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Site-Selective Silylation of Aliphatic C–H Bonds Mediated by [1,5]-Hydrogen Transfer: Synthesis of *α*-Sila Benzamides

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Supporting Information

ABSTRACT: The first example of site-selective silylation of $C(sp^3)$–H bonds mediated by a [1,5]-hydrogen transfer is reported. This reaction occurs selectively at the *α*-position of benzamides with a combination of *tert*-butylmagnesium chloride and a catalytic amount of 4,4′-di-*tert*-butylbipyridine (dtbpy) ligand and provides a facile route for the creation of biologically interesting *α*-sila benzamides. Late-stage functionalization of the incorporated silyl moieties facilitates the synthesis of *N*-formyl, *cis*-enamine, *β*-hydroxyl, amino, and pyrrole-containing derivatives.

The unique reactivity, low toxicity, stability, and pharmacological properties of silicon-containing compounds make them useful in synthetic[1] and medicinal chemistry[2] as well as in materials science.[3] For example, compounds **I**–**IV** containing a silyl moiety at the *α*-position of a benzamide (Figure 1) can be utilized as angiotensin-converting enzyme inhibitors (ACEIs) for the treatment of hypertension.[4] In particular, the silyl moiety can serve as a synthetic handle that facilitates library synthesis by its direct functionalization.[5]

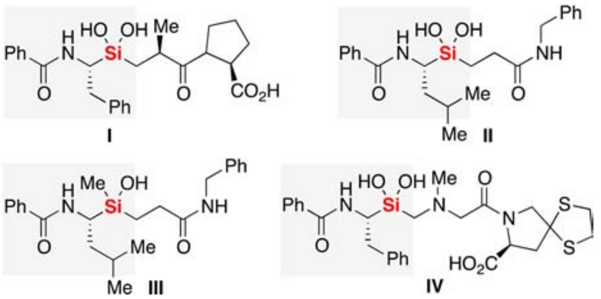
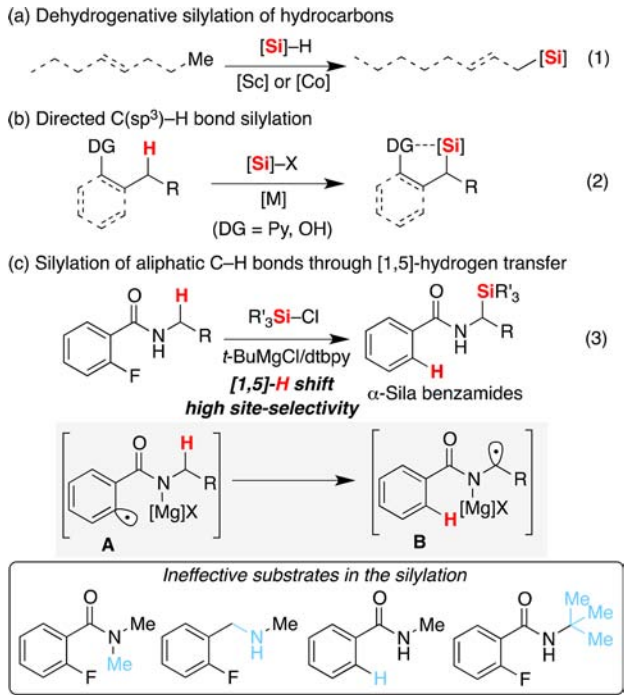


Figure 1. Examples of *α*-sila benzamide-bearing bioactive molecules as angiotensin-converting enzyme inhibitors.

One of the most powerful strategies for the synthesis of organosilicon compounds is the silylation of C–H bonds.[6,7] However, in contrast to the significant achievements in the construction of $C(sp^2)$–Si bonds from aromatic C–H bonds,[8–10] the silylation of aliphatic C–H bonds is less developed.[11] Dehydrogenative silylation incorporates a silyl moiety directly into hydrocarbons (Scheme 1, eq 1).[12] By introducing a pyridyl chelation auxiliary, Kakiuchi pioneered the silylation of benzylic C–H bonds (a general directed strategy is shown in Scheme 1, eq 2).[13,14] Hartwig and coworkers demonstrated that (hydrido)silyl ethers can be generated in situ and serve as directing groups to achieve the silylation of $C(sp^3)$–H bonds.[15] Despite the progress, reactions involving aliphatic C–H bond silylation remain rather limited.

Scheme 1. Strategies for Silylation of Aliphatic C–H Bonds



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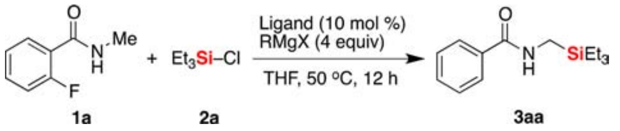
There is no methodology that can install a silyl moiety at the α-position of heteroatoms via C(sp^3)−H bond functionalization. Since its discovery by Curran,[16] the functionalization of a remote C(sp^3)−H bond through a [1,5]-hydrogen transfer has provided a useful tool for the construction of synthetically appealing molecules, generally by mechanisms involving radical intermediates.[17,18] Here we report the site-selective silylation of C(sp^3)−H bonds mediated by a [1,5]-hydrogen transfer, allowing the construction of C−Si bonds specifically at the α-position of benzamides to form α-sila benzamides (Scheme 1, eq 3).

At the outset, we assumed that the selection of a suitable metal to chelate the amidyl group would be vital for achieving the α-silylation of benzamides. The metal was expected to help abstract the *o*-halide to generate a persistent aryl radical species **A**, thus inducing the hydride shift (Scheme 1, eq 3). Because main-group metals such as magnesium possess a unique capacity to activate fluoride,[19] commercially available *tert*-butylmagnesium chloride was treated in the reaction of 2-fluorobenzamide **1a** with chlorotriethylsilane (Table 1, entry 1).

Table 1. Optimization of the Reaction Conditions[a]



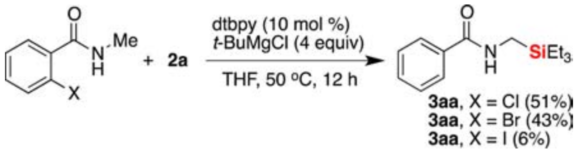
entry	ligand	RMgX	yield of **3aa** (%)
1	–	*t*-BuMgCl	12
2	Phen	*t*-BuMgCl	16
3	Bpy	*t*-BuMgCl	32
4	6,6′-Me_2bpy[b]	*t*-BuMgCl	37
5	4,4′-$(OMe)_2$bpy[c]	*t*-BuMgCl	44
6	dtbpy	*t*-BuMgCl	76
7	TMEDA	*t*-BuMgCl	13
8	dtbpy	*i*PrMgCl	20
9	dtbpy	CyMgCl	28
10	dtbpy	EtMgBr	14
11	dtbpy	MeMgBr	nd[d]
12	dtbpy	$TMSCH_2MgCl$	nd[d]
13	dtbpy	PhMgBr	nd[d]

[a] Conditions: **1a** (0.2 mmol), **2a** (0.8 mmol), ligand (0.02 mmol), RMgX (0.8 mmol), THF, 50 °C, 12 h. [b] 6,6′-Dimethyl-2,2′-bipyridine. [c] 4,4′-Dimethoxy-2,2′-bipyridine. [d] Not detected.

Encouragingly, under these conditions we obtained the desired α-sila benzamide **3aa** in 12% yield. Interestingly, the addition of 10 mol % 1,10-phenanthroline (phen) to the system increased the reaction rate slightly (Table 1, entry 2). Inspired by this result, we explored the effect of bidentate nitrogen ligands on the conversion. In particular, 4,4′-di-*tert*-butylbipyridine (dtbpy) greatly promoted the silylation, giving **3aa** in 76% yield (Table 1, entry 6). The coupling reaction of the Grignard reagent with the C−F bond did not occur. Furthermore, isoindolinone, which may be derived from the cyclization of radical **B**, was not detected (Scheme 1, eq 3).[20] Decreasing the amount of *t*-BuMgCl led to lower yields (see the Supporting Information for details). In addition to serving as a base in the deprotonation of benzamide, we assumed that another 2 equiv of *t*-BuMgCl might be consumed for the C−F bond dissociation and C−Si bond formation. It was found that isopropyl, cyclohexyl, and ethyl Grignard reagents did not increase the level of conversion (Table 1, entries 8−10). However, silylation with MeMgBr, $TMSCH_2MgCl$, or PhMgBr was inhibited, indicating that β-hydride elimination to form an active magnesium species can be considered (Table 1, entries 11−13).

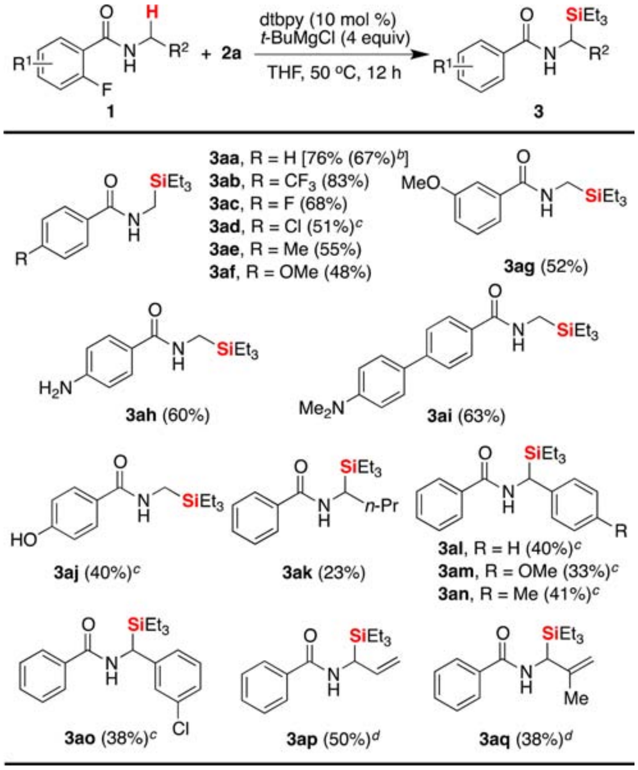
The reactions with 2-fluoro-*N*,*N*-dimethylbenzamide and 1-(2-fluorophenyl)-*N*-methylmethanamine did not take place, and the fluoride moiety was maintained in these molecules (Scheme 1c). These results show that chelation of magnesium to the amidyl group after the deprotonation is required for fluoride activation.[21] Furthermore, the fluoride substituent on *N*-(*tert*-butyl)-2-fluorobenzamide was retained. Silylation with 2-chloro-, 2-bromo-, and 2-iodo-substituted *N*-methylbenzamides gave inferior results (Scheme 2).

Scheme 2. Silylation of 2-Halide-Substituted Benzamides



We then turned our attention to probing the substrate scope for the creation of functionalized α-sila benzamides (Scheme 3). 2-Fluorobenzamides containing CF_3, F, Cl, Me, or OMe substituents on the aromatics underwent the silylation effectively, forming α-sila benzamides **3ab**−**ag** in moderate to good yields. Appealing functionalities such as amino and

Scheme 3. Site-Selective Silylation of Aliphatic C−H Bonds at the α-Position through [1,5]-Hydrogen Transfer[a]



[a] Conditions: **1** (0.2 mmol), **2a** (0.8 mmol), dtbpy (0.02 mmol), *t*-BuMgCl (0.8 mmol), THF, 50 °C, 12 h. [b] The reaction was conducted on a 10 mmol scale. [c] *t*-BuMgCl (1.2 mmol). [d] **1** (0.5 mmol).

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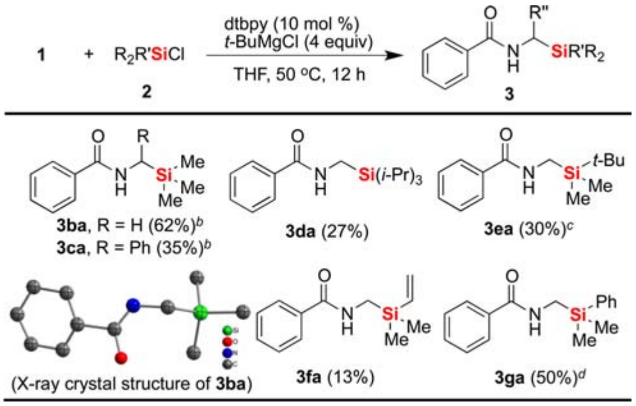
hydroxyl groups were well-tolerated under the reaction conditions (**3ah−aj**). In addition to the functionalization of primary C−H bonds, unactivated secondary C−H bonds were also silylated to produce tertiary C−Si bonds (**3ak−ao**).[22] The compatibility of double bonds with the reaction conditions enabled the silylation of allylic C−H bonds, providing a straightforward construction of γ-silyl-containing allyl scaffolds (**3ap** and **3aq**), which are important building blocks for the total synthesis of cyclic peptides TMC-95A; the synthesis of such motifs previously required a multiple-step reaction sequence.[23] Several silane electrophiles were then examined. Diverse substituted organosilicon functionalities were incorporated in a site-selective manner at the α-position of the benzamide (Scheme 4).[24] The silylation proceeded smoothly on a gram scale to give **3aa** in 67% yield (Scheme 3).

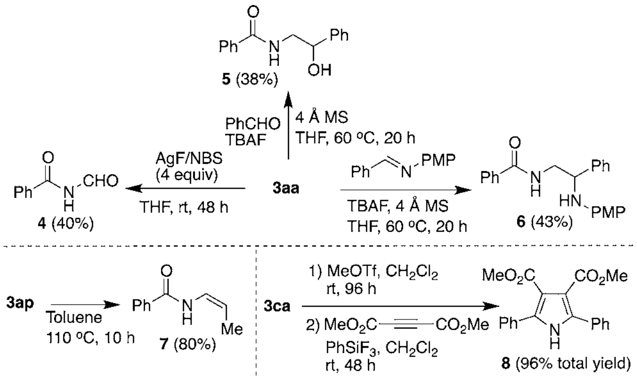
Scheme 4. Synthesis of α-Sila Benzamides[a]



[a]Conditions: **1a** (0.2 mmol), **2** (0.8 mmol), dtbpy (0.02 mmol), *t*-BuMgCl (0.8 mmol), THF, 50 °C, 12 h. [b]TMSCN was used. [c]Me_2(*t*-Bu)SiOTf was used. [d]**1a** (0.5 mmol).

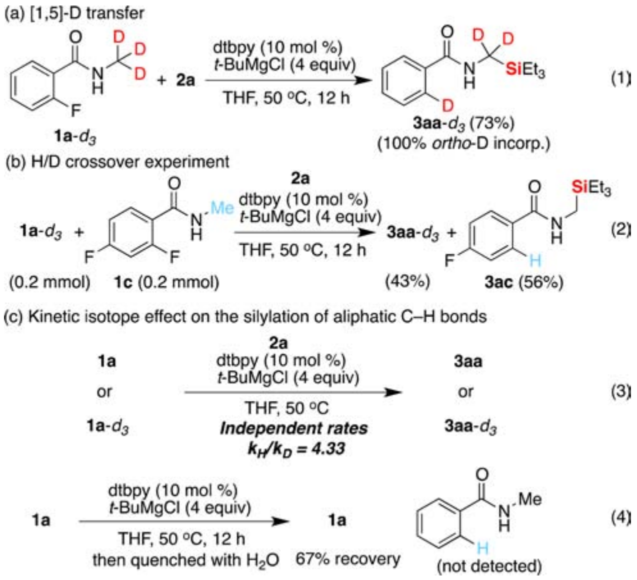
The installed organosilicon motifs are amenable to transformation by late-stage functionalization. In the presence of AgF and NBS, conversion of the silylmethyl moiety into the corresponding aldehyde functionality proceeded smoothly to give *N*-formylbenzamide (**4**) (Scheme 5).[25] Direct additions of α-sila benzamide **3aa** to benzaldehyde and an aromatic imine gave β-hydroxyl- and amino-substituted compound **5** and **6**, respectively.[26] Heating α-silyl *N*-allylbenzamide **3ap** in toluene enabled the preparation of *cis*-enamide compound **7**.[27] Furthermore, multiply substituted pyrrole **8** could be synthesized from **3ca**.[28]

Scheme 5. Functionalization of α-Sila Benzamides



The [1,5]-hydrogen transfer in the silylation was then examined by conducting deuterium experiments with *N*-methyl-deuterated benzamide. It was found that almost 100% of the deuterium was incorporated at the *ortho* position of the product **3aa**-d_3 (Scheme 6, eq 1). Moreover, no intermolecular H/D exchange was detected in H/D crossover experiments (Scheme 6, eq 2), thus providing further evidence for the intramolecular hydride shift process. To measure the initial reaction rates, kinetic isotope effect (KIE) studies with two separate reactions of nondeuterated **3aa** and deuterated **3aa**-d_3 were performed (Scheme 6, eq 3). The results indicated that cleavage of the α-C(sp^3)−H bond, with a KIE value of 4.33, can be considered as the turnover-limiting step. Notably, the *o*-C−F bond on the benzamide was not cleaved without the assistance of chlorosilane (Scheme 6, eq 4).

Scheme 6. Mechanistic Studies



In summary, we have developed a novel silylation of aliphatic C−H bonds that proceeds through a [1,5]-hydrogen transfer. The approach provides a site-selective and scalable method to construct C−Si bonds at the α-position of benzamides, expanding the hydride transfer reactions beyond the construction of C−C, C−O, and C−N bonds. Through the combined use of a catalytic amount of dtbpy ligand and *tert*-butylmagnesium chloride, primary and secondary C−H bonds were silylated in a site-specific manner to form α-sila benzamides, which can be further utilized as building blocks in synthesis by functionalization of the incorporated silyl scaffolds. Additional efforts to elucidate the reaction mechanism with the help of theoretical studies are underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02784.

Detailed optimization data; experimental procedures; characterization data for all new compounds; ORTEP drawing and crystallographic data for **3ba** (PDF)
Crystallographic data for **3ba** (CIF)

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Notes

The authors declare no competing financial interest.

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