Direct Synthesis of Silylcyclopentene under Ball Milling Conditions

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Abstract: The development of innovative methods for synthesizing silylcyclopentene compounds is particularly important for enriching and improving the synthetical toolbox of organosilicon compounds. Herein, a facile approach has been developed for the synthesis of silylcyclopentenes promoted by mechanochemically generated organolithium species as silicon nucleophiles under ball milling conditions, avoiding the requirement of large amounts of bulk solvent. This operationally simple method demonstrates good functional group compatibility, which provides a great opportunity for further exploration of the synthetic applications of silylcyclopentenes. Density functional theory calculations indicated that the transient lithiosilole intermediates undergo a stepwise nucleophilic addition process, which governs this mechanic-force-promoted [4+1] cycloaddition reaction.

Silylcyclopentene compounds, in which an organic skeleton bridges one silicon atom and carbon-carbon double bond, are of significant interest because of their unique structures and excited potential synthetic applications.[1] However, the dearth of efficacious synthetic methodologies under environmentally friendly conditions has relegated silylcyclopentene's practical utility to the realm of unmet potential, consistently relegated to obscurity.

In general, silylcyclopentenes can be synthesized through the reaction of 1,3-diene compounds with silylenes ($R_2Si:$), which have garnered significant interest in the synthesis of organosilicon compounds owing to their capacity to concurrently construct two C-Si σ-bonds. In this regard, silylenes are added to the carbon-carbon double bonds of 1,3-dienes to generate silacyclopropanes, which undergo ring expansion through biradical intermediates. Subsequently, a radical-radical coupling process occurs to afford silylcyclopentene derivatives.[2] Nevertheless, the synthons of silylenes, such as silacyclopropanes,[3] silanorbornenes,[4] disilenes,[5] silylboronic esters,[6] and oligosilanes[7] which typically require multi-step preparation under stringent conditions. Moreover, due to the high-reactive silylcarbene intermediates generated in situ are often difficult to control in terms of chemical selectivity, strictly controlled reaction temperatures, and inner gas protection are required.[8]
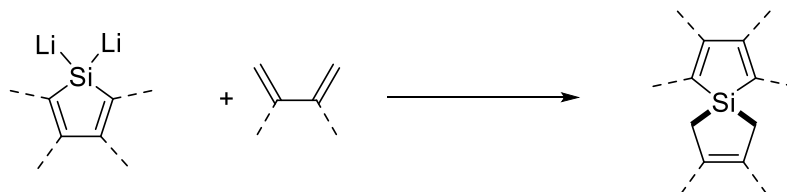
Conventional solution-based methods ————
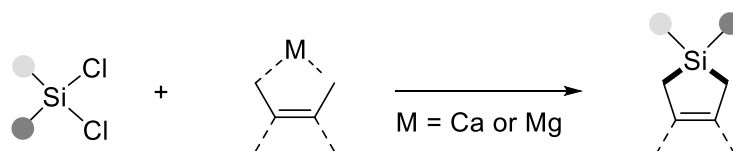
a. Synthesis from silylenes (R$_2$Si:)
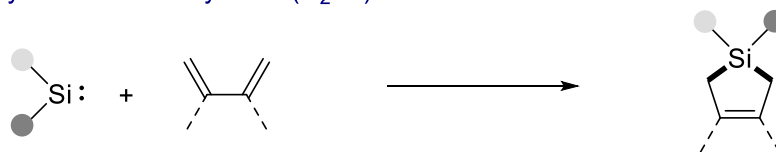
multi-step preparation of Si-carbene precursors

b. Synthesis through *in-situ* generated silole dianions

*constraining substrate diversity for the preservation of Hückel aromaticity*

c. Synthesis of silylcyclopentene using pre-activated Ca/Mg metal

M = Ca or Mg

pre-activation of Ca and Mg using Li/naphthalene (Rieke method)

Direct synthesis under mechanochemical conditions ————

d. *This work*: Optimizing synthesis processes through ball milling techniques

Li
ball milling
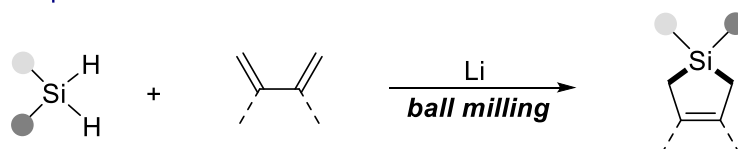
✔ Pre-activation-free   ✔ Operationally simple   ✔ Step economy

✔ Air tolerable   ✔ Reduced solvent waste

Scheme 1. Zero-valent metal mediates the direct synthesis of silylcyclopentene.

In 1990, Joo et al. published the pioneering work on synthesizing silole dianions via potassium reduction of dichlorosilafluorene.[9] Subsequently, by the utilization of the high nucleophilicity of silole dianions, West and co-workers achieved the synthesis of silylcyclopentene compounds from in-situ generated silole dianions species and dienes through the oxidative cyclization process.[10] However, the generation of the silole dianion requires the presence of aromaticity; thus, this method demands specific reactants to fulfil the necessary conditions (Scheme 1b).[11] In addition to silicon-based dianions,

carbon-based organolithium reagents resulting from the reaction of 2,6-dilithio-1,6-heptadienes with tert-butyl lithium also can be employed for synthesizing silylcyclopentene compounds.12 1,3-Diene-calcium complexes, prepared from the direct metalation of alkaline earth metals (Mg or Ca) with conjugated dienes always feature exciting reactivity, originating from the big electronegativity difference between calcium and carbon.13 The 1,4-cyclization products can be obtained from the reaction of dichlorodiphenylsilanes and 1,3-diene-calcium complexes.14 Although this method provides a promising synthetic route, pre-activation of calcium/magnesium metal using lithium with complicated experimental operations is necessary. Furthermore, all experimental operations should be conducted in an inert gas atmosphere, which is greatly inherent in their practical applications (Scheme 1c). Dehydrogenative double silylation of conjugated dienes using lanthanide or titanium catalysts provides an alternative approach to accessing silylcyclopentene compounds. The key intermediate allylic-metal complexes were generated through the addition process of Si-M (M = Yb, Sm or Ti) and dienes, followed by intramolecular cyclization to furnish the products of silylcyclopentene. However, 1,4-disilylative compounds are generally formed as the main products through this catalytic system.15

Although the aforementioned research endeavors have been extensively studied for the synthesis of silole cyclopentenes, the requirements of large amounts of organic solvent and complex experimental operations greatly inhibit their synthetic applications.2-15 The pursuit of sustainable chemistry has stimulated interest in mechanical force as an environmentally friendly and green energy source for organic transformations.16 Mechanical force can be utilized to active zero-valent metals to prepare the corresponding organometallic reagents under ball milling conditions in a straightforward fashion, avoiding the use of large amounts of organic solvents and inert gas protection.17,18 Most notably, in recent years, Ito, Kubota, and their co-workers have made outstanding contributions in the field of the synthesis of organometallic reagents under solvent-less solid-state mechanochemical conditions.19 Furthermore, these operational simple mechanochemical methods have opened up a new and promising avenue for the application of organometallic reagents in synthetic chemistry, which has been highly sought after and meaningful in the past decade. Based on these precedents and related methods of mechanochemically generated organometallic reagents, we successfully achieved the synthesis of silacyclopropane compounds using lithium metal directly through the mechanochemically in-situ generated organolithium species (Scheme 1d).

Table 1. Reaction Optimization.
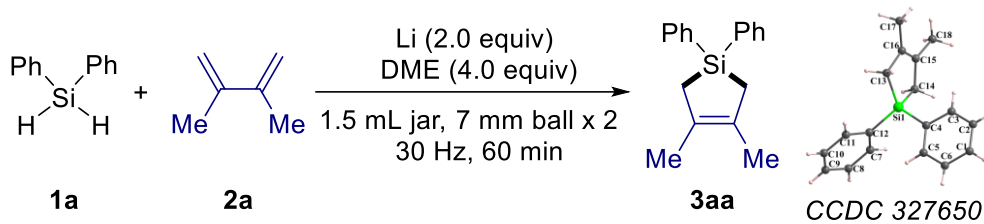
| Entry	Deviation from "standard conditions"	Yield of 2a (%)[b]
1	none	76 (63)[c]
2	without DME	<1
3	THF instead of DME	70
4	2-Me-THF instead of DME	47
5	THP instead of DME	26
6	Et$_2$O instead of DME	38
7	4.0 equiv of 2a	51
8	2.0 equiv of 2a	46
9	Mg instead of Li	32
10	Ca instead of Li	56

[a]Conditions: 1a (0.5 mmol), 2a (1.5 mmol), Li (1.0 mmol), DME (2.0 mmol), in a stainless-steel ball-milling jar (1.5 mL) with two stainless-steel balls (diameter: 7 mm). [b]Yields determined by gas chromatography analysis using biphenyl as an internal standard. [c]Isolated yields are given in brackets.

Scheme 2. Scope of the reaction between 1,3-diene and diarylsilanes.[a]

3ba, 52%

3ca, 51%

3da, 50%

3ea, 55%

3fa, 58%

3ga, 49%

3ha, 53%

3ia, n. d.

3ja, n. d.
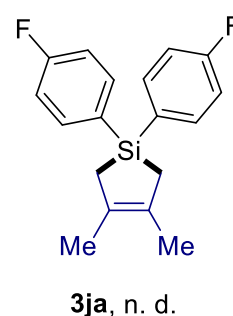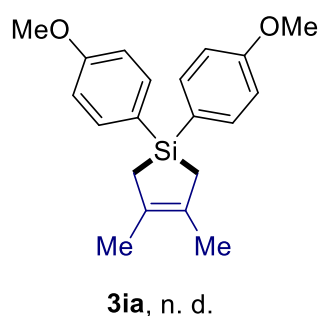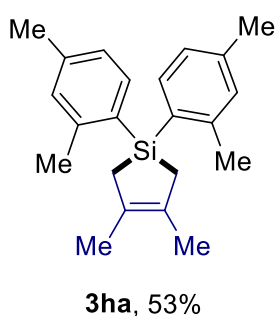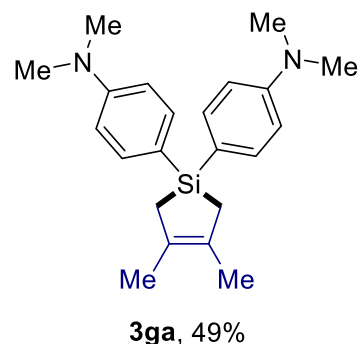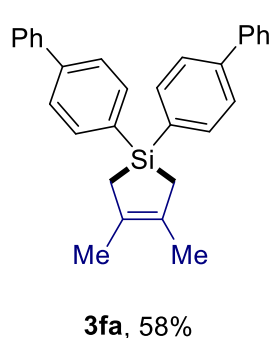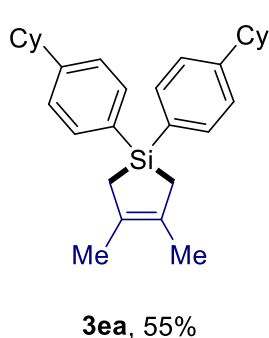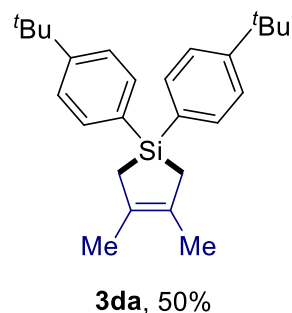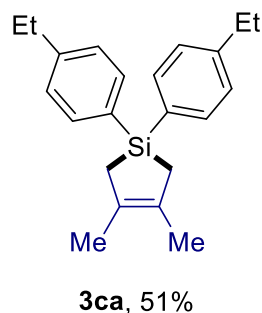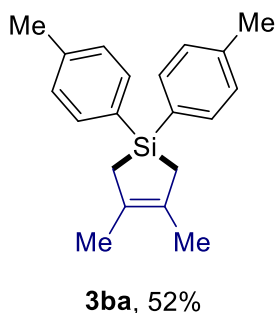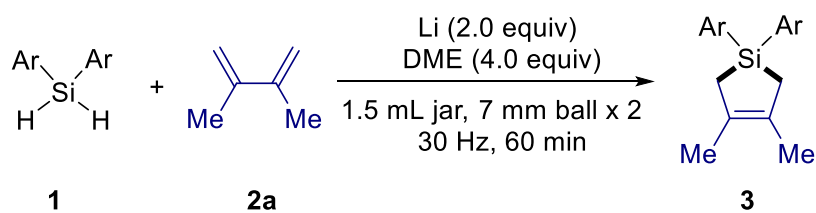
[a]Conditions: 1a (1.5 mmol), 2 (0.5 mmol), Li (1.0 mmol), DME (2.0 mmol), in a stainless-steel ball-milling jar (1.5 mL) with two stainless-steel balls (diameter: 7 mm). Reaction yields correspond to the pure isolated products.

To probe the feasibility of mechanochemical synthesis of silylcyclopentene compounds, the diphenyl silane (1a) and 2,3-dimethyl-1,3-butadiene (2a) were chosen as the modern substrates. 1a (0.5 mmol, 1.0 equiv), 2a (1.5 mmol, 3.0 equiv), lithium metal (1.0 mmol, 2.0 equiv), and 1,2-dimethoxyethane (2.0 mmol, 4.0 equiv) were added to a stainless-steel ball-milling jar (1.5 mL) with two stainless-steel balls (diameter: 7 mm) in air. After

ball milling for 60 minutes, the target product 3aa was obtained in 76% GC yield (Table 1, entry 1). The reaction cannot proceed in the absence of 1,2-dimethoxyethane (DME), which is mainly due to ether additives that can enhance the stability of organolithium species by coordinating with the metal center (Table 1, entry 2). Switching to other ether additives such as tetrahydrofuran (THF), 2-Methyltetrahydrofuran (2-Me-THF), tetrahydropyran (THP) and diethyl ether (Et2O) led to a decrease in reaction efficiency (Table 1, entries 3 to 6). Subsequently, we investigated the amount of the 2,3-dimethyl-1,3-butadiene (2a) needed. We attempted to keep the amount of diphenyl silane (1a) consistent at 0.5 mmol and vary the number of equivalents of 2a, and we found that the yields of the desired product 3aa decreased when the amount of 2a was increased or decreased (Table 1, entries 7 and 8). The mechanical force provided by ball milling can be used to activate calcium and magnesium metal to generate the corresponding organometallic reagents without a pre-activation process.19a and 19d Notably, when the reaction was performed by employing magnesium or calcium instead of lithium, in otherwise same reaction conditions, the reaction efficiency was evidently inhibited (Table 1, entries 9 and 10). This suggests that 1,3-diene-Ca/Mg complexes could potentially form and subsequently engage in a reaction with diphenyl silane, yielding the corresponding [4+1] cycloaddition product under ball milling conditions.14

Under the optimal conditions, we proceeded to examine the substrate scope of this mechanochemical methodology (Scheme 2). We initially focused on the use of 2,3-dimethylbutadiene 2a with various diarylsilanes 1. Methyl group at the para position of the benzyl ring of diphenyl silane 1b showed good compatibility, providing silylcyclopentene product (3ba) in moderate yield. Then, other alkyl groups including ethyl (1c), tert-butyl (1d), and cyclohexyl (1e) were also compatible with this mechanochemical method to generate the corresponding silylcyclopentene products smoothly (3ca–3ea). The phenyl-substituted diphenyl silane (1f) was tolerated, affording the target product (3fa) in good yield. Basic N. N-dimethyl was a feasible group (1g) as well, delivering 3ga in moderate yield. Moreover, the sterically more congested ortho-methyl substituted diaryl silane (1h) participated in the reaction to obtain silylcyclopentene product (3ha) successfully. Unfortunately, perhaps due to coordination competition with ether additives, the final product (3ia) cannot be obtained with a substrate bearing a methoxy group (1i). The presence of a para-fluorine substitution in the substrate (1j) did not proceed and failed to give the corresponding product (3ja).

Scheme 3. Reaction under solution-based conditions.
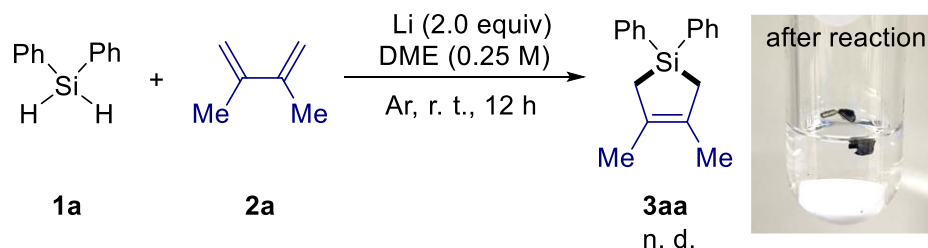
To demonstrate the pivotal role played by the mechanical force generated through ball milling in the synthesis of silacyclopropanes mediated by metallic lithium, a reaction under solution-based conditions was conducted. After stirring for 12 hours in solution under an argon atmosphere, no target product 3aa was obtained, and substantial amounts of lithium metal persisted, primarily attributed to the inhibitory effect of the inert oxidized layer on the lithium metal, impeding the progress of the reaction. Through the application of ball milling, the mechanical force exerted between the balls or between the balls and the vessel walls proved instrumental in supplying ample energy to eliminate the oxide layer, thereby expediting the chemical transformation (Scheme 3).
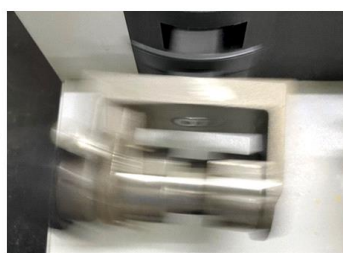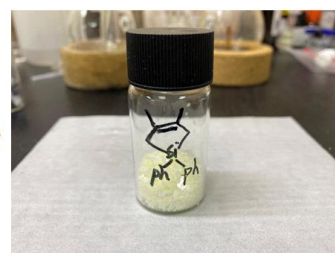
Scheme 4. Up-scale reaction.[a]
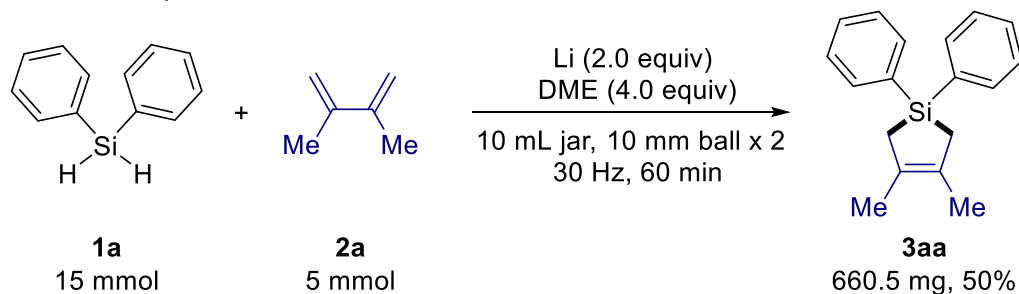
Operation steps

Step 1: All chemicals were added in air

Step 2: Ball milling for 60 min (30 Hz)

Step 3: Isolation of the product

[a]Conditions: **1a** (1.5 mmol), **2a** (0.5 mmol), Li (1.0 mmol), DME (2.0 mmol), in a stainless-steel ball-milling jar (10.0 mL) with two stainless-steel balls (diameter: 10 mm). Reaction yields correspond to the pure isolated products.

The aforementioned attributes of mechanochemical synthesis of silylcyclopentenes are noteworthy due to their potential to facilitate environmentally friendly synthesis. Therefore, achieving a scale-up synthesis becomes crucial. To our satisfaction, a moderate yield of the corresponding product 3aa was successfully obtained during a scale-up experiment,

highlighting the applicability of the solventless designed methodology for practical applications. Furthermore, all chemicals can be added to the milling jar in air, significantly simplifying the entire experimental operation compared to conventional solution-based methods.

To investigate the reaction mechanism, a stepwise experiment was conducted (Scheme 5a). Initially, diphenyl silane (1a) was introduced into a ball milling jar containing lithium and DME. After milling for 20 minutes, the jar was opened, and 2,3-dimethyl-1,3-butadiene (2a) was swiftly added to the mixture in the presence of air. Subsequently, the jar was sealed again and ball milling was continued for another 40 minutes, resulting in the formation of the target product in a moderate yield. The metallic lithium could react with 1,3-diene to generate the corresponding organolithium species, which could potentially serve as a nucleophile to react with diarylsilane to form the [4+1] cycloaddition product. Therefore, to further explore the reaction pathway, 2,3-dimethyl-1,3-butadiene (2a) was initially subjected to ball milling conditions in the presence of lithium and DME, followed by a reaction with diphenyl silane (1a). The yield of 3aa was observed to decrease significantly (Scheme 5b). These findings suggest the likely formation of an organolithium species in situ, which subsequently reacts with 2,3-dimethyl-1,3-butadiene (2a) to yield the [4+1] cycloaddition product (see Supporting Information for details).

Scheme 5. Stepwise experimentation.
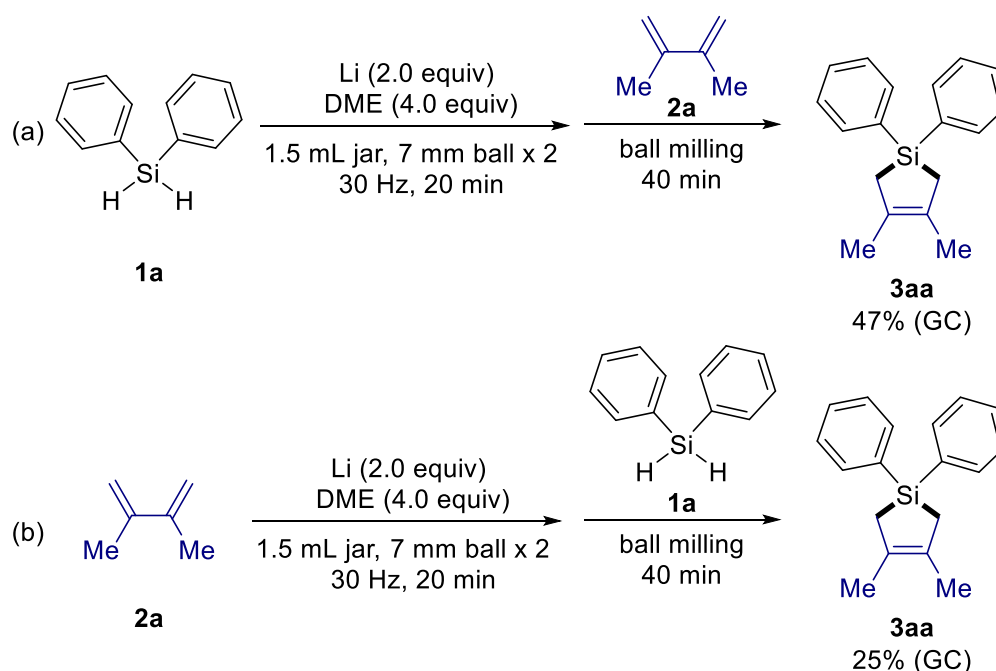
To elucidate the mechanism of this cyclization reaction, Density Functional Theory (DFT) calculations with M06-2X functional were performed on the model reaction of diphenyl silane (1a) and 2,3-dimethyl-1,3-butadiene (2a) (see Supporting Information for details). As shown in Scheme 6, our calculations suggested that the diphenyl silane 1a first reacted with Li to form the lithiosilole intermediate Int1 under ball milling conditions, which can

coordinate with 2,3-dimethyl-1,3-butadiene 2a to provide the intermediary encounter complex Int2. Subsequently, the intermediate Int2 undergoes a nucleophilic addition to butadiene 2a, which is assisted by the complexation of the diene to the Li cation, thus yielding the monoalkylated silane Int3. The barrier for the first step is only 8.4 kcal/mol. Then another molecule of lithium-solvent complex (Li-DME) reacts with Int3 to form the new lithiosilole intermediate Int4, with the release of 1.0 equivalent of lithium hydride (Int4′) byproduct. This is a thermodynamically very favorable process, which is exothermic by 27.9 kcal/mol. Next, the intramolecular nucleophilic attack of the negatively charged carbon atom on the silicon atom of Int4 completes the 1,4-addition sequence with the formation of the silylcyclopentene intermediate Int5. The transformation of Int5 with 1a will effortlessly yield the final product 3aa. The rate-determining step is the second nucleophilic addition process to offer desired silylcyclopentene Int5 via TS2 with a barrier of 21.1 kcal/mol (relative to Int4). The whole reaction is exothermic by 55.8 kcal/mol, which is consistent with our mild experimental conditions.

Scheme 6. DFT calculation
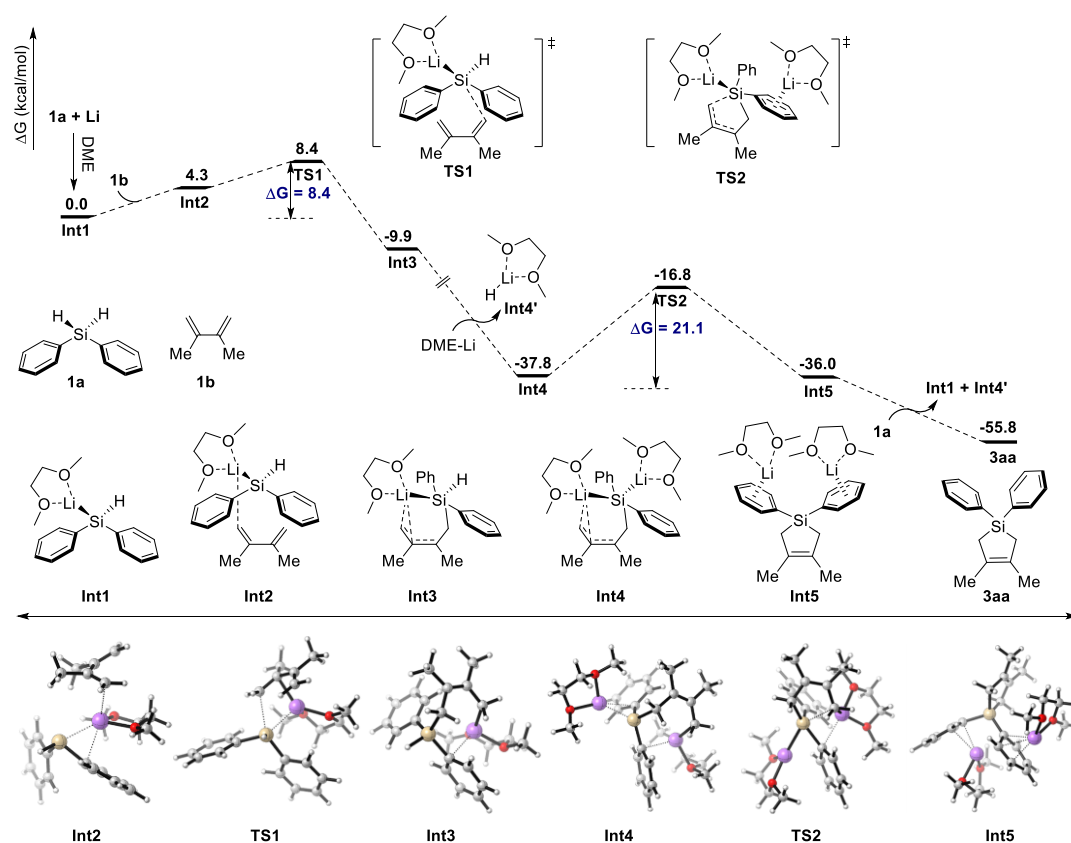
In summary, the direct synthesis of silylcyclopentenes can be readily achieved by ball milling technique without the requirement for bulk organic solvent. Notably, the entire experimental operation has been greatly simplified compared to the conventional solution-based synthesis method. We have effectively scaled up the reaction to the gram level and illustrated the robustness of this method's practical applications. The results from density

functional theory (DFT) calculations and mechanistic stepwise experiments indicated that the in-situ generated lithiosilole species play a crucial role in facilitating this cyclization reaction. We anticipate that this environmentally benign, simple, atom-economical, and efficient mechanochemical strategy will enhance the structural diversification of organosilicon compounds, thereby advancing research in synthetic chemistry and materials science.

Conflicts of interest

There are no conflicts to declare.

Acknowledgments

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