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TfOH-catalyzed intramolecular alkyne–ketone metathesis leading to highly substituted five-membered cyclic enones†‡

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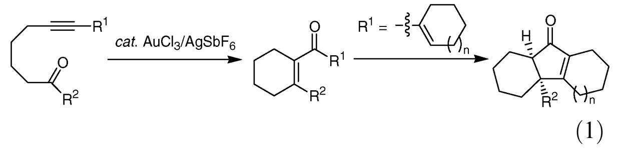
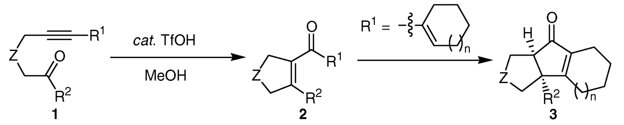
The intramolecular carbocyclization of tethered alkynyl ketones to five-membered cyclic enones is shown to be catalyzed by trifluoromethanesulfonic acid in MeOH, proceeding in good to excellent yields and with high selectivities.

The catalytic addition of C–O double bonds to C–C triple bonds, so-called alkyne–carbonyl metathesis, is an attractive method for the construction of highly substituted enones, because it can be used to construct new C–C and C–O bonds simultaneously in an efficient and atom-economic manner as an alternative to the Wittig reaction. Although Lewis acid- or Brønsted acid-catalyzed inter- and intramolecular alkyne–aldehydes metathesis giving the corresponding enones has been investigated extensively,[1] the alkyne–ketone metathesis was considered to be problematic due to the severe limitations on the structure of the alkynes and ketones.[2] For example, Harding *et al.* reported that BF_3 or HCl promotes intramolecular cyclization of 6-octyn-2-one to give a mixture of five-membered cyclic enone and cyclohexenone.[2f] Recently, Hsung *et al.* reported the BF_3-catalyzed intramolecular cyclization of special ynamide–ketones leading to the five-membered cyclic enones selectively.[2m]

We recently reported an efficient cationic Au(III)-catalyzed alkyne–carbonyl metathesis of carbon tethered alkynyl ketones to form highly substituted six-membered cyclic enones (eqn (1)).[3] Furthermore, we found that when 1,3-enynyl ketones were employed, fused polycyclic enones could be obtained under the same reaction conditions through tandem alkyne–carbonyl metathesis and Nazarov cyclization (eqn (1)).[4] However, unfortunately, when the reaction was applied to the formation of five-membered cyclic enones, we failed to obtain the corresponding products in good yields, instead a complex mixture of products was formed. It occurred to us that the use of a π-electrophilic catalyst other than coinage metals may produce the corresponding five-membered cyclic enones in the alkyne–ketone metathesis. Herein we report that, by the use of TfOH catalyst in MeOH, the intramolecular transformation of the tethered alkynyl ketones **1** into the tetrasubstituted five-membered cyclic enones **2** proceeds in good to excellent yields (eqn (2)). Furthermore, the reaction of 1,3-enynyl ketones produces the fused polycyclic enones **3** containing a cyclopentenone ring efficiently (eqn (2)).



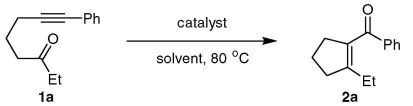
(1)



(2)

Initially, according to the previous results,[3] we focused on screening the reaction conditions, catalysts and solvents, for the selective formation of the tetrasubstituted five-membered cyclic enone **2a** from **1a** (Table 1). The use of $AuCl_3$–$AgSbF_6$, $AgSbF_6$, and TfOH in dichloroethane solvent afforded a complex mixture of products containing a very poor yield of **2a** (entries 1–3). Similarly, the use of other aprotic solvents, such as toluene, THF, CH_3CN, and 1,4-dioxane, gave **2a** in very low yields. Hence, we gave our attention to protic solvents. Fortunately, when MeOH was used as a solvent in

Table 1 Optimization of reaction conditions for the formation of **2a**[a]



Entry	Catalyst (mol%)	Solvent	Time/h	Yield (%)[b]
1	$AuCl_3$–$AgSbF_6$ (2/6)	$(CH_2Cl)_2$	9	30
2	$AgSbF_6$ (5)	$(CH_2Cl)_2$	7	20
3	TfOH (5)	$(CH_2Cl)_2$	9	28
4	$AgSbF_6$ (5)	MeOH	19	87
5	TfOH (5)	MeOH	4	90 (87)
6	Tf_2NH (5)	MeOH	4	90
7	$HClO_4$ (5)	MeOH	18	80
8	$HSbF_6 \cdot H_2O$ (5)	MeOH	22	75
9	HCl (10)	MeOH	22	59
10	CF_3CO_2H (5)	MeOH	22	3
11	TfOH (5)	EtOH	22	68
12	TfOH (5)	^{i}PrOH	22	4
13	TfOH (5)	$(CH_2OH)_2$	22	56

[a] Reaction conditions: **1a** (0.4 mmol), catalyst (2–10 mol%), solvent (0.2 M) at 80 °C. [b] ^1H NMR yield was determined by using CH_2Br_2 as an internal standard. Isolated yield is shown in parentheses.

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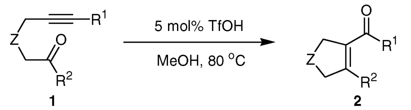
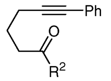
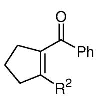
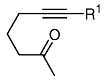
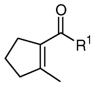
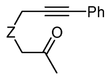
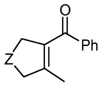
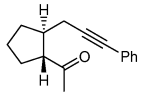
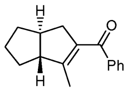
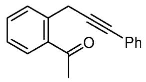
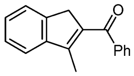
‡ Electronic supplementary information (ESI) available: Experimental procedures and characterization data. See DOI: 10.1039/b905954g

the presence of $AgSbF_6$ catalyst, **2a** was obtained in 87% yield (entry 4). Further investigation of various Lewis acids and Brønsted acids led to the finding that TfOH and Tf_2NH catalysts produce the expected cyclic enone **2a** in a high yield in a shorter reaction time (entries 5 and 6). Other Brønsted acids such as $HClO_4$, $HSbF_6$, and HCl were also effective, while CF_3CO_2H gave a trace amount of **2a** (entries 7–10). It is noteworthy that other protic solvents, such as EtOH, ^{i}PrOH, and ethylene glycol, were less effective (entries 11–13). These results indicate that the use of methanol is crucial for the selective formation of the five-membered cyclic enones.

The substrate scope of TfOH-catalyzed cyclization of the alkynyl ketones **1** is summarized in Table 2. The reaction of **1b** and **1c** bearing a methyl and bulky isopropyl group at R^2 in the presence of 5 mol% of TfOH in MeOH at 80 °C gave the corresponding tetrasubstituted five-membered cyclic enones **2b** and **2c** in 90% and 75% yields, respectively (entries 1 and 2). The electronic characteristics of an aromatic ring at R^1 did not exert a significant influence on the yield of **2**. Substrates **1d** and **1e** having an electron-donating and an electron-withdrawing aromatic group at the alkynyl terminus produced the desired enones **2d** and **2e** in high yields, though the reaction of **1e** required a longer reaction time (entries 3 and 4). Not only the naphthyl substituted alkynyl ketone **1f**, but also hetero-aromatic ring, such as thiophenyl (**1g**) and furanyl (**1h**), substituted alkynyl ketones afforded the corresponding enones in high yields (entries 5–7). The reaction of **1i** and **1j**, having a phenyl substituent and a geminal group in the tethered moiety, proceeded smoothly to give **2i** and **2j** in 89% and 93% yields, respectively (entries 8 and 9). The cyclopentane and benzene tethered alkynyl ketones **1k** and **1l** were suitable substrates for the formation of the bicyclic enones **2k** and **2l** (entries 10 and 11).

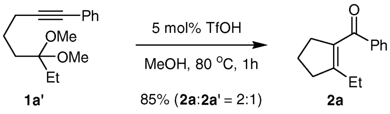
Table 2 TfOH-catalyzed alkynyl ketone cyclization for the formation of **2**[a]



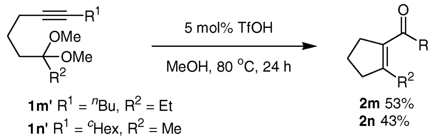
Entry	Substrates	**1**	Time/h	Products	**2**	Yield (%)[b]
1		**1b** R^2 = Me	4		**2b**	90
2		**1c** R^2 = ^{i}Pr	15		**2c**	75
3		**1d** R^1 = 4-MeC_6H_4	4		**2d**	95
4		**1e** R^1 = 4-ClC_6H_4	36		**2e**	88
5		**1f** R^1 = 2-naphthyl	7		**2f**	85
6		**1g** R^1 = 2-thiophenyl	4		**2g**	94
7		**1h** R^1 = 2-furanyl	7		**2h**	89
8		**1i** Z = CHPh	4		**2i**	89
9		**1j** Z = $C(CO_2Me)_2$	36		**2j**	93
10		**1k**	6		**2k**	83
11		**1l**	7		**2l**	91

[a] Reaction conditions: **1** (0.4 mmol), TfOH (5 mol%) in MeOH (0.2 M) at 80 °C in a pressure vial for the time shown in the Table. [b] Isolated yield.

In order to rationalize the role of methanol in this acid-catalyzed alkyne–carbonyl metathesis, we performed the reaction with the tethered alkynyl dimethoxy ketal **1a′**[5] under the standard reaction conditions (eqn (3)). The reaction was accomplished in 1 h, affording a 2 : 1 mixture of the desired enone **2a** and the ketalized product **2a′** in 85% yield. Treatment of the enone **2a** with 5 mol% of TfOH in MeOH at 80 °C did not give the ketalized product **2a′** at all. These experimental results suggest that the present reaction proceeds through *in situ* formation of ketal **1a′**. However **2a′** was not formed in the reaction of **1a**. Perhaps **2a′** might be converted to **2a** under the conditions of Table 2. Accordingly, we thought that not only **1a′** but also the hemi-ketal intermediate ***A*** might be involved as reactive intermediates (Scheme 1). The occurrence of a ketal species was further supported by the following experiment (eqn (4)). In general, the reaction of alkynyl ketones substituted with an alkyl group at R^1 did not proceed well.[6] However, the reaction of the tethered alkynyl dimethoxy ketals **1m′** and **1n′** having a *n*-butyl and *c*-hexyl group at the alkynyl teminus gave the corresponding products **2m** and **2n** in 53% and 43% yields, respectively. This result suggests that a ketal species gives the desired product more easily and efficiently than the corresponding ketone.



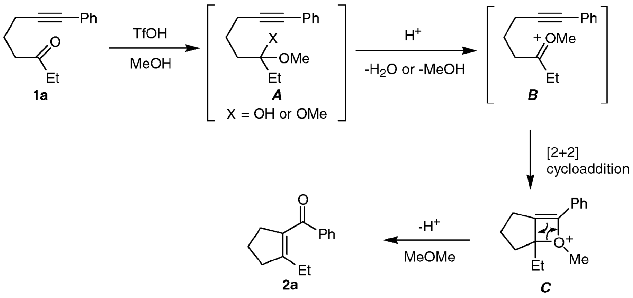
(3)



(4)

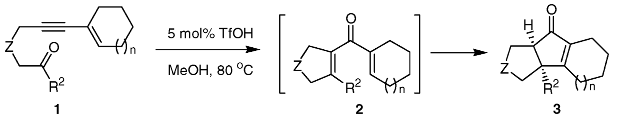
A proposed reaction mechanism is shown in Scheme 1. The reaction of ketone **1a** with TfOH in MeOH generates the dimethoxy ketal and/or hemi-ketal ***A***. Subsequent demethanolation or dehydration affords the oxonium species ***B***. The intramolecular [2 + 2] cycloaddition would form the oxete ***C***,[1b,2f] which leads to **2a** through a ring opening of oxete.[7]

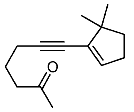
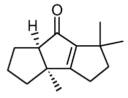
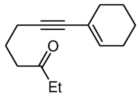
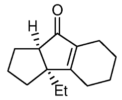
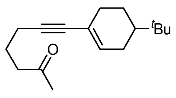
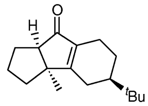
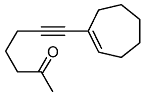
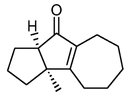
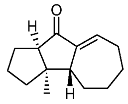
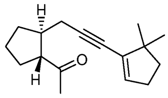
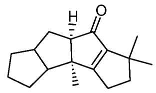
Next, we extended this methodology to the tandem alkyne–carbonyl metathesis and Nazarov reaction[8] of 1,3-enynyl ketones for the synthesis of various fused tri- and tetracyclic enones containing a cyclopentenone ring. The reaction with the enynyl ketones having cyclopentene (**1o**) and cyclohexene



Scheme 1 A proposed mechanism.

Table 3 TfOH-catalyzed tandem cyclization of 1,3-enynyl ketones **1**^{a}



Entry	Substrates	1	Time/h	Products	3	Yield (%)^b
1		**1o**	20		**3o**	68
2		**1p**	7		**3p**	80
3		**1q**	4		**3q**	80 (7 : 1)
4		**1r**	4		**3r**	63
					**3r′**	25
5		**1s**	36		**3s**	63^c (1.7 : 1)

^{a} Reaction conditions: **1** (0.4 mmol), TfOH (5 mol%) in MeOH (0.2 M) at 80 °C in a pressure vial. ^{b} Isolated yield. ^{c} A mixture of two diastereomers.

(**1p**) moieties gave the corresponding linear tricycles **3o** and **3p** in 68% and 80% yield, respectively (Table 3, entries 1 and 2). The enynyl ketone **1q** bearing a sterically bulky *tert*-butyl on the 4-position of the cyclohexene ring was subjected to the reaction conditions affording a 7 : 1 mixture of diastereomers **3q** with the *cis-anti* isomer as a major diastereomer (entry 3). The reaction of the enynyl ketone **1r** having a cycloheptene moiety afforded 63% of the corresponding tricycle **3r** along with 25% of a single diastereomer **3r′**, in which the double bond was away from the ring-fused position (entry 4). Perhaps the double bond migration took place to avoid ring strain. The cyclopentane tethered enynyl ketone **1s** underwent the tandem cyclization smoothly to give a 1.7 : 1 mixture of two diastereomers of the corresponding linear tetracycle **3s** in 63% yield (entry 5).

In conclusion, we have developed an efficient TfOH-catalyzed alkyne–carbonyl metathesis for the selective synthesis of five-membered cyclic enones from tethered alkynyl ketones. The reaction proceeds through hemi-ketals or ketals generated *in situ* in MeOH. Further extension of this method led to the tandem alkyne–carbonyl metathesis and Nazarov cyclization of 1,3-enynyl ketones, forming the fused tri- and tetracyclic enones. Further investigation of mechanistic details and application of the present methodology to the synthesis of biologically active compounds are in progress.

Notes and references

1 (*a*) For alkyne–aldehyde metathesis, see: M. Curini, F. Epifano, F. Maltese and O. Rosati, *Synlett*, 2003, 552; (*b*) J. U. Rhee and M. Krische, *Org. Lett.*, 2005, **7**, 2493; (*c*) A. Saito, M. Umakoshi, N. Yagyu and Y. Hanazawa, *Org. Lett.*, 2008, **10**, 1783; (*d*) G. S. Viswanathan and C.-J. Lee, *Tetrahedron Lett.*, 2002, **43**, 1613; (*e*) C. González-Rodríguez, L. Escalante, J. A. Varela, L. Castedo and C. Saá, *Org. Lett.*, 2009, **11**, 1531.

2 (*a*) C. E. Harding and M. Hanack, *Tetrahedron Lett.*, 1971, **12**, 1253; (*b*) R. J. Balf, B. Rao and L. Weiler, *Can. J. Chem.*, 1971, **49**, 3135; (*c*) M. Hanack, C. E. Harding and J. Derocque, *Chem. Ber.*, 1972, **105**, 421; (*d*) G. L. Lang and T.-W. Hall, *J. Org. Chem.*, 1974, **39**, 3819; (*e*) C. E. Harding and G. R. Stanford, *J. Org. Chem.*, 1989, **54**, 3054; (*f*) C. E. Harding and S. L. King, *J. Org. Chem.*, 1992, **57**, 883; (*g*) J. Siso, A. Balog and D. P. Curran, *J. Org. Chem.*, 1992, **57**, 4341; (*h*) J. R. Grunwell, M. F. Wempe and J. Mitchell, *Tetrahedron Lett.*, 1993, **34**, 7163; (*i*) A. Balog and D. P. Curran, *J. Org. Chem.*, 1995, **60**, 337; (*j*) A. Balog, S. J. Geib and D. P. Curran, *J. Org. Chem.*, 1995, **60**, 345; (*k*) M. F. Wempe and J. R. Grunwell, *J. Org. Chem.*, 1995, **60**, 2714; (*l*) M. F. Wempe and J. R. Grunwell, *Tetrahedron Lett.*, 2000, **41**, 6709; (*m*) K. C. M. Kurtz, R. P. Hsung and Y. Zhang, *Org. Lett.*, 2006, **8**, 231.

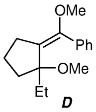
3 T. Jin and Y. Yamamoto, *Org. Lett.*, 2007, **9**, 5259.

4 T. Jin and Y. Yamamoto, *Org. Lett.*, 2008, **10**, 3137.

5 The ketals **1a′**, **1m′**, and **1n′** were prepared according to the literature procedure, see: N. Hamada, K. Kazahaya, H. Shimizu and T. Sato, *Synlett*, 2004, 1074.

6 Under the standard reaction conditions, an alkyl-substituted alkynyl ketone, such as **1m** (R^1 = ^{n}Bu, R^2 = Et, in Table 2), produced the corresponding enone **2m** in 17% NMR yield even at a higher temperature (100 °C) for a prolonged time (48 h).

7 The following mechanism is also conceivable. Interaction of a cationic carbon of ***B***, attached to MeO$^+$, with a triple bond makes it electron-deficient, and then addition of MeOH to the triple bond followed by C–C bond formation produces an intermediate ***D***. Bond reorganization–demethoxylation–ketalization–hydrolysis affords **2a**.



D

8 For recent reviews of Nazarov reaction, see: (*a*) M. A. Tius, *Eur. J. Org. Chem.*, 2005, 2193; (*b*) H. Pellissier, *Tetrahedron*, 2005, **61**, 6479; (*c*) A. J. Frontier and C. Collison, *Tetrahedron*, 2005, **61**, 7577.