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One-Pot Synthesis of Silylated Enol Triflates from Silyl Enol Ethers for Cyclohexynes and 1,2-Cyclohexadienes

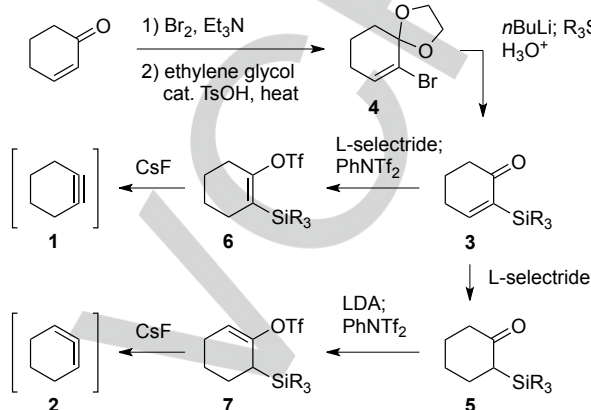
Kazuki Inoue, Ryo Nakura, Kentaro Okano,* and Atsunori Mori

Abstract: Regiocontrolled synthesis of precursors for strained cyclohexynes and 1,2-cyclohexadienes is described based on one-pot rearrangement of silyl enol ether followed by formation of enol triflate. Treatment of silyl enol ether with a combination of LDA and *t*BuOK led to the migration of the silyl group to generate α -silyl enolate, which was treated with Comins' reagent to provide the corresponding enol triflate. The transient α -silyl lithium enolate was smoothly isomerized in the presence of stoichiometric amount of water within one hour at room temperature, providing precursors for cyclohexynes exclusively in one pot. Effects of silyl groups, isomerization of the lithium enolate, and regiocontrolled generation of these precursors for these strained molecules were also investigated.

Strained cyclic compounds, such as benzyne, cyclohexyne (**1**), and 1,2-cyclohexadiene (**2**), are reactive intermediates for synthesizing multiply functionalized organic molecules.^[1–4] Despite their synthetic potentials, preparation of the necessary precursors can present obstacles. Although reactivity and generation of benzyne are extensively investigated for decades, reports on the related cycloalkynes and cycloallenes are still limited. Among various precursors, synthetically useful compounds for such strained intermediates are α -silyl enol triflates because of the unambiguously mild generation conditions (CsF, rt) and broad functional group compatibilities. Precursors for both compounds were first synthesized by Guitián and co-workers and transformed to the cycloalkynes and cycloallenes.^[4] However, this method requires multi-step synthesis of these precursors, and both precursors follow different synthetic routes (Scheme 1). To shorten the synthetic route for these strained intermediates **1** and **2**, we realized that the preparation of α -silyl enone **3** requires multi-step sequence via cyclohexenyl bromide **4**. In addition, the synthetic route toward 1,2-cyclohexadiene (**2**) includes reduction of the C–C double bond in enone **3** followed by triflation of the resultant silyl ketone **5**. In 1980s, Kuwajima^[5] and Corey^[6] independently reported the synthesis of α -silyl cyclohexanone. Encouraged by these literatures, we devised a one-pot synthesis of both silyl enol triflates **6** and **7** from the same silyl enol ether **8**. Based on Corey's report, the base-mediated migration of the silyl group gives lithium enolate **9**, which is converted to the corresponding triflate **7** as a precursor for 1,2-cyclohexadiene (**2**). On the other hand, we focused on the kinetic stability of the transient lithium enolate **9**. In turn, isomerization of the trisubstituted enolate **9** to thermodynamically stable tetrasubstituted enolate **10** gives triflate **6** as a precursor for cyclohexyne (**1**). Herein, we report one-pot synthesis of both precursors through rearrangement of silyl enol ether with/without isomerization of lithium enolate **9**.

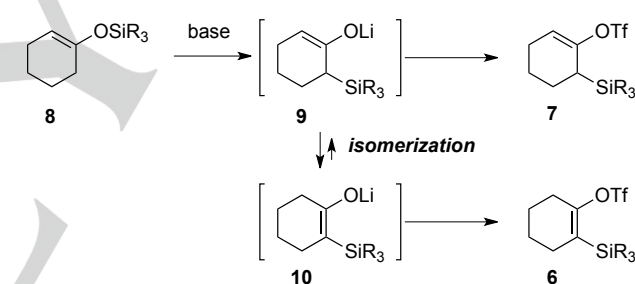
Previous reports

Synthesis of α -silyl enol triflates as precursors for cycloallene/cycloalkyne



This work

One-pot synthesis of α -silyl enol triflates from the same silyl enol ether



Scheme 1. Related previous work, the key objectives of this study and the associated challenges.

We first examined the effectiveness of the combination of *n*BuLi and *t*BuOK with TES enol ether **8a** as a substrate, according to the report by Corey^[6] (Table 1, entry 1). The progress of the migration of the TES group was monitored by TLC, and substantial amount of the starting TES enol ether **8a** was consumed within three hours. However, the subsequent treatment with Comins' reagent **11**^[7] did not produce the desired enol triflate in spite of the extensive optimization of reaction conditions, including screening of the triflating reagents.^[8] In these cases, we isolated α -silyl cyclohexanone **5a** as the major product, which should be generated through protonation of the transient lithium enolate **9a**. These results indicated that the strongly basic Schlosser's conditions^[9] might hamper the triflation, probably due to the undesired nucleophilic addition of butyl lithium toward the triflating reagent. Therefore, we re-examined the reaction conditions that were applicable for our synthetic strategy. We then attempted *t*BuOK-free conditions using butyl lithium. The silicon migration, however, was not facilitated, resulting in 74% recovery of the starting silyl enol ether **8a** (entry 2). The addition of other promoting agents, such as TMEDA, led to the formation of a simple enol triflate derived

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from cyclohexanone in 72% yield,^[10] despite the complete consumption of silyl enol ether **8a** (entry 3). Switching *n*BuLi to *s*BuLi gave a complex mixture of unidentified byproducts (entry 4). Finally, we found that the novel combination of LDA and *t*BuOK^[11] was extremely effective for the one-pot silyl migration followed by treatment of the transient lithium enolate using Comins' reagent **11** to give a precursor **7a** for 1,2-cyclohexadiene (**2**) (entry 5). The control experiments revealed that both LDA and *t*BuOK were essential (entries 6 and 7). Thus, the reaction did not proceed in the absence of *t*BuOK or LDA, resulting in the recovery of the silyl enol ether **8a**.

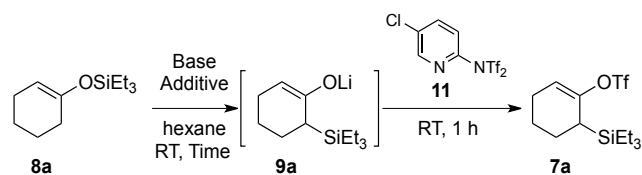
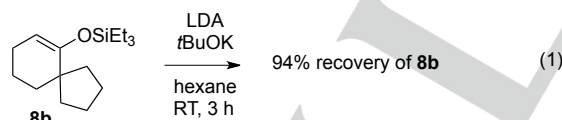


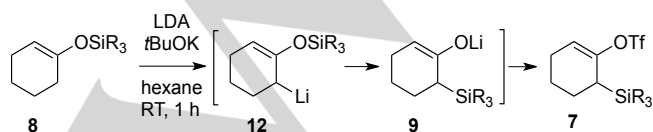
Table 1. Screening of bases for one-pot silyl group migration/triflation^[a]

Entry	Base	Additive	Time	8a [%] ^[b]	7a [%] ^[b]
1	<i>n</i> BuLi	<i>t</i> BuOK	3 h	15	<2
2	<i>n</i> BuLi	–	3 h	74	— ^[c]
3	<i>n</i> BuLi	TMEDA	3 h	— ^[c]	— ^[c]
4	<i>s</i> BuLi	<i>t</i> BuOK	3 h	67	12
5	LDA	<i>t</i> BuOK	1 h	— ^[c]	93
6	LDA	–	3 h	98	— ^[c]
7	–	<i>t</i> BuOK	3 h	89	— ^[c]

[a] Reaction conditions: silyl enol ether **8a** (1 equiv; 0.50 mmol), base (2.5 equiv), additive (2.5 equiv), hexane, RT, then Comins reagent **11** (2.0 equiv). [b] The yield was determined by ¹H NMR spectrum of the crude material with 1,1,2,2-tetrachloroethane as an internal standard. [c] Not detected in the ¹H NMR spectrum of the crude material. TMEDA = *N,N,N',N'*-tetramethylethylenediamine. LDA = lithium diisopropylamide.

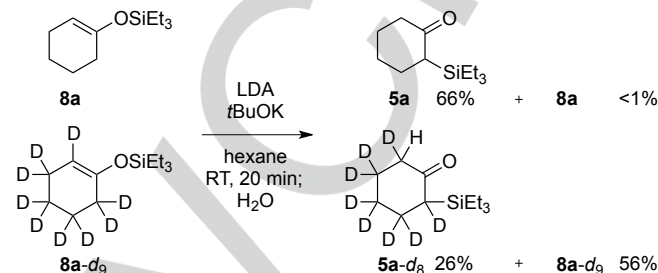


Silyl enol ether **8b** without an allylic α -proton was inert under the conditions (eq 1), which supports that the reaction proceeded through deprotonation of allylic proton rather than olefinic proton.^[6] Thus, the generation of allylic anion **12** led to the formation of thermodynamically more favored α -silyl lithium enolate **9**. Subsequent trapping with Comins' reagent provided **7** as a precursor for 1,2-cyclohexadiene (**2**) (Scheme 2).



Scheme 2. Plausible reaction pathway: favored initial allylic deprotonation.

Kinetic isotope effect of this reaction was also investigated using a 1:1 mixture of **8a** and **8a-d₉** (Scheme 3). After the mixture was treated with the combination of LDA and *t*BuOK at room temperature for 20 min, the reaction was quenched with water. Almost all the silyl enol ether **8a** was consumed to provide the corresponding α -silylketone **5a** in 66% yield, whereas α -silylketone **5a-d₈** was generated in 26% with 56% recovery of silyl enol ether **8a-d₉**. The results indicated that the initial allylic deprotonation was the rate-determining step.



Scheme 3. Kinetic isotope effect of the rearrangement of silyl enol ether.

With the optimal conditions in hand, scope and limitation of this method were investigated (Table 2). The established reaction conditions can be applied to the multi-gram scale synthesis, i.e., 1.3 g of **7a** was isolated in 74% yield. TBS, TIPS, and TBDPS enol ethers **8c–8e** were converted to the corresponding α -silyl enol triflates **7c–7e** in low to moderate yields. Silyl enol ethers **8c–8e** smoothly underwent migration of the silyl group, which was monitored by TLC analysis. In the case of TIPS enol ether **8a**, subsequent triflation of the resulting lithium enolate was slower, probably due to the steric hindrance of the TIPS group. Trimethylsilyl enol ether **8f** was converted to cyclohexanone, through nucleophilic attack to the less hindered silicon atom, causing the cleavage of the Si–O bond. Silyl enol ether **8g** was converted to silyl enol triflates **7g**.

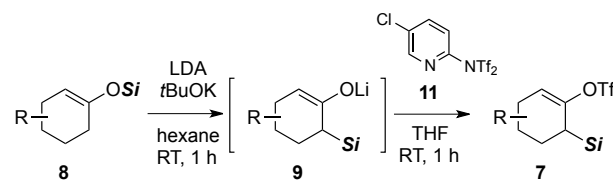
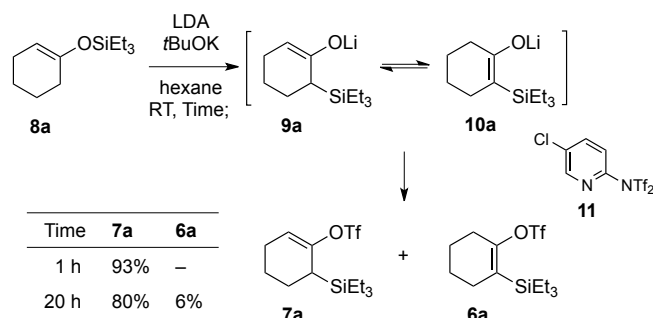


Table 2. Scope of the preparation of precursors for 1,2-cyclohexadiene^[a]

Silyl enol ether	Product	Yield [%] ^[b]
		Si = TES 7a 74 ^[c] TBS 7c 68 TIPS 7d 38 TBDPS 7e 56 TMS 7f –
		70 (dr = 9:1)

[a] Reaction conditions: silyl enol ether **8a** (1 equiv; 0.50 mmol), LDA (2.5 equiv), *t*BuOK (2.5 equiv), hexane, RT, then THF, Comins' reagent **11** (2.0 equiv). [b] Isolated yield. [c] 5 mmol scale.

After the establishment of the one-pot synthesis of precursors for 1,2-cyclohexadiene, we then turned our attention to parallel synthesis of precursors for cyclohexynes through isomerization of the transient anion **9a** (Scheme 4). To promote isomerization of lithium enolate **9a** to **10a**, silyl enol ether **8a** was subjected to the same reaction conditions in a prolonged period (20 h), which provided the desired product **6a** in 6% yield associated with **7a** in 80%.



Scheme 4. Effect of reaction time for isomerization of the transient enolate.

Encouraged by the promising results, we then focused on the isomerization of the transient α -silyl enolate to thermodynamically favored enolate (Table 3). The prolonged reaction time was insufficient for isomerization (Scheme 4 and Table 3, entry 1); however, these results indicated that diisopropylamine, the conjugate acid LDA, should work as an acid in the reaction. We then examined a suitable proton donor that could function as an acid to promote the isomerization of the resulting enolate. Based on the hypothesis, the reaction mixture was treated with diisopropylamine as an additive and was stirred for 20 h at room temperature. The isomerization, however, was not effectively promoted (entry 2). We then investigated other proton sources for the smooth isomerization. Triphenylmethane^[13] was effective, and methanol was proved superior for the reaction (entries 3 and 4). Finally, we found that the subsequent addition of THF and 1.5 equivalents of water provided complete isomerization to give the desired compound exclusively (entry 5). The isomerization was found to complete in a shorter reaction period, even in 10 min with reproducibility (entries 5–8). The isomerization was hampered in the absence of additional THF that was added after the migration of the silyl group (entry 9), probably due to the insufficient solvation of water. Finally, we examined the effect of equivalents of water on the isomerization. When the reaction was run with 0.5 and 1.0 equivalents of water, the desired silyl triflate **6a** was formed in 17% and 54% yields with concomitant generation of silyl triflate **7a** in 68% and 34%, respectively (entries 10 and 11). On the other hand, increased amount of water (3.0 equiv) provided the desired compound **6a** in slightly reduced yield with none of silyl triflate **7a** (entry 12). The yield of the silyl triflate **6a** was evidently reduced to 43% with 5 equivalents of water, and the α -silylated cyclohexanone **6a** was recovered in 57% ¹H NMR yield (entry 13). These results indicated that generated lithium enolate was protonated by the excess water, providing the α -silylated cyclohexanone **6a**.

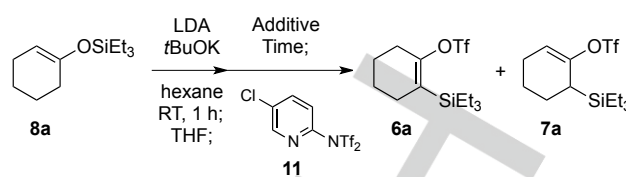


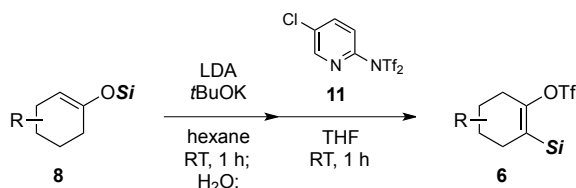
Table 3. Screening of reaction conditions for isomerization of enolate^[a]

Entry	Additive	Equiv	Time	6a [%] ^[b]	7a [%] ^[b]
1	–	–	20 h	6	80
2	<i>i</i> Pr ₂ NH	1.5	20 h	28	54
3	Ph ₃ CH	1.5	20 h	73	10
4	MeOH	1.5	20 h	68	— ^[c]
5	H ₂ O	1.5	20 h	77	— ^[c]
6	H ₂ O	1.5	3 h	81	— ^[c]
7	H ₂ O	1.5	1 h	91	— ^[c]
8	H ₂ O	1.5	10 min	95	— ^[c]
9 ^[d]	H ₂ O	1.5	1 h	13	71
10	H ₂ O	0.5	1 h	17	68
11	H ₂ O	1.0	1 h	54	34
12	H ₂ O	3.0	1 h	76	— ^[c]
13	H ₂ O	5.0	1 h	43	— ^[c]

[a] Reaction conditions: silyl enol ether **8a** (1 equiv; 0.50 mmol), LDA (2.5 equiv), *t*BuOK (2.5 equiv), hexane, RT, 1 h, then THF, additive (1.5 equiv), RT, then Comins' reagent **11** (2.0 equiv). [b] The yield was determined by ¹H NMR spectrum of the crude material with 1,1,2,2-tetrachloroethane as an internal standard. [c] Not detected in the ¹H NMR spectrum of the crude material. [d] No additional THF.

After establishing the isomerization conditions of the double bond in the transient enolate, we then investigated scope and limitation of the transformation (Table 4). Silyl enol ethers **8a** and **8c–8e**, which gave satisfactory results in the synthesis of the precursor for 1,2-cyclohexadiene (**2**), were subjected to the established reaction conditions to provide the corresponding α -silyl enol triflates. In the case of TES enol ether **8a**, the reaction could be performed to provide **6a** in 85% in a 1.4-gram scale. For the synthesis of substituted cyclohexynes, the stereochemical problem should be considered. We then examined TES enol ether **8g** and isolated the corresponding product **6g** in 44% yield as a sole regioisomer. TES enol ether **8h** was also converted to the desired product **6h** in 61% yield.

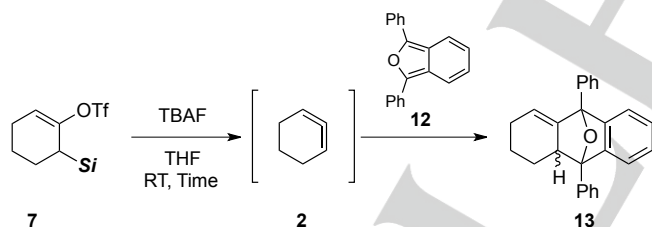
With these α -silyl enol triflates in hand, we then investigated the rate for generation of 1,2-cyclohexadiene (**2**) (Table 5). According to previous reports,^[4b,4c] TES enol triflate **7a** was treated with tetrabutylammonium fluoride (TBAF) in the presence of 1,3-diphenylisobenzofuran (**12**) at room temperature. The starting TES enol triflate **7a** was consumed within one hour and the cycloadducts **13** was isolated in 83% yield as a mixture of 71:29 *endo/exo* adducts (Entry 1). On the other hand, TBS

**Table 4.** Scope of the preparation of precursors for cyclohexyne^[a]

Silyl enol ether	Product	Yield [%] ^[b]
 8a, 8c–8e	 6a, 6c–6e	Si = TES 6a 85 ^[c] TBS 6c 65 TIPS 6d 46 TBDPS 6e 16
 8g	 6g	61
 8h	 6h	44

[a] Reaction conditions: silyl enol ether **8a** (1 equiv; 0.50 mmol), LDA (2.5 equiv), *t*BuOK (2.5 equiv), hexane, RT, then THF, H₂O (1.5 equiv), RT, then Comins' reagent **11** (2.0 equiv). [b] Isolated yield. [c] 5 mmol scale.

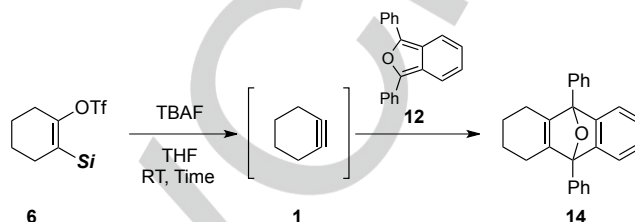
and TIPS enol triflates **7c** and **7d** required a prolonged reaction time (24 h) for consumption to provide **13** in 97% and 98% yields, respectively (Entries 2 and 3). TBDPS enol triflate **7e** was also converted to **13** in 4 h to give **13** in quantitative yield (Entry 4).

**Table 5.** Generation of 1,2-cyclohexadiene^[a]

Entry	Si	Time [h]	7 [%] ^[b]	13 [%] ^[b]	endo/exo
1	TES	1	— ^[c]	quant (83 ^[d])	71:29 (78:22 ^[d])
2	TBS	24	1	97	72:28
3	TIPS	24	— ^[c]	98	71:29
4	TBDPS	4	— ^[c]	quant	72:28

[a] Reaction conditions: silyl enol triflate **7** (1 equiv; 0.20 mmol), 1,3-diphenylisobenzofuran (**12**) (1.5 equiv), THF, RT, then TBAF (1.5 equiv). [b] The yield was determined by ¹H NMR spectrum of the crude material with 1,1,2,2-tetrachloroethane as an internal standard. [c] Not detected in the ¹H NMR spectrum of the crude material. [d] Isolated yield. TBAF = tetrabutylammonium fluoride.

α -Silyl enol triflates **6** were found to generate cyclohexyne (**1**) in the presence of fluoride ion (Table 6). Similarly, among these α -silyl enol triflates **6**, TES enol triflates **6a** was smoothly converted to the corresponding cycloadduct **14** in 94% yield (Entry 1). TBS and TIPS enol triflates **6c** and **6d** were also converted to **14** in good to excellent yields for 24 h (Entries 2 and 3). The reaction of TBDPS enol triflates **6e** furnished to provide cycloadduct **14** for 4 h (Entry 4).

**Table 6.** Generation of cyclohexyne^[a]

Entry	Si	Time [h]	6 [%] ^[b]	14 [%] ^[b]
1	TES	1	— ^[c]	94 (78 ^[d])
2	TBS	24	— ^[c]	87
3	TIPS	24	— ^[c]	73
4	TBDPS	4	— ^[c]	86

[a] Reaction conditions: silyl enol triflate **6** (1 equiv; 0.20 mmol), 1,3-diphenylisobenzofuran (**12**) (1.5 equiv), THF, RT, then TBAF (1.5 equiv). [b] The yield was determined by ¹H NMR spectrum of the crude material with 1,1,2,2-tetrachloroethane as an internal standard. [c] Not detected in the ¹H NMR spectrum of the crude material. [d] Isolated yield. TBAF = tetrabutylammonium fluoride.

In conclusion, we developed the synthesis of precursors for 1,2-cyclohexadienes based on one-pot rearrangement of silyl enol ether followed by the formation of enol triflate. The transient α -silylated lithium enolate was smoothly isomerized in the presence of stoichiometric water at room temperature to give precursors for cyclohexynes. In addition, we investigated the effects of silyl groups on the reaction rates for generating 1,2-cyclohexadiene and cyclohexyne. Further application of these findings will be reported in due course.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: strained molecules • reactive intermediates • cycloalkyne • cycloallene • migration

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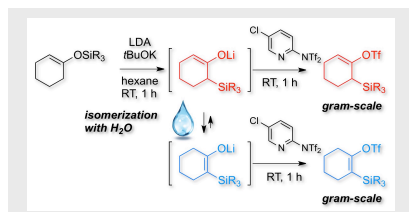
Entry for the Table of Contents

COMMUNICATION

Kazuki Inoue, Ryo Nakura, Kentaro Okano,* and Atsunori Mori

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One-pot Synthesis of Silylated Enol Triflates from Silyl Enol Ethers for Cyclohexynes and 1,2-Cyclohexadienes



Regiocontrolled synthesis of precursors for strained cyclohexynes and 1,2-cyclohexadienes is described based on one-pot rearrangement of a silyl group followed by the formation of enol triflates. The transient α -silylated lithium enolate was smoothly isomerized in the presence of stoichiometric amount of water within one hour at room temperature to provide precursors for cyclohexyne.