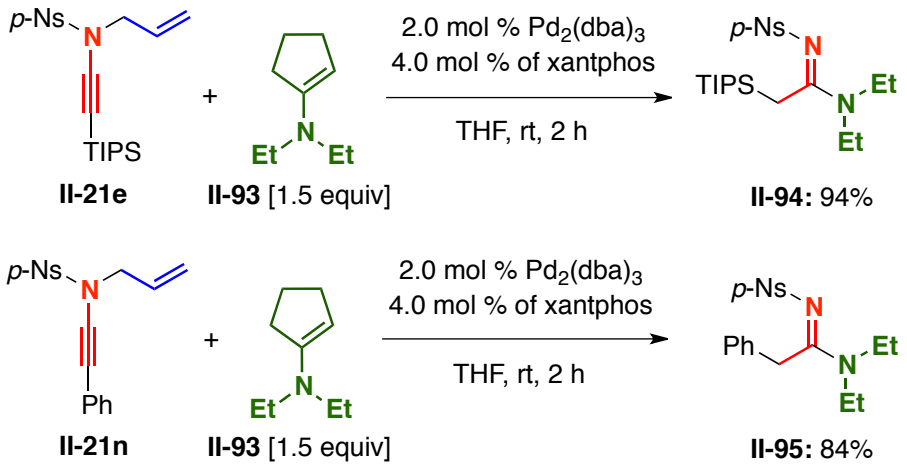
**Table II-8. Vinylogous Amidines *via* Addition of Enamines**

| entry | ynamides | enamines[a] | time [h] | temp [°C] | vinylogous amidines | yield [%][b] |
|---|---|---|---|---|---|---|
| 1 |  **II-21a:** R = Ts |  **II-83** | 2 | 70 |  **II-86** | 52 |
| 2 | **II-21l:** R = MBS | | 2 | 50 | **II-87** | 71[c] |
| 3 |  **II-21e** |  **II-84** | 12 | 70 |  **II-88** | 58[d] |
| 4 |  **II-21c** |  **II-83** | 0.5 | 50 |  **II-89** | 54 |
| 5 |  **II-21m** |  **II-83** | 2 | 25 |  **II-90** | 57 |
| 6 |  **II-21n** |  **II-85** | -- | 25–75 |  **II-91** | -- |
| 7 | |  **II-84** | 2 | 75 |  **II-92** | 62[e] |

[a] Unless otherwise noted, all reactions utilized 3.0 equiv of the enamine, 5.0 mol % $Pd_2(dba)_3$, 10.0 mol % of xantphos, and were run in THF [conc = 0.05 *M*]. [b] Isolated yields. [c] 1.5 equiv of $K_2CO_3$. [d] 1.5 equiv of **II-84**, 2.0 mol % $Pd_2(dba)_3$, and 4.0 mol % of xantphos. [e] 1.5 equiv of $K_2CO_3$ and 1.5 equiv of **II-84**.

To illustrate the problem of enamine hydrolysis, when acyclic enamine **II-93** was used, only des-allyl amidines **II-94** and **II-95** were isolated even when the reactions were run at rt **[Scheme II-10]**.

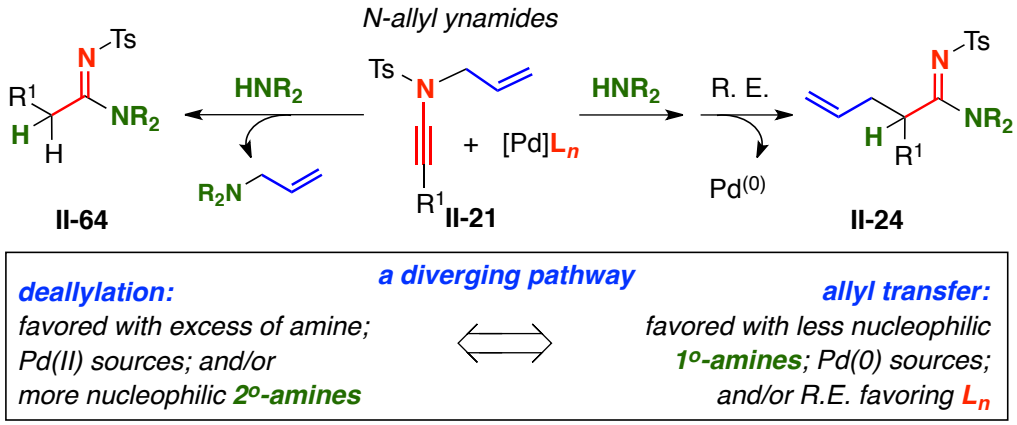
**Scheme II-10. Enamine Hydrolysis–Deallylative Amidine Synthesis**




### 2.2.5 Summary of Allyl Transfer vs. Deallyative Amidine Synthesis

Shown in **Figure II-3** is a summary of our findings on the divergence between *N*-to-*C* allyl transfer and deallylative amidine synthesis. Deallylation was favored with excess of amine, Pd(II) sources, and/or more nucleophilic secondary amines. The allyl transfer pathway was favored with less nucleophilic primary amines or slow addition, Pd(0) sources, and/or reductive elimination promoting phosphine ligands.

**Figure II-3. Dichotomy of Deallylation and Allyl Transfer**




## 2.3 Thermal *Aza*-Claisen Rearrangements of *N*-Allyl Ynamides

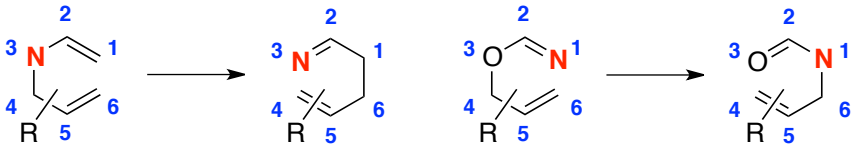
During our course of study with Pd-catalyzed amidine formation, we found that a strictly thermal pathway could also be used to generate ketenimines *in situ* via a rare alkyne 3-*aza*-Claisen rearrangement.[48,49]

### 2.3.1 Introduction to *Aza*-Claisen Rearrangements

The aza-Claisen rearrangement[48] is a nitrogen-analog to the widely studied oxygen-based Claisen[49] and carbon-based Cope rearrangements. Like the Claisen and Cope, the *aza*-Claisen is a loosely concerted [3,3]-sigmatropic rearrangement proceeding through a chair or boat-like 6-membered transition state, allowing chiral information to be transferred during the rearrangement. The two most common types of *aza*-Claisen rearrangement are the 3-*aza*-Claisen and 1-*aza*-Claisen, as dictated by the position of the nitrogen atom [**Figure II-4**]. Unlike the Claisen and Cope rearrangements, thermal 3-*aza*-Claisen rearrangements require very high reaction temperatures. For example, the *aza*-Claisen

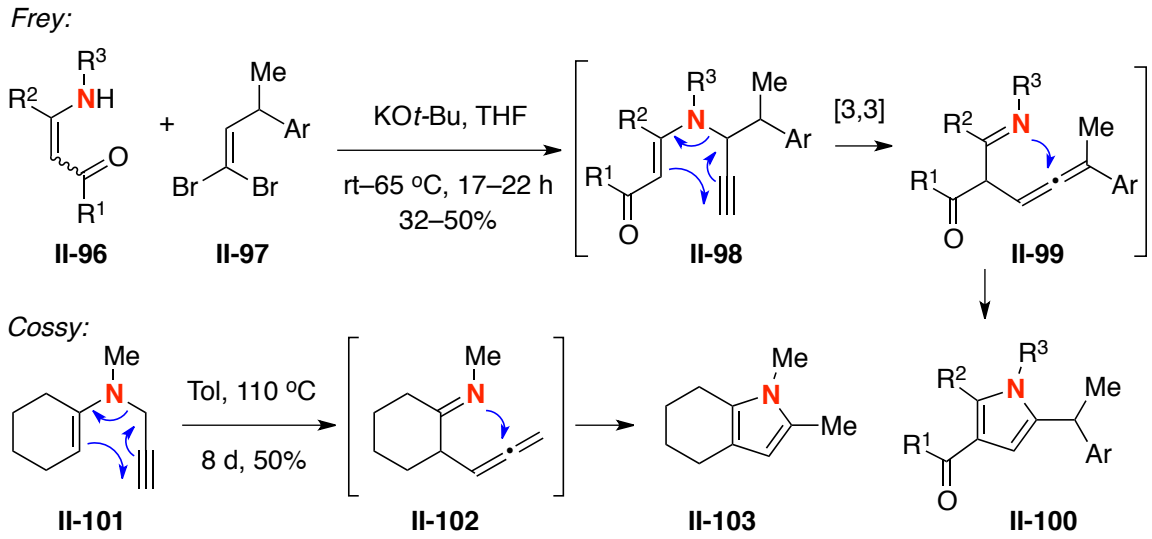
rearrangement of *N*-allyl-*N*-methylisobutenylamine is reported to proceed at ~250 °C.[50] In the last thirty years, huge breakthroughs have been made on lowering this activation barrier, most notably through charge acceleration via Lewis and Bronsted acids catalysis or by employing quaternary ammonium ions.[48] Additionally, alkyne *aza*-Claisen rearrangements have been shown have lower activation barriers than their all alkene counterparts.

**Figure II-4. Nomenclature of *Aza*-Claisen Rearrangements**




To date, there have been only a handful of examples of alkyne *aza*-Claisen rearrangements, though to the best of our knowledge, all involve propargyl amine based systems. Two such examples by Frey[51] and Cossy[52] are shown in Scheme **II-11** for the synthesis of functionalized pyrroles after cyclization through imino-allenes **II-99** and **II-102**. Significantly, both of these alkyne *aza*-Claisen rearrangements occurred at synthetically practical reaction temperatures.

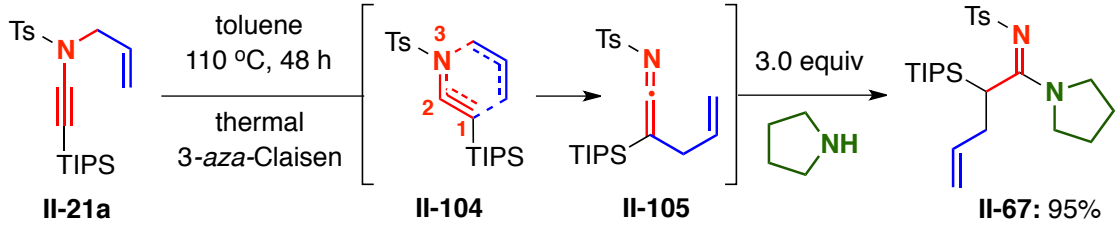
**Scheme II-11. Alkyne *Aza*-Claisen Rearrangements**




### 2.3.2 Addition of *N*-Nucleophiles

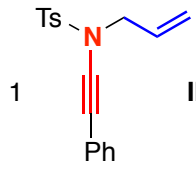
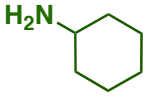
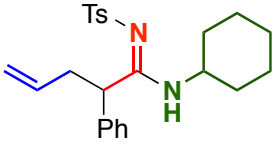
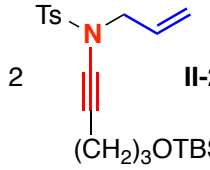
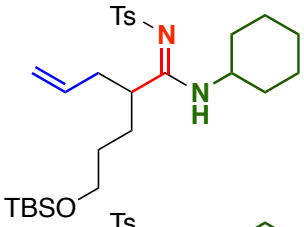
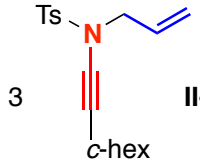
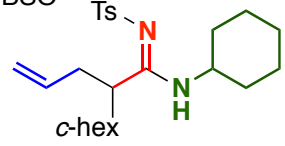
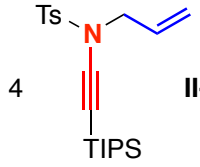
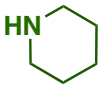
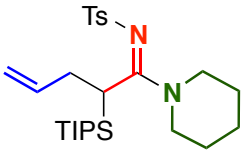
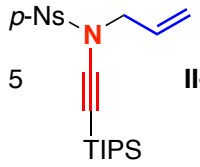
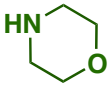
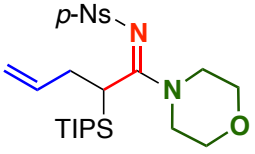
While pursuing our investigations of Pd-catalyzed *N*-to-*C* allyl transfer,[40-42] we realized that an analogous uncatalyzed transformation may be possible via a thermal 3-*aza*-Claisen rearrangement. We were delighted to find that heating of ynamide **II-21a** at 110 °C for 48 h in the presence of pyrrolidine led to exclusive formation of amidine **II-67**, implying the existence of ketenimine **II-105** as a reactive intermediate [**Scheme II-12**].[42]

**Scheme II-12. Discovery of a 3-*Aza*-Claisen Rearrangement for α-Allyl Amidines**



The thermal *aza*-Claisen procedure was quite general and completely avoided the problem of deallylation in all cases studied [**Table II-9**]. Notably, phenyl-terminated ynamide **II-21f**, which was not tolerated under the Pd-catalyzed conditions, led to amidine **II-106** in excellent yield [entry 1]. Alkyl- and silyl-terminated ynamides could also be transformed into the respective amidines in good to excellent yields with both primary and secondary amine nucleophiles [entries 2–5].

**Table II-9. Amidine Synthesis via Thermal *Aza*-Claisen Rearrangement**

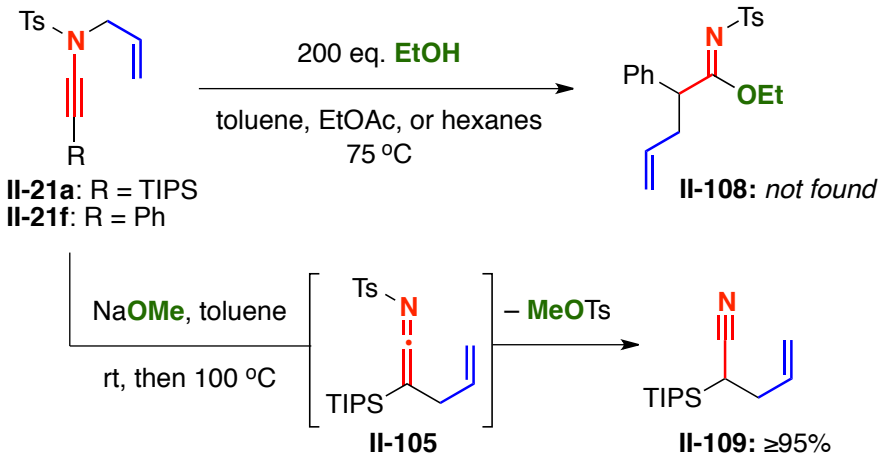
| entry | ynamides | amines[a] | amidine products | yield [%][b] |
|---|---|---|---|---|
| 1 |  **II-21f** |  |  **II-106** | 94 |
| 2 |  **II-21c** | |  **II-80** | 58 |
| 3 |  **II-21k** | |  **II-82** | 77 |
| 4 |  **II-21a** |  |  **II-69** | ≥95 |
| 5 |  **II-21e** |  |  **II-107** | 93 |

[a] Reaction conditions: 3.0 equiv amine, toluene [conc = 0.05 *M*], 110 °C for 24 h, except it was 48 h for entry 4. [b] Isolated yields.

### 2.3.3 Addition of *O*- Nucleophiles

We were excited by the ability to carry out the *aza*-Claisen rearrangement thermally and decided to investigate the use of oxygen nucleophiles as trapping agents for the synthesis of imidates.[53] To our surprise, our initial attempts were met with little success. Heating ynamide **II-21f** in the presence of even 200 equiv of EtOH resulted in no observable formation of imidate **II-108** [**Scheme II-13**]. Instead, a nitrile formed by a competing 1,3-sulfonyl transfer was found [see **Chapter 3**].[41] We reasoned that the alcohol was not nucleophilic enough to trap out the ketenimine, so next investigated the use of alkoxide nucleophiles. Interestingly, instead of adding to the central ketenimine carbon, NaOMe attacked the *ipso* sulfonyl carbon of **II-105**, triggering detosylation and tautomerization to afford nitrile[54] **II-109** in quatitative yield after the MeOTs was removed by filtration.

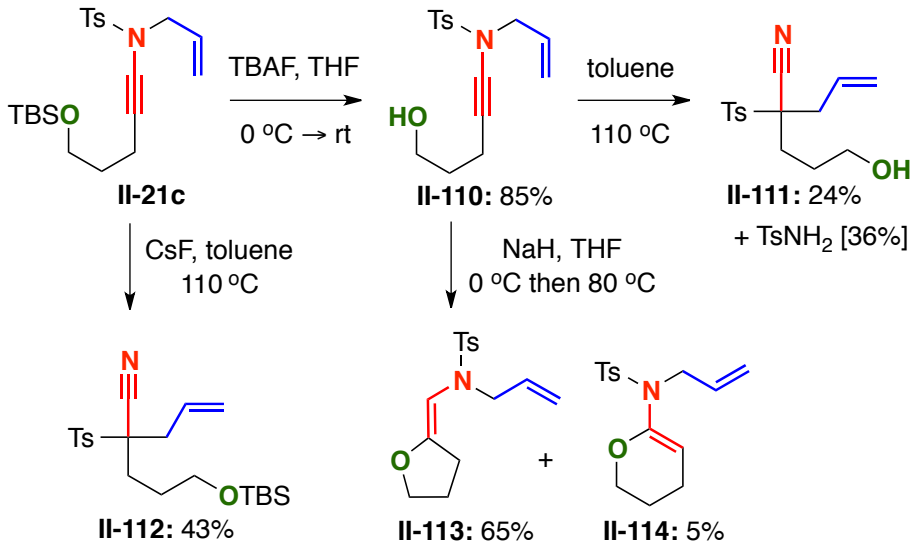
**Scheme II-13. Attempts at Intermolecular Imidate Synthesis**




We subsequently turned our attention towards developing an intramolecular variant, hoping that the lowered entropic barrier may help to overcome the diminished

nucleophilicity [**Scheme II-14**]. Again, we found that heating of ynamide **II-110** bearing a tethered alcohol led only to nitrile **II-111** from the competing 1,3-sulfonyl transfer, as well as hydrolysis of the intermediate ketenimine. By deprotonating the alcohol with NaH, the resulting alkoxide was too nucleophilic and actually added across the alkyne before the *aza*-Claisen occurred to give a separable mixture of enamides **II-113** and **II-114**. This prompted us to explore the possibility of generating the alkoxide at high temperature, ideally as the *aza*-Claisen rearrangement was occurring, via treatment of ynamide **II-21c** with CsF at 110 $^{o}$C. Unfortunately, this too led to nitrile **II-112** along with decomposition, but no detectable imidate formation.

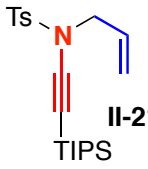
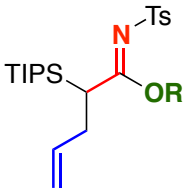
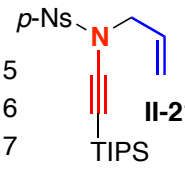
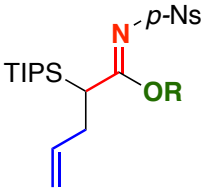
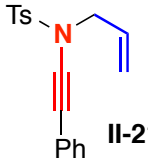
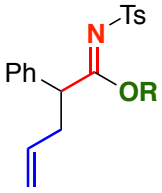
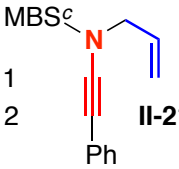
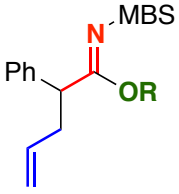
**Scheme II-14. Attempts at Intramolecular Imidate Synthesis**




With our back to the wall, we turned once more to intermolecular imidate synthesis with the hope that using the alcohol as the solvent, we could trap the ketenimine before the 1,3-sulfonyl transfer. Using this protocol, we were finally successful in preparing imidates

from *N*-allyl ynamides [**Table II-10**]. Heating of TIPS-terminated ynamide in MeOH at 75 °C led to formation of imidate **II-115** in 81% yield [entry 1]. Other alcoholic solvents could also be used successfully, though there was a severe steric penalty as clearly seen in entries 8–10. Maintaining the temperature at 75 °C, the use of MeOH gave imidate **II-122** in 95% yield with no competing nitrile observed, whereas *i*-Pr gave imidate **II-123** in 47% yield with ~20% nitrile observed in the crude $^1$H NMR.

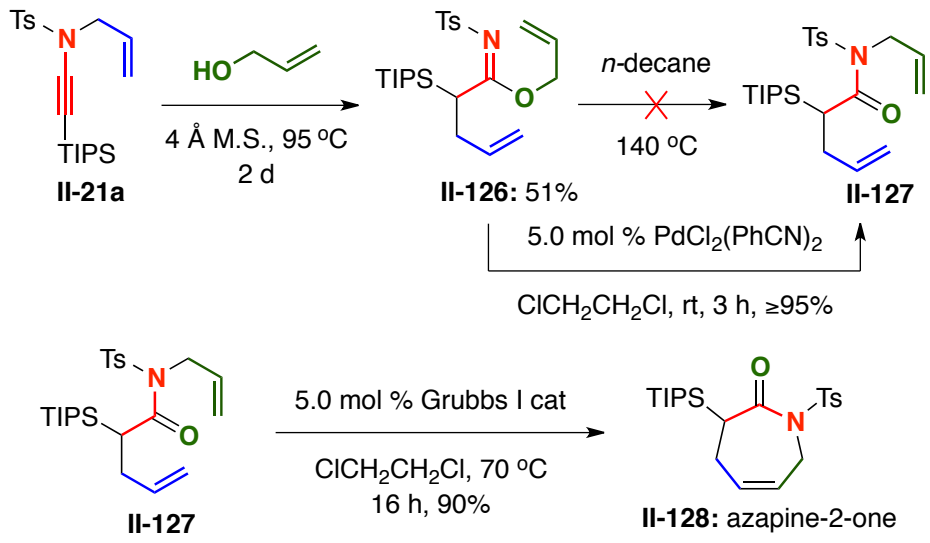
**Table II-10. Imidate Synthesis *via* Aza-Claisen Rearrangement in Alcoholic Solvents**

| entry | ynamides | alcohols[a] | temp [°C] | time [d] | imidate products | | yield [%][b] |
|---|---|---|---|---|---|---|---|
| 1 |  **II-21a** | MeOH | 75 | 2 |  | R = Me | **II-115** | 81 |
| 2 | | EtOH | 75 | 2 | | R = Et | **II-116** | 43 |
| 3 | | *i*-PrOH | 90 | 5 | | R = *i*-Pr | **II-117** | 39 |
| 4 | | *c*-pentanol | 110 | 5 | | R = *c*-pent | **II-118** | 45 |
| 5 |  **II-21e** | EtOH | 85 | 3 |  | R = Et | **II-119** | 76 |
| 6 | | *i*-PrOH | 90 | 4 | | R = *i*-Pr | **II-120** | 76 |
| 7 | | *c*-pentanol | 115 | 4 | | R = *c*-pent | **II-121** | 71 |
| 8 |  **II-21f** | MeOH | 75 | 2 |  | R = Me | **II-122** | 95[d] |
| 9 | | EtOH | 75 | 2 | | R = Et | **II-108** | 75 |
| 10 | | *i*-PrOH | 75 | 2 | | R = *i*-Pr | **II-123** | 47[e] |
| 11 |  **II-21o** | EtOH | 75 | 2 |  | R = Et | **II-124** | 82 |
| 12 | | *c*-pentanol | 75 | 2 | | R = *c*-pent | **II-125** | 38 |

[a] Reaction conditions: Ynamide was heated in respective alcohol as solvent [conc = 0.04 *M*] in the presence of 4 Å M.S. [b] Isolated yields. [c] MBS = *p*-methoxybenzenesulfonyl. [d] No nitrile observed in crude $^1$H NMR. [e] ~ 20% nitrile by crude $^1$H NMR.

Though not especially practical, we were curious if we could carry out a sequential *aza*-Claisen–allyl alcohol addition–Overmann rearrangement[55] for the preparation of di-allyl amides, which followed by ring-closing metathesis [RCM] could lead to azapine-2-ones **[Scheme II-15]**. To that end, we found that ynamide **II-21a** could be heated in allyl alcohol at 95 °C for 2 days to give imidate **II-126**. Despite many attempts to achieve a thermal Overmann rearrangement either in tandem from **II-21a** or stepwise from **II-126**, we were unsuccessful and had to turn to palladium catalysis.[56] Treatment of **II-126** with 5.0 mol % $PdCl_2(PhCN)_2$ cleanly afforded amide **II-127**, which when subjected to 5.0 mol % Grubbs I generation catalyst gave azapine-2-one **II-128** in 90% yield.

**Scheme II-15. Sequential Aza-Claisen–Pd-Cat Overmann–RCM for Azapin-2-ones**

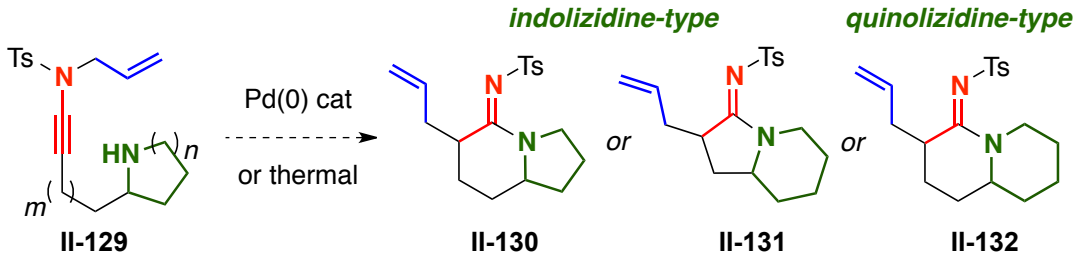


## 2.4 Future Work

### 2.4.1 Intramolecular Variation of Amidine Synthesis

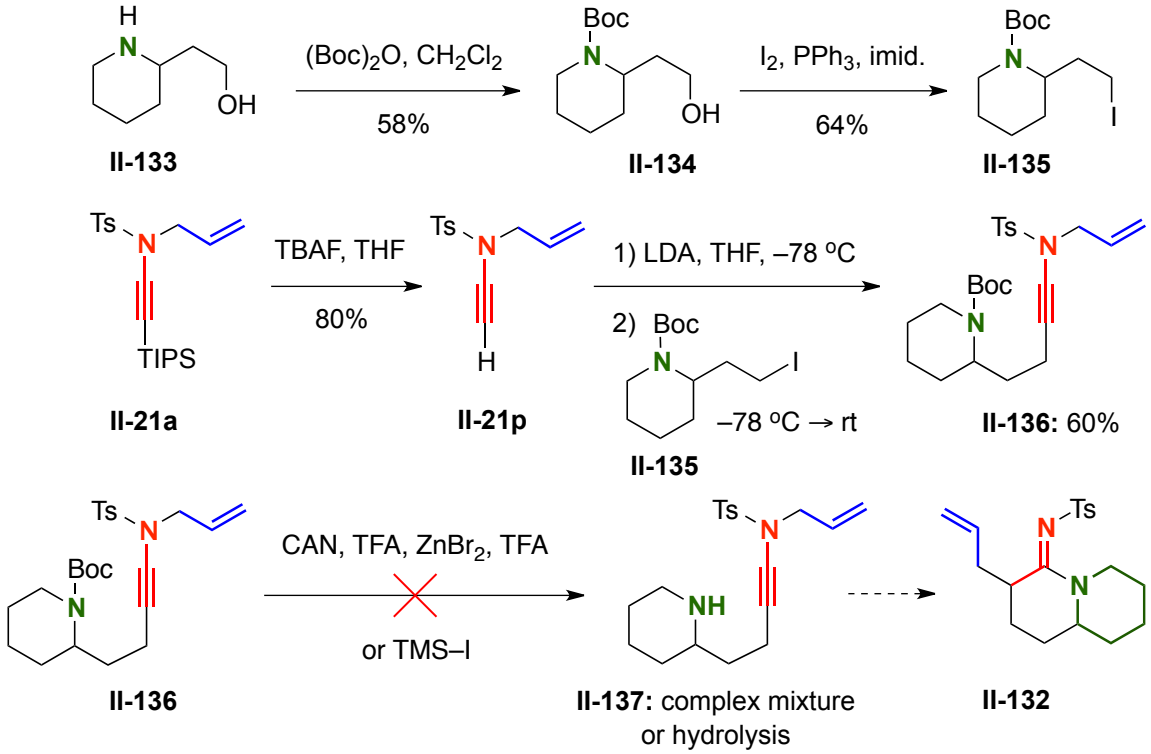
Once we had firmly established the synthesis of amidines using both Pd-catalyzed and thermal conditions, we started to imagine the use of tethered amine nucleophiles for the preparation of azabicycles found in a huge number of indolizidine and quinolizidine-type natural products [**Scheme II-16**].

**Scheme II-16. Potential Applications Towards Alkaloid Scaffolds**




We even began developing a method to prepare the appropriate amine-tethered ynamides [**Scheme II-17**]. Ynamide **II-21a** could be lithiated by lithium diisopropyl amine [LDA] at –78 $^{o}$C, which followed by slow syringe pump addition of alkyl iodide **II-125** led to ynamide **II-136** featuring a tethered *N*-Boc amide in 60% yield. Unfortunately, this is where our investigation dead-ended, as the standard array of methods to remove the Boc protecting group while preserving the ynamide all failed. Other protecting groups should be investigated, especially an alloc protecting group, which may allow for *in situ* deprotection via $Pd(PPh_3)_4$ at low temperature and then the *N*-to-*C* allyl transfer and amidine formation to occur upon warming.

**Scheme II-17. Amide–Tethered Ynamide Synthesis**




## 2.5 Conclusions

We have rigorously investigated the *N*-to-*C* allyl transfer and nucleophilic trapping of *N*-allyl ynamides using both palladium-catalyzed and thermal conditions for the preparation of amidines, vinylogous amidines, and imidates. In addition, we have demonstrated the ability to selectively tune the catalytic system to afford either α-allyl amidines or des-allyl amidines by using either reductive elimination favoring Pd(0) catalytic systems or Pd(II) catalysts.

# Chapter 3. Rearrangements of *N*-Allyl Ynamides

## Chapter 3: Rearrangements of *N*-Allyl Ynamides

*N*-allyl ynamides[2] have been shown to rearrange to ketenimines[57] through both Pd-catalyzed *N*-to-*C* allyl transfers[40-42] and thermal 3-*aza*-Claisen rearrangements.[42,53] In addition, we have demonstrated the ability to trap these ketenimines and Pd-π-allyl ketenimine complexes with amine, enamine, and alcohol nucleophiles to prepare amidines, vinylogous amidines, and imidates. In this chapter, we describe mechanistic details for the rearrangement of ynamides to ketenimines, as well as the fate of these ketenimines when no nucleophile is present.[41]

### 3.1 Rearrangements Through C≡C–N and C=C=N Systems

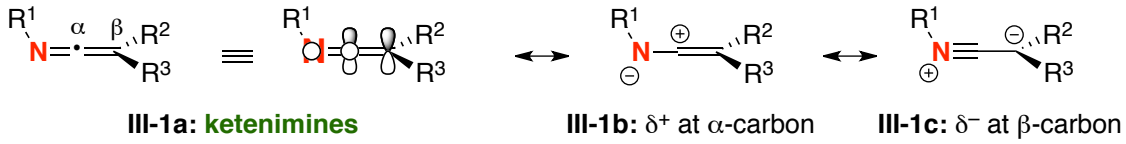
Aside from our work, there are very few examples of ynamide rearrangements in literature. Rearrangements of *ketenimines*,[57] however, have been studied for the last three decades.

#### 3.1.1 Ketenimines and Their Synthesis

Ketenimines are an *aza*-analog to ketenes and, as such, have similar trends in reactivity.[57] Ketenimines **III-1** are comprised of two orthogonal π-systems and can be axially chiral in principle, though the barrier to inversion is too low to be practically useful (~10 kcal/mol). As described in **Figure III-1**, ketenimines possess electrophilic character at the central α-carbon and nucleophilic character at the terminal β-carbon, as shown by resonance structures **III-1b** and **III-1c**, respectively. Employing ketenimines in intermolecular nucleophilic and electrophilic additions has been widely exploited in

literature, though here we will focus only on their ability to participate in intramolecular rearrangements.

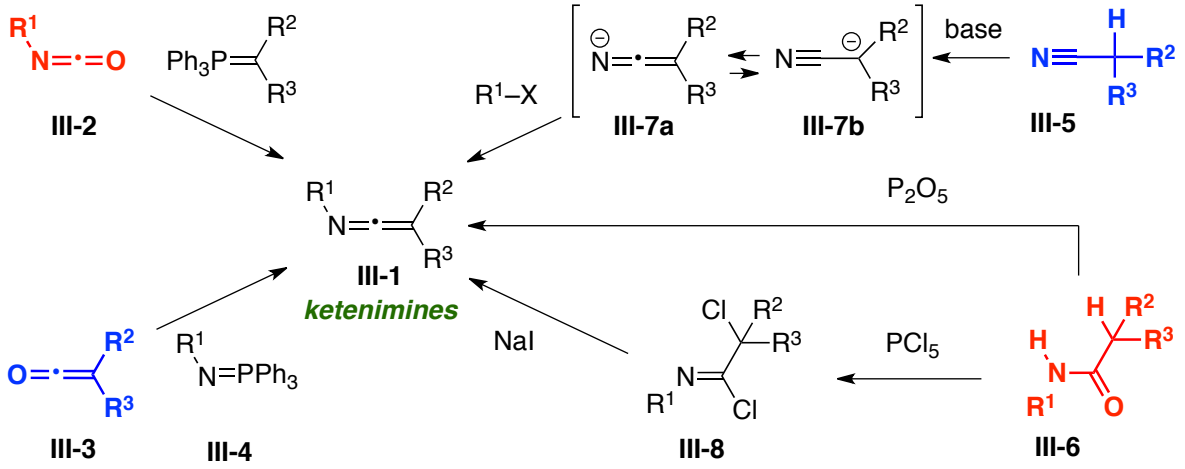
**Figure III-1. Ketenimine Modes of Reactivity**




Staudinger[58] and Meyer reported the first preparation of ketenimines **III-1** in the 1920's by carrying out Wittig olefinations on isocyanates **III-2** [**Scheme III-1**]. A few years later, Staudinger[59] developed an *aza*-Wittig variant by reacting ketenes **III-3** with *aza*-ylides **III-4**. To date, this has remained the most widely used method for preparing ketenimines. However, other noteworthy preparations include the deprotonation of nitriles **III-5** and subsequent trapping of ketenimine **III-7a**,[60] as well as dehydration of amides **III-6** either stepwise through chloro-imine **III-8**[61a] or directly using $P_2O_5$.[61b]

Though ketenimines have been known and studied for nearly a hundred years, it wasn't until the 1970's that they began to truly emerge as a useful functional group. Much of this has to do with their ability to participate in cycloaddition reactions[57e] [not discussed] and propensity to undergo rearrangements for the synthesis of heterocyclic compounds.

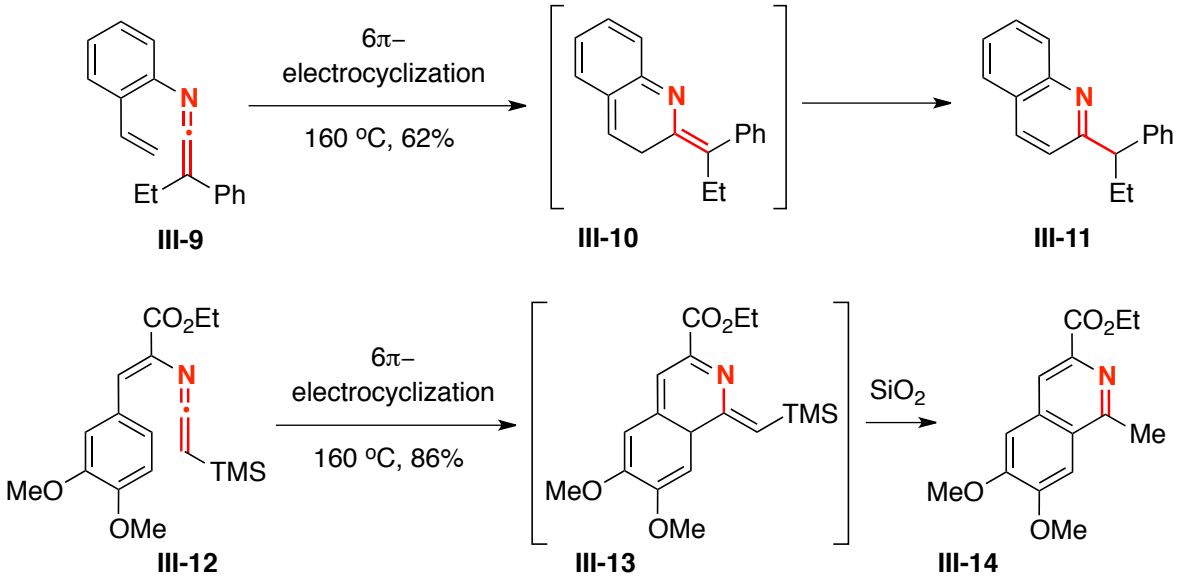
**Scheme III-1. Classical Ketenimine Synthesis**




### 3.1.2 Rearrangements *via* the C=N Bond of Ketenimines

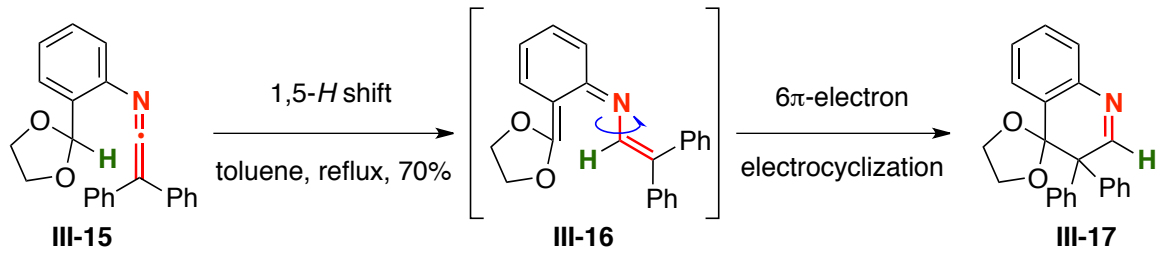
In 1992, Molina and Alajarin[62] first demonstrated the use of a thermal 6π-electron electrocyclic ring closure through the ketenimine C=N bond for the synthesis of alkaloid scaffolds [**Scheme III-2**]. From ketenimine **III-9**, the electrocyclization occurred at 160 °C to give **III-10**, which upon isomerization gave **III-11**. Molina[63] later used a similar methodology to prepare **III-14**, representing a formal synthesis of alkaloid natural product aaptamine.

**Scheme III-2. Ketenimine 6π-Electron Electrocyclization *via* C=N Bond**




Ketenimines have also been used successfully in *sigmatropic* rearrangements through the C=N bond, most notably in 1,5-*H* shifts. Starting from acetalic ketenimine **III-15**, Alajarin[64] was able to carry out a tandem 1,5-*H* shift, followed by a 6π-electron electrocyclic ring closure through the presumed *o*-quinomethanimine intermediate **III-16** to give 4-quinolone **III-17** [**Scheme III-3**]. The authors supported the proposed 1,5-*H* shift through computational calculations, as well.

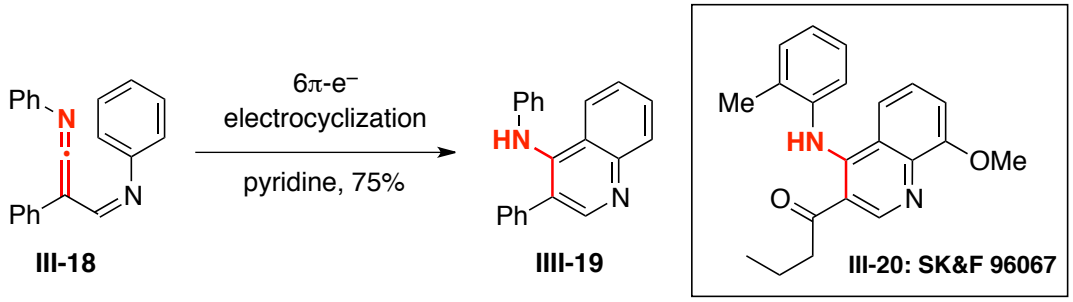
**Scheme III-3. Tandem Ketenimine 1,5-*H* Shift–6π-Electron Electrocyclization**



### 3.1.3 Rearrangements *via* the C=C Bond

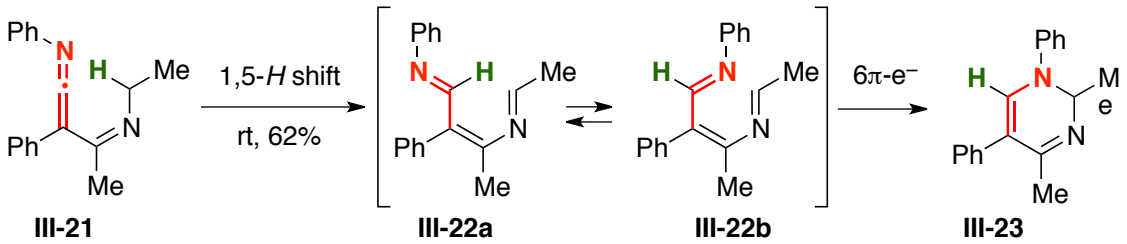
Electrocyclizations through the C=C bond of the ketenimine are less prevalent in literature, though there are still a few. The first by Cauano[65] in 1979 was the 6π-electron electrocyclization of ketenimine **III-18** to give 4-aminoquinoline **III-19** [**Scheme III-4**]. Lewis[66] later applied this methodology to the total synthesis of **III-20** SK&F 96067.

**Scheme III-4. Ketenimine 6π-Electron Electrocyclization *via* C=C Bond**




The first example of a ketenimine 1,5-*H* shift through the C=C bond was by Goerdeler[67] in 1981 [**Scheme III-5**]. As with the previously discussed examples, the intermediate di-imine **III-22a** subsequently underwent bond-rotation and 6π-electron electrocyclization to give **III-23** in 62% yield.

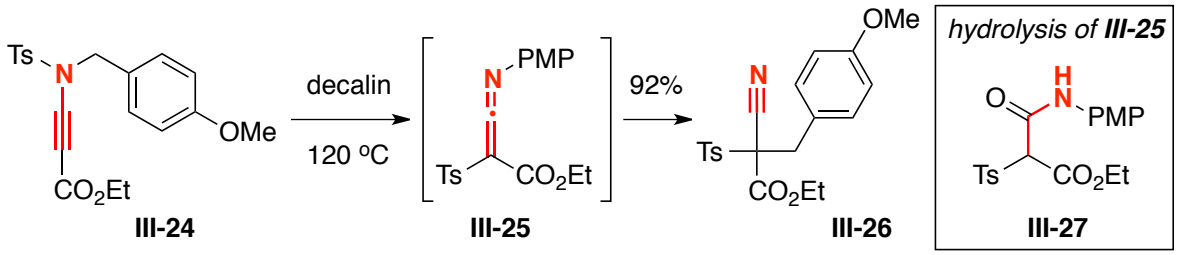
**Scheme III-5. Tandem 1,5-*H* Shift–6π-Electron Electrocyclization**



### 3.1.4 Rearrangements Involving Both the C=C and C=N Bonds

Wudl[68] was the first to showcase a double-barreled *N*-to-*C* 1,3-Ts shift–1,3-PMP shift of ynamide **III-24** to nitrile **III-26** [**Scheme III-6**]. The intermediate ketenimine **III-25** was isolable and stable under inert atmosphere, but upon attempted purification resulted in amide **III-27**, supporting that the sulfonyl rearranged first, followed by the *p*-methoxybenzyl moiety.

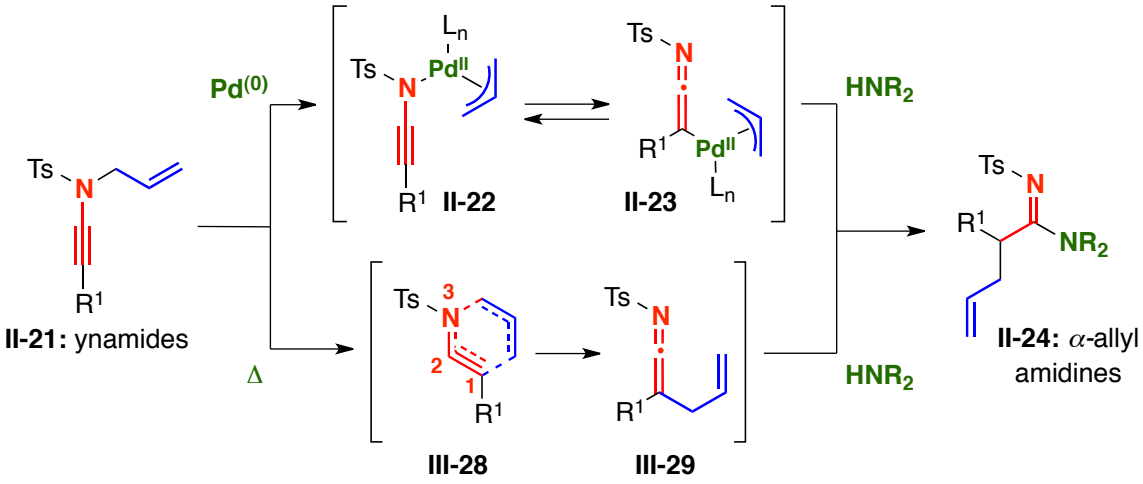
**Scheme III-6. Tandem 1,3-Ts Shift–1,3-PMP Shift**




### 3.1.5 Review of Pd-Catalayzed and Thermal *Aza*-Claisen Rearrangements

We have shown that *N*-allyl ynamides[2] readily undergo both Pd-catalyzed *N*-to-*C* allyl transfers[40-42] and thermally induced 3-*aza*-Claisen rearrangements[42,53] to generate ketenimines **II-23** and **III-29** *in situ* [**Scheme III-7**]. These ketenimines may be trapped by external nucleophiles as shown in **Chapter 2**; however, with no nucleophile present, entirely new reaction pathways become accessible.[41]

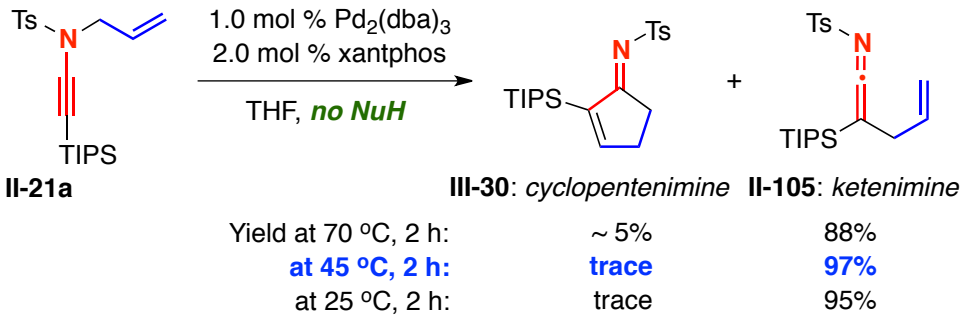
**Scheme III-7. Conversion of Ynamides to Amidines *via* Ketenimine Intermediates**




## 3.2 Mechanistic Studies on Pd-Catalyzed *N*-to-*C* Allyl Transfer

When ynamide **II-21a** was treated with 1.0 mol % $Pd_2(dba)_3$ and 2.0 mol % xantphos in THF with no nucleophile present, ketenimine **II-105** could actually be isolated and even purified by silica gel column chromatography [**Scheme III-8**].[69] The optimal temperature was 45 $^{o}$C, where ketenimine **II-105** could be isolated in quantitative yield. Interestingly though, at 70 $^{o}$C, another reaction pathway was accessible leading to cyclopentenimine **III-30** in 5% yield [see **Chapter 5**]. Regardless, the isolation of **II-105** granted us a wonderful opportunity to study the mechanism for palladium-catalyzed allyl transfer.

**Scheme III-8. Discovery of an Isolable Ketenimine**



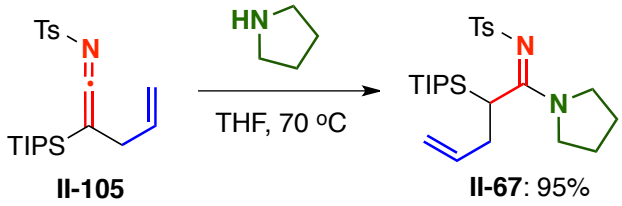

**II-21a**

**III-30**: *cyclopentenimine* **II-105**: *ketenimine*

| | | |
|---|---|---|
| Yield at 70 °C, 2 h: | ~ 5% | 88% |
| **at 45 °C, 2 h:** | **trace** | **97%** |
| at 25 °C, 2 h: | trace | 95% |

In addition to assigning the structure of ketenimine **II-105** via the standard array of spectroscopic techniques, its structure was further supported by trapping with pyrrolidine to give amidine **II-67** [**Scheme III-9**]. As a side note, with respect to characterization, one of the best ways to determine the presence of a ketenimine is by IR spectroscopy; ketenimines possess a very strong, distinct stretch at ~1960 $cm^{-1}$.

**Scheme III-9. Trapping of Ketenimine with Pyrrolidine**




**II-105**

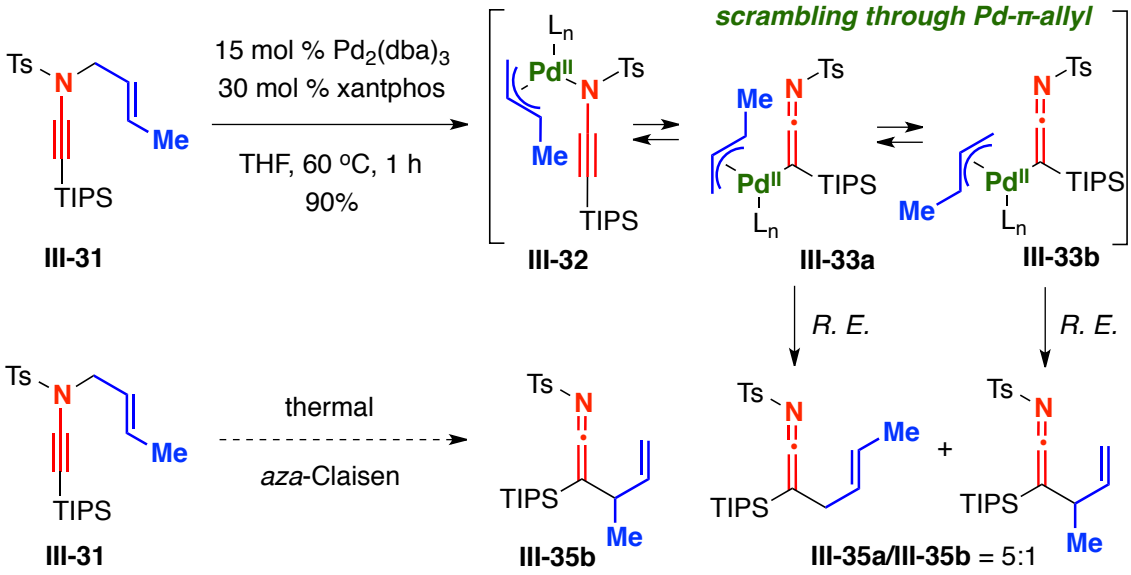
**II-67**: 95%

As mentioned previously, with the isolation of ketenimine **II-105**, it became possible for us to explore the mechanistic details of its formation, specifically: (1) the intermediacy of a Pd-π-allyl complex, and (2) whether the *N*-to-*C* allyl transfer occurred intramolecularly or intermolecularly.

### 3.2.1 Scrambling Through Pd-π-Allyl Complex

Our first challenge was to confirm that a Pd-π-allyl complex was truly involved in the rearrangement, as it was possible that the palladium did not participate and only a thermal *aza*-Claisen was operational [**Scheme III-10**]. To differentiate between these two pathways, we prepared *N*-crotyl ynamide **III-31** and subjected it to 15.0 mol % $Pd_2(dba)_3$ and 30.0 mol % xantphos at 60 °C [at 45 °C, mostly ynamide was recovered]. As desired, ketenimines **III-35a** and **III-35b** were isolated in a 5:1 ratio. The scrambling of the crotyl group was demonstrative of the involvement of Pd-π-allyl complexes, which would allow equilibration between **III-33a** and **III-33b** through bond rotation. Reductive elimination through the less sterically hindered **III-33a** would favor formation of **III-35a**. To further illustrate this point, though not attempted, the thermal *aza*-Claisen rearrangement of **III-31** should produce **III-35b** as the major, likely exclusive, product.

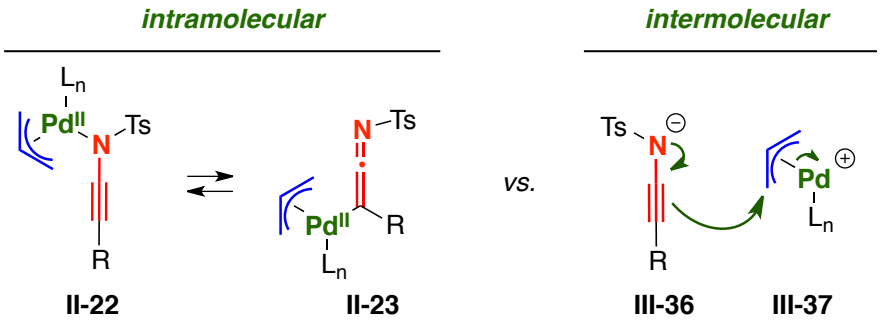
**Scheme III-10. Support for a Pd-π-Allyl Complex During Allyl Transfer**



### 3.2.2 A Cross-over Experiment

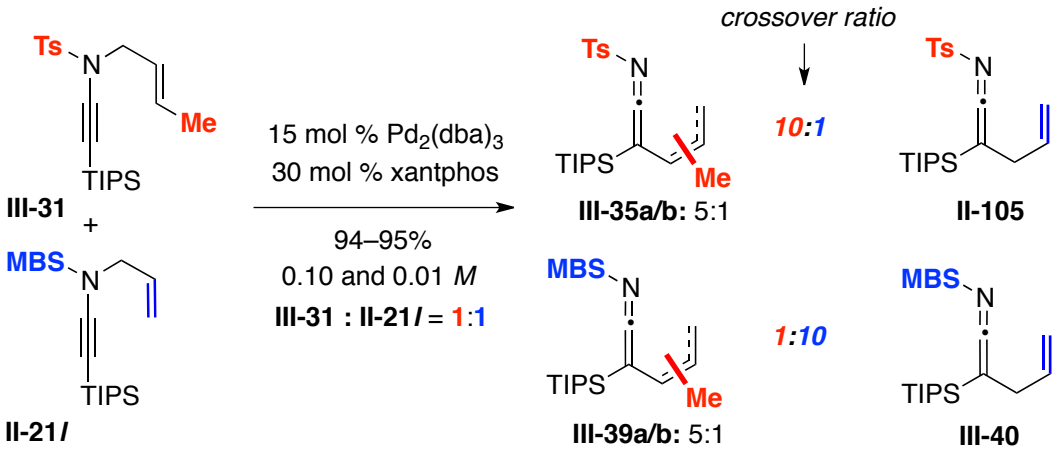
After firmly establishing the intermediacy of Pd-π-allyl complexes in the described rearrangement, we became interested in ascertaining whether the transfer occurred in an intramolecular manner analogous to tautomerization [**II-22→II-23**] or in an intermolecular dissociative manner similar to a Tsuji-Trost[43] reaction [**Scheme III-11**].

**Scheme III-11. Two Possible Allyl Transfer Pathways**




A simple cross-over experiment was used to distinguish between these two reactive pathways. When a 1:1 mixture of *N*-tosyl-*N*-crotyl ynamide **III-31** and *N*-*p*-methoxybenzenesulfonyl-*N*-allyl ynamide **II-21*l*** was treated to our catalytic conditions, we were able to assign four distinct ketenimines in the product mixture: **III-35a/b**, **II-105**, **III-39a/b**, and **III-40** [**Scheme III-12**]. The ratio of **III-35a/b** and **III-39a/b** were both 5:1 due to Pd-π-allyl bond rotation, but more revealing was the 10:1 cross-over ratio, even when the concentration was 0.10 *M*. This implied that the *N*-to-*C* allyl transfer occurred largely as an intramolecular event through tightly coordinated ynamido- and ketenimino-Pd-π-allyl complexes.

**Scheme III-12. Support For an Intramolecular Allyl Transfer**




### 3.2.3. Summary of Mechanistic Studies

We have shown that with TIPS-terminated ynamides, remarkably stable TIPS-substituted ketenimines may be isolated upon treatment with catalytic Pd(0). This allowed us to investigate the role of the palladium catalyst in the *N*-to-*C* allyl transfer, demonstrating that tightly bound ynamido and ketenimino-Pd-π-allyl complexes are involved.

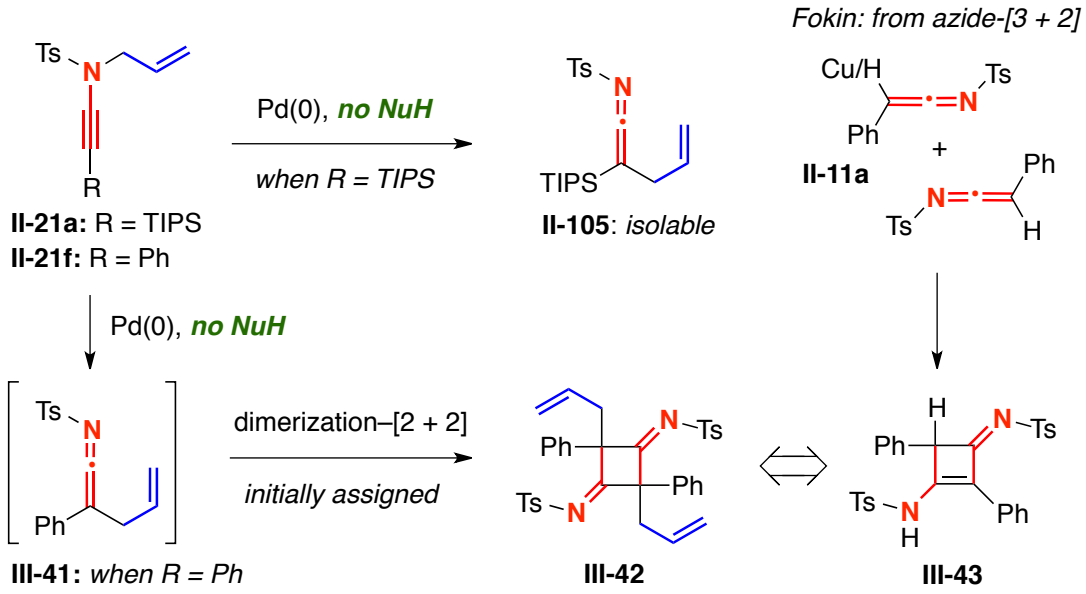
## 3.3 Discovery of a Ketenimine *N*-to-*C* 1,3-Sulfonyl Shift

The fate of ketenimines generated by palladium-catalyzed or thermal rearrangements of *N*-allyl ynamides depends largely on the β-substituent of the ynamides used. Thus far, we have shown that TIPS-terminated ynamides rearrange to isolable TIPS-ketenimines. The ketenimines formed from non-silyl terminated ynamides are not nearly as well behaved.

### 3.3.1 Dimerization Versus 1,3-Sulfonyl Shift

While exploring the trapping of non-silyl ketenimines with sterically hindered amine nucleophiles[40-42] and later with alcohol nucleophiles,[53] we often observed small amounts of an unidentified impurity in the crude reaction mixture. Fokin[38] had reported that ketenimine **II-11a** underwent facile dimerization to give cyclobutane bis-imine **III-43**. So, we tentatively assigned our biproducts as dimers [**Scheme III-13**]. For example, when ynamide **III-21f** was treated with $Pd_2(dba)_3$ and xantphos with no nucleophile present, **III-42** was isolated in 20% yield, curiously as a single isomer [the first hint our assignment was wrong].

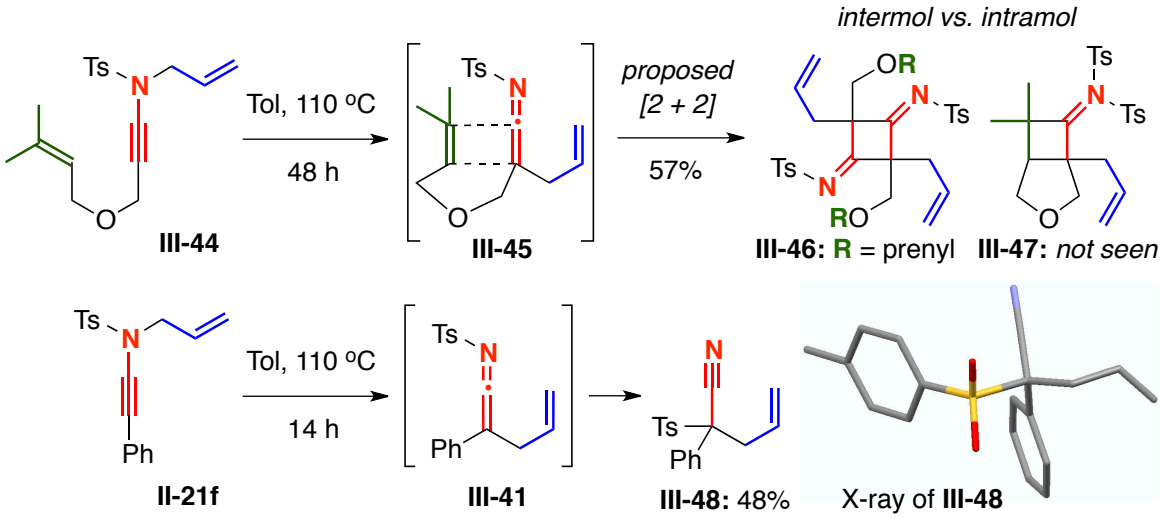
**Scheme III-13. Initially Assigned Dimerization Pathway of Non-Silyl Ynamides**




We wondered if we could outcompete this intermolecular dimerization–[2 + 2] pathway with an intramolecular one, so we prepared ynamide **III-44** bearing a tethered olefin and heated it to 110 °C in toluene [**Scheme III-14**]. Interestingly, the major product

was the one derived from the presumed dimerization pathway [**III-46**]. The remaining mass balance was not the result of an intramolecular [2 + 2], but an intramolecular ene reaction [see **Chapter 6**]. Regardless, the discovery that our proposed *intermolecular* dimerization pathway had outcompeted an intramolecular one led us to reevaluate our assignment of **III-42**. X-ray structural analysis unambiguously confirmed that ynamide **III-21f** led not to cyclobutane bis-imine **III-42**, but to nitrile **III-48**[70] resulting from a rare 1,3-sulfonyl shift[68] through ketenimine **III-41**. Furthermore, palladium was not necessary and the yield of **III-48** could be improved to 48% using thermal conditions.

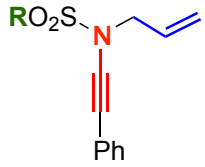
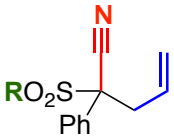
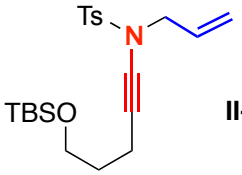
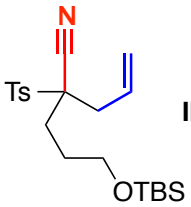
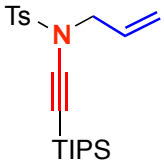
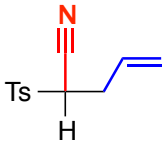
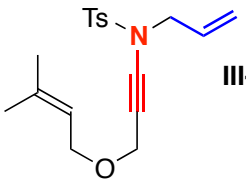
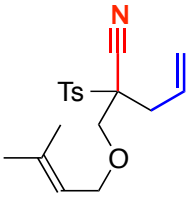
**Scheme III-14. Realization of a 1,3-Sulfonyl Shift**




We were intellectually thrilled with the discovery of a tandem 3-*aza*-Claisen–1,3-sulfonyl shift, but also fully realized that such an exceptionally facile intramolecular rearrangement severely limited the usefulness of our ketenimine intermediates [see **Chapter 4**]. Regardless, by exploiting this rearrangement, we were able to construct a variety of

nitriles bearing quaternary carbon centers [**Table III-1**]. Both electron-rich and electron-deficient arylsulfonyl groups [entries 1 and 2] participated in the rearrangement, as well as a methane-sulfonyl moiety [entry 3]. Further attesting to the stability of TIPS-substituted ketenimines, TIPS-terminated ynamide **III-21a** only led to nitrile **III-53** with concomitant desilylation. No TIPS-substituted nitrile has ever been observed in our system.

**Table III-1. Tandem *Aza*-Claisen–1,3-Sulfonyl Shift for Nitrile Synthesis**

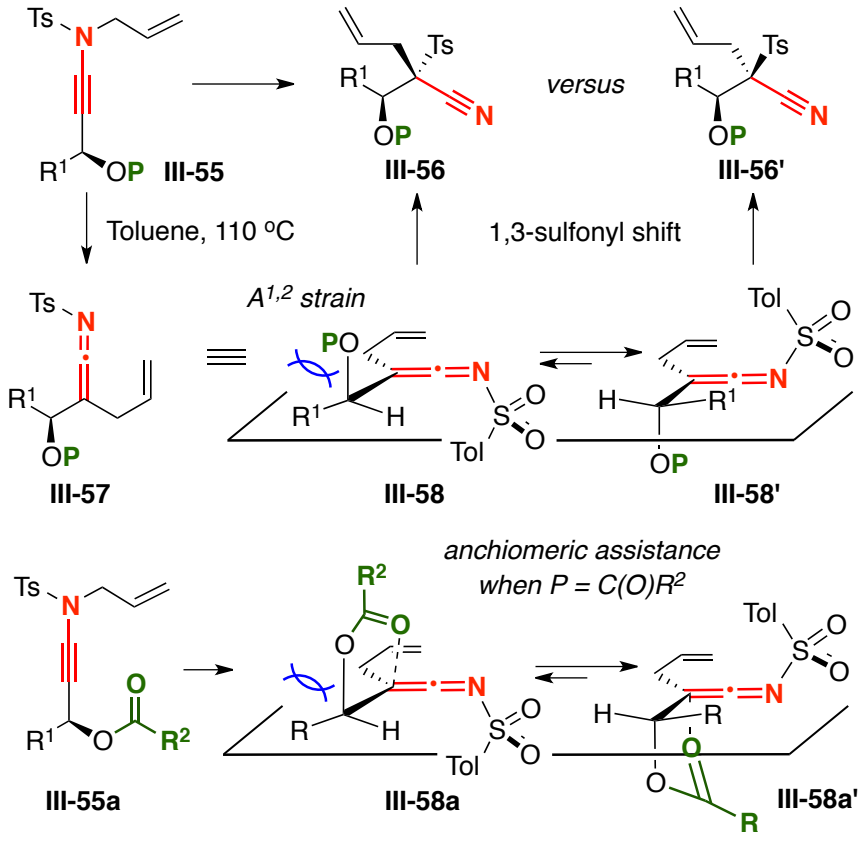
| entry | ynamides | nitriles | yield[a,b] |
|---|---|---|---|
| 1 |  **II-21m:** R = 4-MeO-Ph |  **III-50** | 53 |
| 2 | **II-21n:** R = 4-$NO_2$-Ph | | **III-51** | 53 |
| 3 | **III-49:** R = Me | | **III-52** | 64 |
| 4 |  **II-21c** |  **II-112** | 45 |
| 5 |  **II-21a** |  **III-53** | 57[c] |
| 6 |  **III-44** |  **III-46b** | 57 |

[a] Reaction conditions: Ynamide in toluene [conc = 0.04 *M*] at 110 °C for 14 h. [b] Isolated yields. [c] TIPS substituted nitrile was not found.

### 3.3.2 Attempts at Rendering the Shift Diastereoselective

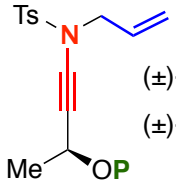
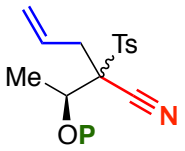
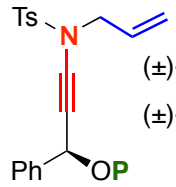
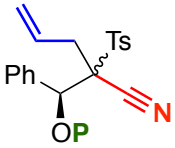
Having established the feasibility of a tandem *aza*-Claisen–1,3-sulfonyl shift, we thought it might be possible to carry out the transformation in a diastereoselective manner [**Scheme III-15**]. After the *aza*-Claisen rearrangement of ynamide **III-55** bearing a propargylic stereocenter, we proposed that ketenimines **III-57** could adopt either conformation **III-58** or **III-58'**, leading to either **III-56** or **III-56'**, respectively. Furthermore, **III-58** should be relatively disfavored due to $A^{1,2}$ strain, making a diastereoselective 1,3-sulfonyl shift possible. We thought this could be further enforced by invoking anchiomeric assistance, as well.

**Scheme III-15. Model for Proposed Diastereomeric Induction**



Unfortunately, the diastereoselectivity observed was modest at best [**Table III-2**]. Ynamides **III-59** and **III-61** led to nitriles **III-63** and **III-65** with diastereomeric ratios of 1.5:1 and 2.0:1, respectively [entries 1 and 3]. Acetyl and pivalyl protected ynamides, which we hoped would invoke anchiomeric assistance to further favor **III-III-58a'** [**Scheme III-15**], exhibited even less diastereomeric induction while also participating in another unexpected [3,3]-sigmatropic rearrangement [see **Scheme III-16**].

**Table III-2. Attempted Diastereoselective 1,3-Sulfonyl Shifts**

| entry | ynamides[a] | nitriles | | yield[b] | *dr* |
|---|---|---|---|---|---|
| 1 |  (±)-**III-59: P** = TIPS |  | **III-63** | 91 | 1.5:1 |
| 2 | (±)-**III-60: P** = Ac | | **III-64** | 50[c] | 1.3:1 |
| 3 |  (±)-**III-61: P** = TIPS |  | **III-65** | ≥95 | 2.0:1 |
| 4 | (±)-**III-62: P** = Piv | | **III-66** | 69[c] | 1.5:1 |

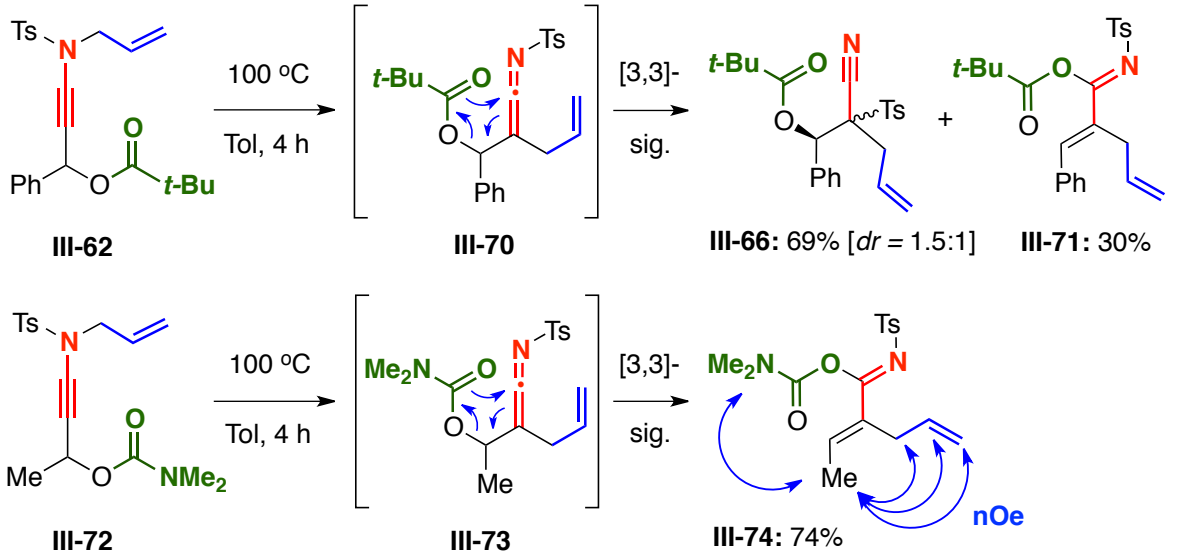
[a] Reaction conditions: Ynamide in toluene [conc = 0.04 *M*] at 110 °C for 2–4 h. [b] Isolated yields. [c] See **Scheme III-16.**

## 3.4 Tandem Aza-Claisen–[3,3]-Sigmatropic Rearrangement

Though ynamide **III-62** did not undergo the 1,3-sulfonyl shift with any useful degree of diastereoselectivity, it did participate in an interesting tandem *aza*-Claisen–[3,3]-sigmatropic rearrangement through ketenimine **III-70** to give α,β-unsaturated mixed anhydride **III-71** in 30% yield [**Scheme III-16**]. By employing the more electron-rich *N*,*N*-

dimethyl carbamate tethered ynamide **III-72**, the [3,3]-sigmatropic rearrangement dominated to give **III-74** in 74% yield, with no nitrile observed. The alkene configuration was confirmed by nOe analysis for both **III-71** and **III-74** [see **Appendix II**].

**Scheme III-16. Tandem *Aza*-Claisen–[3,3]-Sigmatropic Rearrangement**




## 3.5 Conclusions

TIPS-terminated *N*-allyl ynamides undergo Pd-catalyzed *N*-to-*C* allyl transfers to afford stable, isolable silyl-ketenimines. We have shown that the transfer occurs intramolecularly through tightly coordinated Pd-π-allyl complexes. When non-silyl terminated ynamides are subjected to Pd-catalyzed or thermal rearrangement conditions, a facile 1,3-sulfonyl transfer ensues for the synthesis of quaternary nitriles. Though our attempts to carry out the 1,3-sulfonyl shift with facial selectivity were largely unsuccessful, we uncovered a tandem *aza*-Claisen–[3,3]-sigmatropic rearrangement in the process.

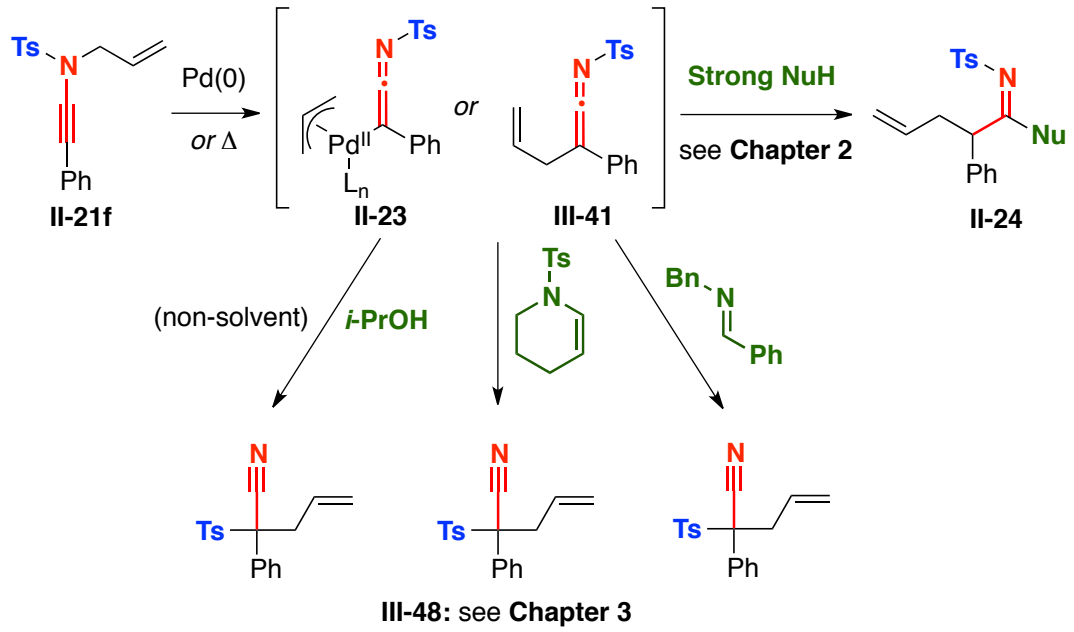
# Chapter 4. Introducing a New Class of *N*-Phosphoryl Ynamides

## Chapter 4: Introducing a New Class of *N*-Phosphoryl Ynamides

### 4.1 Need for a New Ynamide *N*-Electron-Withdrawing Group

*N*-allyl ynamides[2] are excellent precursors for preparing allyl ketenimines[57] *in situ*. Unfortunately, when TIPS-terminated ynamides were used, the corresponding ketenimines were too stable[69] [or sterically hindered] to react with weak nucleophiles and were, in fact, even isolable.[41] On the other hand, non-silyl substituted ketenimines were prone to undergo a facile 1,3-sulfonyl shift resulting in the formation of quaternary nitriles[41-42,53,70] such as **III-48** even when nucleophiles such as enamides and imines were present [**Scheme IV-1**]. While this rare 1,3-sulfonyl shift was fascinating, it precluded us from utilizing the *in situ* generated allyl ketenimines to their full potential. It therefore became necessary to develop this chemistry using non-sulfonyl protecting groups.

**Scheme IV-1. Facile 1,3-Sulfonyl Shift with Non-Silyl Ketenimines**

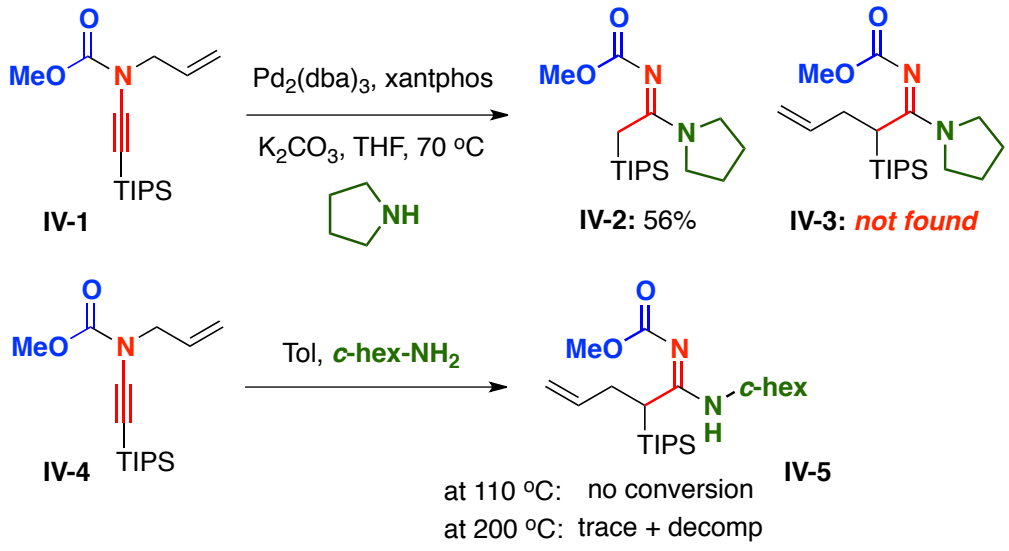


### 4.1.1 Dependence of the *Aza*-Claisen on Electron-Withdrawing Group

We had previously attempted to use non-sulfonyl protecting groups when exploring substrate scope for amidine synthesis and found that even under the optimized palladium-catalyzed conditions,[40-42] the deallylation pathway was once again dominant. For example, carbamate-derived ynamide **IV-1** gave only des-allyl amidine **IV-2** with no **IV-3** found [**Scheme IV-2**]. Alternatively, using thermal conditions, the *aza*-Claisen[48] did not occur at 110 °C, and heating to 200 °C resulted largely in decomposition with only a trace amount of **IV-5** found in the crude $^1$H NMR. The rearrangements were clearly sensitive to the electron-withdrawing capacity of the protecting group.

We next turned our attention to unconventional phosphoryl-derived electron-withdrawing groups [EWG]. We were intrigued by the ability to finely tune their electronegativity as well as the idea of generating ynamides with chirality at the phosphorus atom.[72]

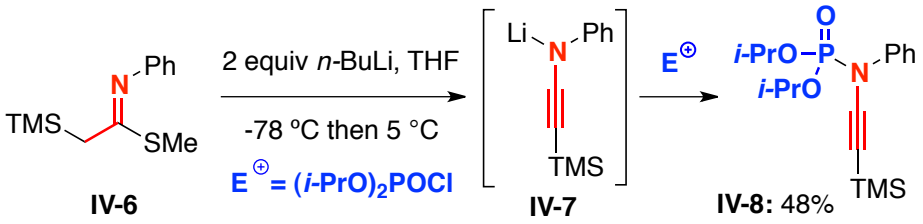
**Scheme IV-2. Problems with Non-Sulfonyl Protecting Groups**



## 4.2 The First *N*-Phosphoryl Derived Ynamide

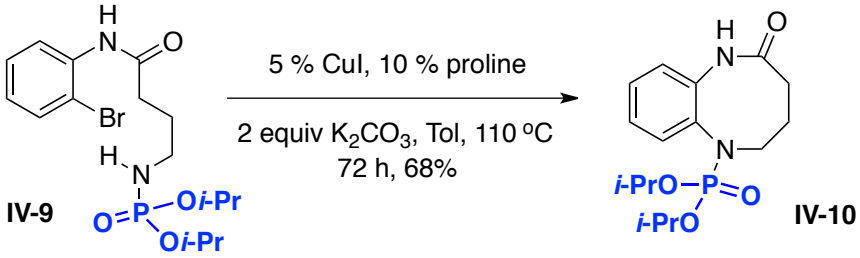
There was one example of an *N*-phosphoryl based ynamide in literature prior to our investigations. Masson[71] found that when thioamidine **IV-6** was reacted with 2 equiv of *n*-BuLi, *in situ* generated metallo-ynamide **IV-7** could be trapped with di-*iso*-propyl phosphoryl chloride to prepare *N*-phosphoryl ynamide **IV-8** in 48% yield [**Scheme IV-3**]. This report served as an excellent proof of principle demonstrating that such ynamides were adequately stable and propelled us to investigate a general method for their preparation based on our amidative cross-coupling strategy.[12-13]

**Scheme IV-3. Masson's Single *N*-Phosphoryl Ynamide Preparation**




To the best of our knowledge, there are no reports on the amidative cross-coupling between an *sp*-C and phosphoramidate.[73] However, the concept was demonstrated by Fu[74] through a series of intramolecular Cu-catalyzed $sp^2$-C–phosphoramidate cross-couplings for the preparation of medium sized rings such as **IV-10** [**Scheme IV-4**].

**Scheme IV-4. Fu's Intramolecular Phosphoramidate Cross-Coupling**

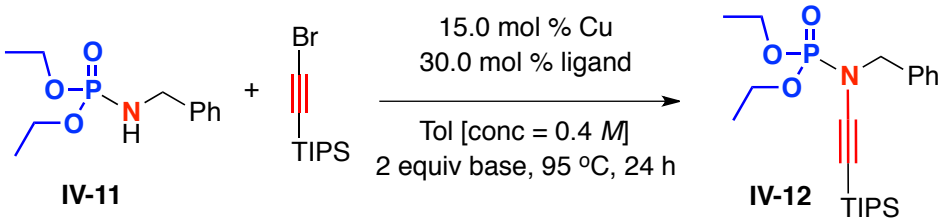



## 4.3 Development of an Amidative Cross-Coupling of Phosphoramidates

### 4.3.1 Optimization of Coupling Conditions

We quickly discovered that phosphoramidate **IV-11** could in fact be coupled with TIPS-alkynyl bromide using 15.0 mol % $CuSO_4 \cdot 5H_2O$, 30.0 mol % 1,10-phenanthroline, and 2 equiv of $K_2CO_3$ in toluene at 70 °C to afford *N*-phosphoryl ynamide **IV-12** in 38% yield [**Table IV-1**, entry 1].[75] By using $K_3PO_4$, a stronger base, the yield could be improved to 68% [entry 3]. Unfortunately, the use of KO*t*-Bu led to complete decomposition [entry 4]. When using CuI and CuCN using dimethylethylenediamine [DMEDA] as the ligand [our first generation coupling conditions],[12] higher temperatures were required and gave lower yields of **IV-12** [entries 5 and 6], clearly demonstrating the superiority of the $CuSO_4 \cdot 5H_2O$ and 1,10-phenanthroline combination.

**Table IV-1. Optimization of Coupling Conditions**



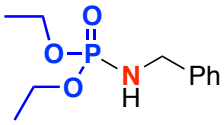
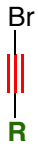
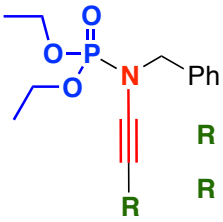
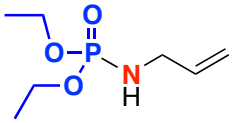
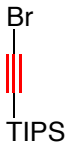
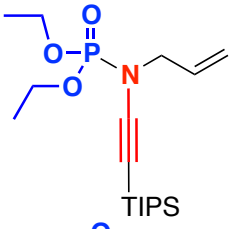
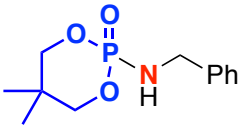
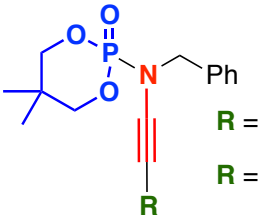
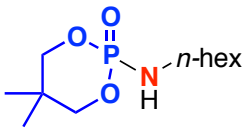
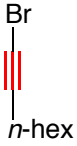
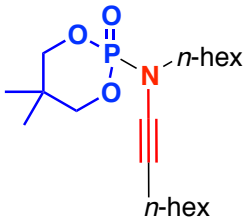
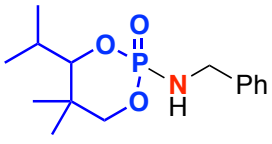
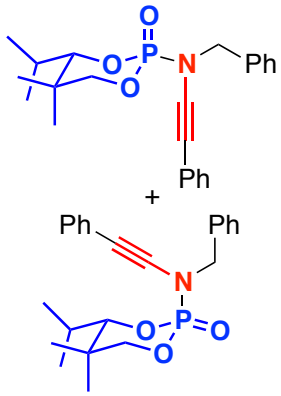

| entry | Cu catalyst | ligand | base | yield [%][a] |
|---|---|---|---|---|
| 1 | $CuSO_4{\cdot}5H_2O$ | 1,10-phenanthroline | $K_2CO_3$ | 38 |
| 2 | $CuSO_4{\cdot}5H_2O$ | 1,10-phenanthroline | $Cs_2CO_3$ | 59 |
| **3** | **$CuSO_4{\cdot}5H_2O$** | **1,10-phenanthroline** | **$K_3PO_4$** | **68** |
| 4 | $CuSO_4{\cdot}5H_2O$ | 1,10-phenanthroline | KO*t*-Bu | – |
| 5 | CuI | DMEDA | $K_3PO_4$ | 25[b] |
| 6 | CuCN | DMEDA | $K_3PO_4$ | 27[b] |

[a] Isolated yields. [b] Reactions run at 110 °C.

### 4.3.2 Synthesis of *N*-Phosphoryl Ynamides

Using the optimized coupling conditions from **Table IV-1**, a small library of *N*-phosphoryl ynamides was prepared [**Table IV-2**]. *N*-benzyl phosphoramidate **IV-11** led smoothly to ynamides **IV-17** and **IV-18** in 61 and 69% yields, respectively [entries 1 and 2]. *N*-allyl-*N*-phosphoryl ynamide **IV-19** could also be successfully prepared [entry 3], though an ensuing *aza*-Claisen–hydrolysis pathway was operational at 75 °C, resulting in a diminished yield [see **Scheme IV-8**]. Cyclic phosphoramidates generally gave higher yields of the corresponding ynamides, likely due to enhanced hydrolytic stability[76] of both the amides and ynamide products [entries 4–7, see **Figure IV-1**]. In addition, a 1:1 mixture of diastereomeric phosphoramidates **IV-16** was used to prepare ynamides **IV-23ax** and **IV-23eq**, differing only in the stereochemistry at phosphorus, in a combined 95% yield.

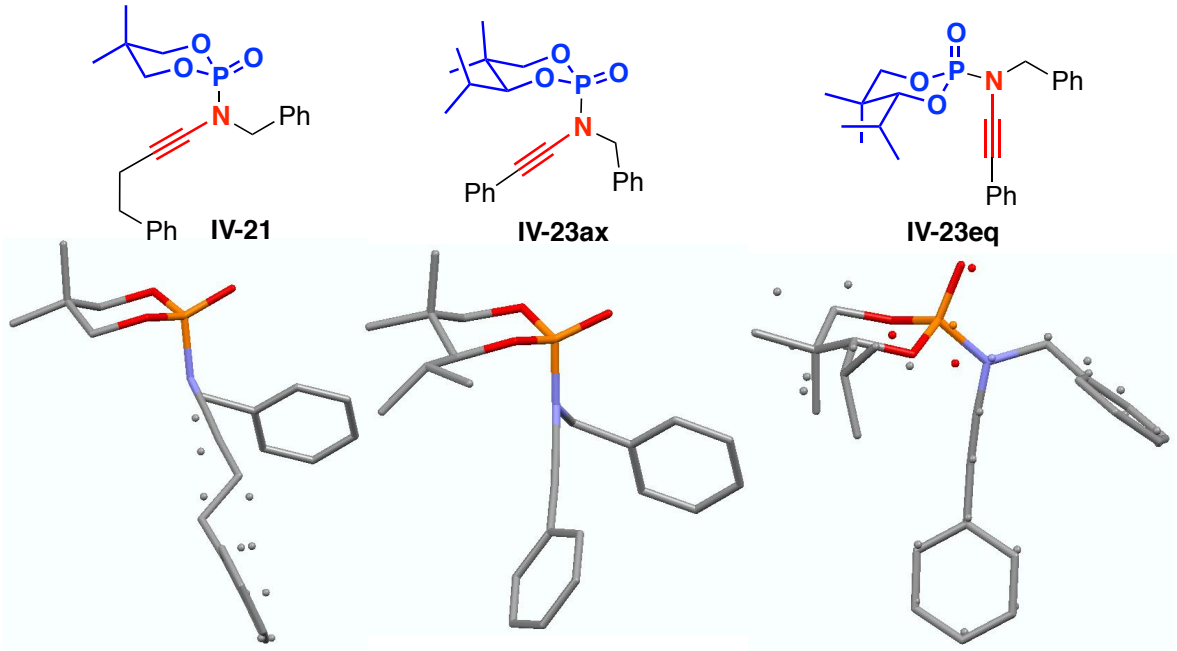
**Table IV-2. Achiral *N*-Phosphoryl Ynamide Preparation**

| entry | phosphoramidate | alkyne | ynamide | | yield [%][b] |
|---|---|---|---|---|---|
| 1 |  **IV-11** |  |  | **R** = $CH_2OTBS$ **IV-17** | 61 |
| 2 | | | | **R** = *n*-hex **IV-18** | 69 |
| 3 |  **IV-13** |  |  | **IV-19** | 39 |
| 4 |  **IV-14** |  |  | **R** = *n*-hex **IV-20** | 84[c] |
| 5 | | | | **R** = $(CH_2)_2Ph$ **IV-21** | 92[c] |
| 6 |  **IV-15** |  |  | **IV-22** | 54[c] |
| 7 |  **IV-16** [1:1 *dr*] |  |  | **IV-23eq** / **IV-23ax** | 95[c] |

[a] Reaction conditions: 15.0 mol % $CuSO_4 \cdot 5H_2O$, 30.0 mol % 1,10-phenanthroline, 1.3 equiv alkynyl bromide, 2 equiv $K_3PO_4$, Tol [conc = 0.4 *M*], 75–100 °C, 24 h. [b] Isolated yields. [c] 48 h reaction time.

These two diastereomeric ynamides were separable by column chromatography and also crystalline, allowing us to assign the stereochemistry of each by single crystal X-ray structural analysis [**Figure IV-1**]. Interestingly, the X-ray structure of cyclic ynamide **IV-21** showed that it adopted a chair configuration such that the *N*-*C*≡C was in the more sterically hindered axial orientation. This allowed the nitrogen lone pair to delocalize into the σ*[P=O] and the two oxygen lone pairs to delocalize into the π*[P=O]. Ynamide **IV-23ax** adopted a similar conformation.

**Figure IV-1. X-ray Structures of Ynamides IV-21, IV-23ax, and IV-23eq**




Unfortunately, the X-ray crystal structure of ynamide **IV-23eq** was convoluted by co-crystallization of both enantiomers in a 90:10 ratio as an example of whole molecule disorder [**Figure IV-1**]. Regardless, it was clear that the *N*-*C*≡C was in an equatorial

orientation with the nitrogen lone pair delocalized into the π*[P=O]. Further attesting to the stability gained by the axial ynamide orientation, **IV-23ax** had a melting point more than 70 $^{o}$C higher than that of **IV-23eq**, though some of that difference may be due to the whole molecule disorder in the crystal of **IV-23eq**.

## 4.4 Coupling of Chiral Phosphordiamidates

In addition to having readily tunable electronegativity, one especially interesting feature of phosphoryl-derived electron-withdrawing groups is that the phosphorus atom *directly* attached to the ynamide may be chiral. This should allow the *N*-phosphoryl group to serve two purposes: (1) as an electron-withdrawing group necessary to stabilize the ynamide, and (2) as a chiral auxiliary.

Chiral phosphordiamidates were readily prepared using a one-pot procedure starting from chiral amino-alcohols [**Scheme IV-5**].[77] For example, *L*-proline **IV-24** was reacted with $POCl_3$ and $NEt_3$ in $CH_2Cl_2$ to first afford phosphoryl chloride **IV-25**. After 3 h, benzyl amine and $NEt_3$ were then be added to finally give proline-derived phosphordiamidate **IV-26** in 89% yield as a single diastereomer. Similarly, a 3:1 mixture of phosphordiamidates **IV-28a** and **IV-28b** was prepared from 1*R*,2*R*-(–)-pseudoephedrine in 90% yield. By recrystallizing from $Et_2O$, the minor diastereomer **IV-28b** was selectively crystallized from the mixture as 1:16 **a/b**, enriching the mother liquor to 5:1 **a/b**. The stereochemistry of **IV-26**, **IV-28a**, and **IV-28b** was determined by nOe analysis [**Figure IV-2**].

**Scheme IV-5. Preparation of Chiral Phosphordiamidates**

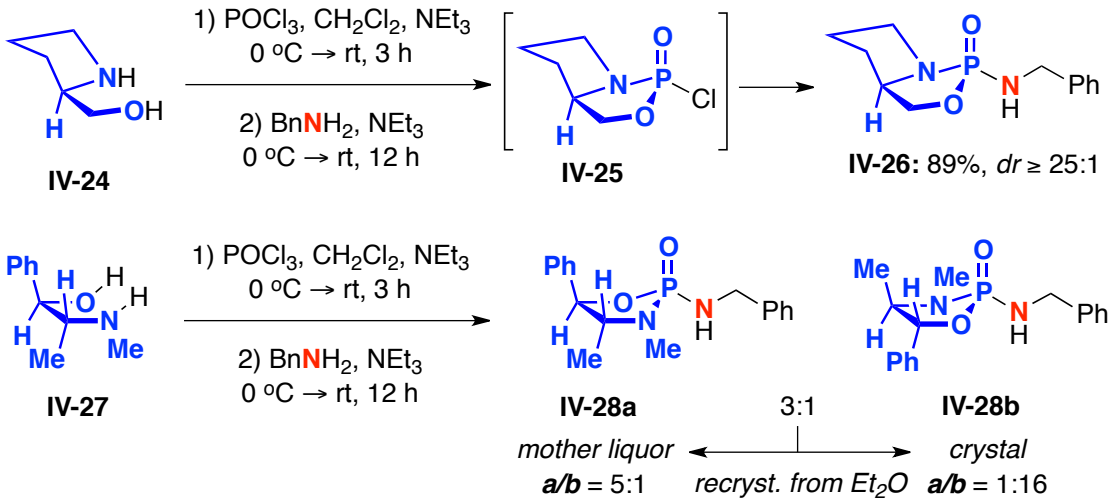
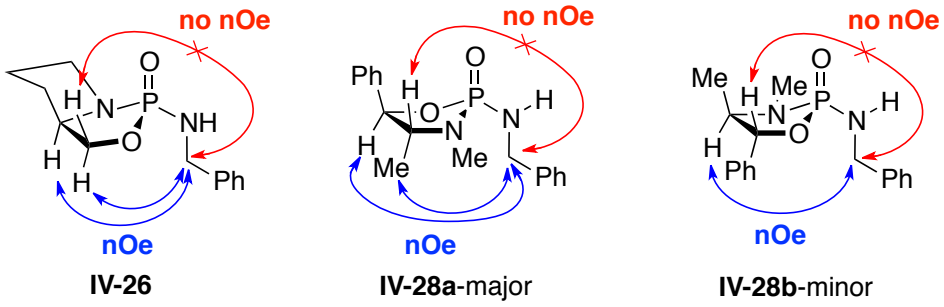



**Figure IV-2. Stereochemical Assignment of Chiral Phosphordiamidates**

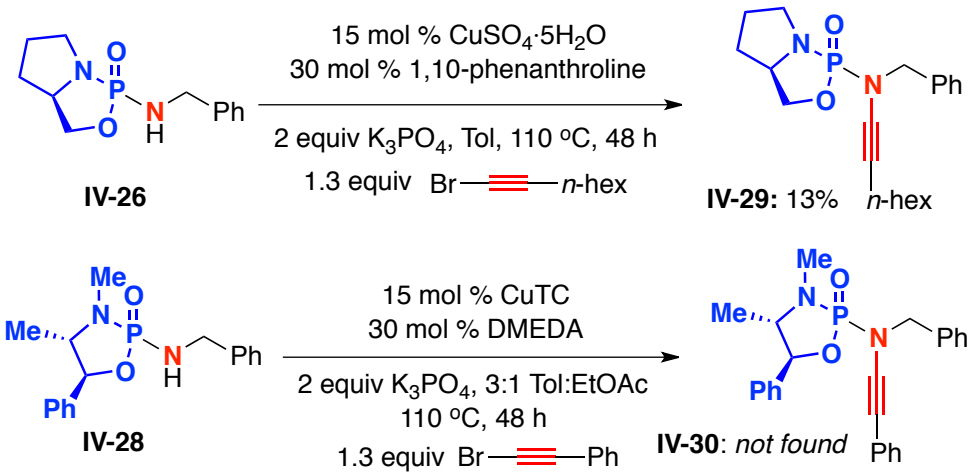



### 4.4.1 Problematic Coupling

Our initial attempts to use prepare chiral *N*-phosphoryl ynamides using our amidative cross-coupling were met with much frustration for we realized that the reactivity of amino-alcohol derived phosphordiamidates was very different from their 1,3-diol derived counterparts. To illustrate this point, the coupling of **IV-26** using the previously established conditions proceeded in a meager 13% yield [**Scheme IV-6**]. Some starting material could

be recovered, but the majority had decomposed. During our course of study, we also experimented with using CuTC [TC = thiophene-2-carboxylate][78] instead of $CuSO_4 \cdot 5H_2O$ to avoid hydrolysis problems. Unfortunately, using 15 mol % CuTC with 30 mol % DMEDA resulted in no coupling of 1*R*,2*R*-(–)-pseudoephedrine derived phosphordiamidate **IV-28**, though 70% of the starting material could be recovered [the use of EtOAc as a co-solvent was for solubility].

**Scheme IV-6. Hydrolysis and Low Reactivity Issues**




### 4.4.2 Synthesis of Chiral *N*-Phosphoryl Ynamides

We finally discovered that the addition of 10 equiv $NEt_3$ to the anhydrous catalytic system [CuTC/DMEDA] allowed for the synthesis of phosphordiamidate derived ynamide **IV-29** in a low but synthetically useful yield [**Scheme IV-7**].

**Scheme IV-7. Use of $NEt_3$ to Increase Reactivity**

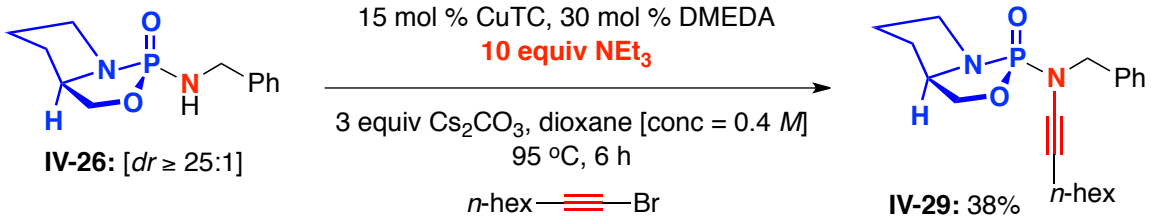
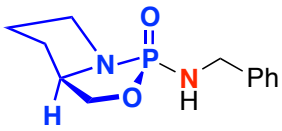
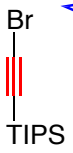
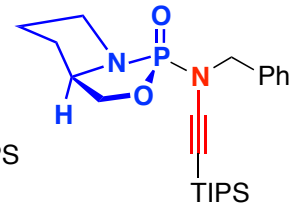
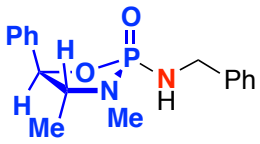
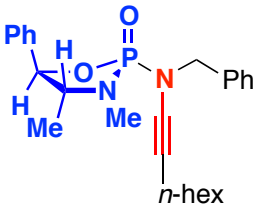
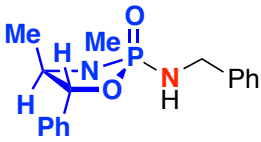
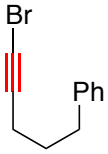
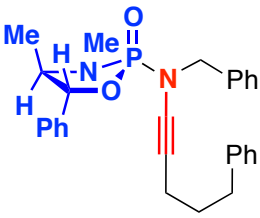
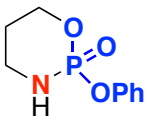
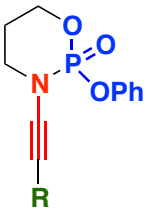



**Table IV-3. Synthesis of Chiral *N*-Phosphoryl Ynamides**

| entry | phosphor(di)amidate | alkyne | ynamide | | yield[b] |
|---|---|---|---|---|---|
| 1 |  **IV-26:** [*dr* ≥ 25:1] |  |  | **IV-32** | 28 |
| 2 |  **IV-28a** [*dr* 5:1] |  |  | **IV-33** | 59 |
| 3 |  **IV-28b** [*dr* 16:1] |  |  | **IV-34** | 41 |
| 4<br>5 |  **IV-31:** *racemic* |  |  | **R** = *n*-hex<br>**R** = TIPS | **IV-35**<br>**IV-36** | 62[c]<br>81[c] |

[a] Reaction conditions: 20.0 mol % CuTC, 40.0 mol % DMEDA, 1.3 equiv alkynyl bromide, 3 equiv $Cs_2CO_3$, 10 equiv $NEt_3$, dioxane [conc = 0.4 *M*], 95 °C, 6–24 h. [b] Isolated yields. [c] Same catalyst, but with 3:1 toluene:EtOAc [conc = 0.4 *M*], 2 equiv $K_3PO_4$, 95 °C, 24 h.

To our relief, the revised coupling conditions were general and could be used to prepare a variety of chiral *N*-phosphoryl ynamides [**Table IV-3**]. Ynamides **IV-33** and **IV-34** could be prepared from the separable mixture of diastereomeric phosphordiamidates **IV-28a** and **IV-28b** in 59% and 41% yield, respectively [entries 2 and 3]. The 1,3-amino alcohol derived phosphoramidate resembling a phosphoryl version of Evans' chiral auxiliary led nicely to ynamides **IV-35** and **IV-36** in moderate yields without the use of $NEt_3$, further demonstrating the difference in reactivity between phosphoramidates and phosphordiamidates.

## 4.5 Applications of *N*-Phosphoryl Ynamides

The discovery and synthesis of a new class of ynamides was interesting, but we needed to assess their utility. We describe here our successes and failures using *N*-phosphoryl ynamides in a variety of cycloaddition reactions.

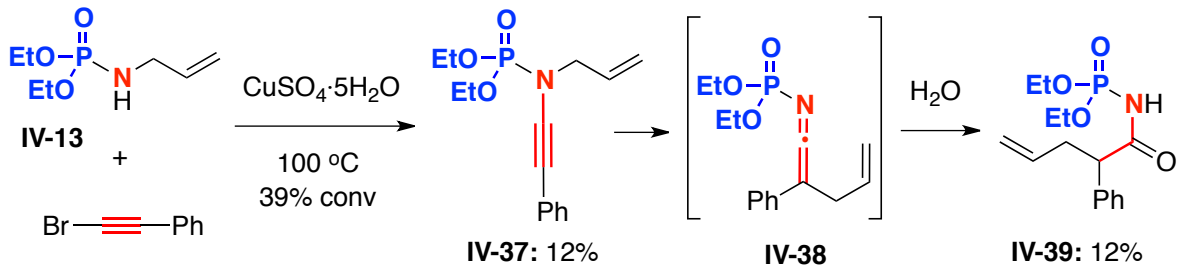
### 4.5.1 Tandem *Aza*-Claisen–Cycloadditions of *N*-Phosphoryl-*N*-Allyl Ynamides

Our initial interest in developing a synthesis of *N*-phosphoryl ynamides was largely for the desire to carry out Pd-catalyzed or thermal rearrangements without the ensuing ketenimine 1,3-sulfonyl shift[41-42,53] seen with *N*-sulfonyl ynamides [see **Chapter 3**]. Therefore, it was critical that an *N*-to-*C* transfer would occur and a 1,3-phosphoryl shift would not.

### 4.5.1.1 Feasibility of an *Aza*-Claisen Rearrangement

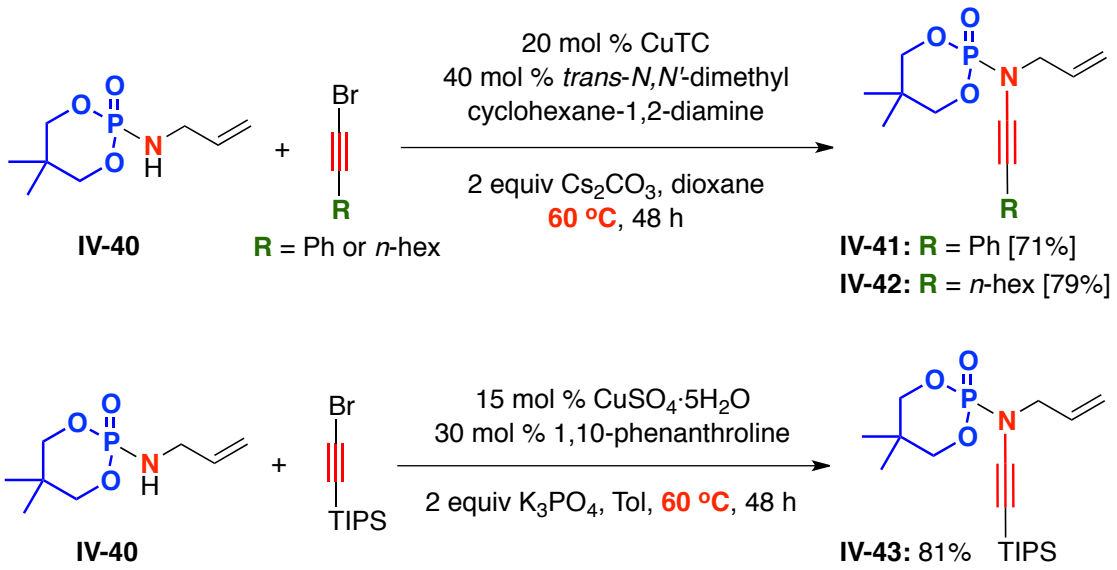
Early in our screening of reaction conditions, we were delighted to isolate amide **IV-39** as a side-product during the synthesis of *N*-allyl ynamide **IV-37** [**Scheme IV-8**]. Formation of amide **IV-39** implied the existence of ketenimine **IV-38** resulting from a thermal 3-*aza*-Claisen rearrangement[48] of ynamide **IV-37**.

**Scheme IV-8. Discovery of an *Aza*-Claisen–Hydrolysis Pathway**




By simply lowering the reaction temperature, the *aza*-Claisen rearrangement could be avoided, allowing for the synthesis of a variety of *N*-phosphoryl-*N*-allyl ynamides [**Scheme IV-9**]. Accordingly, ynamides **IV-41** and **IV-42** were prepared using 20 mol % CuTC with 40 mol % *trans-N,N'*-dimethylcyclohexane-1,2-diamine at 60 °C in 79% and 71%, respectively yield. We later discovered that our original catalytic system [$CuSO_4 \cdot 5H_2O$/1,10-phenanthroline] was equally efficient at 60 °C and far less expensive. Using this method, ynamide **IV-43** was prepared in 81% yield.

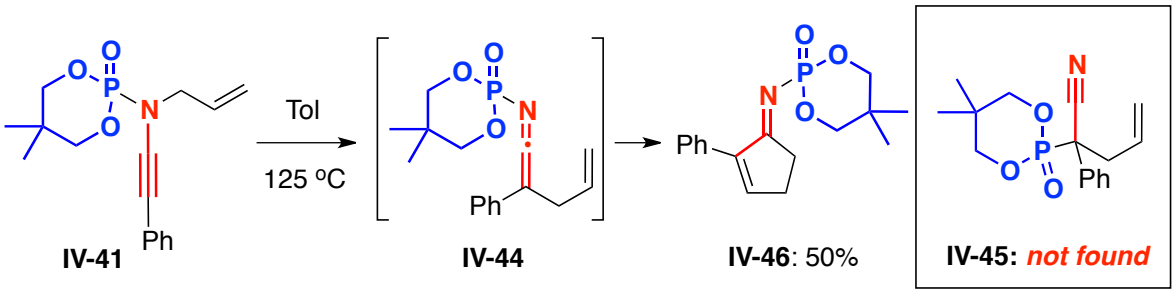
**Scheme IV-9. Avoiding the *Aza*-Claisen in Ynamide Preparation**




### 4.5.1.2 Tandem *Aza*-Claisen–[2 + 2] or [4 + 2]

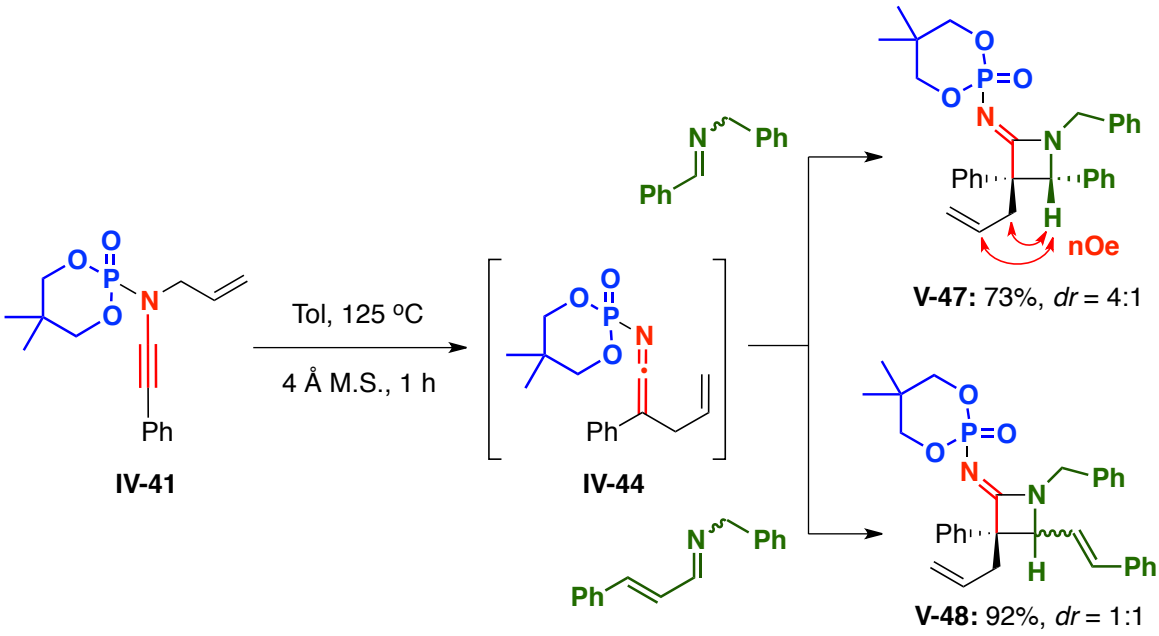
The next issue to address was whether a 1,3-phosphoryl shift was operational after the *aza*-Claisen rearrangement. Fortunately, heating of *N*-phosphoryl-*N*-allyl ynamide **IV-41** to 125 °C in toluene resulted in no observed formation of nitrile **IV-45** [**Scheme IV-10**]. Instead, an unexpected cyclopentenimine **IV-46** was isolated in 50% yield resulting from an intramolecular carbocyclization of the rearranged allyl moiety onto the ketenimine [see **Chapter 5**].

**Scheme IV-10. *Aza*-Claisen, But No 1,3-Phosphoryl Shift**



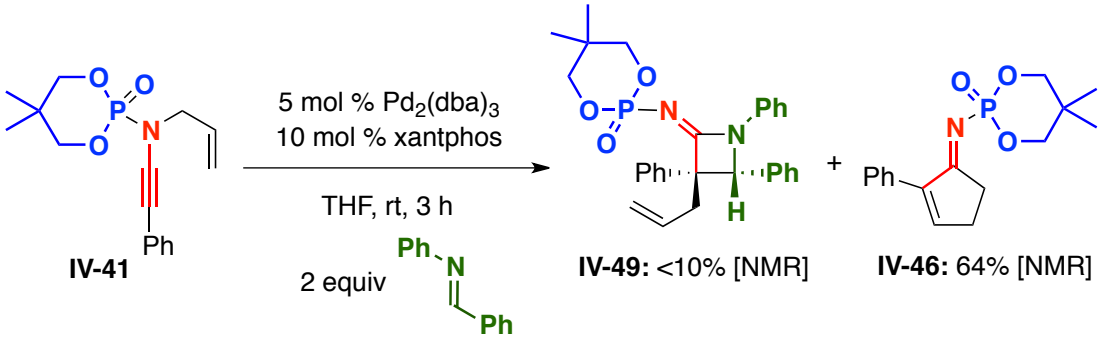

Still, in the presence of nucleophilic imines, the intermediate ketenimine could be successfully trapped to yield heterocyclic products through Staudinger-type cycloadditions[38,57e,79] [**Scheme IV-11**]. When 2 equiv of *N*-benzylidenebenzylamine was used, *N*-phosphoryl azetadine-2-imine **IV-47** was isolated in 73% yield as a 4:1 mixture of diastereomers. Likely, this proceeded through initial coordination of the imine to the electrophilic central ketenimine carbon, followed by a conrotatory 4π-electron electrocyclic ring closure and tautomerization to give the azetidine-2-imine. The stereochemistry of the major diastereomer was confirmed by nOe. Similarly, the use of an analogous unsaturated imine yielded a 1:1 mixture of unsaturated azetidine-2-imines **IV-48** in 92% yield *via* a stepwise–[2 + 2] instead of the possibly competing [4 + 2] cycloaddition to give an imino-piperidine.

**Scheme IV-11. Tandem *Aza*-Claisen–Staudinger Type–[2 + 2] Cycloadditions**




With the *N*-benzyl imines shown in **Scheme IV-11**, the competing cyclopentenimine formation was not a problem. However, when the less nucleophilic fully-conjugated *N*-benzylidineaniline was used, the intramolecular carbocyclization outcompeted the intermolecular [2 + 2] to give mostly cyclopentenimine **IV-46** by $^{1}$H NMR [**Scheme IV-12**].

**Scheme IV-12. Carbocyclization Versus [2 + 2]-Cycloaddition**

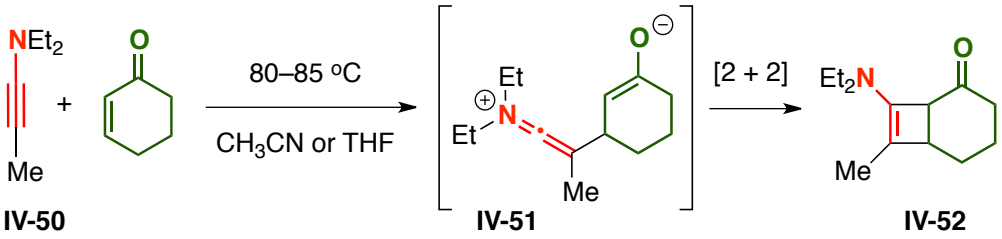


### 4.5.2 Intermolecular Ynamide Ficini–[2 + 2]

#### 4.5.2.1 Original Ynamine Ficini–[2 + 2]

Ficini[80] was a pioneer in the field of ynamine chemistry. In the late 1960's and early 1970's, they reported a series of elegant thermally driven [2 + 2] cycloadditions of ynamines with unsaturated enones for the synthesis of aminocyclobutenes.[80-81] For example, the cycloaddition of **IV-50** with cyclohexenone occurred at 80–85 °C to give **IV-52** presumably through zwitterionic intermediate **IV-51** [**Scheme IV-13**].

**Scheme IV-13. Ficini's Ynamine–[2 + 2] Cycloaddition**

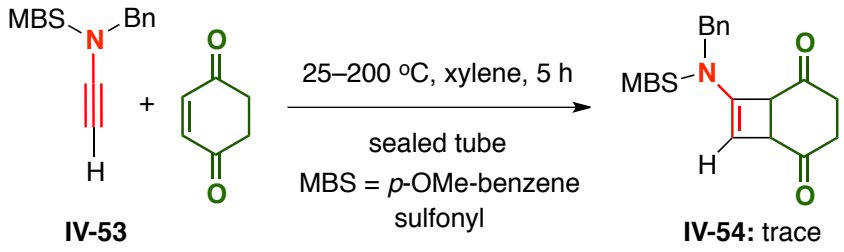



**IV-50** **IV-51** **IV-52**

#### 4.5.2.2 Cu-Catalyzed *N*-Sulfonyl Ynamide Ficini–[2 + 2]

We have been interested in developing an ynamide version of Ficini's intermolecular ynamine–[2 + 2] for the past 15 years. Unfortunately, the same stability that renders ynamides superior functional groups to ynamines also makes them less nucleophilic. All attempts to carry out a thermal ynamide Ficini–[2 + 2] were met with failure. Even heating of the more electron-rich *N*-*p*-methoxybenzenesulfonyl ynamide **IV-53** to 200 °C in xylene with quinone gave only a trace amount of the desired amidocyclobutene **IV-54** [**Scheme IV-14**].

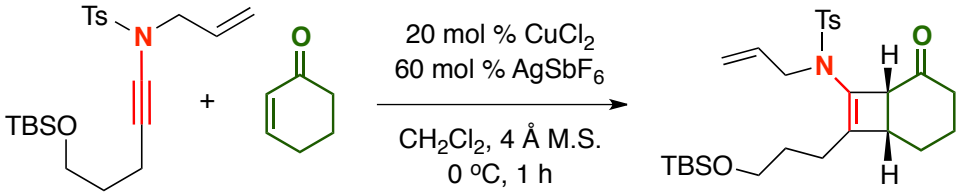
**Scheme IV-14. Problematic Thermal Ynamide Ficini–[2 + 2]**




**IV-53** **IV-54:** trace

In 2010, we discovered and reported the first successful copper-catalyzed Ficini–[2 + 2] cycloaddition of ynamides.[82] Using 20 mol % $CuCl_2$ and 60 mol % $AgSbF_6$, ynamide **II-21c** smoothly underwent an intermolecular [2 + 2] cycloaddition with cyclohexenone at 0 °C to afford **IV-56** in 56 % yield [**Scheme IV-15**]. The method was general for a variety of *N*-sulfonyl ynamides, including electron-deficient *p*-Ns, and both cyclic and acyclic enones in good yields.

**Scheme IV-15. Discovery of a Successful Catalytic System**



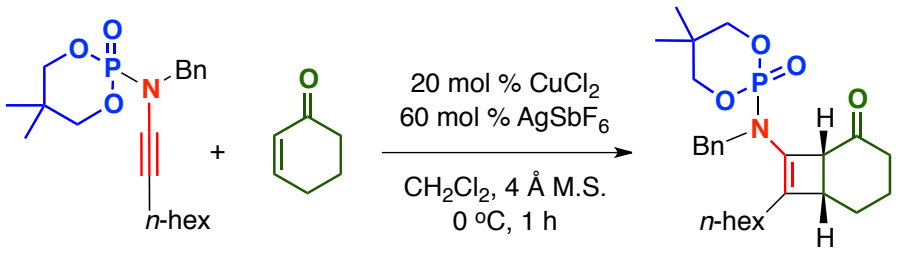

**II-21c** **IV-56**: 56%

### 4.5.2.3 Ficini–[2 + 2] with an *N*-Phosphoryl Ynamide

When we extended this methodology to include the use of *N*-phosphoryl ynamides, we were pleased to discover that the same catalytic system could be employed. Starting from

ynamide **IV-20**, amidocyclobutene **IV-57** was isolated in 44% yield [**Scheme IV-16**]. Notably, there was a significant amount of ynamide hydrolysis observed, as well.

**Scheme IV-16. An *N*-Phosphoryl Ynamide Ficini–[2 + 2] Cycloaddition**

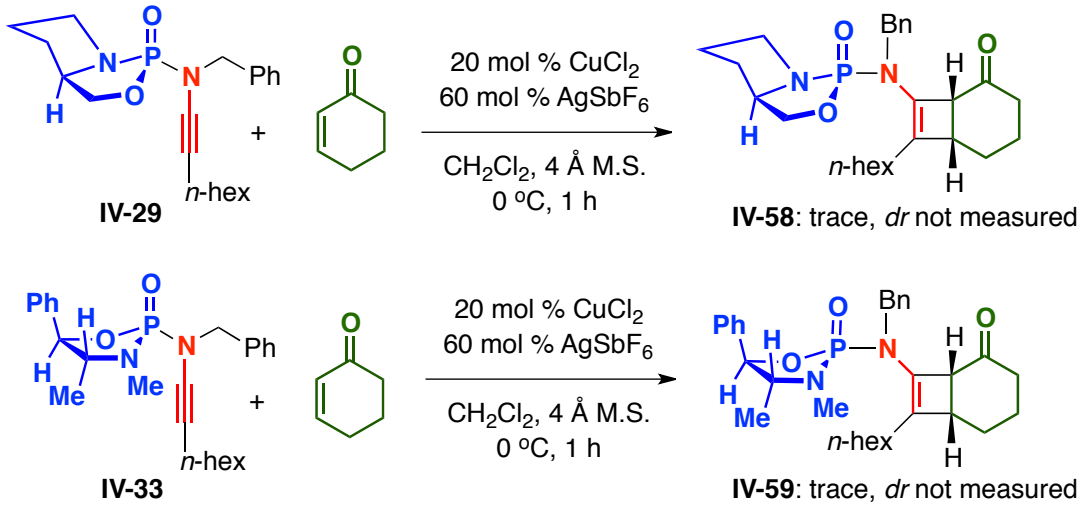



**IV-20** **IV-57**: 44%

### 4.5.2.4 Attempts at a Diastereoselective [2 + 2] Cycloaddition

One inherent feature of *N*-phosphoryl ynamides is their capacity to be chiral.[72] Unfortunately, amino-alcohol derived phosphordiamidates and, likewise, the corresponding ynamides are far less hydrolytically stable[76] than their 1,3-diol derived counterparts. When we attempted the Cu-catalyzed [2 + 2] cycloaddition of ynamides **IV-29** and **IV-33** with cyclohexenone, the corresponding cycloadducts could only be observed in trace amounts and could not be isolated [**Scheme IV-17**]. The instability to Lewis acids presents a clear limitation for the utility of *N*-phosphoryl ynamides.

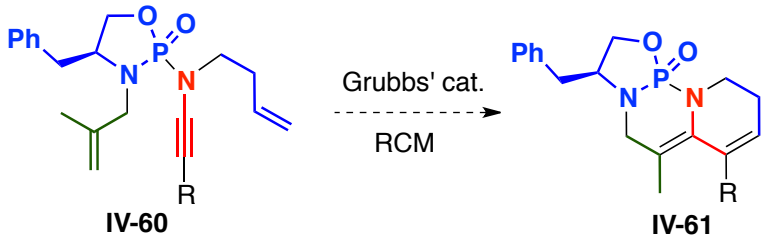
**Scheme IV-17. Hydrolysis With Amino-Alcohol Derived Phosphordiamidates**




### 4.5.3 Potential Applications

In addition to being exploited as chiral auxiliaries, phosphoryl moieties have recently been used as tethers between two or more reactive components.[83] With our system, we imagine that it may be possible to carry out transformations such as ring-closing metathesis cascades from ynamides **IV-60** to prepare unique fused tricycles **IV-61** where the phosphorus is incorporated into the skeleton.

**Scheme IV-18. Tandem Ring-Closing Metathesis Sequence**



## 4.6 Conclusions

We have described the synthesis of a new class of *N*-phosphoryl ynamides via Cu-catalyzed amidative cross-couplings of phosphoramidates and phosphordiamidates with alkynyl bromides. We showed that *N*-phosphoryl-*N*-allyl ynamides participate in a thermal 3-*aza*-Claisen rearrangement for the *in situ* preparation of ketenimines that do not undergo a 1,3-phosphoryl transfer. The ketenimines could, therefore, participate in Staudinger-type cycloadditions with imines and unsaturated imines. The first example of an *N*-phosphoryl ynamide Ficini–[2 + 2] cycloaddition is described, as well as our attempts to use chiral phosphoryl groups to induce diastereoselectivity in the cycloaddition.

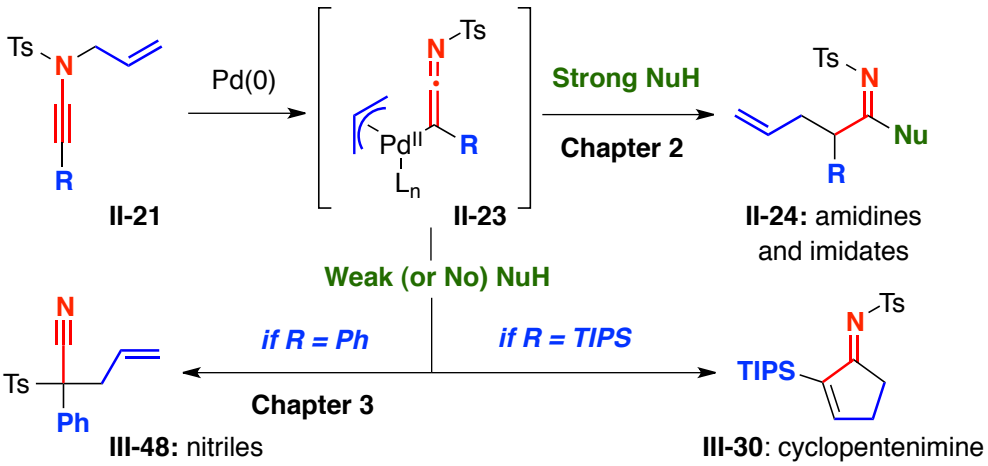
# Chapter 5. Carbocyclizations of *N*-Allyl Ynamides

## Chapter 5: Carbocyclizations of *N*-Allyl Ynamides

### 5.1 Pd-Catalyzed Carbocyclizations of *N*-Sulfonyl-*N*-Allyl Ynamides

Over the last several years, we have thoroughly explored the Pd-catalyzed rearrangement[40-42] of *N*-allyl ynamides[2] to Pd-π-allyl ketenimine complexes and the transformations that ensue. We have shown that these ketenimines may be trapped with strong nucleophiles such as amines, alcohols, and enamines for the synthesis of amidines,[40-42] imidates,[53] and vinyologous amidines,[42] respectively [**Scheme V-1**]. We later found that the ketenimines generated from aryl- and alkyl-terminated ynamides undergo a facile 1,3-sulfonyl shift for the synthesis of nitriles[41] when no nucleophile or weak nucleophiles are present. Interestingly, when a TIPS-terminated ynamide was subjected to Pd(0)-catalyzed conditions with no nucleophile present, instead of observing a corresponding nitrile, cyclopentenimine **III-30** was found, representing a unique carbocyclization of *N*-allyl ynamides.[41]

**Scheme V-1. Initial Discovery of a Pd-Catalyzed Carbocyclization**



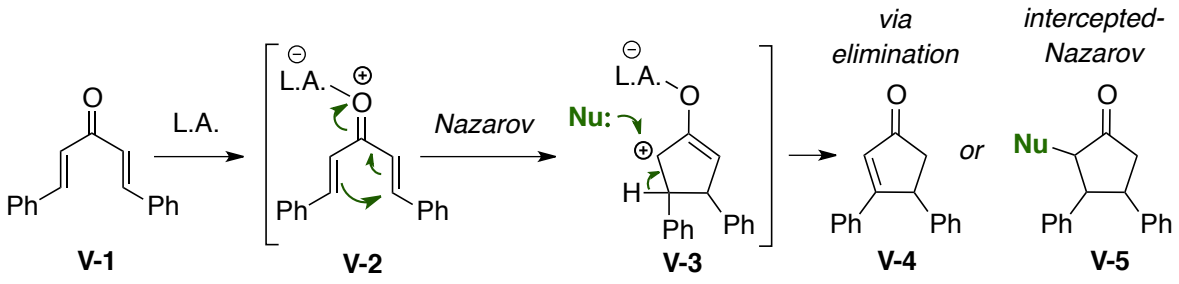
### 5.1.1 Related Carbocyclizations for Cyclopentenone Synthesis

Both concerted and non-concerted carbocyclizations have been extensively used to prepare functionalized cyclopentenes. Among the most well-studied is the Nazarov cyclization,[84] however beautiful examples of iminium ion[85] and ketene[86] promoted cyclizations have also been recently reported.

#### 5.1.1.1 Nazarov Cyclizations

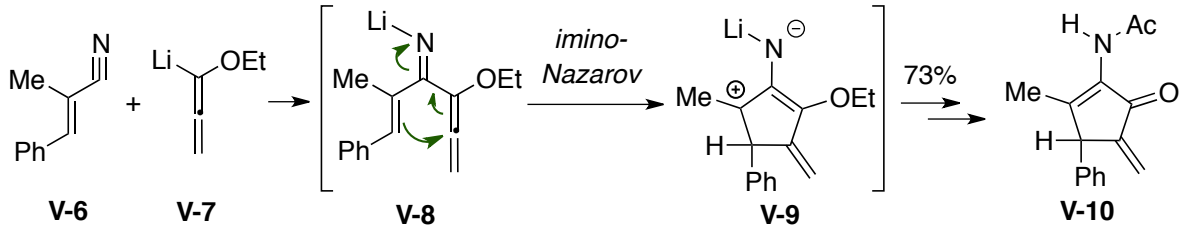
The Nazarov cyclization is a powerful method for preparing α,β-unsaturated cyclopentenones from divinyl ketones. As a representative example, upon treatment of divinyl ketone **V-1** with an oxophilic lewis acid, divinyl oxonium **V-2** is generated. This species may undergo a Nazarov conrotatory 4π-electron electrocyclization to give cationic intermediate **V-3** [**Scheme V-2**]. Typically, elimination follows to afford cyclopentenone **V-4**. Alternatively, there have been many recent examples of using nucleophiles to intercept the cationic intermediates to prepare highly substituted cyclopentanones **V-5**.[87-88]

**Scheme V-2. Nazarov and Intercepted-Nazarov Cyclizations**



One relevant variant of the Nazarov cyclization is the imino-Nazarov,[84] where a nitrogen is used in place of the oxygen atom. Though not nearly as well studied as the Nazarov, there have been several examples of imino-Nazarov cyclizations in literature. In one notable example, the imino-Nazarov was successfully used by Tius[89] to prepare α-aminocyclopentenone **V-10** after the addition of lithiated allene **V-7** to unsaturated nitrile **V-6** [**Scheme V-3**].

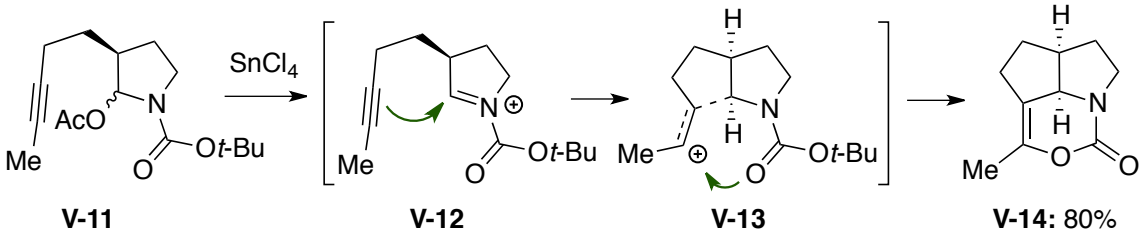
**Scheme V-3. Tius's Imino-Nazarov Cyclization**




### 5.1.1.2 Iminium Ion Promoted Carbocyclization

There are also many examples of carbocyclizations that occur through a non-contiguous π-system. Shown in **Scheme V-4** is an example of an *N*-acyloxyimium ion promoted carbocyclization by Hanessian[85] for the synthesis of azatricycle **V-14**. In this case, the vinyl cation **V-13** was trapped intramolecularly by the *N*-Boc carbonyl, though there are many examples showcasing intermolecular trappings, as well.

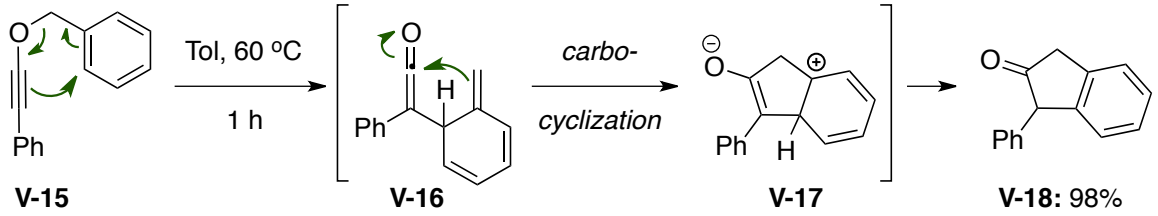
**Scheme V-4. Hanessian's Carbocyclization of *N*-Acyloxyiminium Ions**




### 5.1.1.3 Thermal Ketene Carbocyclization

In 2008, Minehan[86] first reported a tandem Claisen rearrangement–carbocyclization of ynol ether **V-15** for the synthesis of indanone **V-18** [**Scheme V-5**]. In their system, the Claisen rearrangement[49] could be achieved at 60 °C in toluene to afford ketene **V-16**. The subsequent carbocyclization generated zwitterionic intermediate **V-17**, and an ensuing elimination gave **V-18** in near quantitative yield.

**Scheme V-5. Minehan's Ynol Ether Carbocyclization**

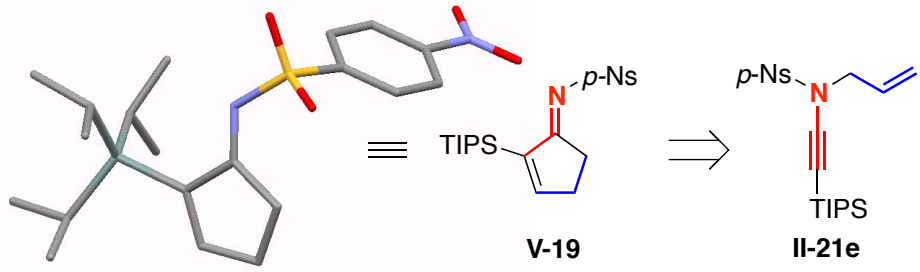



### 5.1.2 Optimization and X-Ray Structure Confirmation

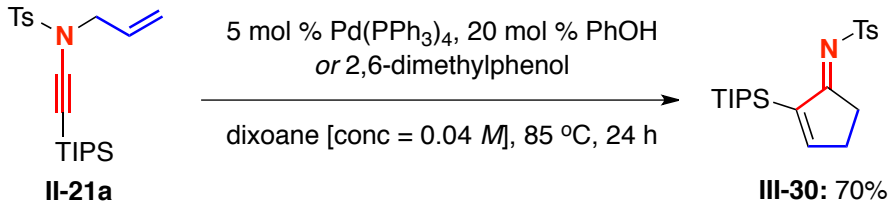
Our initial discovery of cyclopentenimine formation from *N*-allyl ynamides was unexpected and it often appeared in low yield as a byproduct during other reactions.[41] Upon X-ray structural confirmation of *N*-*p*-Ns-cyclopentenimine **V-19** [**Figure V-1**], we

optimized the conditions and found we could prepare cyclopentenimine **III-30** in 70% yield using 5 mol % $Pd(PPh_3)_4$ with 20 mol % phenol or 2,6-dimethylphenol as a co-ligand [**Scheme V-6**].

**Figure V-1. X-Ray of *p*-Ns Cyclopentenimine V-19**




**Scheme V-6. Optimized Conditions for Cyclopentenimine Formation**

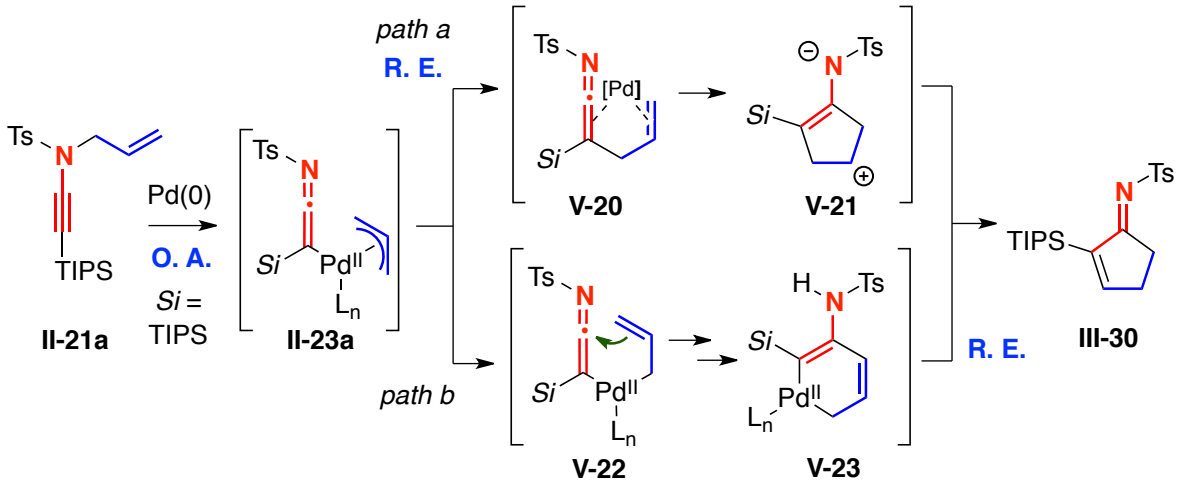



### 5.1.3 Mechanistic Studies

More interesting to us than the cyclopentenimine structure itself was the mechanism by which it formed. Without a palladium catalyst, cyclopentenimine **III-30** has never been isolated from **II-21a**; instead, only nitrile formation with concomitant desilylation has been observed.[42] This implied that the carbocyclization was mediated in some way by palladium. Specifically, we wanted to ascertain whether the carbocyclization occurred before reductive elimination [**Scheme V-7**, *path b*] or after reductive elimination [*path a*]. If the mechanism

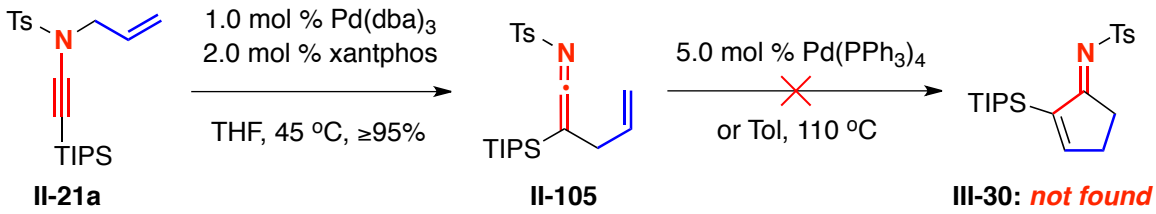
progressed via *path a*, it should involve zwitterionic intermediate **V-21** and an *N*-promoted 1,2-*H* shift to give **III-30**. Alternatively, the cyclization could occur through π-allyl complexes **V-22** and **V-23** followed by reductive elimination and tautomerization to afford **III-30**.

**Scheme V-7. Possible Mechanistic Pathways for Cyclopentenimine Formation**




Fortunately, we previously found that we could cleanly isolate ketenimine **II-105**, thereby providing a means of probing the mechanistic pathway involved in cyclopentenimine formation. First, when **II-105** was treated with 5 mol % $Pd(PPh_3)_4$, no cyclopentenimine was found [**Scheme V-8**]. Second, when **II-105** was heated in toluene at 110 $^{o}$C, again no cyclopentenimine was found. Taken together, this provided strong evidence that the carbocyclization occurred before the reductive elimination [ie. via *path b* and ketenimino-Pd-π-allyl complex **V-22**].

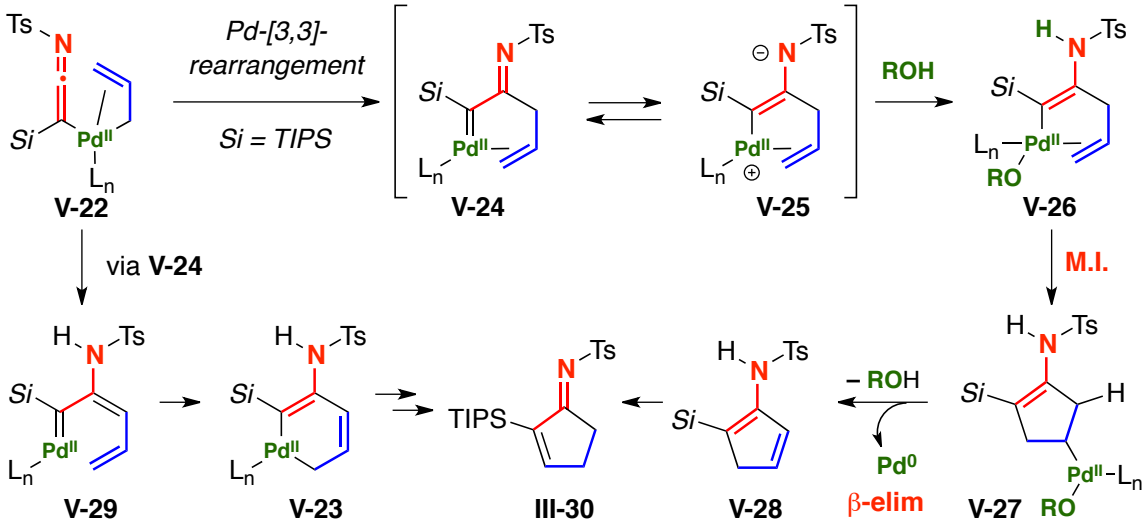
**Scheme V-8. Evidence for Carbocyclization Before Reductive Elimination**




**II-21a** **II-105** **III-30: *not found***

We therefore propose that a likely mechanistic course could involve an *aza*-variant of a Rautenstrauch–Nazarov cyclization[90-91] as shown in **Scheme V-9**. By using conditions in which the reductive elimination is relatively slowed, ketenimino-Pd-π-allyl complex **V-22** may instead undergo a Pd–[3,3] sigmatropic rearrangement to give α-imino palladium carbenoid **V-24.** While a number of possibilities could occur subsequently, one possibility that is consistent with the increased efficiency using PhOH would involve the formation of enamido-Pd-complex **V-26**, which could afford 2-amidocyclopentadiene **V-28** following migratory insertion [M.I.] and β-elimination. A facile 1,2-*H* shift followed by tautomerization could give cyclopentenimine **III-30**. An alternative pathway could proceed through dienyl palladium carbenoid **V-29** derived from tautomerization of **V-24**. A subsequent reductive elimination, 1,2-*H*-shift, and tautomerization would similarly give **III-30**.

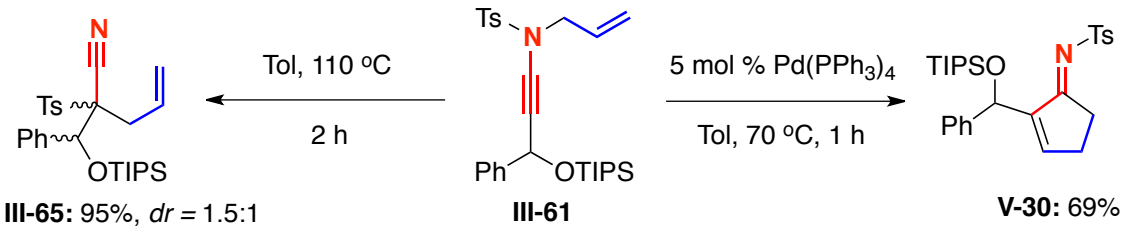
**Scheme V-9. An *Aza*-Rautenstrauch-Nazarov Cyclization Pathway**




### 5.1.4 Carbocyclizations with γ-Branched Ynamides

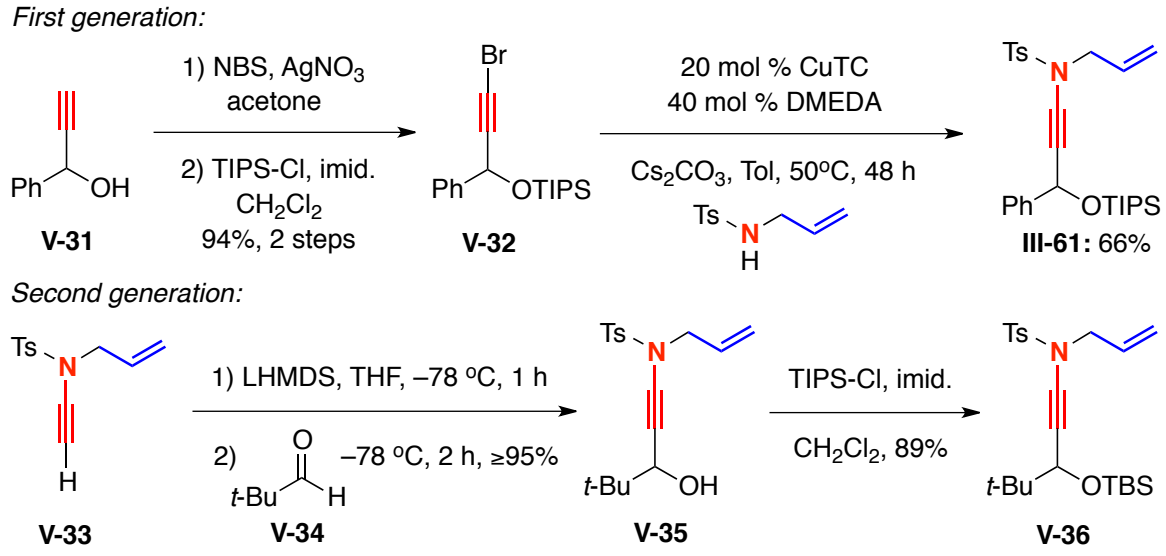
We were fascinated with the synthesis of cyclopentenimine **III-30**, but were unable for quite some time to promote cyclopentenimine formation with any non-silyl terminated ynamides. For example, even using the optimized conditions, phenyl- and alkyl-terminated ynamides resulted in nitrile formation with no desired cyclopentenimine observed.[41-42] It was not until we started exploring diastereoselective 1,3-sulfonyl shifts of γ-branched ynamides [see **Chapter 3**] more than a year later that we discovered another case of cyclopentenimine formation [**Scheme V-10**].[42] When ynamide **III-61** was treated with 5 mol % $Pd(PPh_3)_4$ in toluene at 70 °C, cyclopentenimine **V-30** was isolated in 69% yield. This again illustrated the importance of palladium in this reaction, as thermal conditions gave nitrile **III-65** in near quantitative yield.

**Scheme V-10. Pd(0)-Catalyzed Versus Thermal Conditions**




Isolation of **V-30** came as quite a surprise and prompted further exploration. Unfortunately, the preparation of γ-branched ynamide **III-61** was problematic [**Scheme V-11**]. It involved initial silylation of phenyl-propargyl alcohol **V-31** followed by bromination to afford **V-32.** These alkynyl bromides were not especially stable and are known lachrymators. Furthermore, the anhydrous Cu-catalyzed amidative cross-coupling to give **III-61** was sluggish at 50 °C and still incomplete after 48 h. The use of $CuSO_4 \cdot 5H_2O$ and 1,10-phenanthroline gave **III-61** in 12% yield with hydrolysis prevailing.

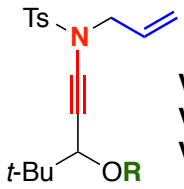
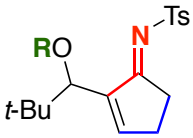
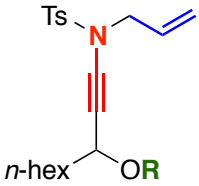
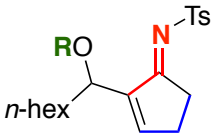
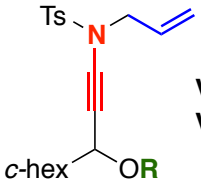
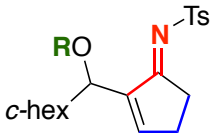
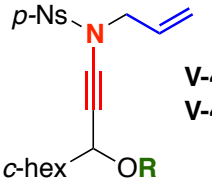
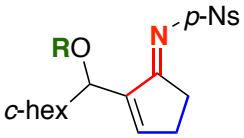
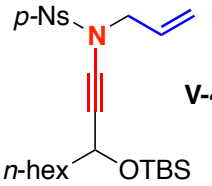
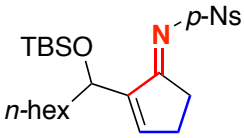
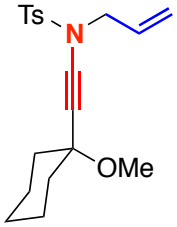
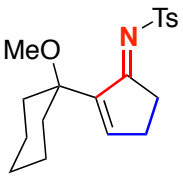
**Scheme V-11. Preparation of γ-Branched Ynamides**



As we soon realized that the cyclopentenimine formation was quite general with branched ynamides, it became necessary to reexamine the route for their preparation. Ideally, the diversification should occur as late as possible. With this in mind, we found that ynamide **V-33** could be lithiated and added to aldehydes such as pivalaldehyde **V-34** to directly prepare γ-hydroxy ynamide[92] **V-35** in excellent yield [**Scheme V-11**]. The alcohol could then be functionalized as desired to afford ynamides such as **V-36**. This allowed us to expediently and fully explore the scope of cyclopentenimine formation.

As shown in **Table V-1**, a variety of functionalized *N*-allyl-γ-branched ynamides could be employed in cyclopentenimine synthesis using 5 mol % $Pd(PPh_3)_4$ in toluene at 70 $^oC$. The reaction nicely tolerated *t*-Bu, *n*-hex, *c*-hex, and even a spirocyclic cyclohexane at the γ-position. The tolerance for functionality on the alcohol moiety was equally general, including methyl, silyl, benzyl, and even trityl protecting groups. Notably, this methodology provided a means of preparing α,β-unsaturated cyclopentenimines analogous to the α,β-unsaturated enones from a Baylis-Hillman[93] type reaction.

**Table V-1. Cyclopentenimines from *N*-Allyl-γ-Branched Ynamides**

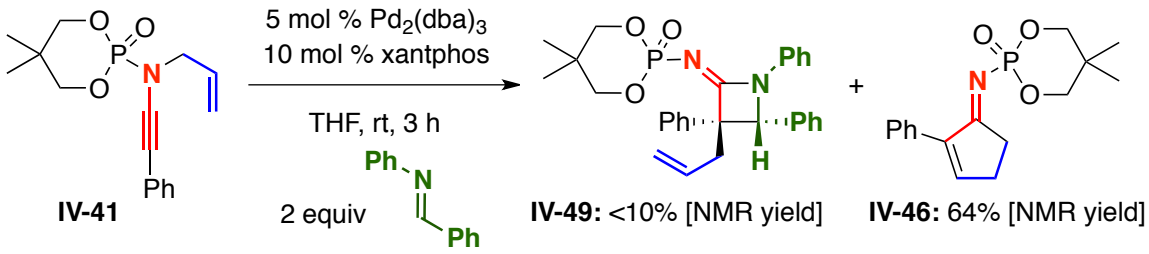
| entry | ynamide | | cyclopentenimine | | yield [%][b] |
|---|---|---|---|---|---|
| 1 |  | **V-36:** **R** = TBS |  | **V-47:** **R** = TBS | 71% |
| 2 | | **V-37:** **R** = Me | | **V-48:** **R** = Me | 77% |
| 3 | | **V-38:** **R** = Bn | | **V-49:** **R** = Bn | 84% |
| 4 |  | **V-39:** **R** = Me |  | **V-50:** **R** = Me | 70% |
| 5 | | **V-40:** **R** = TIPS | | **V-51:** **R** = TIPS | 92% |
| 6 |  | **V-41:** **R** = Me |  | **V-52:** **R** = Me | 88% |
| 7 | | **V-42:** **R** = Bn | | **V-53:** **R** = Bn | ≥95% |
| 8 |  | **V-43:** **R** = TBS |  | **V-54:** **R** = TBS | 80% |
| 9 | | **V-44:** **R** = $CPh_3$ | | **V-55:** **R** = $CPh_3$ | 83% |
| 10 |  | **V-45** |  | **V-56** | 56% |
| 11 |  | **V-46** |  | **V-57** | 34% |

[a] Reaction conditions: 5.0 mol % $Pd(PPh_3)_4$, toluene [conc = 0.04 *M*], 70 °C, 1 h.
[b] Isolated yields.

## 5.2 Carbocyclizations of *N*-Phosphoryl-*N*-Allyl Ynamides

While exploring the Staudinger-type [2 + 2] of *N*-phosphoryl ynamides[2,75] [see **Chapter 4**], we discovered that when using the less nucleophilic *N*-benzylidineaniline in the presence of catalytic amounts of $Pd_2(dba)_3$ and xantphos, the major product by NMR yield [phenanthrene internal standard] was cyclopentenimine **IV-46** instead of the desired azetidine imine **IV-49** [**Scheme V-12**]. This was our first successful carbocyclization of a Ph-terminated ynamide.

**Scheme V-12. An Unexpected Carbocyclization**

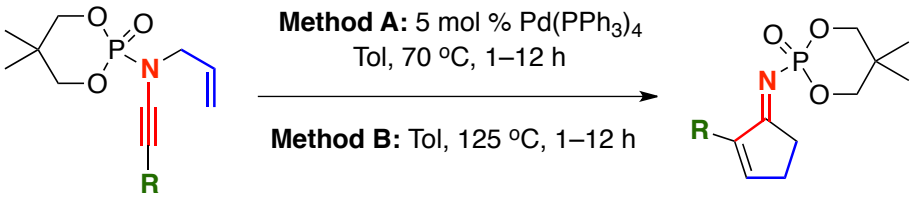



### 5.2.1 Pd-Catalyzed Versus Thermal Carbocyclization

Upon further studies, the yield of cyclopentenimine **IV-46** could be increased to 87% using 5 mol % $Pd(PPh_3)_4$ in toluene at 70 °C [**Table V-2**]. More importantly, the success of our initial discovery using conditions that favored reductive elimination led us to an exciting possibility: the carbocyclization of *N*-phosphoryl ynamides may not require palladium catalysis. This was confirmed when Ph-terminated ynamide **IV-41** gave cyclopentenimine **IV-46** in 50% yield upon heating to 125 °C in toluene while taking extra care to prevent palladium contamination [new reaction vials and magnetic stir bars].[94] Other alkyl-terminated *N*-phosphoryl ynamides could also be used in this transformation using both Pd-

catalyzed and thermal conditions. Curiously, γ-branched ynamide **V-60** gave <10% yield of **V-63** at 70 °C using Pd-catalysis, but 69% yield at 135–140 °C under strictly thermal conditions. This sensitivity to sterics was the first hint that the mechanism for the Pd-catalyzed carbocyclization of *N*-phosphoryl and *N*-sulfonyl ynamides was not necessarily the same.

**Table V-2. Cyclopentenimines from *N*-Phosphoryl-*N*-Allyl Ynamides**

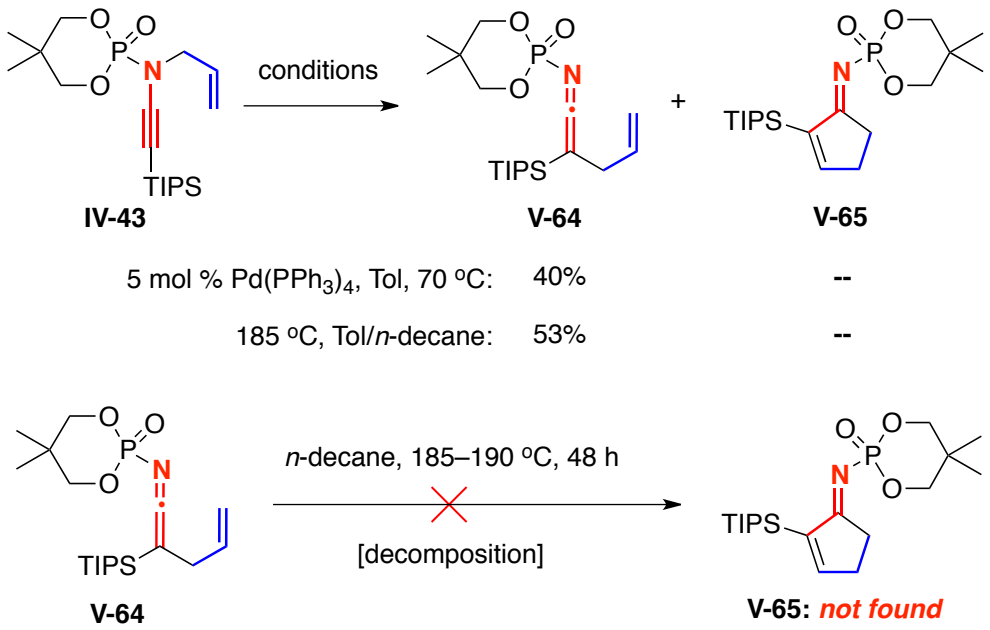



| ynamides | R = | cyclopentenimines | yield [%][a] |
|---|---|---|---|
| **IV-41** | Ph | **IV-46** | **A:** 87<br>**B:** 50 |
| **IV-42** | *n*-hex | **V-61** | **A:** 56<br>**B:** 27 |
| **V-59** | $(CH_2)_4OTBS$ | **V-62** | **A:** 34<br>**B:** 37 |
| **V-60** | *t*-Bu, OTBS | **V-63** | **A:** <10<br>**B:** 69[b] |

[a] Isolated yield. [b] 135–140 °C, 14 h.

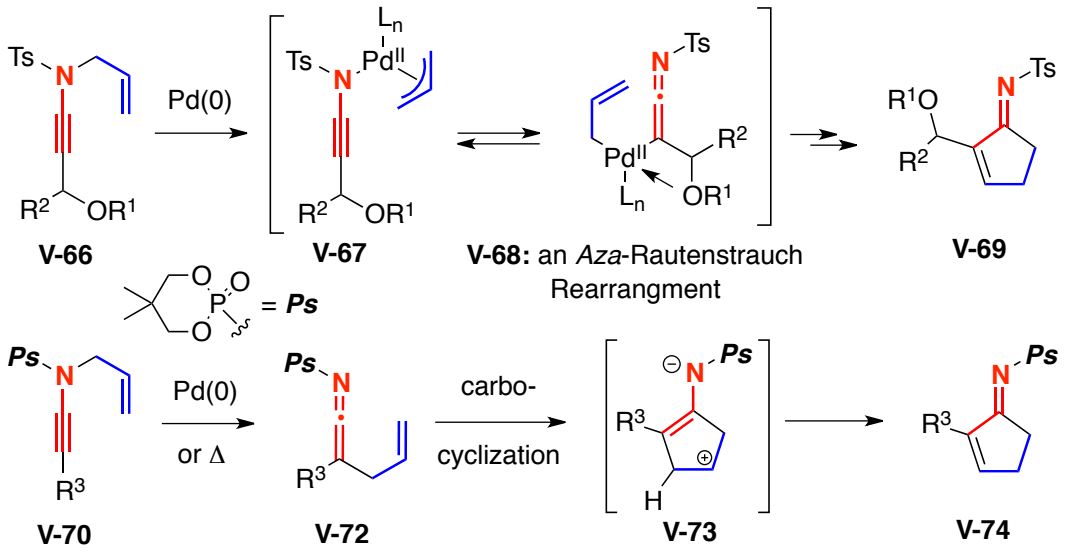
Furthermore, in direct contrast to the *N*-sulfonyl system,[41] when TIPS-terminated *N*-phosphoryl ynamide **IV-43** was subjected to either the standard Pd-catalyzed conditions or even heated to 185–190 °C, no carbocyclization product was found. In fact, ketenimine **V-64** was isolated in both cases [**Scheme V-13**]. Heating of the isolable ketenimine to 185–190 °C similarly led to no discernable cyclopentenimine formation and eventual decomposition.

**Scheme V-13. No Carbocyclization with TIPS-Terminated Ynamide IV-43**




These experiments demonstrated a stark difference in the mechanism for carbocyclization between *N*-sulfonyl and *N*-phosphoryl ynamides. As shown in **Scheme V-14**, the carbocyclization of *N*-sulfonyl ynamides must occur prior to reductive elimination through ketenimino-Pd-π-allyl complexes **V-67** and **V-68**. Alternatively, with *N*-phosphoryl ynamides, it appears that the reductive elimination is faster than the carbocyclization, leading to ketenimines **V-72**. Since there is no operating 1,3-phosphoryl-shift as in sulfonyl systems[41-42,53,75,94] [see **Chapter 4**], the ensuing carbocyclization may occur to give cyclopentenimines **V-74** through zwitterionic intermediate **V-73**. Similarly, the thermal carbocyclization pathway should involve an *aza*-Claisen rearrangement to generate ketenimine **V-72** directly.

**Scheme V-14. *N*-Ts Versus *N*-Phosphoryl Ynamide Carbocyclizations**

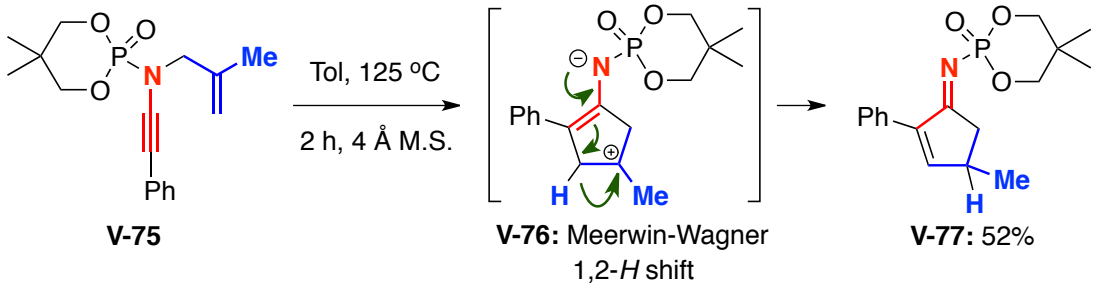



### 5.2.2. Feasibility of a Meerwein-Wagner 1,2-*H* Shift

We were especially excited about the ability to transform *N*-phosphoryl ynamides to cyclopentenimines without the need for palladium. This discovery eliminated any ambiguity in the intermediacy of zwitterionic intermediates and inspired us to consider intercepting the intermediates through Meerwein-Wagner rearrangements and nucleophilic trappings.[87] Also, because palladium was not strictly necessary, it allowed us to explore the use of functionalized allyl moieties in the transformation, without worry of scrambling through the Pd-π-allyl complex[41] [see **Chapter 2**].

First, to demonstrate that other allyl moieties would in fact participate in the *aza*-Claisen–carbocyclization, when ynamide **V-75** was heated to 125 °C in toluene for 2 h, cyclopentenimine **V-77** was isolated in 52% yield, likely via a 1,2-*H* shift through **V-76** [**Scheme V-15**].

**Scheme V-15. A Possible Meerwein-Wagner 1,2-*H* Shift**



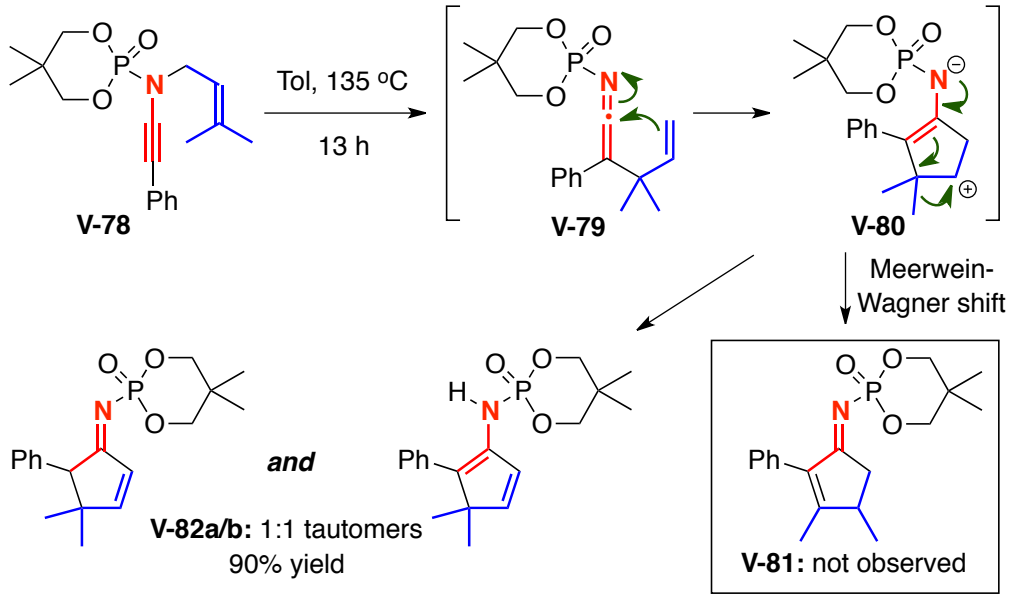

**V-75** **V-76:** Meerwin-Wagner 1,2-*H* shift **V-77:** 52%

### 5.2.3 Other Meerwein-Wagner Rearrangements

#### 5.2.3.1 Failed *Me*-Shift and Discovery of a Cyclopentadiene [4 + 2]

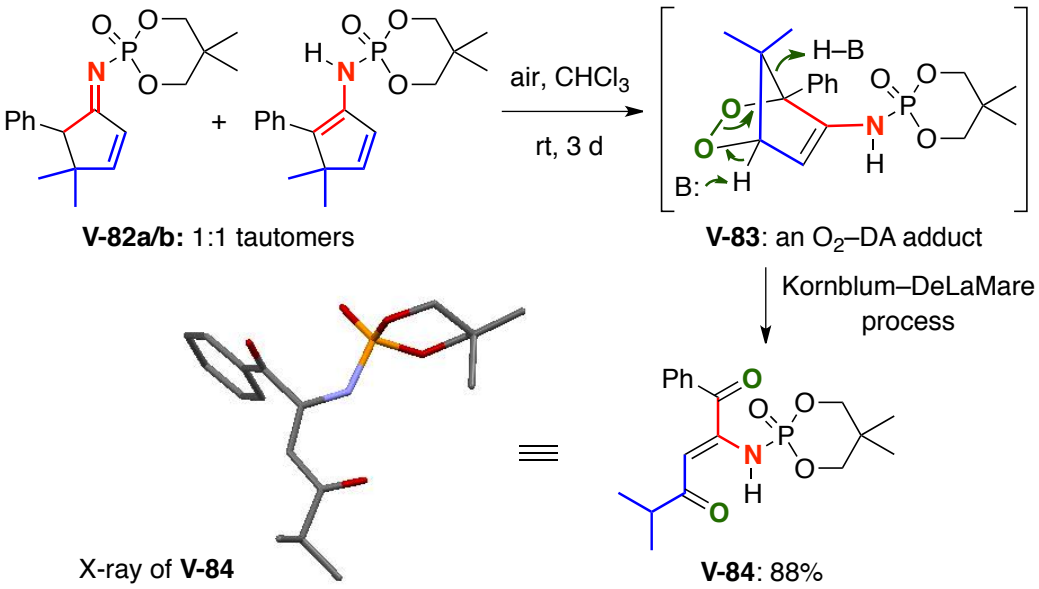
While it is also possible that deprotonation could lead to 1-amido dienes that then tautomerize to the observed cyclopentenimines, we were fascinated with the idea that a 1,2-*H* shift was operating. We therefore wondered if other Meerwein-Wagner shifts could occur following the initial *aza*-Claisen rearrangement and carbocyclization. To explore this possibility, *N*-prenyl ynamide **V-78** was heated to 135 °C, with the hopes of demonstrating a 1,2-methyl shift through the formation cyclopentenimine **V-81** [**Scheme V-16**]. Unfortunately, **V-81** was not observed. Instead, a 1:1 tautomeric mixture of **V-82a** and **V-82b** was isolated in 90% yield caused by deprotonation alpha to the enamide instead of the desired methyl shift.

**Scheme V-16. Attempted 1,2-*Me* Shift**




When the reaction mixture was left open to air for an extended period of time, an unexpected [4 + 2] cycloaddition of **V-82b** with oxygen occurred. By intentionally bubbling air through the tautomeric mixture in $CHCl_3$ over several days, the [4 + 2] cycloaddition could be further facilitated [**Scheme V-17**]. Initially, endo-peroxide **V-83** must have formed, which underwent subsequent fragmentation to afford the isolated ene-dione **V-84**. While this could have been a radical fragmentation and although the reaction conditions involved no base, it was very likely another example of a Kornblum-DeLaMare process.[95-96]

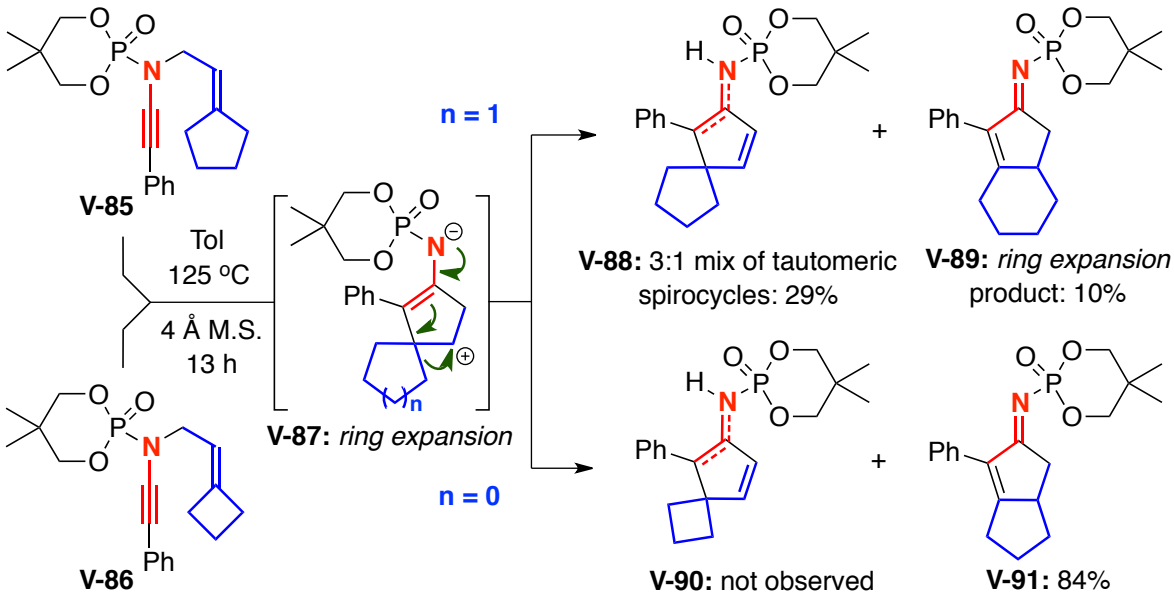
**Scheme V-17. 2-Amidodiene–$O_2$ Diels-Alder and Fragmentation**




### 5.2.3.2 Meerwein-Wagner Ring Expansions

The idea of pursuing [4 + 2] cycloadditions with *in situ* generated 2-amido dienes was intriguing, however we were still very interested in intercepting the zwitterionic intermediates through either Meerwein-Wagner rearrangements or nucleophilic trappings. To explore the former stategy, we prepared ynamides **V-85** and **V-86** bearing a tethered methylcyclopentylidine and methylcyclobutylidine, respectively, reasoning that the added ring strain should favor ring expansion through zwitter ions **V-87** [**Scheme V-18**]. When **V-85** was heated to 135 $^{o}$C, a 3:1 tautomeric mixture of spirocycles **V-88** resulting from elimination dominated; however, fused bicycle **V-89** was also isolated in 10% yield representing a successful ring-expansion. Moreover, ynamide **V-86** with increased ring strain yielded ring-expansion product **V-91** in 84% yield and spirocycle **V-90** was not even observed.

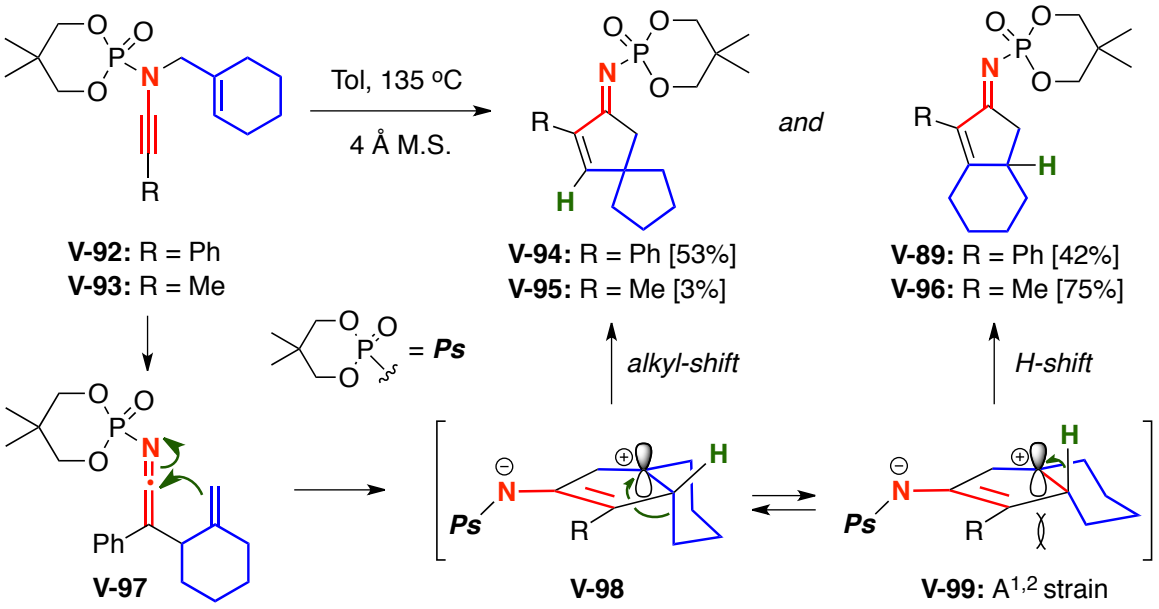
**Scheme V-18. Ring-Expansion Meerwein-Wagner Shift**




### 5.2.3.3 Meerwein-Wagner Ring Contractions

We also, rather unexpectedly, discovered a Meerwein-Wagner ring-contraction when pursuing the carbocyclization of ynamide **V-92** bearing a tethered methylcyclohexene [**Scheme V-19**]. In addition to the anticipated 5,6-fused bicycle **V-89** resulting from a 1,2-*H* shift, 5,5-spirocycle **V-94** was isolated as the major product in 53% yield. It is possible that $A^{1,2}$ strain promoted the C-C bond of the fused cyclohexane ring to adopt a pseudo-axial position as shown in **V-98**, thereby allowing the 1,2-alkyl shift to compete. This notion was further demonstrated by our experimentation with methyl-terminated ynamide **V-93**, whereby the expected 1,2-*H* shift dominated to give **V-96** in 75% yield and only 3% of the spirocycle **V-95**.

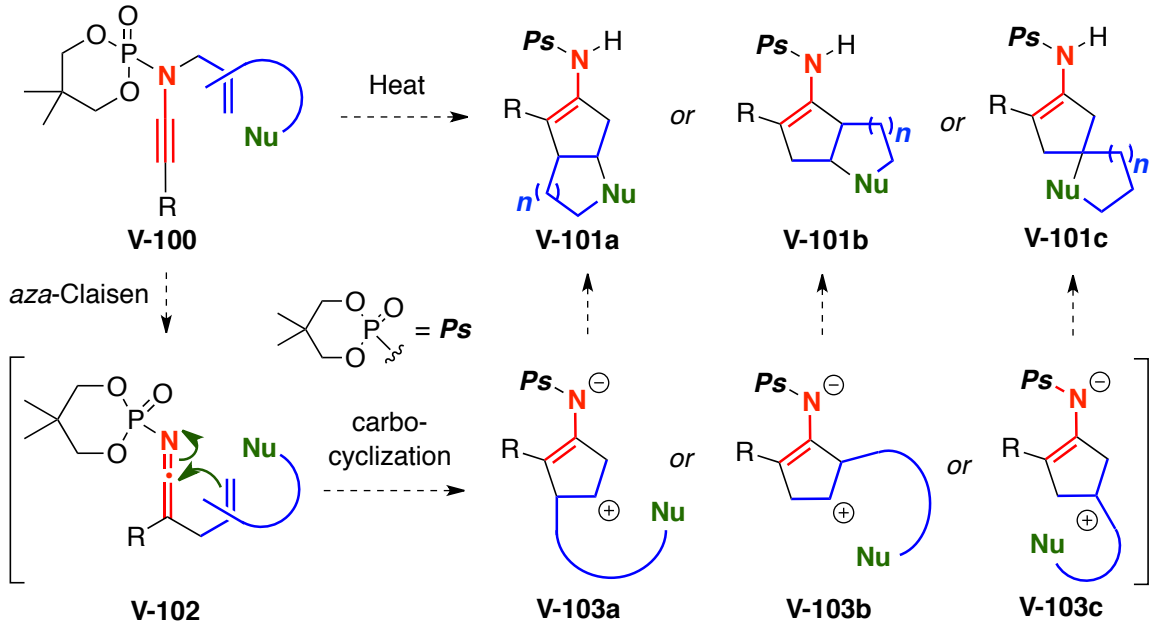
**Scheme V-19. Ring-Contraction Meerwein-Wagner Shift**




### 5.2.4 Intercepted Carbocyclizations

Next, we envisioned the possibility of intercepting the zwitterionic intermediates with tethered nucleophiles,[87] thus using the *aza*-Claisen rearrangement to initiate a carbocyclization cascade.[97-98] By tethering a nucleophile through the allyl moiety as in **V-100**, we reasoned that we could gain access to a host of fused [**V-101a** or **V-101b**] or spiro [**V-101c**] carbo- or heterocycles [**Scheme V-20**].

**Scheme V-20. Intramolecular Nucleophilic Trapping of Cationic Intermediate**

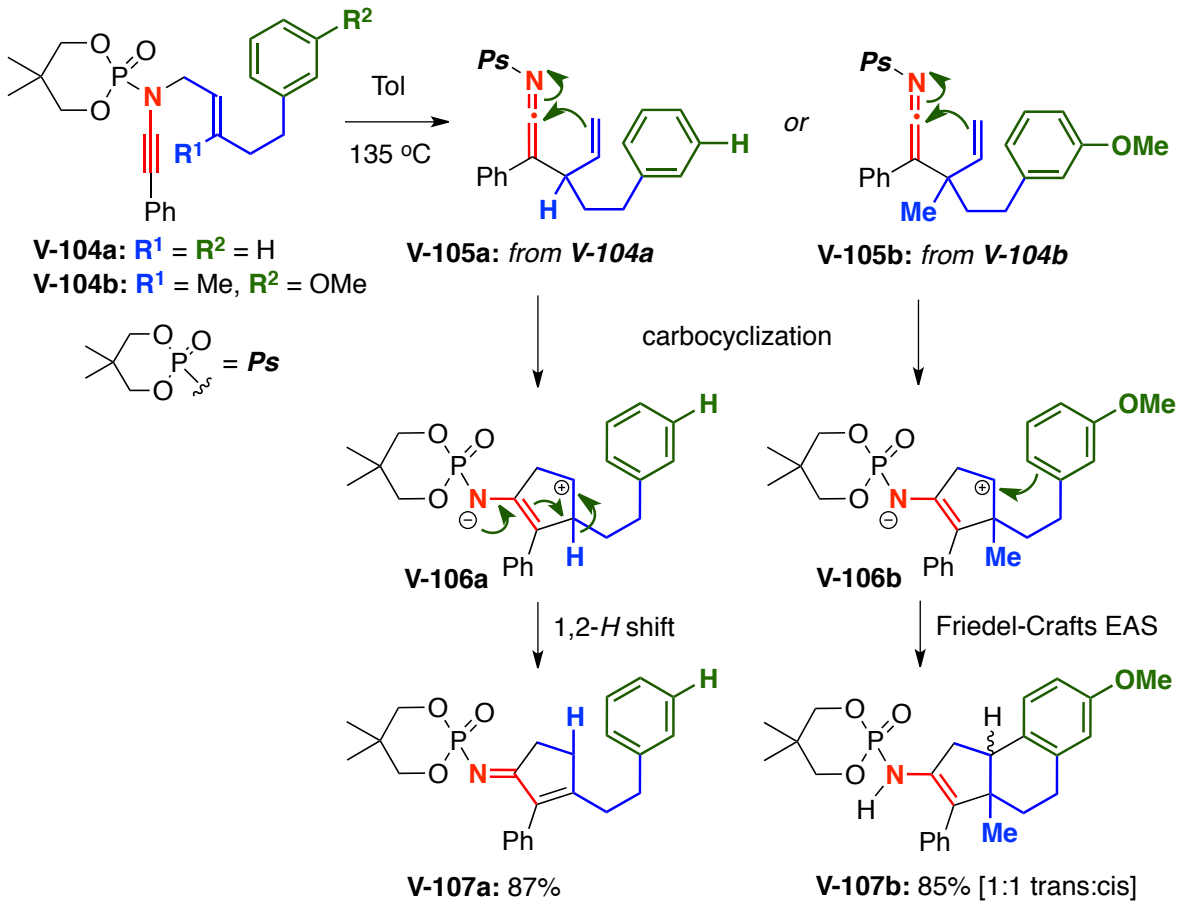



### 5.2.4.1 Tandem *Aza*-Claisen–Carbocyclization–Friedel Crafts EAS

We were most interested in employing tethered carbon nucleophiles to avoid any competing reactions such as amidine[40-42] or imidate[53] formation [see **Chapter 2**]. One of our first attempts to intercept a zwitterionic intermediate was using ynamide **V-104a** bearing a tethered benzene ring. When **V-104a** was heated to 135 °C in toluene, only cyclopentenimine **V-107a** was isolated [**Scheme V-21**]. This demonstrated that the *aza*-Claisen rearrangement and initial carbocyclization were successful; however, the competing 1,2-*H* shift through **V-106a** was very facile. Therefore, it was necessary to suppress the 1,2-*H* shift to favor nucleophilic attack and we had already discovered that the analogous *M*e-shift was slow. Gratifyingly, ynamide **V-104b** featuring a *m*-methoxyphenyl moiety tethered to a *crotyl* fragment cleanly underwent the required 3-*aza*-Claisen rearrangement followed

by carbocyclization and Friedel-Craft electrophilic aromatic substitution to give **V-107b** in 85% yield as a 1:1 mixture of *trans* and *cis* isomers and without any competing alkyl shifts.

**Scheme V-21. Friedel-Craft EAS Versus 1,2-*H* Shift**




### 5.2.4.2 Cationic Polyene Cascade Cyclizations

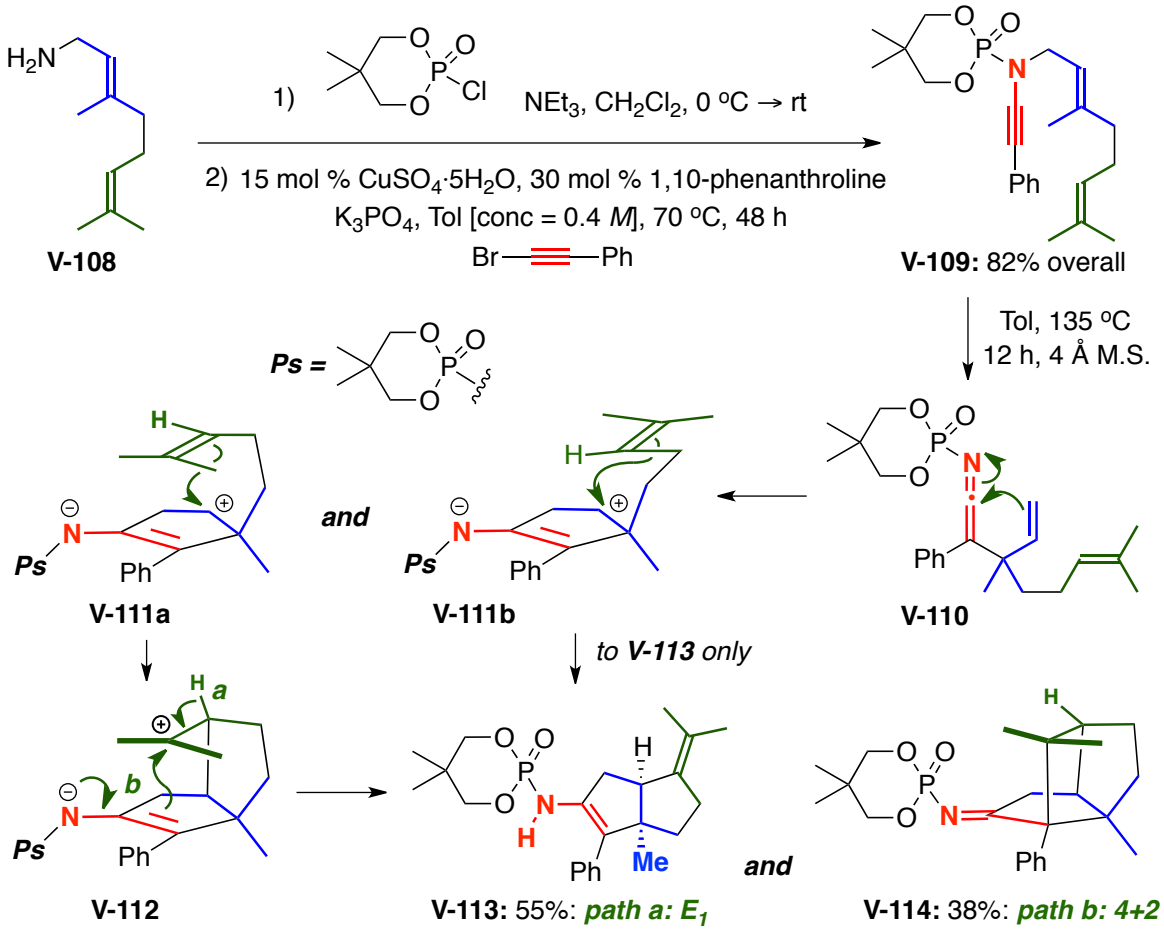
The ability to intercept these zwitterionic intermediates with aryl nucleophiles was exciting and propelled us into exploring other nucleophilic trappings. Inspired by the abundance of beautiful work using terpenes in cationic polyene cascades[97-98] we decided to investigate the possibility of an ynamide-initiated carbocyclization cascade with terpene-

derived ynamides [**Scheme V-22**].

Starting from commercially available geranylamine **V-108**, a simple two-step protocol involving phosphorylation and Cu-catalyzed amidative cross-coupling gave ynamide **V-109** in 82% overall yield. We were amazed to discover that when **V-109** was heated to 135 $^{o}$C for 12 hours, 5,5-*cis*-fused bicycle **V-113** bearing an exocyclic olefin was indeed isolated in 55% yield and as a single diastereomer from an elimination pathway. Of note, the *cis*-fused bicyclic core in **V-113** is prominent in triquinane[99] natural products. As an unexpected but pleasant surprise, in addition to **V-113**, tricycle **V-114** featuring four contiguous stereocenters and three all-carbon quaternary centers was isolated in 38% yield as a single diastereomer. The two products could be mostly separated by silica gel column chromatography and further purified by recrystallization from hexanes and EtOAc. The geometry of both products was determined by nOe analysis.

The divergence between **V-113** and **V-114** was very interesting. As one might imagine, after the initial carbocyclization, the second olefin may add to the carbocation through the facial approach shown in either **V-111a** or **V-111b**, which followed by elimination would give **V-113**. Mechanistically more intriguing is the formal [4 + 2] cycloaddition to afford **V-114**, which must arise through the olefin approach shown in **V-111a**, followed by enamide addition to the resulting tertiary carbocation.

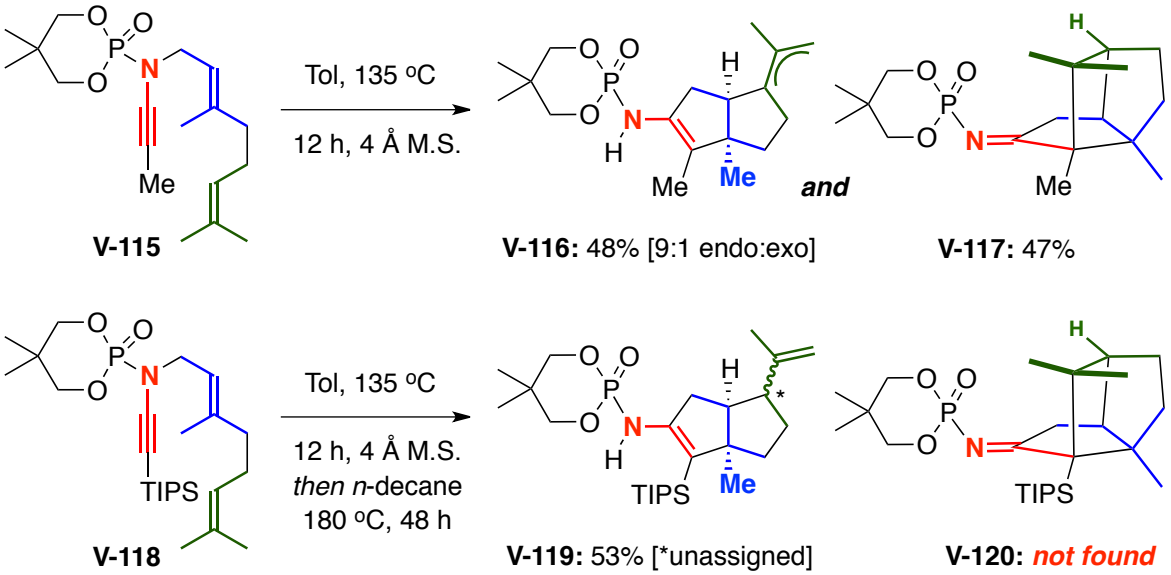
**Scheme V-22. *Aza*-Claisen Initiated Polyene Cascade Cyclization**




Using a phenyl-terminated ynamide was a great proof of concept for the carbocyclization cascade. However, for the transformation to be useful outside of methodology, other functionality more amenable to natural product synthesis needed to be explored. Indeed, the carbocyclization cascade worked equally well with methyl-terminated ynamide **V-115** [**Scheme V-23**]. After 12 hours, 5,5-*cis*-fused bicycle **V-116** was isolated as a 9:1 mixture of endo and exo olefin isomers, as well as tricycle **V-117** as a single diastereomer. When TIPS-terminated ynamide **V-118** was employed, only **V-119** was found,

however the reaction had to be heated to 180 °C in toluene/*n*-decane for 48 h and still some precyclized-ketenimine was seen in the crude $^{1}$H NMR. Likely, the intermediate TIPS-enamide was too sterically hindered to add to the carbocation to give **V-120** as seen previously, so elimination prevailed.

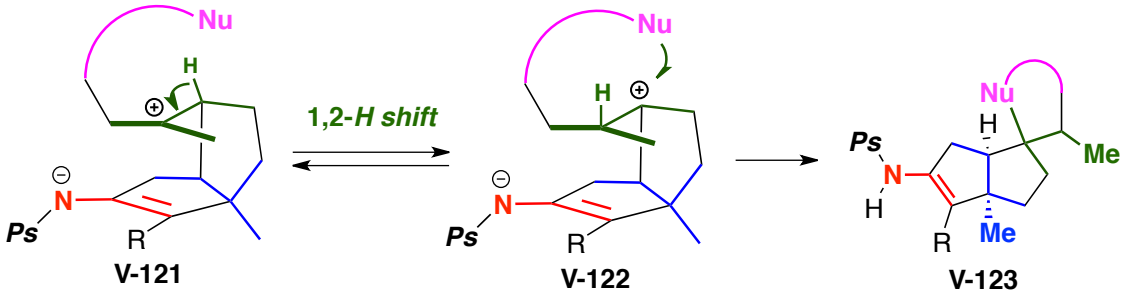
**Scheme V-23. Non-Phenyl Ynamide Cascade Cyclization**




### 5.2.4.3 Farnesyl-Tethered Ynamide Carbocyclization

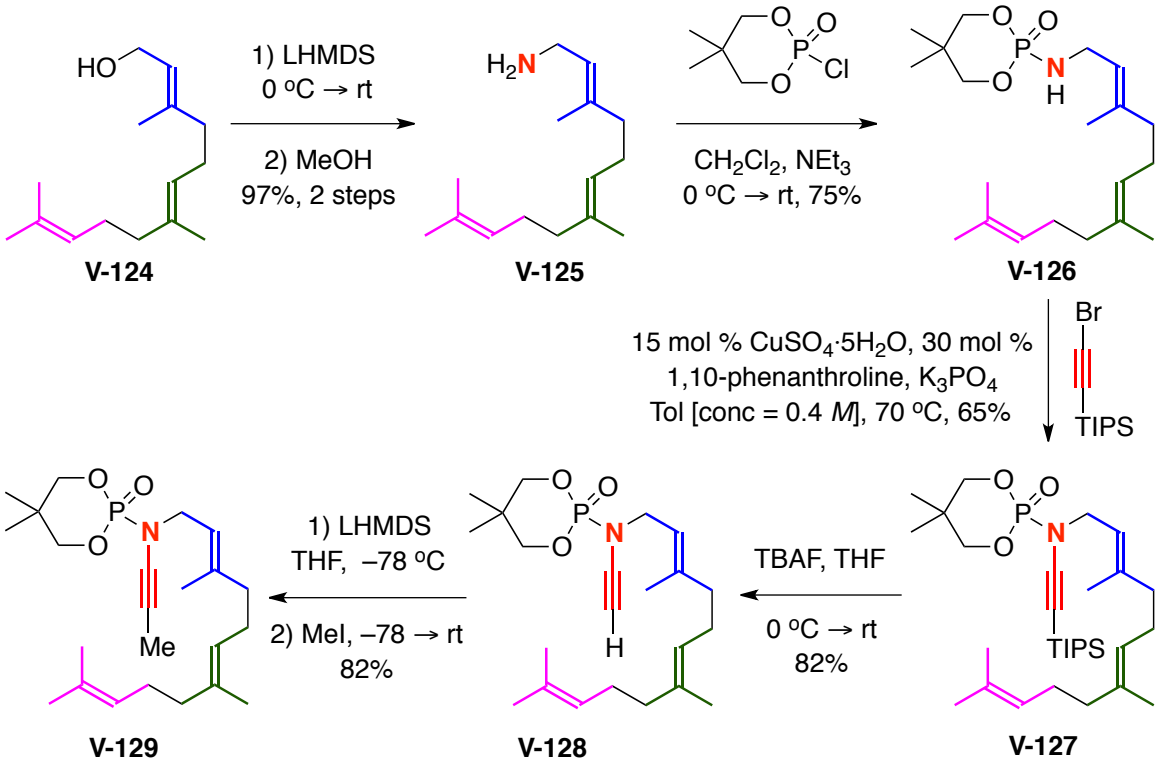
With our success in developing a cationic polyene cascade cyclization, we wanted to investigate how far we could extend the system. Specifically, we wondered if a third cyclization event would be possible by taking advantage of equilibration between **V-121** and **V-122** through a 1,2-*H* shift instead of elimination [**Scheme V-24**].

**Scheme V-24. A Possible 1,2-*H* Shift**



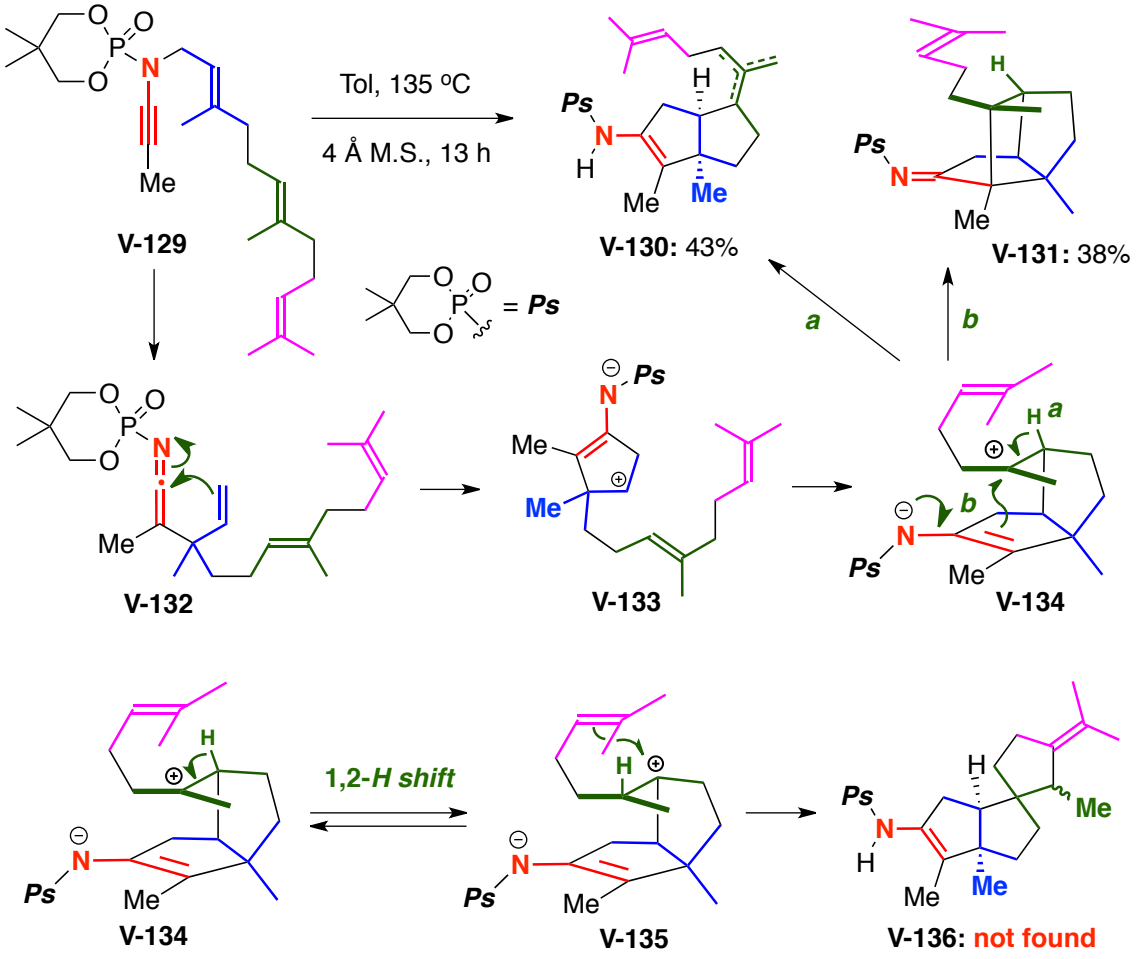

The most straightforward means of testing this hypothesis was to use a farnesyl-derived ynamide. The preparation of methyl-terminated farnesyl-tethered ynamide **V-129** is shown in **Scheme V-25**. Following a known protocol,[100] farnesylamine **V-125** was easily accessible in gram quantities. Phosphorylation proceeded in 75% yield and the Cu-catalyzed amidative cross-coupling with TIPS-alkynyl bromide gave **V-127** in 65% yield. TBAF-mediated desilylation afforded terminally-unsubstituted ynamide **V-128**, which followed by lithiation and addition to MeI gave **V-129** in 82% yield.

**Scheme V-25. Preparation of Farnesyl-Tethered Ynamides**




With ynamide **V-129** in hand, we could ascertain the feasibility of a third cyclization. Unfortunately, **V-136** resulting from the trapping of **V-135** was not found [**Scheme V-26**]. Instead, only tricycle **V-131** could be isolated cleanly from the reaction mixture in 38% yield as a single diastereomer. Also, a complex mixture of bicyclic *endo* and *exo* elimination products **V-130** was isolated, but could not be adequately characterized except to determine that the remote olefin was in fact still intact. The elimination and enamide addition pathways were clearly more facile than the desired 1,2-*H* shift.

**Scheme V-26. Attempted 1,2-*H* Shift in Polyene Cascade**

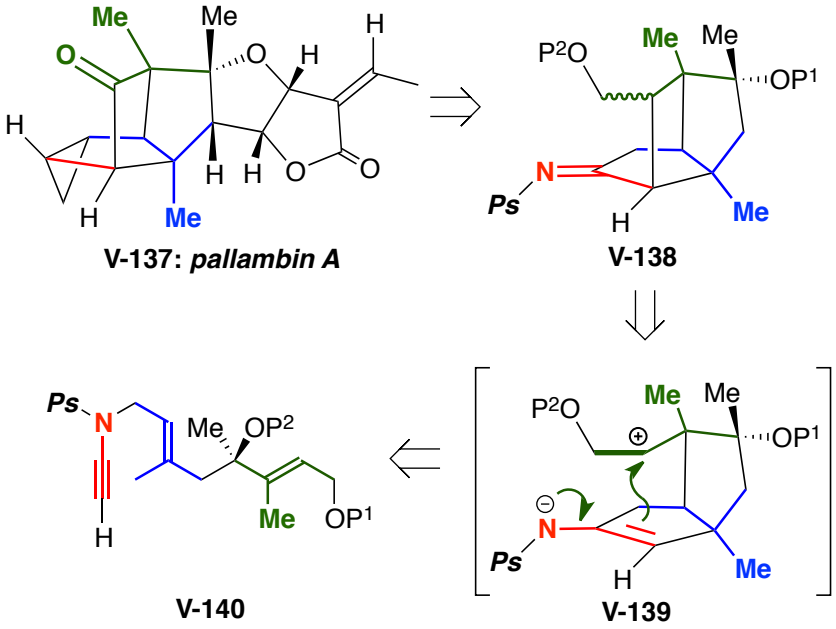



## 5.3 Potential Applications in Total Synthesis

Shortly after communicating our carbocyclizations with geranyl-tethered ynamides, the isolation of pallambin A,[101] a novel 19-*nor*-7,8-secolabdane diterpenoid with an unprecedented tetracyclodecane core, was reported [**Scheme V-27**]. Remarkably, the core is almost perfectly suited for our tandem *aza*-Claisen–double carbocyclization–enamide addition sequence. We envision that ynamide **V-140** with an appropriately functionalized

allyl moiety could provide expedient access to the tricyclic core with the appropriate functional handles to complete the synthesis.

**Scheme V-27. Potential Application Towards Total Synthesis of Pallambin A**




## 5.4 Conclusions

First, we showcased a tandem Pd-catalyzed *N*-to-*C* allyl transfer–carbocyclization of *N*-sulfonyl-*N*-allyl ynamides for the synthesis of α,β-unsaturated cyclopentenimines. Mechanistic studies support the intermediacy of a ketenimino-Pd-π-allyl complex during the cyclization. Second, we extended the system to include *N*-phosphoryl-*N*-allyl ynamides, where the use of palladium was not necessary. This allowed us to exploit the zwitterionic intermediates in Meerwein-Wagner ring-expansions and contractions, as well as to develop

cationic polyene cascade cyclizations for the synthesis of complex bi- and tricyclic scaffolds.

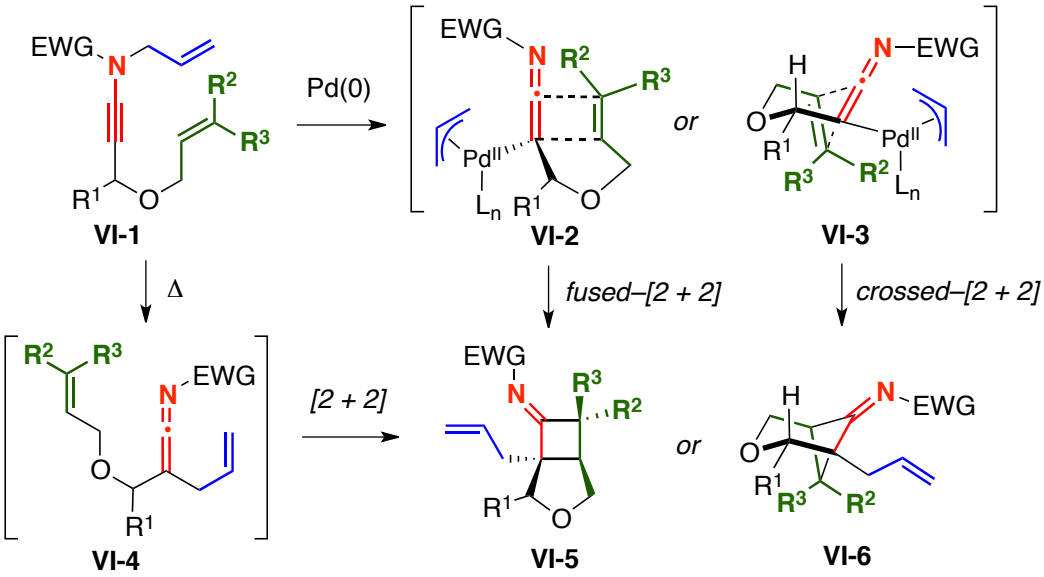
# Chapter 6. Ketenimine–[2 + 2] Cycloadditions From *N*-Allyl Ynamides

## Chapter 6: Ketenimine–[2 + 2] Cycloadditions From *N*-Allyl Ynamides

### 6.1 Feasibility of an Intramolecular [2 + 2] Cycloaddition

Throughout our studies on palladium catalyzed *N*-to-*C* allyl transfer[40-42] and thermal *aza*-Claisen[48-49] rearrangements[41-42,53,75,94] of *N*-allyl ynamides[2] to ketenimines,[57] we were excited by the possibility of effecting tandem intramolecular [2 + 2] cycloadditions with tethered alkenes [**Scheme VI-1**].

**Scheme VI-1. Feasibility of [2 + 2] Cycloadditions with Tethered Alkenes**



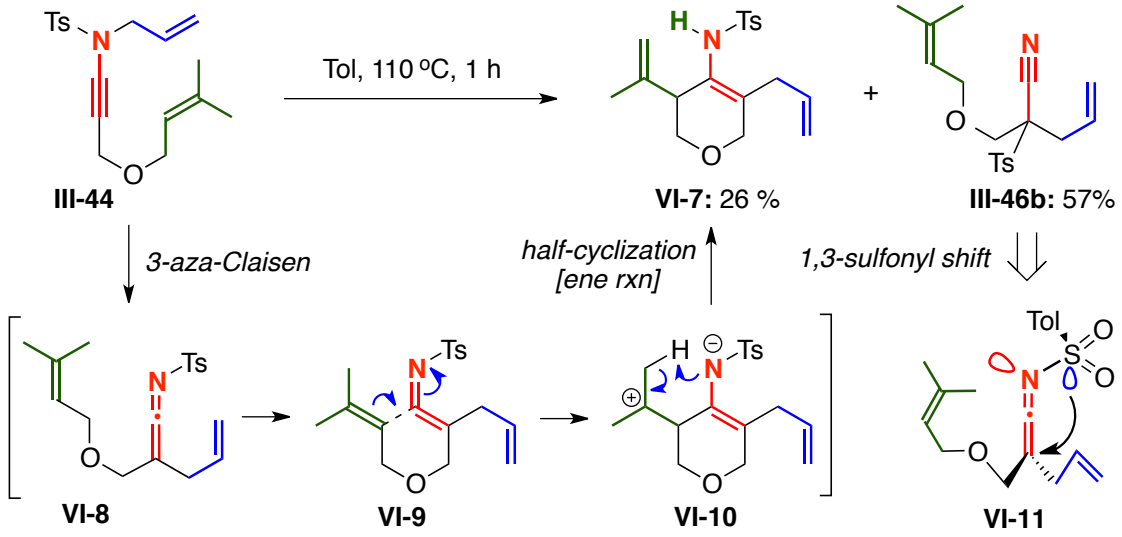

Similar cycloadditions involving ketenes and keteniminium ions[102] have been studied extensively by Marko,[103] Snider,[104] Brady,[105] and recently by Minehan,[106] giving rise to cyclobutanones through fused–[107] and/or crossed–[2 + 2][108] pathways. For our own designs, we imagined that ketenimino-Pd-π-allyl complexes prepared by *N*-to-*C* allyl transfers of *N*-allyl ynamides **VI-1** could participate in similar fused– or, more rarely, crossed–[2 + 2]

cycloadditions to afford highly substituted bicycloimines **VI-5** or **VI-6** *via* intermediates **VI-2** or **VI-3** [**Scheme VI-1**]. Alternatively, thermal 3-*aza*-Claisen rearrangements could be used to initiate the cycloadditions through generation of ketenimines **VI-4**.

### 6.1.1 Tandem *Aza*-Claisen–Half-Cyclization [Ene Reaction]

Our first success in intercepting ketenimines with tethered olefins came during the thermal 3-*aza*-Claisen rearrangement of ynamide **III-44** [**Scheme VI-2**]. At the time of the experiment, we did not yet understand that a 1,3-sulfonyl shift was operational [we later assigned **III-46b** as the nitrile shown, see **Chapter 3**].[41] We still believed that the *in situ* generated ketenimines were undergoing intermolecular [2 + 2] dimerizations,[38] so we hoped that an intramolecular [2 + 2] would be more facile. Interestingly, when ynamide **III-44** was heated to 110 $^{o}$C for 1 h, nitrile **III-46b** was isolated as the major product in 57% yield, however enamide **VI-7** was also found in 26% yield. Most likely, **VI-7** resulted from a stepwise cyclization through zwitterionic intermediate **VI-10** and elimination instead of the desired second-bond formation. Thus, **VI-7** represented a successful half-cycloaddition or a formal ene reaction.[109] We soon after realized that there was, in fact, no competing intermolecular dimerization pathway and that **III-46b** resulted instead from a facile *intramolecular* 1,3-sulfonyl shift, as shown from **VI-11**. We could not overcome the 1,3-shift and our half–[2 + 2] cycloaddition result was shelved.

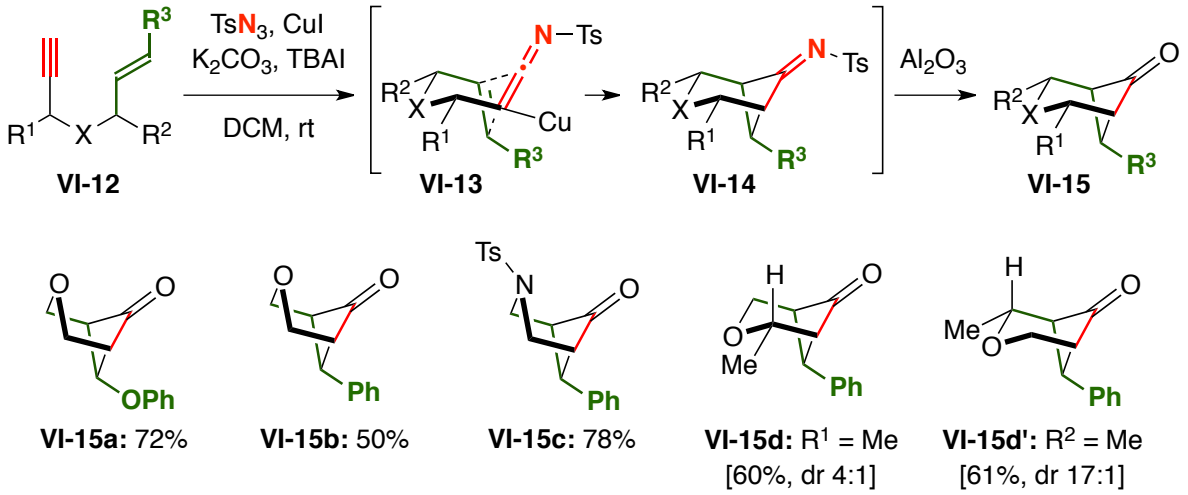
**Scheme VI-2. 1,3-Sulfonyl Shift Versus Half-Cyclization [Ene Reaction]**




### 6.1.2 Tu's Crossed Metallo-Ketenimine–[2 + 2] Cycloaddition

In 2012, Tu[110] reported a series of beautiful intramolecular crossed–[2 + 2] cycloadditions from Cu-ketenimines generated by alkyne azide–[3 + 2] cycloadditions and concomitant expulsion of $N_2$.[26,35-39] [**Scheme VI-3**]. They found that alkynes **VI-12** bearing a variety of electron-rich tethered olefins could be treated with *N*-tosyl azide and CuI to prepare bridged bicycloimines **VI-14** *in situ*. Rather than isolate the imines, they hydrolyzed the crude mixtures with $Al_2O_3$ and isolated the resulting ketones **VI-15**. Nicely, the reaction conditions tolerated both oxygen and nitrogen tethering units in moderate to good yields. When a methyl group was introduced at either the propargylic or allylic position, **VI-15d/VI-15d'** [equivalent by $C_{2v}$ symmetry] could be isolated in 60% or 61%, respectively though the diastereomeric ratio was much lower for the substrate with the propargylic methyl [4:1 compared to 17:1].

**Scheme VI-3. Crossed–[2 + 2] Initiated by an Azide–[3 + 2]**




## 6.2 [2 + 2] Cycloadditions From *N*-Allyl Ynamides

At the time of Tu's report,[110] we were also working towards developing [2 + 2] cycloadditions of metallo-ketenimines. We had found during our work on ynamide carbocyclizations that the problematic 1,3-sulfonyl shifts were not seen with γ-branched ynamides under Pd-catalyzed conditions [see **Chapter 5**]. Inspired by this discovery, we renewed our efforts towards developing intramolecular [2 + 2] cycloadditions initiated by Pd-catalyzed *N*-to-*C* allyl transfers of *N*-allyl ynamides.

### 6.2.1 Tandem Allyl Transfer–Crossed Ketenimine–[2 + 2] Cycloaddition

We were delighted to discover that in the presence of 5.0 mol % $Pd(PPh_3)_4$, γ-branched *N*-allyl ynamide **VI-16** featuring an oxygen tethered styryl moiety underwent the desired Pd-catalyzed rearrangement–cycloaddition sequence to afford bridged bicycloimine **VI-18** in 80% yield as a single diastereomer [**Scheme VI-4**]. Notably, cycloadduct **VI-17**

from the possible fused–[2 + 2] pathway was not found. Unlike in Tu's system,[13] the directly resulting imine was isolable by silica gel column chromatography and also crystalline, allowing for unambiguous determination of its structure by single crystal X-ray analysis [**Figure VI-1**]. By orienting the alkene to engage the orthogonal imine π-system and the bulky *c*-hexyl group into a pseudo-equatorial position, diastereomeric transition states **VI-19** and **VI-19'** can be envisioned. The $A^{1,3}$ strain between the *c*-hex group and imine disfavored **VI-19'**, leading to **VI-18** as the exclusive product with the imine *anti* to the *c*-hexyl.

**Scheme VI-4. Discovery of a Crossed Ketenimine–[2 + 2] Cycloaddition**

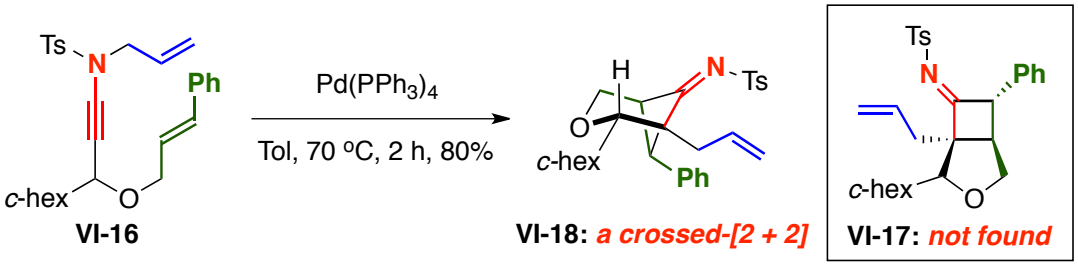
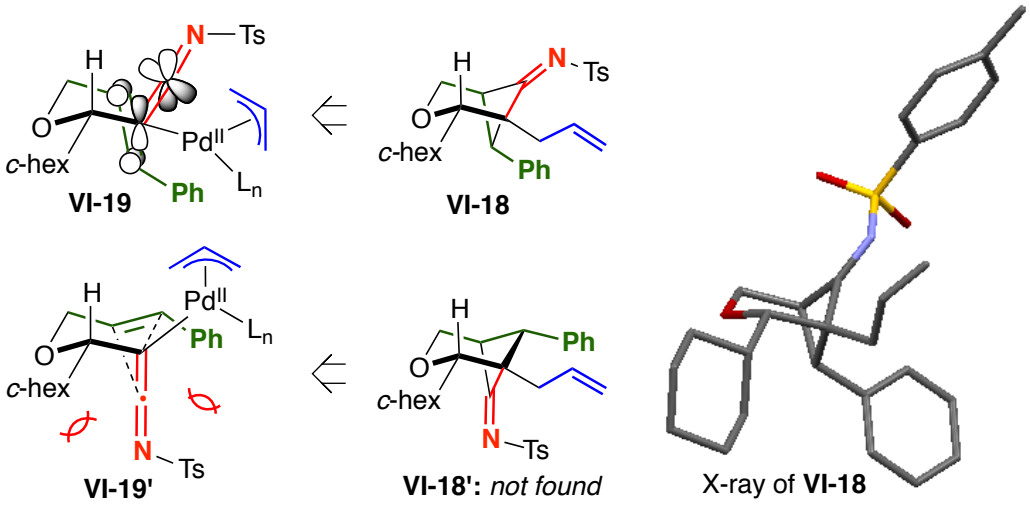
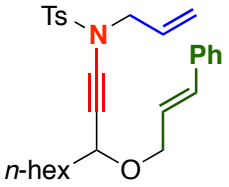
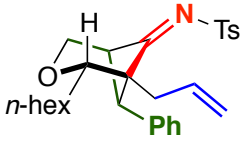
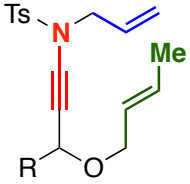
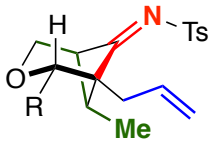
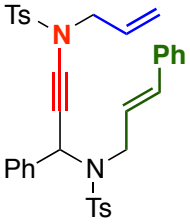
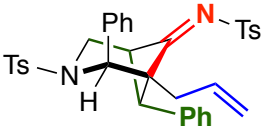



**Figure VI-1. X-ray of VI-18 and Diastereoselectivity Rationale**



The substrate scope proved to be exceptional, tolerating an array of propargylic substitutents and tethered olefins [**Table VI-1**]. Styryl-tethered ynamide **VI-20** led to crossed cycloadduct **VI-30** in near quantitative yield [entry 1]. By utilizing crotyl-tethered ynamides, bicycloimines **VI-31**–**VI-33** were isolated in good yields, though competing carbocyclizations were also observed in 10–20% yield, likely due to decreased alkene electron density [entries 2–4, see **Scheme VI-6**].

**Table VI-1. Crossed Ketenimine–[2 + 2] Cycloadditions**

| entry | ynamide | | crossed–[2+2] cycloadduct | | yield [%][b,c] |
|---|---|---|---|---|---|
| 1 |  | **VI-20** |  | **VI-25** | ≥95 |
| 2 |  | **VI-21:** R = Me |  | **VI-26:** R = Me | 72[d] |
| 3 | | **VI-22:** R = *n*-hex | | **VI-27:** R = *n*-hex | 74 |
| 4 | | **VI-23:** R = *c*-hex | | **VI-28:** R = *c*-hex | 67[d] |
| 5 |  | **VI-24** |  | **VI-29** | 95[e] |

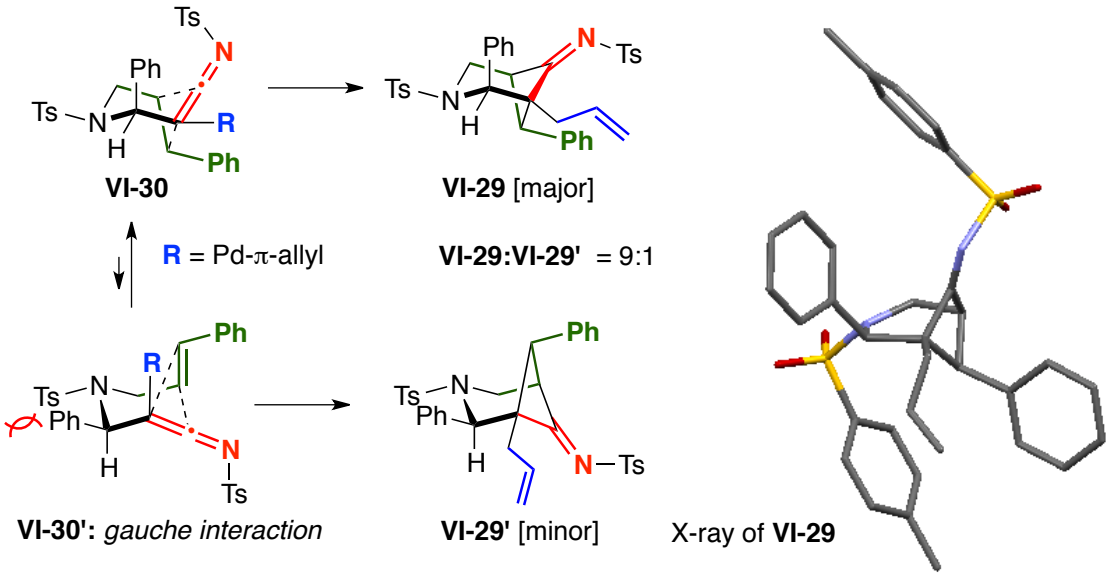
[a] Reaction conditions: 5 mol % $Pd(PPh_3)_4$, Tol [*conc* = 0.1 *M*], 70 °C, 2 h. [b] Isolated yields. [c] ≥20:1 *dr* by $^1H$ NMR unless otherwise noted. [d] 10–20% cyclopentenimine. [e] 9:1 *dr* as measured by $^1H$ NMR.

Nicely, styryl-tethered ynamide **VI-24** featuring an *N*-Ts linkage could also be employed to afford **VI-29** in near quantitative yield as a 9:1 mixture of diastereomers [**Table**

**VI-1**, entry 5]. Interestingly, X-ray analysis showed that the phenyl was *syn* to the imine in **VI-29** [**Figure VI-2**], opposite to the observed stereochemistry in the oxygen-tethered system [see **Figure VI-1**]. Tu reported no such selectivity switch in their system.[110]

The switch in diastereoselectivity for the crossed cycloaddition with *N*-Ts tethered ynamides is likely a result of a gauche interaction between the phenyl and the *N*-sulfonyl moiety as shown in **VI-30'** [**Figure 2**]. Instead, the cycloaddition favored chair-flipped **VI-30** with the phenyl pseudo-axial, explaining the formation of **VI-29** with the imine and phenyl *syn* as the major diastereomer.

**Figure VI-2. X-Ray and Conformational Analysis For VI-29**

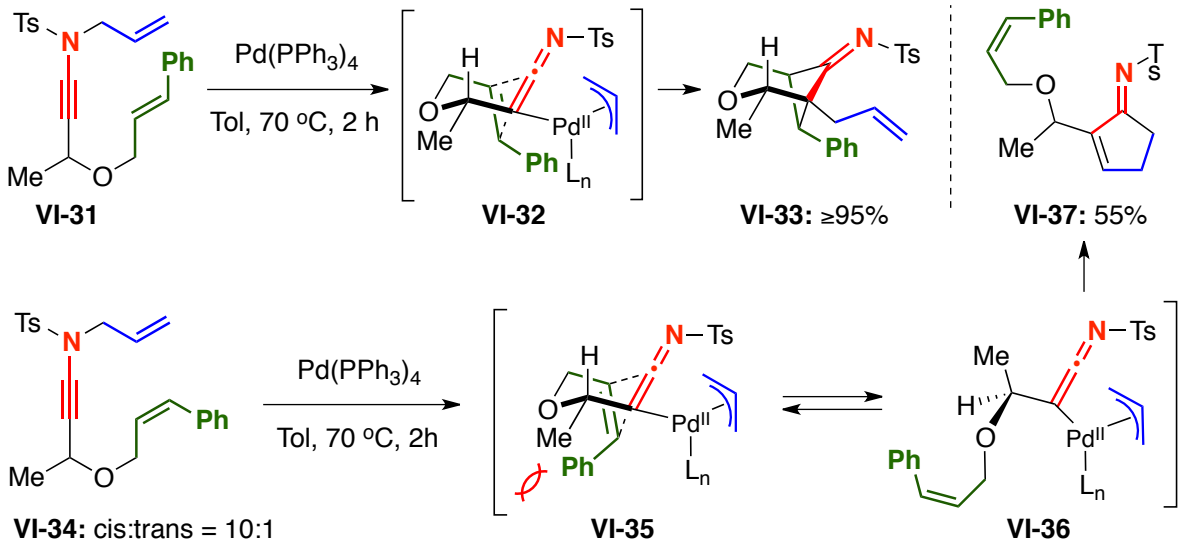



### 6.2.2 Cycloaddition Versus Carbocyclization Dichotomy

In **Table VI-1** and extensively in **Chapter 5**, we revealed that a competing carbocyclization was operational to give cyclopentenimines in 10–20% yield from several of

the γ-branched ynamides. Upon attempting to carry out cycloadditions with tethered *cis* alkenes, this reaction dichotomy was even more drastic [**Scheme VI-5**]. As anticipated, ynamide **VI-31** bearing a tethered *trans*-olefin afforded the desired crossed cycloadduct **VI-33** in ≥95% yield as a single diastereomer. However, the *cis*-olefin tethered analogue **VI-34** [10:1 *cis*:*trans*] gave cyclopentenimine **VI-37** in 55% yield with only a trace amount of cycloadduct **VI-33** observed, which likely arose from the *trans* impurity in the starting ynamide and not from reaction of the *cis* alkene. Clearly, the *cis* olefin geometry would have disfavored the cycloaddition transition state **VI-35**, and instead the carbocyclization through **VI-36** ensued.

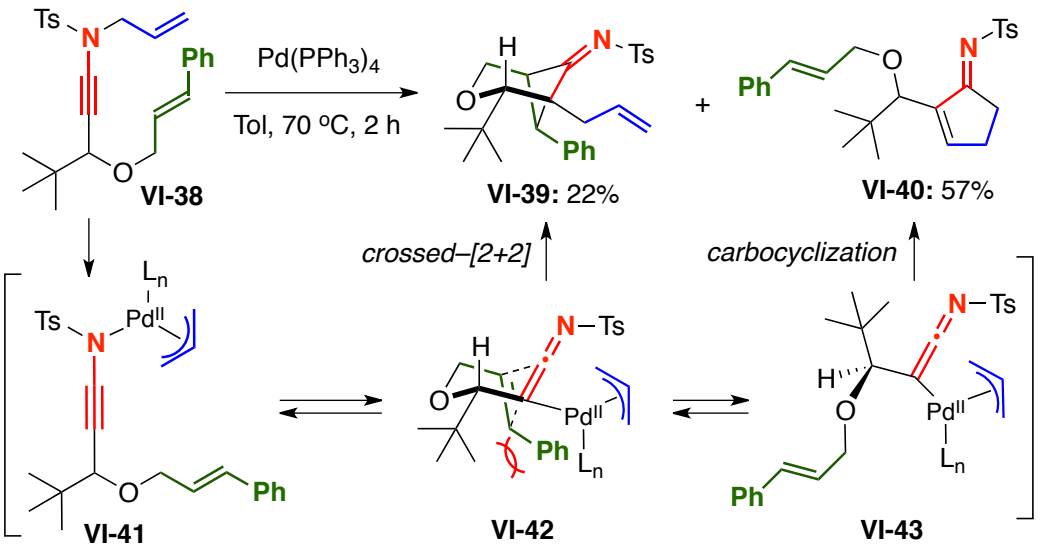
**Scheme VI-5. Dichotomy Based on Olefin Geometry**




Furthermore, when *t*-Bu-substituted ynamide **VI-38** was treated to the reaction conditions, the desired cycloadduct **VI-39** was isolated in only 22% yield, however cyclopentenimine **VI-40** was obtained in 57% yield [**Scheme VI-6**]. This further illustrates

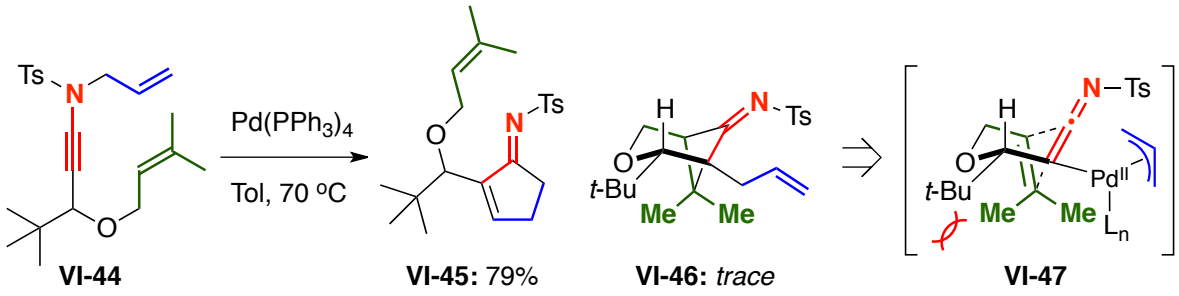
the necessity for the cycloaddition to occur through highly-organized transition state **VI-42**, as disfavorable steric interactions clearly favored carbocyclization through **VI-43**.

**Scheme VI-6. Crossed–[2 + 2] versus Carbocyclization**




In a similar vein, prenyl-tethered ynamide **VI-44** gave cyclopentenimine **VI-45** in 79% yield with only a possible trace amount of **VI-46** from the desired cycloaddition observed, again due to the high degree of steric hindrance in **VI-47** [**Scheme VI-7**].

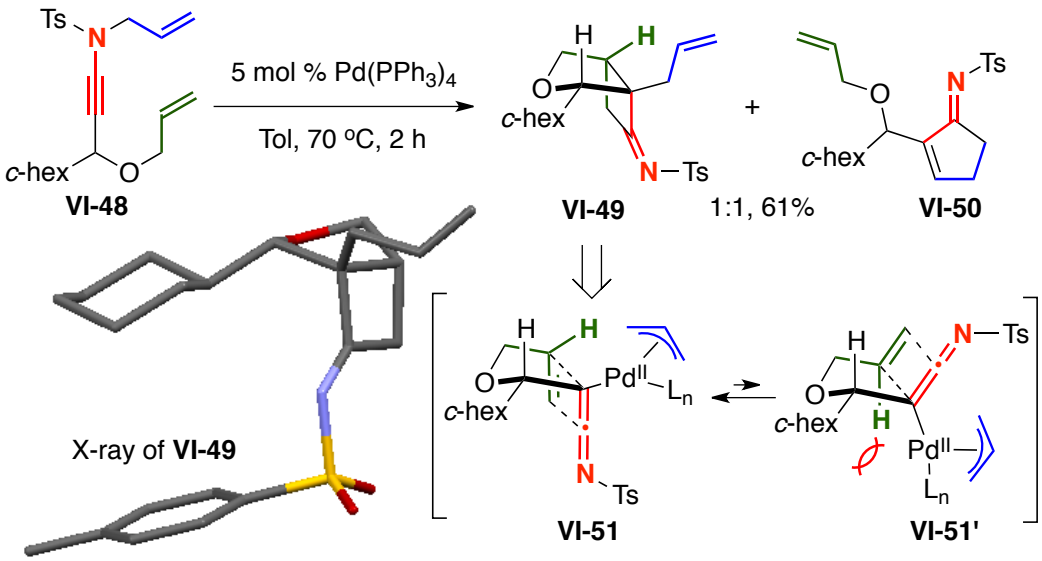
**Scheme VI-7. Trisubstituted Olefin Further Favors Carbocyclization**



### 6.2.3 Discovery of Fused Ketenimine–[2 + 2] Cycloadditions

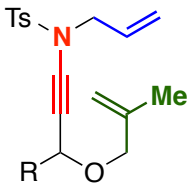
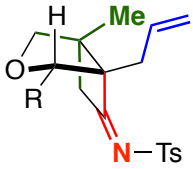
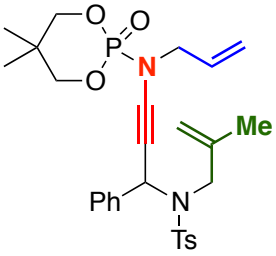
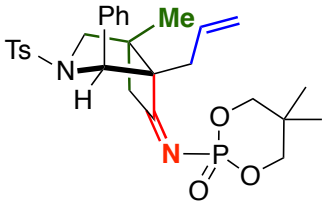
Next, we wondered how an unsubstituted allyl group serving as the cycloaddition partner would fare under the reaction conditions, as Pd-catalyzed deallylation was also possible [**Scheme VI-8**]. Additionally, Tu found unsubstituted alkenes to be unreactive in their system.[13] Interestingly, when ynamide **VI-48** was heated to 70 °C with 5 mol % $Pd(PPh_3)_4$, a 1:1 mixture of cycloadduct **VI-49** and cyclopentenimine **VI-50** was isolated in 61% yield, arising from a competing fused–[2 + 2] cycloaddition and carbocyclization. Fortunately, fused cycloadduct **VI-49** crystallized cleanly from the mixture, allowing us to confirm its structure by X-ray analysis. The cycloaddition was highly diastereoselective, giving **VI-49** with the imine *syn* to the *c*-hexyl as a single diastereomer through **VI-51** to minimize $A^{1,2}$ strain suffered in **VI-51'**.

**Scheme VI-8. Discovery of a Fused–[2 + 2] Cycloadduction**



Similar to what has been well documented for ketene–[2 + 2] cycloadditions,[6] we found that tethered internally substituted alkenes also favored formation of fused cycloadducts in our system [**Table VI-2**]. Ynamides **VI-52–VI-55** featuring a variety of propargylic substituents gave fused cycloadducts **VI-57–VI-60** in good yields with excellent diastereoselectivity. *N*-phosphoryl-*N*-allyl ynamide[75] **VI-56** with an *N*-Ts tethering unit led to fused cycloadduct **VI-61** as a 9:1 mixture of diastereomers, again favoring the isomer with the phenyl and imine *anti*, as shown. The relative stereochemistry of **VI-57** was assigned by nOe analysis [see **Appendix II**].

**Table VI-2. Fused Ketenimine–[2 + 2] Cycloadditions**

| entry | ynamide | fused–[2+2] cycloadduct | yield [%][b,c] |
|---|---|---|---|
| 1 |  **VI-52:** R = Me |  **VI-57:** R = Me | 86 |
| 2 | **VI-53:** R = *n*-hex | **VI-58:** R = *n*-hex | 71[d] |
| 3 | **VI-54:** R = *i*-Pr | **VI-59:** R = *i*-Pr | 85 |
| 4 | **VI-55:** R = $CH_2OTBS$ | **VI-60:** R = $CH_2OTBS$ | 72 |
| 5 |  **VI-56** |  **VI-61** | 85[e] |

[a] Reaction conditions: 5 mol % $Pd(PPh_3)_4$, Tol [*conc* = 0.1 *M*], 70 °C, 2 h. [b] Isolated yields. [c] ≥20:1 *dr* by $^1H$ NMR unless otherwise noted. [d] 10–20% cyclopentenimine. [e] 9:1 *dr* as measured by $^1H$ NMR.

## 6.3 Conclusions

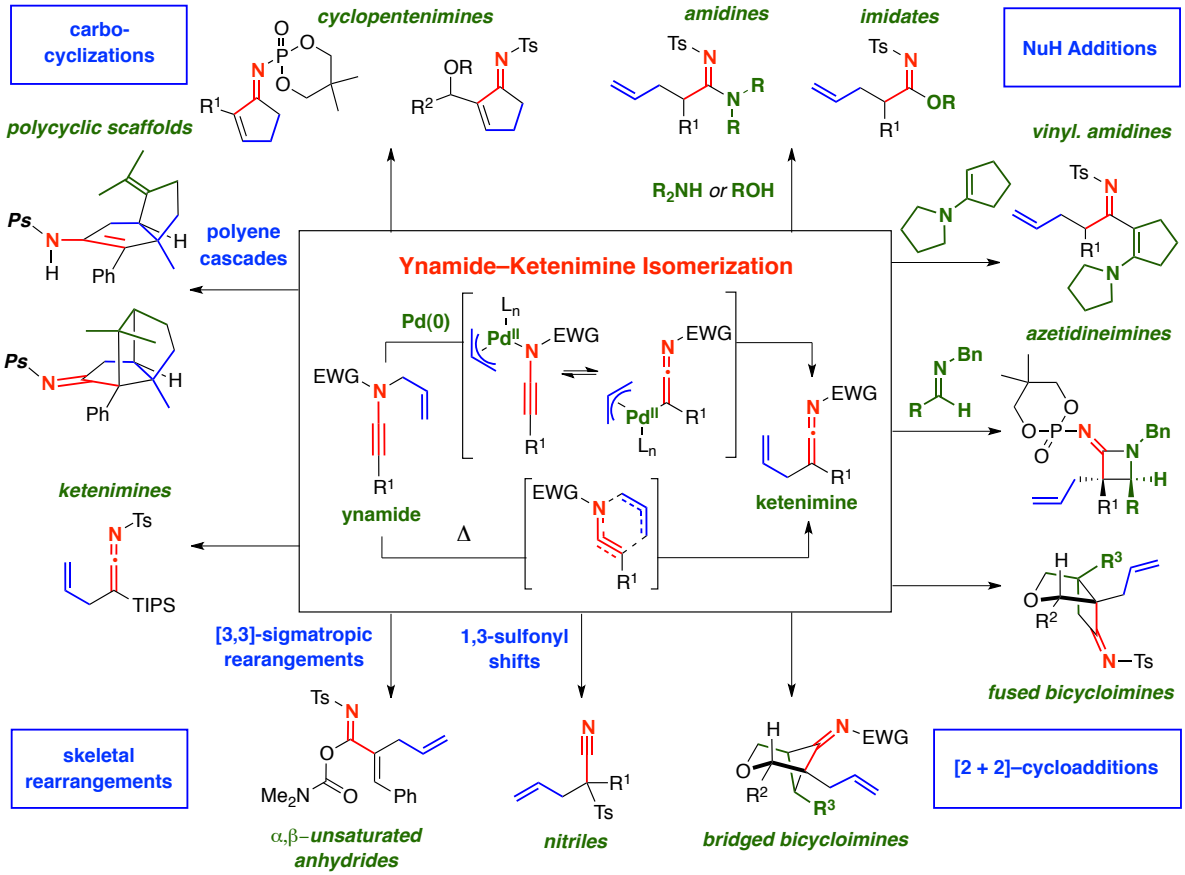
We have showcased here tandem *N*-to-*C* allyl transfer–intramolecular–[2 + 2] cycloadditions of *N*-allyl ynamides for the synthesis of highly functionalized bridged and fused bicycloimines. Interestingly, terminally-substituted alkenes gave exlusively crossed cycloadducts, and internally and unsubstituted alkenes gave fused cycloadducts. In all cases studied, the cycloadditions proceeded with high levels of diastereoselectivity. Furthermore, the major diastereomer was dependant upon the type of linkage used, as oxygen-linked ynamides and *N*-Ts linked ynamides gave alternate relative stereochemistries in the respective cycloadducts. In addition, we discovered a competing carbocyclization pathway when hindered alkenes and sterically demanding propargylic substituents were employed.

# Chapter 7. Conclusions

## Chapter 7. Conclusions

By exploiting the isomerization between ynamides and ketenimines *via* Pd-catalyzed *N*-to-*C* allyl transfers or thermal 3-*aza*-Claisen rearrangements, we have uncovered a surplus of new ynamide reactivity leading to the *de novo* synthesis of amidines, vinylogous amidines, imidates, azetidineimines, bridged and fused bicycloimines, quaternary nitriles, unsaturated mixed anhydrides, isolable silyl-ketenimines, complex polycyclic scaffolds, and a host of α,β-unsaturated cyclopentenimines.

**Scheme VII-1. Summary of *N*-Allyl Ynamide Reactivity**



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