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Free-Radical-Promoted Site-Selective C−H Silylation of Arenes by Using Hydrosilanes

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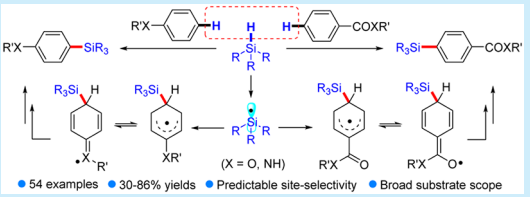
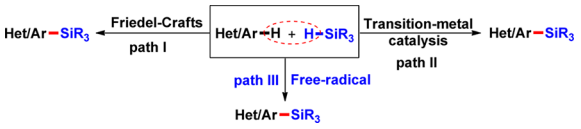
Supporting Information

ABSTRACT: A free-radical-promoted aryl/heteroaryl C−H silylation using hydrosilane was developed. This cross-dehydrogenative silylation enables both electron-rich and electron-poor aromatics to afford the desired arylsilanes in unique selectivity. A "*para*-selectivity" was observed by examination of over 54 examples. This exceptional orientation is quite different from that in Friedel−Crafts C−H silylation or transition-metal-catalyzed dehydrogenative silylation.



Organosilicon compounds find wide applications in synthetic chemistry, material, and polymer science.[1] Direct silylation of inert C−H bonds using hydrosilanes represents the most atom-economic and waste-minimizing access to organosilanes.[2] As depicted in Scheme 1, two main pathways through

Scheme 1. Accesses to Aryl and Heteroaromatic Silanes via C−H Silylation Using Hydrosilane



cross-dehydrogenative coupling (CDC)[3] reactions of arenes/heteroarenes with hydrosilanes have been explored to afford arylsilanes in recent years. One is the Friedel−Crafts C−H silylation via electrophilic aromatic substitution (SEAr).[4,5] Usually, only electron-rich aromatics could be smoothly silylated through this method. The other is the transition-metal-catalyzed dehydrogenative silylation.[6,7] Generally, *ortho*- and *meta*-silylation of aryl C−H bonds could be selectively achieved by this strategy. A directing group and noble metal catalysts as well as hydrogen acceptor are often required in these systems. There is, in fact, a third pathway to aryl C−H silylation. That is free-radical-promoted homolytic aromatic silylation.[8,9] It was considered unpractical because of very low yields and poor selectivities. Recently, Grubbs and Stoltz et al.[10] realized a series of highly efficient radical heteroaryl C−H silylations initiated by alkali metal oxides, which made a significant breakthrough in this area. Although this system is sensitive to oxygen and moisture and aromatics with electron-withdrawing groups were generally not tolerated in this chemistry, the features of unique selectivity, transition-metal-free, and mild conditions enable this radical silylation service to be an elegant alternative to path I and II.

It is well-known that the site-selectivity in radical reactions is unique, which is quite different from that in polar reactions.[11] For example, C2 silylation happened in radical-initiated reaction of indole with hydrosilane as reported by Grubbs.[10] Sila Friedel−Crafts reactions afford C3-silylated products.[4] Previous studies on radical-initiated homolytic aromatic alkylation showed special regioselectivity, which was called "*para*-selectivity".[12] It is believed that the resonance stabilization of the σ-complex might be responsible for this exceptional selectivity. As part of our continuous studies on free-radical-promoted C−Si bond formation,[13] we began to envision whether a similar "*para*-selectivity" could be observed in radical silylation of arenes. Fortunately, we successfully accomplished a direct C−Si bond formation via free-radical reaction of arenes/heteroarenes with hydrosilanes. Furthermore, a unique and predictable selectivity was observed in this homolytic aromatic silylation by examination of over 54 examples. To the best of our knowledge, it is the first time the "*para*-selectivity" in radical-promoted silylation of aryl C−H bond has been revealed.

Initially, we chose *N*-phenylacetamide and triethylsilane as the model compounds to evaluate the regioselectivity in aryl C−H silylation under free-radical initiation (Table 1). It was found that the Cu_2O was more efficient than Cu powder, CuBr, and $Fe(OAc)_2$, etc. (entries 1−5). In the case of the solvent, it seemed that only *t*-BuOH was effective (entries 6−8). Additionally, the peroxide DTBP (di-*tert*-butyl peroxide), used as the radical initiator, is more efficient than DCP (dicumyl peroxide) and BPO (benzoyl peroxide), etc. (entries 9 and 10). Finally, a good isolated yield of *N*-(4-(triethylsilyl)phenyl)acetamide was obtained as the unique product by using a catalytic amount of Cu_2O (entries 11 and 12). The ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra indicated that the *para*-silylation is dominant (>20:1).

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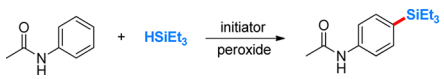
Table 1. Optimization of the Reaction Conditions[a]

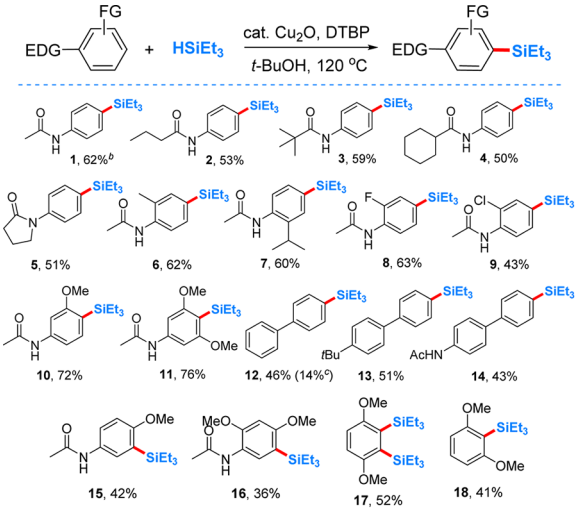


entry	initiator (mol %)	peroxide	solvent	yield[b] (%)
1		DTBP	*t*-BuOH	trace
2	Cu (10)	DTBP	*t*-BuOH	42
3	Cu_2O (10)	DTBP	*t*-BuOH	56
4	CuBr (10)	DTBP	*t*-BuOH	14
5	$Fe(OAc)_2$ (10)	DTBP	*t*-BuOH	trace
6	Cu_2O (10)	DTBP	DMF	NR
7	Cu_2O (10)	DTBP	DMSO	NR
8	Cu_2O (10)	DTBP	TFE	NR
9	Cu_2O (10)	DCP	*t*-BuOH	trace
10	Cu_2O (10)	BPO	*t*-BuOH	trace
11	Cu_2O (5)	DTBP	*t*-BuOH	62
12	Cu_2O (2)	DTBP	*t*-BuOH	51

[a]Reaction conditions: *N*-phenylacetamide (1 equiv, 0.1 mmol), $HSiEt_3$ (12 equiv, 1.2 mmol), peroxide (18 equiv, 1.8 mmol), solvent (0.5 mL), sealed tube, 120 °C (measured temperature of the oil bath), 12 h later, additional portions of $HSiEt_3$ (1.2 mmol) and peroxide (1.8 mmol) were added, refluxing for a further 12 h. [b]Isolated yield.

With the above optimized conditions in hand, we set out to investigate the substrate scope and the site selectivity of this system (Scheme 2). First a set of *N*-phenylalkylamides including

Scheme 2. Silylation of Electron-Rich Arenes with $HSiEt_3$[a]

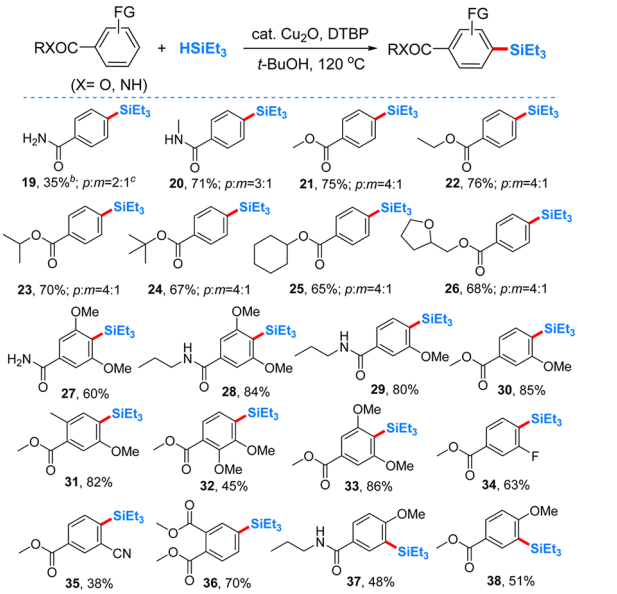


[a]Typical reaction conditions: arene (1 equiv, 0.1 mmol), $HSiEt_3$ (1.2 mmol), DTBP (1.8 mmol), Cu_2O (5 mol %), *t*-BuOH (0.5 mL), sealed tube, 120 °C (measured temperature of the oil bath), 12 h later, additional portions of $HSiEt_3$ (1.2 mmol) and DTBP (1.8 mmol) were added, refluxing for further 12 h. [b]Isolated yield. [c]4,4′-Bis(triethylsilyl)-1,1′-biphenyl.

1-phenylpyrrolidin-2-one were examined to be effective substrates, and all gave the desired *para*-silylated products in moderate to good yields (**1**–**5**). In these cases, no regioisomers were observed by NMR spectra. Next, a series of substituted *N*-phenylacetamides were screened (**6**–**11**). As a result, both *ortho*- and *meta*-substituted *N*-phenylacetamides afforded the corresponding *para*-silylation products. Then 1,1-biphenyl and its derivatives also reacted smoothly with triethylsilane to produce the expected [1,1′-biphenyl]-4-yltriethylsilanes (**12**–**14**). Finally, we examined several *para*-substituted arenes (**15**–**17**). *N*-(4-Methoxyphenyl)acetamide and *N*-(2,4-dimethoxyphenyl)-acetamide yielded *meta*-silylation products **15** and **16**, respectively. A 52% yield of (3,6-dimethoxy-1,2-phenylene)bis(triethylsilane) (**17**) was isolated by using 1,4-dimethoxybenzene. Surprisingly, 1,3-dimethoxybenzene gave **18** as the major product. Silylation occurred at a more hindered position in this case.

To further study the site-selectivity of this radical silylation of aryl C–H, a wide range of electron-deficient aromatics were tested. As demonstrated in Scheme 3, *para*-silylated arenes were

Scheme 3. Silylation of Electron-Poor Arenes with $HSiEt_3$[a]



[a]Typical reaction conditions. [b]Isolated yield. [c]The ratio of regioisomers were determined by ^1H NMR.

also isolated as the major products. Benzamide gave regioisomers in 35% yield with the ratio of p/m = 2/1 (**19**). while a 71% yield of isomers with p/m = 3/1 ratio was obtained with *N*-methylbenzamide (**20**). Gratifyingly, an array of benzoates afforded the products in high yields with p/m = 4/1 ratio (**21**–**26**). Variation of the structure of alcohol in esters could not affect the site-selective ratio. To our delight, *meta*-substituted benzamides and benzoates all generated the desired products in 38–86% yields, and the ratios of *para*/*meta* were up to 20/1 (**27**–**35**). Interestingly, dimethyl phthalate led to a unique silane in 70% yield (**36**). Similarly, *meta*-silylation occurred when the *para*-position of benzamide and benzoate was occupied (**37** and **38**).

In addition, various heterocycles were examined. As depicted in Scheme 4, heteroaromatics such as benzofuran, benzo[*b*]-thiophene, thiophene, indole, pyridine, and pyrrole were amenable to this system. The C2-silylation products were isolated in high yields with C3-substituted benzofurans, benzo[*b*]thiophenes, and thiophenes (**39**–**43**). In contrast, *N*-heterocycles afforded C3-silylated products (**44**–**47**). The possible reason for this C3-selectivity is unclear now, where silyl cation might be involved in these cases.

Finally, a series of hydrosilanes has been screened. It can be seen from Scheme 5 that both alkyl and aryl hydrosilanes are compatible with this system (**48**–**54**). Once again, *para*-silylated

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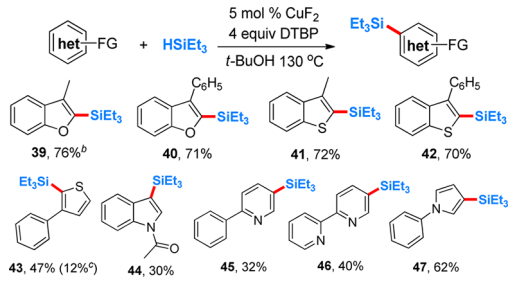
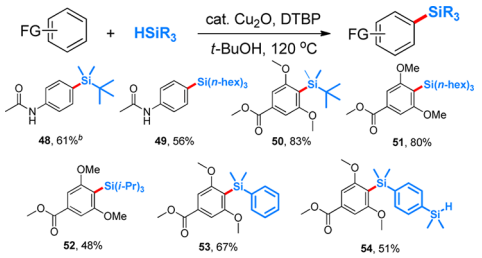
Scheme 4. Silylation of Heteroaromatics with $HSiEt_3$[a]



[a]Reaction conditions: heteroaromatics (1 equiv, 0.2 mmol), $HSiEt_3$ (2.0 mmol), CuF_2 (5 mol %), DTBP (0.8 mmol), *t*-BuOH (3 mL), 130 °C, 12 h. [b]Isolated yield. [c](3-Phenylthiophene-2,5-diyl) bis-(triethylsilane).

Scheme 5. Silylation of Aromatics with Hydrosilanes[a]

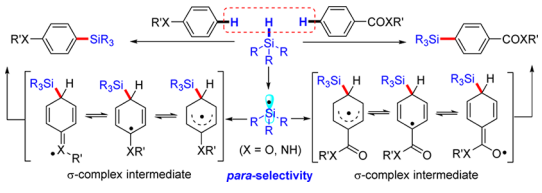


[a]Typical reaction conditions. [b]Isolated yield.

N-phenylacetamides and benzoates were isolated in moderate to high yields.

With these data in hand, we began to discuss the site-selectivity of this chemistry. Pioneering studies by Russell,[14] Giese,[15] and Tedder and Walton[16] et al. suggested that factors such as bond strength, polarity, stereoelectronic effects, and steric effects are critically important to govern the reactivity and orientation of free-radical addition reactions. As mentioned above, previous investigations on homolytic aromatic alkylation indicated a "*para*-selectivity" was found in these reactions.[12] The site-selectivity largely depends on the resonance stabilization of the σ-complex. Clearly a similar "*para*-selectivity" was observed in this radical-promoted aryl C−H silylation. It can be seen from Scheme 6 that the σ-complex intermediates would be formed by

Scheme 6. *Para*-Selectivity in Radical-Promoted Aryl C−H Silylation



addition of the silyl radical to arenes. Although both the *para*- and *ortho*-addition could lead to efficient delocalization that thus stabilize the radical intermediates, *para*-addition would occur prior to *ortho*-addition due to the steric effect. When there is *para*-substituent on the aromatic core, *meta*-addition would occur due to the collective effects of hindrance and polarity.[17]

The silyl-substituted arenes generated from this radical process are known to undergo a variety of powerful synthetic transformations. A number of representative examples are demonstrated here (Figure 1). Diverse transformations from arylsilanes to aryl halides, phenols, and biaryls were achieved by halogenation reactions, oxidation reactions, and cross-coupling reactions.

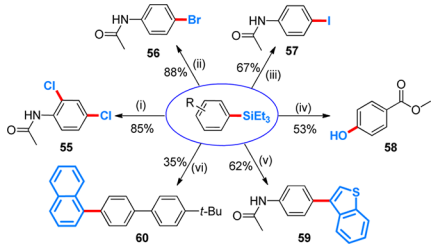
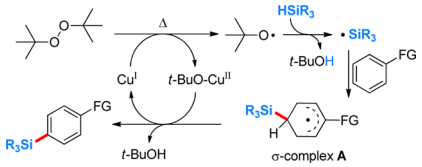


Figure 1. Transformation of the arylsilane products. Reaction conditions: (i) **1** (1 equiv), NCS (5 equiv), N_2, CH_3CN, 40 °C; (ii) **1** (1 equiv), NBS (5 equiv), N_2, CH_3CN, rt; (iii) **1** (1 equiv), NIS (5 equiv), N_2, CH_3CN, rt; (iv) **21** (1 equiv), 5 mol % $Pd(OAc)_2$, $PhI(OCOCF_3)_2$ (1.5 equiv), AcOH, 100 °C; H_2O, 100 °C; (v) Benzo[*b*]thiophene (1 equiv), **1** (2 equiv), 5 mol % of $PdCl_2(CH_3CN)_2$, $CuCl_2$ (2 equiv), N_2, toluene, 100 °C; (vi) naphthalene (1 equiv), **13** (2 equiv), 5 mol % $PdCl_2$, $CuCl_2$ (4 equiv), DCE, 120 °C

On the basis of the above results and previous reports, a plausible mechanism for the present process is proposed and shown in Scheme 7. Initially, heterolysis of the O−O bond in

Scheme 7. Proposed Mechanism



peroxide by Cu(I) would afford *tert*-butoxyl radical and Cu(II) species. Hydrogen abstraction from the hydrosilane by *t*-BuO radical gives *t*-BuOH and a silyl radical, which then adds to arene leading to the σ-complex intermediate **A**. Finally, direct hydrogen-atom transfer from **A** to *tert*-butoxyl radical forms the product, or single-electron oxidation of **A** by Cu(II) would generate a radical anion, which then deprotonates by *tert*-butoxyl anion performs to produce *t*-BuOH and arylsilane. Meanwhile, the Cu(I) is regenerated to enter the next reaction cycle.

In summary, a Cu/peroxide-promoted free-radical aryl/heteroaryl C−H silylation is developed. It allows a site-selective and predictable access to various arylsilanes. Additionally, the experimental results indicated that a "*para*-selectivity" was found in this homolytic aromatic silylation. The exceptional selectivity enables this radical silylation to be an attractive strategy for C−Si formation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02717.

Experimental procedures, characterization, and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

In memory of Prof. You-Cheng Liu.

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