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Cyclization

Triflic Acid-Catalyzed Enynes Cyclization: A New Strategy beyond Electrophilic π-Activation

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Abstract: The cyclization of enynes, catalyzed by a transition metal, represents a powerful tool to construct an array of cyclic compounds through electrophilic π-activation. In this paper, we disclose a new and efficient strategy for enynes cyclization catalyzed by triflic acid. The salient features of this transformation includes a broad substrate scope, metal free synthesis, open flask and mild conditions, good yields, ease of operation, low catalyst loading, and easy scale-up to gram scale. A preliminary mechanism study demonstrated that the activation model of the reaction was σ-activation, which is different from the transition-metal-catalyzed enynes cyclization. Our strategy affords a complementary method to the traditional strategies, which use transition-metal catalysts.

Carbo- and heterocycles are essential and fundamental skeletons found in numerous natural products, biologically active compounds, and drugs. Among reported strategies, a transition-metal-catalyzed cyclization of enynes through electrophilic π-activation has emerged as a general and efficient method to construct various functionalized cyclic compounds from relatively simple linear unsaturated substrates in a single step (Scheme 1 a).[1] However, these transformations usually rely on expensive and even toxic noble metals, such as rhodium, gold, palladium, and so forth. Thus, the development of a metal-free strategy to deliver functionalized cyclic compounds is highly desirable.

Compared to Lewis acids and transition-metal catalysts, Brønsted acids are easy to handle, low price, environment friendly, generally stable toward oxygen and water, and can be stored for a long period of time. Brønsted acids are usually applied to activate carbonyl, imine, alkene, alkyne, and hydroxyl groups, forming oxonium, iminium, carbocation, and vinylic carbocation, all of which can be attacked by nucleophiles. Over the past decades, Brønsted acids exhibited their unique privilege and became more and more commonly used for the carbon-carbon bond-forming reaction.[2] Inspired by biomimetic cationic cyclizations of polyenyne derivatives developed some decades ago and the recent work developed by Yamamoto,[3] we reasoned that the concept of using Brønsted acids could be applied to the cyclization of enynes to synthesize important cyclic compounds, which are beyond traditional electrophilic π-activation catalyzed by metals. We assumed that the carbonyl of alkyne enone derivatives can be activated selectively by Brønsted acids to give allylic carbocation **I-A**. Next, the alkyne group would attack this carbocation to generate alkenyl cation intermediate **I-B**,[4] which subsequently could be intercepted by nucleophiles to furnish the desired cyclic compounds (Scheme 1 b). Herein, we report an unprecedented and attractive triflic acid-catalyzed method, which is beyond the traditional electrophilic π-activation protocol, to synthesize cyclic compounds.

Due to the importance of cyclic 1,5-diketones,[5] which are synthesized from enynes using a ruthenium catalyst, as synthetic synthons,[6] we selected this skeleton as our target. Accordingly, we synthesized enyne **1 a** as the model substrate to test our idea. Because of the efficiency of triflic acid in numerous transformations,[7] we employed it primarily as the catalyst in the reaction of **1 a** with water. To our delight, the reaction was carried out smoothly and afforded the desired product **2 a** in 93% NMR yield with 3:1 d.r. (Table 1, entry 1). Although other Brønsted acids, such as H_2SO_4, CF_3CO_2H, $TsOH{\cdot}H_2O$, were also tested, no better results were obtained (entries 2–4), which indicate that the acidity of the Brønsted acid is vital to this transformation. Besides, the screening of solvents shows that dichloroethane is the best one. It was a little surprising that the reaction did not work in THF and toluene (entry 5 versus 7), which may be attributed to the coordination between oxygen and H^+ in THF and low solubility of triflic acid in toluene. Further optimization revealed that the loading of triflic acid could be reduced to 2.5 mol% (entry 8), resulting in a comparable result. Pleasingly, wet DCE can dramatically accelerate the transformation, and the reaction could be done in one minute, affording the desired **2 a** in 99% yield (entry 9). Then, we wanted to convert the diastereoisomers to only one by treating with bases. Gratifyingly, single *trans* isomer was obtained in 88% yield after the reaction mixture in dichloroethane was treated with DBU (4.0 equiv) at r.t. (entry 10).

With the optimized conditions in hand, a variety of enynes **1** were prepared and subjected to the aforementioned condi-

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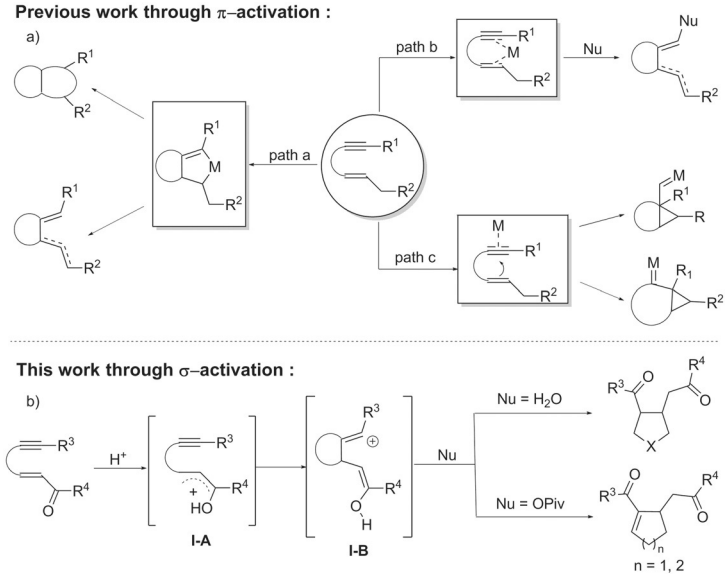
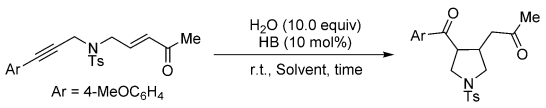


Scheme 1. Previous strategies and our design for the enyne cyclization.

tions. The results are summarized in Scheme 2. When the linkage moiety was TsN, the reaction of substrates **1b**–**1d** with electron-donating groups or weak electron-withdrawing groups at the *para*-position of the phenyl ring attached the alkynyl part could afford the corresponding adducts **2b**–**2d** in good yields. The structure of compound **2c** was further confirmed as the *trans* isomer by single-crystal X-ray crystallography. The reaction of **1e** with a strong electron-withdrawing group (NO_2) at the *para*-position of the phenyl ring afforded **2e** in 60% yield, probably because the conjugated nitro group lowered the nucleophilicity of alkyne moiety and the stability of the forming alkenyl carbocation intermediate. Meanwhile, the position of the substituent had no effect on the yield (e.g., **2f**, **2g**). When the methyl group was introduced to the terminal of the alkyne, substrate **1h** needed higher temperature (70 °C), delivering **2h** in 35% yield, and **2h'** by a further aldol annulation in 38% yield. Compared to the corresponding ketone, the aldehyde substrates (**1i**–**1n**) showed lower reactivity, and the desired products **2i**–**2n** could still be obtained in 51–71% yields at 70 °C that may be attributed to the weaker coordination ability of the aldehyde to the proton and side reactions of the aldehyde under basic conditions with DBU. Besides pyrrole derivatives, both 3,4-disubstituted tetrahydrofurans **2o**–**2q** and all-carbon ring cyclopentanes **2r**–**2t** could be stereoselectively synthesized in moderate to good yields.

To gain mechanistic insights of the reaction, several control experiments were conducted. Because the Brønsted acid-catalyzed hydration of alkynes[8] is well known and an alternative pathway through tandem hydration/Michael addition might be also reasonable for this transformation, intermediate **1a'** was synthesized and subject-

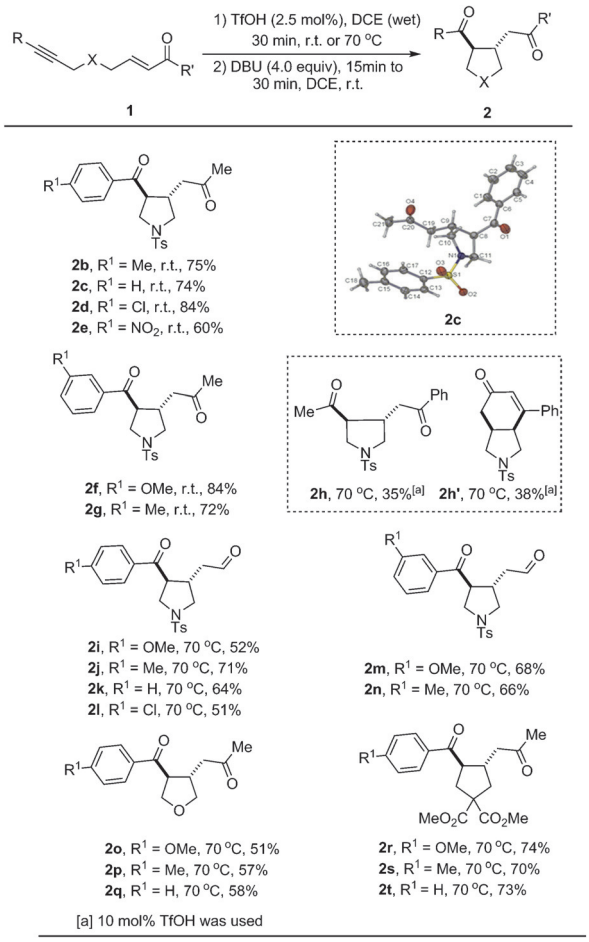
Table 1. Optimization of reaction conditions.[a]



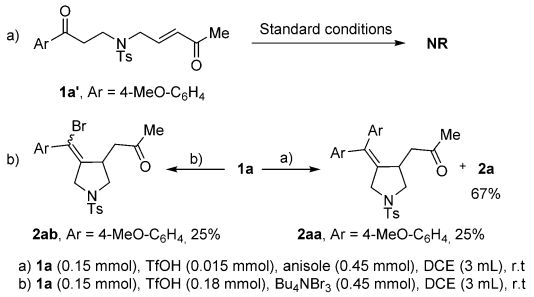
1a **2a**

Entry	HB	Solvent	Time	Yield [%][f]	d.r.
1	TfOH	$Cl(CH_2)_2Cl$	12 h	93	3:1
2	CF_3CO_2H	$Cl(CH_2)_2Cl$	36 h	trace	–
3	H_2SO_4	$Cl(CH_2)_2Cl$	36 h	trace	–
4	$TsOH·H_2O$	$Cl(CH_2)_2Cl$	36 h	67	3:1
5	TfOH	Toluene	36 h	NR	–
6	TfOH	CH_3CN	36 h	70	5:1
7	TfOH	THF	36 h	NR	–
8[b]	TfOH	$Cl(CH_2)_2Cl$	36 h	91	2:1
9[b,c]	TfOH	$Cl(CH_2)_2Cl$	1 min	>99	1:1
10[b,c,d]	TfOH	$Cl(CH_2)_2Cl$	31 min[e]	(88)	

[a] **1a** (0.15 mmol) was dissolved in solvent (3 mL). [b] TfOH (2.5 mol%) was used. [c] Wet dichloroethane (3 mL) was used and no extra water was added. [d] DBU (4.0 equiv) was added after the reaction was complete. [e] The solution of **1a** in DCE was treated with TfOH (2.5 mol%) for 1 min, then DBU was added and stirred at r.t. for 30 min. [f] Yields were determined by ^1H NMR using CH_2Br_2 as internal standard. Numbers in parenthesis are isolated yields. TfOH = triflic acid. DBU = 1,5-diazabicyclo-[4.3.0] non-5-ene.



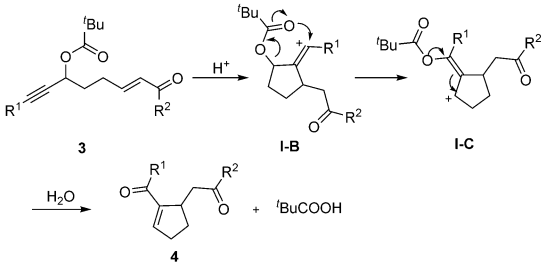
Scheme 2. Synthesis of carbo- and heterocycles.



Scheme 3. Preliminary mechanism study.

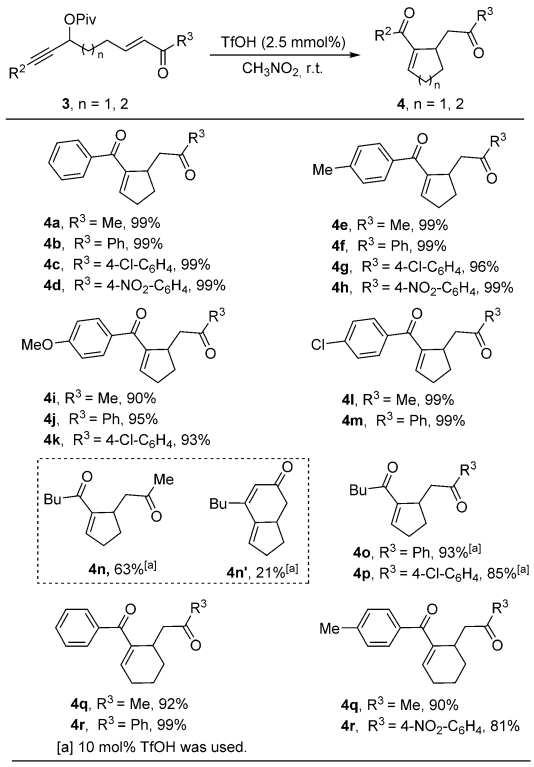
ed to the standard conditions but no desired product was detected (Scheme 3a), which indicated that the hydration/Michael addition pathway through **1a'** might be ruled out. Besides, other nucleophiles, such as anisole and bromide, were also used to trap the alkenyl cation intermediate **I-B**. For the reaction of **1a** and anisole, the desired product **2aa** was obtained in 25% yield along with **2a** (67% yield) due to H_2O in DCE. **1a** was consumed completely and only **2ab** was isolated in 25% yield when **1a** was treated with Bu_4NBr_3 under the standard conditions.

Because the intermolecular trapping of alkenyl cation **I-B** was successful, we next wanted to extend this strategy to intramolecular version. Inspired by the transition-metal-catalyzed propargyl ester rearrangement,[9–12] we envisioned that a pivolate group adjacent to the alkyne moiety that can act as an inner nucleophile, could trap the alkenyl carbocation spontaneously and the resulting intermediate **I-C** could undergo further rearrangement and hydrolysis to offer unsaturated carbocycles (Scheme 4). The formed scaffold (**4**), which is a key synthon in natural products synthesis,[13] is normally synthesized by the Rauhut–Currier reaction,[14] albeit with limited regioselectivity.



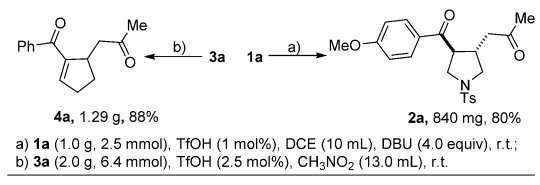
Scheme 4. Our proposal for the intramolecular trapping.

To prove our hypothesis, we chose **3a** as the model substrate.[15] To our delight, the desired product **4a** was obtained (99% yield) in an open flask catalyzed by triflic acid (2.5 mol%) with wet nitromethane as the solvent. Fortunately, our method is applicable to synthesize a series of symmetrical and unsymmetrical unsaturated carbocycles. Of particular note is that our protocol allows to synthesize cycloadducts that would be regioselectively disfavored by the traditional Rauhut–Currier reaction, such as **4a**, **4d**, **4h**, **4i**, and so forth.[16] The scope of the reaction is surveyed in Scheme 5. In general, the desired cycloadducts could be obtained in high to excellent yields. It was found that alkyl substituents and electron-rich and -poor aryl substituents at both R^2 and R^3 positions were tolerated. For butyl-substituted substrate **3n**, 10 mol% loading of the catalyst was required, offering the corresponding product **4n** in 63% yield.

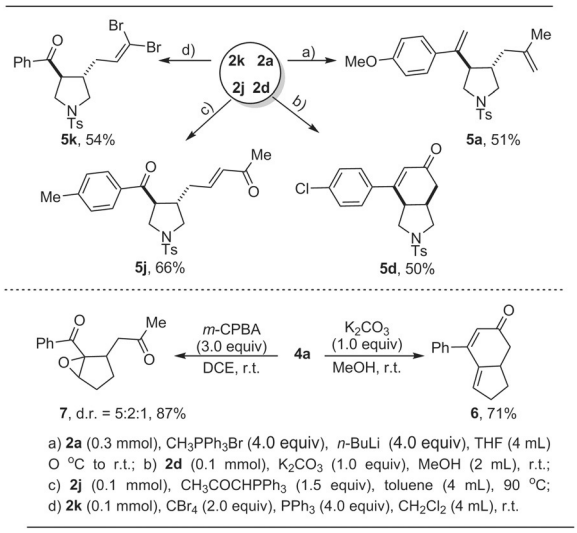


Scheme 5. Preparation of unsaturated carbocycles.

To demonstrate the synthetic value of our methodology, two gram-scale reactions were performed (Scheme 6). Additionally, several further transformations of the products were also conducted (Scheme 7). The Wittig olefin reaction of **2a** and **2j** afforded the desired products **5a** and **5j**, respectively, in moderate yields. Besides, further annulation products **5d** and **6** could be obtained in 50 and 71% yields, respectively, in the presence of K_2CO_3 in methanol. The treatment of aldehyde **2k** with PPh_3 and CBr_4 led to the corresponding homologated dibromoolefin product **5k** in 54% yield. The olefin epoxidation of **4a** with *m*-CPBA delivered **7** in good yield.



Scheme 6. Gram-scale synthesis.



Scheme 7. Products transformations.

In summary, we have developed a novel and efficient triflic acid-catalyzed cyclization of enynes. This method provides a facile access to structurally diverse carbo- and heterocycles in moderate to excellent yields. The salient features of this transformation includes a broad scope of substrates, metal free synthesis, open flask and mild conditions, high yields, ease of operation, low catalyst loading, and easy scale-up to gram scale. A preliminary mechanism study indicated that the activation model was indeed σ-activation rather than the normal π-activation, which is catalyzed by a metal. We believe that our strategy will shine some light on the design of novel pathways for enynes and Brønsted acid-catalyzed reactions.

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Keywords: σ-activation · enynes · organic chemistry · synthetic methods · triflic acid

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