C3–H Silylation of Furfural Derivatives: Direct Access to a Versatile Synthetic Platform Derived from Biomass

Sebastien Curpanen,[a] Giovanni Poli,[a] Alejandro Perez-Luna,*[a] and Julie Oble*[a]

Abstract: The sustainable production of industry-relevant chemicals, ranging from biofuels to pharmaceuticals, requires the development of efficient functionalization of biomass-derived building blocks, such as furan derivatives. Herein we report directed iridium-catalyzed C3–H silylation of furfural compounds, which grants access to versatile synthetic platforms. This transformation was developed on furfuryl derivatives, using imines as directing groups, and trialkylsilanes or bis(trimethylsilyl)methylsilane as silylating agents, in the presence of a hydride scavenger. Subsequently, fluoride-mediated activation strategies were applied to the C3–SiMe(OSiMe3)2 furfural derivatives. This strategy enables a wide range of transformations, namely arylation, alkenylation, alkynylation, allylation and alkylation, as well as halogenation and trifluoromethylation. A variety of high value-added products were thus easily obtained from the same common C3-silylated furfural platform.

Introduction

The preparation of building-block intermediates and value-added compounds from lignocellulosic nonedible biomass rather than from fossil resources has emerged as a relevant tool to develop more eco-compatible synthetic processes.[1,2] In particular, furfural (1) and 5-(hydroxymethyl)furfural (HMF, 2), which are obtained by depolymerization / cyclodehydration of raw biomasses containing C5- and C6-monosaccharides, are two renewable platform molecules of high interest for bulk as well as fine chemistry.[3–11] In recent years, organic chemists have investigated and developed new C–C bond forming protocols on these molecules to obtain new highly functionalized bio-based chemicals or biofuels.[12] In particular, the direct functionalization of furfural, especially through transition metal (TM) catalyzed C–H activation processes,[13–16] is an emerging field that attracts considerable interest. Most of the reported examples address the functionalization at C5 of the furan ring, which is the most electron-rich site of the ring.[17–29] By contrast, C3–H functionalization of the formyl-furan unit via directing groups which allow to bypass the natural C5 preference has been much less studied.[26–29]

Within a broader project directed toward the selective C–H functionalization of furfural derivatives without prior modification of the redox state of the aldehyde function, we established that C3–H activation can be achieved using nucleophilic TM catalysts, which involve a directed oxidative addition as the C–H activation step. On the contrary, electrophilic TM-complexes that elicit Si2Ar or concerted-metalation-deprotonation mechanisms are often unsuccessful. In this context, we reported the Ru(0)-catalyzed C3 functionalization of furylilamines (Scheme 1) – alkylation with vinylsilane or styrene derivatives (eq. 1),[30] arylation with arylboronates (eq. 2),[31,32] acylation under CO atmosphere with vinylsilanes or styrenes (eq. 3)[33] and alkenylation with electron-poor alkenes (eq. 4).[34] Some of these processes (eq. 3 and 4) were also extended to pyrrole 2-carboxaldehydes (not shown in the scheme), which, given their accessibility from furfurals,[35,36] are also potentially biomass-derived building blocks. The success of these processes is highly dependent on the nature of the imine, which acts as directing group, overriding the innate C–H activation of the more reactive C5 position. Thus, a bidentate amino-imine allows hydrofurylation of alkenes (Murai reaction: eq. 1), while electron-rich furylilamines allow a carboxylative Murai reaction (eq. 3), as well as arylation (eq. 2) and alkenylation (Fujiwara-Moritani type reaction: eq. 4) couplings.
Scheme 1. *Previously* developed Ru-catalyzed selective C3–H functionalizations of furfurylimines.

In continuation of these works, we sought to access versatile furfural-derived platforms that could enable a number of C3 functionalizations via simple and reliable transformations. Accordingly, we envisaged a particularly attractive strategy involving the synthesis of C3-silyl furfural derivatives and the subsequent transformation of the newly generated C(sp²)–SiR₃ bond (Scheme 2).

Indeed, it is well established that organo-silanes are robust carbanion surrogates that allow for a number of synthetically useful transformations. Herein, we disclose the C3 selective Ir-catalyzed C–H-to-C–Si bond transformation of furfurylimines. Furthermore, we demonstrate the successful fluoride-mediated C–Si-to-C–C and C–Si-to-C–X (X = halogen) conversion, which enables the synthesis of a broad range of polyfunctionalized furanic synthons.

Scheme 2. Synthesis of C3-silylated furfural derivatives and the subsequent functionalizations of the C–SiR₃ bonds formed: *this work*.

Results and Discussion
Following on our previous studies, initial tests were carried out on furfurylimines derived from 1, using Ru₃(CO)₁₂ as catalyst in the presence of Et₃SiH and a sacrificial hydride acceptor (see SI, Table S1). Unfortunately, with this catalyst, low yields of C3-silylated imines were obtained, along with large amounts of reduced products – furfurylamine-type by-products. We thus turned our attention to other transition metal-based catalysts in a model reaction involving p-methoxyphenyl (PMP)-furfurylimine 3a, Et₃SiH (2.5 equiv.) and 3,3-dimethylbut-1-ene (2 equiv.) as hydrogen acceptor in n-hexane at 120 °C during 6 h (see SI, Table S2). Rhodium-based catalysts – RhCl(COD)₂ and RhCl(PPh₃)₃ – only led to reduction products (3a'). In contrast, switch to the iridium-based catalyst [IrCl(COD)]₂, in the presence of Hünig’s base (20 mol%) in n-hexane at 120 °C provided the desired C3-silylated product 4aA (65%), with no imine reduction (Table 1, entry 1). However, the C3,C5-disilylated product 5aA was
also formed in 20% yield. The decrease of the amount of hydrosilane (1.5 equiv.) and of the reaction time (4 h), allowed to reduce the amount of disilylated product 5aA to only 5% yield, while keeping a good yield of silylated product 4aA (82%) (entry 2). The influence of the imine directing group was then investigated. Electron-rich furfurylimines 3a-b provided the best results with relatively good silylation yields and no trace of the reduction products (entries 2 and 3), with a better selectivity for the C3-silylation over disilylation with PMP-imine 3a. Phenylimine 3c led to significant product degradation (entry 4), while electron-poor furfurylimine 3d was found to be more prone to competing hydrosilylation (giving 3d') (entry 5). To improve the selectivity, different bidentate N,N-amino-imines were also tested. While imines with a terminal N,N-dimethylamine group (3f, entry 7) or a piperidyl group (3g, entry 8) bearing two carbons between the two nitrogen atoms led to poor conversion, the one having a N,N-diethylamine group (3e, entry 6) gave the C3-silylated imine 4eA in 80% yield. In a similar fashion, bidentate imines possessing a three-carbon spacer gave better yields compared to the two-carbon ones (entries 9-10). This result might be due to the requirements of the iridium catalyst, which accommodates best a 6-membered metallacycle, or might be related to a looser complexation of the second amine, which prevents the catalyst poisoning, and allows a better selectivity. In particular, 3i proved to be very selective, as only product 4iA was obtained, with high yield (entry 10). It should be noted that the installation of a temporary imine directing group serves both for the ortho-directing effect, as well as for protecting the aldehyde function toward undesired hydrosilylation or decarbonylation processes. We completed our optimization studies by varying the solvent and the temperature, but no further improvement was achieved (see SI for details).

Table 1. Ir-catalyzed C3-silylation of furfurylimines.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>4 (%)&lt;sup&gt;[a]&lt;/sup&gt;</th>
<th>5 (%)&lt;sup&gt;[b]&lt;/sup&gt;</th>
<th>3&lt;sup&gt;'&lt;/sup&gt; (%)&lt;sup&gt;[c]&lt;/sup&gt;</th>
</tr>
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<tr>
<td>1&lt;sup&gt;[b]&lt;/sup&gt;</td>
<td>+&lt;sup&gt;→&lt;/sup&gt;N=O&lt;sub&gt;3a&lt;/sub&gt; (PMP)</td>
<td>4aA: 65</td>
<td>5aA: 20</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>3a (PMP)</td>
<td>4aA: 82 (47)&lt;sup&gt;[c]&lt;/sup&gt;</td>
<td>5aA: 5</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>+&lt;sup&gt;→&lt;/sup&gt;N=O&lt;sub&gt;3b&lt;/sub&gt;</td>
<td>4bA: 74</td>
<td>5bA: 12</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>+&lt;sup&gt;→&lt;/sup&gt;N=O&lt;sub&gt;3c&lt;/sub&gt;</td>
<td>4cA: 13</td>
<td>-</td>
<td>3&lt;sup&gt;'&lt;/sup&gt;: 25</td>
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<tr>
<td>5</td>
<td>+&lt;sup&gt;→&lt;/sup&gt;N=O&lt;sub&gt;3d&lt;/sub&gt;</td>
<td>4dA: 54</td>
<td>5dA: 16</td>
<td>3&lt;sup&gt;'&lt;/sup&gt;: 19</td>
</tr>
<tr>
<td>6</td>
<td>×&lt;sup&gt;→&lt;/sup&gt;tw&lt;sub&gt;3e&lt;/sub&gt;</td>
<td>4eA: 80 (55)&lt;sup&gt;[c]&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>×&lt;sup&gt;→&lt;/sup&gt;tw&lt;sub&gt;3f&lt;/sub&gt;</td>
<td>4fA: traces</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>×&lt;sup&gt;→&lt;/sup&gt;N=O&lt;sub&gt;3g&lt;/sub&gt;</td>
<td>4gA: 26</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>×&lt;sup&gt;→&lt;/sup&gt;tw&lt;sub&gt;3h&lt;/sub&gt;</td>
<td>4hA: 79</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>×&lt;sup&gt;→&lt;/sup&gt;tw&lt;sub&gt;3i&lt;/sub&gt;</td>
<td>4iA: 85 (46)&lt;sup&gt;[c]&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
</tr>
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</table>

[a] Yield calculated by <sup>1</sup>H NMR using 3,4,5-trimethoxybenzaldehyde as internal standard. [b] With Et<sub>3</sub>SiH (2.5 equiv.) for 6 h. [c] Isolated yield.

The silylation scope was then explored on furfural, 5-methyl furfural and (TBS)-protected HMF on the corresponding PMP-imines (3a, 6a, 7a) (Scheme 3) as well as N,N-dimethylanilines (3i, 6i, 7i) (Scheme 4). The optimized conditions ([IrCl(COD)]<sub>2</sub> (2 mol%), (i-Pr)<sub>2</sub>NEt (20 mol%), HSiR<sub>3</sub> (1.5 equiv.) were then applied in n-hexane (2 equiv.); no traces of reduction products were detected.
equiv.), and 3,3-dimethylprop-1-ene (2 equiv.) in hexane at 120 °C during 4 h] were employed with various hydrosilanes. The reaction crude was subjected to imine hydrolysis, either by HCl treatment (for PMP-imines), or directly by silica gel chromatography (for bidentate amino-imines). Due to the high volatility of the C3-silylated furfuraldehydes (in particular of the C5 unsubstituted furfural derivatives), the ¹H-NMR-yields of the crude silylated furyl aldehydes were also measured in some cases (see SI).

The silylation step was carried out conveniently using trialkysilanes such as HSiEt₃, HSi(i-Pr)₃, HSiMe₂Bn, and HSiMe₂t-Bu (final compounds 8A-D, 9A-D and 10A-D). Using HSiMePh₂ and HSiMe₂Ph, the corresponding products 8F-8G were also formed, albeit in very low yields. The use of more sterically demanding hydrosilanes such as HSi(n-Bu)₃, HSi(SiMe₃)₃, and HSiPh₃ gave no silylation product, which confirmed the high dependence of this coupling upon steric factors. Bidentate amino-imines 3i, 6i and 7i, were found to be highly C3 selective when using small trialkylsilanes, but inefficient when using sterically hindered silanes such as HSi(i-Pr)₃ and HSiMe₂t-Bu. These silanes also evidenced some limitations associated with competing hydrosilylation processes. On their side, PMP-imines 3a, 6a and 7a, although slightly less C3 selective, were found to be less sensitive to hydrosilylation, and could thus be applied with a wider range of silanes, generally affording better yields.

**Scheme 3.** Scope of the C3-silylation of PMP-furfurylimines (3a, 6a, 7a).
In contrast to the bidentate amino-imines, the PMP-imines enabled the silylation reaction using HSiMe(OTMS)$_2$ as the silicon donor, which delivered products 8E, 9E and 10E in synthetically useful yields. Conversely, alkoxysilanes and dihydrosilanes, known to be good reducing agents, led to degradation and/or reduction of the furfurylimines (not shown in the schemes). In general, the C3 silylation of the (TBS)-protected 5-HMF derivatives was less efficient than that of the 5-methyl congeners. With the aim of performing the dehydrogenative silylation in the absence of an external hydrogen acceptor, the use of vinyltrimethylsilane or diphenylallylsilane was also envisaged to fulfil both the role of silicon source and sacrificial hydrogen acceptor. However, no C3-functionalized product could be evidenced and a rather poor conversion was observed (see SI).

Finally, the C3-silylation of the PMP-imine of pyrrole 2-carboxaldehyde 12a was also tested, using HSiEt$_3$ as the silylating agent (Scheme 5). Adopting the previously optimized reaction conditions, after a 16 h reaction time the desired silylated adduct 13A was obtained in 25% yield (46% conversion). Increasing the catalytic loading of [IrCl(COD)]$_2$ to 5 mol% and the temperature to 140 °C improved the yield of 13A to 49%.

**Scheme 4.** Scope of the C3-silylation of N,N-dimethylpropane-furfurylimines (3i, 6i, 7i).

**Scheme 5.** Iridium-catalyzed C3-silylation of PMP-based pyrrole 12a.
In light of our own observations and considering the mechanistic studies performed by Hartwig for the iridium-catalyzed dehydrogenative silylation, we propose the following mechanism for this C3-directed silylation of furfurylimines (Scheme 6). Starting from the pre-catalyst, the formation of a mononuclear complex in the presence of \((i-Pr)_2NET\) would first occur. Subsequent oxidative addition of the Si–H bond of the hydrosilane generates an Ir(III)-intermediate, and following reductive elimination releases DIPEA-HCl and the active-catalytic species, A. Oxidative addition of the hydrosilane to A generates the Ir(III) complex B, likely resting state of the catalytic cycle, and subsequent coordination to the furfurylimine gives complex C. Oxidative addition into the C3–H bond then furnishes a hexacoordinated iridacycle D, which undergoes reductive elimination to generate E. Ligand exchange with 3,3-dimethylbut-1-ene releases the C3-silylated furfurylimine and generates the Ir(III)-dihydride silyl complex F. Subsequent migratory insertion of the alkene into the [Ir]–H bond gives G, which following reductive elimination generates 2,2-dimethylbutane and regenerates the active catalytic species A. For now, the mechanism leading to the formation of the 3,5-bis-silylated furfurylimine is unclear. On the other hand, hydroisilylation of aldmines have been previously been described with cationic [Ir(I)] complex in the presence of HSiEt₃. The generation of an Ir(III) silyl hydride was considered to be responsible of the reduction of imines.

Scheme 6. Proposed mechanism for directed C3-silylation of \(\rho\)-methoxyphenyl-furfurylimine \(3a\).

With the C3-silylated furfural derivatives in hand, we then sought to exploit the C(sp²)–Si bond as a handle for subsequent C3-functionalizations. Given the presence of the rather unstable furanic core and formyl function, we directly opted for mild reaction conditions under fluoride activation. Following some initial failures on Hiyama-Denmark cross-couplings using the C3-(SiMe₂Bn) substituted substrate...
8C, we soon discovered that the C3–SiMe(OSiMe$_3$)$_2$\cite{48} substituted derivatives 8E, 9E and 10E were optimal platforms for such challenging C3-functionalizations.

Halodesilylation was first considered (Scheme 7). After some optimization work, we were pleased to find that treatment of 8E, 9E and 10E with the corresponding N-halosuccinimides (NXS, 2 equiv.) in the presence of AgF (2 equiv.), in acetonitrile at 50 °C, gave smoothly the C3-chlorinated (14-16$_\text{Cl}$), brominated (14-15$_\text{Br}$) and iiodinated (14-16$_\text{I}$) products in fair yields. Note, however, that most of these products are considerably volatile, which significantly complicated their isolation in high yield. Furthermore, in the case of the TBS containing substrate 10E, four equivalents of NXS and AgF were used, to ensure the full activation of the C3(sp$^2$)–Si bond. Very low or no yield of products were obtained with NBS, possibly due to competitive radical bromination. Finally, C–Si-to-C–F conversion from 9E was attempted using N-fluoropyridinium tetrafluoroborate or SelectFluor\cite{49} as electrophilic fluoride sources,\cite{49} but proved unsuccessful.

![Scheme 7. C3-halogenation of C3-silylated furfurals.](image)

The above AgF activation was subsequently applied to achieve cross-coupling reactions with C(sp$^2$)-electrophiles. Accordingly, by adapting literature precedents,\cite{50} treatment of 9E with iodobenzene in the presence of [Pd$_2$dba$_3$-CHCl$_3$ / BINAP] as the catalytic system gave the expected arylated product 18 in an excellent 81% yield (Scheme 8a). The same conditions were applied to the arylation of 8E with iodobenzene, which delivered product 17 in 48% yield. The cross-coupling of 10E occurred in significantly lower yield. Alkenylation of 9E was also performed with β-bromostyrene, which delivered product 20 in 45% yield. Furthermore, by adapting a reported protocol,\cite{51} treatment of 9E with phenylethynyl bromide gave the expected alkynylated product 21, albeit in a poor 19% yield (Scheme 8b).
We then passed to tackle \([\text{C}^3(\text{sp}^2)–\text{Si}]\)-to-\([\text{C}^3(\text{sp}^2)–\text{C}(\text{sp}^3)]\) cross-coupling reactions. As no reaction was observed reacting \(9\text{E}\) with allyl bromide under Pd(0) catalysis in the presence of AgF, we directed our attention to copper-based strategies,\(^{52,53}\) and particularly to the use of Cu–F complexes, known to be able to trigger silicon-to-copper transmetalation. For this purpose, bench-stable \((\text{PPh}_3)_3\text{Cu–F}\) was prepared by the reaction of \(\text{PPh}_3\) and \(\text{CuF}_2\).\(^{54}\) With this promoter, cross-coupling of silylated 5-methyl furfural \(9\text{E}\) was achieved with allyl- and methallyl-bromide, leading to the corresponding allylic substituted products in quite good yields under the optimized conditions (22 62% and 23 67%, respectively) (Scheme 9a). Cinnamyl bromide was also found to be a competent electrophile under the same conditions. However, in this case, competing protodesilylation hampered somewhat the process, leading to a lower yield of the cross-coupled compound 24. The scope was also extended to furfural derivative 8E, which afforded the methallylated product 25 in reasonably good yield.

Alkylation processes were also studied, with methyl iodide and benzyl bromide as electrophiles. Here, the best results were obtained using catalytic amounts of \((\text{PPh}_3)_3\text{Cu–F}\) in the presence of AgF (2 equiv.). Methylated product 26 and benzylated product 27 were formed in respectively 35% and 40% yield, along with small amounts of protodesilylation product (Scheme 9b).

Finally, to further increase the added-value of our platform, we tested the trifluoromethylation of the C3-silylated furfurals. To this end, \((\text{phen})\text{Cu(CF}_3)_3\) was prepared and isolated according to a literature protocol.\(^{55}\) Then, the reaction between \(9\text{E}\) and this copper complex (1.2 equiv.) was performed with AgF as the activating agent under oxygen atmosphere. In these conditions, the desired trifluoromethylated product 28 was obtained in satisfactory yield (Scheme 9c).
a. Allylation

\[
\begin{align*}
\text{R} \quad &\quad + \quad \text{R}^1\text{Br} \quad \xrightarrow{\text{CuF(PPh}_3\text{)}_3 (1.2 \text{ equiv.}) } \quad \text{R} \quad \text{R}^1\text{H} \\
\text{SiMe(OSiMe}_3\text{)}_2 &\quad \text{DMF (0.1 M)} \quad 60 ^\circ \text{C, overnight} \\
\text{R} = \text{H} (8E) &\quad \text{(3 equiv.)} \\
\text{R} = \text{Me} (9E)
\end{align*}
\]

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield</th>
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<tbody>
<tr>
<td>22</td>
<td>62%</td>
</tr>
<tr>
<td>23</td>
<td>67%</td>
</tr>
<tr>
<td>24</td>
<td>53%</td>
</tr>
<tr>
<td>25</td>
<td>64%</td>
</tr>
</tbody>
</table>

* The isolated product contained ~ 10% of 5-Me-furfural.

b. Alkylation

\[
\begin{align*}
\text{Me} &\quad + \quad \text{Me}^+ \quad \xrightarrow{\text{CuF(PPh}_3\text{)}_3 (20 \text{ mol%}) \quad \text{AgF (2 equiv.) }} \quad \text{Me} \quad \text{Me}^+ \\
\text{SiMe(OSiMe}_3\text{)}_2 &\quad \text{DMF (0.1 M)} \quad 60 ^\circ \text{C, overnight} \\
\text{9E} &\quad \text{(3 equiv.)} \\
\text{Me} &\quad + \quad \text{Me}^+ \quad \text{(volatile)} \\
\text{35%} &\quad \text{26} \\
\text{10%} &\quad \text{(b)}
\end{align*}
\]

\[
\begin{align*}
\text{Me} &\quad + \quad \text{Bn}^+\text{Br} \quad \xrightarrow{\text{CuF(PPh}_3\text{)}_3 (20 \text{ mol%}) \quad \text{AgF (2 equiv.) }} \quad \text{Me} \quad \text{Me}^+ \\
\text{SiMe(OSiMe}_3\text{)}_2 &\quad \text{DMF (0.1 M)} \quad 60 ^\circ \text{C, overnight} \\
\text{9E} &\quad \text{(3 equiv.)} \\
\text{Me} &\quad + \quad \text{Me}^+ \\
\text{29%} &\quad \text{(40%)} \text{(b)} \\
\text{20%} &\quad \text{(b)}
\end{align*}
\]

* \text{b} \quad \text{H NMR yield prior to purification.}

**Scheme 9.** Allylation, methylation, benzylation and trifluoromethylation of C3-silylated furfurals.

**Conclusion**

In summary, we have developed an efficient protocol for the selective iridium-catalyzed C3–H silylation of biomass-derived furfurals. This transformation involves the C3–H activation of the furan ring by the transient participation of a monodentate arylimine, or bidentate imino / amine directing group. This chemistry offers a direct access to a library of C3-silylated furfurals, which constitute versatile furanic platforms to access elaborated added-value chemicals. This prospect, important in the context of progress to more sustainable chemical synthesis, was demonstrated for platforms relying on the SiMe(OSiMe3)2 unit, which were converted into the corresponding furfuraldehydes decorated at C3 with halogen, aryl, alkenyl, alkynyl, methyl, benzyl and CF3 groups. This work is expected to further raise the value of the biobased furanic platform molecules.

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**Keywords:** Furfural • Iridium • Silicon • Fluoride • Biomass


[44] The addition of Hünig base is known to promote the formation of a single-nuclear iridium complex. Better yields were thus obtained with the tertiary amine compared to tests in presence of triethylamine or without base (see SI).

[45] The C3 silylation of imine 3a with HSiMe(OTMS)2 was reported under the same conditions but at 80 °C instead of 120 °C (ref 42). Failure to reproduce the reported results (in our hands, unsatisfactory levels of conversion (< 35%) were obtained), led us to reoptimize the protocol.


