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Highly Efficient Brønsted Acid-Catalyzed Cycloisomerizations of Alkynes Bearing Bis(acetoxy) Groups to Indenyl Ketones

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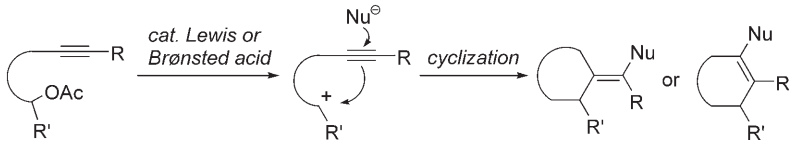
Abstract: A Brønsted acid-catalyzed cycloisomerization of functionalized alkynes is described, which is assumed to be initiated through the formation of a benzylic cation intermediate. The reaction offers a highly efficient and straightforward route to indenyl ketones with a wide range of substituents under mild conditions.

Keywords: alkynes; Brønsted acids; cycloisomerization; indenyl ketones; propargyl esters

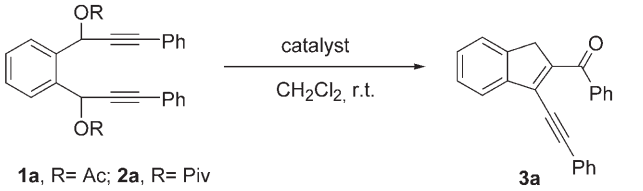
The intramolecular cyclization of alkynes bearing proximate C, O, N nucleophiles has proven to be a powerful synthetic route to the wide variety of carbo- and/or heterocycles. Although much progress has been achieved, most of this chemistry has concentrated on transition metal-catalyzed strategies through the regio- and stereoselective addition of a nucleophile to the activated carbon-carbon triple bond.[1] There are only few examples for the Brønsted acid-catalyzed cyclization or cycloisomerization reactions of alkynes.[2] From both an economical and an environmental point of view, the development of a metal-free methodology for these type of reactions is highly desirable. Several successful approaches for the Brønsted acid-catalyzed transformation of alkynes to cyclic rings have been reported. Kozmin et al. reported the $HNTf_2$-promoted cyclization of siloxyalkynes with arenes, alkenes, or alkynes *via* the intermediacy of highly reactive ketenium ions.[2a–b] Hsung et al. reported a stereoselective arene-ynamide cyclization *via* a novel keteniminium Pictet–Spengler cyclization.[2c] Brønsted acid-catalyzed metathesis reactions of enynes bearing electron-withdrawing groups on the alkyne entity can be also found in the literature.[2d] However, special substituents (OR, NR^1R^2, or EWG) on the alkyne terminus were usually required for these cyclizations. We anticipated that a new domino process initiated by Lewis- or Brønsted acid-induced carbocation formation followed by subsequent nucleophilic attack (Scheme 1) might be achieved. In this communication, we describe our discovery and investigation of the Brønsted acid-catalyzed cycloisomerization of alkynes bearing bis(acetoxy) groups to indenyl ketones.

The substrates, diesters **1a** and **2a**, which were easily prepared in high yields as a diastereomeric mixture through acetylide addition to phthalaldehyde,[3] were chosen to test the hypothesis. In light of the efficient activation of alkynes by gold catalysts[4–6] and our recent report on the gold-catalyzed direct amination of allylic alcohols,[6c] we first examined the reactivity of **1a** in the presence of various gold catalysts. However, only disappointing results were obtained (Table 1, entries 1 and 2). After many efforts, we were delighted to find that, in the presence of 5 mol% of $AgSbF_6$, **1a** cyclized smoothly in CH_2Cl_2 to afford in-



Scheme 1.

Table 1. Optimization studies for the Lewis or Brønsted acid-catalyzed cycloisomerization of alkyne **1a** or **2a**.



1a, R= Ac; **2a**, R= Piv **3a**

Entry	Substrate	Catalyst	Time	Yield [%] of **3a**[a]
1	**1a**	2% $AuCl_3$	1 h	–[b]
2	**1a**	2% $AuCl(PPh_3)$, 2% $AgBF_4$	6 h	–[b]
3	**1a**	5% $AgSbF_6$	20 h	89
4	**1a**	5% $Sc(OTf)_3$	6 h	97
5	**2a**	10% $Yb(OTf)_3$	24 h	NR[c]
6	**1a**	5% TfOH	1 min	>99[d]
7	**2a**	5% TfOH	1 min	>99
8	**1a**	20% CF_3COOH	24 h	NR[c]
9	**1a**	20% TsOH	24 h	–[e]

[a] NMR yields.
[b] Complicated reaction mixture was observed.
[c] NR = no reaction.
[d] Isolated yield is 65%.
[e] We did observe some transformation in this case, however, this reaction was not clean, and we could not obtain pure products.

denyl ketone **3a**[7] incorporating an alkynyl group in 89% NMR yield after stirring at room temperature for 20 h (Table 1, entry 3). Interestingly, using 5 mol% of $Sc(OTf)_3$ reduced the reaction time to 6 h, and a high yield of 97% of **3a** was obtained. Further studies revealed that the conjugate acid of the metal triflates, TfOH, showed excellent catalytic activities to afford >99% NMR yields of the desired product within one minute (Table 1, entries 6 and 7)![8] The efficiency of TfOH was demonstrated also through a comparison with other Brønsted acids such as CF_3COOH or TsOH (Table 1, entries 8 and 9).

Encouraged by these results, we next examined the scope of this cycloisomerization in terms of the alkyne substituent (Table 2, entries 1–6). We were pleased to find that the functionalities like Me, MeO, and Cl groups on the aromatic ring were well tolerated during the reaction, furnishing the corresponding products **3b–d** in 61–76% yields. However, the diacetate **1e**, bearing an *o*-CF_3 group on the aromatic ring, afforded a low yield (32%) of **3e** (Table 2, entry 5). The procedure was also compatible with alkyl-substituted alkyne **1f** to afford **3f** in 51% yield using 15% of TfOH (Table 2, entry 6).

It should be noted that this cycloisomerization process was not limited to bisalkynes, monoalkynes of **1g–1o** also underwent similar cyclization reactions smoothly (Table 2, entries 7–15). However, a double bond isomer of 1,2-disubstituted indene **4** was formed as major product in these cases (isomeric purity >98% except **4m**).[9] Treatment of diacetate **1g** bearing phenyl groups on the alkyne and at the benzylic position with 5 mol% of TfOH in CH_2Cl_2 for 1 min afforded indenyl ketone **4g** in 81% yield (Table 2, entry 7). The aromatic groups at R^1 and/or R^2 bearing various substituents were well accommodated, and the corresponding products **4h–o** were formed in 36–95% yields. The structures of **3** and **4** were unambiguously confirmed by X-ray single-crystal analyses of **3f** and **4l**.[10]

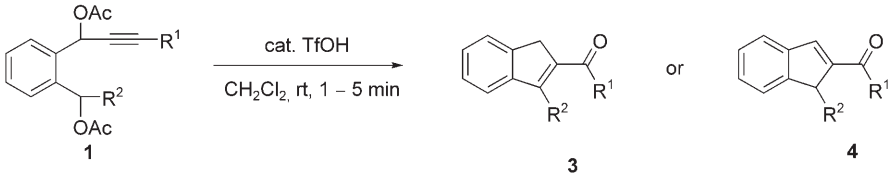
Substrate **5** with a methyl substituent on the aromatic ring was studied to investigate the electronic effects of the substitution on the efficiency of the cyclization reaction (Scheme 2). The cyclization proceeded with complete regioselectivity to give 2,3,6-trisubstituted indene **6** in 73% yield, while its regioisomer **7** was not observed. The structure of **6** was determined by collateral evidence of ^1H-^1H COSY and HMBC spectra.[11] This experimental result supported a cationic mechanism, since a more stable benzyl cation *para* to the methyl group would be formed preferentially. Interestingly, the presented method could be readily extended to the synthesis of tricyclic ketone **9** or its isomer **10** (Scheme 2), and good yields were obtained in each case.

On the basis of the above observations, a possible reaction mechanism is proposed in Scheme 3. As the first step, protonation followed by elimination of a leaving group in **1** is proposed to generate a benzyl cation intermediate **11**.[12] The stability of benzyl cations is well documented and has been the subject of theoretical and experimental study.[13] Benzyl cation-initiated cyclization *via* an intramolecular Friedel–Crafts reaction is also well precedent.[14] Attack of the alkyne moiety onto the resulting carbocation leads to cyclization and affords the alkenyl cation **12**. Nucleophilic attack of HOAc onto **12** followed by deprotonation gives enol acetate **13**. HOAc may also attack the alkyne moiety in **11** directly to furnish **13**. Decomposition of the unstable enol acetate, presumably through an oxocarbonium intermediate **15**, then gives indenyl ketone **4**. Isomerization of **4** upon column chromatography affords the thermodynamically more stable 2,3-disubstituted indene **3** in the cases of bisalkynes.

To probe the mechanistic hypotheses, we next monitored the reaction of **1d** by NMR. ^1H NMR showed a complete conversion to **4d** along with small amounts of **3d**. In addition, Ac_2O could also be detected in 95% NMR yield (Scheme 4).[15]

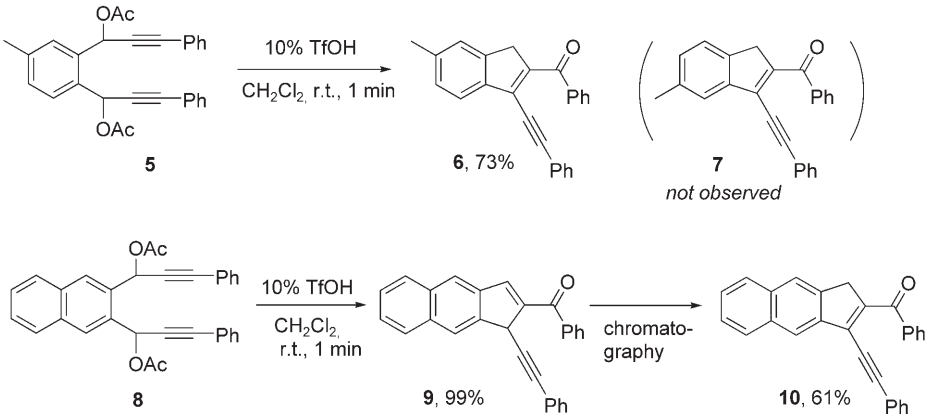
In conclusion, we have developed a highly efficient method for the synthesis of indenyl ketones *via* a Brønsted acid-catalyzed cycloisomerization of functionalized alkynes under extremely mild conditions. The indene derivatives are useful synthetic intermediates, especially as valuable ligand precursors for tran-

Table 2. TfOH-catalyzed cycloisomerization reactions of alkynes.

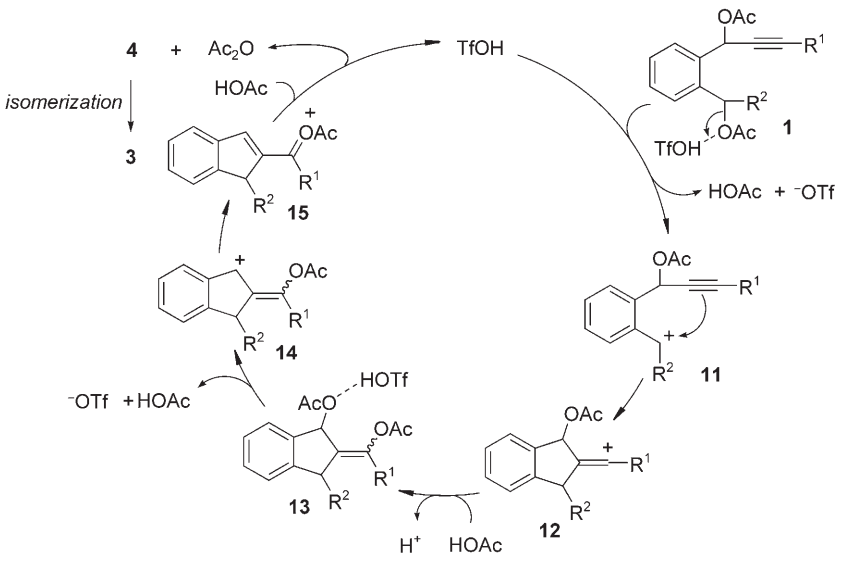


Entry	Substrate	R^1	R^2	Catalyst [mol%]	Product	Yield [%] of **3** or **4**[a]
1	**1a**	Ph	C≡C−Ph	5	**3a**	65[b]
2	**1b**	*p*-MeC_6H_4	C≡C−*p*-MeC_6H_4	5	**3b**	70[b]
3	**1c**	*p*-$MeOC_6H_4$	C≡C−*p*-$MeOC_6H_4$	5	**3c**	76[b]
4	**1d**	*p*-ClC_6H_4	C≡C−*p*-ClC_6H_4	5	**3d**	61[b]
5	**1e**	*o*-$CF_3C_6H_4$	C≡C−*o*-$CF_3C_6H_4$	10	**3e**	32[b]
6	**1f**	Bu	C≡C−Bu	15	**3f**	51[b]
7	**1g**	Ph	Ph	5	**4g**	81
8	**1h**	*p*-MeC_6H_4	Ph	8	**4h**	36
9	**1i**	*p*-ClC_6H_4	Ph	5	**4i**	91
10	**1j**	Ph	*p*-MeC_6H_4	5	**4j**	86
11	**1k**	Ph	*p*-BrC_6H_4	5	**4k**	85
12	**1l**	Ph	*p*-$MeOC_6H_4$	5	**4l**	95
13	**1m**	Ph		5	**4m**	78[c]
14	**1n**	Ph		10	**4n**	43
15	**1o**	Bu	Ph	5	**4o**	75

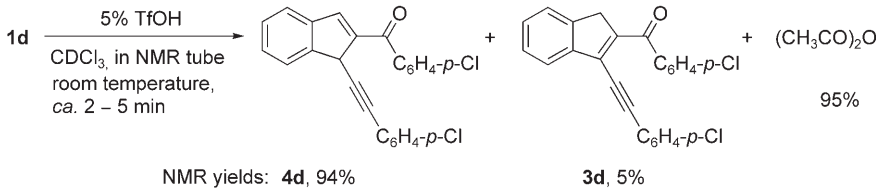
[a] Isolated yields after column chromatography.
[b] Isolated yields after further purification by recrystallization or washing with organic solvents.
[c] The product was obtained as a mixture of two double bond isomers in a ratio of 8:1, **4m** is the major isomer.



Scheme 2.



Scheme 3.



Scheme 4.

sition metal complexes.[16] Further studies to elucidate the reaction mechanism and to extend the scope and synthetic utility are in progress in our laboratory.

Experimental Section

General Procedure for TfOH-Catalyzed Cycloisomerization of Alkynes Bearing Bis(acetoxy) Groups to Indenyl Ketone

To a solution of diacetate **1** (0.4 mmol, in 4 mL dry CH_2Cl_2) was added TfOH (0.02 mmol, 1.8 μL), the color changed immediately to deep brown, and the mixture was stirred at room temperature for 1~5 min. An appropriate amount of silica gel was added to the mixture and the solvent was evaporated under vacuum at room temperature (in some cases, evaporation at higher temperature such as 50 °C resulted in a partial decomposition of the product). The residue was purified by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate) to afford the desired indenyl ketone **3** or **4**. Note: For alkynyl-substituted indenyl ketones **3a**–**3f**, further purification by recrystallization or by washing with the organic solvents was needed to remove the coloring matter.

Phenyl-(3-phenylethynyl-1*H*-inden-2-yl)-methanone (3a): Purification of the crude product by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) followed by recrystallization in petroleum ether/CH_2Cl_2 afforded the title compound as a yellow solid; yield: 104 mg (0.5 mmol scale; 65%); mp116–118 °C. ^{1}H NMR ($CDCl_3$, Me_4Si): $\delta = 4.05$ (s, 2H), 7.03–7.06 (m, 2H), 7.21–7.30 (m, 3H), 7.42–7.51 (m, 4H), 7.55–7.58 (m, 2H), 7.75–7.77 (m, 1H), 7.91–7.94 (m, 2H); ^{13}C NMR ($CDCl_3$, Me_4Si): $\delta = 39.66$, 82.88, 101.68, 121.99, 122.47, 124.20, 127.13, 128.04, 128.17, 128.38, 129.09, 129.60, 131.92, 132.20, 132.40, 138.76, 142.86, 143.43, 145.53, 193.73; HR-MS (EI): $m/z = 320.1209$, calcd for $C_{24}H_{26}O$: 320.1201.

Supporting Information

Experimental details and spectroscopic characterization of all new compounds and X-ray crystal structure of compounds **3f** and **4l** are available as Supporting Information.

Acknowledgements

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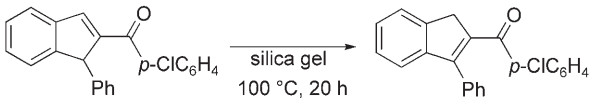
[7] Alkynyl-substituted indenyl ketones such as **3a** are somewhat unstable after evaporation of the solvent, a small amount of colored matter will appear. However, it becomes stable in the solid state. In these cases, the desired products were further purified by recrystallization or by washing with the organic solvents.

[8] We have also tried TfOH-catalyzed reaction of **1a** in the presence of water as suggested by one reviewer. It was found that addition of 1 equiv. of H_2O could afford **3a** in 96% NMR yield, however, in the presence of 5 equiv. of H_2O, only a trace amount of indene was observed.

[9] Interestingly, the isomerization between **4** and its double bond isomer the 2,3-disubstituted indene could be observed through heating a sample loaded on silica gel (200–300 mesh). For example, a double bond isomer was isolated in 72% yield with >99% isomeric purity upon heating **4i** for 20 h.

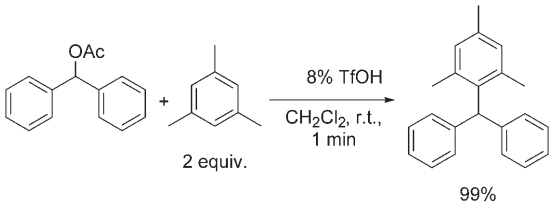


4i **3i**, 72%

[10] Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 668960 (**3f**), CCDC 668961 (**4l**). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif or on application to CCDC, 12Union Road, Cambridge CB21EZ, UK [Fax: int. code +44-(1223–336–033; e-mail: deposit@ccdc.cam.ac.uk].

[11] See Supporting Information.

[12] a) To understand the possible formation of benzylic cation, we tried the reaction of acetic acid benzhydryl ester with mesitylene catalyzed by 8% TfOH; the desired substitution product of 2-diphenylmethyl-1,3,5-trimethylbenzene was obtained in 99% yield; b) for the



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[15] For bisalkynes **1a**–**1f**, the initially formed indenyl ketones **4** are easily isomerized upon flash chromatography on silica gel, or treatment of the reaction mixture with basic solution such as saturated $NaHCO_3$ solution (the detailed procedure is shown in the Supporting Information).

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