β-Silicon Effect Enables Metal-Free Site-Selective Intermolecular Allylic C–H Amination

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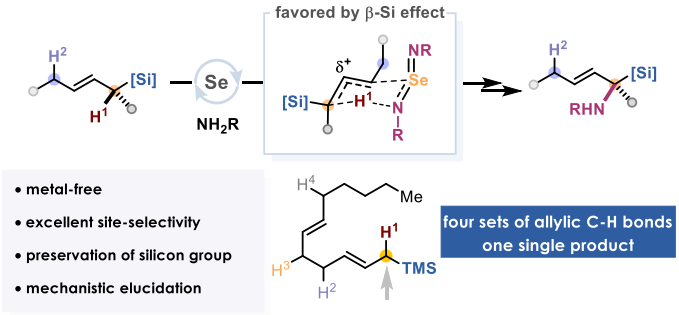
KEYWORDS. α-amino silane, C–H amination, selenium, site-selectivity, β-silicon effect

ABSTRACT: α-Amino silanes and their derivatives play pivotal roles across diverse applications, yet their current synthetic methods often entail intricate functional group manipulations. Despite the widespread use of allyl silanes as carbon nucleophiles in organic synthesis, their participation in allylic C–H functionalization has been underexplored. Herein, we unveil a metal-free intermolecular C–H amination of allyl silanes facilitated by the β-silicon effect. This protocol yields α-amino silanes with exceptional site-selectivity. Notably, a wide array of secondary and tertiary α-amino silanes are synthesized in high yields without desilylation, owing to the mild reaction conditions and a unique reaction pathway. Mechanistic elucidations highlight the activation effect of the silyl moiety on alkenes, alongside its stabilizing influence on adjacent developing positive charges, which selectively drives a closed transition state, ensuring remarkable site-selectivity.



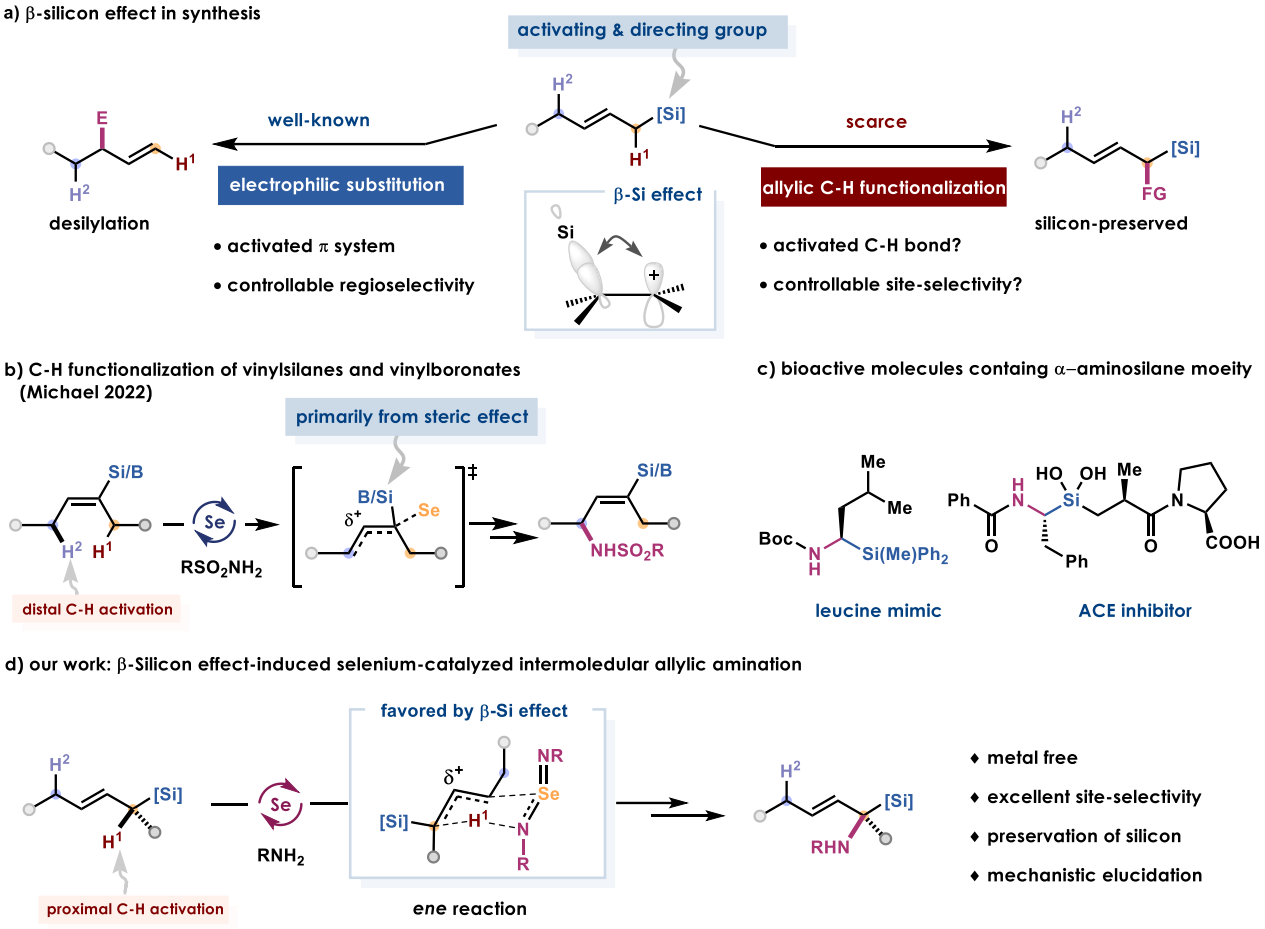
INTRODUCTION

Organosilicon compounds play a crucial role in organic synthesis, serving as synthetic reagents, intermediates, protecting groups, and valuable bioisosteres of carbon.[1-8] Among these compounds, allyl silanes encompass the properties of alkenes and organometallic complexes, making them widely used in organic synthesis.[9-12] Notably, the well-known β-silicon effect,[11,13] which manifests itself in the selective electrophilic substitution of alkenes, is particularly pronounced in the reactivity of allyl silanes. This effect not only enhances the activity and nucleophilicity of alkenes, especially the alkenyl carbons distal to the silyl group, but also effectively controls the regioselectivity through σ(C–Si)-π* hyperconjugation. However, the β-silicon-effect-induced functionalization of allyl silanes primarily targets unsaturated double bonds, resulting in double bond migration and extensive desilylation owing to the susceptibility of silicon groups to nucleophilic attack (left, Scheme 1a).[9,10] While offering substantial promise for the synthesis of functionalized organosilanes, direct allylic C–H functionalization of allyl silanes enabled by silicon effects remain largely underexplored,[14,15] probably due to its propensity to undergo transmetalation with transition metal C–H activation catalysts, and the higher reactivity of the activated π system (right, Scheme 1a).

Allylic C–H functionalization reactions have become essential techniques in organic synthesis, facilitating the efficient construction of diverse molecules with wide-ranging applications.[16-19] However, achieving site selectivity in internal alkenes, which possess two or more sets of similar allylic protons, has long been a significant challenge compared to the well-established functionalization of alkenes with a single set of allylic protons.[20-22] Recent progress in this area has largely stemmed from advances leveraging the negative inductive effect of electron-withdrawing groups (EWGs) or the coordinating influence of heteroatoms.[23-27]

We have recently developed a site-selective allylic C–H functionalization reaction guided by electron-donating B(MIDA) (*N*-methyliminodiacetyl boronate) moiety.[28] The capability of B(MIDA) to stabilize the developing positive charges at β position was proposed to be key for both reactivity and regio-selectivity.[29,30] This method was based on Sharpless's pioneering work in 1976 on metal-free allylic C–H amination of simple alkenes using stoichiometric in situ generated diimidoselenium reagent,[31-32] and more recently Michael's catalytic version using simple sulfonamides as nitrogen sources in combination of a hypervalent iodine oxidant.[33-35] The latter upgraded protocol has been applied in allylic C–H amination of many terpenoids but it still poses challenges for unsymmetrical internal alkenes. Very

Scheme 1. β-Silicon Effect and its application

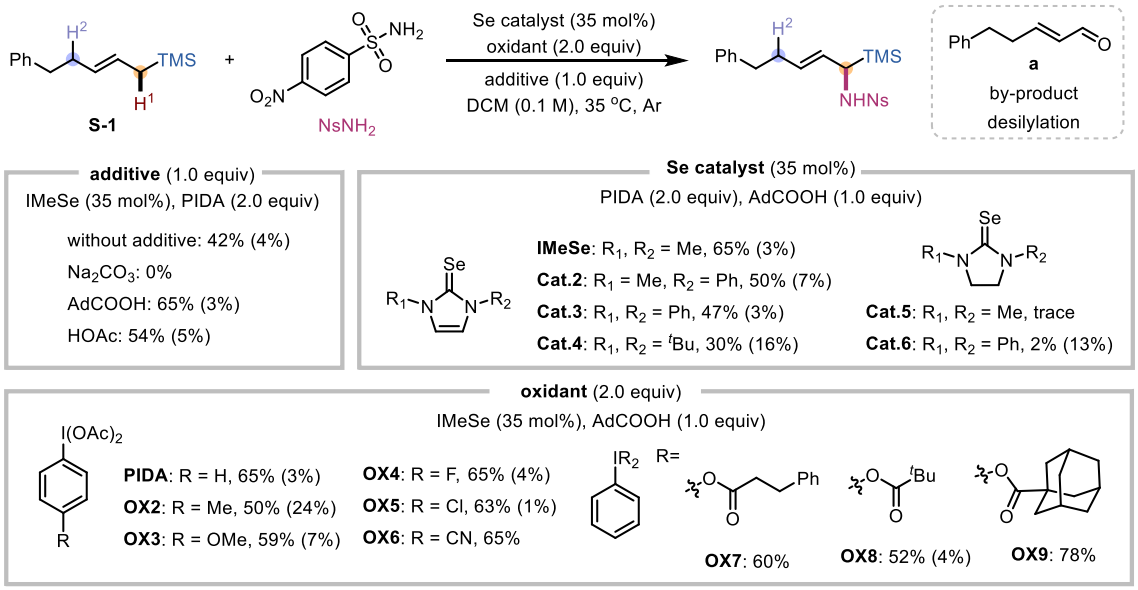


recently, Michael demonstrated an elegant C–H amination of vinylsilanes and vinylboronates using silicon or boron as regioselectivity switch (Scheme 1b).[36] The selective reaction at site distal to the silyl or boryl group was observed. This regio-outcome was believed to result primarily from steric effect, although the electronic effect also plays a positive role. Little or no activating effect on reactivity was found upon silyl or boryl substitution. α-Amino silanes have unique biological activities with low toxicity and good metabolic stability, and are widely used as analogues of α-amino acids in protease inhibitors such as angiotensin-converting enzyme (ACE) inhibitors and serine protease human neutrophil elastase (HNE) inhibitors (Scheme 1c).[37-40] Given their importance, the development of synthetic methods for constructing α-amino silanes has attracted significant interest.[37,38] However, current strategies rely heavily on functional group manipulations.[41-56] Methods via direct C–H functionalization are scarce and still suffer from the use of stoichiometric amounts of strong bases, limited substrate scope, poor regioselectivities, and/or harsh reaction conditions.[57-62] Herein, we report a mild and selective selenium-catalyzed allylic C–H amination reaction of allyl silanes towards the diverse synthesis of allyl α-amino silanes (Scheme 1d). This approach mitigates common desilylation process and exhibits high-level of site selectivities. The reaction mechanism was elucidated through detailed theoretical calculation using density functional theory (DFT), which underscored the significant advantages of the β-silicon effect in enhancing the reactivity and regulating excellent regioselectivity.

To initiate our investigation, we assessed the feasibility of site-selective amination using allyl TMS silane **S-1** as the model substrate and *p*-nitrophenylsulfonamide ($NsNH_2$) as the nitrogen source (Table 1). Our initial findings revealed that the desired α-aminated product could be obtained in 42% yield using IMeSe as the catalyst and PIDA as the oxidant. Additionally, a desilylative oxidation by-product (**a**) was observed at a 4% yield. Interestingly, the inclusion of a basic additive, Na_2CO_3, resulted in a complete shut-down of reactivity, while acidic additives proved beneficial for yield enhancement, with AdCOOH improving the yield to 65%. Screening different NHC-ligated Se catalysts revealed that the originally utilized IMeSe was optimal. Moreover, the reaction displayed insensitivity to the electronic properties of the aryl ring in the hypervalent iodine oxidant. However, substitution of the acetoxyl group with the sterically bulkier 1-adamantanecarboxyl group further enhanced the yield to 78%, with no **a** being found.

Having established the optimal reaction conditions, a variety of allyl silanes were used to evaluated the robustness of the site-selective amination (Scheme 2). As expected, alkenes with two sets of allylic protons (**2**-**6**) are all suitable substrates for reaction, producing the desired α-aminated products in good yields. A variety of commonly encountered

Table 1. Reaction Optimization



Reaction Conditions: allyl silane (0.2 mmol, 1.0 equiv), $NsNH_2$ (0.4 mmol, 2.0 equiv), Se catalyst (35 mol%), additive (1.0 equiv), oxidant (2.0 equiv) and DCM (2 mL), N_2 atmosphere, 35 °C, 24 h.

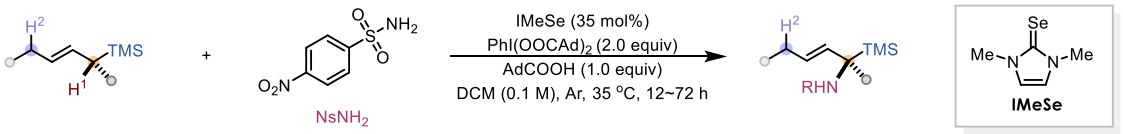
functional groups, such as chloro (**7**), aryl (**1**), ether (**8**, **9**), ester (**10**-**16**), terminal alkenyl (**18**), and even *p*-toluenesulfonate (**17**) are all well tolerated. Interestingly, while the installation of a bulky *tert*-butyl (**19**) or an electron-withdrawing benzyloxy (**22**) group at the other allylic position did not compromise the regioselectivity, other electron-withdrawing group such as phenyl (**20**), naphthyl (**21**) and *tert*-butyl ester groups (**23**) did result in inferior selectivity. A board range of secondary alkyl substituted allyl TMS silanes (**24**-**30**), either cyclic or acyclic, proceeded the desired amination smoothly. The α-allylic C-H bonds of secondary allyl silanes are potentially sterically shielded. Still, however, the *tert*-α-amino silanes (**31**-**34**) were delivered exclusively regardless of in cyclic or acyclic system. In these cases, the use of *o*-CF_3-PhI(OAc)$_2$ as oxidant provided better performance. Not unexpectedly, functionalized allyl TMS silanes derived from probenecid (**35**), naproxen (**36**), gemfibrozil (**37**) and isoxepac (**38**) were all well suited for α-amination, affording the corresponding products without difficulty. The reaction could be run on a 2 mmol scale without erosion of yield and selectivity (**7**). These outcomes highlight the robustness and practicality of the developed method.

The reaction demonstrated compatibility with several phenylsulfonamides (**39**-**41**) and sulfamates (**42**-**46**) possessing varying electronic properties as well (Scheme 3). However, methanesulfonamide and acetamide were not suitable coupling partners. The directing effect of the silyl group appeared to be quite general, as common alkyl or aryl-substituted silyl groups (**47**-**50**) consistently guided the amination at their α positions. Nonetheless, the site-selectivities were compromised due to steric hindrances, a conclusion supported by DFT calculations (vide infra).

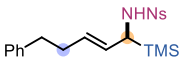
Experimental Mechanistic Studies. Several control experiments were conducted to elucidate the role of silyl moiety in the reaction (Scheme 4). Intermolecular competition experiments between **S-51** and **S-2** led to preferential formation of allyl α-amino silane (Scheme 4a), indicating an activating effect of silyl group to the reactivity. This activating effect was also manifested itself in the reaction of substrate **52** and **53**, both having an additional double bond (E or Z, respectively) and therefore 4 reaction sites. Only the α-aminated allyl silane products were observed. The reaction of *Z*-type allyl silanes **S-1a** results in a *E* product **1**, highlighting the potential for convergent synthesis (Scheme 4b). In principle, the α-anion stabilization from the silyl group may account for the observed regioselectivity by increasing the acidity the α-C–H bond and thereby facilitating the ene step. To test this possibility, alkene bearing an allylic ester group was subjected to the reaction. A preferential reaction at the α position of ester group was observed, but to a negligible extent, indicating the acidity of the concerning C–H bond is not important for reactivity (Scheme 4c). When the TMS moiety was moved from an α position far away to the β position, a significantly decreased regioselectivity (1.7:1) was observed. A significant difference of $^1J_{CH}$ coupling constants for the two competing allylic C–H bonds suggested a strong positive inductive effect of the TMS group (Scheme 4d). The kinetic isotope effect measured via intermolecular competition gave a primary KIE (kH/kD = 3.2), indicating the C–H cleavage is involved in the product-determining step (Scheme 4e).

Computational Mechanistic Studies. To better understand the mechanism, DFT calculations were performed (Scheme 5). Selenium bis(imide) reactive species A and allyl silane B were chosen as the starting points. As depicted in Scheme 5a, the ene reaction occurs through a six-membered ring transition state, and is highly exothermic and therefore irreversible under the reaction conditions, making it the site-selectivity determining step. The reaction at the α C–H bond is associated with a lower activation barrier by 2.5 kcal/mol than the distal one ($\Delta G_\alpha^{\neq}$ = 4.1 kcal/mol vs $\Delta G_\delta^{\neq}$ = 6.6 kcal/mol), in agreement with experimental observations. Next, following a rate-determining [2,3]-sigmatropic

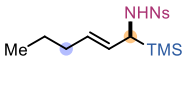
Scheme 2. Site-Selective Amination of Allyl Silanes



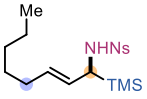
primary allyl silane



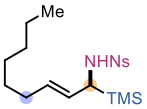
1, 78% (> 20:1 rr)
2 mmol scale: 76% (> 20:1 rr)



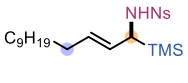
2, 60% (> 20:1 rr)[c]



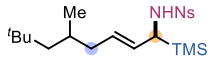
3, 70% (> 20:1 rr)



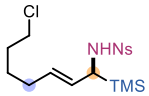
4, 81% (> 20:1 rr)



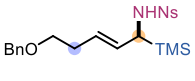
5, 80% (> 20:1 rr)[d]



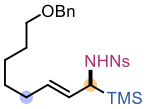
6, 69% (> 20:1 rr, 1.4:1 dr)



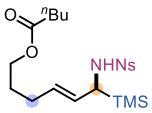
7, 73% (> 20:1 rr)



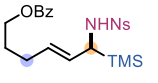
8, 65% (> 20:1 rr)



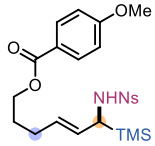
9, 71% (> 20:1 rr)



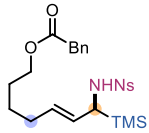
10, 47% (> 20:1 rr)



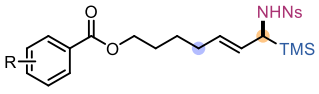
11, 63% (> 20:1 rr)[b]



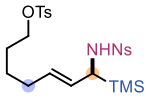
12, 66% (14:1 rr)



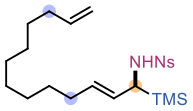
13, 63% (> 20:1 rr)



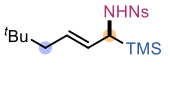
14, R = 4-Br, 68% (> 20:1 rr)
15, R = 4-Cl, 53% (15:1 rr)
16, R = 3-NO_2, 62% (10:1 rr)



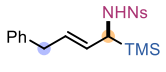
17, 42% (> 20:1 rr)



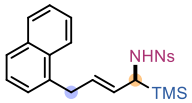
18, 52% (> 20:1 rr)



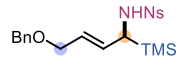
19, 68% (> 20:1 rr)



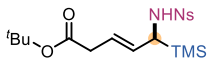
20, 57% (6:1 rr)



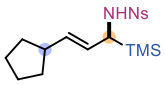
21, 49% (4:1 rr)



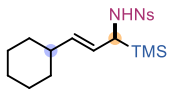
22, 52% (> 20:1 rr)[b]



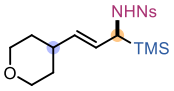
23, 44% (2:1 rr)[b]



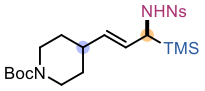
24, 59% (> 20:1 rr)[b]



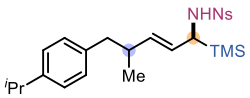
25, 68% (> 20:1 rr)



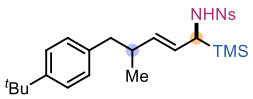
26, 47% (> 20:1 rr)



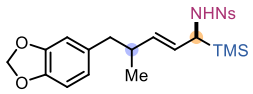
27, 69% (17:1 rr)



28, 82% (> 20:1 rr, 2:1 dr)

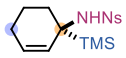


29, 71% (> 20:1 rr, 2:1 dr)

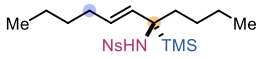


30, 50% (> 20:1 rr, 1.2:1 dr)[e]

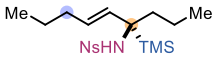
secondary allyl silane



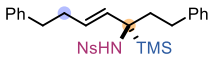
31, 43% (> 20:1 rr)



32, 62% (> 20:1 rr)[b]

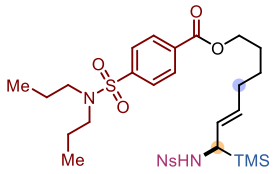


33, 64% (> 20:1 rr)[b]



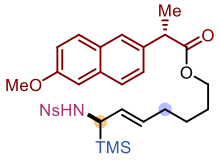
34, 73% (> 20:1 rr)[b]

derived from drug moledules



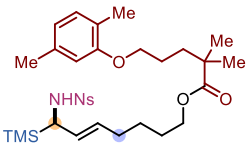
from Probenecid

35, 44% (> 20:1 rr)



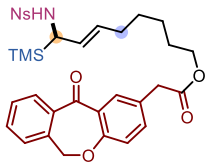
from Naproxen

36, 65% (> 20:1 rr, 3:1 dr)



from Gemfibrozil

37, 65% (> 20:1 rr)



from Isoxepac

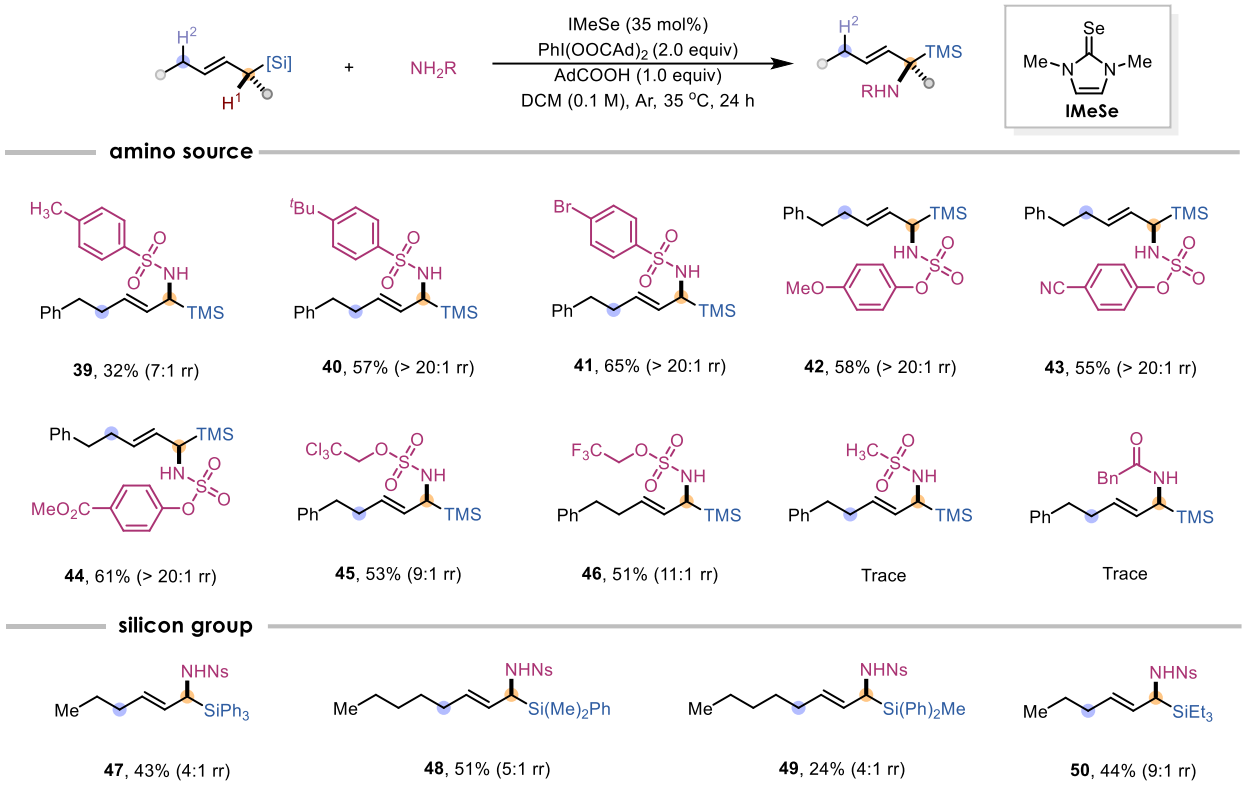
38, 60% (> 20:1 rr)

[a] Reaction Conditions: allyl silane (0.2 mmol, 1.0 equiv), $NsNH_2$ (0.4 mmol, 2.0 equiv), IMeSe (35 mol%), AdCOOH (0.2 mmol, 1.0 equiv), $PhI(O_2CAd)_2$ (0.4 mmol, 2.0 equiv) and DCM (2 mL), N_2 atmosphere; [b] *o*-CF_3-$PhI(OAc)_2$ instead of $PhI(O_2CAd)_2$; [c] without AdCOOH; [d] 40 °C; [e] 60 °C .

rearrangement, the allylic amination product can be formed. For other larger silyl groups, computational results indicate reduced energy difference, with $\Delta\Delta G^{\neq}$ for **$SiEt_3$** decreasing to 2.1 kcal/mol, and for **Si(Ph2Me)** to 1.5 kcal/mol, which translates to poorer selectivity compared to the TMS group in experiments. To further explore the origin of regioselectivity and activating effect of silicon group, distortion/interaction and NBO analysis was carried out. As illustrated in-Scheme 5b, a comparative distortion/interaction analysis between **TS-1** and **TS-1a** reveals that the stability of **TS-1** is

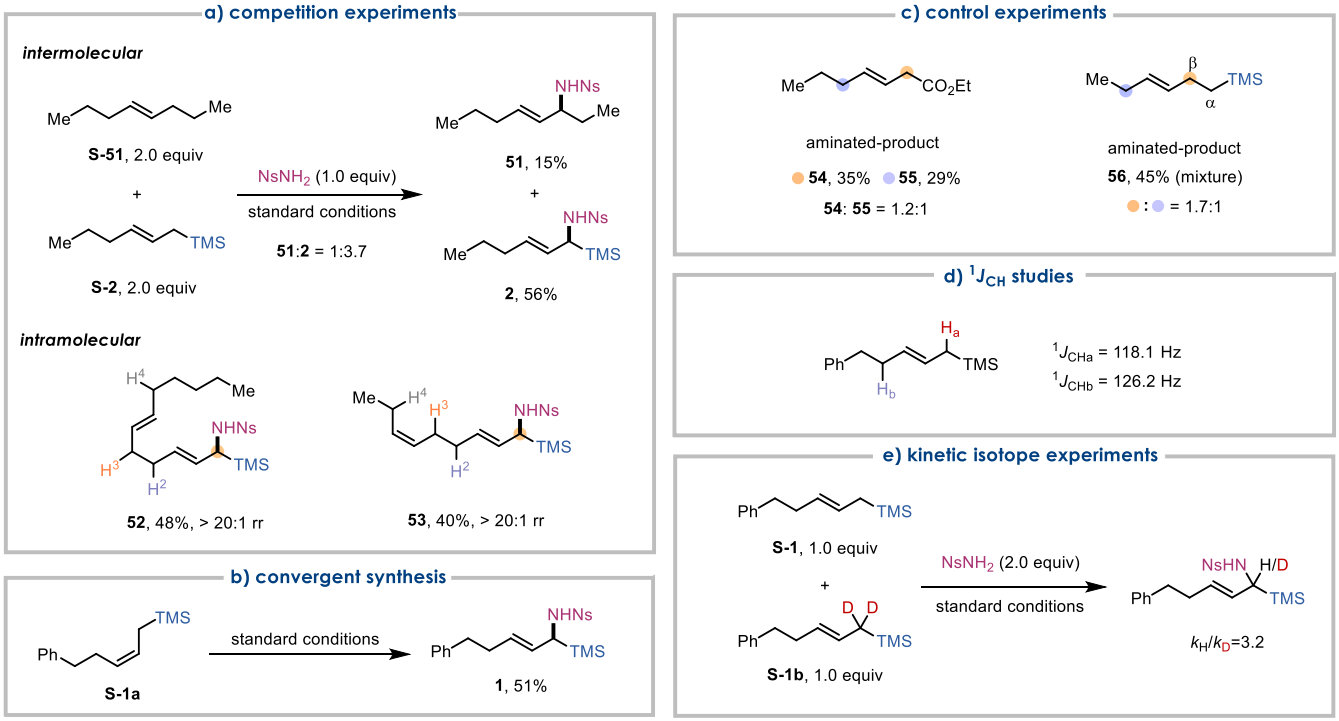
governed by a significantly higher interaction energy ($\Delta\Delta E_{int}$ = -10.8 kcal/mol), although it is substantially counterbalanced by the concurrently increased distortion energy ($\Delta\Delta E_{dist}$ = +8.5 kcal/mol). This increased distortion energy in **TS-1** primarilyoriginates from the deformation of the **TMS** alkyl chain on the alkene ($\Delta\Delta E_{dist(alkene)}$ = +9.3 kcal/mol) to meet the conformational requirements of the six-membered ring transition state (dihedral angle for

Scheme 3. Scope on Amino Sources and Silicon Groups



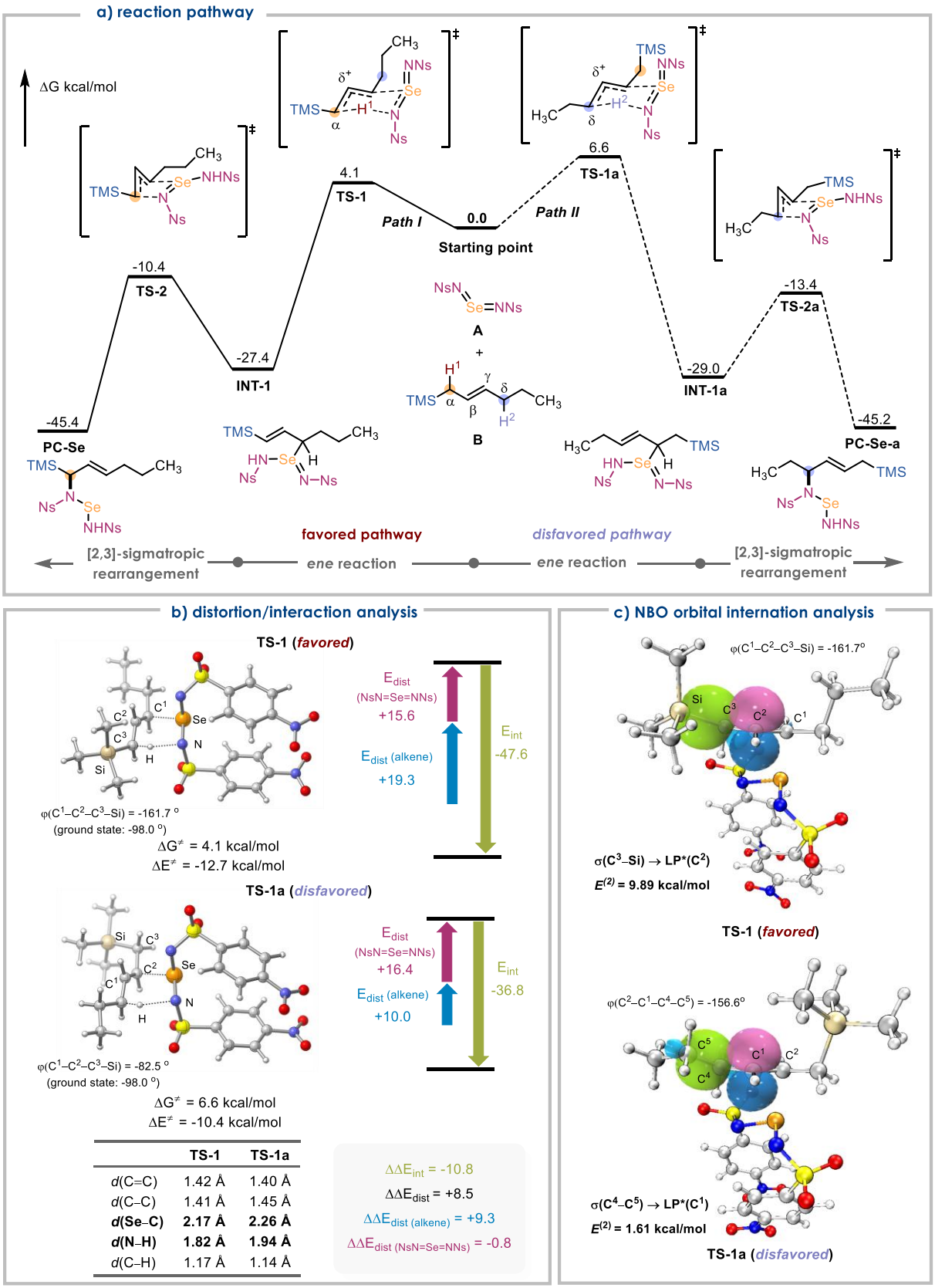
Reaction Conditions: allylsilane (0.2 mmol, 1.0 equiv), RNH_2 (0.4 mmol, 2.0 equiv), IMeSe (35 mol%), AdCOOH (0.2 mmol, 1.0 equiv), $PhI(O_2CAd)_2$ (0.4 mmol, 2.0 equiv) and DCM (2 mL), N_2 atmosphere, 35 °C, 24 h.

Scheme 4. Experimental Mechanistic Studies



https://doi.org/10.26434/chemrxiv-2024-84xr4 **ORCID:** https://orcid.org/0000-0002-9648-6759

Scheme 5. Computational Studies



	TS-1	TS-1a
d(C=C)	1.42 Å	1.40 Å
d(C–C)	1.41 Å	1.45 Å
***d*(Se–C)**	**2.17 Å**	**2.26 Å**
***d*(N–H)**	**1.82 Å**	**1.94 Å**
d(C–H)	1.17 Å	1.14 Å

C=C–C–Si in **Ts-1** (-161.7 °), **Ts-1a** (-82.5 °), and ground state (-98.0 °)). Conformational analysis of similar transition states indicates that in **TS-1**, the key distances Se–C (0.09 Å) and N–H (0.12 Å) are shorter, while the C–H distance (0.03 Å) is longer, correlating with a greater interaction energy between the alkene and the Se catalyst. NBO

analysis (Scheme 5c) reveals that **TS-1** is associated with a stronger hyperconjugative stabilization with a second-order perturbation energy ($E^{(2)}$) of 9.89 kcal/mol for the σ(C–Si)→LP*(C) orbital interaction, whereas the analogous σ(C–C)→LP*(C) orbital interaction in **TS-1a** ismuch weaker ($E^{(2)}$ = 1.61 kcal/mol). And finally, the removal of the silyl group (common alkenes) resulted in a higher ene activation barrier ($\Delta G^{\neq}$ = 9.8 kcal/mol) than both **TS-1** and **TS-1a**. Taken together, the above results uncover a remarkable β-silicon effect in tuning regioselectivity and reactivity, and this effect is largely a result of electronic reasons.

CONCLUSIONS

In summary, we've established a selenium-catalyzed direct C–H amination reaction of allyl silane. This protocol provides an efficient pathway to various highly functionalized α-amino silanes, including tertiary ones and those derived from bioactive compounds. The mild reaction conditions and unique reaction pathway circumvent undesired desilylation, preserving silicon as a valuable carbon bioequivalent. The remarkable site selectivity observed is attributed to the β-silicon effect, which governs a site-selectivity determining ene reaction, a conclusion supported by detailed DFT calculations.

ASSOCIATED CONTENT

Supporting Information.

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Notes

The authors declare no competing financial interest.

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