How to cite: *Angew. Chem. Int. Ed.* **2021**, *60*, 23335–23341
International Edition: doi.org/10.1002/anie.202109252
German Edition: doi.org/10.1002/ange.202109252

Photocatalysis

Direct Access to α-Aminosilanes Enabled by Visible-Light-Mediated Multicomponent Radical Cross-Coupling

*Xiaoye Yu, Constantin G. Daniliuc, Fatmah Ali Alasmary, and Armido Studer**

Dedicated to Professor Gerhard Erker on the occasion of his 75th birthday

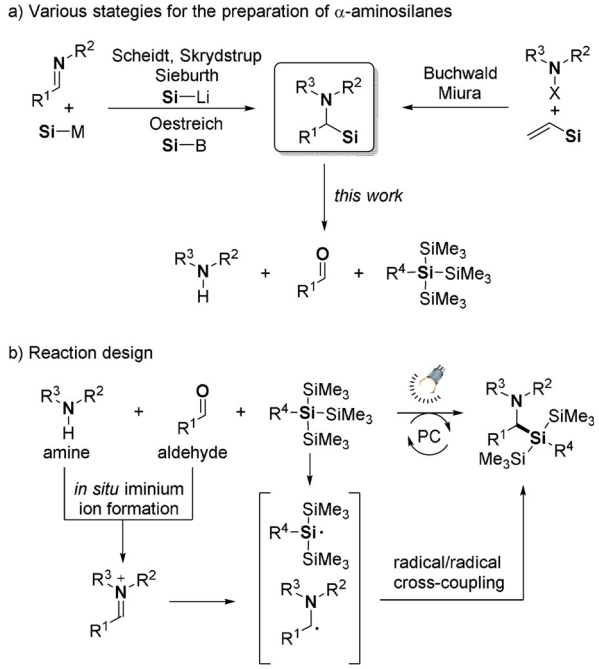
Abstract: *α-Aminosilanes are an important class of organic compounds that show biological activity. In this communication, a new approach to α-aminosilanes that utilizes photoredox catalysis to enable three-component coupling of organo(tristrimethylsilyl)silanes with feedstock alkylamines and aldehydes is presented. A wide range of highly functionalized α-aminosilanes can be obtained in good yields under mild conditions. Both primary amines and secondary amines are compatible with this transformation. Moreover, optically pure α-aminosilanes are accessible by using chiral amines. Mechanistic studies indicate that reactions proceed through radical/radical cross-coupling of silyl radicals with α-amino alkyl radicals.*

Introduction

Organosilicon compounds are of great interest in organic synthesis as they appear as valuable reagents, as protecting groups, as bioactive compounds and also in functional materials.[1] In this context, α-aminosilanes belong to a valuable Si-containing subclass which can not only serve as mimics of natural α-amino acids in several protease inhibitors, but have been incorporated into peptide isosteres.[2] Given their importance, development of mild and robust protocols to access such α-aminosilanes has attracted considerable interest. Traditionally, α-aminosilanes have been prepared by nucleophilic addition of silyl anions to imines (Scheme 1 a). For example, the Scheidt,[3] Skrydstrup[2j,4] and Sieburth[2c,g,i] groups utilized in situ generated functionalized metallated Si-nucleophiles for diastereoselective addition to C=N bonds. However, these processes suffer from limitations: a) they require activating groups at the imine nitrogen atom and b) use air-sensitive organometallic Si-reagents which significantly restricts substrate scope. Oestreich and other groups successfully prepared α-aminosilanes from imines by using air-sensitive Si-B reagents[5] through copper-catalysis.[6] An alternative disconnection strategy uses the addition of nitrogen-based reagents across vinylsilanes, which has been exploited by the groups of Buchwald and Miura to circumvent some of the inherent shortcomings of the Si-anion protocols.[7] Despite of these achievements, new and efficient strategies for the construction of functionalized α-aminosilanes remain highly attractive and demanded.

In recent years, photoredox catalysis[8] has emerged as a valuable branch of modern organic synthesis that offers unique opportunities to develop novel transformations. Compounds that are constructed through unusual bond connections by harnessing the great potential of reactive radical intermediates can be accessed. Along these lines, silyl radicals serve as valuable intermediates which have been widely used in synthesis.[9]

We wondered whether α-aminosilanes can be prepared via direct coupling of silyl radicals with in situ generated α-amino alkyl radicals. Such α-amino alkyl radicals can be readily generated by reduction of iminium ions that are



Scheme 1. Different approaches towards α-aminosilanes and reaction design.

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derived from aldehydes and amines.[10] These nucleophilic alkyl radicals are generally trapped by alkenes in C–C bond forming processes, as shown by Gaunt and others.[10,11] Moreover, reductively generated α-amino alkyl radicals can dimerize or also couple with ketyl radicals.[12] As compared to radical alkene additions, radical/radical cross-couplings show very low activation barriers and sterically encumbered σ-bonds can be constructed via such an approach. However, the selective cross-coupling of two reactive radicals is highly challenging, but control can be achieved if one of the coupling partners represents a longer-lived radical, following the concept of the persistent radical effect (PRE).[13]

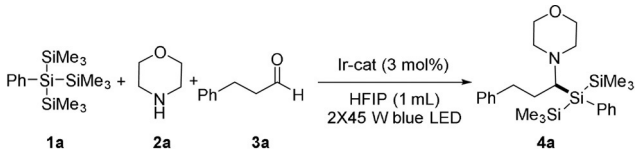
Our group recently developed visible-light-mediated hydrosilylation of electron-deficient alkenes with organo(tristrimethylsilyl)silanes.[9p] Si-radicals are generated through oxidative cleavage of a trimethylsilyl-polysilanyl Si–Si bond with the assistance of hexafluoroisopropanol (HFIP). We reasoned that such an operationally simple catalytic process could be applied to couple organo(tristrimethylsilyl)silanes with alkylamine and aldehyde feedstocks which would offer a facile and modular route to highly functionalized α-aminosilanes. This novel strategy would represent a complementary approach to existing methodology and would obviate some of the current limitations such as relatively harsh reaction conditions and narrow scope. Moreover, α-aminopolysilanes available by this approach are a novel class of polysilanes.

Based on literature precedence,[11a,b] we hypothesized that an iminium ion, formed in situ through condensation of an alkylamine with an aldehyde, should engage in single electron transfer (SET) reduction by a photoredox catalyst (Scheme 1b). The resulting α-aminoalkyl radical should then cross-couple with a silyl radical that is concomitantly formed by SET oxidation of an oligosilane to eventually give an α-aminosilane. For iminium ions derived from aliphatic aldehydes, deprotonation to the corresponding enamines must be suppressed, since enamines are known to undergo SET oxidation to give the corresponding radical cations.[14]

Results and Discussion

We began our investigations by exploring three-component radical α-aminosilane synthesis using phenyltris(trimethylsilyl)silane **1a**, morpholine **2a** and hydrocinnamaldehyde **3a** as representative coupling partners. After careful optimization of the reaction parameters,[15] the desired α-aminosilane **4a** was obtained in 70% yield by using [Ir(dF(CF$_3$)ppy)$_2$(5,5′-d(CF$_3$)bpy)]PF$_6$ as photocatalyst (PC, 3 mol%) and HFIP as solvent under 2×45 W blue LED irradiation (Table 1, entry 1). With 4czlPN or [Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ in place of [Ir(dF(CF$_3$)ppy)$_2$(5,5′-d(CF$_3$)bpy)]PF$_6$, yield of **4a** decreased (Table 1, entry 2 and 3). Solvent screening showed the importance of HFIP, since in DMF, CH$_3$CN or EtOH, no conversion or only trace amount of the targeted product was observed (Table 1, entry 4–6). Notably, the use of a 10 W blue LED instead of two 45 W blue LEDs led to a significantly reduced yield (44%, Table 1, entry 7) and control experiments indicated the necessity of both the photocatalyst and light irradiation (Table 1, entry 8 and 9). In these reactions, we could not identify the homodimer (hexamethyl-2,3-diphenyl-2,3-bis(trimethylsilyl)-tetrasilane) derived from **1a**.

Table 1: Reaction optimization.[a]

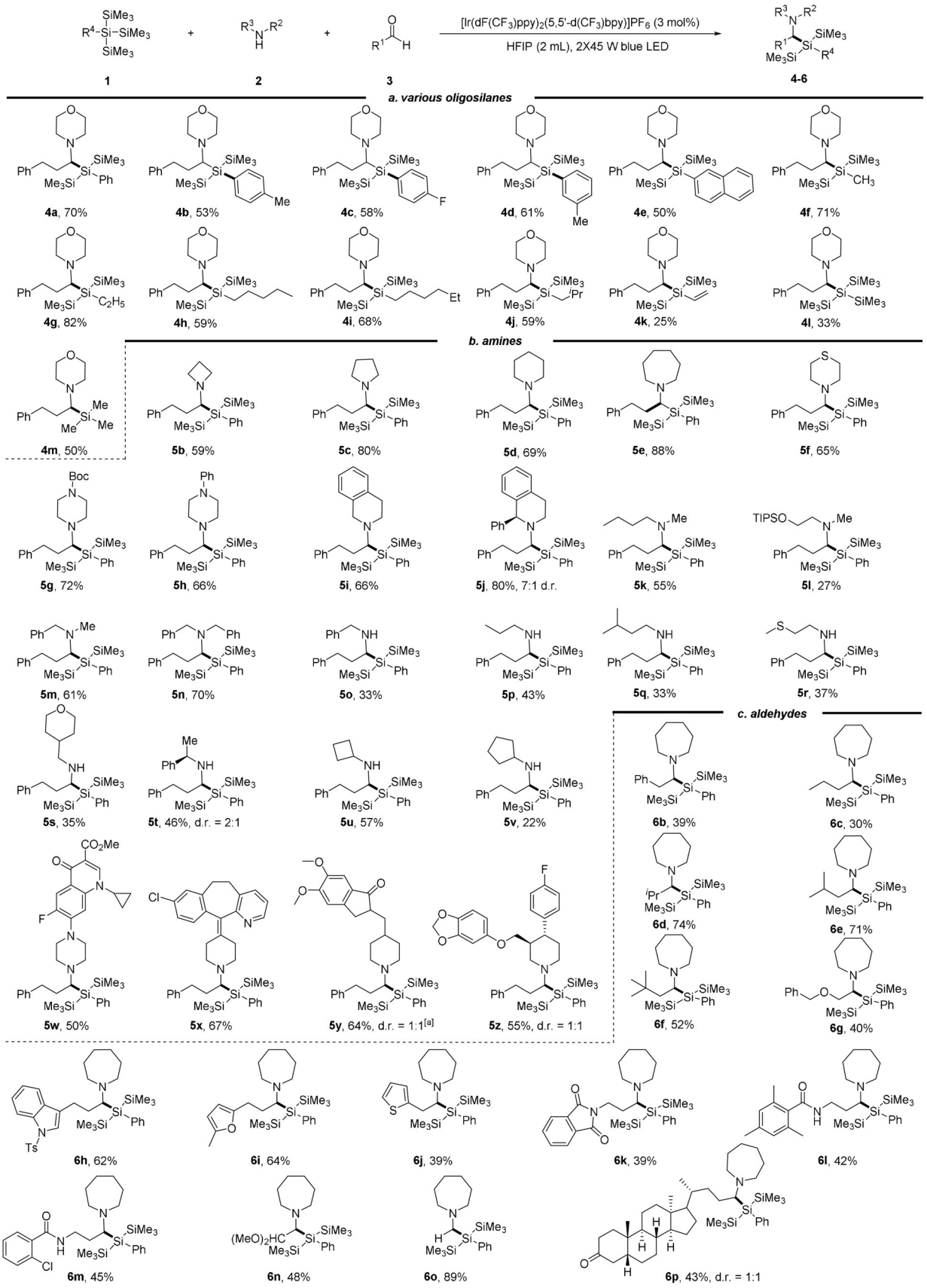


1a **2a** **3a** **4a**

Entry	Variation from standard conditions	Yield [%][b]
1	none	70
2	4czlPN instead of [Ir(dF(CF$_3$)ppy)$_2$(5,5′-d(CF$_3$)bpy)]PF$_6$	15
3	[Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ instead of [Ir(dF(CF$_3$)ppy)$_2$(5,5′-d(CF$_3$)bpy)]PF$_6$	trace
4	DMF instead of HFIP	nd
5	CH$_3$CN instead of HFIP	nd
6	EtOH instead of HFIP	trace
7	10 W instead of 2X45 W blue LED	44
8	Without PC	no reaction
9	Without visible light irradiation	no reaction

[a] Reaction conditions: **1a** (0.15 mmol), **2a** (0.15 mmol), **3a** (0.1 mmol) and [Ir(dF(CF$_3$)ppy)$_2$(5,5′-d(CF$_3$)bpy)]PF$_6$ (3 mol%) in HFIP (1 mL) at rt under irradiation of 2X45 W blue LEDs for 10 h. [b] Isolated yields. bpy = 2,2′-bipyridyl. ppy = 2-phenylpyridine. HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol. DMF = *N*,*N*-dimethylformamide. nd = not detected.

With the optimal conditions identified, we next investigated the generality of the photocatalytic three-component radical α-aminosilane synthesis (Scheme 2). Along with model product **4a**, we found aryltris-(trimethylsilyl)silanes bearing electron donating (Me) and accepting (F) *para*-substituents at the aryl moiety were compatible, furnishing the desired α-aminosilanes **4b** and **4c** in 53% and 58% yield, respectively. As slightly better yield was obtained for the *meta*-methyl congener (see **4d**, 61%). Reaction of **2a** and **3a** with 2-naphthyltris-(trimethylsilyl)silane **1e** gave **4e** in a reasonable yield. Notably, the substrate scope with respect to the polysilane component could be further expanded to alkyl substituted tris-(trimethylsilyl)silanes. For example, methyl (**1f**), ethyl (**1g**), pentyl (**1h**), hexyl (**1i**), and isobutyl (**1j**) substituted tris-(trimethylsilyl)silanes engaged in the three-component reaction to afford the α-aminosilanes **4f**–**4j** in good to very good yields (59–82%). However, a worse yield was achieved with the vinyltris-(trimethylsilyl)silane **1k** as Si-radical precursor (see **4k**, 25%). Commercially available tetrakis(trimethylsilyl)silane (**1l**) and hexamethyldisilane (**1m**) proved to be eligible coupling partners to provide the products **4l** and **4m** in 33% and 50% yield. Notably, we also examined hexakis(trimethylsilyl)disilane and hexamethyl-2,3-diphenyl-2,3-bis(trimethylsilyl)tetrasilane as Si-radical

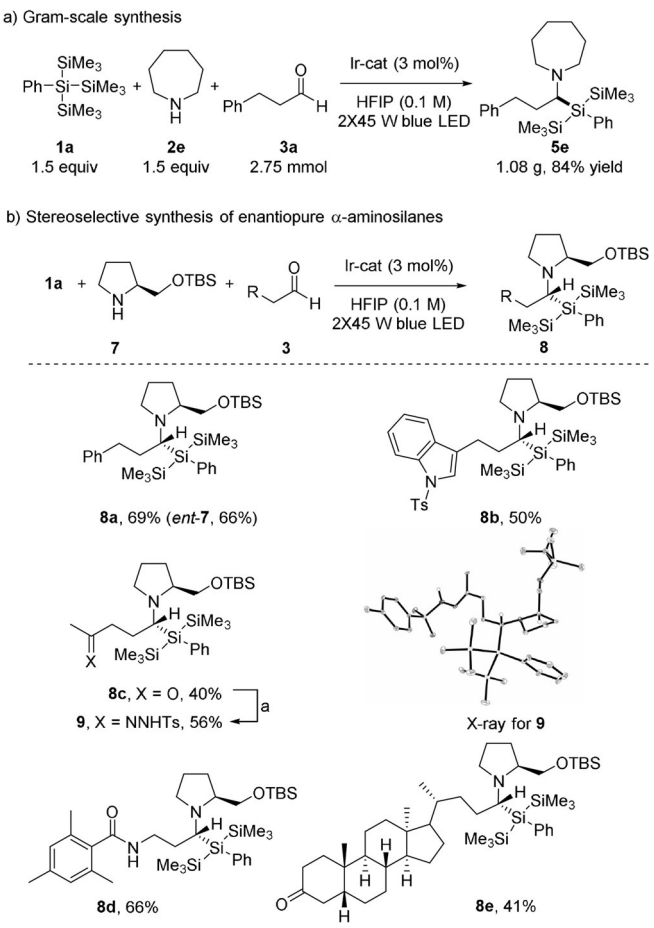


Scheme 2. Substrate scope. Conditions: **1** (0.3 mmol, 1.5 equiv), **2** (0.3 mmol, 1.5 equiv), **3** (0.2 mmol, 1.0 equiv) and $[Ir(dF(CF_3)ppy)_2(5,5'\text{-}d(CF_3)bpy)]PF_6$ (3 mol%) in HFIP (2 mL), rt, 12 h, 2X45 W blue LED. Yields given correspond to isolated products. [a] Reaction performed with 2.0 equiv of Na_2CO_3. bpy = 2,2′-bipyridyl. ppy = 2-phenylpyridine. HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol. ^{i}Pr = Isopropyl.

precursors, but the desired products were not detected (see SI for detailed information).

The amino component was varied next using **1a** and **3a** as reaction partners and we were pleased to find that the photocatalytic process was effective for a diverse array of primary and secondary alkyl amines. Thus, cyclic amines varying in ring size including four-, five-, six- and seven-membered amines could be successfully used for this radical cross-coupling (**5b**–**5e**, 59% to 88%). Replacing the oxygen atom in morpholine with sulfur or nitrogen did not influence reaction efficiency and the targeted α-aminosilanes **5f**–**5h** were obtained in 65–72% yield. Tetrahydroisoquinoline provided **5i** in 66% yield and three-component coupling with 1-phenyl-tetrahydroisoquinoline provided the α-aminotrisilane **5j** in 80% yield with 7:1 diastereoselectivity.[16] Non-cyclic secondary amines displaying linear alkyl substituents such as methyl, butyl, benzyl etc. participated in this reaction to afford the desired α-aminosilanes **5k**–**5n** with moderate to good yield (27–70%). Of note, a wide range of primary amines **2o**–**2v** bearing linear and branched alkyl substituents were suitable coupling partners to give the trisilanes **5o**–**5v** (22–57%). As compared to the secondary amines, primary amines generally provide lower yields. This methodology was also applicable to late-stage functionalization of medicinally interesting compounds (*ciprofloxacin* **2w**, *desloratidine* **2x**, *donepezil* intermediate **2y** and *paroxetine* **2z**) to provide access to a family of valuable α-aminosilanes **5w**–**5z** in yields ranging from 50 to 67%. Aromatic amines were found to be problematic substrates, likely due to failed formation of the iminium ion under the applied conditions. We therefore tested *N*-aryl imines as starting materials in two-component couplings. However, only for an electron-poor imine the targeted product was formed in low yield (see SI for detailed information). Thus, protonation to form the corresponding iminium ion might be another problem in these cases.

By using phenyltris(trimethylsilyl)silane **1a** and feedstock azepane **2e**, the aldehyde component was varied next. Interestingly, not only the linear aliphatic aldehydes **3b**–**3c**, but also the branched aldehydes **3d**–**3f** performed well in the cascade and the α-aminosilanes **6b**–**6f** were isolated with moderate to good yield. 2-(Benzyloxy)acetaldehyde **3g** was successfully coupled with **1a** and **2a** to afford the trisilane **6g** (40%). Moreover, aliphatic aldehydes **3h**–**j** bearing electron-rich arenes such as indole, furan, thiophene were compatible and the α-aminosilanes **6h**–**6j** were isolated in reasonable yield (39–64%). Of note, various aromatic aldehydes bearing electron-withdrawing and electron-donating groups did not engage in this reaction under the standard conditions (see SI for detailed information). We also examined a set of aldehydes containing differently substituted amides and found that all tested substrates could be transformed to the targeted products **6k**–**6m** (39–45%). α-Aminosilane synthesis also worked with glyoxal dimethyl acetal **3n** (**6n**, 48%) and paraformaldehyde reacted with **1a** and **2a** to give **6o** in high yield (89%). The lithocholic acid derived aldehyde **3p** was successfully converted to the α-aminosilane **6p** (43%) documenting that the method is valuable for conjugation of complex natural product-derived aldehydes.

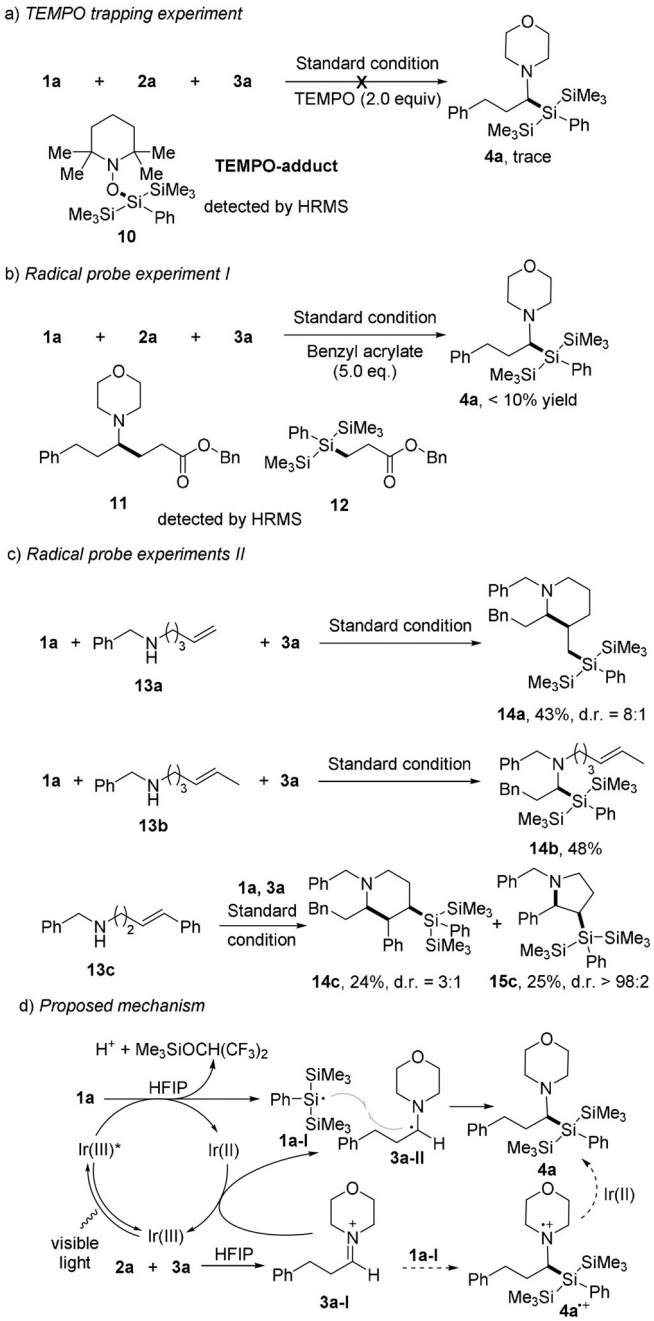


Scheme 3. Large scale experiment and stereoselective coupling to enantiopure α-aminosilanes. a) Reaction conditions: **1a** (4.13 mmol, 1.5 equiv), **2e** (4.13 mmol, 1.5 equiv), **3a** (2.75 mmol, 1.0 equiv) and $[Ir(dF(CF_3)ppy)_2(5,5'\text{-}d(CF_3)bpy)]PF_6$ (3 mol%) in HFIP (27.5 mL), rt, 12 h, 2X45 W blue LED. b) Reaction conditions: **1a** (0.3 mmol, 1.5 equiv), (*S*)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)pyrrolidine **7** (0.3 mmol, 1.5 equiv), **3** (0.2 mmol, 1.0 equiv) and $[Ir(dF(CF_3)ppy)_2(5,5'\text{-}d(CF_3)bpy)]PF_6$ (3 mol%) in HFIP (2 mL), rt, 12 h, 2X45 W blue LED. [a] $TsNHNH_2$ (2.0 equiv), MeOH (0.05 M), rt, 10 h. TBS = *tert*-butyldimethylsilyl. Ts = *p*-toluenesulfonyl.

To demonstrate the robustness of the cascade, a gram scale experiment was carried out (Scheme 3a). It was found that the product **5e** was obtained under the standard condition with no erosion of yield. Considering the significance of enantiopure α-aminosilanes,[2] we targeted optically pure α-aminosilanes by diastereoselective radical cross-coupling of the readily available chiral prolinol derivative **7**, phenyltris(trimethylsilyl)silane **1a** and five selected aldehydes **3** bearing additional functionalities (Scheme 3b). Pleasingly, in all cases the product silanes (**8a**–**8e**) were formed with complete control of the diastereoselectivity (d.r. > 98:2). Starting with the enantiomeric prolinol derivative *ent*-**7**, the enantiomeric series is available, as documented by the successful preparation of *ent*-**7**. After treatment of compound **8c** with *p*-toluenesulfonyl hydrazide, the hydrazone **9** could be obtained in good yield. The relative configuration in **9** was unambiguously assigned by X-ray

structure analysis,[17] and all other compounds in this series were assigned in analogy.

To shed light on the mechanism, several control experiments with model substrates **1a**, **2a** and **3a** were conducted (Scheme 4). When 2.0 equivalents of the radical scavenger TEMPO were added, only a trace amount of the desired product **4a** was formed and the radical trapping product **10** was detected by HRMS (Scheme 4a). Moreover, in the presence of 5.0 equivalents of benzyl acrylate, we could detect adducts **11** and **12** by HRMS along with small amounts of **4a** (Scheme 4b). These findings demonstrated that the phenylbis(trimethylsilyl)silyl radical **1a-I** and the α-amino alkyl radical **3a-II** are likely intermediates in the three-component coupling. Additionally, we carried out a series of radical probe experiments (see SI for detailed information).[15] Reaction of pentenylamine **13a** with **1a** and **3a** provided the piperidine **14a** as a mixture of diastereoisomers (Scheme 4c). Product **14a** can be formed via radical/radical cross coupling of the cyclized radical or alternatively via initial Si-radical addition to the terminal alkene of the intermediate iminium ion followed by a 6-*endo*-cyclization and reduction. To suppress Si-radical addition to the alkene moiety, a methyl (see **13b**) or a phenyl group (see **13c**) was installed at the terminus of the double bond. With the amine **13b** as coupling partner, the non-cyclized product **14b** was isolated and by using amine **13c**, the piperidine **14c** was isolated in moderate yield as a mixture of diastereoisomers. In addition, **15c** (25%) was formed likely via Si-radical addition to the alkene **13c** followed by oxidation to the corresponding benzylic cation and subsequent ionic cyclization. Stern–Volmer quenching experiments showed that phenyltris(trimethylsilyl)silane **1a** in the presence of HFIP can effectively quench the excited state of the Ir-photocatalyst (see SI for detailed information).



Scheme 4. Control experiments and proposed mechanism.

Based on these experiments, we propose a plausible mechanism that is shown in Scheme 4d. The cascade begins with visible light irradiation of the Ir^{III} PC, leading to the formation of the photoexcited Ir^{III}*-complex. Then, SET oxidation of **1a** by the excited state PC $^{*}Ir^{III}$ generates the silyl radical **1a-I** along with the corresponding reduced Ir^{II}-complex. Importantly, Si-radical generation is likely assisted by the solvent HFIP to give $Me_3SiOCH(CF_3)_2$ which was identified as a byproduct. The iminium ion **3a-I**, that is formed in situ by the condensation of **2a** with **3a**, is then reduced by the Ir^{II}-complex to deliver the α-aminoalkyl radical **3a-II** through a single electron transfer process, regenerating ground-state Ir^{III}-complex. Since no acid is required, we assume that HFIP also mediates iminium ion formation and therefore has a dual role in this cascade. Finally, radical/radical cross-coupling of **3a-II** and **1a-I** leads to product **4a**. Since some phenylbis(trialkylsilyl)silyl radicals are known to be persistent species,[18] we assume that the Si-radical **1a-I** is a longer-lived intermediate and accordingly the cross-coupling to be controlled by the persistent radical effect.[13] An alternative pathway involving addition of the silyl radical **1a-I** to the in situ-generated alkyliminium ion **3a-I** to give the radical cation of **4a** followed by reduction with the Ir^{II}-complex cannot be ruled out (see dashed arrows). Considering this second mechanistic option and our probe experiments (Scheme 4c), direct addition of the bulky silyl radical **1a-I** onto an iminium ion would be slower than addition onto a terminal alkene (see **14a**), slower than addition to a β-substituted styrene derivative (see **14c**) but faster than addition onto a non-activated internal alkene (see **14b**).

Conclusion

In summary, we developed a straightforward and effective photochemical protocol to access α-aminosilanes by direct coupling of organo(tristrimethylsilyl)silanes with primary and secondary alkylamine and aldehyde feedstocks. These cas-

cades proceed under mild conditions, shows high functional group tolerance and broad substrate scope. The reaction is amenable to gram-scale synthesis of α-aminosilanes. By using chiral secondary amines, optically pure α-aminosilanes can be obtained with excellent stereocontrol. Moreover, the introduced method provides a new disconnection strategy for the synthesis of a diverse range of α-aminosilanes that are difficult to prepare using existing methods.

Acknowledgements

This work was supported by the Distinguished Scientist Fellowship Program (DSFP) at King Saud University, Riyadh, Saudi Arabia and the Alexander von Humboldt foundation (postdoctoral fellowship to X.Y.). Open Access funding enabled and organized by Projekt DEAL.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: photocatalysis · radical cross-coupling · silyl radicals · α-aminoalkyl radicals · α-aminosilanes

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Manuscript received: July 12, 2021
Revised manuscript received: August 13, 2021
Accepted manuscript online: August 25, 2021
Version of record online: September 17, 2021

