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Inter- and Intramolecular [4 + 3] Cycloadditions Using Epoxy Enol Silanes As Functionalized Oxyallyl Cation Precursors

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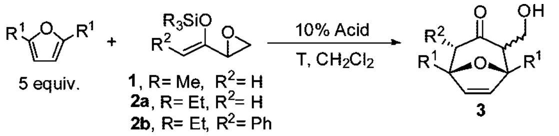
The [4 + 3] cycloaddition of allyl cations and dienes is a direct and efficient strategy for the assembly of seven-membered rings.[1,2] Moreover, cycloaddition with cyclic dienes such as furan and cyclopentadiene provide stereochemically defined oxabicyclic and carbobicyclic scaffolds where subsequent stereocontrolled functionalizations and ring opening reactions afford useful intermediates for the syntheses of natural products.[3,4] The development of strategies to afford optically pure [4 + 3] cycloadducts[5] and novel methods to generate allyl cations as the three-carbon unit[6] are topics of ongoing research.

Mild and chemoselective methods to assemble and generate the oxyallyl cation are necessary for maximum functional group compatibility, to extend its application to intramolecular reactions and to late stages of the synthesis of complex natural products. In addition, functionalized oxyallyl cations that can engage in cycloaddition are also desirable to furnish more complex cycloadducts with added synthetic potential. Herein we describe the use of epoxy enol triethylsilanes as oxyallyl cation precursors that are conveniently assembled and, under catalysis by silyl triflates and acids, can afford hydroxylated cycloadducts diastereoselectively and in optically enriched forms.

The only use of epoxy enol silanes as oxyallyl cation precursors for [4 + 3] cycloaddition with furan had been by Ohno et al., who reported that **1** reacted to produce hydroxymethylenated cycloadduct **3a** in the presence of TMSOTf.[7] However, a yield of only 12% rendered the reaction impractical for application in synthesis (Table 1, entry 1). A rationalization of the low yield may be that the epoxide cleavage of **1** comcomitantly generates a nucleophile in the putative oxyallyl cation, which could conceivably be quenched by intramolecular cyclization before engaging in any intermolecular reaction.[8]

Table 1. Intermolecular [4 + 3] Cycloaddition Reactions

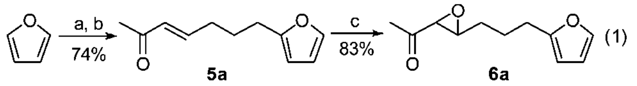


entry	**1/2**	furan	acid	*T* (°C)	**3** (isolated yield)
1	**1**	$R^1 = H$	TMSOTf	−50	**3a** (12%)[a]
2	**2a**	$R^1 = H$	TESOTf	−94	**3a** (75%)
3	**2a**	$R^1 = Me$	TESOTf	−94	**3b** (31%)[b]
4	**2b**	$R^1 = H$	TESOTf	−50	**3c** (61%)[c]

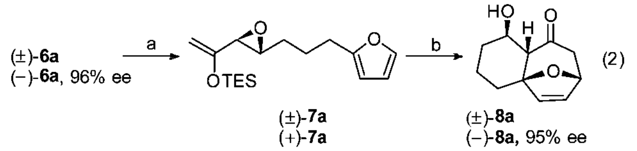
[a] Reference 7. [b] Accompanied by alkylated furan **4b** (32%); see Supporting Information (SI). [c] Accompanied by alkylated furan **4c** (24%); see SI.

In our studies, however, we have determined that the desired cycloaddition was precluded by the lability of the TMS enol ether, as well as the rapid decomposition of the trimethylsiloxyallyl cation after it was generated. The formation and cycloaddition of this kind of oxyallyl cation are facilitated by employing the more bulky triethylsilyl group.[9] Furthermore, together with the use of low reaction temperatures, the reaction of enol triethylsilane **2a** with furan resulted in a 6-fold improvement to 75% in the yield of the cycloaddition (Table 1, entry 2). Either alcohol **3a** or TES-protected **3a** can be obtained as the sole or major product by varying the workup conditions.[10] A screening of acids showed that TMSOTf, Tf_2NH, and TfOH also catalytically promoted the cycloaddition.[11] The sterically demanding 2,5-dimethylfuran was reluctant toward undergoing cycloaddition, giving diminished yields of **3b** along with alkylated furan resulting from the interrupted cycloaddition as a side product (Table 1, entry 3).[2e] With 2-methylfuran, the reaction was messy and even less successful (<15% yield). Substitution on the enol triethylsilane is tolerated (Table 1, entry 4), but in all cases, the diastereoselectivity at the hydroxymethylene group remained low (~1.2−2:1), similar to previous findings.[7,12]

To effectively capture the highly electrophilic siloxyallyl cation, the intermolecular cycloaddition employed an excess of the diene. It was anticipated that the cycloaddition should proceed with greater efficiency intramolecularly. On the other hand, the outcomes of the reactions involving substituted furans clearly indicate that subtle electronic and steric differences in the substrate could significantly alter the course and the yield of the cycloaddition. To study the intramolecular cycloaddition, a series of substrates **7a−h** were readily prepared as exemplified by the synthesis of **7a** in eqs 1 and 2.



Reaction conditions: (a) (i) *n*-BuLi, –50 to 0 °C; ,(ii) 5-bromopentene; (b) cat. Grubbs' 2nd generation catalyst, MVK; (c) NaOH, H_2O_2, MeOH.



Reaction conditions: (a) (i) LHMDS, –78 °C, THF; (ii) TESCl, 76-79%; (b) 10% TESOTf, CH_2Cl_2, –94 °C, 10-15 minutes, 82-83%.

In the event, the cycloaddition of **7a** in the presence of TESOTf was complete in minutes to afford an 83% yield of tricyclic hydroxyenone **8a**. In contrast to the lack of diastereoselectivity in the intermolecular reaction, we were delighted to find that this cycloaddition furnished **8a** as *a single diastereomer* (eq 2).[13] Accordingly, this methodology is amenable to the synthesis of enantiomerically pure cycloadducts. Using optically enriched (+)-**7a**, obtained from epoxy ketone (−)-**6a**, cycloaddition was directed by the stereochemistry of the epoxide to afford in one step cycloadduct (−)-**8a** bearing four stereocenters in 95% ee (eq 2).

The scope of this reaction has been examined for several intramolecular cycloaddition substrates (Table 2). Under similar

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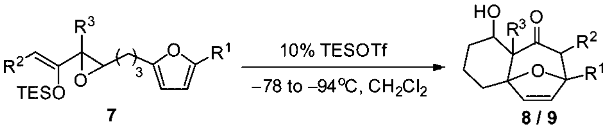
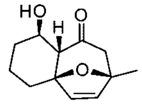
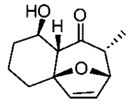
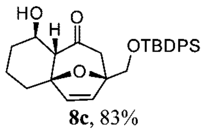
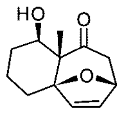
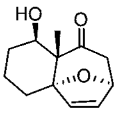
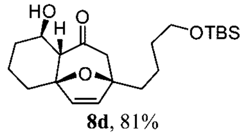
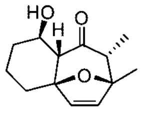
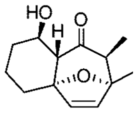
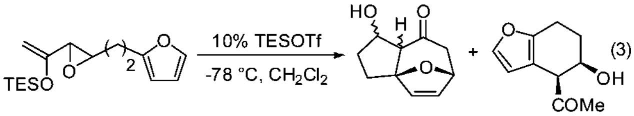
Table 2. Intramolecular [4 + 3] Cycloadditions of **7b**−**g**



Entry	Cycloadduct, yield[a]	Entry	Cycloadduct, yield[a]
1	 **8b**, 76%	4	 **8e**, 70%
2	 **8c**, 83%	5	  **8f**, 52% + **9f** 7%
3	 **8d**, 81%	6	  **8g**, 40% + **9g**, 57%

[a] Isolated yields.

reaction conditions, the [4 + 3] cycloadditions of epoxy enol silanes **7b**−**g** all proceeded efficiently in good to excellent yields. Analogous to **7a**, substrates **7b**−**f** bearing three-atom tethers undergo cycloaddition with high diastereoselectivies (entries 1−5). Cycloadducts include **8b**−**d** derived from disubstituted furans ($R^1 \neq H$), **8e** bearing five stereocenters ($R^2 \neq H$), and **8f** bearing an additional quaternary stereocenter ($R^3 \neq H$). Only in the case of the hindered substrate **7g** was the reaction high-yielding but unselective. The cycloaddition of **7h** also proceeded with low diastereoselectivity, presumably due to strain in the transition state leading to the 5,7-fused ring system, as a significant amount of intramolecularly alkylated furan **10** was also isolated (eq 3).

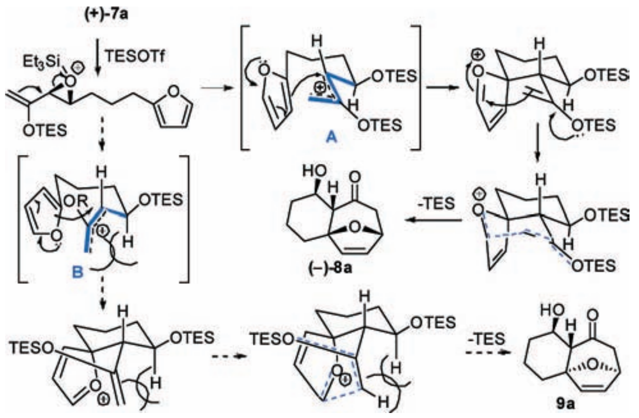


(3)

7h **8h/9h,** 58% yield **10,** 23% yield

The proposed mechanism of the cycloaddition is shown in Scheme 1 for (+)-**7a**. Activation of the epoxide by acid generates a siloxyallyl cation.[14] Adopting preferentially a W-type configuration, this intermediate initiates cycloaddition asynchronously with furan[2e] through a compact-endo transition state **A** in which the tether adopts a chairlike conformation, to afford the observed diastereomer **8a**. This pathway typically predominates over the alternative, less favored endo transition state **B** in which the siloxyallyl cation is in a sickle configuration, resulting in isomeric cycloadduct **9a**.[15]

Scheme 1. Proposed Mechanism for [4 + 3] Cycloaddition of (+)-**7a**



In summary, the acid-catalyzed [4 + 3] cycloaddition using epoxy enol triethylsilanes as oxyallyl cation precursors is a useful reaction to produce hydroxylated cycloheptanoids, particularly carbobicyclo[5.4.0] systems, which can be obtained in optically enriched forms. Together with numerous well-precedented, stereoselective reactions that can be executed on such rigid scaffolds, this reaction should find application in the asymmetric synthesis of complex natural products. Our continued efforts to develop and apply this reaction will be reported in due course.

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Supporting Information Available: Procedures for the syntheses and characterizations of all substrates and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) Recent examples:(a) Antoline, J. E.; Hsung, R. P.; Huang, J.; Song, Z.; Li, G. *Org. Lett.* **2007**, *9*, 1275–1278. (b) Pascual, M. V.; Proemmel, S.; Beil, W.; Warchow, R.; Hoffmann, H. M. R. *Org. Lett.* **2004**, *6*, 4155–4158. (c) Föhlisch, B.; Flogaus, R.; Henle, G. H.; Sendelbach, S.; Henkel, S. *Eur. J. Org. Chem.* **2006**, *216*, 0–2173. (d) Harmata, M.; Wacharasindhu, S. *Org. Lett.* **2005**, *7*, 2563–2565.
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(9) The TES enol ether **2** appears to be optimized for reactivity, as the TBS-analogue reacts sluggishly resulting in lower yields, while the TMS-derivative **1** is too reactive.
(10) TES-**3a** is obtained by quenching with Et_3N, and **3a** is obtained by quenching with aqueous $NaHCO_3$ and fluoride (TBAF or HF−pyridine).
(11) Other acids [$Yb(OTf)_3$, $Sc(OTf)_3$, $BF_3 \cdot Et_2O$, Bu_2BOTf, BBr_3, $SnCl_4$, $TiCl_4$] induced the cycloaddition stoichiometrically or in poor yields.
(12) An extended Table 1 showing results of experiments for optimization and scope appears in the SI.
(13) The relative stereochemistries of **8a**−**g** were determined by NOE correlations, and the structures of **8a**, desilylated-**8c**, **8g**, and **9g** have been additionally confirmed by X-ray crystallography.
(14) For simplicity, Scheme 1 shows full C−O bond cleavage at the epoxide to afford the siloxyallyl cation. However, the actual extent of bond dissociation may or may not be complete prior to C−C bond formation.
(15) Transition state **B** accounts for the formation of **9f** and **9g**. Apparently the selectivity for cycloaddition via transition state **A** is disfavored only when the substrate is hindered, as in **7g** in which both the enol ether and the furan are substituted.

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