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The First Addition of Silyl Enol Ethers to Internal Unactivated Alkynes

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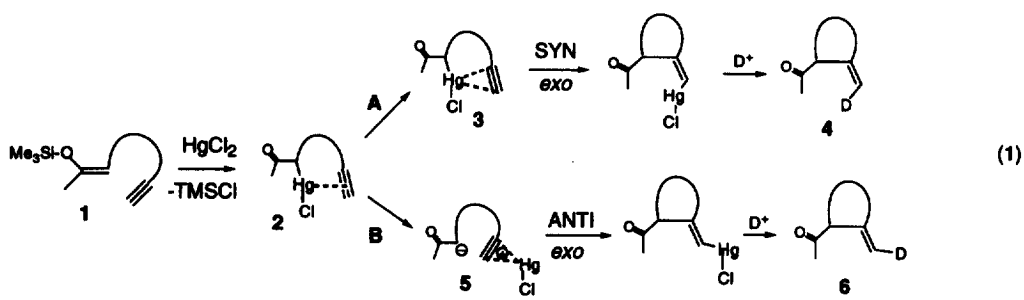
Abstract: The $EtAlCl_2$-mediated intramolecular addition of silyl enol ethers to both terminal and internal unactivated alkynes, bearing alkyl and phenyl susbstituents at the alkyne moiety, proceeded *exclusively* in the *endo*-fashion to give mono- and bicyclic β,γ-unsaturated ketones in good to excellent yields. The mechanism of this regiospecific Lewis acid-assisted carbocyclization is proposed. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Lewis acid; silyl enol ethers; carbocyclization; alkynes

The development of new selective carbocyclization methodologies is an important task for synthetic organic chemists.[1] Carbocyclization of alkynes is of interest since it provides an access to unsaturated carbo- and heterocycles.[2] In particular, the intramolecular addition of silyl enol ethers to acetylenes is an effective synthesis of medium-sized carbocycles. Two approaches are known to date for encouraging a weak nucleophile, such as a silyl enol ether, to add intramolecularly across a carbon-carbon triple bond.[3] The first is a well explored $HgCl_2$-mediated *exo*-carbocyclization (eq 1),[4,5] in which mercury activates the enolate moiety of **1** by forming a transient α-keto mercurial species **2**. Either the product **4** or the isomeric trans-addition product **6** is obtained through syn-addition of the enolate to the η^2 neutral **3** (pathway **A**) or anti-addition to the η^2 cationic **5** (pathway **B**) species, respectively (eq 1).[4,5]



(1)

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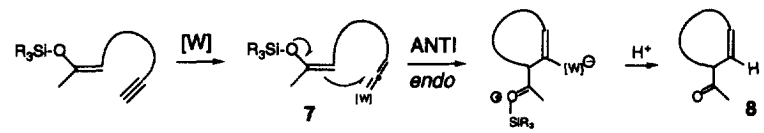
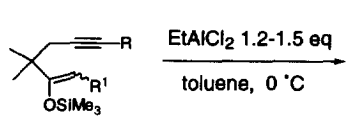
The second is a very recent approach (eq 2)[6] where a W complex catalytically activates an alkyne moiety (toward nucleophilic addition of an enolate) *via* formation of the alkyne-vinylidene intermediate **7**, which, after concomitant anti-addition of the silyl enol ether to its electrophilic central carbon, forms an *endo*-carbocyclization product **8** (eq 2).[6]

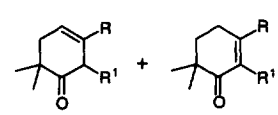


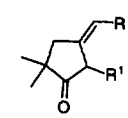
(2)

Despite the obvious synthetic importance of the above mentioned methodologies,[7] the scope of their application is limited to the use of terminal[4-6] and masked terminal (silyl-protected)[4c-d,7] alkynes. Herein we wish to report the first examples of a third alternative approach: Lewis acid-mediated intramolecular addition of silyl enol ethers to both terminal and internal unactivated alkynes.

We have recently developed an efficient and highly *endo*-selective Lewis acid-catalyzed intramolecular allylsilylation of alkynes.[8] These reactions proceed through electrophilic activation of the alkyne by the Lewis acid making it able to react with the modestly nucleophilic allylsilane moiety. Moreover, internal alkynes underwent the carbocyclization much more effectively than terminal ones.[8] Inspired by this successful Lewis acid-catalyzed intramolecular allylsilylation of internal alkynes[8] and motivated by the importance of development of new and general carbocyclization processes as mentioned above, we attempted to apply the Lewis acid-alkyne activation motif for the intramolecular addition of silyl enol ethers to internal alkynes. The initial experiments on cyclization of **9a** in the presence of $HfCl_4$ (the best Lewis acid system for the inter-[9] and intramolecular[8] allylsilylation of alkynes) indicated no reaction, whereas the use of stoichiometric amounts of $EtAlCl_2$[10] afforded the desired cyclization product **10a** in 57% isolated yield (eq 3). The carbocyclizations of butyl- (**9b**) and phenyl-substituted (**9c,d**) alkynyl silyl enol ethers also proceeded smoothly to give the β,γ-unsaturated ketones **10b-d** in 80, 75, and 76 % yields, respectively (eq 3). In all the above cases, the β,γ-unsaturated ketones **10a-d** were accompanied with detectable amounts of the isomeric α,β-unsaturated cyclohexenones **11a-d**, which are obviously the thermodynamic products (eq 3).[11]







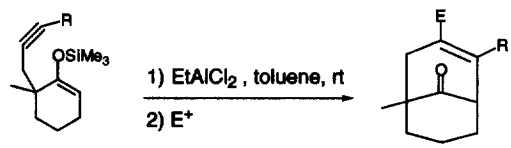
(3)

9a-d	**10a-d**	**11a-d**	**12**
			not detected
a: R=Me, R^1=H	57%	11%	
b: R=Bu, R^1=H	80%	6%	
c: R=Ph, R^1=H	75%	4%	
d: R=Ph, R^1=Me	76%	8%	

It should be pointed out that in all cases the carbocyclizations proceeded in exclusive *endo*-fashion and no traces of the *exo*-cyclization products **12** were detected by GC-MS and NMR analyses of the crude reaction mixtures. The experimental procedure for carbocyclization of **9c** is representative. $EtAlCl_2$ (1.2 equiv.) was added to a stirred solution of **9c** (139 mg, 0.5 mmol) in toluene (5 mL, 0.1 M) at 0 °C under an argon

atmosphere. After being stirred for 3 hours the mixture was quenched (Et_2NH), diluted ($NaHCO_3$ sat), extracted (Et_2O-H_2O), dried ($MgSO_4$) and concentrated. Separation by column chromatography (silica gel, eluent: hexane-ethyl acetate) gave 77 mg (75 %) of **10c** and 4 mg (4 %) of **11c**.[12]

The $EtAlCl_2$-mediated carbocyclization of the cyclic substrates **13** (eq 4) similarly proceeded in exclusive *endo*-fashion to give bicyclic β,γ-cyclohexenones **14** in good yields.



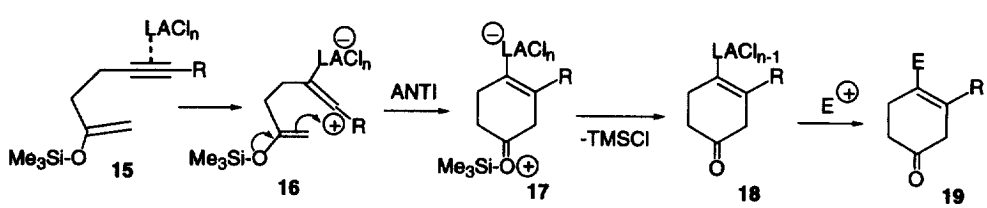
(4)

13a,b
a: R=H
b: R=Me

14a-d
a: R=E=H, 78%
b: R=H, E=D, 71%
c: R=Me, E=H, 84%
d: R=Me, E=I, 75%

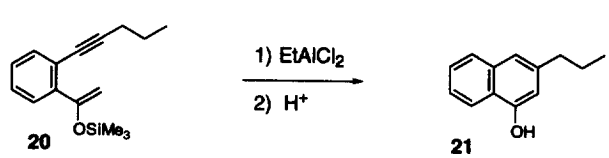
Substrates possessing both terminal (**13a**) and internal (**13b**) alkynyl moieties effectively cyclized under the reaction conditions shown above to give the bicyclic **14a** and **14c** in 78 and 84% isolated yields, respectively (eq 4). Furthermore, quenching the reaction mixtures with electrophiles, such as D_2O or I_2, afforded the corresponding D- (**14b**) and I-containing (**14d**) products in good yields (eq 4).

We propose the following mechanism for the observed Lewis acid-mediated exclusively *endo*-carbocyclization of carbon tethered alkynyl silyl enol ethers. As we previously proposed for the Lewis acid-catalyzed hydro-[13] and allylstannation[14] and hydro-[15] and allylsilylation[8,9] of alkynes, the coordination of the Lewis acid to the triple bond of **15** would form zwitterionic intermediate **16** (eq 5). The vinyl cation of **16** would then attack the double bond of the silyl enol ether moiety at the most nucleophilic terminal position in an *anti-fashion* affording the *endo-cyclization* product **17**. The elimination of TMSCl from **17** would form the vinylmetal complex **18**, which, after trapping with an electrophile, would produce **19**.



(5)

Initial experiments demonstrated that naphthol **21** could be also synthesized through the present methodology from the unsaturated analogue **20**, although in modest unoptimized yield (40 % by ^1H NMR, eq 6).



(6)

In conclusion, we have demonstrated for the first time addition of silyl enol ethers to both terminal and internal unactivated alkynes. The present *endo*-selective method can be used for the construction of mono- and bicyclic compounds possessing a cyclohexenone framework.

References and Notes

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3. There are reports on the intermolecular addition of silyl enol ethers to terminal alkynes mediated by $SnCl_4$-Bu_3N system and by $GaCl_3$, proceeding *via syn*-addition of metal enolates to metalacetylides. See: (a) Yamamguchi, M.; Hayashi, A.; Hirama, M. *J. Am. Chem. Soc.* **1993**, *115*, 3362. (b) Tsukagoshi, T.; Kido, Y.; Arisawa, M.; Sugihara, T.; Yamaguchi, M. In *5th International Symposium on Carbanion Chemistry* (ISCC-5); Sendai 1998; p 144.
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6. While this project was under investigation in our labs, a paper describing a W-catalyzed *endo*-selective carbocyclization of silyl enol ethers with terminal alkynes has appeared. See: Maeyama, K.; Iwasawa, N. *J. Am. Chem. Soc.* **1998**, *120*, 1928.
7. Mercury-mediated carbocyclization approach was recently successfully used for natural products synthesis. See: (a) Frontier, A. J.; Raghavan, S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 6686. (b) See also ref 5c.
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10. Other Lewis acids such as $ZrCl_4$, $B(C_6F_5)_3$, and $InCl_3$ did not mediate this carbocyclization, whereas the use of $AlBr_3$, $MeAlCl_2$, Et_2AlCl, and $GaCl_3$ in some cases gave the carbocyclization products although the chemical yields with these Lewis acids were low (≤ 40 %).
11. The control experiments have confirmed that β,γ-enone **10** is the kinetic product, which isomerizes into the thermodynamic product, α,β-enone **11**, under the reaction conditions. Thus, normally the carbocyclization of **9c** gives about a 95:5 ratio of **10c**:**11c** (eq 3); after being stirred for an additional 3 hours at room temperature the ratio changes to 44:56, whereas after 12 hours the isomeric **11c** becomes the major reaction product accompanied by a trace amount of **10c**.
12. **10c**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.25 (m, 5H), 6.22 (tt, J = 4.2, 1.8 Hz, 1H), 3.31 (dt, J = 1.8, 1.8 Hz, 2H), 2.46 (dt, J = 4.2, 1.8 Hz, 2H), 1.20 (s, 6H). ^{13}C NMR (75.5MHz, $CDCl_3$) δ 213.4, 139.4, 134.2, 128.5 (×2), 127.5, 124.9 (×2), 122.1, 43.3, 40.8, 40.1, 24.3 (×2). IR (neat) 1714, 1672, 1599, 751, 694 cm^{-1}. HRMS calcd for $C_{14}H_{16}O$ 200.1201, found 200.1211. Anal. Calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 83.91; H, 8.01.
11c: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58-7.52 (m, 2H), 7.44-7.38 (m, 3H), 6.35 (t, J = 1.5 Hz, 1H), 2.79 (td, J = 6.1, 1.5 Hz, 2H), 1.98 (t, J = 6.1 Hz, 2H), 1.18 (s, 6H). ^{13}C NMR (75.5MHz, $CDCl_3$) δ 204.7, 157.3, 138.5, 129.8, 128.7 (×2), 126.0 (×2), 123.8, 40.4, 36.4, 25.2, 24.1 (×2). IR (CCl_4) 1667, 1611, 1573, 725, 693 cm^{-1}. HRMS calcd for $C_{14}H_{16}O$ 200.1201, found 200.1201.
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