Modular synthesis of 2-furyl carbinols from 3-benzyl-dimethylsilylfurfural platforms relying on oxygen-assisted C–Si bond functionalization

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Introduction
Progress towards the use of nonedible renewable feedstock to replace fossil resources as starting material for high-value chemicals is an important endeavor of modern synthesis [1-3]. As part of this effort, exploitation of furfural and corresponding derivatives attracts continuous attention [4-7]. In this area, we have actively investigated catalytic C–H activation reactions [8-14], and as part of this work, we have recently developed an iridium-based protocol for the catalytic C3–H silylation of furfurylimines [15]. This method allows to install a C–Si bond poised for further functionalization on the furfural unit, and thereby leads to synthetic platforms useful to access elaborated furans. This prospect was demonstrated with platforms relying
on the SiMe(OSiMe$_3$)$_2$ unit, which were readily converted through Pd- or Cu-catalyzed electrophilic substitution reactions into an array of furfurals decorated at C3 with carbon- or heteroatom-containing substituents (Scheme 1). Conversely, all of our subsequent efforts to achieve cross-coupling reactions from C3-silylated furfurals with triorganosilane units have failed so far.

2-Furyl carbinols represent a useful class of furanic synthetic intermediates that have given rise to a number of synthetically relevant transformations, such as the Piancatelli and aza-Piancatelli reactions [16,17] or the Achmatowicz rearrangement [18]. Addition reactions of nucleophiles to the C–O double bond of furfurals represent an obvious synthetic approach to 2-furyl carbinols. We reasoned that for carbinols derived from C3-triorganosilyl-substituted furfurals, the OH unit could be exploited to assist C–Si bond activation [19]. Therewith, C3-triorganosilyl-substituted furfurals could be suitable platforms to develop a two-step modular approach to 3-substituted 2-furyl carbinols, entailing nucleophilic addition to the aldehyde function and oxygen-assisted electrophilic substitution of the C–Si bond (Scheme 1).

Results and Discussion

Synthesis of 3-silylated 2-furyl carbinols

C3-silylated furfurals 1a–c and 2c are accessible from furfural or 5-methylfurfural [20], respectively, according to our previously reported protocol for selective catalytic C3 silylation [15]. The addition of organolithium [21] or Grignard reagents [22,23] to these substrates was uneventful and allowed for the preparation of 2-furylalkyl (see 3a–c, 4c), -aryl (see 5c, 6c), and -allyl carbinols (see 7c) having furan rings with various triorganosilyl substituents at C3 in a synthetically useful yield and on an appropriate scale (Scheme 2).

With the 3-silylated 2-furyl carbinol substrates at hand, we then considered C–Si bond activation strategies relying on the assistance of the oxygen atom to promote electrophilic substitution reactions with carbon electrophiles.
C3–Si bond functionalization through intramolecular activation by alkoxides

We first contemplated the possibility to promote C3–Si bond functionalization through intramolecular activation by alkoxides [15]. It was reported that lithium alkoxides A undergo 1,4-silyl migration (Brook rearrangement) to generate C2-lithiated furans C, which in turn can react in the presence of electrophiles to deliver product D, resulting from the overall C2–Si functionalization (Scheme 3, top) [24,25]. The key to the viability of this process is the formation of pentavalent silicon intermediate B. This suggested that a related pentavalent intermediate F could be similarly accessible from E, and thus affording the C3-lithiated furan derivative G upon 1,4-silyl migration as well as the electrophilic substitution product H in the presence of an appropriate electrophile (Scheme 3, bottom).

However, treatment of aldehyde 1b with n-BuLi, followed by addition of benzaldehyde in THF/DMPU [25], afforded only the addition product 3b without any detectable formation of product 9, expected from 1,4-silyl migration/electrophilic substitution of 8 (Scheme 4, top).

Conversely, treatment of alcohol 3a with t-BuOCu in the presence of allyl chloride, according to conditions developed by Takeda et al. for the reaction of γ-trimethylsilyl-substituted allylic alcohols [26,27] or ortho-silylated aryl carbinols [28], did provide C3-functionalized compound 10, albeit in very low yield (6%) and along with the O-allylated product 11 (11%), as well as products 12 (4%) and 13 (4%) [29] (Scheme 4, bottom). In spite of extensive experimentation to find better conditions, this result could not be improved.

Nevertheless, important information came from an experiment involving furyl carbinol 4c, having a benzyltrimethylsilyl unit (Scheme 5). Here, treatment with t-BuOCu-Li in the presence of benzaldehyde led to the formation of adduct 14 (in 75% yield), which arose from the addition of a benzyl carbanion 17 to benzaldehyde. The generation of such a nucleo-

Scheme 3: C–Si bond functionalization of 2,3-disubstituted furyl carbinols by 1,4-silyl migration.

Scheme 4: Attempts of C3–Si bond functionalization promoted by intramolecular activation via alkoxide.
phile strongly suggests the formation of pentavalent silicon intermediate 15 \[27\], which then produced a (stabilized) benzylic carbanion (by exocyclic cleavage) rather than a 3-furanyl anion (by endocyclic cleavage). As a consequence, the failure to promote C3–Si activation of intermediates E (SiR3 = SiEt3 or SiMe2t-Bu) according to our initially envisaged scenario depicted in Scheme 3, did not seem to be related to the difficulty to form pentavalent silicon intermediates F. Instead, the reason was probably a too low intrinsic stability of C3-lithiated furans G, which thwarted 1,4-silyl migration. Conversely, this experiment provided evidence that cyclic siloxanes (e.g., 16), which are potential nucleophilic partners for cross-coupling chemistry \[30,31\], could be accessed from 2-[(3-benzyl(dimethyl)silyl)furyl] carbinol.

**Scheme 5: Alkoxide-promoted cyclic siloxane formation from 2-[(3-benzyl(dimethyl)silyl)furyl] carbinol 4c.**

**C3–Si bond functionalization through siloxane formation**

In an attempt to isolate cyclic siloxane 16, we then considered a protocol reported by Anderson and co-workers to prepare cyclic siloxanes by debenzylation/cyclization of benzyl(dimethyl)silyl-substituted allylic alcohols \[32\]. To that end, carbinol 4c was treated with TBAF·3H2O (1.0 equiv), which resulted in the formation of 16 in 86% yield (along with toluene, Scheme 6). Alkene 5-membered cyclic dimethyl(alkenyl)siloxanes, 16 was found to be highly sensitive towards silica gel column chromatography, and all of our attempts to isolate it failed. For this reason, we went on to consider C3–Si functionalization strategies of alcohols 4c–7c relying on the formation of cyclic siloxanes and subsequent in situ cross-coupling.

We first briefly investigated Pd-catalyzed arylation reactions (Scheme 7). Fluoride-promoted arylation reactions of benzyl(dimethyl)(alkenyl)silanes have been reported, and it is established that they proceed through the cleavage of the benzyl moiety from the benzyl(dimethyl)silyl groups, leading to either dimethylsilanols or cyclic siloxanes (as for substrates with pending hydroxy units) \[32-35\]. To the best of our knowledge, no analogous cross-coupling reactions from aryl- or heteroaryl-substituted benzyl(dimethyl)silanes have been disclosed. We were thus delighted to find that using Pd2(dba)3 as precatalyst (2.5 mol %) in combination with Cul (20 mol %), cross-coupling between 4c and iodobenzene was achieved, giving 18 in reasonably good yield (70%). 4-Iodoanisole could also be coupled (giving 19 in 57% yield), but not electron-deficient 1-iodo-4-nitrobenzene. At this point, it should be mentioned that treatment of aldehyde 2c under the same reaction conditions led predominantly to decomposition products and only 5-methylfurfural (resulting from protodesilylation) was recovered in low yield (~20%). Hence, intramolecular hydroxy activation seems decisive to obtain productive cross-coupling reactions with this system. Also, it is important to underscore that the copper cocatalyst was crucial for the success of this transformation as without, only protodesilylation products were obtained. This behavior is in contrast to that of dimethyl(alkenyl)dimethyilsiloxanes, which do not require copper to undergo cross-coupling \[30,32\].

**Scheme 6: TBAF-promoted cyclic siloxane formation from 2-[(3-benzyl(dimethyl)silyl)furyl] carbinol 4c.**

This requirement for copper prompted us to test copper-catalyzed C(sp2)–C(sp3) cross-coupling reactions, as reported by Takeda et al., to achieve allylation reactions of benzyl(dimethyl)(alkenyl)silanes [36]. Treatment of 4c with methallyl chloride in the presence of TBAF·(t-BuOH)4 (2.4 equiv), Cul
Investigating the scope of this transformation (Scheme 8), we established that the reaction performed well with other 5-methylfuryl carbinols. As such, products 23 and 24, arising from phenyl- and allyl-substituted substrates 6c and 7c, respectively, were isolated in 56% and 65% yield, respectively. Somewhat lower yields were noted with butyl- and phenyl-substituted carbinols 3c and 5c, respectively, bearing C5-unsubstituted furan rings, which gave products 25 and 26 in 42% and 40% yield, respectively. Electrophiles other than methallyl chloride could also be used. C3-Allylation of substrate 4c, leading to 27, was achieved in 52% yield by reaction with allyl chloride and in a better 61% yield using allyl bromide. It should be mentioned that competing protodesilylation could not always be fully suppressed in the above described reactions. Furthermore, purification was troublesome for products 25–27, which could only be isolated in the presence of the protodesilylated side products (see Supporting Information File 1 for details). We also contemplated the use of alkyl iodides as electrophiles. Methylation with methyl iodide was efficient, as shown through the preparation of 28 in 61% yield from 4c. In contrast, higher alkyl iodides, such as ethyl iodide, failed to provide the alkylated products (i.e., 29) and only protodesilylation was observed (even at 50 °C).

Conclusion

In conclusion, we have shown that 3-silylated 2-furyl carbinols are readily accessible in three steps from furfural and 5-methyl-furfural, and the hydroxy unit of these adducts can be used to

| Table 1: Optimization of the reaction conditions for Cu-catalyzed methallylation of 2-[(3-benzyldimethylsilyl)furyl] carbinol 4c. |
|---|---|---|---|---|---|
| entry | Cu source | ligand | conditions | 21<sup>a</sup> (%) | 22<sup>a</sup> (%) |
| 1 | Cul (1.5 equiv) | P(OEt)<sub>3</sub> (1.5 equiv) | DMF, 24 h | 68 | 9 |
| 2<sup>b</sup> | Cul (1.5 equiv) | P(OEt)<sub>3</sub> (1.5 equiv) | DMF, 24 h | 38 | 32 |
| 3<sup>c</sup> | Cul (1.5 equiv) | P(OEt)<sub>3</sub> (1.5 equiv) | DMF, 24 h | 41 | 20 |
| 4 | Cul (1.5 equiv) | P(OEt)<sub>3</sub> (1.5 equiv) | DMF, 2 h | 68 | 0 |
| 5 | Cul (1.5 equiv) | — | DMF, 2 h | 40 | 23 |
| 6 | Cul (1.5 equiv) | PPh<sub>3</sub> (1.5 equiv) | DMF, 2 h | 80 | 0 |
| 7 | Cul-PPh<sub>3</sub> (1.5 equiv) | | DMF, 2 h | 79 (65)<sup>d</sup> | 0 |
| 8 | Cul-PPh<sub>3</sub> (1.5 equiv) | | THF, 2 h | 71 | 20 |
| 9 | Cul-PPh<sub>3</sub> (20 mol %) | | DMF, 2 h | 84 (78)<sup>d</sup> | 0 |

<sup>a</sup>Yield measured prior to purification by <sup>1</sup>H NMR analysis using Me<sub>2</sub>SO as internal standard. <sup>b</sup>TBAF-(t-BuOH)<sub>4</sub> (1.2 equiv) was used. <sup>c</sup>TBAF (1 molar solution in THF, 2.4 equiv) was used. <sup>d</sup>Isolated yield.
promote C(sp^2)–Si bond functionalization. Although intramolecular activation by alkoxides did not prove useful, C3–Si bond functionalization is achieved from benzyl-dimethylsilyl units upon siloxane formation in the presence of TBAF. Protocols for fluoride-promoted Pd/Cu-catalyzed arylation, as well as Cu-catalyzed allylation and methylation, have been developed. Overall, we have demonstrated that C3-benzyl-dimethylsilyl-appended furfurals are useful platforms that offer modular access to 3-substituted 2-furyl carbinols. This strategy represents a new, simple, and selective way to decorate the biomass-derived furan nucleus, allowing to reach synthetically relevant building blocks.

**Experimental**

**Procedure for the addition of n-BuLi to C3-silylated furfurals (preparation of compounds 3a–c and 4c)**

In a flame-dried round-bottom flask under argon was placed the appropriate C3-silylated furfural [15] and dissolved in freshly distilled THF (0.3 M). The solution was cooled to −78 °C, and then n-BuLi (1.2 equiv in hexane) was added dropwise. The reaction mixture was allowed to stir at −78 °C for 30 min and then quenched with aq saturated NH_4Cl/NH_3 2:1 solution. Et_2O was added, and the aqueous layer was extracted three times. The combined organic layer was washed with brine, dried over MgSO_4, filtered, concentrated under reduced pressure, and purified by silica gel column chromatography.

**Procedure for the addition of Grignard reagents to C3-silylated furfurals (preparation of compounds 5c, 6c, and 7c)**

In a flame-dried round-bottom flask under argon was placed the appropriate C3-silylated furfural [15] and dissolved in freshly distilled THF (0.2 M solution). The solution was cooled to 0 °C, and then the Grignard reagent (1.3 equiv in Et_2O) was added dropwise (the rate of addition was equal to, or lower than 0.125 mL/min). The reaction mixture was allowed to stir at 0 °C for 1 h and then allowed to reach room temperature. Upon consumption of the starting material, the reaction mixture was quenched with saturated NH_4Cl. CH_2Cl_2 was added, and the aqueous layer was extracted three times using CH_2Cl_2. The combined organic layer was dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by silica gel column chromatography.

**Procedure for the Pd/Cu-catalyzed arylation of C3-benzyl(dimethyl)silyl-substituted 2-furyl carbinol 4c (preparation of compounds 18 and 19)**

A flame-dried Schlenk tube was charged with CuI (20 mol %) and Pd_2(dba)_3 (2.5 mol %) and heated gently under vacuum using a heat gun. In another Schlenk tube, the appropriate iodoarene (1.5 equiv) and 4c (1 equiv) were dissolved in freshly distilled THF (0.63 mL). The solution was degassed in three freeze–pump–thaw cycles, and degassed anhydrous TBAF (1 M in THF, 2.2 equiv) was added. The mixture was allowed to stir for 10 min at 0 °C and transferred via cannula to the Schlenk tube containing the catalytic mixture. The resulting mixture was stirred for 2 h at rt, then filtered through a short pad of silica gel, and concentrated. The residue was purified by silica gel column chromatography.

**Procedure for the Cu-catalyzed allylation and methylation of C3-benzyl(dimethyl)silyl-substituted 2-furyl carbinols (preparation of compounds 21 and 23–28)**

Cul–PPh_3 [37] (20 or 120 mol %) was introduced to a flame-dried microwave vial, which was then placed under an argon at-
mosphere and sealed. In a Schlenk tube, the appropriate C3-benzylidemethylsilyl-substituted 2-furyl carbom (0.3 mmol, 1 equiv) was dissolved in CH2Cl2 (1 mL), concentrated under reduced pressure, and placed under argon. DMF (3.0 mL) was then added, and the solution was degassed in three freeze–pump–thaw cycles. TBAF(–BuOH)4 [38] (402 mg, 0.72 mmol) was then added along with the corresponding electrophile (3 equiv). The mixture was stirred for 2–3 min at rt and then cannulated into the vial containing the copper complex. The mixture was stirred for 2 h at 30 °C and then quenched with aq KOH (6 M, 1 mL). The mixture was extracted with cyclohexane/CH2Cl2 9:1 (4 × 10 mL), and the combined organic layer was washed with water (10 mL), dried over MgSO4, and concentrated under reduced pressure. The residue was purifed by silica gel column chromatography.

### Supporting Information

#### Supporting Information File 1

General information, characterization data, and copies of NMR spectra.

[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-18-131-S1.pdf](https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-18-131-S1.pdf)

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