JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Synthesis of Cyclopentenimines from *N*-Allyl Ynamides via a Tandem Aza-Claisen Rearrangement−Carbocyclization Sequence

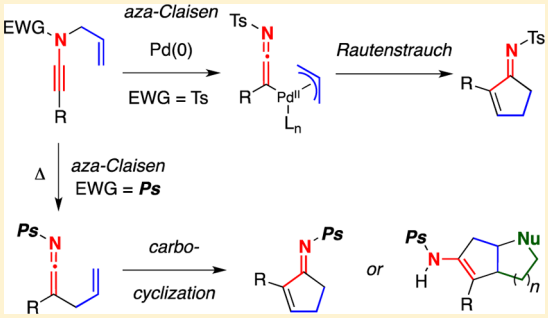
Xiao-Na Wang,[†] Gabrielle N. Winston-McPherson,[†] Mary C. Walton,[†] Yu Zhang,[†] Richard P. Hsung,*[,†] and Kyle A. DeKorver*[,‡]

[†]Division of Pharmaceutical Sciences and Department of Chemistry, 777 Highland Avenue, University of Wisconsin, Madison, Wisconsin 53705-2222, United States

[‡]Dow AgroSciences, LLC, 9330 Zionsville Road, Indianapolis, Indiana 46268, United States

Supporting Information

ABSTRACT: We describe here details of our investigations into Pd-catalyzed and thermal aza-Claisen−carbocyclizations of *N*-allyl ynamides to prepare a variety of α,β-unsaturated cyclopentenimines. The nature of the ynamide electron-withdrawing group and β-substituent plays critical roles in the success of this tandem cascade. With *N*-sulfonyl ynamides, the use of palladium catalysis is required, as facile 1,3-sulfonyl shifts dominate under thermal conditions. However, since no analogous 1,3-phosphoryl shift is operational, *N*-phosphoryl ynamides could be used to prepare similar cyclopentenimines under thermal conditions through zwitter ionic intermediates that undergo *N*-promoted *H*-shifts. Alternatively, by employing ynamides bearing tethered carbon nucleophiles, the zwitter ionic intermediates could be intercepted, giving rise rapidly to more complex fused bi- and tricyclic scaffolds.

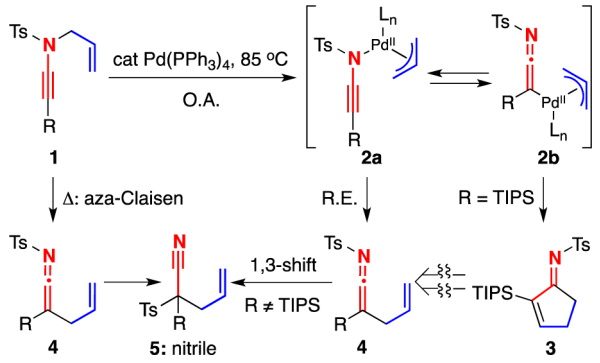


INTRODUCTION

We have been involved with the chemistry of ynamides for the last 17 years, and this burgeoning field has attracted an immense amount of attention from the synthetic community in recent decade.[1−3] In our own effort during the past several years, we have been heavily interested in using Pd-catalyzed and thermal aza-Claisen[4,5] rearrangements as a means of activating *N*-allyl ynamides toward (1) nucleophilic additions of amines[6] and alcohols,[7] (2) inter-[8] and intramolecular[9] [2 + 2] cycloaddition reactions, (3) skeletal rearrangements yielding nitriles,[6c] and (4) carbocyclizations[10] and cationic polyene cascades.

We previously reported the initial discovery of a tandem cascade of Pd-catalyzed aza-Claisen rearrangement and carbocyclization of TIPS-terminated *N*-allyl ynamide **1** to cyclopentenimine[6b] **3** upon exposure to 5 mol % $Pd(PPh_3)_4$ [Scheme 1]. Interestingly, our only success in achieving this transformation was using TIPS-terminated ynamides; alkyl and aryl-terminated ynamides underwent facile 1,3-sulfonyl shifts to generate quaternary nitriles **5**.[6b,c] Furthermore, we demonstrated that the pathway leading to cyclopenteimine **3** involved tautomeric Pd-π-allyl ynamide and ketenimine complexes **2a** and **2b**, as treatment of the isolable TIPS-ketenimine[11] **4** to either Pd(0) or thermal conditions gave no cyclopentenimine **3**. We wish to disclose here details of this Pd-catalyzed or thermal aza-Claisen−carbocyclization sequence using *N*-allyl ynamides and the impact of the ynamide electron-withdrawing group and β-substituents on this tandem cascade.

Scheme 1. Initial Discovery of a Pd-Catalyzed Carbocyclization



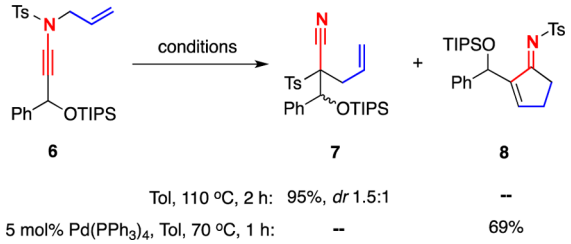
RESULTS AND DISCUSSION

While attempting to render the 1,3-sulfonyl shift leading to nitrile formation diastereoselective, we uncovered a fascinating reaction dichotomy with γ-branched ynamides. Upon heating ynamide **6** in toluene at 110 °C, nitrile **7** was isolated in near quantitative yield, albeit with modest diastereoselectivity[6c] [Scheme 2]. Alternatively, treatment of **6** with 5 mol % $Pd(PPh_3)_4$ gave cyclopentenimine **8** in 69% yield, and nitrile **7**

Received: May 6, 2013
Published: May 29, 2013

   dx.doi.org/10.1021/jo400960e | J. Org. Chem. 2013, 78, 6233−6244

Scheme 2. 1,3-Sulfonyl Shift versus Carbocyclization Dichotomy



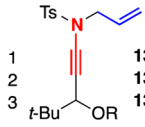
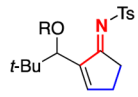
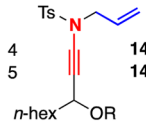
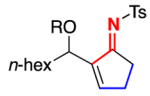
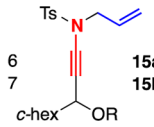
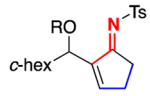
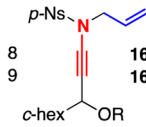
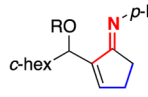
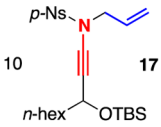
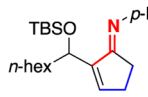
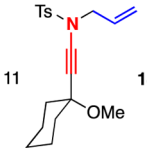
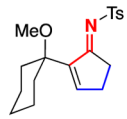
was not found. This represented the first time we had observed a carbocyclization of a nonsilyl terminated *N*-sulfonyl ynamide.

We were intrigued by the possibility of using γ-branched ynamides as carbocyclization precursors and wanted to further probe the substrate scope. Unfortunately, the preparation of γ-branched ynamide **6** was problematic [Scheme 3]. It involved initial silylation of 3-phenyl-propargyl alcohol **9** followed by bromination to afford **10**. The ensuing standard 15 mol % $CuSO_4{\cdot}5H_2O$ and 30 mol % 1,10-phenanthroline-catalyzed amidative cross-coupling gave **6** in only 12% yield, likely because of the steric bulk of the alkynyl bromide. We later discovered that using 20 mol % CuTC and 40 mol % DMEDA could improve the yield of the cross coupling to 66%. Still, assessing the reaction scope using this protocol would have been a lengthy endeavor.

Alternatively, inspired by a report by Saá,[12] we found that ynamide **11**, which was readily accessible in gram quantities, could be lithiated using LHMDS and added to aldehydes such as pivalaldehyde to directly prepare γ-hydroxy-ynamide **12a** in excellent yield [Scheme 3]. The alcohol could then be functionalized as desired to afford ynamides such as **13a**. This allowed us to expediently and fully explore the scope of cyclopentenimine formation.

We soon discovered that the substrate scope for the Pd-catalyzed carbocyclization was quite broad. As shown in Table 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 °C. 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. Also, both *N*-Ts and *N*-Ns containing ynamides underwent the desired carbocyclization in comparable yields. Notably, this methodology provided a means of preparing α,β-unsaturated cyclopentenimines analogous to the α,β-unsaturated enones from a Baylis–Hillman[13] type reaction.

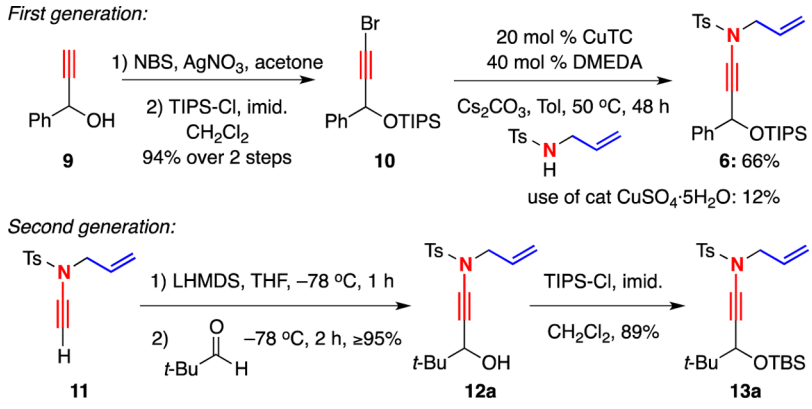
Table 1. Synthesis of α,β-Unsaturated Cyclopentemines from *N*-Allyl Ynamides[a]

entry	ynamide	cyclopentenimine	yield [%][b]
1	 **13a:** R = TBS	 **19a:** R = TBS	71%
2	**13b:** R = Me	**19b:** R = Me	77%
3	**13c:** R = Bn	**19c:** R = Bn	84%
4	 **14a:** R = Me	 **20a:** R = Me	70%
5	**14b:** R = TIPS	**20b:** R = TIPS	92%
6	 **15a:** R = Me	 **21a:** R = Me	88%
7	**15b:** R = Bn	**21b:** R = Bn	≥95%
8	 **16a:** R = TBS	 **22a:** R = TBS	80%
9	**16b:** R = CPh_3	**22b:** R = CPh_3	83%
10	 **17**	 **23**	56%
11	 **18**	 **24**	34%

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

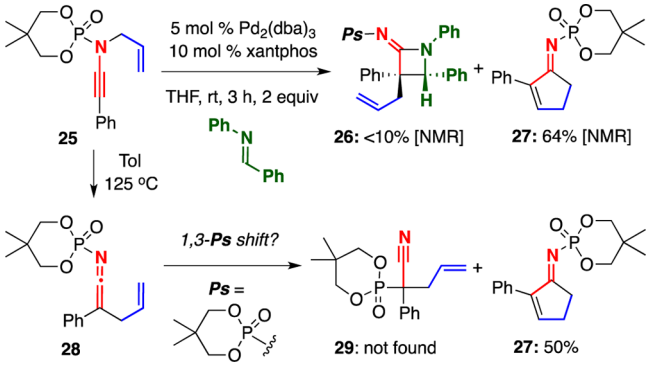
While exploring a potential Staudinger-type [2 + 2] cycloaddition of *N*-phosphoryl *N*-allyl ynamides to give azetidinimines **26**,[14] we discovered another case of cyclopentenimine formation [Scheme 4]. When a mixture of *N*-phosphoryl ynamide **25** and *N*-benzylidineaniline was subjected to 5 mol % $Pd_2(dba)_3$ and 10 mol % xantphos, conditions which favor reductive elimination of the intermediate Pd-π-allyl

Scheme 3. Preparation of γ-Branched Ynamides



dx.doi.org/10.1021/jo400960e | J. Org. Chem. 2013, 78, 6233–6244

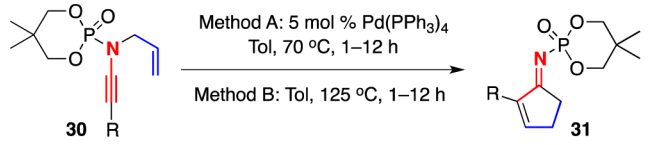
Scheme 4. Unexpected Carbocyclization of an *N*-Phosphoryl Ynamide



ketenimine in our hands, the major product by ^{1}H NMR using phenanthrene as an internal standard was cyclopentenimine **27**. This was the first time we had observed the carbocyclization of a phenyl-terminated ynamide. In the analogous phenyl-terminated *N*-sulfonyl ynamide, the 1,3-sulfonyl shift leading to nitriles dominated the carbocyclization pathway. However, because there was no competing 1,3-phosphoryl shift, heating of *N*-phosphoryl ynamide **25** to 125 °C in toluene led to cyclopentenimine **27** in an isolated 50% yield.

We soon found that the yield of cyclopentenimine **27** could be increased to 87% yield using 5 mol % $Pd(PPh_3)_4$ in toluene at 70 °C [Scheme 5]. Ynamides **30b** and **30c** bearing terminal

Scheme 5. Pd-Catalyzed versus Thermal Carbocyclizations of *N*-Phosphoryl Ynamides



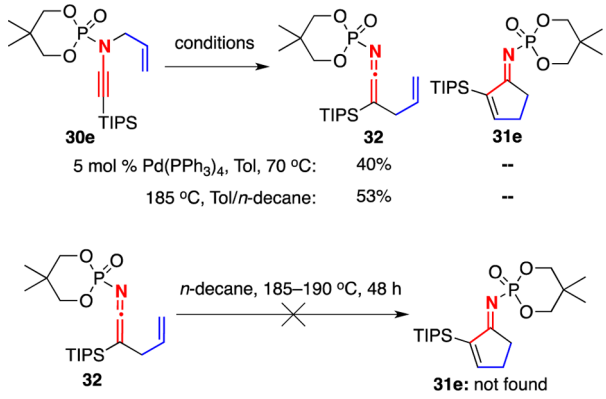
ynamides	R =	cyclopentenimines	yield [%][a]
30a	Ph	**31a**	A: 87 B: 50
30b	*n*-hex	**31b**	A: 56 B: 27
30c	$(CH_2)_4OTBS$	**31c**	A: 34 B: 37
30d	*t*-Bu, OTBS	**31d**	A: <10 B: 69[b]

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

n-hexyl and TBS-ether moieties were also tolerated using both thermal and Pd-catalyzed conditions, though the yields were slightly diminished. Interestingly, the Pd-catalyzed carbocyclization of γ-branched ynamide **30d** was sluggish, giving <10% yield of the desired cyclopentenimine. The yield could be improved to 69% by heating to 135 °C in toluene. The difference in reactivity of γ-branched *N*-sulfonyl and *N*-phosphoryl ynamides under Pd-catalyzed conditions was the first indication that the carbocyclization pathways may be different.

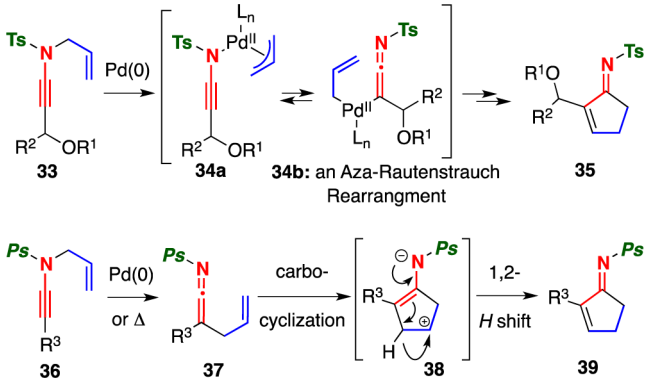
Furthermore, treatment of TIPS-terminated *N*-phosphoryl ynamide **30e** with 5 mol % $Pd(PPh_3)_4$ led to no discernible formation of cyclopentenimine **31e**; only ketenimine **32** resulting from reductive elimination of the intermediate Pd-π-allyl complex was isolated [Scheme 6]. Also, heating of **32** to 185–190 °C for two days did not result in any formation of **31e**.

Scheme 6. Mechanistic Studies Employing an Isolable TIPS-Ketenimine



Collectively, the experimental evidence indicated that the carbocyclization mechanisms for *N*-sulfonyl and *N*-phosphoryl ynamides, even under Pd-catalysis, were unique [Scheme 7].

Scheme 7. Unique Carbocyclization Pathways for *N*-Sulfonyl and *N*-Phosphoryl Ynamides

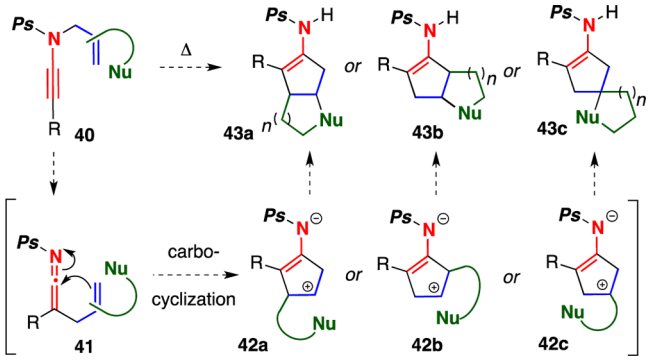


We propose that the carbocyclization of *N*-sulfonyl ynamides **33** occurs through Pd-π-allyl ketenimines **34b** via a Rautenstrauch rearrangement.[15,16] In contrast, it seems that the carbocyclization of *N*-phosphoryl ynamides **36** occurs through ketenimine **37** under both palladium-catalyzed and thermal conditions because of the lack of a competing 1,3-phosphoryl shift. Following the carbocyclization[17,18] that generates zwitter ionic intermediate **38**, a *N*-promoted 1,2-*H* shift gives cyclopentenimine **39**.

We were especially excited by the discovery that *N*-phosphoryl ynamides participated in the carbocyclization without the need for palladium catalysis, thereby avoiding any potential scrambling[6b] of the allyl moiety through the Pd-π-allyl intermediates. In suitably substituted *N*-phosphoryl ynamides, we demonstrated that *N*-promoted Meerwein–Wagner alkyl shifts could compete with the 1,2-*H* shift leading to fused or spiro bicyclic products.[10] In addition to exploiting the zwitter ionic intermediates via *N*-promoted ring expansions and contractions, we envisioned the possibility of intercepting[19] the intermediates with tethered nucleophiles to prepare a variety of bicyclic scaffolds such as **43a–43c** [Scheme 8].

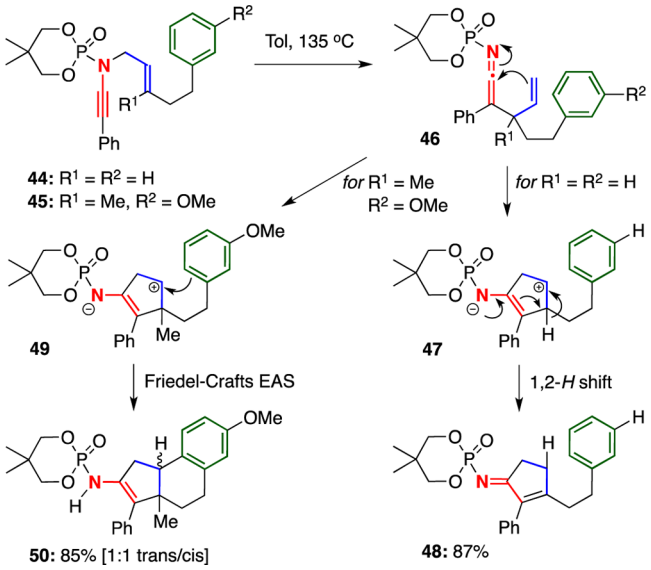
dx.doi.org/10.1021/jo400960e | J. Org. Chem. 2013, 78, 6233–6244

Scheme 8. Potential Carbocyclization Cascades of *N*-Phosphoryl Ynamides



Our initial attempts at trapping the zwitter ionic intermediates employed tethered carbon nucleophiles, thereby eliminating any undesired side reactions such as amidine[6] or imidate[7] formation. When ynamide **44** featuring a tethered benzene ring was heated to 135 °C in toluene, only cyclopentenimine **48** resulting from a 1,2-*H* shift through **47** was isolated [Scheme 9]. To allow the nucleophilic addition to occur, it was clear that we needed to slow the 1,2-*H* shift. By introducing a methyl at R^1 and tethering a more electron-rich *m*-methoxy benzene, ynamide **45** cleanly underwent the desired thermal aza-Claisen/Friedel–Craft electrophilic aromatic substitution reaction sequence to give **50** in 85% yield as a mixture of *cis* and *trans* isomers at the ring juncture.[10]

Scheme 9. Carbocyclization Cascade vs 1,2-*H* Shift



In addition, we had previously demonstrated that geranyl-tethered ynamides such as **51** could be used in thermal carbocyclization cascades to prepare a readily separable mixture of *cis*-fused bicycle **52** as a 9:1 mixture of alkene isomers and tricycle **53** [Scheme 10].[10]

Working from our success thus far in developing carbocyclization cascades[20,21] of geranyl-tethered ynamides, we wondered if we could extend the cyclization to include farnesyl-tethered ynamides. The ynamide synthesis is straightforward and outlined in Scheme 11. Following a literature procedure,[22] farnesol amine **55** could be prepared from farnesol **54** in 97% over two steps. Then, phosphorylation of farnesol amine gave **56**, which could be subjected to our optimized amidative cross-coupling conditions to yield TIPS-terminated ynamide **57** in 65% yield. TBAF-mediated desilylation gave the terminally unsubstituted ynamide **58**, which could then be lithiated and quenched with MeI to prepare the desired farnesyl-tethered ynamide **59**.

With ynamide **59** in hand, we were able to investigate the outcome of the intended polyene carbocyclization cascade. As described in Scheme 12, our hypothesis was that a facile 1,2-*H* shift could occur to allow equilibration between carbocationic intermediates **61a** and **61b**, which may be followed by a third cyclization to afford tricycle **64**. Unfortunately, when ynamide **59** was heated to 135 °C in toluene, only bicycle **62** resulting from elimination of **61a** and tricycle **63** resulting from a formal [4 + 2] cycloaddition could be found.

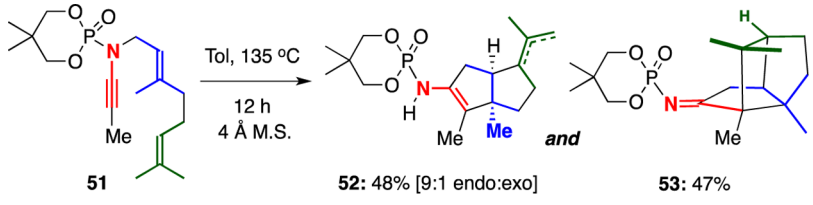
CONCLUSIONS

We have described here a fascinating study of Pd-catalyzed and thermal carbocyclizations of *N*-sulfonyl and *N*-phosphoryl ynamides to prepare *α,β*-unsaturated cyclopentenimines. In the case of *N*-sulfonyl ynamides, the use of palladium catalysis is necessary, as the carbocyclization occurs through Pd-*π*-allyl complexes via a Rautenstrach rearrangement; with *N*-phosphoryl ynamides, thermal conditions may be employed to yield cyclopentenimines via *N*-promoted 1,2-*H* shifts through zwitter ionic intermediates. We also demonstrated the ability to intercept the zwitter ionic intermediates with tethered alkenyl and aryl nucleophiles to prepare a variety of fused bicyclic and tricyclic scaffolds.

EXPERIMENTAL SECTION

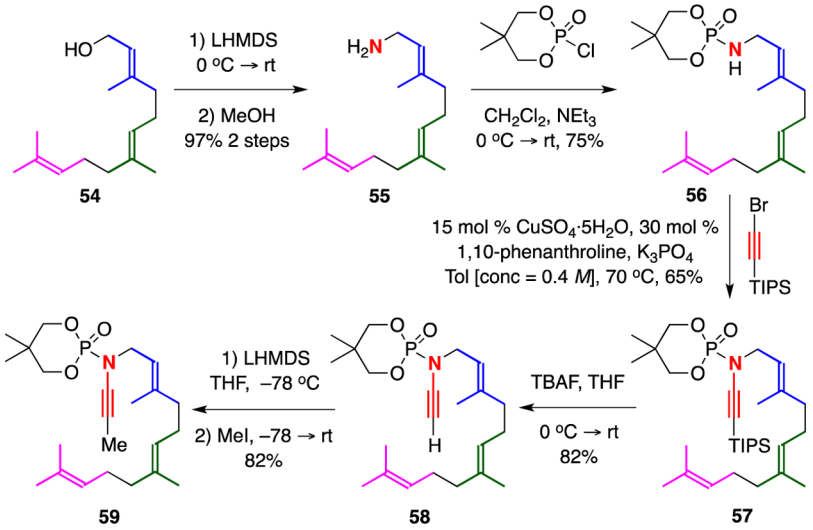
All reactions were performed in flame-dried glassware under a nitrogen atmosphere. Solvents were distilled prior to use. Chromatographic separations were performed using 60 Å SiO_2. ^1H and ^{13}C NMR spectra were obtained on spectrometers using $CDCl_3$ with TMS or residual solvent as standard unless otherwise noted. Infrared spectra were obtained on FTIR, and relative intensities are expressed qualitatively as s (strong), m (medium), and w (weak). TLC analysis was performed using 254 nm polyester-backed plates (60 Å, 250 μm) and visualized using UV and a suitable chemical stain. Low-resolution mass spectra were obtained using LC/MSD and APCI.

Scheme 10. Carbocyclization Cascade of Geranyl-Tethered Ynamides

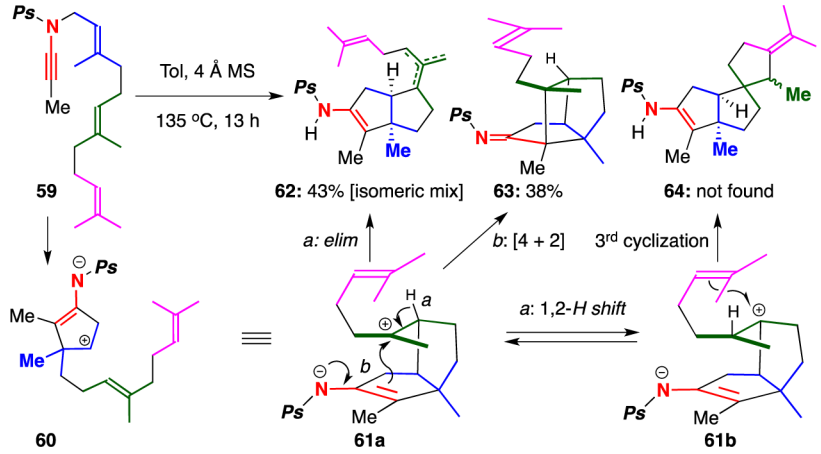


dx.doi.org/10.1021/jo400960e | J. Org. Chem. 2013, 78, 6233–6244

Scheme 11. Synthesis of a Farnesyl Tethered Ynamide



Scheme 12. Attempted Carbocyclization Cascade of Farnesol-Tethered Ynamide 59



General Procedure for the Preparation of γ-Hydroxy-ynamides. To a flame-dried 50-mL RB-flask was added ynamide **11** (470.0 mg, 2.00 mmol) and THF (20 mL). The solution was cooled to −78 °C [− 50 °C works equally well], and LHMDS (3.0 mL, 3.0 mmol, 1 M in THF) was added dropwise over ∼1 min. The reaction mixture was stirred at −78 °C [or −50 °C] for 1 h to ensure complete lithiation of the ynamide, and then pivalyl aldehyde was added dropwise over ∼1 min. After 20 min, the cooling bath was removed, and the reaction was allowed to come to rt. The reaction was monitered by TLC, and when progress appeared to be complete after ∼2 h, the mixture was diluted with EtOAc (20 mL) and quenched with water (15 mL). The phases were separated, and the aqueous phase extracted with EtOAc (20 mL) once. The organic phases were combined, washed with brine, dried over Na_2SO_4, and concentrated by rotary evaporation. The crude residue was purified by flash silica gel column chromatography (isocratic eluent: 4:1 hexanes/EtOAc + 2% NEt_3 [to buffer the column]) to afford the γ-hydroxy-ynamide **12a** (656.0 mg, 2.00 mmol, ≥95%) as a colorless oil.

12a: (656.0 mg, ≥95%); R_f = 0.27 [3:1 hexanes:EtOAc]; colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.95 (s, 9H), 2.45 (s, 3H), 3.96 (dq, 2H, *J* = 1.5, 6.5 Hz), 4.11 (brs, 1H), 5.21 (dq, 1H, *J* = 1.5, 10.0 Hz), 5.24 (dq, 1H, *J* = 1.5, 17.0 Hz), 5.72 (ddt, *J* = 6.5, 10.0, 17.0 Hz), 7.34 (d, 2H, *J* = 8.0 Hz), 7.79 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 25.6, 36.4, 54.3, 71.0, 71.7, 78.1, 120.2, 127.9, 129.9, 131.1, 134.9, 144.9; IR (film) cm^{-1} 3519brm, 2956m, 2869w, 2244m, 1597m, 1478m, 1462m, 1362s; mass spectrum (ESI) *m*/*e* (% relative intensity) 336 (100) $(M - H_2O + MeOH + H)^+$; HRMS (QTOF MS ESI) *m*/*e* calcd for $C_{17}H_{23}NO_3SNa$ $[M + Na]^+$ 344.1291, found 344.1307.

12b: (413.2 mg, 79%); (R_f = 0.28 [3:1 hexanes:EtOAc]; pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, 3H, *J* = 6.8 Hz), 1.23−1.42 (m, 8H), 1.59−1.73 (m, 2H), 1.87 (brs, 1H), 2.45 (s, 3H), 3.95 (ddt, 1H, *J* = 1.2, 6.4, 14.4 Hz), 4.01 (ddt, 1H, *J* = 1.2, 6.4, 14.4 Hz), 4.48 (t, 1H, *J* = 6.8 Hz), 5.22 (dq, 1H, *J* = 1.6, 10.0 Hz), 5.26 (dq, 1H, *J* = 1.6, 16.4 Hz), 5.77 (ddt, 1H, *J* = 6.4, 10.0, 16.4 Hz), 7.35 (d, 2H, *J* = 8.4 Hz), 7.80 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 21.8, 22.7, 25.3, 29.1, 31.9, 38.0, 54.3, 62.8, 72.4, 78.2, 120.2, 127.9, 129.9, 131.0, 134.8, 144.8; IR (film) cm^{-1} 3376brm, 2925m, 2857m, 2243m, 1597m, 1494w, 1466m, 1419m, 1364s; mass spectrum (ESI) *m*/*e* (% relative intensity) 364 (100) $(M - H_2O + MeOH + H)^+$; HRMS (QTOF MS ESI) *m*/*e* calcd for $C_{19}H_{27}NO_3SNa$ 372.1604, found 372.1612.

12c: (211.0 mg, 81%); R_f = 0.21 [3:1 hexanes/EtOAc]; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97−1.33 (m, 6H), 1.64−1.83 (m, 5H), 2.45 (s, 3H), 3.94 (ddt, 1H, *J* = 1.2, 5.6, 14.0 Hz), 3.99 (ddt, 1H, *J* = 1.2, 5.6, 14.0 Hz), 4.26 (d, 1H, *J* = 4.0 Hz), 5.21 (dq, 1H, *J* = 1.4, 7.2 Hz), 5.25 (dq, 1H, *J* = 1.4, 14.0 Hz), 5.73 (ddt, 1H, *J* = 6.4, 10.4, 16.8 Hz), 7.34 (d, 2H, *J* = 8.4 Hz), 7.79 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 26.0, 26.1, 26.5, 28.2, 28.8, 44.5, 54.3, 67.5, 71.4, 78.9, 120.2, 127.9, 129.9, 131.1, 134.8, 144.9; IR (film) cm^{-1} 2925m, 2853m, 2244m, 1597w, 1364s; mass spectrum (ESI) *m*/*e* (% relative intensity) 362 (100) $(M - H_2O + MeOH + H)^+$. HRMS (TOF MS ESI) *m*/*e* calcd for $C_{19}H_{26}NO_3S$ $[M + H]^+$ 348.1628, found 348.1639.

dx.doi.org/10.1021/jo400960e | J. Org. Chem. 2013, 78, 6233−6244

12d: (184.0 mg, 65%); R_f = 0.30 [3:1 hexanes/EtOAc]; orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97−1.30 (m, 4H), 1.50−1.57 (m, 2H), 1.66−1.84 (m, 5H), 4.02 (ddt, 1H, J = 1.2, 6.4, 14.4 Hz), 4.07 (ddt, 1H, J = 1.2, 6.4, 14.4 Hz), 4.28 (t, 1H, J = 5.6 Hz), 5.25 (dq, 1H, J = 1.2, 10.4 Hz), 5.28 (dq, 1H, J = 1.2, 16.8 Hz), 5.72 (ddt, 1H, J = 6.4, 10.4, 16.8 Hz), 8.10 (d, 2H, J = 9.2 Hz), 8.40 (d, 2H, J = 9.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.9, 26.0, 26.5, 28.2, 28.7, 44.4, 54.7, 67.3, 72.1, 77.6, 120.9, 124.5, 129.1, 130.3, 143.2, 150.8; IR (film) cm^{-1} 3401brm, 2928m, 2854m, 2247m, 1532s, 1372s; mass spectrum (APCI) m/e (% relative intensity) 393 (100) (M − H_2O + MeOH + H)$^+$.

12e: (55.4 mg, 58%); R_f = 0.25 [3:1 hexanes/EtOAc]; pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, 3H, J = 7.2 Hz), 1.22−1.44 (m, 8H), 1.61−1.76 (m, 2H), 1.80 (brs, 1H), 4.01 (ddt, 1H, J = 1.2, 6.4, 14.8 Hz), 4.05 (ddt, 1H, J = 1.2, 6.4, 14.8 Hz), 4.49 (t, 1H, J = 6.4 Hz), 5.24 (dq, 1H, J = 1.2, 10.4 Hz), 5.27 (dq, 1H, J = 1.2, 16.8 Hz), 5.72 (ddt, 1H, J = 6.4, 10.4, 16.8 Hz), 8.10 (d, 2H, J = 9.2 Hz), 8.41 (d, 2H, 9.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 22.8, 25.4, 29.1, 32.0, 38.1, 54.8, 62.7, 73.3, 77.0, 121.0, 124.6, 129.2, 130.3, 143.2, 150.9; IR (film) cm^{-1} 3379brm, 2928m, 2858m, 2246m, 1607s, 1348s; mass spectrum (APCI) m/e (% relative intensity) 395 (100) (M − H_2O + MeOH + H)$^+$; HRMS (QTOF MS ESI) m/e calcd for $C_{18}H_{24}N_2O_5SNa$ 403.1298, found 403.1292.

12f: (507.9 mg, ≥95%); R_f = 0.38 [4:1 hexanes/EtOAc]; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06−1.16 (m, 1H), 1.30−1.59 (m, 7H), 1.80 (d, 2H, J = 12.4 Hz), 2.36 (s, 3H), 3.10 (s, 1H), 3.86 (d, 2H, J = 6.4 Hz), 5.09−5.17 (m, 2H), 5.58−5.68 (m, 1H), 7.27 (d, 2H, J = 8.0 Hz), 7.72 (d, 2H, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 23.0, 24.9, 39.7, 53.8, 68.5, 74.1, 77.2, 119.7, 127.5, 129.5, 130.6, 134.2, 144.5; IR (film) cm^{-1} 3496w, 3399w, 2933s, 2857m, 2242m, 1597w, 1447w, 1362s; mass spectrum (APCI) m/e (% relative intensity) 334 (24) (M + H)$^+$.

General Procedure for the Silylation of γ-Hydroxy-ynamides. To a flame-dried screw-cap vial was added ynamide **12a** (64.8 mg, 0.20 mmol) and CH_2Cl_2 (0.57 mL, 0.35 M in ynamide). The solution was cooled to 0 °C, and then imidazole (34.0 mg, 0.50 mmol) and TBSCl (37.5 mg, 0.25 mmol) were added. The reaction mixture was allowed to warm to rt. The reaction was monitered by TLC, and when the starting material was consumed after ∼45 min, the mixture was diluted with CH_2Cl_2 (3 mL) and quenched with water (3 mL). The phases were separated and the aqueous phase extracted with CH_2Cl_2 (3 × 5 mL). The organic phases were combined, washed with brine, dried over Na_2SO_4, and concentrated by rotary evaporation. The crude residue was purified by flash silica gel column chromatography (isocratic eluent: 15:1 hexanes/EtOAc + 2% NEt_3 [to buffer the column]) to afford ynamide **13a** (78.0 mg, 0.18 mmol, 89%).

13a: (78.0 mg, 89%); R_f = 0.48 [8:1 hexanes:EtOAc]; pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.04 (s, 3H), 0.86 (s, 9H), 0.91 (s, 9H), 2.44 (s, 3H), 3.97 (d, 2H, J = 6.4 Hz), 4.03 (s, 1H), 5.21 (dd, 1H, J = 1.2, 10.0 Hz), 5.25 (dd, 1H, J = 1.2, 16.8 Hz), 5.77 (ddt, 1H, J = 6.4, 10.0, 16.8 Hz), 7.33 (d, 2H, J = 8.0 Hz), 7.80 (d, 2H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.2, −4.3, 18.3, 21.7, 25.7, 25.9, 37.0, 54.4, 71.5, 71.9, 77.7, 120.0, 127.9, 129.8, 131.3, 135.2, 144.6; IR (film) cm^{-1} 2954m, 2929m, 2856m, 2243w, 1598w, 1462m, 1367s, 1292w, 1250m; mass spectrum (ESI) m/e (% relative intensity) 336 (100) (M − OTBS + MeOH + H)$^+$.

General Procedure for the Alkylation of γ-Hydroxy-ynamides. To a flame-dried screw-cap vial was added ynamide **12a** (96.0 mg, 0.30 mmol) and THF (1.0 mL, 0.3 M in ynamide). The solution was cooled to 0 °C, and NaH (16.0 mg, 0.39 mmol, 60% dispersion in mineral oil) was added carefully. The reaction mixture was stirred at 0 °C for 30 min to ensure complete deprotonation of the alcohol, and then MeI (24.0 μL, 0.78 mmol) was added dropwise over ∼1 min. After 30 min, the cooling bath was removed, and the reaction was allowed to come to rt. The reaction was monitered by TLC, and when progress appeared to be complete after ∼2 h, the mixture was diluted with EtOAc (3 mL) and quenched with water (3 mL). The phases were separated, and the aqueous phase extracted with EtOAc (10 mL) once. The organic phases were combined, washed with brine, dried over Na_2SO_4, and concentrated by rotary evaporation. The crude residue was purified by flash silica gel column chromatography (isocratic eluent: 15:1 hexanes/EtOAc + 2% NEt_3 [to buffer the column]) to afford ynamide **13b** (86.0 mg, 0.256 mmol, 86%). *Note: For displacement of alkyl bromides, DMF was used as the solvent. During workup, the organic phase was washed with brine 5 times to remove DMF.*

13b: (86.0 mg, 86%); R_f = 0.16 [15:1 hexanes/EtOAc]; colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (s, 9H), 2.45 (s, 3H), 3.31 (s, 3H), 3.63 (s, 1H), 3.94 (ddt, 1H, J = 1.0, 6.5, 14.5 Hz), 4.01 (ddt, 1H, J = 1.0, 6.5, 14.5 Hz), 5.21 (dq, 1H, J = 1.0, 10.0 Hz), 5.24 (dq, 1H, J = 1.0, 17.0 Hz), 5.74 (ddt, 1H, J = 6.5, 10.0, 17.0 Hz), 7.33 (d, 2H, J = 8.0 Hz), 7.79 (d, 2H, J = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.9, 26.1, 36.0, 54.5, 57.3, 68.9, 79.5, 81.1, 120.2, 128.0, 129.9, 131.3, 135.0, 144.9; IR (film) cm^{-1} 2956m, 2926m, 2820w, 2240m, 1597w, 1366s; mass spectrum (APCI) m/e (% relative intensity) 336 (100) (M + H)$^+$; HRMS (QTOF MS ESI) m/e calcd for $C_{18}H_{25}NO_3SNa$ [M + Na]$^+$ 358.1447, found 358.1447.

Ynamide **13c** was prepared from **12a** following the general procedure for alkylation.

13c: (98.0 mg, 79%); R_f = 0.17 [15:1 hexanes/EtOAc]; colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (s, 9H), 2.41 (s, 3H), 3.78 (s, 1H), 3.95 (ddt, 1H, J = 1.0, 6.5, 14.5 Hz), 4.01 (ddt, 1H, J = 1.0, 6.5, 14.5 Hz), 4.38 (d, 1H, J = 12.0 Hz), 4.68 (d, 1H, J = 12.0 Hz), 5.22 (dq, 1H, J = 1.0, 10.0 Hz), 5.25 (dq, 1H, J = 1.0, 17.0 Hz), 5.74 (ddt, 1H, J = 6.5, 10.0, 17.0 Hz), 7.24−7.34 (m, 5H), 7.28 (d, 2H, J = 8.0 Hz), 7.79 (d, 2H, J = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.8, 26.2, 36.0, 54.5, 69.1, 70.7, 77.9, 79.6, 120.3, 127.6, 127.9, 128.0, 128.4, 129.9, 131.3, 135.0, 138.7, 144.9; IR (film) cm^{-1} 2956m, 2867m, 2241m, 1597w, 1495w, 1365s; mass spectrum (APCI) m/e (% relative intensity) 336 (100) (M − HOBn + MeOH + H)$^+$, 412 (20) (M + H)$^+$; HRMS (QTOF MS ESI) m/e calcd for $C_{24}H_{29}NO_3SNa$ [M + Na]$^+$ 434.1760, found 434.1759.

Ynamide **14a** was prepared from **12b** following the general procedure for alkylation.

14a: (70.0 mg, 96%); R_f = 0.41 [4:1 hexanes/EtOAc]; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, 3H, J = 6.8 Hz), 1.21−1.34 (m, 6H), 1.34−1.43 (m, 2H), 1.58−1.74 (m, 2H), 2.45 (s, 3H), 3.30 (s, 3H), 3.93 (ddt, 1H, J = 1.2, 6.4, 14.4 Hz), 4.01 (ddt, 1H, J = 1.2, 6.4, 14.4 Hz), 4.04 (t, 1H, J = 6.4 Hz), 5.20 (dq, 1H, J = 1.2, 10.0 Hz), 5.24 (dq, 1H, J = 1.2, 16.4 Hz), 5.73 (ddt, 1H, J = 6.4, 10.0, 16.4 Hz), 7.34 (d, 2H, J = 8.4 Hz), 7.79 (d, 2H, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 21.9, 22.8, 25.5, 29.2, 32.0, 36.0, 54.4, 56.3, 70.1, 71.7, 79.1, 120.2, 128.0, 129.9, 131.1, 134.9, 144.9; IR (film) cm^{-1} 2926m, 2858m, 2240m, 1465w, 1367s; mass spectrum (APCI) m/e (% relative intensity) 364 (100) (M + H)$^+$.

Ynamide **14b** was prepared from **12b** following the general procedure for silylation.

14b: (101.0 mg, ≥95%); R_f = 0.56 [4:1 hexanes/EtOAc]; colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, 3H, J = 7.0 Hz), 1.03 (d, 18H, J = 5.0 Hz), 1.05−1.07 (m, 3H), 1.24−1.34 (m, 7H), 1.34−1.47 (m, 3H), 1.66 (td, 2H, J = 6.0, 8.0 Hz), 2.44 (s, 3H), 3.94 (ddt, 1H, J = 1.5, 5.5, 14.0 Hz), 3.98 (ddt, 1H, J = 1.5, 5.5, 14.0 Hz), 4.56 (t, 1H, J = 6.0 Hz), 5.18 (dq, 1H, J = 1.0, 10.0 Hz), 5.22 (dq, 1H, J = 1.0, 17.0 Hz), 5.73 (ddt, 1H, J = 6.5, 10.0, 17.0 Hz), 7.31 (d, 2H, J = 8.0 Hz), 7.77 (d, 2H, J = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.5, 14.4, 18.0, 18.3, 18.3, 21.9, 22.9, 25.2, 29.3, 32.1, 39.4, 54.5, 63.5, 73.0, 119.9, 128.0, 129.9, 131.4, 135.2, 144.7; IR (film) cm^{-1} 2941s, 2864s, 2242m, 1597w, 1463m, 1369s; mass spectrum (APCI) m/e (% relative intensity) 364 (100) (M − HOTIPS + MeOH + H)$^+$.

Ynamide **15a** was prepared from **12c** following the general procedure for alkylation.

15a: (60.0 mg, 79%); R_f = 0.11 [15:1 hexanes/EtOAc]; colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.03−1.26 (m, 5H), 1.58 (tdt, 1H, J = 3.0, 6.0, 12.0 Hz), 1.65 (d, 1H, J = 12.0 Hz, 1H), 1.74 (t, 4H, J = 14.0 Hz), 2.45 (s, 3H), 3.29 (s, 3H), 3.83 (d, 1H, J = 6.0 Hz), 3.94 (dd, 1H, J = 6.5, 14.5 Hz), 4.02 (dd, J = 6.5, 14.5 Hz), 5.22 (dq, 1H, J = 1.0, 10.0 Hz), 5.25 (dq, 1H, J = 1.0, 17.0 Hz), 5.74 (ddt, 1H, J = 6.5, 10.0, 17.0 Hz), 7.33 (d, 2H, J = 8.0 Hz), 7.79 (d, 2H, J = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.9, 26.2, 26.2, 26.7, 28.6, 29.2, 43.0, 54.5, 56.6, 69.1, 76.7, 79.7, 120.2, 128.0, 129.9, 131.2, 134.9, 144.9; IR

dx.doi.org/10.1021/jo400960e | J. Org. Chem. 2013, 78, 6233−6244

(film) cm^{-1} 2924m, 2853m, 2239m, 1449m, 1367s; mass spectrum (APCI) *m/e* (% relative intensity) 362 $(M + H)^+$.

Ynamide **15b** was prepared from **12c** following the general procedure for alkylation.

15b: (72.0 mg, 63%); R_f = 0.49 [3:1 hexanes/EtOAc]; white solid; mp = 62−64 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80−1.28 (m, 5H), 1.56−1.84 (m, 6H), 2.42 (s, 3H), 3.95 (ddt, 1H, J = 1.2, 6.4, 14.4 Hz), 3.96 (d, 1H, J = 6.2 Hz), 4.03 (ddt, 1H, J = 1.2, 6.4, 14.4 Hz), 4.53 (ABq, 2H, $\Delta\nu_{AB}$ = 33.6 Hz, J_{AB} = 11.8 Hz), 5.23 (dq, 1H, J = 1.2, 10.0 Hz), 5.26 (dq, 1H, J = 1.2, 17.2 Hz), 5.76 (ddt, 1H, J = 6.4, 10.0, 17.2 Hz), 7.24−7.35 (m, 7H), 7.80 (d, 2H, J = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 26.1, 26.1, 26.6, 28.7, 29.2, 43.0, 54.4, 69.3, 70.3, 73.9, 79.7, 120.2, 127.6, 127.9, 128.0, 128.4, 129.8, 131.2, 134.8, 138.4, 144.8; IR (film) cm^{-1} 2925m, 2852m, 2243m, 1597w, 1451m, 1363s; mass spectrum (APCI) *m/e* (% relative intensity) 362 (100) (M − BnOH + MeOH + H)$^+$.

Ynamide **16a** was prepared from **12d** following the general procedure for silylation.

16a: (81.0 mg, 82%); R_f = 0.57 [3:1 hexanes/EtOAc]; white solid; mp = 61−62 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 3H), 0.03 (s, 3H), 0.85 (s, 9H), 0.90−1.30 (m, 6H), 1.45 (dtt, 1H, J = 2.8, 6.2, 18.0 Hz), 1.61−1.79 (m, 4H), 4.00 (ddt, 1H, J = 1.2, 6.2, 14.8 Hz), 4.04 (ddt, 1H, J = 1.2, 6.2, 14.8 Hz), 4.18 (d, 1H, J = 6.0 Hz), 5.22 (dq, 1H, J = 1.2, 10.4 Hz), 5.25 (dq, 1H, J = 1.2, 16.8 Hz), 5.70 (ddt, 1H, J = 6.4, 10.0, 16.8 Hz), 8.08 (d, 2H, J = 9.2 Hz), 8.37 (d, 2H, J = 9.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.0, −4.4, 18.3, 25.8, 26.1, 26.1, 26.6, 28.7, 28.7, 45.3, 54.8, 67.8, 72.8, 76.5, 120.8, 124.4, 129.2, 130.5, 143.5, 150.7; IR (film) cm^{-1} 2929m, 2855m, 2248m, 1535s, 1376m, 1349m; mass spectrum (APCI) *m/e* (% relative intensity) 393 (100) (M − HOTBS + MeOH + H)$^+$; HRMS (QTOF MS ESI) *m/e* calcd for $C_{24}H_{36}N_2O_5SSiNa$ $[M + Na]^+$ 515.2006, found 515.1992.

Ynamide **16b** was prepared from **12d** following the general procedure for silylation, but with Ph_3C−Cl (1.3 equiv), NEt_3 (2 equiv), and DMAP (0.1 equiv) in CH_2Cl_2.

16b: (89.0 mg, 55%); R_f = 0.51 [3:1 hexanes/EtOAc]; yellow foam; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.09−1.19 (m, 6H), 1.43 (d, 1H, J = 10.0 Hz), 1.63 (t, 2H, J = 8.0 Hz), 1.72 (d, 1H, J = 6.5 Hz), 1.86 (d, 1H, J = 10.0 Hz), 3.70 (dd, 1H, J = 6.5, 15.0 Hz), 3.79 (d, 1H, J = 3.5 Hz), 3.88 (dd, 1H, J = 6.5, 15.0 Hz), 5.16 (d, 1H, J = 16.5 Hz), 5.18 (d, 1H, J = 10.0 Hz), 5.53 (ddt, 1H, J = 6.5, 10.0, 16.5 Hz), 7.11−7.31 (m, 9H), 7.47 (d, 6H, J = 8.0 Hz), 8.00 (d, 2H, J = 9.0 Hz), 8.34 (d, 2H, J = 9.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.3, 26.3, 26.8, 28.0, 29.3, 43.6, 54.6, 69.3, 71.5, 78.3, 87.5, 120.3, 124.5, 126.9, 127.2, 127.5, 127.8, 128.2, 128.2, 128.5, 128.6, 129.2, 129.2, 129.7, 130.8, 143.7, 144.9, 147.1, 150.7; IR (film) cm^{-1} 3059w, 3031w, 2930m, 2853m, 2246m, 1717m, 1605m, 1531s, 1491m, 1447m, 1348s; mass spectrum (APCI) *m/e* (% relative intensity) 293 (100) (*p*-Ns-allylamine+H)$^+$, 393 (10) (M − $HOCPh_3$ + MeOH + H)$^+$.

Ynamide **17** was prepared from **12e** following the general procedure for silylation.

17: (88.4 mg, 90%); R_f = 0.36 [8:1 hexanes/EtOAc]; colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.05 (s, 3H), 0.87 (s, 9H), 1.22−1.41 (m, 10H), 1.57−1.69 (m, 3H), 4.01 (ddt, 1H, J = 1.0, 6.5, 14.5 Hz), 4.05 (ddt, 1H, J = 1.0, 6.5, 14.5 Hz), 4.44 (t, 1H, J = 6.5 Hz), 5.23 (dq, 1H, 1.0, 10.0 Hz), 5.26 (dq, 1H, J = 1.0, 17.0 Hz), 5.71 (ddt, 1H, J = 6.5, 10.0, 17.0 Hz), 8.09 (d, 2H, J = 9.0 Hz), 8.38 (d, 1H, J = 9.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.8, −4.3, 14.3, 18.4, 22.8, 25.5, 26.0, 29.2, 32.1, 39.0, 54.9, 63.3, 73.8, 76.1, 120.9, 124.5, 129.2, 130.5, 143.5, 150.8; IR (film) cm^{-1} 2954m, 2928m, 2857m, 2245m, 1606w, 1534s, 1377m, 1348s; mass spectrum (APCI) *m/e* (% relative intensity) 395 (100) (M − HOTBS + MeOH + H)$^+$; HRMS (QTOF MS ESI) *m/e* calcd for $C_{24}H_{38}N_2O_5SSiNa$ $[M + Na]^+$ 517.2163, found 517.2158.

Ynamide **18** was prepared from **12f** following the general procedure for alkylation.

18: (596.6 mg, ≥95%); R_f = 0.38 [6:1 hexanes/EtOAc]; white solid; mp = 50−51 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23−1.28 (m, 1H), 1.39−1.54 (m, 5H), 1.59−1.63 (m, 2H), 1.84−1.88 (m, 2H), 2.45 (s, 3H), 3.26 (s, 3H), 3.97 (dt, 2H, J = 6.4, 1.2 Hz), 5.19−5.26 (m, 2H), 5.68−5.77 (m, 1H), 7.34 (d, 2H, J = 8.0 Hz), 7.79 (d, 2H, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 22.8, 25.4, 36.8, 50.5, 54.1, 71.4, 74.3, 79.3, 119.9, 127.8, 129.6, 130.9, 134.5, 144.6; IR (film) cm^{-1} 2934s, 2857w, 2360w, 2341w, 2240m, 1447m, 1366s; mass spectrum (APCI) *m/e* (% relative intensity) 348 (43) $(M + H)^+$; HRMS (QTOF MS ESI) calcd for $C_{19}H_{25}NO_3SNa$ $[M + Na]^+$ 370.1447, found 370.1450.

General Procedure for the Carbocyclization of γ-Branched-*N*-Allyl Ynamides. To a flame-dried screw-cap vial containing 4 Å MS was added ynamide **6** (50.0 mg, 0.100 mmol), $Pd(PPh_3)_4$ (5.8 mg, 0.005 mmol), and toluene (2.5 mL, 0.04 M in ynamide). The vial was sealed under nitrogen and heated to 70 °C for 1 h, at which time TLC analysis showed consumption of the starting material. The reaction mixture was cooled to rt, filtered through Celite and purified by flash silica gel column chromatography (isocratic eluent: 8:1 hexanes/EtOAc) to afford cyclopentenimine **8** (34.5 mg, 0.069 mmol) in 69% yield.

8: (34.5 mg, 69%); R_f = 0.11 [8:1 hexanes/EtOAc]; colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (d, 9H, J = 7.0 Hz), 0.94 (d, 9H, J = 7.0 Hz), 1.01 (sept, 3H, J = 7.0 Hz), 2.44 (s, 3H), 2.63 (ddt, 1H, J = 2.5, 6.0, 20.5 Hz), 2.73 (ddt, 1H, J = 2.5, 6.0, 20.5 Hz), 3.06 (ddd, 1H, J = 1.5, 6.0, 20.5 Hz), 3.20 (ddd, 1H, J = 1.5, 6.0, 20.5 Hz), 5.57 (s, 1H), 7.15 (dd, 2H, J = 2.0, 5.0 Hz), 7.29 (d, 2H, J = 8.0 Hz), 7.30−7.32 (m, 3H), 7.57 (td, 1H, J = 1.5, 2.5 Hz), 7.75 (d, 2H, J = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.3, 18.1, 18.2, 21.8, 30.9, 33.2, 70.0, 126.7, 127.2, 127.4, 128.0, 129.5, 138.5, 143.1, 143.5, 151.4, 157.2, 189.4; IR (film) cm^{-1} 2942m, 2865m, 1591s, 1461m, 1317s; mass spectrum (APCI) *m/e* (% relative intensity) 498 (100) $(M + H)^+$.

19a: (54.1 mg, 71%); R_f = 0.26 [8:1 hexanes:EtOAc]; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.24 (s, 3H), −0.04 (s, 3H), 0.78 (s, 9H), 0.84 (s, 9H), 2.43 (s, 3H), 2.70−2.73 (m, 2H), 3.11 (ddd, 1H, J = 2.4, 5.6, 20.4 Hz), 3.29 (ddd, 1H, J = 2.4, 5.6, 20.4 Hz), 4.27 (s, 1H), 7.31 (d, 2H, J = 8.0 Hz), 7.38 (t, 1H, J = 2.4 Hz), 7.84 (d, 2H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.2, −4.5, 18.1, 21.7, 25.7, 25.9, 30.9, 32.4, 36.3, 72.9, 127.1, 129.4, 138.4, 143.4, 149.5, 160.4, 190.9; IR (film) cm^{-1} 2954m, 2928m, 2857w, 1587s, 1471m, 1438m, 1389m, 1304m; mass spectrum (ESI) *m/e* (% relative intensity) 436 (100) $(M + H)^+$; HRMS (QTOF MS ESI) calcd for $C_{23}H_{37}NO_3SSiNa$ $[M + Na]^+$ 458.2156, found 458.2165.

19b: (49.4 mg, 77%); R_f = 0.25 [4:1 hexanes/EtOAc]; white solid, mp = 113−114 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.79 (s, 9H), 2.43 (s, 3H), 2.78 (dq, 2H, J = 3.0, 5.0 Hz), 3.12 (dddd, 1H, J = 1.0, 3.0, 5.0, 21.0 Hz), 3.14 (s, 3H), 3.35 (dddd, 1H, J = 1.0, 3.0, 5.0, 21.0 Hz), 3.82 (s, 1H), 7.31 (d, 2H, J = 8.5 Hz), 7.35 (t, 1H, J = 3.0 Hz, 1H), 7.84 (d, 2H, J = 8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.8, 25.9, 31.1, 32.7, 35.8, 57.8, 82.6, 127.2, 129.6, 138.5, 143.6, 146.3, 160.1, 192.2; IR (film) cm^{-1} 2955m, 2870m, 1586s, 1315s; mass spectrum (APCI) *m/e* (% relative intensity) 336 (100) $(M + H)^+$; HRMS (QTOF MS ESI) calcd for $C_{18}H_{26}NO_3S$ $[M + H]^+$ 336.1628, found 336.1637.

19c: (65.9 mg, 84%); R_f = 0.31 [4:1 hexanes/EtOAc]; pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (s, 9H), 2.44 (s, 3H), 2.67−2.78 (m, 2H), 3.11 (ddd, 1H, J = 2.8, 5.6, 20.4 Hz), 3.31 (ddd, 1H, J = 2.8, 5.6, 20.4 Hz), 4.05 (s, 1H), 7.22−7.29 (m, 5H), 4.29 (ABq, 2H, $\Delta\nu_{AB}$ = 18.5 Hz, J_{AB} = 11.8 Hz), 7.31 (d, 2H, J = 8.0 Hz), 7.38 (td, 1H, J = 0.8, 2.8 Hz), 7.84 (d, 2H, J = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.8, 26.0, 31.1, 32.6, 35.9, 71.8, 80.2, 127.2, 127.6, 127.8, 128.4, 129.6, 138.5, 138.9, 143.6, 146.5, 160.5, 191.8; IR (film) cm^{-1} 2955m, 2867m, 1584s, 1364m, 1314s; mass spectrum (APCI) *m/e* (% relative intensity) 412 (100) $(M + H)^+$; HRMS (QTOF MS ESI) calcd for $C_{24}H_{29}NO_3SNa$ $[M + Na]^+$ 434.1760, found 434.1779.

20a: (48.3 mg, 70%); R_f = 0.17 [4:1 hexanes/EtOAc]; pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (t, 3H, J = 7.2 Hz), 1.18−1.26 (m, 8H), 1.43−1.63 (m, 2H), 2.43 (s, 3H), 2.72−2.76 (m, 2H), 3.20 (ddd, 1H, J = 2.8, 5.2, 20.4 Hz), 3.25 (s, 3H), 3.27 (ddd, 1H, J = 2.8, 5.2, 20.4 Hz), 4.03 (dddt, 1H, J = 1.8, 2.8, 4.4, 5.8 Hz), 7.31 (d, 2H, J = 8.0 Hz), 7.33 (td, 1H, J = 1.2, 2.8 Hz), 7.86 (d, 2H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 21.8, 22.8, 25.2, 29.3, 31.0, 31.9, 33.1, 34.8, 57.6, 76.2, 127.2, 129.6, 138.5, 143.6, 148.1, 157.6, 191.0; IR (film) cm^{-1} 2924m, 2864m, 1587s, 1464m, 1381m, 1316s; mass spectrum (APCI) *m/e* (% relative intensity) 364 (100) $(M + H)^+$;

dx.doi.org/10.1021/jo400960e | J. Org. Chem. 2013, 78, 6233−6244

HRMS (QTOF MS ESI) calcd for $C_{20}H_{29}NO_3SNa$ $[M + Na]^+$ 386.1760, found 386.1758.

20b: (92.0 mg, 92%); R_f = 0.43 [4:1 hexanes/EtOAc]; colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97 (d, 9H, J = 5.5 Hz), 0.99 (d, 9H, J = 4.5 Hz), 1.05 (s, 3H), 1.53−1.67 (m, 2H), 2.43 (s, 3H), 2.66−2.74 (m, 2H), 3.17 (dt, 1H, J = 4.0, 20.5 Hz), 3.23 (dt, 1H, J = 4.0, 20.5 Hz), 4.70 (td, 1H, J = 1.0, 5.0 Hz), 7.30 (d, 2H, J = 8.5 Hz), 7.42 (td, 1H, J = 1.0, 2.5 Hz), 7.83 (d, 2H, J = 8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.5, 14.3, 17.9, 18.3, 18.3, 21.8, 22.9, 23.8, 29.6, 30.8, 32.0, 33.2, 36.9, 67.5, 127.2, 129.6, 138.6, 143.5, 151.0, 158.6, 190.2; IR (film) cm^{-1} 2925m, 2865m, 1587s, 1463m, 1382m, 1317m; mass spectrum (APCI) m/e (% relative intensity) 506 (100) $(M + H)^+$; HRMS (QTOF MS ESI) calcd for $C_{28}H_{47}NO_3SSiNa$ $[M + Na]^+$ 528.2938, found 528.2949.

21a: (52.1 mg, 88%); R_f = 0.24 [3:1 hexanes/EtOAc]; pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87−0.97 (m, 1H), 1.00−1.18 (m, 4H), 1.43 (d, 1H, J = 12.0 Hz), 1.50 (tdt, J = 3.2, 5.6, 11.2 Hz), 1.55−1.73 (m, 4H), 2.44 (s, 3H), 2.75−2.78 (m, 2H), 3.17 (ddd, 1H, J = 3.2, 4.8, 20.4 Hz), 3.19 (s, 3H), 3.29 (ddd, 1H, J = 3.2, 4.8, 20.4 Hz), 3.88 (dd, 1H, J = 0.8, 5.6 Hz), 7.32 (d, 2H, J = 8.0 Hz), 7.85 (d, 2H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 26.3, 26.4, 26.6, 28.1, 29.2, 31.1, 33.0, 42.6, 57.9, 80.2, 127.2, 129.6, 138.5, 143.6, 146.8, 158.7, 191.5; IR (film) cm^{-1} 2925m, 2851m, 1586s, 1449m, 1314s; mass spectrum (APCI) m/e (% relative intensity) 362 (100) $(M + H)^+$; HRMS (QTOF MS ESI) calcd for $C_{20}H_{27}NO_3SNa$ $[M + Na]^+$ 384.1604, found 384.1615.

21b: (88.5 mg, ≥95%); R_f = 0.31 [3:1 hexanes/EtOAc]; pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80−1.18 (m, 5H), 1.41 (d, 1H, J = 10.0 Hz), 1.49−1.72 (m, 4H), 1.74 (d, 1H, J = 12.8 Hz), 2.44 (s, 3H), 2.70−2.76 (m, 2H), 3.17 (ddd, 1H, J = 3.6, 4.4, 20.4 Hz), 3.27 (ddd, 1H, J = 3.6, 4.4, 20.4 Hz), 4.09 (d, 1H, J = 5.2 Hz), 4.32 (ABq, 2H, $\Delta\nu_{AB}$ = 20.2 Hz, J_{AB} = 11.7 Hz), 7.22−7.29 (m, 5H), 7.31 (d, 2H, J = 8.4 Hz), 7.36 (t, 1H, J = 2.7 Hz), 7.85 (d, 2H, J = 8.4 Hz);^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 26.2, 26.4, 26.6, 28.3, 29.4, 31.1, 32.9, 42.8, 71.9, 77.9, 127.2, 127.7, 127.9, 128.5, 129.6, 138.5, 138.7, 143.6, 147.3, 159.2, 191.3; IR (film) cm^{-1} 2925m, 2852m, 1585s, 1451m, 1314s, 1302s; mass spectrum (APCI) m/e (% relative intensity) 438 (100) $(M + H)^+$; HRMS (QTOF MS ESI) calcd for $C_{26}H_{31}NO_3SNa$ $[M + Na]^+$ 460.1917, found 460.1919.

22a: (39.6 mg, 80%); R_f = 0.21 [8:1 hexanes/EtOAc]; white solid; mp = 137−140 °C [decomp]; ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.15 (s, 3H), −0.02 (s, 3H), 0.86 (s, 9H), 0.98−1.15 (m, 5H), 1.35−1.45 (m, 2H), 1.48 (d, 1H, J = 13.2 Hz), 1.54−1.73 (m, 3H), 2.72−2.82 (m, 2H), 3.23 (ddd, 1H, J = 3.2, 4.4, 20.4 Hz), 3.30 (ddd, 1H, J = 3.2, 4.4, 20.4 Hz), 4.27 (d, 1H, J = 2.9 Hz), 7.44 (td, 1H, J = 1.2, 2.8 Hz), 8.16 (d, 2H, J = 8.8 Hz), 8.38 (d, 2H, J = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9, −4.4, 18.3, 25.9, 26.3, 26.5, 26.6, 26.9, 29.9, 31.0, 33.7, 43.4, 71.2, 124.2, 126.5, 128.3, 133.6, 150.0, 161.1, 192.0; IR (film) cm^{-1} 2931m, 2855m, 1557s, 1384s, 1348s; mass spectrum (APCI) m/e (% relative intensity) 493 (100) $(M + H)^+$; HRMS (QTOF MS ESI) calcd for $C_{24}H_{36}N_2O_5SSiNa$ $[M + Na]^+$ 515.2006, found 515.2013.

22b: (73.4 mg, 83%); R_f = 0.26 [5:1 hexanes/EtOAc]; white solid; mp = 93−95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.43 (qd, 1H, J = 3.6, 12.4 Hz), 0.97 (qt, 1H, J = 3.2, 12.8 Hz), 1.12 (qt, 1H, J = 3.2, 12.8 Hz), 1.20−1.34 (m, 2H), 1.37 (d, 1H, J = 12.4 Hz), 1.54 (d, 1H, J = 12.4 Hz), 1.62 (d, 1H, J = 12.4 Hz) 1.78 (d, 1H, J = 12.8 Hz), 1.84 (ddt, 1H, J = 3.6, 12.0, 19.6 Hz), 2.01−2.13 (m, 2H), 2.43 (dd, 1H, J = 6.0, 19.6 Hz), 2.69 (dd, 1H, J = 6.0, 20.4 Hz), 2.87 (dd, 1H, J = 6.0, 20.4 Hz), 4.38 (d, 1H, J = 4.0 Hz), 7.03 (t, 1H, J = 3.6 Hz), 7.17−7.27 (m, 11H), 7.35−7.40 (m, 4H), 8.02 (d, 2H, J = 8.8 Hz), 8.30 (d, 2H, J = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.3, 26.6, 26.7, 26.8, 29.6, 31.1, 32.9, 44.3, 71.1, 87.3, 124.2, 127.3, 128.1, 128.3, 129.1, 144.6, 146.4, 147.3, 150.1, 162.9, 192.22; IR (film) cm^{-1} 3058w, 3032w, 2929m, 2853m, 1736m, 1576s, 1530s, 1448m, 1349s; mass spectrum (APCI) m/e (% relative intensity) 605 (100) $(M + H)^+$; HRMS (QTOF MS ESI) calcd for $C_{37}H_{36}N_2O_5SNa$ $[M + Na]^+$ 643.2237, found 643.2262.

23: (27.8 mg, 56%); R_f = 0.23 [6:1 hexanes/EtOAc]; pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.08 (s, 3H), 0.00, (s, 3H), 0.83 (t, 3H, J = 7.2 Hz), 0.87 (s, 9H), 1.12−1.29 (m, 8H), 1.41−1.61 (m, 2H), 2.55−2.92 (m, 3H), 3.21−3.35 (m, 2H), 4.44 (tdt, 1H, J = 1.6, 3.2, 5.2 Hz), 7.48 (td, 1H, J = 1.2, 3.2 Hz), 8.16 (d, 2H, J = 8.8 Hz), 8.37 (d, 2H, J = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.7, −4.5, 14.2, 18.3, 22.8, 24.8, 26.0, 29.3, 31.0, 31.9, 33.9, 36.9, 67.7, 124.3, 128.5, 147.1, 150.3, 151.0, 160.2, 191.8; IR (film) cm^{-1} 2954m, 2928m, 2857m, 1580s, 1531s, 1348s; mass spectrum (APCI) m/e (% relative intensity) 495 (100) $(M + H)^+$; HRMS (QTOF MS ESI) calcd for $C_{24}H_{38}N_2O_5SSiNa$ $[M + Na]^+$ 517.2173, found 517.2190.

24: (23.8 mg, 34%); R_f = 0.17 [6:1 hexane/EtOAc]; pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42−1.73 (m, 10H), 1.96 (td, 2H, J = 13.6, 4.8 Hz), 2.44 (s, 3H), 2.67−2.70 (m, 2H), 3.14 (s, 3H), 3.25−3.27 (m, 2H), 7.27−7.33 (m, 3H), 7.88 (d, 2H, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 21.5, 25.3, 29.9, 32.1, 33.5, 49.9, 76.5, 126.8, 129.4, 138.7, 143.2, 149.3, 159.2, 190.2; IR (film) cm^{-1} 2931s, 2856m, 1585s, 1448m, 1302s, 1153s; mass spectrum (APCI) m/e (% relative intensity) 348 (64) $(M + H)^+$; HRMS (QTOF MS ESI) calcd for $C_{19}H_{25}NO_3SNa$ $[M + Na]^+$ 370.1447, found 370.1452.

Preparations of Ynamides 30b, 30c, and 44. *Method A.* To a flame-dried screw-cap vial was added (in the following order) the appropriate phosphoramidate (309.0 mg, 1.50 mmol), CuTC (58.0 mg, 0.30 mmol), Cs_2CO_3 (976.0 mg, 3.00 mmol), dioxane (3.9 mL, 0.4 M in amide), (±)-*N*,*N*′-dimethyl-1,2-cyclohexanediamine (94.0 μL, 0.60 mmol), and the alkynyl bromide (369.0 mg, 1.95 mmol) under a nitrogen atmosphere. The vial was evacuated under a vacuum and flushed with nitrogen three times, and then sealed under nitrogen and heated to 60 °C. When the reaction was judged to be complete by TLC after 48 h, the mixture was cooled to rt, filtered through Celite, and purified by flash silica gel column chromatography (isocratic eluent: 2:1 hexanes/EtOAc + 2% NEt_3) to afford ynamide **30b** (373.0 mg, 1.19 mmol, 79%).

30b: (373.0 mg, 79%); R_f = 0.36 [1:1 hexanes/EtOAc]; pale yellow solid; mp = 47−49 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, 3H, J = 6.8 Hz), 1.05 (s, 3H), 1.16 (s, 3H), 1.24−1.31 (m, 5H), 1.37 (pent, 2H, J = 7.2 Hz), 1.47 (pent, 2H, J = 7.2 Hz), 2.22 (td, 2H, J = 3.2, 7.2 Hz), 3.87 (ddt, 2H, J = 1.6, 6.2, 9.2 Hz), 4.08 (dd, 2H, J = 11.2, 14.4 Hz), 4.21 (dd, 2H, J = 9.6, 11.2 Hz), 5.24 (dd, 1H, J = 1.6, 10.4 Hz), 5.31 (dq, 1H, J = 1.6, 17.2 Hz), 5.90 (ddt, 1H, J = 6.2, 10.4, 17.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 18.5, 21.4 (d, J = 11.3 Hz), 22.7, 28.6, 29.3, 31.5, 32.3 (d, J = 6.4 Hz), 53.4 (d, J = 6.3 Hz), 60.5, 65.2, 75.3, 77.9 (d, J = 6.4 Hz), 118.6, 133.0 (d, J = 1.5 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 0.63; IR (film) cm^{-1} 2929m, 2895m, 2855m, 2256m, 1469m, 1367m, 1255s; mass spectrum (APCI) m/e (% relative intensity) 314 (20) $(M + H)^+$, 346 (100) $(M + MeOH + H)^+$.

30a: (231.7 mg, 71%); R_f = 0.23 [1:1 hexanes:EtOAc]; pale yellow solid; mp = 108−109 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (s, 3H), 1.19 (s, 3H), 4.02 (ddt, 2H, J = 1.6, 6.2, 9.2 Hz), 4.14−4.22 (m, 4H), 5.30 (d, 1H, J = 10.4 Hz), 5.39 (dd, 1H, J = 1.6, 17.2 Hz), 5.97 (ddt, 1H, J = 6.2, 10.4, 17.2 Hz), 7.23−7.30 (m, 3H), 7.31−7.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 21.5, 32.5, 53.9 (d, J = 6.1 Hz), 66.3 (d, J = 5.7 Hz), 78.3 (d, J = 6.3 Hz), 85.3 (d, J = 4.1 Hz), 119.2, 123.7 (d, J = 2.1 Hz), 127.5, 128.5, 131.2 (d, J = 1.5 Hz), 132.8 (d, J = 1.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 1.01; IR (film) cm^{-1} 3081w, 2970w, 2896w, 2244s, 1370m, 1326m, 1254s; mass spectrum (ESI) m/e (% relative intensity) 306 (100) $(M + H)^+$;

30e: (86.3 mg, 57%); R_f = 0.17 [2:1 hexanes:EtOAc]; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (s, 18H), 1.06 (s, 3H), 1.08 (s, 3H), 1.14 (s, 3H), 3.93 (dd, 2H, J = 6.8, 8.8 Hz), 4.11−4.25 (m, 4H), 5.27 (d, 1H, J = 10.0 Hz), 5.35 (d, 1H, J = 16.8 Hz), 5.96 (ddt, 1H, J = 6.8, 10.0, 16.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.5, 18.7, 21.2, 21.4, 32.3 (d, J = 6.8 Hz), 53.8 (d, J = 6.1 Hz), 60.4, 63.4 (d, J = 4.6 Hz), 78.3 (d, J = 6.9 Hz), 99.5 (d, J = 3.8 Hz), 119.1, 132.3 (d, J = 1.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ −2.20; IR (film) cm^{-1} 2942m, 2865m, 2163m, 1740w, 1464m, 1373w, 1313m, 1277s; mass spectrum (APCI) m/e (% relative intensity) 386 (100) $(M + H)^+$.

Method B. To a flame-dried screw-cap vial was added (in the following order) the appropriate phosphoramidate (554.0 mg, 2.70 mmol), $CuSO_4 \cdot 5H_2O$ (103.0 mg, 0.41 mmol), 1,10-phenanthroline (145.8 mg, 0.81 mmol), K_3PO_4 (1.14 g, 5.40 mmol), toluene (6.8 mL, 0.4 M in amide), and the alkynyl bromide (1.02 g, 3.51 mmol) under a

dx.doi.org/10.1021/jo400960e | J. Org. Chem. 2013, 78, 6233−6244

nitrogen atmosphere. The vial was evacuated under a vacuum and flushed with nitrogen three times, and then sealed under nitrogen and heated to 60 °C. When the reaction was judged to be complete by TLC after 48 h, the mixture was cooled to rt, filtered through Celite, and purified by flash silica gel column chromatography (isocratic eluent: 2:1 hexanes/EtOAc + 2% NEt_3) to afford ynamide **30c** (253.1 mg, 0.61 mmol, 23%).

30c: (253.1 mg, 23%); R_f = 0.51 [3:1 hexanes/EtOAc]; brown solid; mp = 42−43 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.77 (s, 9H), 0.94 (s, 3H), 1.04 (s, 3H), 1.40−1.50 (m, 4H), 2.12−2.15 (m, 2H), 3.49 (t, 2H, J = 6.0 Hz), 3.74 (t, 2H, J = 7.6 Hz), 3.97 (dd, 2H, J = 12.4, 14.0 Hz), 4.07 (dd, 2H, J = 10.4 Hz), 5.11 (d, 1H, J = 10.4 Hz), 5.19 (dd, 1H, J = 1.6, 17.2 Hz), 5.72−5.82 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.6, 17.9, 18.0, 20.9, 21.0, 25.4, 25.7, 31.7, 31.8 (d, J = 6.1 Hz), 53.0 (d, J = 6.9 Hz), 62.3, 64.5 (d, J = 5.4 Hz), 75.1 (d, J = 4.5 Hz), 77,5 (d, J = 6.9 Hz), 118.1, 132.5 (d, J = 1.5 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 0.24; IR (film) cm^{-1} 2929m, 2858m, 2256w, 1472m, 1309w, 1255s; mass spectrum (APCI) m/e (% relative intensity) 416.3 (43) $(M + H)^+$; HRMS (QTOF MS ESI) calcd for $C_{20}H_{38}NO_4PSiNa$ $[M + Na]^+$ 438.2200, found 438.2182.

Ynamide **44** was prepared via following Method B.

44: (1.20 g, 28%); R_f = 0.51 [1:1 hexanes/EtOAc]; pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (s, 3H), 1.16 (s, 3H), 2.40 (q, 2H, J = 7.2 Hz), 2.70 (dt, 2H, J = 8.4, 7.2 Hz), 3.93−3.97 (m, 2H), 4.18 (ABX, 4H, $\Delta\nu_{AB}$ = 25.8 Hz, J_{AB} = 10.8 Hz, J_{AX} = 10.8 Hz, J_{BX} = 13.2 Hz), 5.61−5.69 (m, 1H), 5.84 (dt, 2H, J = 15.2, 6.8 Hz), 7.14−7.18 (m, 4H), 7.23−7.34 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.77, 20.80, 31.7 (d, J = 6.1 Hz), 33.7, 35.1, 52.6 (d, J = 6.1 Hz), 65.8 (d, J = 6.1 Hz), 77.7 (d, J = 6.1 Hz), 85.0 (d, J = 4.6 Hz), 124.4 (d, J = 1.6 Hz), 125.5, 126.9, 127.9, 128.0, 128.06, 128.10, 130.5 (d, J = 1.5 Hz), 134.9, 141.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ −1.02; IR (film) cm^{-1} 2966w, 2933m, 2239s, 1371m, 1274s; mass spectrum (APCI) m/e (% relative intensity) 410 (21) $(M + H)^+$. HRMS (QTOF MS ESI) calcd for $C_{24}H_{28}NO_3PNa$ $[M + Na]^+$ 432.1699, found 432.1705.

Preparation of Ynamide 30d. To a flame-dried 25-mL RB-flask was added ynamide **30e** (493.0 mg, 1.30 mmol) and THF (8.5 mL, 0.15 M in ynamide). The flask was cooled to 0 °C, and TBAF (1.65 mL, 1.65 mmol, 1.0 M in THF) was added dropwise. After the addition was complete, the reaction was allowed to warm to rt. The reaction was judged to be complete by TLC analysis after 2 h, and the solvent was removed by rotary evaporation. The crude residue was purified by flash silica gel column chromatography (isocratic eluent: 1:1 hexanes/EtOAc + 2% NEt_3) to afford ynamide **30f** (290.0 mg, 1.27 mmol, 97%) as a white solid.

30f: (290.0 mg, 97%); R_f = 0.26 [1:1 hexanes/EtOAc]; white solid; mp = 55−57 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (s, 3H), 1.07 (s, 3H), 2.39 (d, 2H, J = 4.0 Hz), 3.82−3.86 (m, 2H), 4.10 (ABX, 4H, $\Delta\nu_{AB}$ = 25.8 Hz, J_{AB} = 10.8 Hz, J_{AX} = 11.2 Hz, J_{BX} = 10.4 Hz), 5.21 (d, 1H, J = 10.4 Hz), 5.28 (d, 1H, J = 17.2 Hz), 5.84 (ddt, 1H, J = 6.2, 10.4, 17.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 21.3, 32.3 (d, J = 6.3 Hz), 53.2 (d, J = 5.3 Hz), 54.0 (d, J = 5.6 Hz), 78.2 (d, J = 6.3 Hz), 78.7 (d, J = 4.8 Hz), 119.0, 132.2 (d, J = 1.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 0.64; IR (film) cm^{-1} 2972m, 2923m, 2134m, 1473m, 1373m, 1308s, 1276s; mass spectrum (APCI) m/e (% relative intensity) 230 (10) $(M + H)^+$, 261 (100) $(M + MeOH + H)^+$.

Ynamide **30g** was prepared from **30f** following the general procedure for preparation of γ-hydroxy-ynamides.

30g: (206.3 mg, 51%); R_f = 0.25 [3:1 hexanes/EtOAc]; white solid; mp = 45−46 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (s, 3H), 1.09 (s, 3H), 1.13 (s, 3H), 2.16 (br, 1H), 3.87−3.92 (m, 2H), 4.09−4.21 (m, 5H), 5.26 (dd, 1H, J = 1.2, 10.4 Hz), 5.33 (dd, 1H, J = 1.2, 16.8 Hz), 5.90 (ddt, 1H, J = 6, 10.4, 16.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 21.2, 25.4, 32.1 (d, J = 6.9 Hz), 36.0, 53.3 (d, J = 5.3 Hz), 65.4 (d, J = 6.1 Hz), 71.5, 77.9 (dd, J = 3.0, 6.1 Hz), 80.9 (d, J = 4.6 Hz), 118.9, 132.4 (d, J = 2.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ −0.62; IR (film) cm^{-1} 3402brm, 2966s, 2870m, 2246s, 1474m, 1363w, 1273s; mass spectrum (APCI) m/e (% relative intensity) 316.2 (39) $(M + H)^+$.

Ynamide **30d** was prepared from **30g** following the general procedure for silylation

30d: (218.8 mg, 72%); R_f = 0.25 [3:1 hexanes/EtOAc]; white solid; mp = 45−46 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.08 (s, 3H), 0.85 (s, 9H), 0.89 (s, 9H), 1.06 (s, 6H), 3.81−3.88 (m, 2H), 3.98 (d, 1H, J = 3.6 Hz), 4.01−4.15 (m, 4H), 5.20 (dq, 1H, J = 1.1, 10.4 Hz), 5.28 (dq, 1H, J = 1.6, 17.2 Hz), 5.85 (ddt, 1H, J = 6.0, 10.4, 17.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.4, −4.4, 18.1, 21.2, 25.5, 25.7, 32.1 (d, J = 6.1 Hz), 36.6, 53.3 (d, J = 6.1 Hz), 65.6 (d, J = 6.1 Hz), 71.8, 77.7 (dd, J = 6.9, 14.6 Hz), 80.0 (d, J = 5.3 Hz), 118.6, 132.6 (d, J = 1.5 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ −0.45; IR (film) cm^{-1} 1255s, 1275s, 2247m, 2858m, 2892m, 2931m, 2957m; mass spectrum (APCI) m/e (% relative intensity) 330 (100) (M − TBS + MeOH + H)$^+$. HRMS (TOF MS ESI) m/e calcd for $C_{21}H_{44}N_2O_4PS_i$ $[M + NH_4]^+$ 447.2803, found 447.2820.

General Procedure for the Carbocyclization of *N*-Phosphoryl Ynamides. *Method A.* To a flame-dried screw-cap vial containing ~60 mg 4 Å MS was added ynamide **30a** (61.2 mg, 0.20 mmol), $Pd(PPh_3)_4$ (11.6 mg, 0.01 mmol), and toluene (5.0 mL, 0.04 M in ynamide). The vial was sealed under nitrogen and heated to 70 °C for 90 min, at which time TLC analysis showed consumption of the starting material. The reaction mixture was cooled to rt, filtered through Celite, and purified by flash silica gel column chromatography (isocratic eluent: 1:3 hexanes/EtOAc) to afford cyclopentenimine **31a** (53.0 mg, 0.17 mmol) in 87% yield.

Method B. To a flame-dried screw-cap vial containing ~60 mg 4 Å MS was added ynamide **30a** (61.2 mg, 0.20 mmol) and toluene (5.0 mL, 0.04 M in ynamide). The vial was sealed under nitrogen and heated to 125 °C for 2 h, at which time TLC analysis showed consumption of the starting material. The reaction mixture was cooled to rt, filtered through Celite, and purified by flash silica gel column chromatography (isocratic eluent: 1:3 hexanes/EtOAc) to afford cyclopentenimine **31a** (30.8 mg, 0.10 mmol) in 50% yield.

31a: (Method A: 53.0 mg, 87%); R_f = 0.17 [1:2 hexanes/EtOAc]; pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83 (s, 3H), 1.32 (s, 3H), 2.77 (dd, 2H, J = 3.5, 7.5 Hz), 3.15 (dd, 2H, J = 3.5, 7.5 Hz), 3.89 (dd, 2H, J = 10.5, 19.5 Hz), 4.17 (d, 2H, J = 10.5 Hz), 7.34−7.40 (m, 2H), 7.47 (t, 1H, J = 7.5 Hz), 7.62−7.70 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.0, 22.5, 29.8, 32.7 (d, J = 5.8 Hz), 35.6 (d, J = 10.0 Hz), 77.9 (d, J = 7.3 Hz), 128.3 (d, J = 11.1 Hz), 128.5, 128.8 (d, J = 12.3 Hz), 132.4 (d, J = 9.8 Hz), 145.9 (d, J = 28.3 Hz), 159.0, 194.6 (d, J = 2.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 0.64; IR (film) cm^{-1} 2962m, 2884m, 1638s, 1593m, 1276s; mass spectrum (APCI) m/e (% relative intensity) 306 (100) $(M + H)^+$; HRMS (QTOF MS ESI) calcd for $C_{16}H_{20}NO_3PNa$ $[M + Na]^+$ 328.1073, found 328.1079.

31b: (Method A: 35.2 mg, 56%); R_f = 0.19 [1:1 hexane/EtOAc]; pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87−0.91 (m, 3H), 0.90 (s, 3H), 1.29−1.32 (m, 6H), 1.31 (s, 3H), 1.48−1.54 (m, 2H), 2.22−2.26 (m, 2H), 2.60−2.62 (m, 2H), 2.91−2.94 (m, 2H), 3.92 (ddt, 2H, J = 1.2, 10.8, 18.8 Hz), 4.18 (dd, 2H, J = 4.0, 10.4 Hz), 7.15−7.17 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 20.7, 22.0, 22.5, 25.5, 27.7, 29.1, 29.5, 31.6, 32.4 (d, J = 5.3 Hz), 34.2 (d, J = 10.0 Hz), 77.5 (d, J = 6.9 Hz), 148.0 (d, J = 28.4 Hz), 156.3, 197.1 (d, J = 3.1 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 1.44; IR (film) cm^{-1} 2959m, 2928s, 2857m, 1638s, 1615s, 1470w, 1275s; mass spectrum (APCI) m/e (% relative intensity) 314 (100) $(M + H)^+$.

31c: (Method A: 21.1 mg, 34%); R_f = 0.18 [1:1 hexane/EtOAc]; pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.89 (s, 12H), 1.30 (s, 3H), 1.54−1.57 (m, 4H), 2.25 (t, 2H, J = 6.4 Hz), 2.59−2.60 (m, 2H), 2.91−2.94 (m, 2H), 3.62 (t, 2H, J = 6.2 Hz), 3.92 (ddd, 2H, J = 1.2, 9.6, 18.8 Hz), 4.16 (dd, 2H, J = 3.6, 10.4 Hz), 7.15−7.17 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.3, 18.3, 20.8, 22.0, 24.0, 25.2, 25.9, 29.5, 32.4 (d, J = 6.1 Hz), 32.6, 34.3 (d, J = 10.0 Hz), 62.9, 77.5 (d, J = 6.8 Hz), 147.8 (d, J = 28.5 Hz), 156.3, 197.0; ^{31}P NMR (162 MHz, $CDCl_3$) δ 1.39; IR (film) cm^{-1} 2954m, 2928m, 2858m, 1615m, 1471w, 1257s; mass spectrum (APCI) m/e (% relative intensity) 416 (100) $(M + H)^+$; HRMS (QTOF MS ESI) calcd for $C_{20}H_{38}NO_4PSiNa$ $[M + Na]^+$ 438.2200, found 438.2197.

31d: (41.4 mg, 69%); R_f = 0.14 [1:1 hexanes/EtOAc]; pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.18 (s, 3H), 0.84 (s, 3H), 0.85 (s, 9H), 0.86 (s, 9H), 1.32 (s, 3H), 2.57−2.71 (m, 2H), 2.84 (ddt, 1H, J = 2.8, 6.0, 20.0 Hz), 3.04 (ddt, 1H, J = 2.8, 6.0, 20.0 Hz), 3.82−3.93

dx.doi.org/10.1021/jo400960e | J. Org. Chem. 2013, 78, 6233−6244

(m, 2H), 4.14 (ddd, 2H, J = 2.4, 10.8, 21.2 Hz), 4.36 (s, 1H), 7.40 (dd, 1H, J = 2.8, 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) −5.1, −4.4, 18.2, 20.8, 22.3, 25.9 (d, J = 3.9 Hz), 29.8, 32.5 (d, J = 6.0 Hz), 34.5 (d, J = 10.0 Hz), 36.3, 73.1, 77.5 (d, J = 7.9 Hz), 150.0 (d, J = 27.1 Hz), 160.2, 196.0 (d, J = 2.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 0.84; IR (film) cm^{-1} 2957m, 2930m, 2885m, 2857m, 1632m, 1613m, 1472m, 1281m, 1257m; mass spectrum (APCI) m/e (% relative intensity) 430 (100) $(M + H)^+$; HRMS (QTOF MS ESI) calcd for $C_{21}H_{40}NO_4PSiNa$ $[M + Na]^+$ 452.2356, found 452.2359.

48: (71.2 mg, 87%); R_f = 0.41 [1:1 DCM/EtOAc]; pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.73 (s, 3H), 1.26 (s, 3H), 2.75 (t, 2H, J = 4.0 Hz), 2.82−2.85 (m, 4H), 3.04−3.07 (m, 2H), 3.77 (ddd, 2H, J = 1.2, 9.6, 19.6 Hz), 4.01 (dd, 2H, J = 1.6, 10.4 Hz), 7.08−7.12 (m, 4H), 7.19−7.35 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 22.1, 32.2 (d, J = 6.1 Hz), 32.5, 33.2 (d, J = 1.6 Hz), 33.7, 33.8 (d, J = 10.8 Hz), 77.5 (d, J = 7.7 Hz), 126.3, 127.5, 127.7, 128.1, 128.5, 129.5, 132.4, 140.4, 142.7 (d, J = 29.2 Hz), 173.5, 195.1 (d, J = 1.5 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 0.79; IR (film) cm^{-1} 2963w, 2929w, 1617s, 1592s, 1268s; mass spectrum (APCI) m/e (% relative intensity) 410 (100) $(M + H)^+$; HRMS (QTOF MS ESI) calcd for $C_{24}H_{28}NO_3PNa$ $[M + Na]^+$ 432.1699, found 432.1699.

Characterization of *N*-Phosphoryl-TIPS-Ketenimine 32. 32: (41.1 mg, 53%); R_f = 0.17 [4:1 hexanes:EtOAc]; yellow wax; mp = 47−50 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (s, 3H), 1.13 (d, 18H, J = 6.0 Hz), 1.18 (sept, 3H, J = 6.0 Hz), 1.29 (s, 3H), 2.77 (ddt, 2H, J = 1.2, 6.8, 8.0 Hz), 3.95 (dd, 2H, J = 11.2, 22.0 Hz), 4.18 (d, 2H, J = 10.4 Hz), 5.10 (dd, 1H, J = 1.2, 10.0 Hz), 5.21 (dq, 1H, J = 1.6, 3.2, 17.2 Hz), 5.98 (ddt, 1H, J = 6.4, 10.0, 16.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.9, 17.9, 18.7, 20.5, 22.2, 29.0 (d, J = 5.4 Hz), 32.4 (d, J = 6.1 Hz), 40.0 (d, J = 15.3); 76.9 (d, J = 31.3 Hz), 116.3 (d, J = 3.8 Hz), 136.1 (d, J = 3.1 Hz), 187.9; ^{31}P NMR (162 MHz, $CDCl_3$) δ −9.05; IR (film) cm^{-1} 2943m, 2890w, 2866m, 1993s, 1464m, 1372w, 1341w, 1301s; mass spectrum (ESI) m/e (% relative intensity) 387 (100) $(M + H)^+$; HRMS (QTOF MS ESI) calcd for $C_{19}H_{36}NO_3PSiNa$ $[M + Na]^+$ 408.2094, found 408.2091.

Preparation of Farnesyl-Tethered Ynamide 59. To a flame-dried 25-mL RB-flask was added CH_2Cl_2 (7.0 mL, 0.5 M in allyl amine), farnesyl amine (752.0 mg, 3.39 mmol), and NEt_3 (0.70 mL, 5.09 mmol) under a nitrogen atmosphere. The reaction flask was cooled to 0 °C, and 2-chloro-5,5-dimethyl-1,3,2-dioxaphosphorinane 2-oxide (753.0 mg, 4.07 mmol) was added slowly dropwise. Once the addition was complete, the reaction was allowed to warm to rt and stir overnight. After the reaction was judged to be complete by TLC, water (10 mL) was added, the organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic phase was washed with sat. NaCl and dried over Na_2SO_4. The crude material was purified by flash silica gel column chromatography (1:1 EtOAc:CH_2Cl_2) to afford phosphoramidate **56** (943.0 mg, 2.56 mmol, 75%).

56: (943.0 mg, 75%); R_f = 0.20 [1:1 EtOAc/CH_2Cl_2]; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (s, 3H), 1.21 (s, 3H), 1.60 (s, 6H), 1.65 (s, 3H), 1.68 (s, 3H), 2.12−1.94 (m, 8H), 2.65 (brs, 1H), 3.59 (dt, 2H, J = 6.8, 9.2 Hz), 3.81 (ddt, 2H, J = 1.2, 11.2, 19.6 Hz), 4.29 (dd, 2H, J = 4.4, 11.2 Hz), 5.09 (t, 2H, J = 6.8 Hz), 5.25 (tq, 1H, J = 1.6, 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.1, 16.3, 17.8, 20.9, 22.1, 25.8, 26.4, 26.8, 32.0 (d, J = 5.2 Hz), 39.2, 39.6, 39.8, 76.2 (d, J = 5.5 Hz), 122.0 (d, J = 7.3 Hz), 123.8, 124.4, 131.4, 135.5, 139.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ 6.37; IR (film) cm^{-1} 3210brm, 2965m, 2917m, 1447m, 1374m, 1231m; mass spectrum (APCI) m/e (% relative intensity) 370 (100) $(M + H)^+$. HRMS (TOF MS ESI) m/e calcd for $C_{20}H_{37}NO_3P$ $[M + H]^+$ 370.2506, found 370.2523.

57: (298.0 mg, 65%); R_f = 0.16 [3:1 hexanes/EtOAc]; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (s, 18H), 1.03−1.06 (m, 3H), 1.06 (s, 3H), 1.14 (s, 3H), 1.59 (d, 3H, J = 1.2 Hz), 1.60 (d, 3H, J = 0.8 Hz), 1.68 (d, 3H, J = 1.2 Hz), 1.69 (d, 3H, J = 1.2 Hz), 1.94−2.17 (m, 8H), 3.94 (t, 2H, J = 7.6 Hz), 4.15 (ABX, 4H, $\Delta\nu_{AB}$ = 32.8 Hz, J_{AB} = 11.2 Hz, J_{AX} = 10.7 Hz, J_{BX} = 10.9 Hz), 5.06−5.14 (m, 2H), 5.38 (tq, 1H, J = 1.2, 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.6, 16.1, 16.7, 17.8, 18.8, 18.8, 21.3, 21.6, 25.8, 26.5, 26.9, 32.4 (d, J = 6.9 Hz), 39.8, 48.7 (d, J = 5.4 Hz), 63.0 (d, J = 4.5 Hz), 77.4, 78.3 (d, J = 6.8 Hz), 118.8 (d, J = 2.3 Hz), 124.0, 124.5, 131.4, 135.4, 141.4; ^{31}P NMR (162 MHz, $CDCl_3$) δ 1.65; IR (film) cm^{-1} 2923m, 2864m, 2161m, 1463m, 1380m, 1235m; mass spectrum (APCI) m/e (% relative intensity) 370 (70) $(M - C{\equiv}CTIPS + H)^+$, 571 (10) $(M + H)^+$.

To a flame-dried 10-mL RB-flask was added ynamide **57** (298.0 mg, 0.54 mmol) and THF (2.2 mL, 0.25 M in ynamide). The flask was cooled to 0 °C, and TBAF (0.65 mL, 0.65 mmol, 1.0 M in THF) was added dropwise. After the addition was complete, the reaction was allowed to warm to rt. The reaction was judged to be complete by TLC analysis after 2 h, and the solvent was removed by rotary evaporation. The crude residue was purified by flash silica gel column chromatography (isocratic eluent: 2:1 hexanes/EtOAc + 2% NEt_3) to afford ynamide **58** (174.0 mg, 0.44 mmol, 82%) as a colorless oil.

58: (174.0 mg, 82%); R_f = 0.29 [2:1 hexanes/EtOAc]; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (s, 3H), 1.12 (s, 3H), 1.60 (s, 3H), 1.60 (s, 3H), 1.68 (d, 3H, J = 0.8 Hz), 1.71 (d, 3H, J = 0.8 Hz), 1.97 (t, 2H, J = 7.6 Hz), 2.01−2.14 (m, 6H), 2.40 (d, 1H, J = 3.6 Hz), 3.94 (t, 2H, J = 7.6 Hz), 4.15 (ABX, 4H, $\Delta\nu_{AB}$ = 23.5 Hz, J_{AB} = 10.9 Hz, J_{AX} = 11.0 Hz, J_{BX} = 8.8 Hz), 5.07−5.13 (m, 2H), 5.37 (tq, 1H, J = 1.2, 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.2, 16.6, 17.8, 21.3, 21.4, 25.8, 26.5, 26.9, 32.4 (d, J = 6.3 Hz), 39.8, 39.8, 48.2 (d, J = 5.0 Hz), 53.8 (d, J = 5.8 Hz), 77.4, 78.1 (d, J = 6.3 Hz), 118.6 (d, J = 2.3 Hz), 123.9, 124.5, 131.4, 135.4, 141.9; ^{31}P NMR (162 MHz, $CDCl_3$) δ 0.22; IR (film) cm^{-1} 2965m, 2920m, 2133m, 1769w, 1666w, 1448m, 1305s, 1275s; mass spectrum (APCI) m/e (% relative intensity) 394 (100) $(M + H)^+$.

To a flame-dried 25-mL RB-flask was added ynamide **58** (174.0 mg, 0.44 mmol) and THF (4.4 mL, 0.1 M in ynamide) under a nitrogen atmosphere. The flask was cooled to −78 °C, and LHMDS (0.89 mL, 0.88 mmol, 1 M in THF) was added dropwise. The reaction was kept at −78 °C for 1 h to ensure complete deprotonation, and then MeI (83.0 μL, 1.32 mmol) was added dropwise. The reaction was allowed to warm to rt overnight, at which time TLC analysis showed consumption of the starting material. The reaction was diluted with EtOAc (5 mL) and quenched with water (5 mL). The layers were separated, the aqueous layer was extracted with EtOAc (3 × 10 mL), and then the combined organic layers were washed with brine and dried over Na_2SO_4. Purification of the crude residue by flash silica gel column chromatography (isocratic eluent: 1:1 hexanes/EtOAc + 2% NEt_3) afforded ynamide **59** (147.2 mg, 0.36 mmol, 82%).

59: (147.2 mg, 82%); R_f = 0.16 [2:1 hexanes/EtOAc]; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (s, 3H), 1.17 (s, 3H), 1.60 (s, 6H), 1.68 (s, 3H), 1.70 (d, 3H, J = 0.8 Hz), 1.85 (d, 1H, J = 3.2 Hz), 1.97 (t, 2H, J = 7.6 Hz), 2.04−2.14 (m, 6H), 3.89 (t, 2H, J = 8.0 Hz), 4.03 (dd, 2H, J = 11.2, 14.8 Hz), 4.20 (dd, 2H, J = 9.2, 10.8 Hz), 5.07−5.14 (m, 2H), 5.36 (tq, 1H, J = 1.2, 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.2 (d, J = 1.9 Hz), 16.1, 16.5, 17.8, 21.3, 21.4, 25.8, 26.5, 26.9, 32.3 (d, J = 6.1 Hz), 39.8 (d, J = 4.4 Hz), 48.2 (d, J = 3.7 Hz), 60.2 (d, J = 5.8 Hz), 74.6 (d, J = 4.6 Hz), 77.6 (d, J = 6.2 Hz), 78.0 (d, J = 3.7 Hz), 119.3 (d, J = 2.2 Hz), 123.9, 124.5, 131.4, 135.3, 141.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ 1.41; IR (film) cm^{-1} 2968m, 2919m, 2262w, 1737m, 1447m, 1373m, 1271m; mass spectrum (APCI) m/e (% relative intensity) 408 (100) $(M + H)^+$; HRMS (QTOF MS ESI) calcd for $C_{23}H_{38}NO_3PNa$ $[M + Na]^+$ 430.2482, found 430.2489.

Carbocyclization of Farnesyl-Tethered Ynamide 59. 62: (41.7 mg, 43%); R_f = 0.18 [1:2 hexanes/EtOAc]; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) *all isomers* δ 0.98 (s, 9H), 1.08 (s, 3H), 1.09 (s, 3H), 1.11 (s, 3H), 1.13 (s, 3H), 1.14 (s, 3H), 1.19−1.37 (m, 6H), 1.47 (s, 3H), 1.48 (s, 3H), 1.48 (s, 3H), 1.60 (s, 12H), 1.67 (s, 6H), 1.69 (s, 6H), 1.70−1.75 (m, 2H), 1.91−2.11 (m, 16H), 2.17−2.38 (m, 6H), 2.40−2.49 (m, 1H), 2.53−2.60 (m, 1H), 2.62−2.72 (m, 2H), 2.91−3.00 (m, 2H), 3.87 (ddd, 6H, J = 1.5, 11.5, 16.5 Hz), 4.18−4.30 (m, 8H), 4.33 (d, 2H, J = 8.0 Hz), 4.68 (s, 1H), 4.83 (s, 1H), 5.94−5.19 (m, 3H); ^{31}P NMR (162 MHz, $CDCl_3$) *all isomers* δ 1.56, 1.57, 1.63; IR (film) cm^{-1} 2962m, 2930m, 1737s, 1670m, 1456m, 1373m; mass spectrum (APCI) m/e (% relative intensity) 408 (100) $(M + H)^+$. HRMS (TOF MS ESI) m/e calcd for $C_{23}H_{39}NO_3P$ $[M + H]^+$ 408.2663, found 408.2675.

63: (36.8 mg, 38%); R_f = 0.47 [1:2 hexanes/EtOAc]; colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) 0.76 (s, 3H), 0.80 (s, 3H), 0.86 (s, 3H),

dx.doi.org/10.1021/jo400960e | J. Org. Chem. 2013, 78, 6233−6244

0.93 (s, 3H), 0.93 (ddd, 1H, J = 6.0, 11.0, 13.5 Hz), 1.13 (ddd, 1H, J = 6.0, 11.0, 13.5 Hz), 1.30 (s, 3H), 1.43 (t, 2H, J = 11.0 Hz), 1.52 (ddt, 1H, J = 3.0, 5.5, 11.5 Hz), 1.56 (s, 3H), 1.63 (s, 3H), 1.65−1.76 (m, 1H), 1.88 (ddd, 2H, J = 6.5, 13.5, 19.0 Hz), 1.92 (s, 1H), 2.00 (s, 1H), 2.69 (t, 2H, J = 3.0 Hz), 3.87 (dddd, 2H, J = 3.0, 11.0, 19.0, 41.0 Hz), 4.16 (ddd, 2H, J = 3.5, 11.0, 43.0 Hz), 4.97−5.00 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.3, 16.6, 17.8, 20.2, 20.9, 22.3, 23.7, 25.9, 27.3, 30.0, 32.6 (d, J = 5.7 Hz), 36.1 (d, J = 11.3 Hz), 40.3 (d, J = 6.6 Hz), 47.1, 49.9, 56.9, 64.3 (d, J = 23.1 Hz), 77.8 (d, J = 7.5 Hz), 124.8, 131.4, 206.0 (d, J = 7.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 1.71; IR (film) cm^{-1} 2959m, 2931m, 2877m, 1738m, 1689m, 1460m, 1374m; mass spectrum (APCI) m/e (% relative intensity) 408 (100) (M + H)$^+$; HRMS (QTOF MS ESI) calcd for $C_{23}H_{38}NO_3PNa$ [M + Na]$^+$ 430.2482, found 430.2486.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data for all new compounds, and ^{1}H/^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: rhsung@wisc.edu, kadekorver@dow.com.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Authors thank the NIH [GM066055] for financial support. K.A.D. thanks the American Chemical Society for a Division of Medical Chemistry Predoctoral Fellowship.

■ REFERENCES

(1) For current leading reviews on chemistry of ynamides, see: (a) Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2840. (b) DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064. For reviews partially accounting chemistry of ynamides, see: (c) Ackermann, L.; Potukuchi, H. K. *Org. Biomol. Chem.* **2010**, *8*, 4503. (d) Domínguez, G.; Perez-Castells, J. *Chem. Soc. Rev.* **2011**, *40*, 3430. (e) Weding, N.; Hapke, M. *Chem. Soc. Rev.* **2011**, *40*, 4525. (f) Madelaine, C.; Valerio, V.; Maulide, N. *Chem.—Asian J.* **2011**, *6*, 2224. For reviews on syntheses of ynamides, see: (g) Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P. *Synlett* **2003**, 1379. (h) Dehli, J. R.; Legros, J.; Bolm, C. *Chem. Commun.* **2005**, *43*, 973. (i) Tracey, M. R.; Hsung, R. P.; Antoline, J. A.; Kurtz, K. C. M.; Shen, L.; Slafer, B. W.; Zhang, Y. In *Science of Synthesis, Houben-Weyl Methods of Molecular Transformations*; Weinreb, S. M., Ed.; Georg Thieme Verlag KG: Stuttgart, Germany, 2005; Chapter 21.4. (j) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054. (k) Evano, G.; Jouvinb, K.; Coste, A. *Synthesis* **2013**, 17.

(2) For syntheses of ynamides published in 2012, see: (a) Jin, X.; Yamaguchi, K.; Mizuno, N. *Chem. Lett.* **2012**, *41*, 866. (b) Jin, X.; Yamaguchi, K.; Mizuno, N. *Chem. Commun.* **2012**, *48*, 4974. (c) Jouvin, K.; Heimburger, J.; Evano, G. *Chem. Sci.* **2012**, *3*, 756. (d) Jouvin, K.; Coste, A.; Bayle, A.; Legrand, F.; Karthikeyan, G.; Tadiparthi, K.; Evano, G. *Organometallics* **2012**, *31*, 7933. (e) Tong, X.; Ni, G.; Deng, X.; Xia, C. *Synlett* **2012**, *23*, 2497. (f) Wang, M.-G.; Wu, J.; Shang, Z.-C. *Synlett* **2012**, *23*, 589. (g) Laouiti, A.; Jouvin, K.; Bourdreux, F.; Rammah, M. M.; Rammah, M. B.; Evano, G. *Synthesis* **2012**, *44*, 1491. For syntheses of novel structural analogues of ynamides, see: (h) Yne-sulfoxyimines: Wang, L.; Huang, H.; Priebbenow, D. L.; Pan, F.-F.; Bolm, C. *Angew. Chem., Int. Ed.* **2013**, *52*, 3478. (i) Yne-hydrazides Beveridge, R. E.; Batey, R. A. *Org. Lett.* **2012**, *14*, 540. (j) Yne-imines: Laouiti, A.; Rammah, M. M.; Rammah, M. B.; Marrot, J.; Couty, F.; Evano, G. *Org. Lett.* **2012**, *14*, 6. (k) Ynimides: Souto, J. A.; Becker, P.; Iglesias, Á.; Muñiz, K. *J. Am. Chem. Soc.* **2012**, *134*, 15505. (l) Ynimides: Sueda, T.; Oshima, A.; Teno, N. *Org. Lett.* **2011**, *13*, 3996. (m) Ynimides: Sueda, T.; Kawada, A.; Urash, Y.; Teno, N. *Org. Lett.* **2013**, *15*, 1560. (n) Diamino-acetylenes: Petrov, A. R.; Daniliuc, C. G.; Jones, P. G.; Tamm, M. *Chem.—Eur. J.* **2010**, *16*, 11804. (o) Amidinyl-ynamides: Li, J.; Neuville, L. *Org. Lett.* **2013**, *15*, 1752.

(3) Given the volume, for ynamide chemistry published since September of 2012, see: (a) Karmakar, R.; Mamidipalli, P.; Yun, S. Y.; Lee, D. *Org. Lett.* **2013**, *15*, 1938. (b) Brioche, J.; Meyer, C.; Cossy, J. *Org. Lett.* **2013**, *15*, 1626. (c) Yun, S. Y.; Wang, K.-P.; Lee, N.-K.; Mamidipalli, P.; Lee, D. *J. Am. Chem. Soc.* **2013**, *135*, 4668. (d) Heffernan, S. J.; Beddoes, J. M.; Mahon, M. F.; Hennessy, A. J.; Carbery, D. R. *Chem. Commun.* **2013**, *49*, 2314. (e) Kong, Y.; Jiang, K.; Cao, J.; Fu, L.; Yu, L.; Lai, G.; Cui, Y.; Hu, Z.; Wang, G. *Org. Lett.* **2013**, *15*, 422. (f) Yavari, I.; Nematpour, M.; Sodagar, E. *Synlett* **2013**, *24*, 161. (g) Yavari, I.; Nematpour, M. *Synlett* **2013**, *24*, 165. (h) Bhunia, S.; Chang, C.-J.; Liu, R.-S. *Org. Lett.* **2012**, *14*, 5522. (i) Minko, Y.; Pasco, M.; Lercher, L.; Botoshansky, M.; Marek, I. *Nature* **2012**, *490*, 522. (j) Hoye, T. R.; Baire, B.; Niu, D.; Willoughby, P. H.; Woods, B. P. *Nature* **2012**, *490*, 208. (k) Cao, J.; Kong, Y.; Deng, Y.; Lai, G.; Cui, Y.; Hu, Z.; Wang, G. *Org. Biomol. Chem.* **2012**, *10*, 9556. (l) Greenaway, R. L.; Campbell, C. D.; Chapman, H. A.; Anderson, E. A. *Adv. Synth. Catal.* **2012**, *354*, 3187. (m) Jiang, Z.; Lu, P.; Wang, Y. *Org. Lett.* **2012**, *14*, 6266. (n) Gati, W.; Rammah, M. M.; Rammah, M. B.; Evano, G. *Beilstein J. Org. Chem.* **2012**, *8*, 2214. (o) Smith, D. L.; Chidipudi, S. R.; Goundry, W. R.; Lam, H. W. *Org. Lett.* **2012**, *14*, 4934. (p) Heffernan, S. J.; Carbery, D. R. *Tetrahedron Lett.* **2012**, *53*, 5180.

(4) For reviews on Claisen rearrangements, see: (a) Castro, A. M. M. *Chem. Rev.* **2004**, *104*, 2939. (b) Ito, H.; Taguchi, T. *Chem. Soc. Rev.* **1999**, *28*, 43. (c) Enders, D.; Knopp, M.; Schiffers, R. *Tetrahedron: Asymmetry* **1996**, *7*, 1847. (d) Wipf, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. *5*, p 827. (e) Hill, R. K. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984.

(5) For leading reviews on aza-Claisen rearrangments, see: (a) Majumdar, K. C.; Bhayyacharyya, T.; Chattopadhyay, B.; Nandi, R. K. *Synthesis* **2009**, 2117. (b) Nubbemeyer, U. *Top. Curr. Chem.* **2005**, *244*, 149.

(6) (a) Zhang, Y.; DeKorver, K. A.; Lohse, A. G.; Zhang, Y.-S.; Huang, J.; Hsung, R. P. *Org. Lett.* **2009**, *11*, 899. (b) DeKorver, K. A.; Hsung, R. P.; Lohse, A. G.; Zhang, Y. *Org. Lett.* **2010**, *12*, 1840. (c) DeKorver, K. A.; Johnson, W. L.; Zhang, Y.; Hsung, R. P.; Dai, H.; Deng, J.; Lohse, A. G.; Zhang, Y.-S. *J. Org. Chem.* **2011**, *76*, 5092.

(7) DeKorver, K. A.; North, T. D.; Hsung, R. P. *Synlett* **2010**, 2397.

(8) DeKorver, K. A.; Walton, M. C.; North, T. D.; Hsung, R. P. *Org. Lett.* **2011**, *13*, 4862.

(9) DeKorver, K. A.; Hsung, R. P.; Song, W.-Z.; Wang, X.-N.; Walton, M. C. *Org. Lett.* **2012**, *14*, 3214.

(10) DeKorver, K. A.; Wang, X.-N.; Walton, M. C.; Hsung, R. P. *Org. Lett.* **2012**, *14*, 1768.

(11) For reviews on the chemistry of ketenimines, see: (a) Krow, G. R. *Angew. Chem., Int. Ed.* **1971**, *10*, 435. (b) Gambaryan, N. P. *Usp. Khim.* **1976**, *45*, 1251. (c) Dondoni, A. *Heterocycles* **1980**, *14*, 1547. (d) Barker, M. W.; McHenry, W. E. In *The Chemistry of Ketenes, Allenes and Related Compounds*; Patai, S., Ed.; Wiley-Interscience: Chichester, UK, 1980; Part 2, pp 701−720. (e) Alajarín, M.; Vidal, A.; Tovar, F. *Targets Heterocycl. Syst.* **2000**, *4*, 293.

(12) Rodríguez, D.; Martínez-Esperón, M. F.; Castedo, L.; Saá, C. *Synlett* **2007**, *12*, 1963.

(13) For a review, see: Basavaiah, D.; Jaganmohan Rao, A.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811.

(14) For a related report, see: Whiting, M.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2006**, *45*, 3157.

(15) Rautenstrauch, V. *J. Org. Chem.* **1984**, *49*, 950.

(16) For a leading reference on Rautenstrauch rearrangements, see: Shi, X.; Gorin, D. J.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 5802.

(17) For a related imino carbocyclization, see: Hanessian, S.; Tremblay, M.; Marzi, M.; Del Valle, J. R. *J. Org. Chem.* **2005**, *70*, 5070.

(18) For related carbocyclizations of ketenes, see: (a) Sosa, J. R.; Tudjarian, A. A.; Minehan, T. G. *Org. Lett.* **2008**, *10*, 5091. (b) Tudjarian, A. A.; Minehan, T. G. *J. Org. Chem.* **2011**, *76*, 3576.
(19) 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.
(20) For reviews on polyene cyclizations, see: (a) Johnson, W. S. *Acc. Chem. Res.* **1968**, *1*, 1. (b) Johnson, W. S. *Angew. Chem., Int. Ed.* **1976**, *15*, 9. (c) For a key account, see: Johnson, W. S.; Telfer, S. J.; Cheng, S.; Schubert, U. *J. Am. Chem. Soc.* **1987**, *109*, 2517.
(21) 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.
(22) Coppola, G. M; Prashad, M. *Syn. Commun.* **1993**, *23*, 535.