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Nickel-catalyzed insertions of vinylidenes into Si–H bonds†

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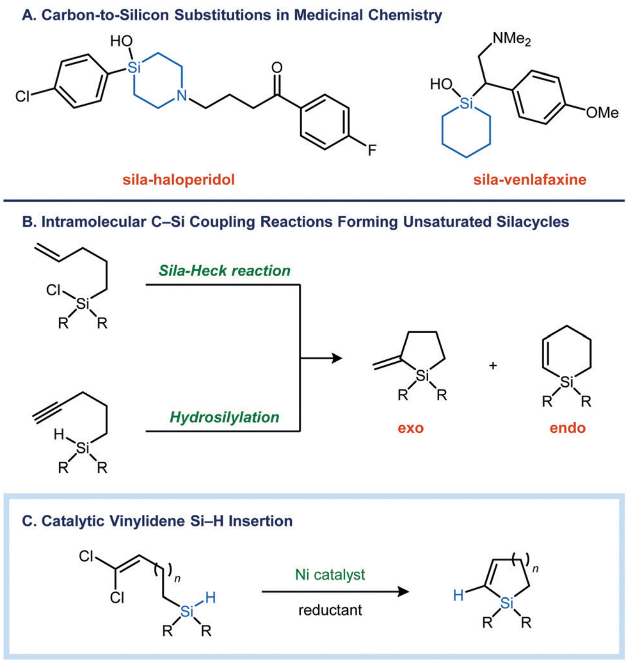
A nickel-catalyzed reductive cyclization of 1,1-dichloroalkenyl silanes is reported. The products of this reaction are unsaturated five- or six-membered silacycles. Intermolecular variants are also described, providing access to trisubstituted vinyl silanes that are not accessible by alkyne hydrosilylation or sila-Heck-type processes. A variety of silanes can be utilized, including those that serve as nucleophilic partners in Hiyama cross-coupling reactions. Mechanistic studies using deuterium-labelled silanes are described.

Substitutions of carbon for silicon have attracted the interest of medicinal chemists as an avenue to optimize the potency and pharmacokinetic properties of lead compounds (Fig. 1A).[1] The larger atomic radius of silicon causes subtle changes in geometry and conformation, impacting target binding affinity.[2] Silicon substitution generally increases lipophilicity, which can improve cellular uptake with polar compounds.[3] Finally, the incorporation of silicon into five- and six-membered rings blocks oxidative aromatization, a common metabolic liability.[4] Despite these potential benefits, the effect of silicon substitution is often unpredictable, and there are currently no silicon-containing drugs and only a few silicon-containing agrochemicals[5] that have successfully reached market. Future investigations of silicon in biologically active molecules will depend on the availability of robust synthetic methods that facilitate the construction of Si–C bonds.[6]

Unsaturated silicon heterocycles are commonly synthesized using intramolecular C–C bond forming reactions, where silicon is incorporated into the acyclic precursor as a tethering atom.[7] Alternatively, direct intramolecular Si–C coupling can be carried out using an alkyne hydrosilylation[8] or a sila-Heck type process (Fig. 1B).[9] In both of these approaches, *endo* and *exo* cyclization modes are possible, and the selectivity is dependent on myriad factors, such as the tether length, the substitution pattern of the π-bond, steric effects, and the presence of functional groups that impart electronic bias.

Recently, we have showed that transition metal vinylidene complexes can be generated from 1,1-dichloroalkenes and a metal reductant such as Zn.[10] We reasoned that the intramolecular insertion of such $M{=}C{=}CR_2$ species into a Si–H bond[11] would yield an unsaturated silacycle without the regioselectivity issues that arise with additions across alkenes and alkynes. To that end, we report here a nickel-catalyzed reductive cyclization of 1,1-dichloroalkenyl silanes to form five- and six-membered silacycles (Fig. 1C). The catalytic reductive Si–H insertion can also be carried out in an intermolecular context to provide trisubstituted vinyl silanes, which are not accessible by alkyne hydrosilylation.


A. Carbon-to-Silicon Substitutions in Medicinal Chemistry

B. Intramolecular C–Si Coupling Reactions Forming Unsaturated Silacycles

C. Catalytic Vinylidene Si–H Insertion

Fig. 1 Nickel-catalyzed reductive insertions of 1,1-dichloroalkenes into Si–H bonds as a route to unsaturated silacycles.

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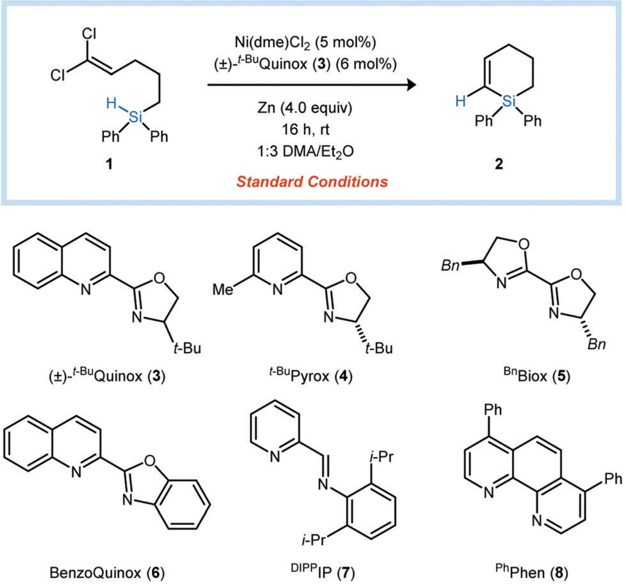
Table 1 Catalytic reductive insertions of vinylidenes into Si–H bonds: effect of reaction parameters



(±)-$^{t\text{-Bu}}$Quinox (3) $^{t\text{-Bu}}$Pyrox (4) $^{\text{Bn}}$Biox (5)

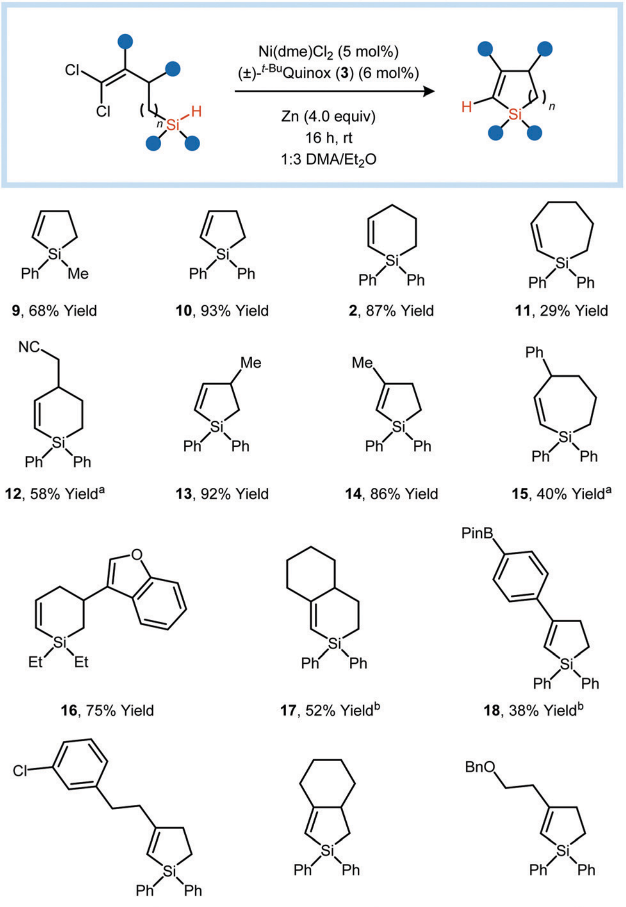
BenzoQuinox (6) $^{\text{DIPP}}$IP (7) $^{\text{Ph}}$Phen (8)

Entry	Deviation from standard conditions[a]	Yield (2) (%)
1	None	91
2	No Zn	0
3	No Ni(dme)Cl$_2$	0
4	No (±)-$^{t\text{-Bu}}$Quinox (3)	0
5	Mn instead of Zn	85
6	DMA only instead of Et$_2$O/DMA	36
7	$^{t\text{-Bu}}$Pyrox (**4**) instead of **3**	50
8	$^{\text{Bn}}$Biox (**5**) instead of **3**	17
9	BenzoQuinox (**6**) instead of **3**	83
10	$^{\text{DIPP}}$IP (**7**) instead of **3**	45
11	$^{\text{Ph}}$Phen (**8**) instead of **3**	43

[a] Reaction conditions: **1** (0.1 mmol, 1.0 equiv.), Ni(dme)Cl$_2$ (0.05 equiv.), (±)-$^{t\text{-Bu}}$Quinox (0.06 equiv.), Zn (4.0 equiv.), DMA (0.2 mL), Et$_2$O (0.6 mL), rt, 16 h. Yields were determined by ^{1}H NMR integration against a mesitylene internal standard.

The dichloroalkenyl silane **1** was selected as a model substrate for the development of a catalytic reductive vinylidene Si–H insertion reaction. Under optimized conditions, ($^{t\text{-Bu}}$Quinox)NiCl$_2$ (5 mol%) promotes the cyclization of **1** to form the six-membered unsaturated silacycle **2** in 91% yield (entry 1). Control experiments indicated that the reductant, metal source, and supporting ligand are required for the reaction to proceed. Mn is a viable reductant but is slightly less effective than Zn (entry 5). A combination of Et$_2$O and a polar amide solvent, such as DMA, gave the highest yields, and the use of DMA alone resulted in a significant decrease in product formation (entry 6). $^{t\text{-Bu}}$Quinox (**3**) proved to be the optimal ligand. However, other bidentate nitrogen-donor ligands also promoted the formation of **2**, with yields ranging from 17–83% (entries 7–11).

With optimized conditions in hand, we investigated the substrate scope of the reaction (Fig. 2). Five- and six-membered rings could be generated in high yield. Two examples of seven-membered ring-forming reactions were demonstrated, providing products **11** and **15** in modest yields of 29% and 40%, respectively. The substituents on Si could be alkyl, aryl, or a combination of the two.



9, 68% Yield **10**, 93% Yield **2**, 87% Yield **11**, 29% Yield

12, 58% Yield^a **13**, 92% Yield **14**, 86% Yield **15**, 40% Yield^a

16, 75% Yield **17**, 52% Yield^b **18**, 38% Yield^b

19, 32% Yield^b **20**, 73% Yield^b **21**, 66% Yield^b

Fig. 2 Substrate scope studies. Reactions were conducted using the standard conditions shown in Table 1. ^{a}10 mol% catalyst loading. ^{b}20 mol% catalyst loading; 50 °C temperature.

Intermolecular variants of the vinylidene Si–H insertion were also investigated (Fig. 3A). In order to obtain high yields, it was necessary to make minor modifications to the reaction conditions developed for the intramolecular reaction: the catalyst loading was increased from 5 mol% to 10 mol%, the co-solvent was changed from Et$_2$O to THF, and the reaction temperature and concentration were increased. Under this set of conditions, vinylsilane **22** was obtained in 75% yield from a tropinone-derived 1,1-dichloroalkene and dimethylphenylsilane. Other tertiary silanes and other ketone-derived 1,1-dichloroalkenes also proved to be viable as reaction partners. Benzyldimethylsilane could be used as a substrate, and the Si–H insertion product can engage in Hiyama cross-coupling reactions (Fig. 3B).[12]

Sequential C–Si bond-forming reactions were carried out using a secondary organosilane. Catalytic hydrosilylation of methyl eugenol (**32**) using diphenylsilane yielded a primary organosilane,[13] which could then be used in an intermolecular Si–H insertion reaction to form **32** in 47% yield over two steps (Fig. 3C).

Experiments using a deuterium labelled silane were carried out in order to gain insight into the mechanism of Si–H insertion.[14] As expected, the reaction between 1,1-dichloroalkene **33** and Ph$_2$MeSiD yielded product **26-*d*$_1$** with >99% deuterium

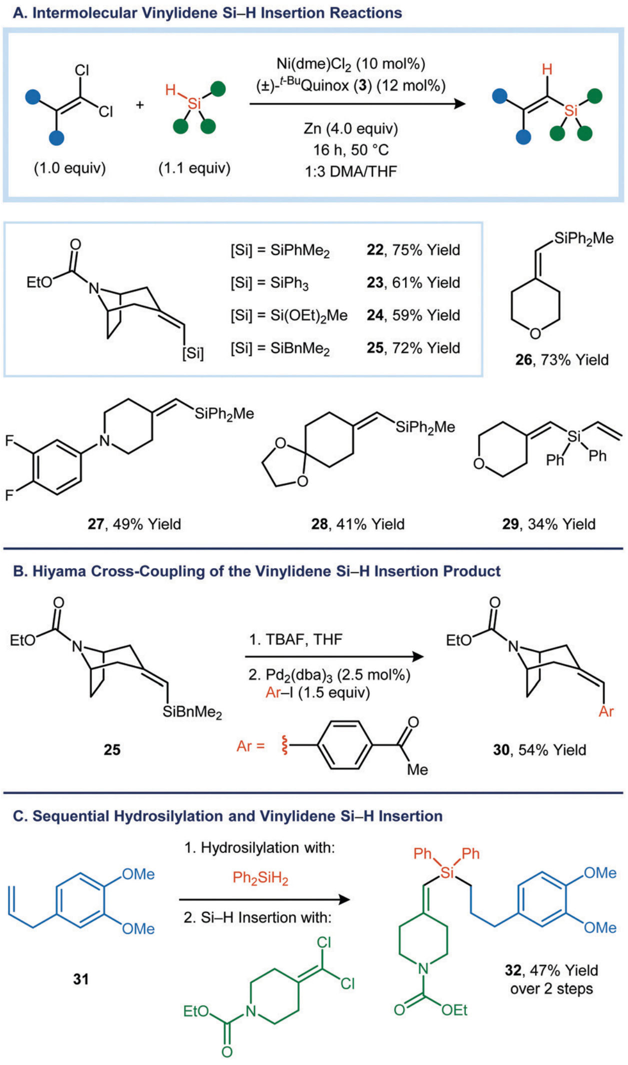


Fig. 3 (A) Intermolecular vinylidene Si–H insertion reactions, providing trisubstituted vinylsilanes. (B) Synthesis of a vinylsilane that can be utilized as a nucleophilic partner in a Hiyama cross-coupling reaction. (C) Sequential hydrosilylation and vinylidene Si–H insertion reactions of a secondary organosilane.

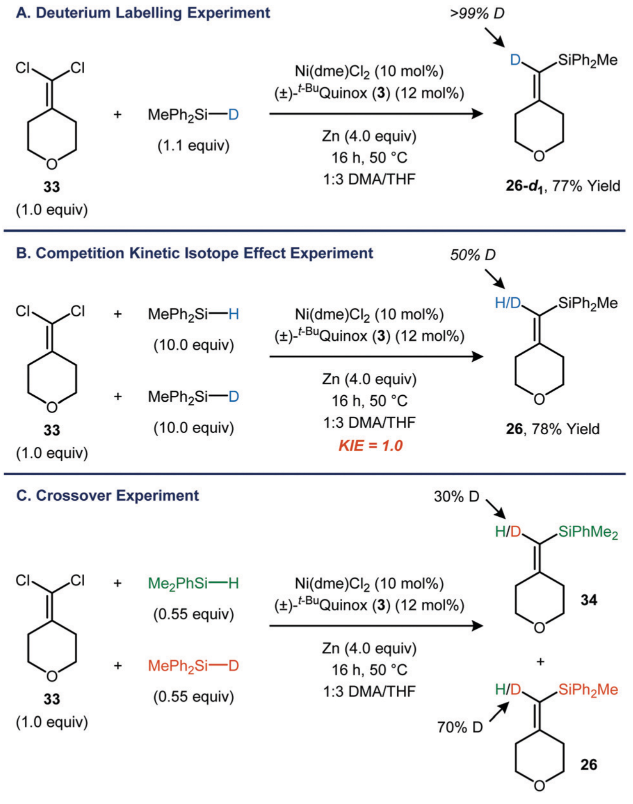


Fig. 4 Mechanistic studies using a deuterium-labelled silane.

incorporation at the vinyl position (Fig. 4A). A kinetic isotope effect (KIE) competition experiment was carried out using a 1 : 1 mixture of Ph_2MeSiH and Ph_2MeSiD (Fig. 4B). The product (**26**) contained a 1 : 1 mixture of H and D at the vinyl position, indicating a k_H/k_D of 1.0. This result appears to be inconsistent with a concerted insertion of a metal vinylidene into the Si–H bond, regardless of whether the insertion is rate-determining or occurs in a fast step following rate-determining generation of the metal vinylidene.[15,16]

Interestingly, scrambling was observed when a reaction was carried out using a 1 : 1 mixture of $PhMe_2SiH$ and Ph_2MeSiD (Fig. 4C). The $PhMe_2Si$-substituted product contains 30% D, and the Ph_2MeSi-substituted product is correspondingly enriched in H. When the $PhMe_2SiH/Ph_2MeSiD$ mixture was subjected to the standard catalytic conditions in the absence of the 1,1-dichloroalkene **33**, H/D scrambling was also observed, indicating that the catalyst is able to activate the Si–H bond without having to generate a metal vinylidene. One scenario that would be consistent with both the KIE and scrambling experiments is a pre-equilibrium Si–H oxidative addition that occurs prior to the rate-limiting step. This rate-limiting step could involve activation of the 1,1-dichloroalkene or formation of the C–Si bond.

In summary, (Quinox)Ni catalysts promote reductive insertions of 1,1-dichloroalkenes into Si–H bonds. One synthetic application of this transformation is in the synthesis of unsaturated five- and six-membered silacycles. Additionally, moderate yields were obtained for the synthesis of seven-membered silacycles, which have not previously been prepared by other methods of ring-closure. Ongoing investigations are aimed at elucidating the mechanism of Si–H insertion and extending this reactivity to other bond insertion reactions.

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Conflicts of interest

There are no conflicts to declare.

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