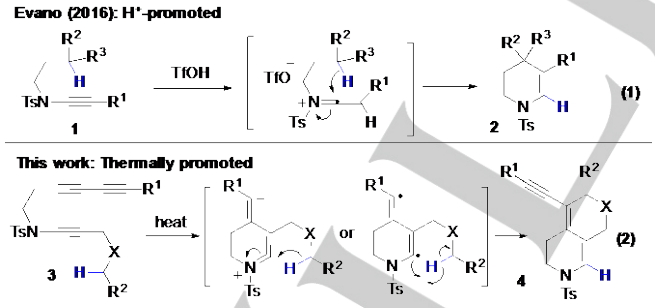
Cyclization of Ynamide-tethered 1,3,8-Triynes

Venkata R. Sabbasani,[§[a]] Hyunjin Lee,[§[a]] Peipei Xie,[[b]] Yuanzhi Xia,*[[b]] and Daesung Lee*[[a]]

This article is dedicated to Professor Paul A. Wender on the celebration of his 70th birthday

Abstract: A facile thermal cyclization of ynamide-tethered 1,3,8-triynes to form 3,5,6,7-tetrahydro-1*H*-pyrano[3,4-*c*]pyridine skeleton is described. Although the mechanism of this unusual reaction is yet to be defined the formation of either a strained keteniminium or a biradical intermediate followed a 1,5-hydride or -hydrogen shift is tentatively proposed as the key elementary steps in the reaction sequence. Appropriate electronic activation at the carbon center donating a hydride or hydrogen is crucial for successful cyclization.

Ynamides play an important role in the synthesis of indole-based natural products via metal-catalyzed benzannulation reactions.[1] Also, various ring-closure reactions catalyzed by various π-philic Lewis acids employ ynamides as a crucial building block.[2] In these reactions, the favorable reactivity of ynamides originates from the electron-rich nitrogen-substituted triple bond,[3] which allows for the formation of a reactive keteniminium[4] intermediate in the presence of an electrophilic species. The recently reported novel ring-forming reaction by Evano nicely illustrates this characteristic reactivity of ynamides (Scheme 1),[5] where, initial protonation of ynamide **1** generates a keteniminium intermediate, which undergoes a [1,5]-hydride shift followed by ring-closure to generate final product **2** (Eq 1). In our attempt to synthesize ynamide-tethered 1,3,6-triyne **3** under the known coupling conditions, an unexpected bicyclic product **4** was obtained instead (Eq 2). Prompted by this initial discovery, we further investigated this unprecedented cyclization ynamide-containing triynes, and herein we report the general scope of the reaction.



Scheme 1. Ring-closures of ynamides via keteniminium formation

[a] V. R. Sabbasani, H. Lee, Prof. D. Lee
Department of Chemistry
University of Illinois at Chicago
845 West Taylor Street, Chicago, IL 60607 (USA)
E-mail: dsunglee@uic.edu
[b] Prof. Y. Xia
College of Chemistry and Materials Engineering
Wenzhou University
Wenzhou, Zhejiang Province 325035 (P.R. China)
E-mail: xyz@wzu.edu.cn
[§] Both authors contributed equally to this work.
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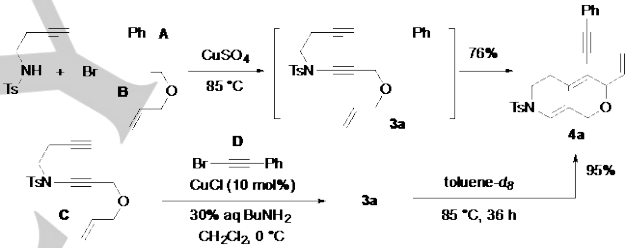
The initial discovery of the ring closure was made from the coupling of building blocks **A** and **B** to prepare enyne derivative **3a**. Upon subjecting sulfonamide **A** and bromoalkyne **B** to typical coupling conditions (15 mol % $CuSO_4 \cdot 5H_2O$, 30 mol % 1,10-phenanthroline, K_2CO_3, toluene, 85 °C, 36 h),[6] a clean conversion occurred to provide a product in 76% yield (Scheme 2). However, the isolated compound was found to be bicycle **4a** rather than the expected ynamide **3a**. We surmised that ynamide **3a** was generated, but due to its unique reactivity to undergo a thermal transformation, this compound could not be isolated. To confirm that **3a** is indeed a precursor for **4a**, an alternative coupling between **C** and **D** was carried out at low temperature to isolate **3a**. Heating of purified **3a** in toluene at 85 °C for 36 h provided compound **4a** in nearly quantitative yield (>95%). This result not only suggests that **3a** is a direct precursor of **4a** but also its formation is purely a thermal process not involving any other reagents such as the copper species used for the coupling reaction as a catalyst.

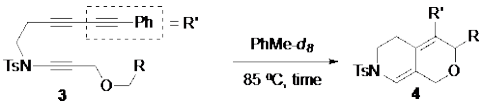


Scheme 2. Initial observation of unexpected transformation in the coupling of sulfonamide with bromoalkyne

Recognizing the involvement of C–H bond cleavage in this reaction from the α-carbon of the allyl ether moiety in the substrate, our exploration commenced with the preparation of a range of substrates containing a differently substituted ether linkage followed by examination of their effect in on the reaction (Table 1). With a phenyl substituent at the 1,3-diyne terminus of **3**, the reaction efficiency of forming product **4** was examined with the variation of substituent R on the ether linkage. Substrates **3a–3e** containing an allylic (entries 1–3), benzylic (entry 4), and cyclohexyl (entry 5) ether moiety provided products **4a–4e** with similar yields except **4e**, which was obtained in slightly lower yield. One noticeable difference between these substrates is their reaction time. While substrates **3a–3c** containing an allylic ether took 36 h for its complete consumption, substrate **3d** with a benzylic ether took somewhat shorter time (24 h). On the contrary, substrate **3e** containing a cyclohexylmethyl ether took significantly longer time (48 h). This trend may imply that the bond strength of the C–H bond at the α-carbon of the ether moiety in substrate **3** is crucial for the formation of a putative intermediate as well as the overall efficiency of the cyclized product **4**.

Having initial set of promising results in hand, the next question we want to address is what structural change in

Table 1. Cyclization of ynamide-tethered triynes with different ethers



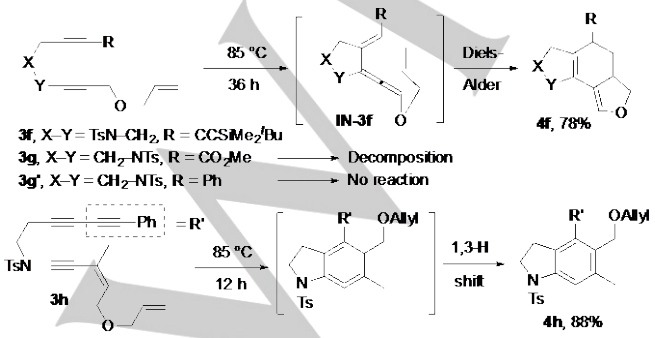
entry	substrate	R	time (h)	product	yield (%)[a]
1	**3a**		36	**4a**	95
2	**3b**		36	**4b**	81
3	**3c**		36	**4c**	81
4	**3d**		24	**4d**	95
5	**3e**		48	**4e**	76

[a] Isolated yields.

substrate **3** would lead to the alteration of reactivity of these ynamides. To answer this question, three probes **3f–3h** were examined (Scheme 3). Triyne **3f** containing an NTs tether but not as a form of ynamide underwent smooth cyclization but through an initial Alder-ene reaction to generate a putative intermediate **IN-3f** followed by an intramolecular Diels-Alder reaction to generate tricycle **4f** in 78% yield.[7] In contrast, ynamide-tethered diynes **3g** or **3g′** containing a carboxylate or a phenyl moiety led to either decomposition or no reaction under the same conditions. In case of ynamide **3h** containing a conjugated 1,3-enyne moiety underwent facile didehydro Diels-Alder reaction,[8] providing **4h** in 88% yield.

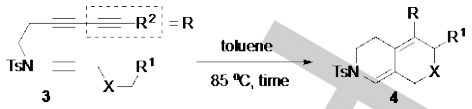
These results clearly indicate that the newly discovered cyclization to form 3,5,6,7-tetrahydro-1*H*-pyrano[3,4-*c*]pyridine skeleton strictly requires an ynamide-based 1,3,8-triyne framework bearing an appropriate hydride- or hydrogen-donating functionality.[9] Otherwise, no reaction or different types of thermal reactions of the multiple unsaturated framework outcompete to generate products of alternative cyclization.

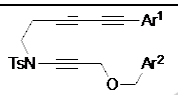
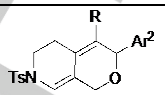
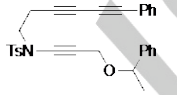
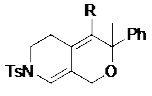
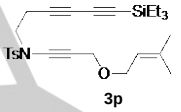
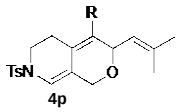
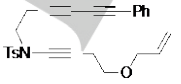
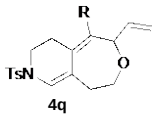
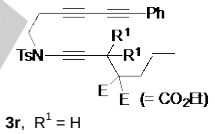
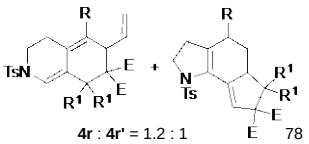
On the basis of the different modes of cyclization induced by altered structural elements shown in Scheme 3, further structural variations were introduced onto the parent framework of an ynamide-based 1,3,8-triyne to examine the scope of the reaction (Table 2). The reaction of benzylic ether-containing substrates **3i–3l** containing different *para*-substituent (OMe, NO_2, CF_3, Cl) afforded products **4i–4l** with similar yields and reaction time (entries 1–4). The X-ray structure of **4l** further secures the



Scheme 3. Cyclizations of triynes of different unsaturation patterns

Table 2. Cyclization reactions of ynamide-tethered triynes



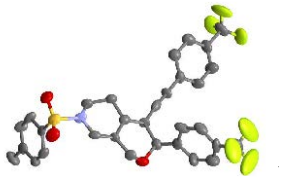
entry	ynamide	time (h)	product	yield (%)[a]
				
1	**3i**, Ar^1, Ar^2 = Ph, 4-$MeOC_6H_4$	23	**4i**, Ar^2 = 4-$MeOC_6H_4$	83
2	**3j**, Ar^1, Ar^2 = Ph, 4-$NO_2C_6H_4$	24	**4j**, Ar^2 = 4-$NO_2C_6H_4$	88
3	**3k**, Ar^1, Ar^2 = Ph, 4-$CF_3C_6H_4$	23	**4k**, Ar^2 = 4-$CF_3C_6H_4$	89
4	**3l**, Ar^1, Ar^2 = 4-$CF_3C_6H_4$	23	**4l**, Ar^2 = 4-$CF_3C_6H_4$	92
5	 **3m**	28	 **4m**	83
6	**3n**, R = H	48	**4n**, R = H	81
7	**3o**, R = Me	48[b]	**4o**, R = Me	78
8	 **3p**	28	 **4p**	84
9	 **3q**	120	 **4q**	68
10	 **3r**, R^1 = H	72	 **4r** : **4r′** = 1.2 : 1	78
11	**3s**, R^1 = Me	72[c]	no reaction	---

[a] Isolated yields. [b] The reaction was heated at 100 °C. [c] No reaction was observed even at 120 °C.

structural assignment of these products (Figure 1).[10] Adding a methyl group at the benzylic carbon in **3m** did not affect the yield of **4m** (entry 5). On the other hand, introducing a methyl group at the propargylic carbon in **3n** significantly slowed down the reaction (48 h, 81%) (entry 6). The *gem*-dimethyl group in **3o** further deactivates the system such that higher temperature (100 °C) was required to generate **4o** in 78% after 48 h (entry 7). Replacing a phenyl substituent with a triethylsilyl group in **3p** (entry 8) slightly improved the yield and shortened the reaction time (28 h, 84%) compared to the reaction with **3b** (36 h, 81%; entry 2 in Table 1). As expected, elongation of the ether tether in **3q** significantly slowed the reaction, which took 120 h for full conversion to generate **4q** in 68% yield (entry 9). Replacement of the ether tether with an all-carbon linker in **3r** and **3s** also changed their cyclization behaviour. The reaction of **3r** provided two product **4r** and **4r′** in 78% yield with a 1.2:1 ratio (entry 10). The formation of product **4r′** is the consequence of an initial

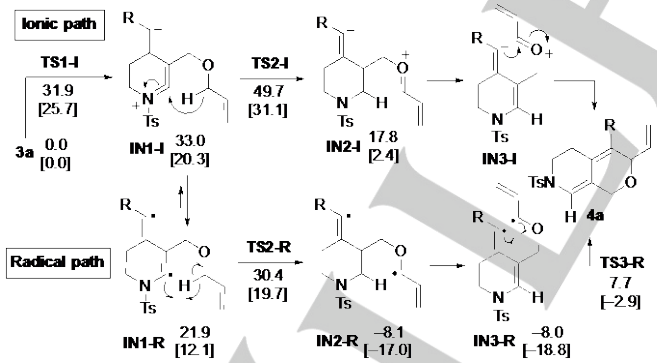
Alder-ene followed Diels-Alder reaction sequence[6] (entry 11). The reaction with *gem*-dimethyl-containing system **3s** did not proceed even at 120 °C and only the unreacted starting material was recovered unchanged after 72 h (entry 11). The lack of

Figure 1. X-ray structure of **4l**



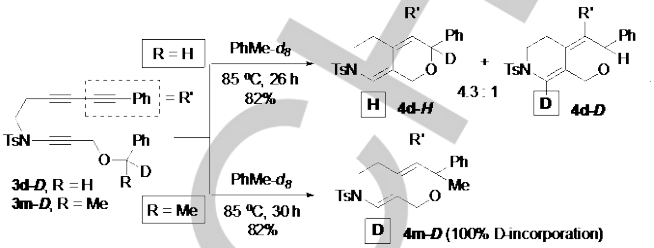
reactivity of **3s** is most likely due to the steric bulk of the *gem*-dimethyl moiety, which prohibits the interaction between the ynamide and the 1,3-diyne counterparts.

Based on these observations, we formulated two plausible mechanistic pathways and performed DFT calculations at the (SMD)/M06-2X/6-311+G(d,p)//B3LYP/6-31G(d) level of theory (Scheme 4). The cyclization of **3a** via an ionic transition state generates zwitterionic intermediate **IN1-1** endergonically, from which the 1,5-hydride shift[11] requires an overall barrier of 49.7 kcal/mol to afford intermediate **IN2-I**. The rotation of the C–O bond in **IN2-I** occurs synchronously with the C–C bond formation to generate product **4a**. The radical pathway is calculated to be energetically more favourable. Although the transition state for the biradical-mediated cyclization[12] of **3a** was not located, biradical **IN1-R** could be formed from **IN1-I** due to a large (11.1 kcal/mol) thermodynamic driving force. The 1,5-hydrogen shift[13] requires 30.4 kcal/mol of activation barrier to generate **IN2-R** exergonically, which is 19.3 kcal/mol lower than that of the ionic pathway. From **IN3-R**, a conformational isomer of **IN2-R**, facile ring closure occurs via **TS3-R** to generate **4a**.

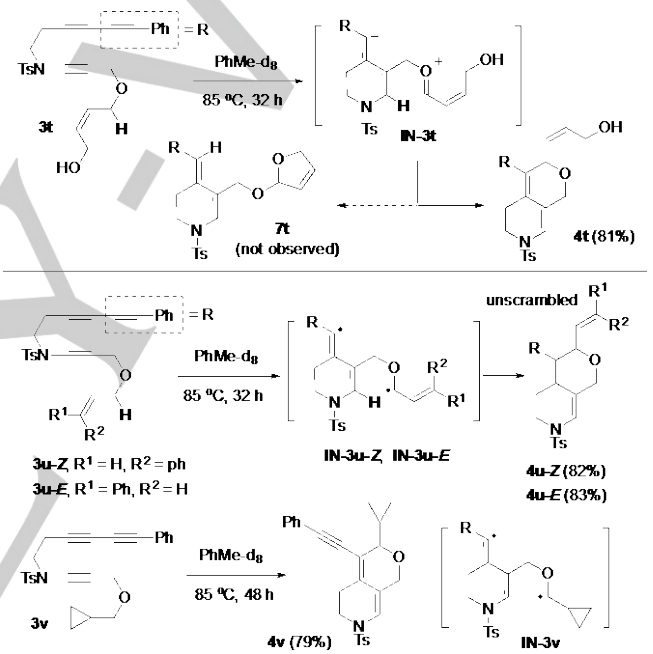


Scheme 4. Relative free energies in toluene solution and in the gas phase (in bracket) are in kcal/mol.

To gain further insight into the reaction mechanism, two deuterium-labeled probes **3d-*D*** and **3m-*D*** were prepared to examine the deuterium-labelling patterns in the product (Scheme 5). The reaction of **3d-*D*** afforded two products **4d-*H*** and **4d-*D*** in a 4.3:1 ratio (82%), and **3n-*D*** provided a single product **4m-*D*** (82%). The comparison of NMR signal of these deuterium-labelled compounds with unlabelled **3d** and **3m** proved that deuterium transfer occurred only to the sp^2-hybridized carbon connected to the Ts*N*-group. Thus, we consider that the current bicyclization reaction proceeds via a concerted 1,5-hydride or hydrogen atom transfer but more information is needed to differentiate these mechanisms.



Scheme 5. Mechanistic hypotheses and deuterium-labelling studies



Scheme 6. Probing cationic and radical mechanisms

At this juncture, we surmised that the reactions of **3t–3v** may provide a clue to differentiate an ionic mechanism involving hydride transfer and a radical mechanism involving hydrogen transfer (Scheme 6). If the reaction of **3t** proceeds through intermediate **IN-3t**, the oxonium moiety and the nearby hydroxyl group would collapse to generate a dihydrofuran-containing product **7t**. The isolated compound from this reaction, however, was identified as **4t** (81%) with the *Z*-alkenyl side chain unscrambled. This observation together with a notable reactivity trend of substrates **3i–3l** where 4-CF_3-containing substrate **3l** afforded the highest yield would disfavour the involvement of oxonim intermediate of type **IN-3t**. On the other hand, if the reaction proceeds through radical intermediates, the putative allylic radical with the *Z*-alkene would isomerize to corresponding *E*-alkenyl radical. To examine this possibility *Z*-styryl substrate **3u-*Z*** and *E*-styryl counterpart **3u-*E*** were prepared and subject to the typical reaction conditions. To our

surprise, in the isolated products **3u-*Z*** (82%) and **3u-*E***, the *Z*- and *E*-styryl configurations were found intact without any scrambling. Also, a cyclopropyl group-containing system **3v** afforded product **4v** (79%) without opening of the cyclopropane moiety, which suggests that the reaction might not proceed via a cyclopropylmethyl radical[14] in intermediate **IN-3v** although it cannot be excluded. The outcomes from the cyclizations of purposefully designed substrates **3t–3v** seem perplexing, especially considering the energetically favourable biradical pathway in DFT-calculation. Except for the biradical-mediated 1,5-hydrogen transfer or the ionic mechanism involving a 1,5-hydride transfer, no other mechanisms reasonably justify the observed cyclization event that involves a remote C–H bond activation to form a new C–C bond under a relatively mild thermal condition.

In conclusion, we discovered an unprecedented thermal ring-closure reaction of ynamide-tethered 1,3,8-triynes to form 3,5,6,7-tetrahydro-1*H*-pyrano[3,4-*c*]pyridine skeleton. Based on the DFT calculation results, we surmise that, instead of forming highly strained keteniminium ion intermediate followed its 1,5-hydride shift, the biradical pathway involving a 1,5-hydrogen shift is the more favorable pathway. However, the experimental data for the cyclization behaviors of substrates containing Z-styryl group (**3u-*Z***) and cyclopropyl group (**3v**) are not fully consistent with the biradical mechanism. Regardless of the actual mechanism, appropriate electronic activation at the hydrogen- or hydride-donating carbon leading to a stabilized radical or oxonium species is crucial for successful cyclization.

Acknowledgements

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Keywords: ynamide • 1,3-diyne • keteniminium • cyclization • hydride transfer • tetrahydro-1*H*-pyrano[3,4-*c*]pyridine

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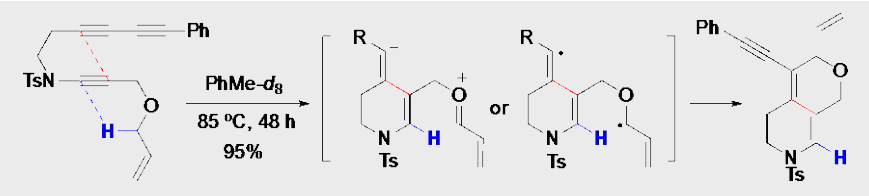

Zwitterion or biradical: Thermal activation of ynamide-tethered 1,3,8-triynes induces a ring-closure to form a 3,5,6,7-tetrahydro-1*H*-pyrano[3,4-*c*]pyridine skeleton. A strained keteniminium or a biradical formation followed a 1,5-hydride or a hydrogen shift are the key elementary steps and appropriate electronic activation at the hydrogen- or hydride-donating carbon leading to a stabilized oxonium or a radical species is crucial for effective cyclization.

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Cyclization of Ynamide-tethered 1,3,8-Triynes