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Olefination

Non-Ionic Peterson-Type Olefination Reactivity and its Use in a Silicon-Promoted Carbonyl-Carbonyl Cross Coupling Reaction

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Abstract: The [2+2] cycloaddition reaction between the Si=C double bond of adamantylsilene and the carbonyl group of aliphatic, aromatic or acetylenic ketones and aldehydes is demonstrated. The product of this reaction that is central to a non-ionic version of the Peterson olefination is an unusual four-membered 1,2-silaoxetane heterocycle that was characterized spectroscopically and crystallographically. In the presence of SiO_2, the silaoxetane undergoes retro-cycloaddition with the formation of alkene products. As the [2+2] cycloaddition proceeds without the necessity of any base, enolizable ketones can be converted into olefins. In addition, it is shown that the adamantylsilene can be produced *in situ* by a sila-Peterson reaction, providing valuable input for the development of a new one-pot silicon-based reductive carbonyl-carbonyl cross coupling methodology.

The conversion of carbonyl compounds into alkenes continues to be an important transformation in organic chemistry, both from a fundamental and applied viewpoint.[1] For example, carbonyl olefinations such as the Wittig[2] and Horner–Wadsworth–Emmons (HWE)[3] reactions (Figure 1, upper row) are crucial chain-prolonging strategies in the industrial production of vitamin A or certain statins, both of which are conducted on a multi-ton scale.[4] The two reactions differ fundamentally in that the olefination reagents are overall neutral and ionic, respectively, lending the two types of reagents different reactivity and substrate scopes. A formal change in the oxophilic element in the HWE reagent from phosphorus to silicon results in the Peterson reaction, which is probably the most well-established, phosphorus-free carbonyl olefination reaction.[5] The analysis in Figure 1 leaves a vacant quadrant, that is, the reaction of neutral silicon-based reagents with carbonyl compounds. To the best of our knowledge, this quadrant is entirely unexplored for its potential in olefination reactions, would however provide attractive opportunities compared to the established name reactions. Most importantly, its non-ionic nature would allow the reaction with enolizable carbonyl compounds, i.e. carbonyl compounds with α-protons, such as acetophenone or acetone. At the same time, a new strategy towards tetra-substituted alkenes that are notoriously difficult to obtain by *P*-based olefination strategies may be within reach.

In this work, we report a proof-of-concept study that populates the forth quadrant, and shows that silenes engage in [2+2] cycloaddition reactions with a variety of aliphatic, aromatic and acetylenic aldehydes and ketones. This reactivity is leveraged for the preparation of highly substituted alkenes. The discovery of the [2+2] cycloaddition between silenes and carbonyl compounds adds to our understanding of recently reported heavier analogues of the above-mentioned name reactions such as the phospha-Wittig,[6] the phospha-bora-Wittig,[7] the phospha-HWE,[8] the sila-Wittig reaction,[9] and the related phosphaalkene dimerization strategy.[10] In particular, a crucial mechanistic question that has often been subject of intense debate is the role of putative four-membered heterocylic intermediates that stem

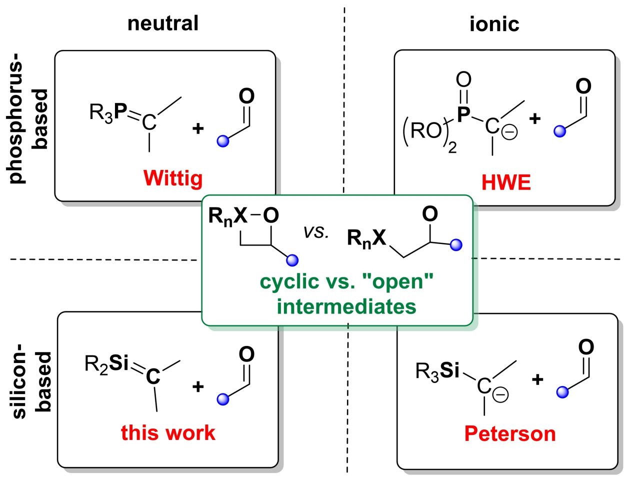

Figure 1. C–C bond formation reactivity of the Wittig (drawn is the resonance structure that emphasizes the double bond character), Horner–Wadsworth–Emmons (HWE) and Peterson olefination reactions, grouped by the oxophilic element in the reagents (P vs. Si), and its charge character (neutral vs. ionic). The quadrant in the bottom left is the present work, and describes the [2+2] cycloaddition between a silene and a carbonyl compound in a non-ionic Peterson-type olefination.

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from the formal [2+2] addition of the olefination reagent to the carbonyl compound (center of Figure 1). Such intermediates may form under certain conditions, but their existence and experimental identification is often challenging due to their transient nature and high reactivity. The four-membered intermediates can undergo retro-cycloaddition reactions to give a final alkene product. In context of the present work, it is shown that a non-ionic Peterson olefination pathway goes through a 1,2- silaoxetane which arises from the [2+2] cycloaddition reaction between the adamantylsilene and a ketone.

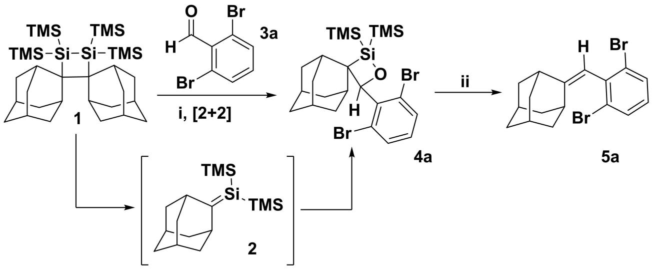
Moreover, a proof-of-concept study is presented that explores the discovered reactivity for the development of a one-pot reductive carbonyl-carbonyl cross coupling reaction in which the silene olefination reagent is formed *in situ* from a second carbonyl compound in a sila-Peterson reaction.

The reactivity between silenes and carbonyl compounds was investigated on adamantylsilene which was previously shown to be easily prepared and thermally stable. In accordance to the original report,[11] the reaction of adamantanone with the lithium salt of tris(trimethylsilyl)silane affords a 1,2-disilacyclobutane **1** which is the head-to-head dimerization product of the initially formed silene **2** (Scheme 1). Monomeric silene **2** itself could not be isolated or characterized, its identity however proven indirectly by trapping reactions with butadiene to give Diels–Alder type products.[11] In our hands, the preparation of **1** proceeds smoothly with 80 % isolated yield (Scheme 1). Interestingly, dimer **1** is in chemical equilibrium with the monomeric silene **2**, and heating of **1** in benzene-D$_6$ pushes the equilibrium towards the monomeric silene, as evident by the appearance of new resonances at $\delta = 3.25$ and 0.26 ppm in the ^{1}H NMR spectrum (see Figure **S2**).

With reliable access to the silene reagent, its reactivity towards carbonyl compounds was explored. In the literature, there are sporadic reports on cycloaddition reactions of silenes that are in thermal equilibrium with their dimeric 1,2-disilacyclobutanes. These silenes, all of which possess $OSi(CH_3)_3$ substituents at the silene-*C* can be reacted with non-enolizable carbonyl compounds to form 1-oxa-2-silacyclobutanes.[12] The latter could be characterized by X-ray crystallography only in one instance,[13] but are generally described to be unstable and their reactivity hard to study due to multiple decomposition pathways. Controlled and systematic studies of retro-cycloaddition reactions that would lead to olefin products are not reported.

Heating dimer **1** in the presence of 2,6-dibromobenzaldehyde to 80 °C consumes the starting material under the formation of a new species that is identified as the four-membered 1,2-silaoxetane **4a** (Scheme 2). The ^{1}H NMR spectrum of **4a** features a singlet at 6.4 ppm which is assigned to the proton at the silaoxetane ring (see Figure **S7**). All protons of the adamantyl substituent are magnetically non-equivalent as a result of the low symmetry of the silaoxetane ring. A similarly complex picture can be observed in the ^{13}C NMR spectrum of compound **4a**, with all adamantyl carbons being non-equivalent. The resonances of the silaoxetane carbon centers are observed at 64.5 ppm (<u>C</u>SiOCH) and 91.4 ppm (CSiO<u>C</u>H), (Figure 2, top spectrum). The spectroscopic characterization of the 1,2- silaoxetane is remarkable, as such compounds have very limited literature precedence and are mostly postulated to be non-isolable intermediates. The [2+2] cycloaddition is independent of the presence or absence of light, and is thus a thermal ground state reaction that does not involve excited state energy surfaces.

Formation of the silaoxetane heterocycle during the reaction could unambiguously be confirmed by single crystal X-ray diffraction (Figure 3).[14] Crystals suitable for this analysis were obtained by recrystallisation of the crude reaction mixture from pentane at −30 °C. In the solid state, the silaoxetane adopts a bent structure with the oxygen



Scheme 2. Reaction between silene **2** and 2,6-dibromobenzaldehyde **3a**. Reaction conditions: i) toluene, 80 °C, 24 h; ii) silica gel, pentane/EtOAc.

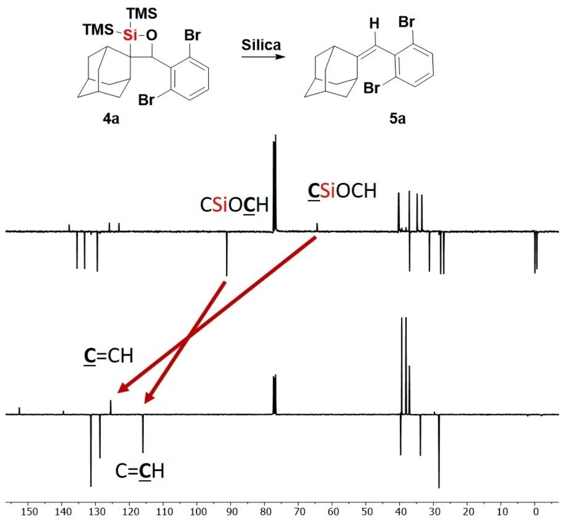
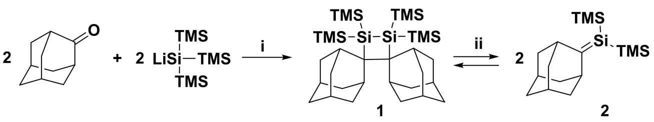


Figure 2. APT ^{13}C NMR spectra of 1,2-silaoxetane **4a** and its retro-cycloaddition product **5a**.



Scheme 1. Preparation of the 1,2-disilabutane **1** and the equilibrium with silene **2**. Reaction conditions: i) toluene, r.t., 3 h, ii) Benzene-D$_6$, 80 °C.

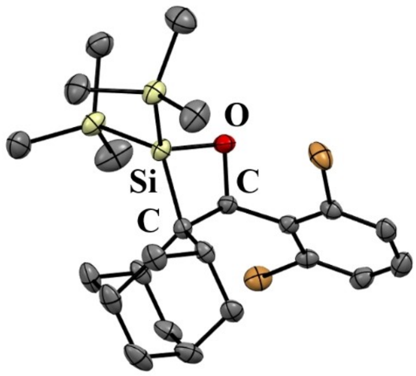


Figure 3. Solid state structure of silaoxetane **4a**. Selected bond lengths: Si–O 1.699 Å, O–C 1.462 Å, C–C 1.588 Å and C–Si 1.926 Å.

center being out of the plane defined by the silicon and two carbon centers by 21 degrees.

The silaoxetane resembles the 1,2-oxasiletanide intermediate[15] in the Peterson olefination.[5b] Both compounds possess the same core structure, but differ in their charge (neutral for silaoxetane, and negative for oxasiletanide with the charge mainly localized at the silicon center). Also, the valency of the silicon center is different between the two species, with the Si center in the silaoxetane and oxasiletanide being four- and five-coordinated, respectively. The hypervalent silicon in the oxasiletanide of the ionic Peterson reaction contributes to the high chemical reactivity which results in the spontaneous retro-cycloaddition and formation of the alkene product. In contrast, the 1,2-silaoxetane is more stable, but its collapse can be initiated by the addition of a Lewis acid such as SiO_2 (Scheme 2).

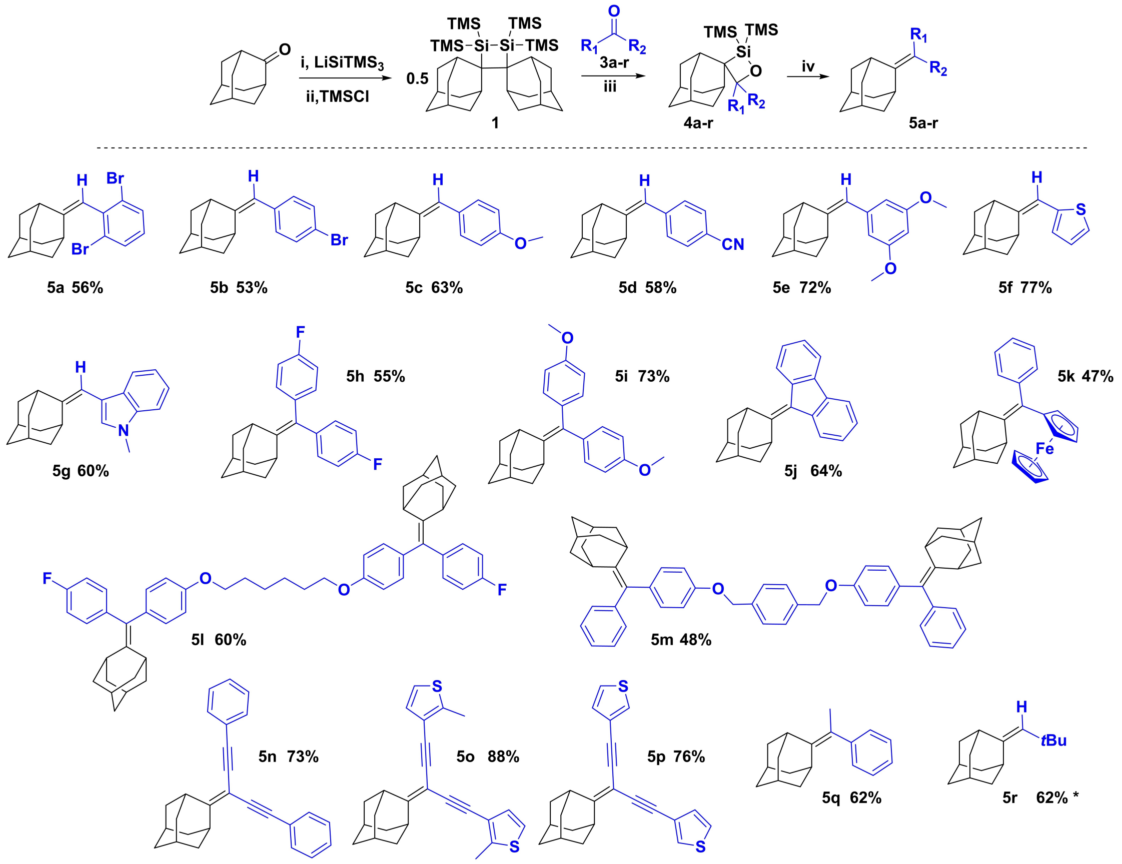
Thus, upon purification of the silaoxetane **4a** by silica gel column chromatography, the retro [2+2] cyclisation is triggered and alkene **5a** is obtained. Retro [2+2] cyclisation of silaoxetane was mentioned in the literature as plausible decomposition pathway of this heterocycle,[11,13] but has not been systematically studied or explored. The retro-cycloaddition reaction is illustrated in the ^{13}C NMR spectroscopic characterization in Figure 2, bottom spectrum, which shows new diagnostic resonances at $\delta = 125.5$ and 116.0 ppm that are assigned to the carbons of the C=C double bond. Correspondingly, a resonance at $\delta = 5.86$ ppm that is assigned to the proton of the double bond emerges in the ^{1}H NMR spectrum of **5a** (see Figure **S9**).

A closer inspection of the reaction conditions for the preparation of the silene (Scheme 1) and its use in the carbonyl olefination reaction (Scheme 2) reveals that they could be compatible, and that the two transformations could be performed consecutively in a one-pot reaction. The result would be a novel type of reductive cross coupling reaction between two carbonyl compounds under the formation of an alkene product.

Hence, silene **2** was prepared *in situ* from the reaction of adamantanone and $LiSi(TMS)_3$, and directly exposed to a second carbonyl compound. Interestingly, initial studies using ketones as coupling partners produced the corresponding alkenes in considerably lower yields as compared to the reactions from isolated **1**. For example, the yield of alkene formation from 4-bromobenzaldehyde and acetophenone declined from 59 and 61 % from isolated **1** to 44 and 21 % in the one-pot reaction, respectively. This observation suggests that silene formation is accompanied by a by-product that is detrimental to the silaoxetane intermediate, and, in extension, alkene formation. With the [2+2] cycloaddition between the silene and the carbonyl compound being a pericyclic reaction between two non-ionic species, we hypothesized that the LiOTMS salt that is formed during silene formation may act as a nucleophile and cause undesired side reactions. Thus, TMS–Cl was added to the reaction prior to the addition of the carbonyl compound to quench any ionic species. Indeed, this procedure resulted in completely restored yields for bromobenzaldehyde and acetophenone olefination of 53 and 62 %, very similar to those of the reaction from isolated **1**. The most remarkable effect of TMS–Cl addition was observed in the preparation of **5n** from 1,5-diphenylpenta-1,4-diyn-3-one **3n**, the yield of which increased from 33 % to 73 %. Such a difference in the reaction outcome can be explained by side reactions which are promoted by ionic species especially at elevated temperatures. Examples of such side reactions include attack at the Si=C double bond followed by polymerization, head-to-tail dimerization or formation of ionic intermediates not active towards carbonyl compounds.[16] From a mechanistic viewpoint, the necessity of the step to quench any ionic intermediates is consistent with the proposed mechanism of the [2+2] cycloaddition reaction as a pericyclic reaction between two neutral, non-ionic species.

With the optimized procedure in hand, the scope of the reaction was explored, the results of which are summarized in Scheme 3. The reaction can be applied to a relatively large variety of substrates, including aldehydes and ketones. Substituted benzaldehyde derivatives give good yields of the olefinic products ranging from 53 % to 72 % independent of the electronic nature of the aryl groups (63 % for electron donating p-OMe benzaldehyde **3c** and 58 % for electron withdrawing p-CN benzaldehyde **3d**). Aliphatic aldehydes also engage in the olefination step, and pivaldehyde **3r** is converted to the corresponding alkene **5r** in 62 % yield. Product **5q** can be obtained from acetophenone **3q** in 62 % isolated yield, illustrating that the method is compatible with enolizable ketones as substrates. Diaromatic ketones give yields ranging from 55 to 73 % (compounds **5h–g**), with the ferrocene derivative **5k** giving a slightly lower yield of 43 %. Double olefinations as in **5l**, **m** can also be performed, and the products obtained in good yields. This is even more remarkable, considering that bis-ketones **3l**, **m** are not very soluble in the reaction media. For example, in case of the ketone **3m** which has very limited solubility in toluene, product **5m** was isolated in 48 % yield.

Application of the reaction conditions to acetylenic ketones **3n–p** results in the formation of the olefin products **5n–p** with excellent yields reaching up to 88 %. Remarkable with these acetylenic substrates is the chemoselectivity of the [2+2] cycloaddition reaction which could, in principle, also occur at the triple bonds of the substrates. In particular,



Scheme 3. Substrate scope for the one-pot silene formation/carbonyl olefination sequence. Reaction conditions: i: toluene, r.t., 3 h; ii: 1.5 eq. of TMSCl, 10 min, r.t., iii: 1 eq. of carbonyl compound **3a–r**, toluene, 80°C, 24 h; iv) silica gel column chromatography, pentane/EtOAc). *crude yield of **4r** determined by quantitative ^{1}H NMR spectroscopy using an internal standard (see ESI for details).

ionic olefination agents that operate by a nucleophilic mechanism have been shown to attack such substrates in a Michael addition, giving rise to altered regiochemistry.[17]

Subsequent studies using carbonyl compounds different from adamantanone for silene formation illustrate the importance of the adamantyl group to follow the reaction mechanistically. For example, diphenylsilene that is produced from benzophenone is less stable than the adamantyl analogue, and gives rise to multiple side products (see ESI for details). Nevertheless, alkene products can be observed also in these cases, supporting the notion that the reported reactivity is general. In addition, these preliminary results encourage further studies to slow down the side reactions and to increase the substrate scope also of the carbonyl compounds that are used for silene formation.

In conclusion, we could show that silenes engage in [2+2] cycloaddition reactions with aromatic, aliphatic and acetylenic ketones and aldehydes. The resulting silaoxetanes that arise from this non-ionic reaction are considerably more stable than the anionic oxasiletanide analogue of the ionic Peterson olefination, and can be spectroscopically and structurally characterized. Exposure of the silaoxetane to SiO_2 triggers a retro-cycloaddition reaction under the liberation of the desired alkene product. Silene formation and its reaction with the carbonyl compounds can be combined in a one-pot procedure as long as any ionic intermediates that are formed in the first stage of the reaction are quenched by the addition of TMS–Cl prior to the addition of the carbonyl compounds **3a–r**. Using this optimized procedure, (hetero)aromatic and aliphatic aldehydes, substituted benzophenones and acetophenone as well as structurally more complex diacetylenic ketones can be converted to the corresponding alkenes in good to very good yields.

The proof-of-concept study that is presented herein provides inspiration for the development of a non-ionic Peterson-type olefination that will have the potential to overcome limitations of existing olefination strategies, in particular by being compatible with enolizable ketones and able to promote the formation of tetra-substituted alkenes. From a synthetic versatility viewpoint, the stability of the silene intermediate is of crucial importance. In the present proof-of-concept work, this issue was remedied by the bulky adamantyl group in **1**, but we hypothesize that increased steric bulk at the *Si*- substituents of the silyl lithium reagent will have a similar stabilizing effect, thereby open the methodology to a broader scope of silenes.

Supporting Information

The data that support the findings of this study are available in the supplementary material of this article. The authors have cited additional references within the Supporting Information.[18]

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Olefination · Carbonyl-carbonyl cross coupling · Silene · Silaoxetane · Reaction mechanism

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