The Emergence of Allenamides in Organic Synthesis

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Received February 11, 2003

ABSTRACT

This Account highlights recent studies describing utility of allenamides in stereoselective inter- and intramolecular synthetic methodologies. It is written to raise interest in the chemistry of allenamides.

1. Introduction

1.1. An Overview. Allenes represent a versatile functional group that can be utilized as a useful building block in a variety of synthetic transformations, leading to complex structures that are useful for constructing natural and unnatural products.[1] Subgroups of allenes are those substituted at the terminal carbon with a heteroatom such as oxygen, sulfur, or nitrogen. Despite the synthetic potential of allenes, heteroatom-substituted allenes, and in particular allenamines, have received relatively little attention.[1]
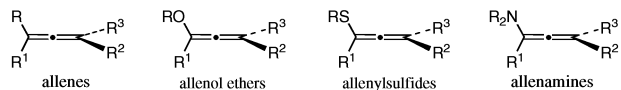
Conceptually, allenamines should be synthetically useful because they are electron-rich and can be readily activated in the presence of an electrophile [E⊕]. More significantly, the nitrogen atom can donate its lone pair toward the allenic moiety to render transformations involving additions of electrophiles [E⊕] and nucleophiles [Nuʸ] highly regioselective, which is a challenge in general with reactions involving allenes [Figure 1].

There are a few literature examples of synthetic transformations involving allenamines, suggesting that allenamines can be useful in organic synthesis. These examples, as highlighted in Scheme 1, include α- or γ-lithiation of allenamines [umpolung equivalents: see the box],[5,6] additions,[7] 1,3-dipolar,[8] [2 + 2],[9,10] and hetero [4 + 2] cycloadditions.[10,11] Other examples [not shown here] would include cyclizations,[12] dimerizations,[13] and rearrangement.[14]

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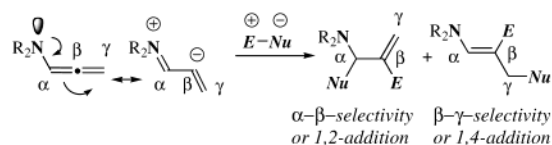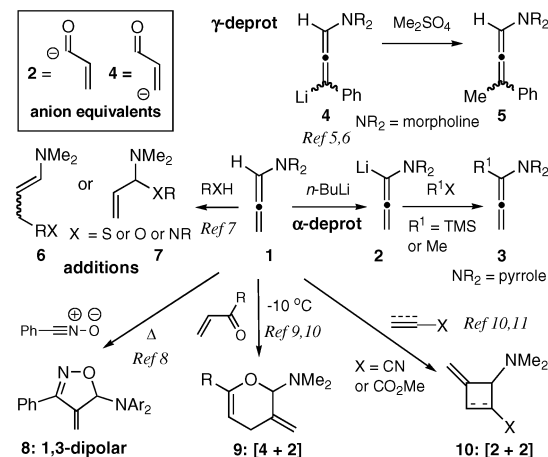
FIGURE 1. An overview.

Scheme 1. Precedents

However, allenamines are also known to be sensitive to hydrolysis, polymerization, and isomerization even at low temperatures, thereby creating serious difficulties in their preparation and handling.[1] Consequently, unlike enamines, which are corresponding subgroups of alkenes, the extent of synthetic applications of allenamines has remained limited for the last 30–40 years.[2–4]
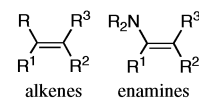
1.2. Potential Significance of Allenamines. Transformations involving allenamines are not only regioselective and stereoselective, but also, more importantly, the resulting products all possess nitrogen functionalities [Scheme 1]. Nitrogen-containing structures are prevalent among medicinally interesting natural and unnatural products and, thus, are useful in developing new therapeutics. Therefore, efforts in developing the chemistry of allenamines and identifying an allenamine-equivalent that possesses the right balance between stability and reactivity can be significant and rewarding.

1.3. Introduction of Allenamides. Allenol ethers, with their oxygen atom being less able to donate the lone pair, are less reactive but represent a more stable allenic system. Thus, they have been more visible in synthesis

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Hui Xiong received his B.S. from Peking University in 1998 and his Ph.D. in 2003 from the University of Minnesota under the supervision of Professor Hsung. His Ph.D. work involves cycloadditions of chiral allenamides, and he is currently a postdoctoral fellow at Scripps Research Institute.

Scheme 2. Dickinson's First Synthesis

a. NaOMe in MeOH or in toluene; or NaH in toluene; or pyrrolidine in dioxane

Scheme 3. Bogentoft's Isomerization


Scheme 4. Overman's Claisen Rearrangement

R = H: [85%]; R = Me [38%]

R = H, Me, Et, *n*-Pr, *i*-Pr, *i*-Bu, *t*-Bu, Bn, *neo*-pentyl; R^1 = H, Ph, *n*-Pr, *t*-Bu.

Scheme 5. First Chiral Allenamides

X = CH$_2$, O, and NMe: Yields: 40% to 95%
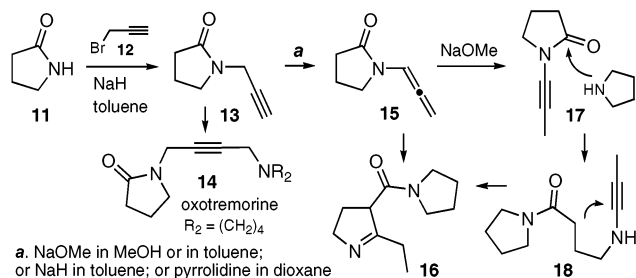
than allenamines.[1,15] By extrapolation, electron-deficient allenamines, such as allenamides, have the potential to function as an allenamine-equivalent. The electron-withdrawing group on the nitrogen atom should diminish its donating ability and lead to improved stability.

electron deficient
allenamines

acyclic allenamides

cyclic allenamides

X = CH$_2$, O, or NR^5
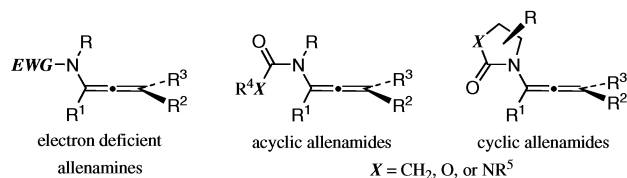
Allenamides had been studied rarely until recently.[1] After Dickinson's first preparation of 1,2-propadienyl-2-pyrrolidinone in 1967,[16] there were very few reports until 1989.[17-20] Since then, there has been an emerging interest in the chemistry of allenamides that ranges from medicinal studies,[21-23] to materials using living polymerization,[24] to synthetic methodologies.[25-44] These efforts support the notion that allenamides are becoming a proven allenamine-equivalent with the right balance of stability and reactivity.

We wish to highlight in this account recent development in the chemistry of allenamides with an emphasis on synthetic methods and with the intention of provoking further interest in the chemistry of allenamides.

2. Part I. Synthesis of Allenamides

2.1. Historical Examples. To repeat an earlier preparation of propargyl amide **13** en route to oxotremorine **14**,[45] a potent muscarinic agent,[46] Dickinson[16] reported in 1967 the first preparation of allenamide **15** from lactam **11** and propargyl bromide **12** under basic conditions [Scheme 2]. Allenamide **15** could also be prepared from **13** using NaOMe or NaH. This based-induced isomerization protocol is one of the most efficient methods for allenamide synthesis.

Subsequently, allenamide **15** was found to give **16** in the presence of NaOMe and pyrrolidine with, interestingly, ynamide **17**[47,48] postulated as a key intermediate.
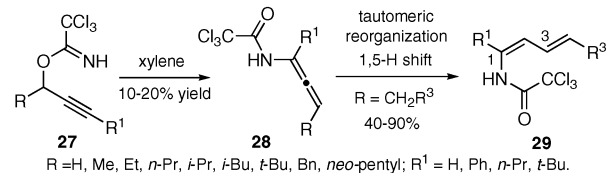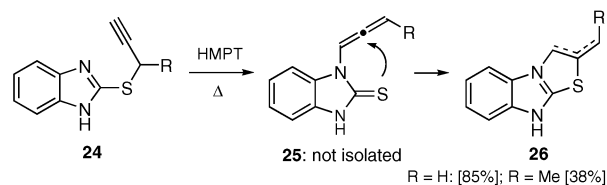
In 1969, Bogentoft[17] prepared allenamide **21** via isomerization in 50% yield. Oxazole **23** was also isolated, and likely derived from allenamide **22** after ring opening of the quinazolone [Scheme 3].

2.2. Sigmatropic Rearrangement. Claisen-type rearrangement of propargyl thiol benzimidazole **24** was found
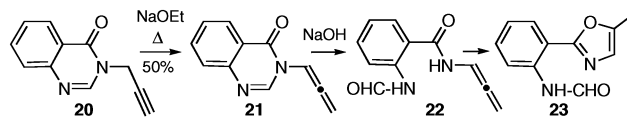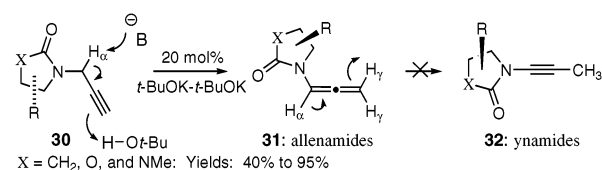
to give thiazole **26**, with allenamide **25** being postulated as a key intermediate [Scheme 4].[19]

In 1979, Overman[20] first demonstrated that Claisen rearrangement of propargyl trichloroacetyl imidates **27** could afford allenamides **28** in 10−20% isolated yields [Scheme 4]. Allenamides **28** could further isomerize to 1*Z*-3*E*-dienamides **29** in a highly stereoselective manner. This protocol represents an attractive method for the synthesis of highly substituted chiral allenamides.

2.3. Base-Induced Isomerization. *2.3.1. Cyclic Propargyl Amides.* We became involved with allenamide chemistry because of our interest in ynamides.[47,48,49−52] We attempted to prepare ynamides **32** via the based-induced isomerization of propargyl amides **30** [Scheme 5]. However, ynamides **32** were not found. Instead, the isomerization gave achiral and chiral allenamides **31**.[41,53]

There are very few examples of isomerizations of propargyl amides to ynamides. The only case in which the ynamide has been isolated is the preparation of vinylogous ynamide **35**[54] [Scheme 6], although allenamide **34** is still found on occasions.[21−22,49,53−55]

In most cases, isomerizations of propargyl amides provided only allenamides especially with propargyl amides in which the nitrogen atom is part of aromatic heterocycles [their isomerization would lead to the corresponding allenamides **36−39**].[21−23] This poses an interesting fundamental question as to why the thermodynamically more stable ynamide [based on our own experience with ynamides[47,50,53]] was not found if these isomerizations involved an equilibration mechanism.

2.3.2. Acyclic Propargyl Amides. Corbel in 1976[18] reported the first example of an acyclic allenamides **41** and

Scheme 6. Heteroaromatic Allenamides

33 → 0.2 eq KOH, DMSO, rt, 90% → **34** → 95% → **35** Me₂N

36: NaHCO₃/EtOH aq
78-86%

37: TBAF
60%

38: KOt-Bu
80%

39: KOt-Bu/DMF
<55%
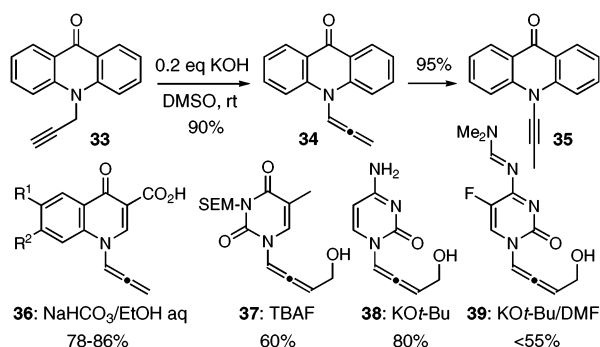
Scheme 7. Corbel's Isomerization

40a → NaH, THF, quantitative, R = Me, Et, Bn → **41**

40b → **42** + **43**
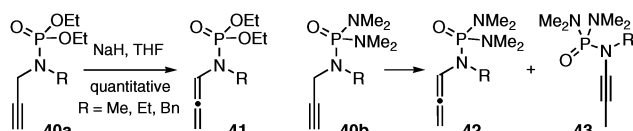
Scheme 8. First Chiral Acyclic Allenamides

44a: R = Bn, R¹ = H
44b: R = R¹ = Me

45a: [75%]
45b: [60%]

46a: R = Me
46b: R Ph

47a: [83%]
47b: [50%]

a. THF [0.1 *M* in concentration], 20 mol% KOt-Bu, rt.

Scheme 9. De Meijere's Isomerization

48 → THF, NaH, 0 °C, propargyl bromide, Ts = Tosyl → **49**: 49% + **50**: 19%

Scheme 10. Tanaka and Farina's Eliminations

51: R¹ = PMB or CHPh₂
52: 98%: *Tanaka*
53: 87%: *Farina*

R = CH₂OPh
R¹ = CHPh₂ or PNB [*para*-nitro benzene]
R² = Ts or 2-mercapto-benzothiazole
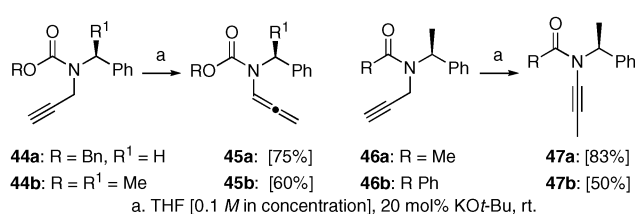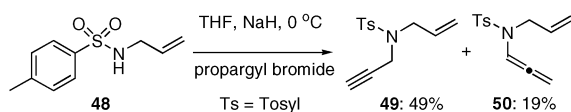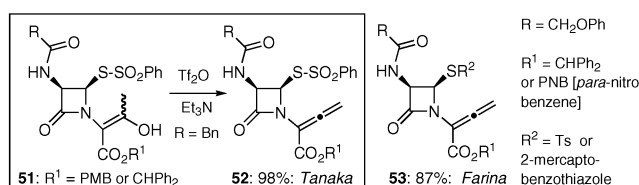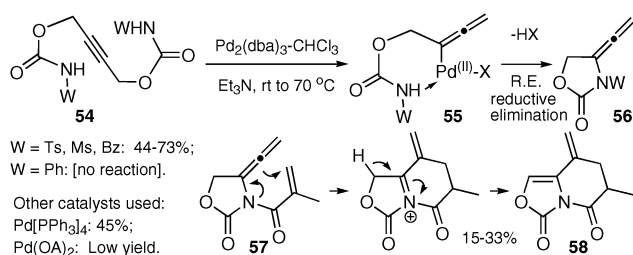
42 via the isomerization of *N*-propargyl phosphoramides **40a** and **40b**, respectively, with the latter providing also ynamide **43** in the mixture [Scheme 7].

Inspired by these results, we examined isomerizations of acyclic propargyl urethanes **44a,b** and found they again gave allenamides **45a,b** using 20 mol % KOt-Bu/t-BuOH [Scheme 8]. However, in contrast, propargyl amides **46a,b** did isomerize successfully to ynamides **47a,b** in 83% and 50% yield, respectively, for the first time.[50]
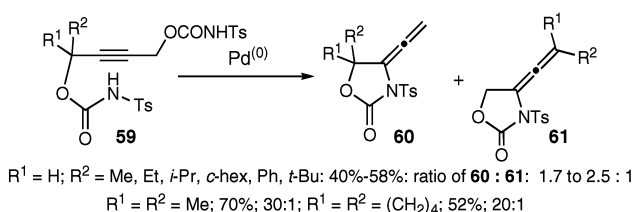
de Meijere[56] also reported an acyclic *N*-tosyl allenamide **50** as a byproduct when preparing propargyl amide **49** from the sulfonamide **48** [Scheme 9].

2.4. Elimination. Tanaka[29] and Farina[30] both communicated an elimination protocol for preparations of β-lactam-based α,α-disubstituted allenamides **52** and **53**, respectively, [Scheme 10] from enol triflates. These allenamides were specifically designed to access cepham analogues [see below].[29,30]
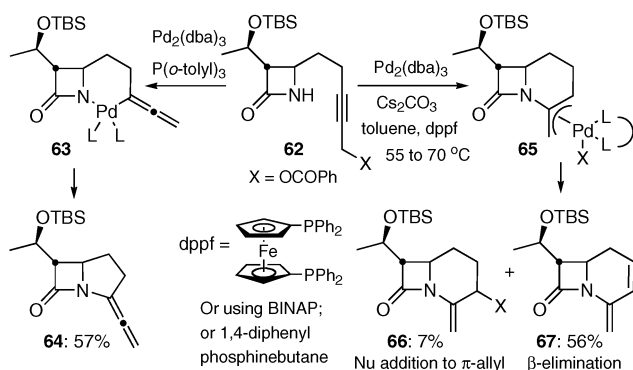
Scheme 11. Tamaru's Allenamides

54 → Pd₂(dba)₃-CHCl₃, Et₃N, rt to 70 °C → **55** → -HX, R.E. reductive elimination → **56**

W = Ts, Ms, Bz: 44-73%;
W = Ph: [no reaction].

Other catalysts used:
Pd[PPh₃]₄: 45%;
Pd(OA)₂: Low yield.

57 → 15-33% → **58**

Scheme 12. Tamaru's Allenamides

59 → Pd⁽⁰⁾ → **60** + **61**

R¹ = H; R² = Me, Et, *i*-Pr, *c*-hex, Ph, *t*-Bu: 40%-58%: ratio of **60** : **61**: 1.7 to 2.5 : 1
R¹ = R² = Me; 70%; 30:1; R¹ = R² = (CH₂)₄; 52%; 20:1

Scheme 13. Mori's Carbapenam Synthesis

63 → Pd₂(dba)₃, P(*o*-tolyl)₃ ← **62** → Pd₂(dba)₃, Cs₂CO₃, toluene, dppf, 55 to 70 °C → **65**

X = OCOPh

64: 57%

dppf =

Or using BINAP; or 1,4-diphenyl phosphinebutane

66: 7%
Nu addition to π-allyl

67: 56%
β-elimination

2.5. Aminocyclization. Some interesting cyclic urethane substituted allenamides **56** via palladium catalyzed intramolecular cyclization of propargyl bis-urethanes **54** were reported recently by Tamaru [Scheme 11].[39,57] Allenamide **57** could further cyclize to give **58**.

The direction of oxidative addition of Pd⁽⁰⁾ en route to allenyl palladium intermediates **55** is not relevant if **54** is symmetrical. Asymmetric bis-urethanes **59** did give a mixture of **60** and **61** [Scheme 12]. The oxidative addition of Pd⁽⁰⁾ was found to be in favor of the less hindered propargyl carbon, leading to **60** with the level of selectivity depending upon the size of R¹ and R².

Mori[58] recently showed a fascinating study in a similar palladium catalyzed aminocyclization of the propargyl carbamate **62** [Scheme 13].

When the ligand was P(*o*-tolyl)₃ or other monodentate phosphines, allenamide **64** with a carbapenam skeleton was found in 57% yield via the allenyl palladium complex **63**. On the other hand, a mixture of **66** and **67** containing the carbacepham skeleton were found in 7% and 56% yields, respectively, when the bidentate ligand dppf was used.

Evidently, an amide coordinated allenyl palladium intermediate like **63** was not possible sterically when a bidentate ligand was used, presumably due to sterics. Instead, attack by the amide nitrogen at the central carbon

Scheme 14. Mori's Allenamides

R = H: β-elimination and
Nu addition to π-allyl

R = OTBS: Only Nu
addition to π-allyl
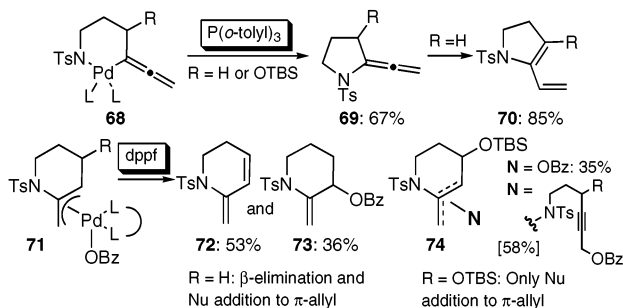
Scheme 15. Corbel's Deprotonation

Scheme 16. α-Substituted Chiral Allenamides

Scheme 17. Allenamide Pauson—Khand

Scheme 18. g-Deprotonation

diastereomeric ratio: 2 : 1

blocked α-position

Scheme 19. Seebach's 1,2-Additions

of the allenyl palladium intermediate [i.e., uncoordinated **63**] would lead to π-allyl complex **65**. Subsequent nucleophilic addition would give **66** and β-elimination would give **67**.

This trend was also found in a more general system where P(*o*-tolyl)₃ led to cyclic *N*-tosyl allenamide **69** in 67% yield that further isomerized to **70** if R = H [Scheme 14].[58] Using dppf provided **72** via β-elimination and **73** [R = H] and **74** [R = OTBS] via nucleophilic addition.

3. Part II. Reactions of Allenamides

3.1. Deprotonations and Addition Reactions. *3.1.1. α-Deprotonation.* Corbel[18] provided the earliest example where allenamides **75** could be deprotonated at α- and γ-positions sequentia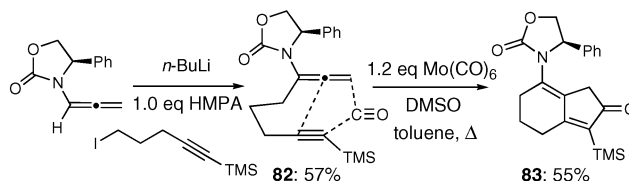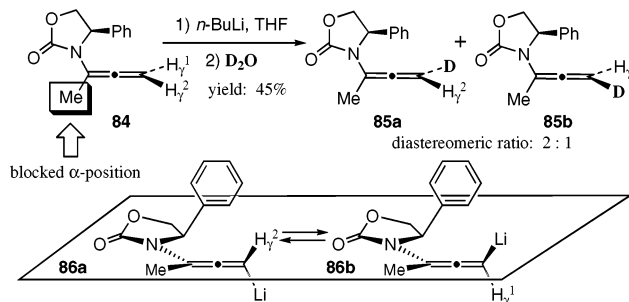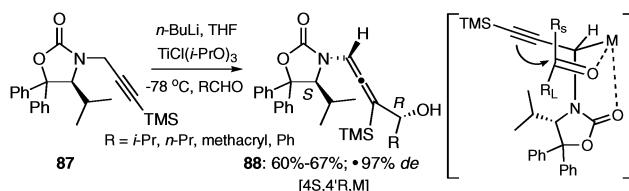lly. The lithiated allenamides **76** and **77** were configurationally stable and could be trapped with electrophiles such as MeI and BnI [Scheme 15].

We embarked on developing this deprotonation method because of its potential as an efficient entry to more functionalized allenamides. After screening a variety of bases, *n*-BuLi was found to be the most suitable, leading to exclusively α-lithiation of **79**, as evident by deuterium quenching [Scheme 16].[25] This led to synthesis of a variety of new α,α-disubstituted chiral allenamides, including chiral allenyl stannanes and allenyl silanes useful for transition metal mediated reactions.[25]

An application of these new allenamides in regioselective allenic Pauson—Khand cycloadditions[59] was carried out using allenamide **82** [Scheme 17].

3.1.2. γ-Deprotonation. γ-Deprotonation of **84**, having the α-position blocked with a methyl group, led to diastereomeric allenamides **85a/b** [Scheme 18] in modest yield.[25] The ratio is only 2:1, implying that either there was very little diastereoselectivity during the deprotonation or the diastereomeric allenyllithium anions **86a** and **86b** equilibrated rapidly even at low temperature.

Seebach[26] recently elegantly demonstrated that lithiated chiral allenamides could be useful in stereoselective additions to aldehydes and ketones. The chiral propargyl amide substituted with Seebach's chiral auxiliary **87** was treated with *n*-BuLi at low temperatures, and upon addition of a variety of aldehydes, γ,γ-disubstituted allenamides were isolated in good yields and high diastereoselectivities [Scheme 19]. The stereochemical outcome was rationalized using the complex as shown in the bracket.

3.2. Cyclizations. *3.2.1. Non-Transition Metal Mediated.* Hackesell reported the first cyclization involving an allenamide.[27] Attempts to methylate propargyl amides **89** led to isolation of the oxazole **90** when R² = *p*-NO₂Ph, and the desired allenamides **91** were isolated when R² = *p*-MeOPh or Ph [Scheme 20]. This cyclization occurred for all substrates when MeI was not added, and presumably, **92** and **93** were key intermediates. Cyclization is actually faster than methylation when R² = *p*-NO₂Ph.

Gericke[28] showed an interesting cyclization involving 2-pyridone substituted allenamides **97a** and **97b** gener-

Scheme 20. Hackesell's Cyclization

89: R^1 = CH$_3$, CF$_3$ **90**: R^2 = *p*-NO$_2$Ph   **91**: R^2 = *p*-MeOPh or Ph   50-60%

R^2 = Ph, *p*-NO$_2$Ph: 78-93%; R^2 = H, CH$_3$, *p*-MeOPh: 5-16%

Scheme 21. Gericke's Cyclization

95: NR$_2$ = 2-pyridone   **96**: 69%

98: 43%

97a: P = H [16%]   **97b**: P = Ac [77%]

100

99: 48%

Scheme 22. Tanaka's Cephem Synthesis

101   **102**   **103**: 23-64%

Scheme 23. Farina's Cephem Synthesis

104: 87%   **105**: 60-70%   **106**

X =
105a
105b: X = *p*-tosyl   **105c**: 31%   found the presence of 1.5 eq 1-methyl-2-mercapto-tetrazolate

Scheme 24. Farina's Cepham

107   **108**   **109**
When using with R^1 = Me, Ph, or *Z*-propenyl: 75-95%

Scheme 25. Noguchi's Cyclization

110   R = H, Me, Ph   **111**   **112**

Scheme 26. Grigg's Pd-Catalyzed Cyclization-Addition

113   **114**   **115**: 54-61%
R = Ph, thiophenyl, PhCH$_2$

116: 88%   **117**

a: N = NEt$_2$: 93%
b: N = N$_3$: 70%
c: N = piperidinyl: 93%

Scheme 27. Grigg's Cyclization-Cycloaddition

118   **119**   **122**

121   56-60%   **120**

R$_2$ = Et$_2$, [CH$_2$]$_4$, or [CH$_2$]$_5$

ated from chromene **95** via deprotonation using LDA [Scheme 21]. While **97a** reverted readily to **95** via a 1,5-H shift and pericyclic ring-closure, **97b** led to benzofuran **98** and **99** upon heating in DMSO and toluene, respectively. Both **98** and **99** were likely derived from the common intermediate **100** with [Ac$^+$] activated DMSO as a proton source leading to the former, and Ac$^+$ trapping and [3,3]-sigmatropic rearrangement leading to the latter.

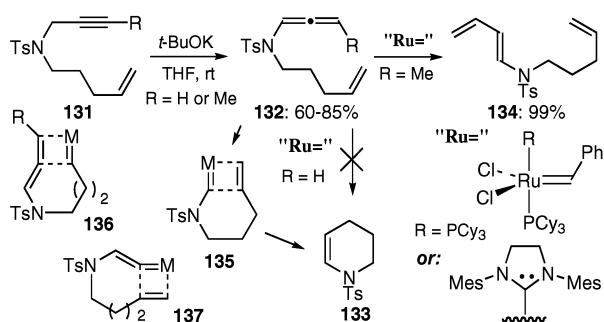Tanaka[29] and Farina[30a] both embarked on preparation of cephem analogues using β-lactam substituted allenamides **101** and **104** [Scheme 22 and Scheme 23, respectively]. In Tanaka's work, a 1,4-addition of an external

nucleophilic amine to the central carbon of allenamide occurred with assistance of CaCl$_2$ followed by a vinylogous enolate addition to the disulfide in **102**.

In Farina's work, an internal attack of the disulfide by the allenamide [functioning as an enamide] occurred, transferring the X group to the central carbon of allenamide followed by an intramolecular 1,4-addition of the resulting sulfide anion to *N*-acyl vinyl iminium **106**. Farina[30b] also reported cuprate additions to allenamide **107** via a mechanistic pathway [see **109**] similar to Tanaka's work en route to cepham **108** [Scheme 24].

Noguchi[31] demonstrated that iodine could promote cyclization of allenamide **110** leading to **111** via a 6-*endo*-trig pathway [Scheme 25]. It was postulated that the iodine activation took place at the terminal olefin [distal from the nitrogen atom] shown in **112**.

3.2.2. Palladium Catalyzed Cyclizations. Grigg[32–35] reported a series of highly creative designs in palladium-catalyzed cyclizations of allenamides [Schemes 26–29].

Reaction of allenamide **113** with Pd(OAc)$_2$ led to the π-allyl complex **114** that could be captured with various nucleophiles [Scheme 26]. Transmetalation of **114** with boronic acids gave isoquinolones **115** in a regioselective manner.[32b] Addition of amines to **114**, in the presence

Scheme 28. Grigg's Hydrostannylation-Cyclization

123 → 124 → 125: 72%

52%   50%   41%   R = SO₂Ph; X = NR or O

Scheme 29. Grigg's Cyclization—Addition

129   Pd(0)   45-63%   130

Nu = NBn, N-cyclopropyl, N-1-phenylethyl, N-1-naphthyl-ethyl, O, C(CO₂Me)₂

Scheme 30. RCM

131 → 132: 60-85% → 134: 99%

136   135   137   133

R = PCy₃

Scheme 31. Epoxidation of Allenamides

for R = H   m-CPBA   CH₂Cl₂   -70 °C to rt

138: R = H
139: R = (CH₂)₄-OH

140   94%; S : R = 91 : 9   Ar = -3-chlorophenyl

fast - pseudo intramolecular

for R = (CH₂)₄-OH   m-CPBA

141

139   1) DMDO, -40 °C   2) TBDPSCl

142   TBDPSO   *AND*   143   *Not Found*

Without PPTS: d.r.: 9 : 1 [72% over 2 steps]   d.r.: 5 : 1
With PPTS [0.5 equiv]: { d.r.: 3.5 : 1   Ratio of 142 : 143: 3 : 1 [96% overall yield]

Scheme 32. A Model

A   138 or 139   1.47 Kcal·mol⁻¹   B   [O]

fast
in the absence of furan or non-acidic conditions

144: Evidenced by Trapping

145: Evidenced by Trapping   R = H   146

of AgCO₃, occurred at the endo position to give **116**, whereas the use of K₂CO₃ led to **117** resulting from exo additions.[32a,c]

By using allenamide **118**, amino diene **120** was obtained and trapped successfully using *N*-methyl maleimide to give **121** in a highly stereoselective manner [Scheme 27].[33] Tetracycle **122** could also be obtained in a similar manner.
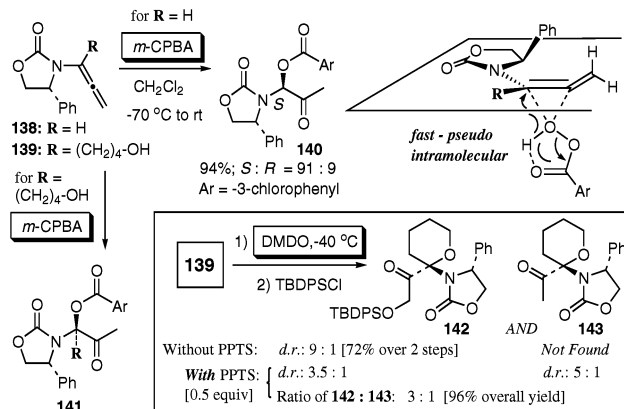
Hydrostannylation of allenamide **123** led to allyl stannane **124** that cyclized to give **125** and a series of other useful heterocycles [Scheme 28].[34] Such strategy could be realized in a tandem manner using allenamide **129** in which the π-allyl intermediate could be trapped intramolecularly [Scheme 29].[35]

This methodology demonstrates the potential of allenamides in transition metal mediated reactions for constructing complex structures.
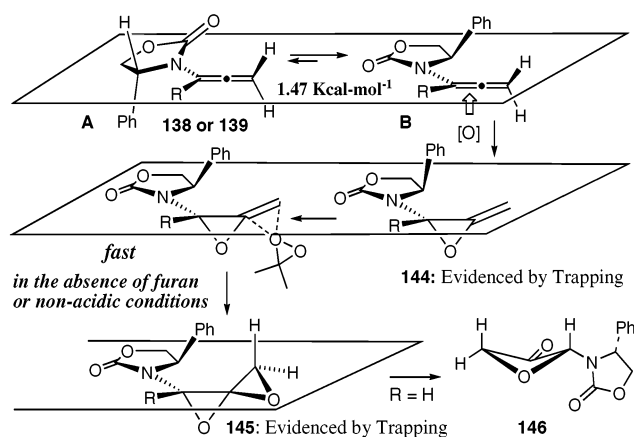
3.3. Ring-Closing Metathesis. Given the power of ring-closing metathesis [RCM],[60] Rutjes[36] attempted RCM using allenamides **132** [Scheme 30]. However, the desired RCM product **133** was not found using either Generation-I or II Ru catalyst. Instead, diene **134**, an isomerization product, was obtained quantitatively when R = Me, thereby implying that the Ru-alkylidene complex **135** was not formed. One wonders if instead the Ru complex **136** or **137** were formed, in what way they would proceed to give RCM-type products.

3.4. Cycloadditions. 3.4.1. [2 + 1]. The only known [2 + 1]-type cycloaddition involved epoxidation of allenamides that was done in our lab in pursuit of [4 + 3] oxyallyl cation cycloaddition.[37] To the best of our knowl-

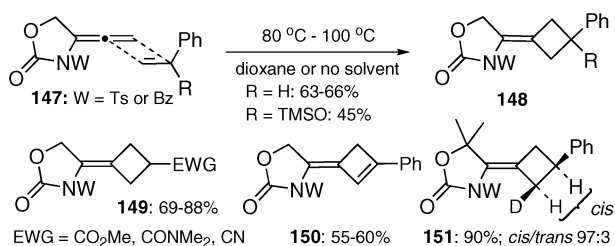edge, epoxidation of heteroatom substituted allenes in general is not well precedented.[61-63]

Epoxidation of allenamides **138** and **139** with *m*-CPBA led to aminals **140** and **141**, repectively, in a highly stereoselective manner via a pseudo intramolecular trapping of the allene oxide intermediate [Scheme 31]. The pseudo intramolecular trapping by *m*-chlorobenzoate anion was actually faster than trapping by the hydroxyl group in **139**.

DMDO [dimethyldioxirane] epoxidations of **139** in the absence of pyridinium *para*-toluenesulfonic acid [PPTS] provided only the pyran **142** [after silylating the primary hydroxyl group], suggesting the presence of the bis-epoxidized intermediate. In the presence of PPTS, both **142** and **143** were isolated, implying that epoxidation had led to the bis- and monoepoxides.
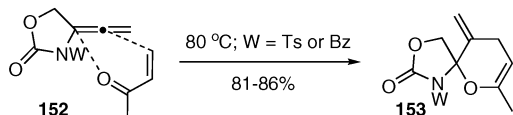
Our studies suggest that DMDO would likely approach from the bottom face of allenamide **138** or **139** in the more favored conformer **B** [Scheme 32]. The resulting mono-epoxide **144** was observed by low temperature ¹H NMR spectroscopy and isolated by intramolecular trapping [see **143**]. The second epoxidation also occurred rapidly at low temperatures in nonacidic conditions leading to bis-spiro-epoxide **145** that could be trapped [see **142**], or rearrange to 3-oxetanone **146**, when R = H, as observed in the low temperature ¹H NMR spectrum.

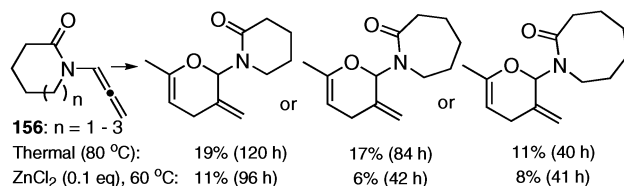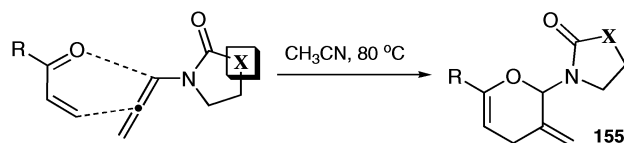This study also indicated that the second epoxidation by DMDO was again slow in the presence of furan,

Scheme 33. [2 + 2] Cycloaddition

147: W = Ts or Bz

80 °C - 100 °C
dioxane or no solvent
R = H: 63-66%
R = TMSO: 45%

148

149: 69-88%
EWG = CO₂Me, CONMe₂, CN

150: 55-60%

151: 90%; *cis/trans* 97:3

Scheme 34. Tamaru's Hetero-[4 + 2]

152

80 °C; W = Ts or Bz
81-86%

153

Scheme 35. Hetero-[4 + 2]

CH₃CN, 80 °C

155

154a: X = NMe   Time: 3-5 h   R = H [52%]; R = CH₃ [62%]
154b: X = O   Time: 24 h   R = H [41%]; R = CH₃ [40%]
154c: X = CH₂   Time: 64 h   R = H [27%]; R = CH₃ [31%]

156: n = 1 - 3
Thermal (80 °C):   19% (120 h)   17% (84 h)   11% (40 h)
ZnCl₂ (0.1 eq), 60 °C: 11% (96 h)   6% (42 h)   8% (41 h)

Scheme 36. Stereoselective Hetero-[4 + 2]

157
R = H: 70% [87:13]; R = Me: 60% [95:5].

CH₃CN, 85 °C
10 - 20 h

158

159a: 78% [●96 : 4]   159b: 60% [94 : 6]   160: 53% [67 : 33]
ZnCl₂ [10 mol%] or 120 °C

Scheme 37. A Proposed Model

Further Away   161   *Much Closer*   157

thereby allowing the subsequent [4 + 3] cycloaddition [see below].

3.4.2. [2 + 2]. An excellent study describing the feasibility of [2 + 2] cycloaddition reactions of allenamides was reported recently by Tamaru.[3b] Allenamides **147** underwent [2 + 2] cycloadditions with alkenes to give cyclobutane **148**. Even electron deficient alkenes and alkynes reacted to give **149** and **150**, respectively. These reactions are also both highly regioselective and stereoselective, as shown in the cycloadduct **151** derived from reactions with *cis*-2-D-styrene.

3.4.3. [4 + 2]. Tamaru[39] carried out the first inverse electron-demand hetero [4 + 2] cycloaddition reaction, as shown in Scheme 34, in which the cycloaddition actually favored the internal olefin of allenamide **152**.[39]
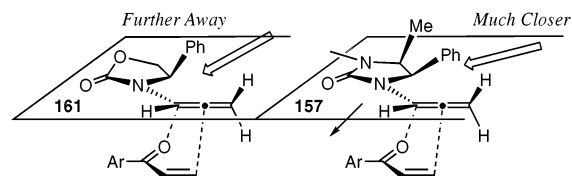
We have studied this hetero Diels–Alder reaction in detail.[41,42] It was found that cycloadditions using our allenamides **154** led to pyrans **155** with the same regiochemistry as reported by Tamura[39] [Scheme 35].

The substitutent pattern of these cyclic amides also impacts the reactivity of allenamides. Urea substituted allenamide **154a** was the most reactive in [4 + 2] cycloadditons with acrolein or methy vinyl ketone [MVK], and γ-lactam substituted allenamide **154c** [X = CH₂] was the least and required the longest reaction time. This is directly related to the extent of delocalization of the nitrogen lone pair into the amide carbonyl. The ring size of the lactam also has an effect on the reactivity.

The [4 + 2] cycloaddition could be rendered highly stereoselective using chiral allenamide **157** that can lead to pyrans **158** and **159a,b** [Scheme 36], representing the first highly stereoselective inverse demand hetero [4 + 2] cycloaddition of a chiral enamide. Control experiments showed that the observed isomeric ratio was not a result of the thermodynamic distribution of final cycloadducts.

In contrast, oxazolidinone substituted allenamides afforded pyranyl heterocycles such as **160** in lower yields and moderate stereoselectivity. This contrast is likely attributed to the fact that oxazolidinone substituted allenamides [see **161** in the lowest-energy conformer: PM3-Spartan Model[TN]] provide less facial differentiation with the phenyl ring being further away from the internal olefin of the allene [Scheme 37]. In the imidazolidinone-substituted allenamide **157**, the phenyl ring is much closer, thereby providing a greater facial bias that would favor the hetero diene approaching preferentially from the bottom face.
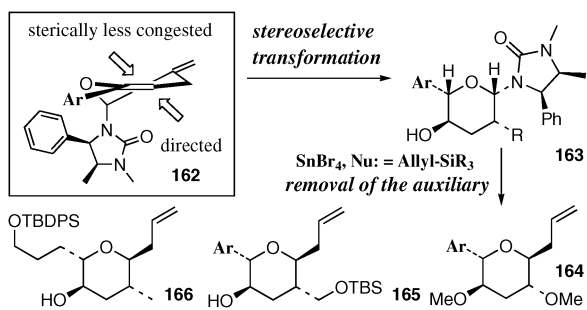
It is noteworthy that oxazolidinone-substituted allenamides are more robust than imidazolidinone-substituted allenamides because the former can tolerate Lewis acidic conditions as well as much higher temperatures [than 80 °C], whereas the latter would decompose under the same conditions.

Applications for these stereoselective cycloaddition products have been examined. The planarity of pyranyl heterocycle **162** [Scheme 38] allowed highly stereoselective transformation of both the sterically accessible *exo*-cyclic olefin and electron-rich *endo*-cyclic olefin leading to **163**. The selectivity could be rationalized as a result of electrophile or nucleophile preferring the less hindered face away from the chiral imidazolidinone group.
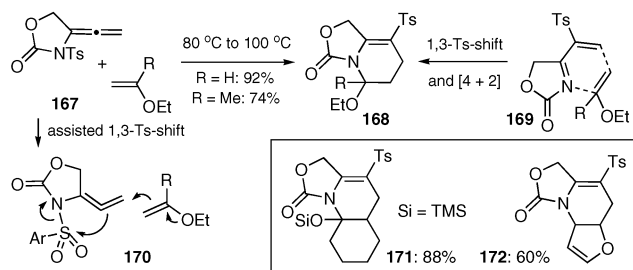
The imidazolidinone group in **163**, serving as an auxiliary, could be removed [and recovered] using a mild Lewis acid [SnBr₄] and replaced with allylsilanes.

These applications provide a new approach to *C*-glycosides[64,65] [**164**−**166**] with the pyranyl heterocycles serving as excellent chiral templates. A major advantage
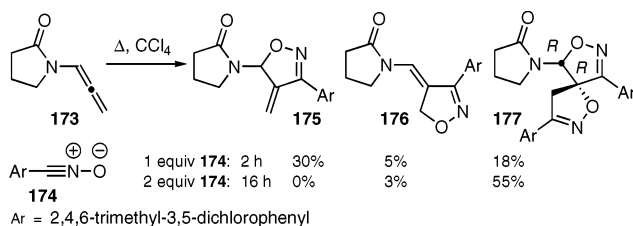
Scheme 38. Applications of Hetero-[4 + 2]

Scheme 39. Tamaru's Formal [4 + 2]

Scheme 40. Zecchi's [3 + 2]

			175	176	177
1 equiv **174**:	2 h	30%		5%	18%
2 equiv **174**:	16 h	0%		3%	55%

Ar = 2,4,6-trimethyl-3,5-dichlorophenyl

Scheme 41. An Overview of [4 + 3]

Scheme 42. Tandem Epoxidation/[4 + 3] Cycloaddition

Scheme 43. Synthetic Applications

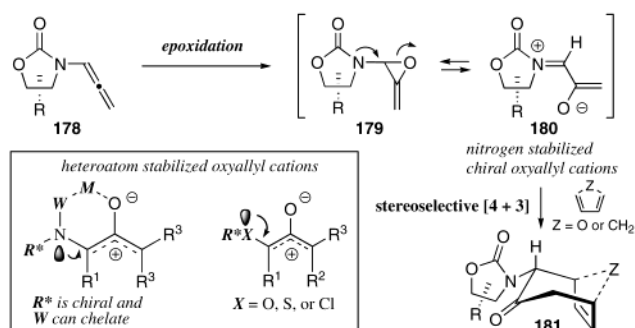of this approach is that protection and deprotection steps can be avoided.[66,67]

Tamura[40] communicated a formal [4 + 2] cycloaddition of allenamide **167** with enol ethers [Scheme 39], leading to **168** [also see **171**-**172**]. This reaction was also stereoselective. Mechanistically, it most likely involved a 1,3-Ts shift that either simply led to an aza-diene **169** that could be added to enol ethers in a [4 + 2] cycloaddition fashion, or was assisted by the enol ether [shown as **170**] followed by a cyclization.

3.4.4. [3 + 2]. Zecchi[43] showed the first example of a 1,3-dipolar cycloaddition utilizing allenamides. Allenamide **173** reacted with aryl nitrile oxide **174** efficiently under various conditions that led to [3 + 2] cycloadducts **175**, **176**, and **177** resulting from addition to internal, terminal olefin, and double addition, respectively [Scheme 40]. Yields and ratios varied with reaction times and equivalents of **174** used.
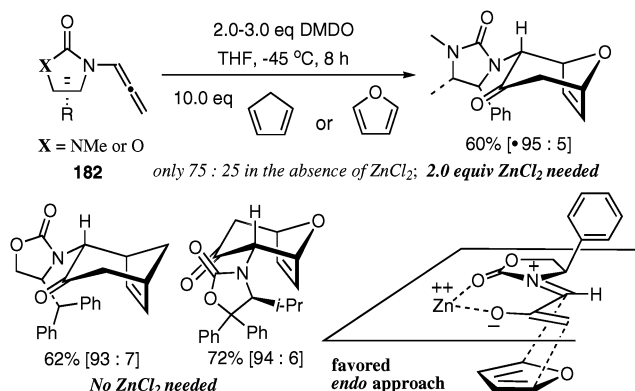
3.4.5. [4 + 3]. On the basis of our studies in epoxidation of allenamides shown earlier [Scheme 32], we were able to explore whether allene oxide **179** and/or nitrogen stabilized chiral oxyallyl cations **180** could be efficiently trapped by dienes in a highly stereoselective manner [Scheme 41]. Achieving highly stereoselective [4 + 3] cycloadditions remains a challenge in the area of oxyallyl cation cycloaddition.[68,69]

While heteroatom stabilized oxyallyl cations are known,[69] the nitrogen stabilized *chiral* oxyallyl cation has not been
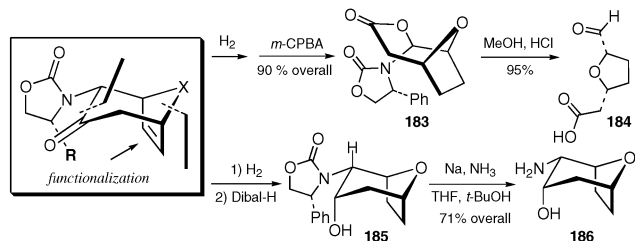
reported.[70−72] The trivalent nature of the nitrogen atom allows simultaneous tethering of a chirality inducing unit and a coordination unit, leading to greater rigidity of the oxyallyl cation species, and thus, also better stereochemical outcome in the cycloaddition. This feature is an advantage over other heteroatom stabilized oxyallyl cations.[69] In addition, we believe that the readily accessible chiral allenamides could serve as excellent sources for nitrogen stabilized chiral oxyallyl cations.

DMDO epoxidation of allenamides **182** in the presence of various dienes led to corresponding [4 + 3] cycloadducts in a highly stereoselective manner [Scheme 42].[44] In some cases, 2.0 equiv of $ZnCl_2$ was needed to achieve high levels of selectivity. This was rationalized using a mechanistic model in which the Zn cation was coordinated to both oxygen atoms, providing greater conformational rigidity of the oxyallyl cation.

These cycloadducts can be excellent building blocks for constructing five-, six-, or seven-membered rings. This methodology has been specifically applied to synthesis of furan **184** and chiral amino alcohol **186** [Scheme 43].[44]

4. Conclusion

We have highlighted recent studies describing utility of allenamides in organic synthesis. Although chemistry involving other heteroatom-substituted allenes is of high impact and value, nitrogen substituted allenes offer some advantages. The trivalent nature of the nitrogen atom allows (1) tethering of a chirality-inducing unit to introduce new stereocenters, (2) inclusion of a coordination unit to provide conformational rigidity, and (3) a greater flexibility in designing intramolecular reactions. These features are attractive for developing stereoselective synthetic methods, and the future of allenamide chemistry should be promising. We hope this Account will provide further interest in the chemistry of allenamides.

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AR030029I