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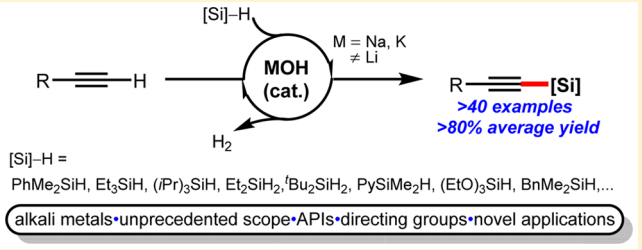
Alkali Metal-Hydroxide-Catalyzed C(*sp*)−H Bond silylation

Anton A. Toutov,[†] Kerry N. Betz,[†] David P. Schuman, Wen-Bo Liu, Alexey Fedorov,[‡] Brian M. Stoltz,* and Robert H. Grubbs*

Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States

Supporting Information

ABSTRACT: Disclosed is a mild, scalable, and chemoselective catalytic cross-dehydrogenative C−H bond functionalization protocol for the construction of C(*sp*)−Si bonds in a single step. The scope of the alkyne and hydrosilane partners is substantial, providing an entry point into various organosilane building blocks and additionally enabling the discovery of a number of novel synthetic strategies. Remarkably, the optimal catalysts are NaOH and KOH.



INTRODUCTION

The catalytic transformation of C−H bonds into a variety of useful functional groups has revolutionized chemical synthesis.[1] However, the necessity of precious metal catalysts for these transformations remains a fundamental and longstanding limitation.[2] With the aim of developing a suite of new methods for powerful, sustainable, and cost-effective chemical synthesis, we became interested in the use of Earth-abundant metal salts for catalytic cross-dehydrogenative C−H bond functionalization reactions.[3] Toward this end, we recently reported the direct C(sp^2)−H silylation of aromatic heterocycles with hydrosilanes using catalytic potassium *tert*-butoxide (KO*t*-Bu).[4] Building upon this concept, we sought to evaluate alkali metal salts as catalysts for the preparation of alkynylsilanes. These important building blocks are used in the construction of electronically and structurally interesting materials,[5] employed as substrates in metathesis reactions[6] and cycloadditions,[7] and as precursors to heterocycles[8] and polycyclic aromatic frameworks.[9] Moreover, alkynylsilane nucleophiles and cross-coupling partners react under mild conditions[10] and therefore are commonly utilized as versatile intermediates en route to complex molecules.[11] Recently, di-*tert*-butylfluorosilyl alkynes have been proposed as a novel functionality in the development of next generation radiofluorinated positron emission tomography (i.e., [^{18}F]PET) probes with high in vivo stability for noninvasive biomedical imaging applications.[12]

Strategies for the synthesis of alkynylsilanes have employed strong bases (Scheme 1a, route A)[13] or have relied on stoichiometric[14] or catalytic transition metal species (Scheme 1a, Route B)[15] and typically use various preactivated organosilicon coupling partners such as [Si−Cl],[13a,b,14a,b] [Si−I],[15f] [Si−NR_2],[14c] [Si−Si],[13d] and [Si−OTf].[15c] Inexpensive and convenient hydrosilanes have been investigated for C(*sp*)−H silylation;[13c−e,g,15a,b,d,f] however, the requisite in situ Si−H bond activation has thus far necessitated additional exogenous bases,[15b,d] sacrificial hydrogen acceptors[15f] or external oxidants,[15a,d] and elevated temperatures.[13c−e,15d,f] Moreover, undesired hydrosilylation of the alkyne can be competitive,[15a,d,f] further complicating catalyst and reaction design. Interestingly, highly basic species such as MgO,[13c,e,f] KNH_2/Al_2O_3,[13g] $LiAlH_4$,[13c,e] *n*-BuLi,[13c] and even alkoxides[13c] have shown some catalytic activity in the dehydrocoupling of hydrosilanes and alkynes. However, these reports are limited to only a handful of unfunctionalized examples, the reactions give modest yields and selectivities, and the chemistry typically requires elevated temperatures (i.e., 80−120 °C), severely lowering the practical utility of these strong base-catalyzed methods. Moreover, basic functionalities such as *N*-heterocycles and aliphatic amines have been absent in all of the aforementioned reports, likely owing, in most cases, to the necessity for Lewis-

Scheme 1. Approaches to C−H Silylation of Alkynes

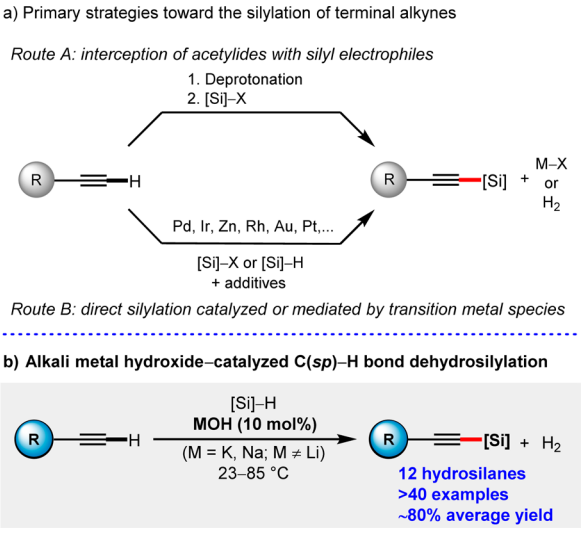


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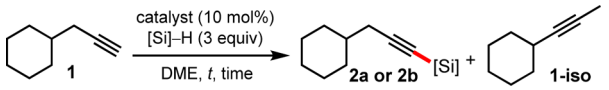
Table 1. Reaction Discovery and Catalyst Evaluation[a]



entry	catalyst	[Si]–H	t (°C)	time (h)	**2** (yield, %)	**1-iso** (yield, %)
1	KO*t*-Bu	Et_3SiH	85	24	**2a** (89)	**9**
2	NaO*t*-Bu	Et_3SiH	85	24	**2a** (46)	**52**
3	LiO*t*-Bu	Et_3SiH	85	24	**2a** (<1)	–
4	pyridine	Et_3SiH	85	48	–	–
5	KOH	Et_3SiH	85	48	**2a** (95)	**3**
6	KOH	$PhMe_2SiH$	25	48	**2b** (89)	–
7	NaOH	$PhMe_2SiH$	25	48	**2b** (93)	–
8	LiOH	$PhMe_2SiH$	25	48	–	–

[a]Reactions were conducted on 0.5 mmol scale with 0.5 mL solvent at the prescribed temperature. DME = 1,2-dimethoxyethane. Entries 1–4, 8: yields determined by GC-FID analysis with tridecane as an internal standard. Entries 5–7: yields of analytically pure isolated materials. Reaction does not proceed without catalyst.

acidic metal centers and/or electrophilic silicon sources in those reactions. An NHC/NaH-catalyzed protocol that is tolerant of *N*-heterocycles has been reported; however, the use of CF_3SiMe_3 (Ruppert–Prakash reagent) as the silicon source is a disadvantage from the perspective of reagent stability, cost, and, in particular, scope of the silicon partner.[16]

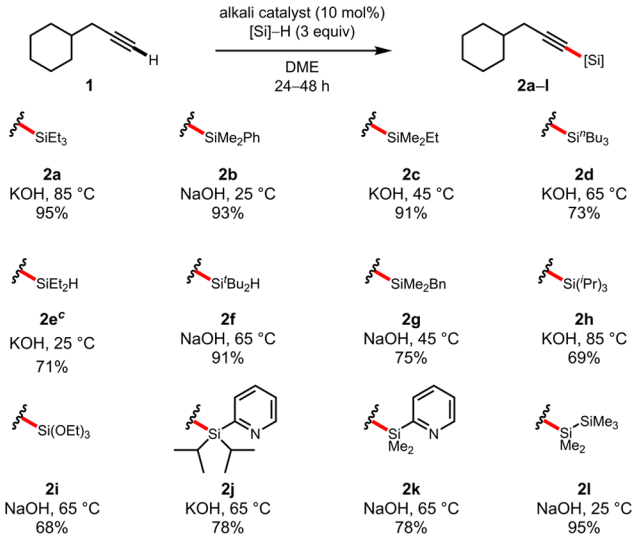
Herein, we disclose a mild, efficient, and general catalytic C(sp)–H bond silylation of unprecedented scope. The method avoids the fundamental limitations of previous strategies, including classical stoichiometric deprotonation and catalytic transition metal–catalyzed approaches, and uses readily available KOH or NaOH as the optimal catalysts (Scheme 1b).

RESULTS AND DISCUSSION

We initiated investigations with the silylation of alkyne **1** using Et_3SiH under our previously reported KO*t*-Bu-catalyzed C(sp^2)–H silylation conditions[4a−c] and gratifyingly observed alkynylsilane **2a** in good yield; however, 9% of undesired alkyne migration product **1-iso** was also isolated (Table 1, entry 1).[17] NaO*t*-Bu (entry 2) and LiO*t*-Bu (entry 3) show poor reactivity, and pyridine (entry 4) gives no reaction. KOH is superior to KO*t*-Bu (entry 5), generating the desired product in 95% yield with decreased quantities (3%) of the undesired **1-iso**. Moving from Et_3SiH to $PhMe_2SiH$ permits the reaction to occur at ambient temperature while still maintaining high yield (entry 6). In sharp contrast to our previously reported heteroarene C(sp^2)–H silylation protocol wherein the catalyst was essentially limited to KO*t*-Bu,[4a−c] the ideal catalysts for the C(sp)–H silylation were KOH and NaOH affording **2b** in 89% and 93% yield, respectively (entries 6 and 7). By contrast, LiOH (entry 8) does not catalyze the reaction.

We next proceeded to evaluate the scope of the hydrosilane partner (Scheme 2) and found that alkyl- and phenyl-substituted hydrosilanes of varying steric demand readily undergo coupling providing alkynylsilanes **2a–d** in high yields. The mild conditions of this reaction enabled the facile preparation of alkynylsilanes containing synthetically versatile hydride- (**2e** and **2f**), benzyldimethyl- (**2g**), triisopropyl- (**2h**), and even triethoxy- (**2i**) and 2-dialkylpyridyl (**2j** and **2k**) moieties in good yield. Alkynyl dimethylsilylpyridines such as **2k** can be advanced to di-, tri-, and tetra-substituted olefins by sequential transition metal-catalyzed protocols making them highly valuable C(sp)–Si functionalities.[18] However, these moieties are currently prepared by stoichiometric metal acetylide chemistry, which may have contributed to their

Scheme 2. Scope of the Hydrosilane[a,b]



[a]Reactions were conducted on 0.5 mmol scale with 0.5 mL of solvent at the prescribed temperature. DME = 1,2-dimethoxyethane. Yields are of analytically pure isolated products. [b]Reactions are run for 48 h, except 24 h for **2c** and **2e**. [c]THF used as the solvent.

apparent underutilization in synthesis.[18] The bulky di-*tert*-butylsilane could also be introduced by catalytic C–H silylation yielding **2f** in excellent yield, providing a point of entry into novel alkynylsilyl [^{18}F]PET radiopharmaceutical moieties.[12] Using $Me_3Si–SiHMe_2$ as a polysilane model compound and subjecting it to our cross-dehydrogenative silylation at ambient temperature gave **2l** in 95% yield, providing a new synthetic strategy for the construction of advanced polysilane materials.[19] At the time of preparation of this manuscript and to the best of our knowledge, this is the most diverse scope of hydrosilanes reported to date for any single catalytic C–H silylation system. The scope of the alkyne coupling partner was likewise substantial, affording products containing electron-rich and electron-deficient aryl (**4a–j**), heteroaryl (**4k–m**), ferrocenyl (**4n**), and aliphatic (**4o–y**) groups (Scheme 3). Substrates containing sensitive functional groups such as aryl halides (**4b–d**), an alkyl chloride (**4v**), and a cyclopropane (**4r**) are tolerated without any undesired side reactions. Molecules bearing acidic functionalities such as propargylamines and propargyl alcohols also react well, providing **4w** and bis-silylated **4x**[20] respectively

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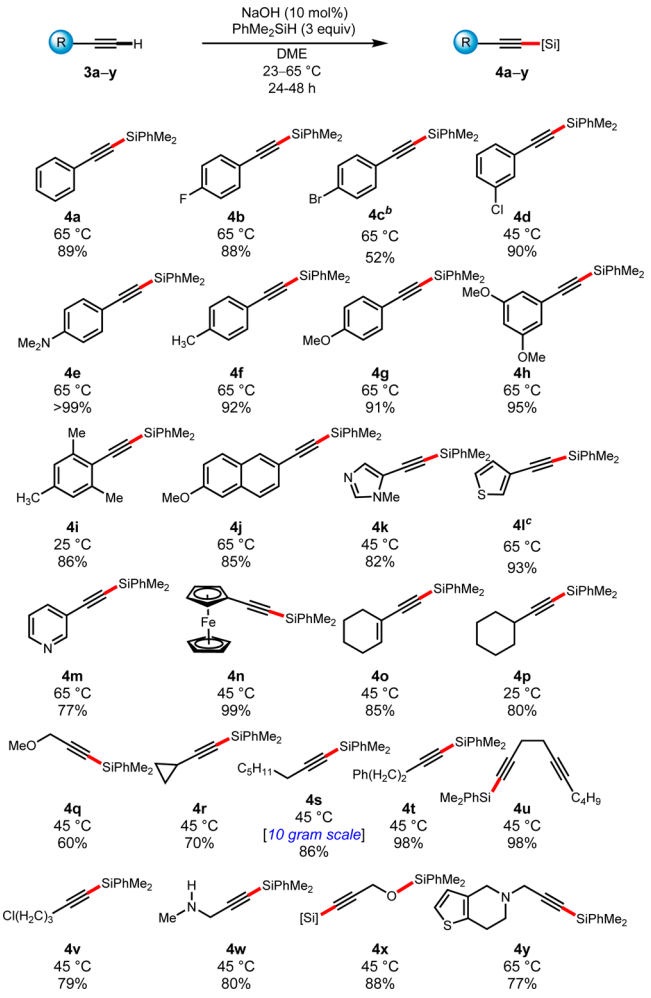
Scheme 3. Scope of the Alkyne Partner[a]



[a]Reactions were conducted on 0.5 mmol scale with 0.5 mL of solvent for 24 or 48 h at the prescribed temperature. DME = 1,2-dimethoxyethane. Yields are of analytically pure isolated products. [b]96 h for **4c**. [c]72 h for **4l**.

in high yields. Unprecedented catalytic cross-dehydrogenative silylation of *N*-heterocyclic systems, such as those substrates containing an imidazole and a pyridine, are also successful affording the corresponding silylated building blocks **4k** and **4m** without any observed Minisci-type reactivity. Substrates containing C–H bonds that are susceptible to our KO*t*-Bu-catalyzed silylation,[4a−c] or those that could be engaged under a variety of other C–H functionalization chemistries react specifically at the terminal alkyne C–H bond. Thus, alkynylsilane products bearing toluene (**4f**), anisole (**4g**), thiophene (**4l** and **4y**), propargyl ether (**4q**), and phenylethyl (**4t**) moieties could be readily accessed. In particular, electron-rich systems are excellent substrates and undergo the desired C(*sp*)–H silylation to furnish alkynylsilanes containing aniline (**4e**), dimethoxybenzene (**4h**), and ferrocene (**4n**) fragments without any byproducts derived from electrophilic silylation. The reaction scales well as demonstrated by the production of 19 g of **4s** using 1.5 mol equiv of the hydrosilane.

SYNTHETIC UTILITY OF THE PRODUCTS

We next proceeded to investigate novel applications of our catalytic method. Symmetrical aliphatic or aromatic diynes can either undergo bis-functionalization (Scheme 4a) to yield **5b** and **6b** or can undergo catalytic monosilylation to yield valuable desymmetrized building blocks **5a** and **6a** by using an excess of substrate (see the Supporting Information). Hydroxide-catalyzed silylation followed by treatment with a borane (i.e., HBPin) leads to a one-pot catalytic *geminal* difunctionalization of terminal alkynes (Scheme 4b). This protocol gives access to trisubstituted olefins **7a–e** containing both a vinyl C–Si and C–B bond as a single olefin isomer from inexpensive, commercially available materials. Combinations of both alkyl- and aryl-substituted silanes and alkynes are amenable to this reaction, though instability in some of the products has been observed during purification, resulting in decreased yields despite high conversions.[21]

Sila-drug analogues in some cases demonstrate improved pharmacokinetic properties relative to the corresponding all-carbon compounds and are garnering increased attention from medicinal chemists.[22] To evaluate our method for late-stage C–H silylation applications, we subjected the monoamine oxidase (MAO) inhibitor pargyline, the estrogen prodrug mestranol, and third-generation oral contraceptive desogestrel to the catalytic silylation conditions, successfully providing novel sila-drug analogues **8**, **9**, and **10** respectively (Scheme 4c).

Si-tethered diynes have a rich history in organometallic chemistry and organic synthesis.[23] They can be readily advanced to substituted arenes, enones, dienes, and aromatic *N*-heterocycles as well as siloles, polysiloles or silole-heterocycle copolymers.[8b,23,24] However, synthesis in general remains challenging and no stoichiometric or catalytic methodology for the direct preparation of unsymmetrical variants has been detailed. Using the title silylation methodology, symmetrical alkyl- (**11a** and **11b**) and aryl-substituted (**11c**) variants could be readily accessed (Scheme 4d). This strategy also enabled an unprecedented unsymmetrical coupling affording variants **12a** and **12b** containing aliphatic, aromatic, and heteroaromatic substituents (see Supporting Information).

PRELIMINARY MECHANISTIC CONSIDERATIONS

A number of mechanisms for the C(*sp*)–H silylation reaction occurring under various conditions with different catalyst systems have been proposed;[13,14a,15b−f,16] however, the mechanistic details of this alkali metal hydroxide–catalyzed dehydrosilylation are not well understood at this point. Nevertheless, a number of experiments were conducted to gain insight into the underlying manifolds involved. As a first investigation, we conducted our reaction in the presence of the radical traps TEMPO and galvinoxyl (Scheme 5).

Neither additive completely thwarted the alkyne C–H silylation: TEMPO did not inhibit the reaction at 10% loading but lowered the silylation yield at 300% loading; the addition of 10 mol % galvinoxyl almost completely inhibited the reaction. Although these stable radical reagents could decrease the yield of the ethynylsilane **2a**, these data certainly cannot conclude whether the reaction is anionic in nature or whether it proceeds via single electron species. One can only conclude that galvinoxyl and TEMPO do inhibit the reaction and that the former is a more effective inhibitor.

We also studied the effect of potassium and sodium chelating agents in the silylation reaction to investigate the importance of the cation in the catalysis. When 18-crown-6 and 15-crown-5 were added to reactions using KOH and NaOH as the catalysts respectively, quantitative silylation was still observed when using triethylsilane as the silicon partner, suggesting either that

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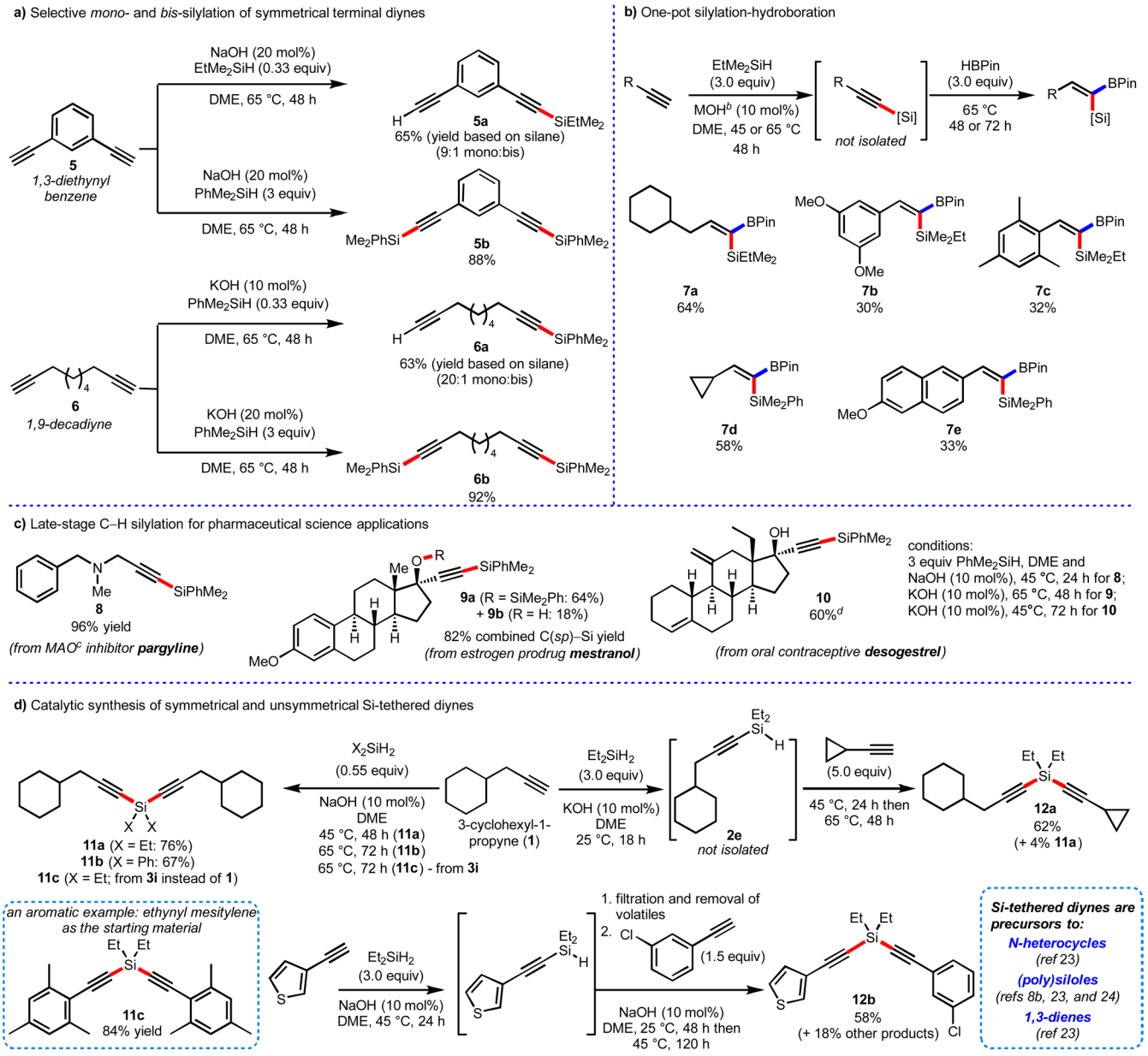
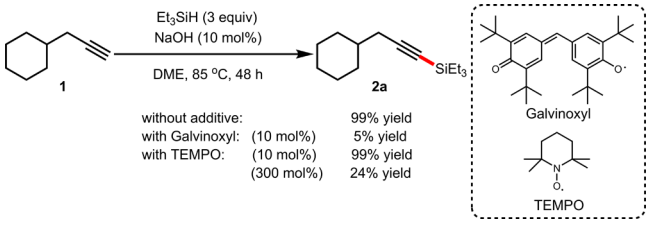
Scheme 4. Novel Applications Enabled by Alkali Hydroxide-Catalyzed C(*sp*)–H Silylation[a]



[a]Reactions were conducted on 0.5 mmol scale with 0.5 mL of solvent at the prescribed temperature unless otherwise stated and yields are of analytically pure isolated materials. DME = 1,2-dimethoxyethane. See SI for optimization and detailed experimental conditions. [b]For **7a**–**7c** M = K; for **7d** and **7e**: M = Na. See SI for specific conditions. [c]MAO = monoamine oxidase. [d]<5% of Si–O product was detected.

Scheme 5. Influence of Radical Scavengers[a]



[a]Reactions were conducted on 0.5 mmol scale with 0.5 mL of solvent at the prescribed temperature and for the prescribed length of time. DME = 1,2-dimethoxyethane. Yields are determined by GC analysis using tridecane as an internal standard.

ineffective chelation of the metal ion had occurred or that the cation was not necessary to the reactivity in this particular case (Scheme 6a).

However, in the case of triethoxysilane, the addition of the chelating agent shut down reactivity, suggesting that the sodium ion is indeed necessary for the silylation of alkynes with this particular silane (Scheme 6b). In this case, the only product when crown ethers are added is $(EtO)_4Si$, which indicates that sequestration of the alkali metal cation from the system shuts down the productive C–H silylation pathway and induces disproportionation of the silane. While the counterion effect is pronounced in this case and also in a number of others (see Tables 2 and 3), the exact role of the counterion in such alkali metal salt–catalyzed C–H functionalization reactions has become an active area of research in our labs.

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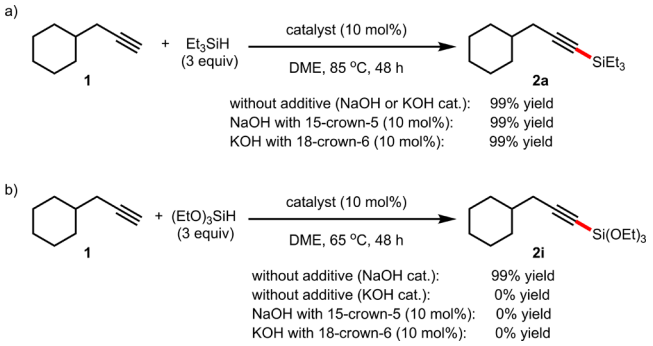
Scheme 6. Impact of Alkali Metal Ion Chelators[a]



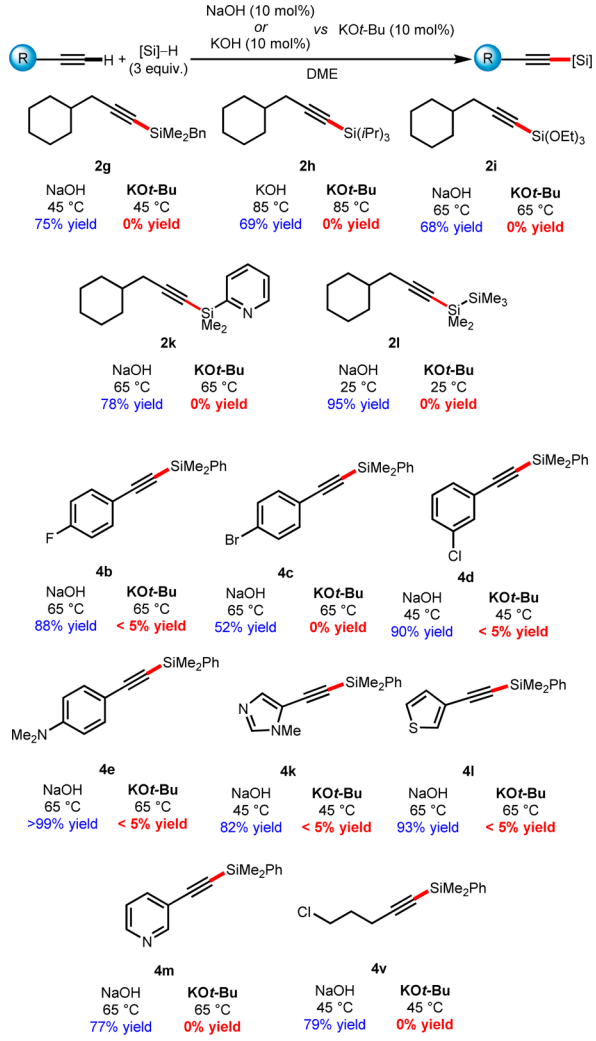
[a]Reactions were conducted on 0.5 mmol scale with 0.5 mL of solvent at the prescribed temperature and for the prescribed length of time. DME = 1,2-dimethoxyethane. Yields are determined by GC analysis using tridecane as an internal standard.

Nevertheless, it is becoming increasingly apparent that the identity of the base catalyst in this dehydrocoupling is unusually important and extends far beyond a simple consideration of basicity. For a number of substrates, we have directly compared several catalysts: KO*t*-Bu, which is an adept silylation catalyst in our recently reported cross-dehydrogenative C−H silylation of aromatic heterocycles and initially showed good reactivity for the title reaction (Table 1),[4a−c] and KOH and NaOH, which are exceptional catalysts for the silylation of C(*sp*)−H bonds in this report.

To perform this comparison, several alkyne substrates and silanes were subjected to the reaction using KO*t*-Bu as a catalyst, with the corresponding MOH-catalyzed reaction performed in parallel. In the reaction of cyclohexylpropyne **1** with triethylsilane, KO*t*-Bu successfully produced the silylated alkyne in moderate yield (recall Table 1, entry 1). However, in virtually all other investigated cases, KO*t*-Bu failed to convert the starting material or produced only trace quantities of the desired dehydrocoupling product (Table 2). These data were striking and unanticipated and suggest that the acetylinic silylation described in this report and the heterocyclic silylation described previously require different catalysts and very well may proceed via distinct mechanisms. These results also suggest that catalysts that do not lie within an optimal pK_a range (whether too basic or not basic enough) perform poorly; this in turn may explain why the superbase-catalyzed (i.e., MgO, KNH_2/Al_2O_3, $LiAlH_4$, *n*-BuLi, metal alkoxide) protocols discussed in the Introduction[13c−f] have suffered from such poor substrate scope.

Next, we were interested in directly comparing the reactivity of NaOH and KOH in the dehydrosilylation since during our evaluation of the hydrosilane scope (Scheme 2) we had observed that depending on the nature of the hydrosilane employed, either NaOH or KOH was preferred. In order to conduct a more detailed study of this phenomenon, we subjected a variety of hydrosilanes and alkyne substrates to the standard reaction conditions employing NaOH and KOH as the catalysts in parallel. These data, which are presented in Table 3, clearly demonstrate the marked difference in the reactivity of the substrates presented depending on the choice of alkali hydroxide employed. However, in our opinion, there appears to be no immediately discernible trend (i.e., basicity, aggregation states, solubilities) that explains the difference in the performance of the two catalysts. The differences between

Table 2. Comparison of Reactivity between KO*t*-Bu and Alkali Metal Hydroxide Catalysts[a]



[a]Reaction conditions are equivalent to those given in Schemes 2 and 3 for each particular hydrosilane and alkyne. Yields are of analytically pure isolated products. DME = 1,2-dimethoxyethane.

NaOH and KOH are most pronounced when using different silanes (Table 3, entries 1−6); however, most substrates studied performed better using NaOH, rather than KOH, except for the notable cases of the steroidal derivatives (entries 14 and 15), which displayed no silylation when using NaOH. To date, the nature of this remarkable effect is unclear and experimentation remains the best method to determine the optimal catalyst-substrate combination.

In conclusion, we have disclosed an alkali metal-hydroxide −catalyzed cross-dehydrogenative C(*sp*)−H silylation method. The chemistry proceeds under mild conditions and enables the direct synthesis of a wide array of useful alkynylsilanes, with high tunability in both the alkyne and hydrosilane, many of which are challenging to prepare by alternate means. The preliminary mechanistic studies and empirical results point to a mechanism that is likely distinct from previously disclosed cross-dehydrogenative C−H silylation reactions in general, including the recently reported KO*t*-Bu-catalyzed C(sp^2)−H silylation of heteroarenes.[4a−c] Although the mechanism currently remains elusive, it is likely that the presumed avoidance of conventional superbase, electrophilic silylation,

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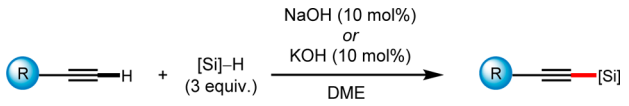
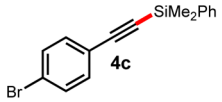
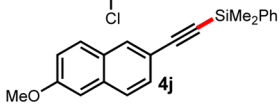
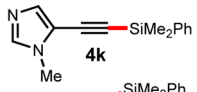
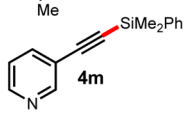
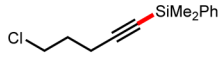
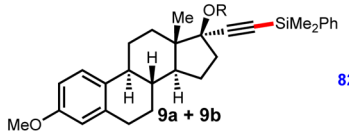
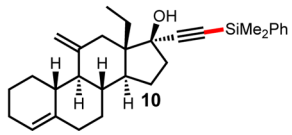
Table 3. Comparison of Reactivity between NaOH and KOH Catalysts[a]



Entry	Product	Yield KOH	Yield NaOH
1	[Si] = $SiEtMe_2$ (**2c**)	91%	14%
2	= $Si(n\text{-}Bu)_3$ (**2d**)	73%	22%
3	= $Si(i\text{-}Pr)_3$ (**2h**)	68%	0%
4	= $Si(i\text{-}Pr)_2Py$ (**2j**)	78%	0%
5	= $Si(OEt)_3$ (**2i**)	0%	68%
6	= $SiMe_2$–$SiMe_3$ (**2l**)	0%	95%
7	 **4c**	<5%	52%
8	 **4d**	38%	90%
9	 **4j**	12%	85%
10	 **4k**	19%	82%
11	 **4m**	7%	77%
12	 **4q**	0%	60%
13	 **4v**	0%	79%
14	 **9a + 9b**	82%	0%
15	 **10**	60%	0%

[a]Reaction conditions are equivalent to those given in Schemes 2 and 3 for each particular hydrosilane and alkyne. Yields are of analytically pure isolated materials. R = $PhMe_2Si$ (**9a**); R = H (**9b**). DME = 1,2-dimethoxyethane.

and C–H insertion mechanisms, which have been the focus of prior strategies, must be at least partly responsible for the title method's unprecedented scope and reactivity profile. Additionally intriguing is the dramatic effect of the nature of the basic catalyst on reaction outcome as evidenced by the difference in dehydrosilylation reactivity between alkali metal hydroxides and KO*t*-Bu and between NaOH and KOH. Detailed mechanistic studies by computational and experimental methods are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b12114.

Experimental details, analytics, and supporting experiments (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*rhg@caltech.edu

*stoltz@caltech.edu

ORCID

Alexey Fedorov: 0000-0001-9814-6726

Brian M. Stoltz: 0000-0001-9837-1528

Present Address

‡A.F.: Department of Chemistry and Applied Biosciences, ETH Zürich, Vladimir-Prelog-Weg 2, CH-8093, Zürich, Switzerland.

Author Contributions

†A.A.T. and K.N.B. contributed equally.

Notes

The authors declare no competing financial interest.

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