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Lewis Acid-Catalyzed Conjugate Addition−Cyclization Reactions of Ethenetricarboxylates with Substituted Propargyl Alcohols: Stereoselectivity in the Efficient One-Pot Synthesis of Methylenetetrahydrofurans

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Oxygen-containing heterocyclic systems are important structures in organic chemistry because of their presence in many biologically active compounds. In this work, a Lewis acid-catalyzed cyclization of ethenetricarboxylate derivatives **1** with substituted propargyl alcohols to give methylenetetrahydrofurans was investigated. Reaction of **1** and γ-silicon-substituted propargyl alcohols **4** with $ZnBr_2$ at 80−110 °C led to (*Z*)-silicon-substituted products stereoselectively. Reaction of **1** and γ-ester-substituted propargyl alcohol **7** in the presence of various Lewis acids gave ester-substituted methylenetetrahydrofurans stereoselectively. Interesting Lewis acid dependency on stereoselectivity for the reaction of **7** was found. Reaction of α-substituted propargyl alcohols also gave cyclized products.

Introduction

Increasing examples of oxygen heterocycles in various biologically interesting natural products require the development of diverse and efficient synthetic strategies.[1] Various new synthetic strategies to construct tetrahydrofurans have been studied recently.[2] Among them, propargyl alcohol has been effectively utilized as a C−C−O component in one-pot formal [3+2] cycloadditions. *n*BuLi/Pd, Cu-promoted, and Zn-promoted reactions of alkylidenemalonates with propargyl alcohol (excess amounts) gave methylenetetrahydrofurans.[3] However, stereoselectivities for various propargylic alcohols with substituents have not been examined in detail.[3,4] Recently, we have reported zinc- and indium-promoted formal [3+2] cycloadditions of ethenetricarboxylates **1** with 1 equiv (to the substrates **1**) of propargyl alcohol **2** to afford oxygen-containing five-membered rings **3** (eq 1), as well as reactions with propargylamines to afford nitrogen-containing five-membered rings.[5] In those reactions, the Lewis acid possibly coordinates to both

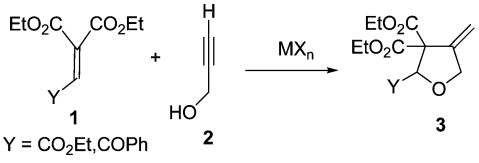

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TABLE 1. Reaction of 1 with Silicon-Substituted Propargyl Alcohols 4

entry	1	Y	4	SiR_3	MXn	conditions	5 (% yield)	3 (% yield)
1	**1a**	CO_2Et	**4a**	$SiMe_3$	$ZnBr_2$	80 °C, 16 h, $ClCH_2CH_2Cl$	**5a** (72)	
2	**1a**	CO_2Et	**4a**	$SiMe_3$	$InBr_3$	80 °C, 16 h, $ClCH_2CH_2Cl$	**5a** (trace)	**3a** (63)
3	**1b**	COPh	**4a**	$SiMe_3$	$ZnBr_2$	80 °C, 16 h, $ClCH_2CH_2Cl$	**5b** (74)	
4	**1b**	COPh	**4a**	$SiMe_3$	$InBr_3$	80 °C, 16 h, $ClCH_2CH_2Cl$	**5b** (13)	**3b** (60)
5	**1a**	CO_2Et	**4b**	$SiMe_2Ph$	$ZnBr_2$	110 °C, 8 h, toluene	**5c** (92)	
6	**1b**	COPh	**4b**	$SiMe_2Ph$	$ZnBr_2$	80 °C, 14 h, $ClCH_2CH_2Cl$	**5d** (76)	
7	**1a**	CO_2Et	**4c**	$SiMePh_2$	$ZnBr_2$	110 °C, 17 h, toluene	**5e** (89)	
8	**1a**	CO_2Et	**4d**	$SiPh_3$	$ZnBr_2$	110 °C, 17 h, toluene	**5f** (53)	
9	**1a**	CO_2Et	**4e**	$SiMe_2CH{=}CH_2$	$ZnBr_2$	110 °C, 17 h, toluene	**5g** (80)	
10	**1a**	CO_2Et	**4f**	$SiMe_2CH_2Ph$	$ZnBr_2$	110 °C, 17 h, toluene	**5h** (84)	
11	**6**	Ph	**4a**	$SiMe_3$	$ZnBr_2$	110 °C, 17 h, toluene	**5i** (63)[a]	
12	**6**	Ph	**4b**	$SiMe_2Ph$	$ZnBr_2$	110 °C, 17 h, toluene	**5j** (68)[b]	

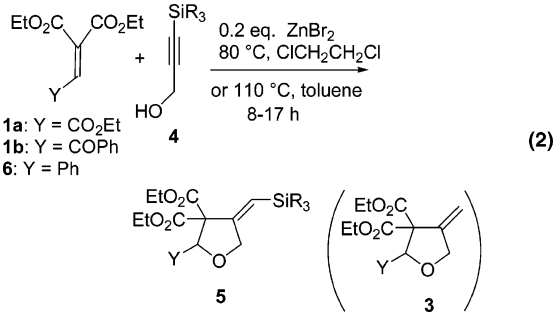
[a] **6** (22%) was recovered. A trace amount of desilylated cyclized product was detected. [b] **6** (20%) was recovered.

carbonyl groups and alkynes. The highly electrophilic reactivity of ethenetricarboxylates led to an efficient one-pot reaction. In this study, various propargylic alcohols with substitutents were examined in order to increase synthetic applicability and the resulting stereoselectivity was discussed.

Results and Discussion

A. γ-Silicon-Substituted Propargyl Alcohols. To explore the reaction of substituted propargyl alcohols, at first, various Lewis acids (0.2 equiv) were examined, in addition to the catalytic conditions (0.2 equiv of $InBr_3$) for eq 1 reported in our previous paper.[5] Reaction of **1** and **2** in the presence of $ZnBr_2$ (0.2 equiv) at 80 °C in $ClCH_2CH_2Cl$ gave good yields (Y = CO_2Et, 81%; Y = COPh, 89%). Use of $AlCl_3$ and $SnCl_4$ gave a small amount of **3**, accompanied by the noncyclized adduct (Y = CO_2Et, triethyl 1-(prop-2-ynyloxy)ethane-1,2,2-tricarboxylate)[5] and starting material **1**. Then, a Lewis acid-catalyzed cyclization of ethene-tricarboxylate derivative with γ-substituted propargyl alcohols to give methylenetetrahydrofurans was investigated. $ZnBr_2$-, $Zn(OTf)_2$-, and $InBr_3$-catalyzed reaction of triethyl ethenetricarboxylate **1** and 3-phenyl-2-propyn-1-ol or 2-butyn-1-ol gave recovered starting material, a noncyclized adduct, or a complex mixture.[6]

Silicon-substituted propargyl alcohols were investigated next, since silyl groups can be considered to activate alkynes toward electrophilic reactions.[7] The silyl group in the resulting cyclized products with a vinylsilane moiety can be used for further synthetic elaboration.[8] Reaction of **1** and 3-silyl-2-propyn-1-ols **4** in the presence of a catalytic amount of $ZnBr_2$ (0.2 equiv) in $ClCH_2CH_2Cl$ or toluene at 80−110 °C gave (*Z*)-silyl-substituted methylenetetrahydrofurans **5** stereoselectively (eq 2,



(2)

Table 1). The (*Z*)-structure of **5** was determined by the presence of NOE peaks between $SiCH_3$ and OCH_2 (except for **5f**) and the absence of NOE peaks between =C*H* and OCH_2 in the NOESY spectra. Use of $InBr_3$ as a Lewis acid catalyst in the reaction of **1** and 3-trimethylsilyl-2-propyn-1-ol gave desilylated cyclized products **3** preferentially (entries 2 and 4). Various silyl groups were examined. Reaction of **1** with TMS-, $PhMe_2Si$-, Ph_2MeSi-, Ph_3Si-, $CH_2{=}CHMe_2Si$-, and $PhCH_2Me_2Si$-substituted propargyl alcohols gave cyclized products **5** in 53−92% yield. On the other hand, reaction of **1a** with $^tBuMe_2Si$-, $^tBuPh_2Si$-, and $(Me_3Si)_3Si$-substituted propargyl alcohols under similar conditions did not give cyclized products effectively. These results probably arise from the combination of electronic and steric effects of substituents on silicon. The reaction of less reactive diethylbenzilidenemalonate **6** with **4a** and **4b** in the presence of $ZnBr_2$ also gave cycloadducts **5i** and **5j** in 63% and 68% yields, respectively.

B. γ-Ester-Substituted Propargyl Alcohols. Next, ester-substituted propargyl alcohols, which are expected to be highly activated in the electrophilc acetylene moiety, were examined. One-pot reactions to construct tetrahydrofurans by base (*t*-BuOK)-catalyzed reaction of nitroalkene with electron-withdrawing group-substituted propargyl alcohols such as methyl 4-hydroxy-2-butynoate (**7**) have been reported already.[4] The base (*t*-BuOK)-catalyzed reaction does not give high stereoselectivity. In addition, 2 equiv of **7** were used because of the instability of **7** under the basic reaction conditions. Lewis acid-catalyzed conditions may solve these problems. Reaction of **1** and methyl 4-hydroxy-2-butynoate (**7**)[9] in the presence of a catalytic amount of ZnX_2, $InCl_3$, $FeCl_3$, and $AlCl_3$ (0.2 equiv)

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(6) Reaction of **1a** (Y = CO_2Et) with 2-butyn-1-ol in the presence of 0.2 equiv of $ZnBr_2$ or $Zn(OTf)_2$ at 80 °C in $ClCH_2CH_2Cl$ gave a noncyclized adduct, triethyl 1-(prop-1-ynyloxy)ethane-1,2,2-tricarboxylate in 42−49% yield, along with starting material **1a** (27−30%).

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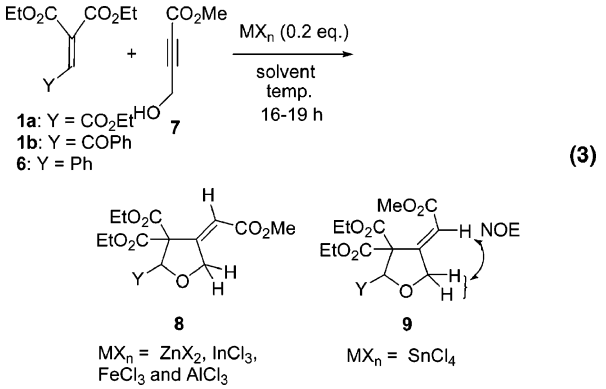
TABLE 2. Reaction of 1 (or 6) with Methyl 4-Hydroxy-2-butynoate (7)

entry	1/6	Y	MX_n	temp/solvent[a]	8 (% yield)	9 (% yield)
1	**1a**	CO_2Et	$ZnBr_2$	110 °C/toluene	**8a** (81)	
2	**1a**	CO_2Et	ZnI_2	110 °C/toluene	**8a** (89)	
	1a	CO_2Et	$ZnCl_2$	110 °C/toluene	**8a** (52)[b]	
3	**1a**	CO_2Et	$InCl_3$	110 °C/toluene	**8a** (54)	
4	**1a**	CO_2Et	$FeCl_3$	110 °C/toluene	**8a** (85)	
5	**1a**	CO_2Et	$AlCl_3$	80 °C/$ClCH_2CH_2Cl$	**8a** (64)	
6	**1a**	CO_2Et	$AlCl_3$	rt/CH_2Cl_2	**8a** (77)	
7	**1b**	COPh	$ZnBr_2$	80 °C/$ClCH_2CH_2Cl$	**8b** (98)	
8	**1b**	COPh	$AlCl_3$	rt/CH_2Cl_2	**8b** (60)	
9	**6**	Ph	$ZnBr_2$	110 °C/toluene	**8c** (55)	
10	**1a**	CO_2Et	$SnCl_4$	80 °C/$ClCH_2CH_2Cl$		**9a** (45)
11	**1a**	CO_2Et	$SnCl_4$	rt/CH_2Cl_2		**9a** (74)
12	**1b**	COPh	$SnCl_4$	rt/CH_2Cl_2		**9b** (49)
13	**1b**	COPh	$SnCl_4$	0 °C/CH_2Cl_2		NR[c]

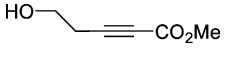
[a] The reaction was carried out for 16−19 h. [b] **1a** (25%) was recovered. [c] NR = no reaction.

gave *Z*-ester-substituted methylenetetrahydrofurans **8** stereoselectively in 52−98% yield (eq 3, Table 2). Use of $InBr_3$, $GaCl_3$,

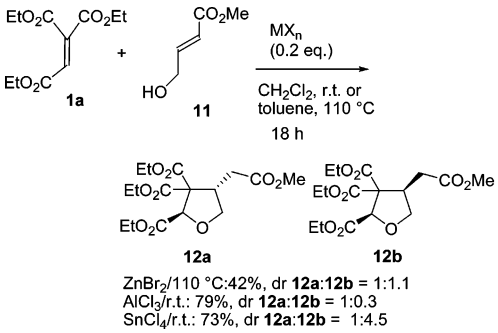


$Sc(OTf)_3$, and $Sn(OTf)_2$ gave complex mixtures. On the other hand, reaction of **1** and **7** in the presence of $SnCl_4$ at room temperature in CH_2Cl_2 gave *E*-isomer **9** exclusively in 45−74% yield. The (*Z*)- and (*E*)-structures were confirmed by the presence or absence of NOE peaks between =C*H* and OC*H*$_2$ in the NOESY spectra. Thus, interesting Lewis acid dependency on stereoselectivity was found. The reaction of diethyl benzylidenemalonate (**6**) and **7** in the presence of various Lewis acids was examined under various conditions. It was found that the reaction with $ZnBr_2$ gave only (*Z*)-cyclized product **8c** in 55% yield (entry 9).

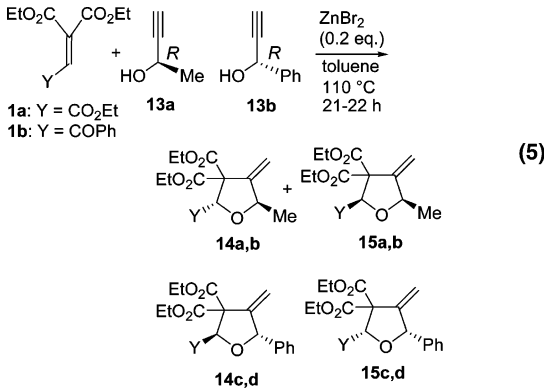
Attempts to synthesize a six-membered ring failed. Reaction of **1** and methyl 5-hydroxy-2-pentynoate (**10**)[10] in the presence of a catalytic amount of $ZnBr_2$, $AlCl_3$, or $SnCl_4$ (0.2 equiv) did not proceed and the starting materials were recovered under similar conditions.



To compare the reactivity of an electron-withdrawing alkene and consider the Lewis acid-catalyzed mechanism, reaction of the corresponding allylic alcohol, (*E*)-methyl 4-hydroxybut-2-enoate (**11**),[11] was also examined. Reaction of **1a** and **11** with $AlCl_3$ or $SnCl_4$ gave tetrahydrofuran products **12** in 73−79% yield as 1:0.3 and 1:4.5 (2,4-*trans*-**12a** and 2,4-*cis*-**12b**) diastereomer mixtures, respectively (eq 4).[12] The stereochemisry of **12a** and **12b** was determined by NOESY spectra, such as the absence (for **12a**) and the presence (for **12b**) of NOE peaks between C*H*CO_2Et and C*H*CH_2CO_2Me, 2,4-ring protons. $AlCl_3$ and $SnCl_4$ showed better results than $ZnBr_2$. Reaction of **1a** and allyl alcohol with $AlCl_3$, $SnCl_4$, and $ZnBr_2$ did not give cyclized products.



C. α-Substituted Propargyl Alcohols. To examine the further stereochemical course of the cyclization with propargyl alcohols, reaction of **1a** with α-substituted propargyl alcohols was investigated. Reaction of triester **1a** and enantiomerically pure (*R*)-3-butyn-2-ol (**13a**) in the presence of a catalytic amount of $ZnBr_2$ (0.2 equiv) in toluene at 110 °C for 22 h gave two stereoisomers **14a** and **15a** in 62% yield in a 1.1:1 ratio and both products demonstrated >95% ee (eq 5). Reaction of ketone



derivative **1b** and (*R*)-3-butyn-2-ol **13a** gave stereoisomers **14b** and **15b** in 73% yield in a 2.3:1 ratio and both products demonstrated >95% ee. The reaction of **1a**,**b** with enantiomerically pure (*R*)-1-phenyl-2-propyn-1-ol (**13b**) was also examined and gave products in >95% ee as well. The diastereomer ratios of **14** to **15** increased in the reaction of **1b** compared to that of **1a**, probably for steric reasons. Thus, the utility of the reaction for synthesis of enantiomerically pure substituted tetrahydrofurans has been shown.

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(12) The opposite preference in the 2,4-trans and cis stereoselectivity for $AlCl_3$ and $SnCl_4$ might be related to formation of $SnCl_4$ chelete intermediate of 2,4-substitutents with esters in the tetrahydrofuran ring.

TABLE 3. Reaction of 1 and Chiral α-Substituted Propargyl Alcohols 13

entry	1	Y	13	14 + 15 (% yield)[a]	14:15
1	**1a**	CO_2Et	**13a** (*R*)	**14a** + **15a** (62)	1.1:1
2	**1b**	COPh	**13a** (*R*)	**14b** + **15b** (73)	2.3:1
3	**1a**	CO_2Et	**13b** (*R*)	**14c** + **15c** (65)	0.9:1
4	**1b**	COPh	**13b** (*R*)	**14d** + **15d** (81)	2.8:1

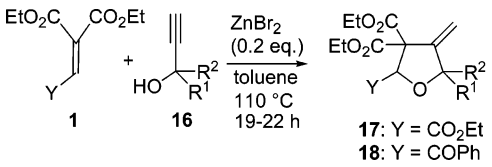
[a] **14** and **15** were separated by column chromatography. The ee % of **14** and **15** was determined as >95% ee by chiral HPLC (CHIRALPAK AS-H), respectively.

TABLE 4. Reaction of 1 and Tertiary α,α′-Substituted Propargyl Alcohols 16

entry	1	Y	16	R^1/R^2	17/18 (% yield)
1	**1a**	CO_2Et	**16a**	Me/Me	**17a** (45)[a]
2	**1b**	COPh	**16a**	Me/Me	**18a** (30)
3	**1a**	CO_2Et	**16b**	$(CH_2)_4$	**17b** (47)
4	**1a**	CO_2Et	**16c**	$(CH_2)_5$	**17c** (63)
5	**1a**	CO_2Et	**16d**	Ph/Ph	**17d** (14)[b]

[a] **1a** (23%) was recovered. [b] **1a** (60%) was recovered.

The reaction of **1** with tertiary α,α′-substituted propargyl alcohols **16a**−**d** was also examined and the reaction gave cyclized products **17** and **18** (eq 6, Table 4). Some cases gave

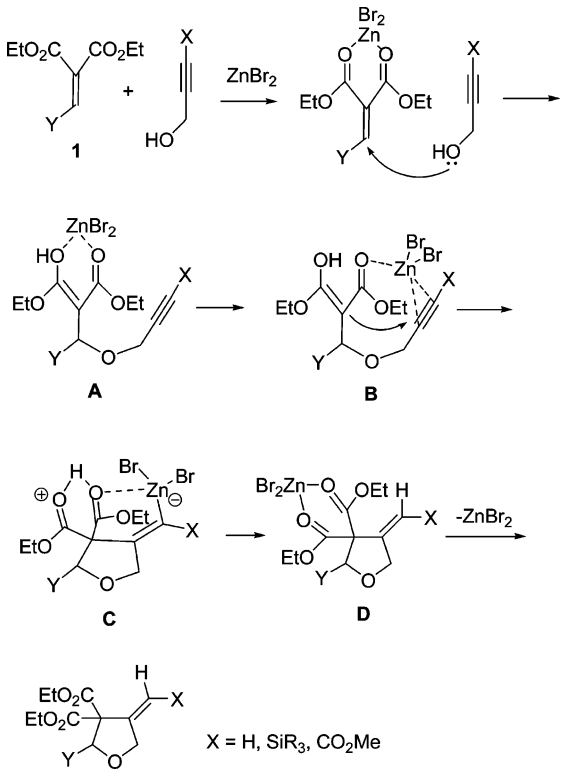


(6)

lower yields, probably by steric hindrance in the initial addition step and possible competing processes.[13] These tertiary substituted tetrahydrofuran skeletons are seen in some biologically interesting compounds[14] and further efforts to improve yields and transformation to them are under investigation.

D. Reaction Mechanism. The Zn-promoted reaction mechanism is considered next. The probable mechanism for formation of the five-membered ring is shown in Scheme 1. Conjugate addition of oxygen of propargyl alcohol to zinc-coordinated **1** in the diester moiety and proton transfer give intermediate **A**.[15] Zinc transfer to alkyne leads to intermediate **B**, and the following cyclization gives **C**. Protonation of sp^2 carbon in intermediate **C** by generated proton and zinc coordination to diester moiety gives more stable intermediate **D**. The intermediate **D** furnishes the five-membered rings along with the release of the zinc

SCHEME 1



catalyst. The facile cyclization by zinc Lewis acid can be explained by the dual activation ability of the carbonyl and alkyne moieties.[16]

The proposed mechanism agrees with the observed *Z*-selectivity for the zinc Lewis acid promoted reaction of **1** and γ-substituted propargyl alcohols: γ-silicon-substituted propargyl alcohols **4** and 4-hydroxy-2-butynoate (**7**). Thus, the alkenyl zinc intermediate **C** retains the configuration.

The observed (*E*)-selectivity for $SnCl_4$ can be explained as shown in Scheme 2. Initial adduct **E**, which is the same type as intermediate **A** in Scheme 1, would transform to intermediate **F** not intermediate **B**-type in Scheme 1, because harder Sn^{4+} may prefer carbonyl oxygen to carbon.[17] Ring closure may occur from the intermediate **F** leading to intermediate **G**. Intermolecular protonation (or protonation by liberated H^+) from outside would lead to Sn diester chelete intermediate **H**. Further study on the $ZnBr_2$- and $SnCl_4$-promoted mechanisms is underway.

In summary, a Lewis acid-catalyzed cyclization of ethenetricarboxylate derivative **1** with substituted propargyl alcohols gave methylenetetrahydrofurans stereoselectively. Reaction of **1** and γ-silicon-substituted propargyl alcohols **4** with $ZnBr_2$ at 80−110 °C leads to (*Z*)-silicon-substituted products. Zinc halides and $AlCl_3$-promoted reaction of **1** and γ-ester-substituted propargyl alcohol **7** gave (*Z*)-ester-substituted methylenetetrahydrofurans. $SnCl_4$-promoted reaction of **1** and γ-ester-substituted propargyl alcohol **7** gave (*E*)-ester-substituted methylenetetrahydrofurans. Interesting Lewis acid dependency on stereoselectivity was found. The present reaction to utilize highly electrophilic substrates provided an efficient stereoselective cyclization method. Further transformation of the products to potentially useful compounds and investigation of new prop-

(13) Possible isomerization of propargylic alcohols, such as via Meyer−Schuster and Rupe rearrangements, may occur in preference to the expected reaction with **1**. (a) Bigi, F.; Carloni, S.; Maggi, R.; Muchetti, C.; Sartori, G. *J. Org. Chem.* **1997**, *62*, 7024. (b) Luzung, M. R.; Tosle, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 15760. (c) Zhao, W.; Carreira, E. M. *Org. Lett.* **2003**, *5*, 4153. (d) Narasaka, K.; Kusama, H.; Hayashi, Y. *Chem. Lett.* **1991**, 1413. (e) Lorber, C. Y.; Osborn, J. A. *Tetrahedron Lett.* **1996**, *37*, 853. (f) Chabardes, P. *Tetrahedron Lett.* **1988**, *29*, 6253.

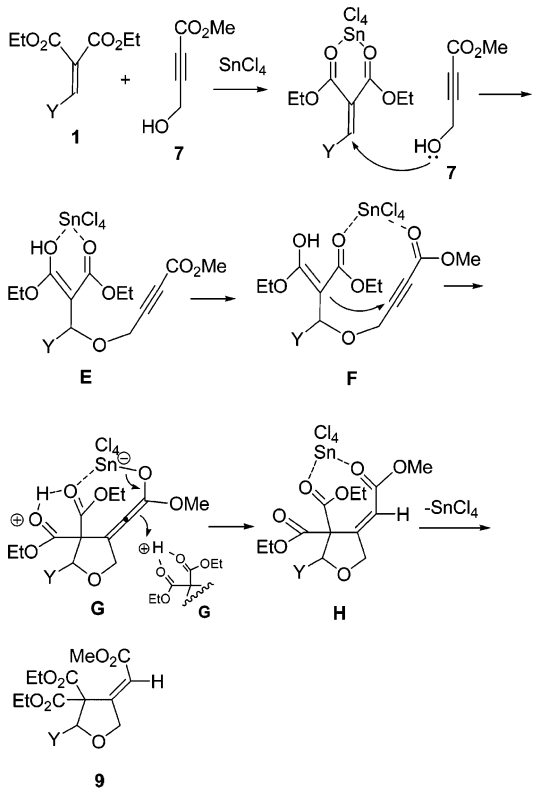
(14) For examples see: (a) Johnson, C. R.; Elliot, R. C.; Meanwell, N. A. *Tetrahedron Lett.*. **1982**, *23*, 5005. (b) Jackson, R. F. W.; Raphael, R. A. *Tetrahedron Lett.* **1983**, *24*, 2117. (c) Sakurai, K.; Takahashi, K.; Yoshida, T. *Agric. Biol. Chem.* **1983**, *47*, 1249. (d) Kaiser, R. *Helv. Chim. Acta* **1984**, *67*, 1198. (e) Hirasawa, Y.; Morita, H.; Shiro, M.; Kobayashi, J. *Org. Lett.* **2003**, *5*, 3991. (f) Trost, B. M.; Mao, M. K.-T.; Balkovec, J. M.; Buhlmayer, P. *J. Am. Chem. Soc.* **1986**, *108*, 4965. (g) Uenishi, J.; Kawahama, R.; Yonemitsu, O. *J. Org. Chem.* **1997**, *62*, 1691.

(15) In ref 3c, zinc alkoxide (in the presence of Et_3N) attack leading to anionic zinc coordinate enolate-ester is suggested. The detailed reaction mechanism including neutral alcohol or alkoxide attack is under investigation.

(16) Takita, R.; Fukuta, Y.; Tsuji, R.; Ohshima, T.; Shibasaki, M. *Org. Lett.* **2005**, *7*, 1363.

(17) Ho, T.-L. *Hard and Soft Acids and Bases Principle in Organic Chemistry*; Academic Press: New York, 1977.

SCHEME 2



argylic and allylic three-atom components for cycloadditions are ongoing and will be reported in due course.

Experimental Section

Typical Experimental Procedure (Table 1, Entry 5). To a solution of **1a** (137 mg, 0.56 mmol) in toluene (1.0 mL) was added 3-(phenyldimethyl)silylpropyn-1-ol (**4b**) (116 mg, 0.61 mmol) and $ZnBr_2$ (25 mg, 0.11 mmol). The mixture was heated at 110 °C and stirred for 8 h. The reaction mixture was cooled to room temperature and evaporated in vacuo. The residue was purified by column chromatography over silica gel with hexane−ether as eluent to give **5c** (225 mg, 92%).

5c: R_f 0.4 (hexane−ether 1:1); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.383 (s, 3H), 0.385 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H), 1.28 (t, J = 7.1 Hz, 3H), 4.15−4.33 (m, 7H), 4.49 (ddd, J = 13.6, 2.5, 0.6 Hz, 1H), 5.04 (d, J = 0.4 Hz, 1H), 6.14 (t, J = 2.5 Hz, 1H), 7.32−7.39 (m, 3H), 7.49−7.53 (m, 2H); selected NOEs are between δ 0.383, 0.385 ($Si(CH_3)_2$) and δ 4.15−4.33, 4.49 (OCH_2, assigned by COSY and HSQC); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) −1.90 (q), −1.88 (q), 13.9 (q), 14.0 (q), 14.1 (q), 61.4 (t), 62.2 (t), 62.5 (t), 68.7 (s), 71.2 (t), 82.0 (d), 123.9 (d), 128.1 (d), 129.5 (d), 133.8 (d), 137.5 (s), 152.0 (s), 166.6 (s), 167.4 (s), 168.8 (s); selected HMBC correlations are between δ 5.04 ($CHCO_2Et$) and δ 71.2 (OCH_2), 68.7 ($C(CO_2Et)_2$), and 152.0 (C=CHSi); IR (neat) 2982, 1739, 1633, 1428, 1368, 1250, 1114, 1027 cm^{-1}; MS (EI) m/z 434 (M^+, 4.1) 419 (18), 361 (93), 333 (66), 135 (100%); HRMS M^+ 434.1762 (calcd for $C_{22}H_{30}O_7Si$ 434.1761). Anal. Calcd for $C_{22}H_{30}O_7Si$: C, 60.81; H, 6.96. Found: C, 60.70; H, 7.10.

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Supporting Information Available: Additional experimental procedures, spectral data, and computational data. This material is available free of charge via the Internet at http://pubs.acs.org.

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