



A formal [3+2] cycloaddition for the synthesis of bicyclo[3.2.1]octanes

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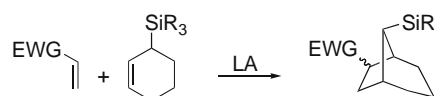
ABSTRACT

A new and a direct synthetic method for the construction of the bicyclo[3.2.1]octane system is envisioned by assembling cyclic allylsilanes with electron-deficient double bonds in a single step via a formal diastereoselective Lewis acid-promoted [3+2] cycloaddition.

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The Lewis acid-promoted [3+2] cycloaddition of allylsilanes with saturated and α,β -unsaturated carbonyl compounds has been shown to be a useful tool for the stereoselective preparation of four- and five-membered carbo- and heterocyclic compounds.¹ This type of cycloaddition was first reported as a side reaction of the Hosomi–Sakurai allylation.² The switch from the Hosomi–Sakurai allylation reaction to the cycloaddition was achieved by using allylsilanes bearing larger substituents at the silicon atom such as SiMe_2Ph , or $\text{Si}(i\text{Pr})_3$ among others.³ The allylsilanes explored in these cycloaddition reactions were almost exclusively acyclic. Herein, we report a formal [3+2] cycloaddition of cyclic allylsilanes with α,β -unsaturated carbonyl compounds that offers an attractive method to form the bicyclo[3.2.1] ring system (Scheme 1).

Such a ring system provides an electron-withdrawing group for further transformations and the ability to carry out an oxidation of the silyl group. The mild conditions required allows for the inclusion of additional substitution on either the allylsilane or the electrophilic olefin. Very few examples of this type of cycloaddition with cyclic allylsilanes have been reported.^{4–7} Some of these examples include an intramolecular reaction of a cyclic allylsilane with an enone as the key step in the construction of the dolastane skeleton;⁴ the annulation of triethylsilyl cyclohexene with methyl propiolate that provides the bicyclo[3.2.1]oct-6-en system;⁵ the annulation of a cyclohexadienyl silane with chlorosulfonyl isocyanate that forms the 6-azabicyclo[3.2.1]octane core;⁶ and the annulation of a substituted cyclohexenyl silane with α -(benzyloxy) acetaldehyde that provides the 6-oxabicyclo[3.2.1]octane system.⁷ Due to its occurrence in many natural and unnatural pharmacologically important compounds such as sesqui-⁸ and diterpenes,⁹ bridged steroids¹⁰ and alkaloids,¹¹ the bicyclo[3.2.1]octane system is the center of considerable synthetic interest. Although a large number of synthetic methods¹² have been developed for the synthesis of this bicyclic subunit, there is always a need for conceptually new methods. Given the utility of this formal [3+2]

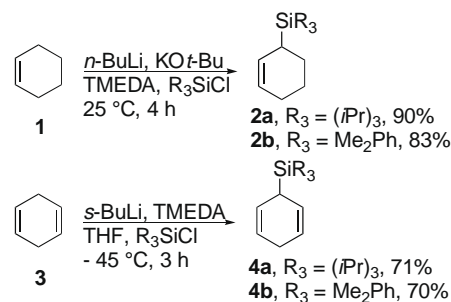


Scheme 1. Formal [3+2] cycloaddition of cyclic allylsilanes.

cycloaddition, we have carried out an initial examination of the scope of this reaction.

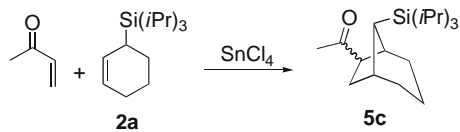
The cyclic allylsilanes used as starting materials in this study were synthesized as shown in Scheme 2. We had initially examined a variety of methods including the reaction between the corresponding Grignard reagent of 3-cyclohexenyl halides with silyl chlorides¹³ and the allylic substitution of cyclic allylic substrates employing reagents containing silicon–metal bonds.^{14,15} However, none of these methods worked well in our hands to provide the desired allylsilanes.

The successful approach involved metallation of cyclohexene **1** with Schlosser's base^{16,17}, followed by silylation with triisopropylsilyl chloride to provide **2a**¹⁸ in 90% yield. This facile and high yielding route also worked well for the preparation of allylsilane **2b**¹⁹ that was obtained in 83% yield. The allylsilanes **4a**²⁰ and **4b**²¹ were prepared from cyclohexa-1,4-diene **3** following a related known procedure.²²



Scheme 2. Synthesis of cyclic allylsilanes.

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Scheme 3. The formal [3+2] cycloaddition of 3-triisopropylsilyl-cyclohexene with methyl vinyl ketone.

Studies on the formal [3+2] cycloaddition of cyclic allylsilanes were initiated by examining the reaction of 3-triisopropylsilyl-cyclohexene **2a** with methyl vinyl ketone (Scheme 3) using TiCl_4 , following the standard procedure reported by Knölker.³ This procedure involves the formation of the Lewis acid/enone complex at -20°C . The temperature is then lowered to -78°C , and a solution of allylsilane in methylene chloride is added. The reaction mixture is then stirred at -20°C for 19 h. In our hands this procedure provided unsatisfactory results.

Since this type of cycloaddition reaction has been reported to be strongly dependent on the Lewis acid used,^{7,23} a series of Lewis acids including SnCl_4 , EtAlCl_2 , AlMe_3 , Et_2AlCl , and $\text{BF}_3\cdot\text{Et}_2\text{O}$ were examined. It was gratifying to see that the use of SnCl_4 provided the expected product albeit in low yield (25%), while all other Lewis acids failed to give cycloadducts. The procedure was modified at this point, and the Lewis acid was added to a mixture of allylsilane and electrophile.²⁴ This provided a somewhat improved yield, and we proceeded with a brief reaction optimization by changing the ratio of the electrophile to nucleophile and the reaction temperature. When an excess (200 mol %) of the nucleophile was used the yield decreased to 7%, while an excess of the electrophile (200 mol %) improved the yield to 52%. Varying the reaction temperature from -40°C to 40°C did not show significant differences in terms of the yields of the reactions, and -20°C seemed to be the optimal temperature (GC yield 71%).

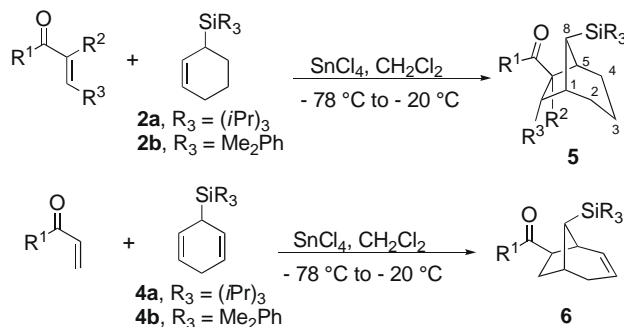
With a viable and somewhat optimized method in hand, further investigations of this formal [3+2] cycloaddition reaction were conducted with additional cyclic allylsilanes and a variety of electrophiles. The results are summarized in Table 1.

In comparing simple substrates for these reactions, methyl vinyl ketone proved to be considerably better than either acrolein or methyl acrylate regardless of the allylsilane. Of the four different allylsilanes paired with these initial electrophiles, the triisopropylsilyl derivatives (**2a** and **4a**) were in general better than the phenyldimethylsilyl derivatives, **2b** and **4b**. This is not entirely unexpected as the silicon of the phenyldimethylsilyl group is more prone to nucleophilic attack than the silicon of the triisopropylsilyl group.³ For example, the reaction of **2b** with methyl vinyl ketone (entry 6) afforded only 10% (isolated yield) of the cycloadduct **5d** and 6% of the Sakurai product, and considerable amounts of PhMe_2SiOH were detected. We can also observe that allylsilane **2b** or **4b** with an additional double bond can sometimes provide improved yields of the annulated product (entry 8 vs entry 6).

With an examination of simpler reaction substrates completed, the examination of additional electrophiles was carried out. While acrolein itself provides a very poor yield (31%), the reaction of crotonaldehyde (entry 10) provides a much better yield of annulation product **5f** (48%). The introduction of a methyl group to the 4-position of methyl vinyl ketone (entry 11 vs entry 5) provides a decrease in yield but an increase in the stereoselectivity of the annulation reaction. The 3-pentene-2-one used in this reaction is trans, and our expectation was that the double bond geometry would be retained.²⁴ NMR studies have confirmed that the double bond geometry is largely (16:1) retained.²⁵ The addition of a methyl group to the 3-position of methyl vinyl ketone (entry 12) provides a further decrease in yield relative to methyl vinyl ketone.²⁶

Table 1

The formal [3+2] cycloaddition of cyclic allylsilanes **2a**, **2b**, **4a**, and **4b** with various electrophiles



| Entry | R ¹ | R ² | R ³ | Allylsilane | Product | Yield ^a (%), <i>exo:endo</i> ratio ^b |
|-------|--------------------------------|----------------|----------------|-------------|-----------|--|
| 1 | H | H | H | 2a | 5a | 31 (8:1) |
| 2 | H | H | H | 2b | 5b | 5 ^c |
| 3 | H | H | H | 4a | 6a | 31 (4:1) ^c |
| 4 | H | H | H | 4b | 6b | 9 ^c |
| 5 | Me | H | H | 2a | 5c | 66 (8:1) |
| 6 | Me | H | H | 2b | 5d | 16 (0.6:1) ^d |
| 7 | Me | H | H | 4a | 6c | 66 (4:1) ^c |
| 8 | Me | H | H | 4b | 6d | 50 (1.5:1) ^c |
| 9 | OMe | H | H | 2a | 5e | 17 ^c |
| 10 | H | H | Me | 2a | 5f | 48 (16:4:1) |
| 11 | Me | H | Me | 2a | 5g | 50 (16:1) |
| 12 | Me | Me | H | 2a | 5h | 45 (9:1) |
| 13 | C ₆ H ₁₁ | H | H | 2a | 5i | 71 (100:0) |
| 14 | C ₆ H ₁₁ | H | H | 2b | 5j | 42 (1.5:1) ^d |
| 15 | C ₆ H ₁₁ | H | H | 4b | 6e | 40 (1.5:1) |
| 16 | Ph | H | H | 2a | 5k | 76 (100:0) |
| 17 | Ph | H | H | 2b | 5l | 50 (3.5:1) ^{c,d} |
| 18 | Ph | H | H | 4b | 6f | 25 (1.8:1) |

^a Isolated chemical yields.

^b The ratio of *exo:endo* was determined by GC of the purified product.

^c The ratio *exo:endo* and the yields were determined by GC using decane as an internal standard.

^d The ratio of Sakurai product:*exo* cycloadduct.

Given the apparent steric influence on the yield and stereoselectivity observed in entries 10–12, two additional ketones with sterically larger groups were studied. Both cyclohexyl vinyl ketone (entry 13) and phenyl vinyl ketone (entry 16) provided excellent yields (71% and 76%, respectively) and a single diastereomeric product upon reaction with allylsilane **2a**. The reactions of both of these ketones with allylsilanes **2b**, and **4b** provided more modest yields and lower diastereoselectivity in the annulation reaction. Surprisingly, the cycloaddition reaction of these ketones with allylsilane **2b** (entries 14 and 17) afforded the Sakurai product as the major product.

The relative stereochemistry of the silyl group is expected to be anti to the electrophile providing products with the stereochemistry shown in Figure 1. However, the relative stereochemistry of the ketone (or other activating groups) was not readily predicted. NOESY and COSY experiments were carried out to determine the relative stereochemistry. The diastereoisomers of **6d** were separable by chromatography, and provided two stereochemically pure cycloadducts for structural elucidation.²⁷

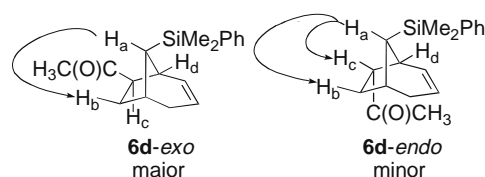


Figure 1. Structure of major and minor cycloadducts and observed NOESY cross peaks.

The NOESY spectrum of isomer **6d-endo** shows a cross peak between H_a and H_c, while this cross peak is not observed in the spectrum of isomer **6d-exo**. This proves that the orientation of the C(O)CH₃ group is as shown in Figure 1. The proton H_a attached to the bridged carbon shows a cross peak with proton H_b in the spectrum corresponding to the **6d-exo** isomer, and there is no coupling observed with H_c. In the spectrum corresponding to the **6d-endo** isomer, proton H_a shows a cross peak with protons H_b and H_c. This proves that the silyl group for both isomers is oriented over the six-membered ring of the bicyclic system as expected. Confirmation of the relative stereochemistry of the *endo* and *exo* isomers was obtained via an examination of the COSY spectra.²⁸

In conclusion, a new type of Lewis acid-mediated allylic formal [3+2] cycloaddition reaction was developed involving cyclic allylsilanes and α,β -unsaturated carbonyls. The reaction is a useful diastereoselective synthetic method for the construction of the bicyclo[3.2.1]octane system, an important structural entity of many pharmacologically important natural products. This reaction constitutes an extension of allylic formal [3+2] cycloadditions as well as an expansion of the methodologies known today for the direct assembly of bicyclo[3.2.1]octane ring system.

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- In the NOESY spectrum of **5g**, cross peaks were observed between proton H_c and methylene groups C3 and C4, while proton H_b shows no cross peaks with these groups. This shows that the carbonyl group is in the *exo* orientation, and that the methyl group at position R³ is in the *endo* orientation.
- The major product was identified as the *exo* cycloadduct **5h** from a NOESY experiment, where a cross peak was observed between the methyl group at position R² and the methylene groups C3 and C4.
- We chose to investigate cycloadduct **6d** because it was possible to isolate both its diastereoisomers, and because the NMR signal corresponding to the bridged proton H_a is clearly observed. For the cycloadducts with (iPr)₃Si group, the NMR signal corresponding to proton H_a is in close proximity or overlaps with the signal corresponding to the iPr group, which makes it difficult to analyze the coupling of proton H_a with other protons in the structure.
- In the COSY spectrum of the isomer **6d-endo**, a cross peak is observed between protons H_c and H_d suggesting a vicinal coupling between the two protons. This cross peak is missing from the COSY spectrum of the **6d-exo** isomer. When two adjacent C–H σ bonds are orthogonal, as for the **6d-exo** isomer, no coupling is observed between H_c and H_d in accordance with the Karplus relationship. The calculated dihedral angle between H_c and H_d for the **6d-endo** structure is 20.5°, and it is 90.3° for the **6d-exo**. The dihedral angles were calculated using SPARTAN '04 Macintosh v1.0. Coupling data have been previously used to determine the relative stereochemistry of bicyclo[2.2.1]heptanes^{29,30} and bicyclo[3.2.1]octanes.^{31,32}
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