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Carbocyclization Cascades of Allyl Ketenimines via *Aza*-Claisen Rearrangements of *N*-Phosphoryl-*N*-allyl-ynamides

Kyle A. DeKorver,* Xiao-Na Wang, Mary C. Walton, and Richard P. Hsung*

Division of Pharmaceutical Sciences and Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53705, United States

dekorver@wisc.edu; rhsung@wisc.edu

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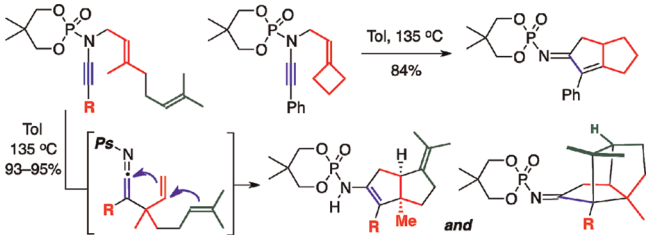
ABSTRACT



A series of carbocyclization cascades of allyl ketenimines initiated through a thermal *aza*-Claisen rearrangement of *N*-phosphoryl-*N*-allyl ynamides is described. Interceptions of the cationic intermediate via Meerwein–Wagner rearrangements and polyene-type cyclizations en route to fused bi- and tricyclic frameworks are featured.

We recently reported a new class of ynamides[1−3] bearing a phosphoryl group as the required electron-withdrawing component.[4] Most notably, it was demonstrated that *N*-phosphoryl-*N*-allyl ynamides **1** [for EWG = $PO(OR)_2$] could undergo a thermal 3-*aza*-Claisen rearrangement[5,6] to generate allyl ketenimine[7] intermediates **2** *in situ* without suffering a subsequent facile 1,3-shift observed in related *N*-sulfonyl systems [**1**→**4** when EWG = $ArSO_2$], leading to an effective formation of structurally unique quaternary nitriles **5**[8,9] (Scheme 1). While such a 1,3-sulfonyl shift can be of immense interest,[10] it precluded us from developing a useful carbocyclization of allyl ketenimines **4**.[8,9] Consequently, in lieu of a 1,3-phosphoryl shift, we envisioned that carbocyclizations of **2** could take place to afford cyclopentenyl zwitter ionic intermediates **6**, which would allow us to construct cyclopentenimine derivatives **7** via a

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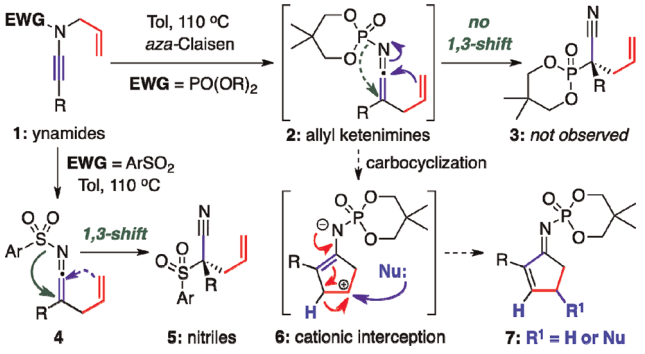
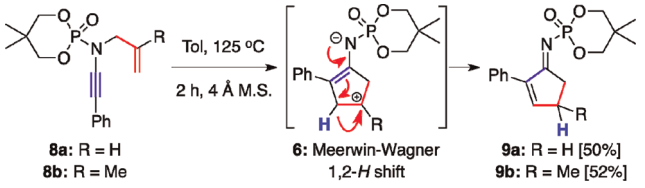
Scheme 1. A Carbocyclization of Allyl Ketenimines



1,2-*H* shift, or more powerfully, nucleophilic trapping[11−13] of **6**. We report herein our success in intercepting these intermediates.

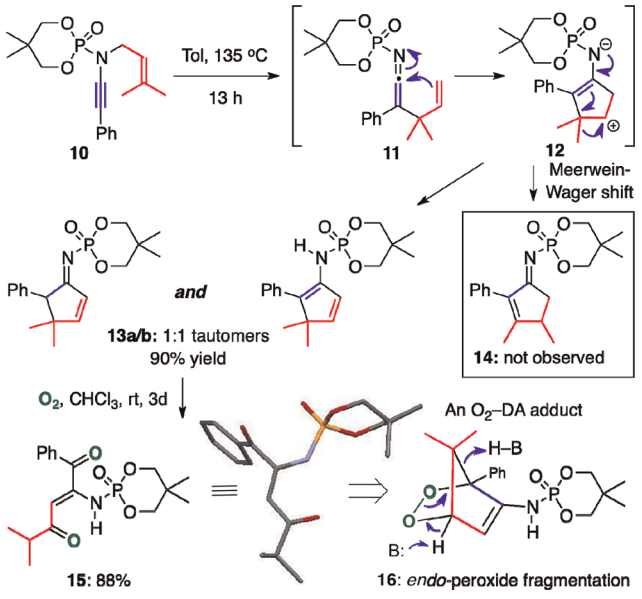
Scheme 2. Feasibility of the Carbocyclization



Our first success with an ynamide-initiated thermal carbocyclization was the rearrangement of ynamide **8a** to α,β-unsaturated cyclopentenimine **9a** in 50% yield (Scheme 2). We were fascinated with this discovery, as it implied that a 1,2-*H* shift through zwitter ionic intermediate **6** may be in operation. Furthermore, ynamide **8b** also underwent the tandem *aza*-Claisen rearrangement−carbocyclization to give **9b**, presumably through a tertiary carbocation intermediate.

While it is also possible that deprotonation could lead to 1-amido dienes that then tautomerized to the observed cyclopentenimines, the idea of a 1,2-*H* shift was enticing. We therefore wondered if other Meerwein−Wagner shifts could occur following the initial *aza*-Claisen rearrangement and carbocyclization (Scheme 3). To explore this possibility, *N*-prenyl ynamide **10** was heated to 135 °C, with the hopes of demonstrating a 1,2-methyl shift through the formation of cyclopentenimine **14**. Unfortunately, **14** was not observed. Instead, a 1:1 tautomeric mixture of **13a** and **13b** was isolated in 90% yield caused by deprotonation α to the enamide instead of the desired methyl shift. Remarkably, when air was bubbled through the tautomeric mixture at rt in $CHCl_3$, a [4 + 2] cycloaddition of 2-amido diene **13b** with O_2 ensued to first give endoperoxide

Scheme 3. Attempts at a 1,2-Alkyl Shift: An Unexpected [4 + 2]



16 that subsequently fragmented to the isolated ene-dione **15**. While this could be a radical fragmentation, although the reaction conditions involved no base, it is very likely another example of a Kornblum−DeLaMare process.[14,15]

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 zwitter ionic intermediates through either Meerwein−Wagner rearrangements or nucleophilic trappings. To explore the former, we prepared ynamides **17** and **21** bearing a tethered

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(9) DeKorver, K. A.; Hsung, R. P.; Lohse, A. G.; Zhang, Y. *Org. Lett.* **2010**, *12*, 1840.

(10) For leading references on synthetic applications of nitriles, see: (a) Fleming, F. F.; Liu, W. *Eur. J. Org. Chem.* **2009**, 699. (b) Fleming, F. F.; Wei, G.; Steward, O. W. *J. Org. Chem.* **2008**, *73*, 3674. (c) Mermerian, A. H.; Fu, G. C. *Angew. Chem., Int. Ed.* **2005**, *44*, 949.

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(13) For related examples of intercepted Nazarov cyclizations, see: (a) Giese, S.; Kastrup, L.; Stiens, D.; West, F. G. *Angew. Chem., Int. Ed.* **2000**, *39*, 1970. (b) Giese, S.; West, F. G. *Tetrahedron* **2000**, *56*, 10221. (c) Wang, Y.; Schill, B. D.; Arif, A. M.; West, F. G. *Org. Lett.* **2003**, *5*, 2747. (d) Huang, J.; Leboeuf, D.; Frontier, A. J. *J. Am. Chem. Soc.* **2011**, *133*, 6307. (e) For a recent review, see: Grant, T. N.; Rieder, C. J.; West, F. G. *Chem. Commun.* **2009**, 5676.

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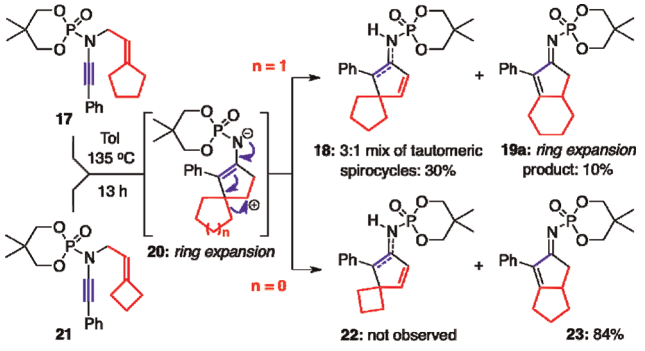
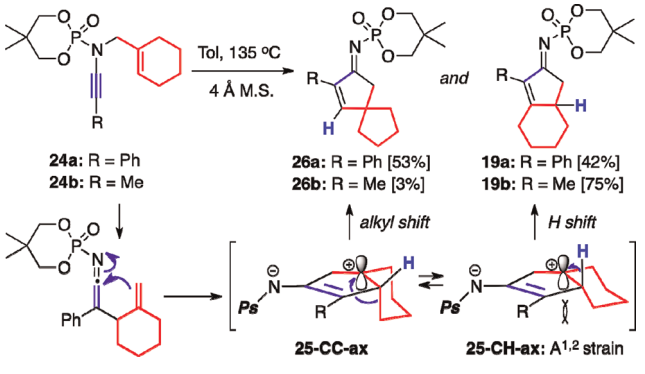
methylcyclopentylidine and methylcyclobutylidine, respectively, reasoning that the added ring strain should favor ring expansion through zwitter ions **20** (Scheme 4). When **17** was heated to 135 °C, spirocycles **18** resulting from elimination dominated; however bicycle **19a** was also isolated in 10% yield representing a successful ring expansion. Moreover, ynamide **21** with increased ring strain yielded ring-expansion product **23** in 84% yield and spirocycle **22** was not observed.

Scheme 4. Ring Expansion through Meerwein–Wagner Shift



We also, rather unexpectedly, discovered a Meerwein–Wagner ring contraction when pursuing the carbocyclization of ynamide **24a** bearing a tethered methylcyclohexene (Scheme 5). In addition to the anticipated 5,6-fused bicycle **19a** resulting from a 1,2-*H* shift, 5,5-spirocycle **26a** 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 pseudoaxial position in

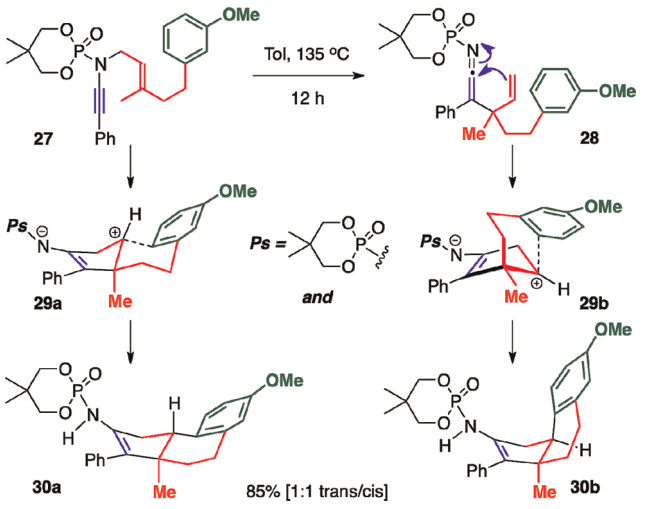
Scheme 5. Ring Contraction through Meerwein–Wagner Shift



25-CC-ax, thereby allowing the 1,2-alkyl shift to compete. This notion was furthered by our experimentation with methyl-terminated ynamide **24b**, where the expected 1,2-*H* shift dominated to give **19b** in 75% yield and only 3% of the spirocycle **26b**.

After successfully completing several examples of intercepting the zwitter ionic intermediates via Meerwein–Wagner rearrangements, we wanted to explore the possibility of using the *aza*-Claisen rearrangement to initiate a carbocyclization cascade with tethered carbon nucleophiles. Gratifyingly, ynamide **27** featuring a *m*-methoxyphenyl moiety tethered to the allyl fragment cleanly underwent the required 3-*aza*-Claisen rearrangement followed by carbocyclization and Friedel–Craft electrophilic aromatic substitution to give **30a** and **30b** as a 1:1 mixture of trans and cis isomers without any competing alkyl shifts (Scheme 6).

Scheme 6. Friedel–Craft Trapping of Cationic Intermediate



The ability to intercept these cationic 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[16,17] we decided to investigate the possibility of an ynamide-initiated carbocyclization cascade with terpene-derived ynamides (Scheme 7).

Starting from commercially available geranylamine **31**, a simple two-step protocol involving phosphorylation and Cu-catalyzed amidative cross-coupling gave ynamide **32** in 82% overall yield. When **32** was heated to 135 °C for 12 h, 5,5-*cis*-fused bicycle **36** bearing an exocyclic olefin was isolated in 55% yield as a single diastereomer. Of note, the *cis*-fused bicyclic core in **36** is prominent in triquinane[18] natural products. In addition to **36**, tricycle **37** featuring four contiguous stereocenters and three all-carbon quaternary centers was isolated in 38% yield as a single diastereomer. The geometry of both products was determined by NOE analysis.

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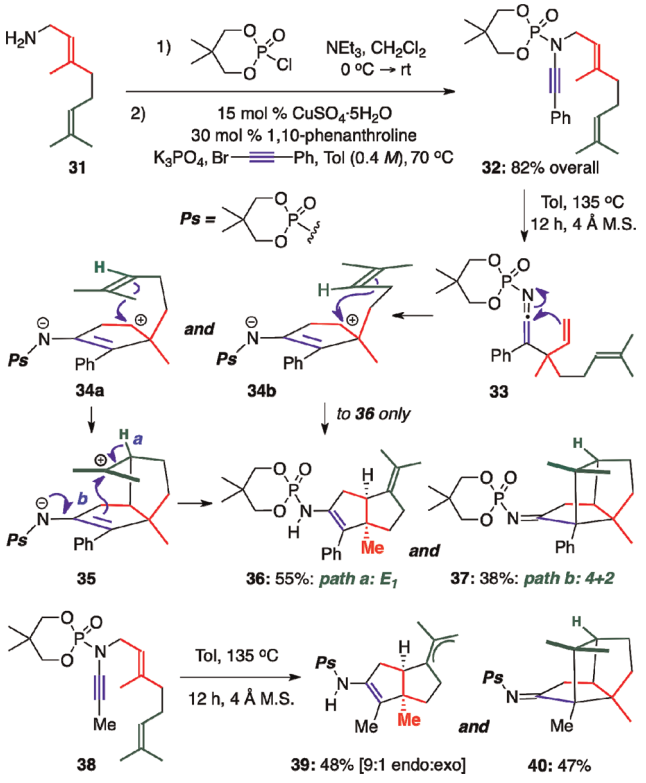
(17) Also see: (a) Stork, G.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1955**, *77*, 5068. (b) Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta* **1955**, *38*, 1890. (c) Stadler, P. A.; Eschenmoser, A.; Schinz, H.; Stork, G. *Helv. Chim. Acta* **1957**, *40*, 2191.

(18) For a review on triquinane synthesis: Mehta, G.; Srikrishna, A. *Chem. Rev.* **1997**, *97*, 671.

Scheme 7. Ynamide Initiated Cationic Polyene Cascade



The divergence in reaction pathways leading to the bi- and tricylic products was interesting. As one might imagine, after the initial carbocyclization, the second olefin may add to the carbocation through the facial approach shown in either **34a** or **34b**, which followed by elimination would give **36**. Mechanistically more intriguing is the formal [4 + 2] cycloaddition to afford **37**, which must arise through the olefin approach shown in **34a**, followed by enamide addition to the resulting tertiary carbocation.

The described carbocyclization cascade worked equally well with methyl-terminated ynamide **38**. After 12 h, 5, 5-*cis*-fused bicycle **39** was isolated as a 9:1 mixture of endo and exo olefin isomers, as well as tricycle **40** as a single diastereomer.

We have showcased here a tandem *aza*-Claisen–carbocyclization for the synthesis of α,*β*-unsaturated cyclopentenimines from *N*-phosphoryl-*N*-allyl ynamides. Furthermore, we have demonstrated the ability to intercept the zwitter ionic intermediates through Meerwein–Wagner ring expansions and contractions, as well as with tethered carbon nucleophiles to afford bi- and tricyclic scaffolds. Applications of these carbocyclization cascades in total synthesis are currently underway.

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Supporting Information Available. Experimental procedures as well as NMR spectra, and characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.