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Brønsted Acid-Catalyzed Cascade Cycloisomerization of Enynes via Acetylene Cations and sp^3-Hybridized C−H Bond Activation

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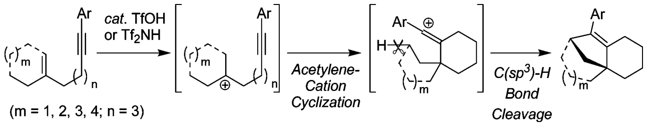
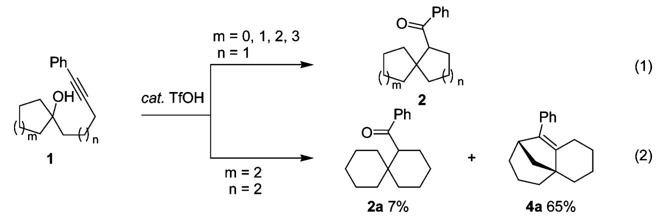
Catalytic functionalization of sp^3-hybridized C−H bonds is a straightforward and potentially powerful transformation in organic chemistry.[1−3] Activation of C(sp^3)−H bonds is still considered a difficult challenge because of their high dissociation energy, but some versatile catalytic transformations have been developed in the past few years. To date, use of transition-metal catalysts has emerged as a valuable alternative to conventional C−C bond-forming reactions through cleavage of activated or inactive C(sp^3)−H bonds.[1] Most recently, Lewis acid catalysts such as gold or platinum salts and BF_3OEt_2 have been demonstrated to cleave some *activated* C(sp^3)−H bonds.[2,3] However, to the best of our knowledge, the Brønsted acid-catalyzed cleavage of an *inactive* C(sp^3)−H bond has never been reported.[3g] Herein, we report an unprecedented Brønsted acid-catalyzed cascade cycloisomerization of 1,6- or 1,7-enynes that affords tri- or bicyclic compounds in good to high yields. The reaction most likely proceeds through a vinyl cation that is formed by acetylene cation cyclization, and subsequent ring closure of the benzylidene cation with an sp^3-hybridized carbon occurs via the cleavage of an entirely inactive C(sp^3)−H bond (Scheme 1).

Scheme 1

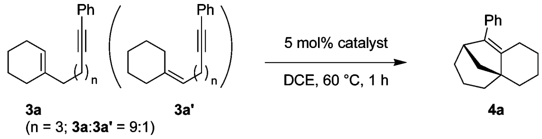


We recently reported that alkynyl cyclic tertiary alcohols **1** (*n* = 1, eq 1) undergo triflic acid-catalyzed acetylene cation cyclization to give various spirocycles **2**:[4]



During this study, we noticed that when 1-(6-phenylhex-5-ynyl)-cyclohexanol (**1a**; *m* = 2, *n* = 2, eq 2) was used, the tricylic product **4a** was formed as the major product instead of the anticipated spirocycle **2a**. It occurred to us that the chemical yield of this interesting product **4a** would be enhanced by the use of the corresponding dehydrated enyne as a substrate.[5] Consequently, a brief optimization was carried out by treating 1,7-enynes **3a** (containing 10% 1,6-enyne **3a′**) with several Brønsted acids and cationic gold catalysts, as shown in Table 1. TFA and *p*-TsOH were completely ineffective, while the use of $HSbF_6$ gave a low yield of **4a** (entries 1−3). Triflic acid exhibited the highest catalytic activity, affording **4a** in 87% yield (entry 5).[6] Tf_2NH catalyst was also effective, although the yield was lower than that with triflic acid (entry 4). Cationic gold catalysts were also effective, giving **4a** in moderate yields (entries 6−9) without formation of any byproducts arising from ordinary alkyne activation.[7] The results indicated unambiguously that TfOH or Tf_2NH catalyst was indispensable for this cascade cyclization.

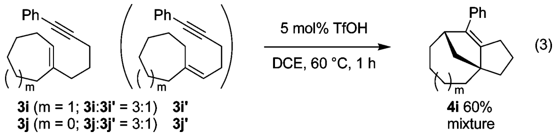
Table 1. Optimization of the Catalyst[a]



entry	catalyst	yield of 4a (%)[b]
1	CF_3CO_2H	0[c]
2	p-TsOH·H_2O	0[c]
3	$HSbF_6\cdot 6H_2O$	15[c]
4	Tf_2NH	68
5	TfOH	87[d]
6	$AuClPPh_3/AgOTf$	40
7	$AuClPPh_3/AgSbF_6$	55
8	$AuClP(^n\mathrm{Bu})_2(o\text{-Bip})/AgSbF_6$	57
9	$AuClPPh_3/AgNTf_2$	50

[a] Catalyst (5 mol %) was added to a 1,2-dichloroethane (DCE) solution (0.2 M, 2 mL) of **3a**/**3a′** (9:1, 0.4 mmol), and the mixture was stirred at 60 °C for 1 h. [b] ^{1}H NMR yields determined using CH_2Br_2 as an internal standard. [c] Recovery of enynes. [d] Isolated yield.

The scope of the TfOH-catalyzed cascade cyclization of cyclic enynes **3** is summarized in Table 2. Substrates **3** having various electron-withdrawing aromatic groups at the alkynyl terminus produced the desired tricycles **4b**−**d** in high yields (entries 1−3). It is noteworthy that when R was an electron-donating aromatic group such as *p*-tolyl, an inseparable mixture of the corresponding tricycle and an unknown product was obtained. Cyclization of enynes having a cycloheptene (**3e**, **3f**), cyclooctene (**3g**), or cyclononene (**3h**) moiety gave the corresponding tricycles **4e**−**h** in good to excellent yields (entries 4−7). Enyne **3i** tethered with a shorter carbon chain efficiently furnished the corresponding tricycle **4i**, although the cyclohexene-substituted enyne **3j** gave a complex mixture of products (eq 3). These experiments indicate that substrates having carbocycles larger than six-membered rings (*m* = 1) are suitable for the formation of the corresponding tricyles.



The cyclization reaction was extended to acyclic 1,7-enynes **5**, as shown in Table 3. To our delight, the TfOH-catalyzed reaction

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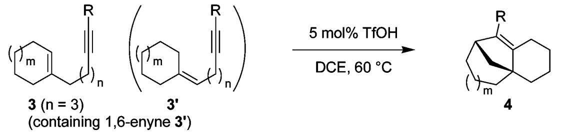
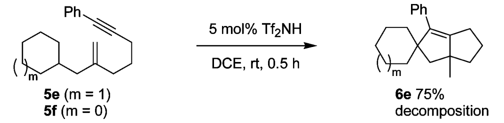
Table 2. TfOH-Catalyzed Cascade Cyclization of Cyclic Enynes[a]



entry	*m*	R	**3/3′** (ratio)[b]	time (h)	**4**	yield (%)[c]
1	1	4-ClC$_6$H$_4$	**3b/3b′** (10:1)	2	**4b**	91
2	1	4-CF$_3$C$_6$H$_4$	**3c/3c′** (8:1)	2	**4c**	86
3	1	4-BsOC$_6$H$_4$[d]	**3d/3d′** (13:1)	4	**4d**	90
4	2	2-naphthyl	**3e/3e′** (3:1)	1	**4e**	99
5	2	C$_6$H$_5$	**3f/3f′** (2.3:1)	4	**4f**	96
6	3	C$_6$H$_5$	**3g/3g′** (10:1)	1	**4g**	95
7	4	C$_6$H$_5$	**3h/3h′** (6:1)	9	**4h**	83

[a] TfOH (5 mol %) was added to a DCE solution (0.2 M, 2 mL) of enynes (0.4 mmol), and the mixture was stirred at 60 °C. [b] Ratio of 1,7-enyne **3** and 1,6-enyne **3′**. Ratio was determined by ^{1}H NMR spectroscopy. [c] Isolated yields. [d] Bs = brosyl.

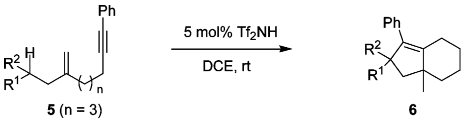
of the simple 1,7-enyne **5a** bearing an ethyl group at the olefin side chain gave bicyclic hydrocarbon **6a** in 33% yield at 40 °C (entry 2), but the use of Tf$_2$NH catalyst afforded a 41% yield of **6a** (entry 1). Thus, Tf$_2$NH was chosen as the catalyst in the following acyclic enyne cyclization. Substrate **5b** having a tertiary C−H bond at the side chain produced the corresponding bicycle **6b** in good yield at room temperature (entry 3).[8] Cyclization of enynes **5c** and **5d** having a cyclic tertiary C−H bond efficiently afforded the expected bicycles **6c** and **6d**, respectively, in high yields (entries 4 and 5). The reaction also worked well with the cyclohexyl-substituted 1,6-enyne **5e**, although the cyclopentyl-substituted 1,6-enyne **5f** did not furnish the expected product; the reaction resulted in decomposition of the enyne substrate (eq 4):



(4)

Acyclic enynes **5** (Table 3) showed a higher reactivity than cyclic enynes **3** (Table 2).

Table 3. Tf$_2$NH-Catalyzed Cascade Cyclization of Acyclic Enynes[a]

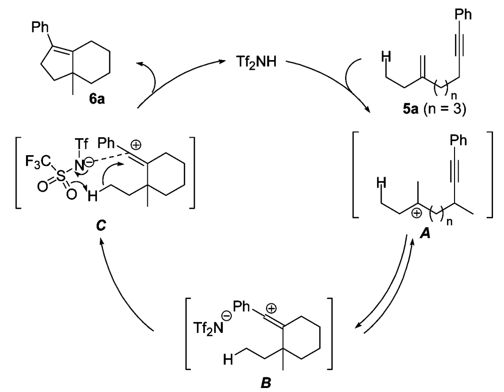


entry	R^1, R^2	**5**	time (h)	**6**	yield (%)[b]
1	H, H	**5a**	1	**6a**	41
2	H, H	**5a**	1	**6a**	33[c]
3	Me, Me	**5b**	1	**6b**	74
4	−(CH$_2$)$_4$−	**5c**	0.5	**6c**	82
5	−(CH$_2$)$_5$−	**5d**	0.5	**6d**	98

[a] Tf$_2$NH (5 mol %) was added to a DCE solution (0.2 M, 2 mL) of enyne (0.4 mmol), and the mixture was stirred at room temperature. [b] Isolated yields. [c] TfOH was used as a catalyst instead of using Tf$_2$NH.

A proposed reaction mechanism is shown in Scheme 2. Activation of the alkene moiety of the enyne by the Brønsted acid leads to the stable tertiary carbocation intermediate **A**. Attack of the alkyne moiety at the cation in **A** affords the benzylidene cation **B**. The interaction between the anion and the benzylidene cation in **C** should lower the energy of C−H bond cleavage,[9] probably through formation of a weak hydrogen bond. The bond rearrangement as shown in **C** affords the corresponding product and regenerates the Brønsted acid. On the other hand, an alternative stepwise mechanism such as a 1,5-hydride shift[3] in **B** followed by an addition/elimination pathway cannot be ruled out.[10]

Scheme 2. Proposed Mechanism



Irrespective of the precise mechanism, we have demonstrated that a Brønsted acid catalyst promotes the cleavage of an entirely inactive C(sp^3)−H bond to form a new C−C bond. Further investigation of mechanistic insight and extension to the activation of sp^2-hybridized C−H bonds are in progress.

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Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(3) For selected C(sp^3)−H bond activation via a 1,5-hydride shift, see: (a) Vadola, P. A.; Sames, D. *J. Am. Chem. Soc.* **2009**, *131*, 16525. (b) McQuaid, K. M.; Sames, D. *J. Am. Chem. Soc.* **2009**, *131*, 402. (c) Pastine, S. J.; McQuaid, K. M.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 12180. (d) Tobisu, M.; Nakai, H.; Chatani, N. *J. Org. Chem.* **2009**, *74*, 5471. (e) Shikanai, D.; Murase, H.; Hata, T.; Urabe, H. *J. Am. Chem. Soc.* **2009**, *131*, 3166. (f) Odedra, A.; Datta, S.; Liu, R.-S. *J. Org. Chem.* **2007**, *72*, 3289. (g) Zhang, C.; Murarka, S.; Seidel, D. *J. Org. Chem.* **2009**, *74*, 419.

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(5) For Brønsted acid-mediated enyne cyclization, see: Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 10204.

(6) Other solvents, such as THF, toluene, and acetonitrile, were almost ineffective even under heating conditions (80 °C). Also, see ref 4.

(7) (a) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (b) Michelet, V.; Toullec, P. Y.; Genêt, J.-P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268.

(8) Secondary C(sp^3)−H bonds were also cleaved in the present reaction. When R^1 was an ethyl group in **5** (R^2 = H; Table 3), the reaction reached completion in 0.5 h at room temperature, giving an inseparable mixture of the corresponding two diastereomeric bicycles **6** and its double-bond-migrated product in 85% total yield (see the Supporting Information).

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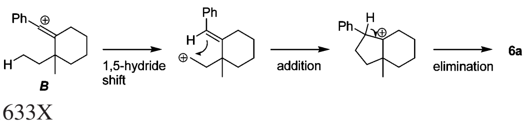
(10) An alternative 1,5-hydride shift mechanism is shown below:



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