# Intramolecular Carbolithiation of 3-Lithioxy-5-alkenyllithiums as a Platform for Cyclopentanols and Cyclopentanones

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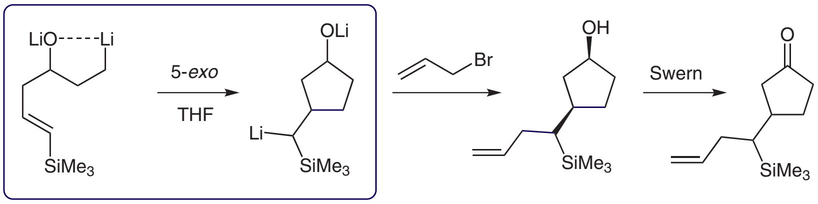

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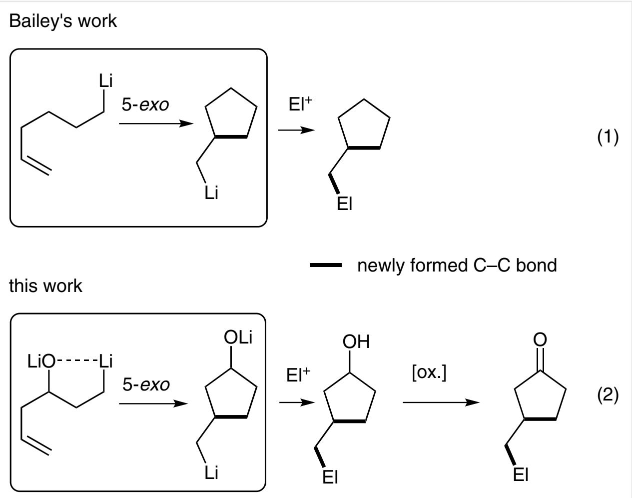
**Abstract** Intramolecular carbolithiation of 3-lithioxy-5-hexenyllithiums was studied. Unlike the case of 5-hexenyllithium, the cyclization of 3-lithioxy-5-hexenyllithium was very sluggish. Acceleration was observed when lithium chloride was added, suggesting that intramolecular lithioxy coordination would hinder the cyclization. Introduction of a silyl or thiophenyl group at the olefin terminus caused smooth cyclization. The resulting dianions having a cyclopentane framework are subjected to C–C bond-forming reaction with electrophiles to give 3-substituted cyclopentanols. Coupled with the Swern oxidation, the overall protocol served as a platform for 3-substituted cyclopentanones.

**Key words** intramolecular carbolithiation, dianion, cyclopentanols, cyclopentanones

Five-membered carbocycles are frequently found in both natural and unnatural compounds.[1] Two decades ago, Bailey and co-workers reported that 5-hexenyllithium undergoes 5-*exo* cyclization leading to cyclopentylmethyllithium on warming at 25 °C (Scheme 1, eq. 1).[2] This finding has triggered a number of useful studies of intramolecular carbolithiation leading to five-membered rings,[3] which involve asymmetric carbolithiation based on (–)-sparteine.[4] During the course of our study on ketone dilithio dianion chemistry,[5] it occurred to us that intramolecular carbolithiation, when applied to the lithioxy-tethered 5-alkenyllithiums, the synthetic usefulness would be further expanded, since the resulting five-membered-ring products are ready to be transformed into cyclopentanols and cyclopentanones, a basically important class of building blocks in organic synthesis (Scheme 1, eq. 2). Herein we report the reactivity of 3-lithioxy-5-alkenyllithiums towards the intramolecular carbolithiation.



**Scheme 1** Concept: Carbocyclization of 3-lithioxy-5-hexenyllithium as a platform for 3-substituted cyclopentanols and cyclopentanones

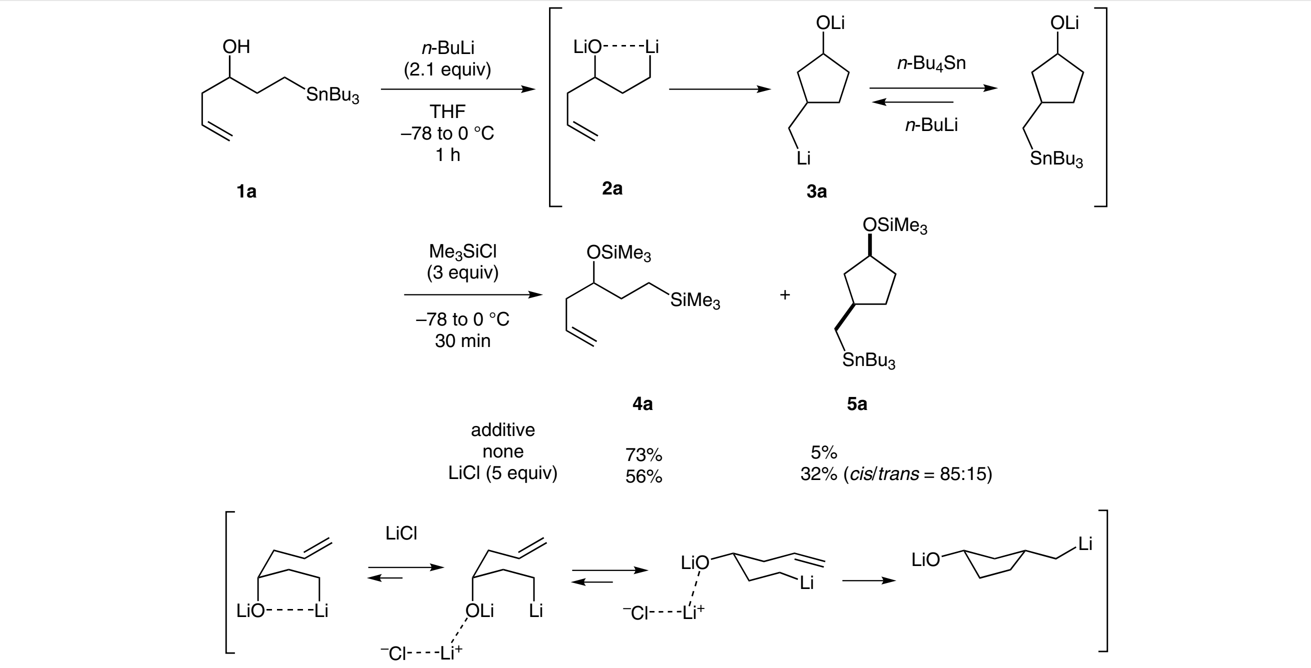
Firstly we examined the reaction of the simplest dilithio dianion, 3-lithioxy-5-hexenyllithium (**2a**), which was generated from 1-tributylstannyl-5-hexen-3-ol (**1a**) and *n*-BuLi (2.1 equiv) in THF (Scheme 2). Tin–lithium exchange reaction was carried out at –78 °C, and then the reaction mixture was allowed to warm to 0 °C. Disappointingly, recooling the mixture to –78 °C and quenching by TMSCl resulted in the formation of uncyclized product **4a** in 73% yield, and only 5% yield of the cyclized product **5a** was obtained. Tin-containing **5a** would be formed by the reaction of the cyclized dianion **3a** with tetrabutyltin. The observed reluctant carbolithiation of **2a** led us to posturate intramolecular coordination of a lithioxy group to alkyllithium in **2a**. To alter the unfavorable intramolecular Li–O–Li coordination, we examined the experiment in the presence of LiCl (5 equiv),[6] which resulted in the increase of the yield of **5a** to 32% yield with 85:15 (*cis*/*trans*) ratio. The promotion of the cyclization and *cis* preference may be due to chairlike conformation allowed by LiCl-caused liberation of the intramolecular Li–O–Li coordination (Scheme 2).

Since carbolithiation of ketone dilithio α,β-dianions onto vinylsilane proceeds efficiently,[5e,7] we next examined dianion **2b** having a silane moiety (Scheme 3). Unlike the parent **2a**, the cyclization of **2b** leading to **3b** proceeded smoothly even without the addition of LiCl to give the desired cyclopentanol **5b** in 85% isolated yield with 94:6 (*cis*/*trans*) ratio after aqueous treatment.[8] We then examined the reaction of thus generated **3b** with carbon electrophiles, such as allyl bromide, benzyl bromide, and benzaldehyde, which gave good yields of the corresponding 3-functionalized cyclopentanols **6**, **7**, and **8**. Swern oxidation was examined to convert cyclopentanols **5b** and **6** into the corresponding cyclopentanones **5b′** and **6′**, which worked quite well. Acidic treatment (sulfuric acid in THF) of the diastereomer mixture (23:23) of diol **8** caused Peterson olefination to give 91% yield of **8′**. The reaction of **3b** with CO was also carried out in the hope of causing acyllithium to lithium enolate conversion accompanied by 1,2-*Si* shift.[9] As our expectation, after aqueous treatment, the desired acylsilane **11** was obtained in 63% yield.

To extend the present dianion-based cyclization strategy to the construction of 2,3-dihydro-1-indenols, we turned our attention to aryllithiums having an *ortho*-lithioxy tether (Scheme 4).[10] The dianion **13a** was prepared from aryl bromide **12a** and *n*-BuLi via Li–Br exchange, however, unlike the case of the dianion **2a**, the cyclization of **13a** did not occur at all even when the LiCl was added. On the other hand, the cyclization reaction of **13b** having a vinylsilane moiety did proceed, yet sluggish, giving a 2:1 mixture of uncyclized **15b** and cyclized **16b**. The addition of LiCl was effective to accelerate the cyclization, giving 76% yield of **16b** with an 82:18 diastereomeric ratio. The Swern oxidation of **16b** gave the corresponding 2,3-dihydro-1-indenone **16b′** in quantitative yield.

We then examined aryllithium **13c** having a vinyl sulfide moiety (Scheme 5). Again the addition of LiCl was necessary to promote the carbocyclization of **13c** leading to **14c**. In this case, however, the expected cyclization product **16c** was detected in a trace amount and instead **17c**, in which a butyl group was incorporated at α position to the PhS group, was obtained as the cyclization product (57% with 5 equiv of LiCl, −78 °C, 30 min). This could be formed by the cyclized anion **14c** with *n*-BuBr, in situ formed by Li–Br exchange reaction between **12c** and *n*-BuLi. Since no such reaction with *n*-BuBr was observed in TMS-attached anion **14b**, the observed reactivity difference is intriguing, and we are now examining the generality.

In summary, we have studied the intramolecular carbolithiation of 3-lithioxy-5-hexenyllithiums. In contrast to the case of Bailey's 5-hexenyllithium, the cyclization was generally inefficient presumably due to the intramolecular coordination. With an exception of aryllithium **13a**, the addition of LiCl was effective to promote the cyclization and this is due to dissociation of the intramolecular coordination. Introduction of a silyl group at the olefin terminus pushed smooth intramolecular carbolithiation, and the resulting



| additive | 4a | 5a |
|---|---|---|
| none | 73% | 5% |
| LiCl (5 equiv) | 56% | 32% (*cis*/*trans* = 85:15) |

**Scheme 2** Carbocyclization of 3-lithioxy-5-hexenyllithium (**2a**)

dianions are subjected to C–C bond-forming reaction with electrophiles to give the corresponding 3-substituted cyclopentanols. Coupled with the subsequent Swern oxidation, the overall protocol served as a platform for β-substituted cyclopentanones.

## Acknowledgment

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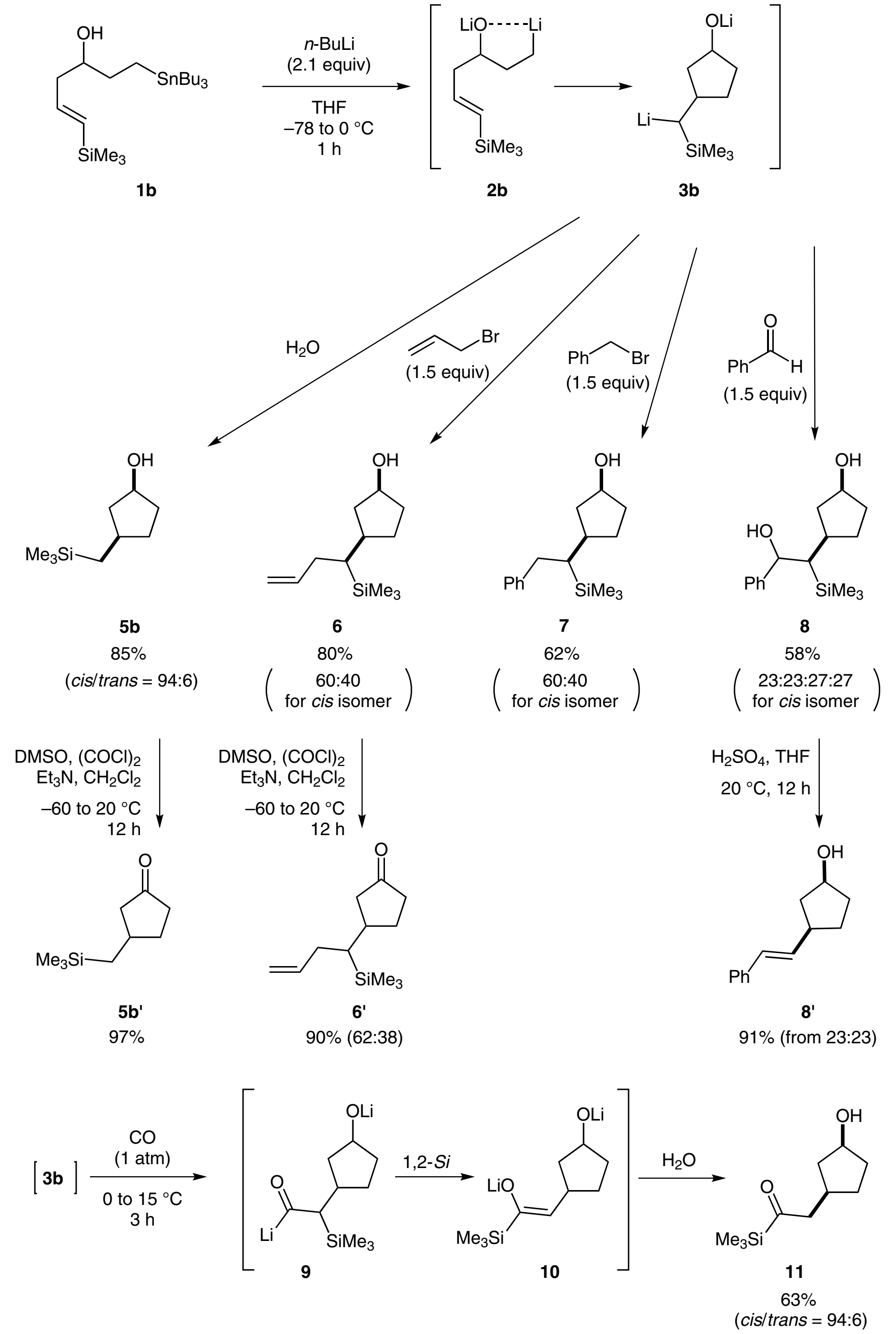
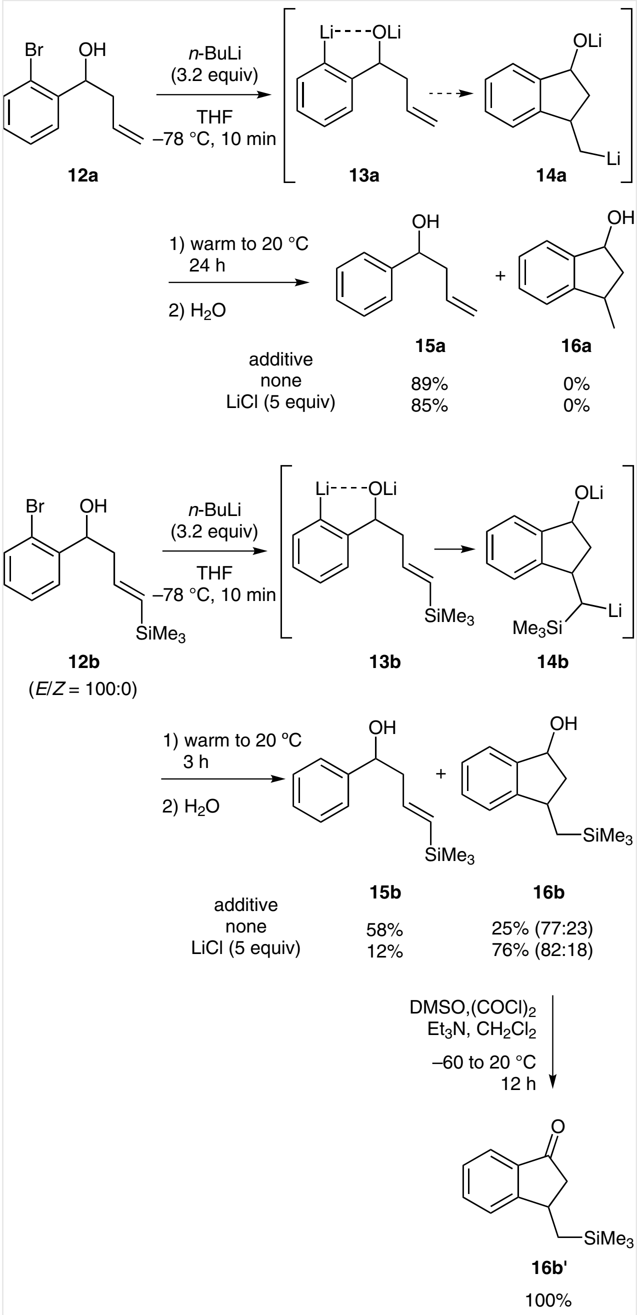


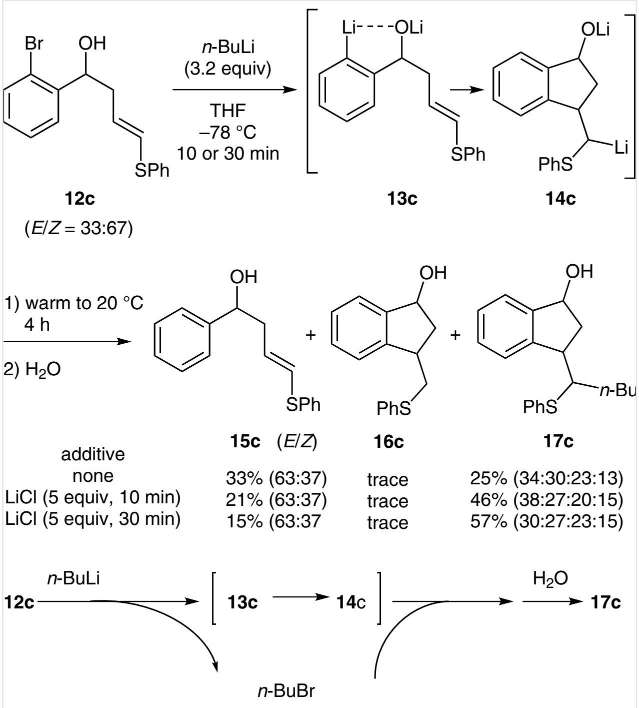
**Scheme 3** Carbocyclization of 3-lithioxy-6-trimethylsilyl-5-hexenyllithium (**2b**) and the use as a platform for 3-substituted cyclopentanols and cyclopentanones



**Scheme 4** Carbocyclization of aryllithiums **13a** and **13b** having an *o*-lithioxybutenyl tether

## Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560170.



**Scheme 5** Carbocyclization of aryllithium **13c** having an *o*-lithioxybutenyl tether

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(8) **3-Trimethylsilylmethylcyclopentanol (5b); Typical Procedure**

To a solution of γ-stannylalcohol **1b** (221 mg, 0.48 mmol) in THF (3 mL) was added *n*-BuLi (0.63 mL, 1.57 M solution in hexane, 1.01 mmol) dropwise over a period of 5 min at –78 °C. This solution was allowed to warm to 0 °C and stirred for 1 h. The resulting solution was quenched with $H_2O$ and extracted with $Et_2O$ twice. The combined organic solution was washed with sat. aq $NH_4Cl$ and dried over $MgSO_4$ and then concentrated under reduced pressure. Purification by flash chromatography (elution with hexane–$Et_2O$, 2:1) provided the desired 3-trimethylsilylmethylcyclopentanol (**5b**, 70 mg, 85%) with 94:6 (*cis*/*trans*) ratio as a colorless oil. $R_f$ = 0.2 (hexane–$Et_2O$, 3:1). $^1H$ NMR (270 MHz, $CDCl_3$ for *cis* isomer): δ = –0.01 (s, 9 H), 0.71 (d, 2 H, *J* = 7.3 Hz), 1.06–1.16 (m, 1 H), 1.33–1.43 (m, 1 H), 1.60–1.90 (m, 5 H), 2.16–2.26 (m, 1 H), 4.25–4.29 (m, 1 H). $^{13}C$ NMR (68 MHz, $CDCl_3$ for *cis* isomer): δ = –0.74, 24.53, 33.99, 35.06, 35.70, 45.90, 73.78. MS (EI): *m*/*z* (%) = 157 (13) $[M^+ - CH_3]$, 139 (29), 91 (32), 73 ($Me_3Si$, 100). IR (KBr): 837, 1248, 3348 $cm^{-1}$. HRMS: *m*/*z* calcd for $C_8H_{17}OSi$ $[M^+ - CH_3]$: 157.1049; found: 157.1037. Anal. Calcd for $C_9H_{20}OSi_3$: C, 62.72; H, 11.70. Found: C, 62.48; H, 11.69.

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