Spirocyclization

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Triflic Acid Catalyzed Synthesis of Spirocycles via Acetylene Cations**

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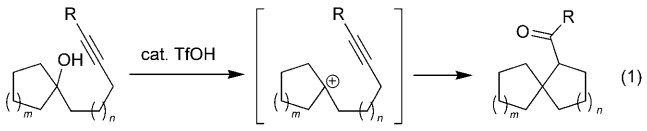
Spirocyclic hydrocarbon frameworks are found in many natural products with a wide range of biological activities. Such compounds often become candidates for medicines, perfumes, and agricultural chemicals.[1] Therefore, many synthetic methodologies for constructing functionalized spirocycles have been developed, such as intramolecular alkylation, transition-metal-based cyclization, cycloaddition, and rearrangement methods.[1] Recently, new preparative methods have been reported.[2] However, the development of a catalytic, efficient method for the synthesis of spirocycles with control over ring size would be highly desirable.

The Brønsted acid mediated cyclization of acetylene cations is an attractive method for the synthesis of polycycles with quaternary carbon centers,[3] because new C–C and C–O bonds can be constructed simultaneously in an efficient and atom-economic manner. To our knowledge, the use of this method for the construction of spirocyclic frameworks has never been reported. Herein, we report that a trifluoromethanesulfonic acid (TfOH) catalyzed cyclization of alkynyl cyclic tertiary alcohols **1** via an acetylene cation produces spirocyclic compounds **2** with rings of various sizes in good to high yields under mild conditions [Eq. (1)].

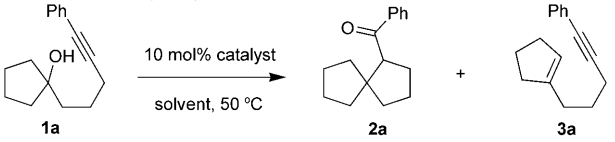


(1)

1: $m = 0, 1, 2, 3$; $n = 1, 2$ — **2**

In preliminary studies, we screened reaction conditions for the formation of the spirocycle **2a** from **1a**. We investigated the use of a series of Brønsted acid catalysts and various solvents at 50 °C (Table 1). Among the Brønsted acids tested in dichloroethane (DCE), TfOH exhibited the highest catalytic activity to produce **2a** in 90 % yield (Table 1, entry 5). Other Brønsted acids, such as HBF_4, $HNTf_2$, and $HSbF_6$, were also effective (Table 1, entries 2–4), although the use of *p*-TsOH gave the dehydrated 1,6-enyne **3a** in 90 % yield without the formation of **2a** (Table 1, entry 1). The investigation of various solvents in the presence of the TfOH catalyst revealed that dichloromethane was also effective; the use of CH_3CN led to a mixture of **2a** and **3a** (Table 1, entries 6 and 7). Interestingly, the use of toluene and THF afforded the enyne **3a** in high yield along with a small amount of **2a** (Table 1, entries 8 and 9).

Table 1: Optimization of the Brønsted acid catalyst and the solvent for the formation of spirocycle **2a**.[a]

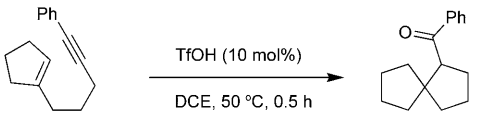


1a — **2a** — **3a**

Entry	Catalyst	Solvent	*t* [h]	Yield of **2a** [%][b]	Yield of **3a** [%][b]
1	*p*-TsOH·H_2O	DCE	24	0	90
2	HBF_4	DCE	24	84	3
3	$HNTf_2$	DCE	1	(75)	0
4	$HSbF_6$·H_2O	DCE	1.5	85	0
5	TfOH	DCE	1	(90)	0
6	TfOH	CH_2Cl_2	1	82	0
7	TfOH	CH_3CN	24	47	29
8	TfOH	toluene	24	8	82
9	TfOH	THF	24	2	90

[a] Reaction conditions: **1a** (0.4 mmol), catalyst (10 mol %), solvent (2 mL, 0.2 M), 50 °C. [b] The yield was determined by ^{1}H NMR spectroscopy by using CH_2Br_2 as an internal standard. Yields in parentheses are the yield of the isolated product. Ts = toluenesulfonyl, Tf = trifluoromethanesulfonyl, DCE = dichloroethane.

These results suggest that the spirocycle **2a** is formed via the 1,6-enyne **3a** with an appropriate π-electrophilic acid. Hence, we tested the reaction of enyne **3a** with TfOH (10 mol %) in DCE at 50 °C. As expected, the reaction proceeded to completion within 30 min in the presence of H_2O (1 equiv) to give the spirocycle **2a** in 96 % yield [Eq. (2)]; in the absence of H_2O, only a trace amount of **2a** was produced. This result indicates clearly that a strong Brønsted acid, such as TfOH, activates the alkene moiety of 1,6-enynes to promote a subsequent nucleophilic carbocycloaddition. Recently, TfOH-catalyzed hydroamination and hydroalkoxylation reactions of unactivated alkenes were



3a — **2a** 96%

(2)

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reported independently by the research groups of Hartwig and He.[4] However, Brønsted acid catalyzed carbocyclization reactions of enynes have rarely been described.[5] Kozmin and Zhang reported the first $HNTf_2$-mediated carbocyclization of siloxy 1,5-enynes, in which the Brønsted acid was proposed to activate the alkyne moiety.[6]

The TfOH-catalyzed synthesis of spirocycles with rings of various sizes is summarized in Table 2. The reactions of alkynes substituted with an electron-donating or electron-withdrawing aromatic ring, a naphthyl group, or a conjugated olefin moiety produced the corresponding spiro[4.4]nonanes **2b–e** in good to excellent yield (Table 2, entries 1–4). Other cyclic tertiary alcohols with a cyclobutyl, cyclohex(en)yl, or cycloheptyl ring were transformed into the expected spiro-[3.4]octane **2f**, spiro[5.4]decanes **2g–i**, and spiro-[6.4]undecane **2j** in good yield (Table 2, entries 5–9). In the case of the isopropyl-substituted tertiary cyclic alcohol **1h** and the tertiary cyclohexenyl alcohol **1i**, the product was formed as a nearly 1:1 mixture of two diastereomers (Table 2, entries 7 and 8).

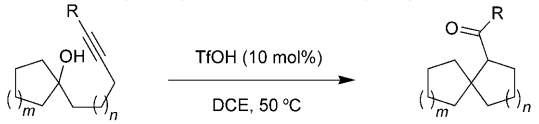
When the number of methylene carbon atoms in the tether between the ring and the alkyne was increased, the reaction still proceeded smoothly. Thus, compounds **1k** and **1l** were converted into the corresponding spiro[4.5]decane **2k** and spiro[3.5]nonane **2l** in 64 and 71% yield, respectively, at 80°C (Table 2, entries 10 and 11).

Substrates **1m** and **1n**, which contain a benzyl or methyl ether group on one of the tether carbon atoms, were transformed under the standard conditions into the corresponding spirocycles **2m** (and **2m′**) and **2n** (and **2n′**) in good yield as a 1.2:1 or 1:1 separable diastereomeric mixture (Table 2, entries 12 and 13). Remarkably, the presence of both a double bond and an oxygen atom in substrate **1o** was also tolerated: The desired spirocyles **2o** and **2o′** were obtained in 61% yield as a 1:1 mixture of diastereomers (Table 2, entry 14). Unfortunately, the reaction of substrates with a carbonyl or *tert*-butyldimethylsilyl ether functional group resulted in decomposition. Additional studies revealed that, in contrast to substrates with an aryl or conjugated alkenyl group at the alkyne terminus, alkynes substituted with an alkyl group at this position did not undergo the present catalytic cyclization to give the desired products.[7]

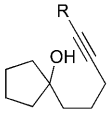
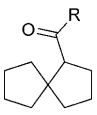
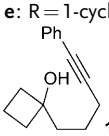
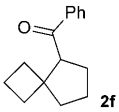
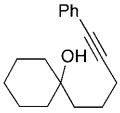
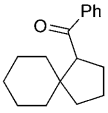
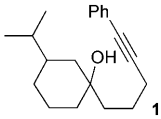
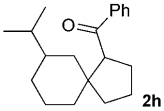
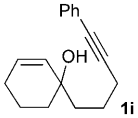
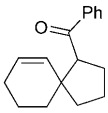
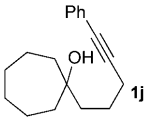
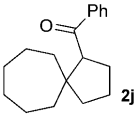
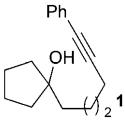
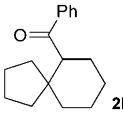
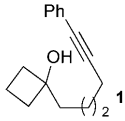
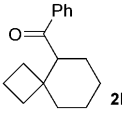
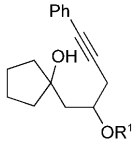
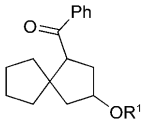
Interestingly, the reaction of the diastereomeric alkynyl tertiary alcohols **1p** and **1p′** under the standard conditions gave the same [3.2.1] bicyclic ketone **4p** as a single diastereomer [Eqs. (3) and (4)]. The reaction of **1q**, with two methylene carbon atoms in the tether (rather than one, as in **1p**), gave the corresponding [3.3.1] bicyclic ketone **4q** in 66% yield as a single diastereomer [Eq. (5)]. On the other hand, a mixture of diastereomers **1r** was converted into a mixture of diastereomers **4r** in a 1.1:1 ratio [Eq. (6)]. These results demonstrate that the newly developed method can be applied to the synthesis of bicyclocarbocycles containing a one-carbon-atom bridge.

A proposed reaction mechanism is shown in Scheme 1: Protonation of the tertiary hydroxy group of **1a** with a Brønsted acid leads to the tertiary carbocation intermediate **A**, which is converted rapidly into the corresponding enyne **3a** through β elimination. There may be an equilibrium

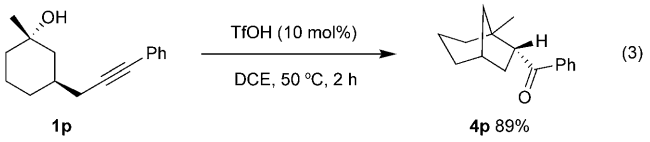
Table 2: TfOH-catalyzed synthesis of various spirocycles **2**.[a]

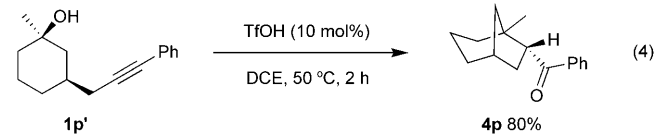


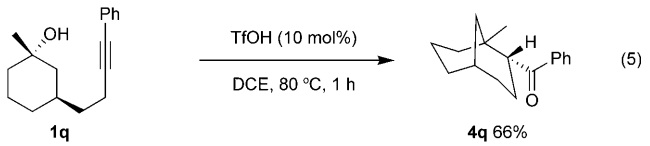
1: m = 0, 1, 2, 3; n = 1, 2 — **2**

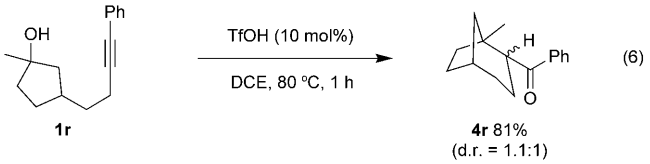
Entry	**1**	t [h]	**2**	Yield [%][b]
				
1	**1b**: R = 4-MeC_6H_4	1	**2b**	79
2[c]	**1c**: R = 4-ClC_6H_4	1	**2c**	96
3[c]	**1d**: R = 1-naphthyl	1	**2d**	93
4	**1e**: R = 1-cyclohexenyl	1	**2e**	55
5	 **1f**	10	 **2f**	71
6	 **1g**	4	 **2g**	75
7	 **1h**	5	 **2h**	64[d] (1:1)
8	 **1i**	1	 **2i**	80[d] (1.2:1)
9	 **1j**	4	 **2j**	45
10[c]	 **1k**	4	 **2k**	64
11[c]	 **1l**	1	 **2l**	71
				
12	**1m**: R^1 = Bn	5	**2m/2m′**	60[d] (1.2:1)
13	**1n**: R^1 = Me	5	**2n/2n′**	60[d] (1:1)
14	**1o**: R^1 = allyl	5	**2o/2o′**	61[d] (1:1)

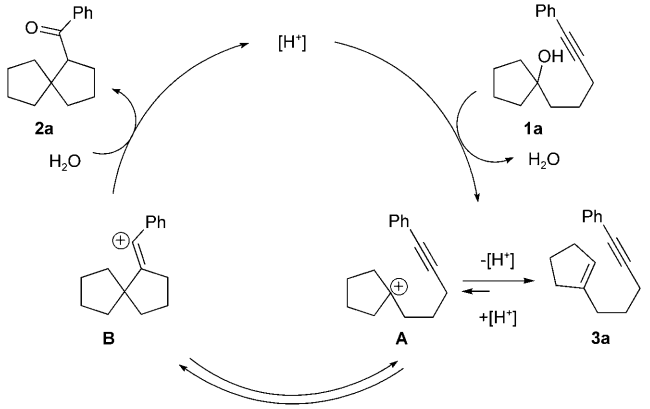
[a] Reaction conditions: **1** (0.4 mmol), catalyst (10 mol%), dichloroethane (2 mL, 0.2 M), 50°C. [b] Yield of the isolated product. [c] The reaction was carried out at 80°C. [d] The total yield is given for a mixture of two diastereomers. Bn = benzyl.











Scheme 1. Proposed mechanism of the TfOH-catalyzed cyclization of alkynyl-substituted cyclic tertiary alcohols via acetylene cations.

between **A** and **3a**. Attack of the alkynyl moiety onto the cation in **A** affords the benzylidene cation **B**. This high-energy intermediate **B** may be stabilized by charge delocalization involving the phenyl group.[3h,i,7,8] The subsequent reaction of cation **B** with H_2O produces the spirocyclic ketone **2a** and regenerates the Brønsted acid.

In summary, we have developed an efficient and general method for the synthesis of spirocycles through the cyclization of acetylene cations. Spirocyclic compounds with rings of various sizes can be obtained under mild reaction conditions. This method was applied to the formation of bridged bicyclic ketones with high stereoselectivity. Investigations into the extension of the present methodology to the construction of a variety of useful carbocycles containing quaternary carbon atoms and into a Brønsted acid catalyzed enyne cycloisomerization are in progress.

Experimental Section

Representative procedure: TfOH (0.04 mmol, 3.5 μL) was added to a solution of 1-(5-phenylpent-4-ynyl)cyclopentanol (**1a**; 0.4 mmol, 91 mg) in dichloroethane (2 mL) at room temperature in a pressure vial, and the resulting mixture was stirred at 50 °C for 1 h. The reaction mixture was then cooled to room temperature, filtered through a short Florisil pad, and eluted with diethyl ether. The filtrate was concentrated, and the residue was purified by chromatography on silica gel to afford phenyl spiro[4.4]non-1-ylmethanone (**2a**; 82 mg, 90 %) as a yellow oil.

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