C3–H Silylation of Furfurylimines: Direct Access to a Novel Biobased Versatile Synthetic Platform Derived from Furfural

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Abstract: Herein we report directed iridium-catalyzed C3–H silylation of furfuryl imines, 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–$SiMe(OSiMe_3)_2$ furfural derivatives to achieve a wide range of transformations of the C3–Si bond. Arylation, alkenylation, alkynylation, allylation and alkylation, as well as halogenation and trifluoromethylation were achieved in modest to high yields. A variety of high value-added products were thus easily obtained from the same common C3-silylated furfural-based platform.

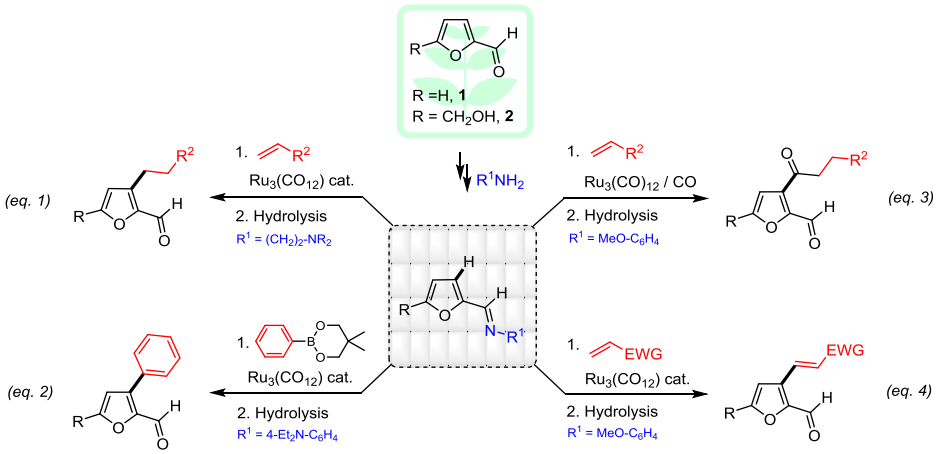
Introduction

The preparation of building-block intermediates and value-added compounds from lignocellulosic nonedible biomass rather than from fossil resources has emerged as a significant tool to develop more eco-compatible synthetic processes.[1,2] In particular, the sustainable production of industry-relevant chemicals, ranging from biofuels to pharmaceuticals, requires the development of efficient functionalization of furan derivatives such as furfural (**1**) and 5-(hydroxymethyl)furfural (HMF, **2**). These molecules, 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.[13] Similarly, the biomass-derived furan rings are found in several drugs – such as ranitidine a well-known anti-ulcer agent – but are exclusively substituted in 2- and/or 5 position.[12] Indeed, functionalizations of furfural at the formyl function - or *via* electrophilic substitutions at the C5 position – are common transformations. On the other hand, the functionalization of furfurals at the C3 position, which is less common, could open the way to new potential drug candidates.

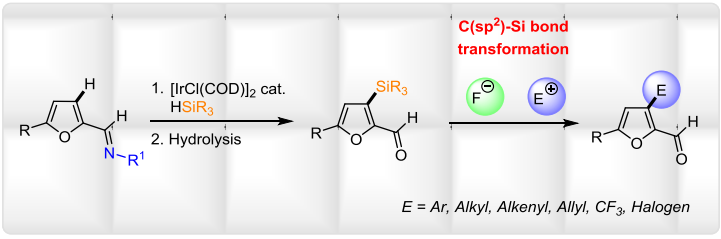
The direct functionalization of furfural, especially through transition metal (TM) catalyzed C–H activation processes,[14–17] is an emerging field that attracts considerable interest. Most of the reported examples address the functionalization at C5 of the furan ring, which is the most electron-rich site of the ring.[18–26] 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.[27–30]

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 S_EAr or concerted-metalation-deprotonation mechanisms are often unsuccessful. In this context, we reported the Ru(0)-catalyzed C3 functionalization of furfurylimines (Scheme 1) – alkylation with vinylsilane or styrene derivatives (*eq. 1*),[31] arylation with arylboronates (*eq. 2*),[32,33] acylation under CO atmosphere with vinylsilanes or styrenes (*eq. 3*),[34] and alkenylation with electron-poor alkenes (*eq. 4*).[35] 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,[36,37] 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 furfurylimines allow a carbonylative Murai reaction (*eq. 3*), as well as arylative (*eq. 2*) and alkenylative (Fujiwara-Moritani type reaction: *eq. 4*) couplings.

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 $C(sp^2)$–SiR_3 bond (Scheme 2).[38,39] Indeed, it is well established that organosilanes are robust carbanion surrogates that allow to perform a number of synthetically useful transformations.[40–42] Herein, we disclose the C3 selective Ir-catalyzed C–H-to-C–Si bond transformation of furfurylimines.[43] 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 1. *Previously* developed Ru-catalyzed selective C3–H functionalizations of furfurylimines.



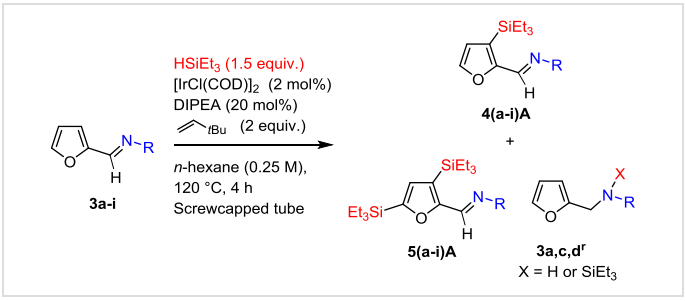
Scheme 2. Synthesis of C3-silylated furfural derivatives and the subsequent functionalizations of the C–SiR_3 bonds formed: *this work*.

Results and Discussion

Following on our previous studies, initial tests were carried out on furfurylimines derived from **1**, using $Ru_3(CO)_{12}$ as catalyst in the presence of Et_3SiH 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.[44] We thus turned our attention to other transition metal-based catalysts in a model reaction involving *p*-methoxyphenyl (PMP)-furfurylimine **3a**, Et_3SiH (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 $RhCl(PPh_3)_3$ – only led to reduction products (**3a^r**). In contrast, switch to the iridium-based catalyst $[IrCl(COD)]_2$, in the presence of Hünig's base (20 mol%)[45] in *n*-hexane at 120 °C provided the desired C3-silylated product **4aA** (65%), with no imine reduction (Table 1, entry 1).[46] 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%) (Table 1, 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^r**) (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 carbon atoms 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 thereby allowing 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 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).

The silylation scope was then explored on the corresponding PMP-imines (**3a**, **6a**, **7a**) as well as *N*,*N*'-dimethylpropanimines (**3i**, **6i**, **7i**) of furfural (Scheme 3), and 5-methyl furfural and (TBS)-protected HMF (Scheme 4), respectively. The optimized conditions [$[IrCl(COD)]_2$ (2 mol%), $(i\text{-}Pr)_2NEt$ (20 mol%), $HSiR_3$ (1.5 equiv.), and 3,3-dimethylprop-1-ene (2 equiv.) in hexane at 120 °C during 4 h] were employed with various hydrosilanes.

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



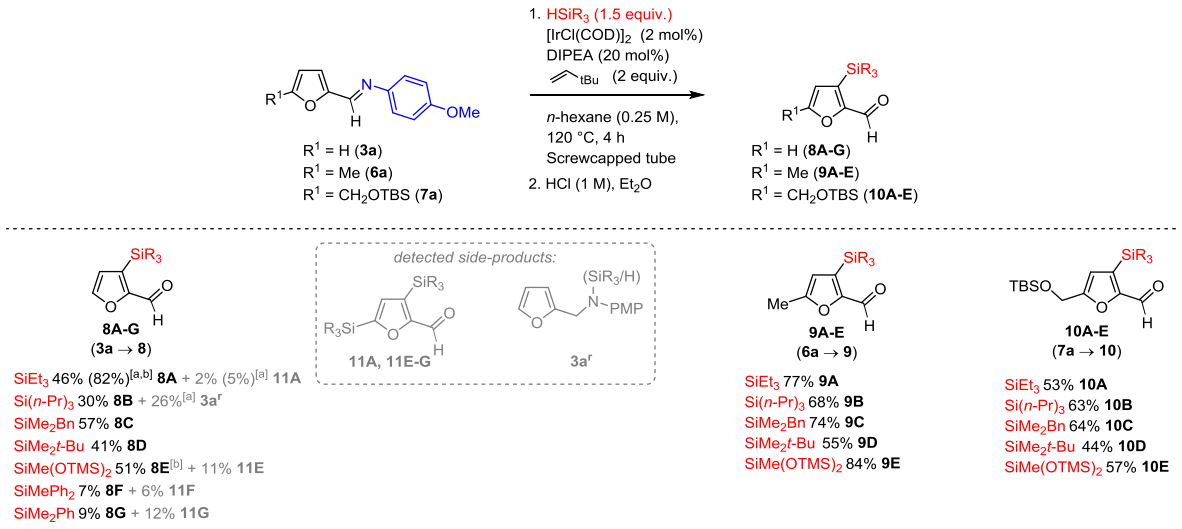
Entry	R	4 (%)[a]	5 (%)[a]	3^r (%)[a]
1[b]	 **3a (PMP)**	**4aA**: 65	**5aA**: 20	-
2	**3a** (PMP)	**4aA**: 82 (47)[c]	**5aA**: 5	-
3	 **3b**	**4bA**: 74	**5bA**: 12	-
4	 **3c**	**4cA**: 13	-	**3c^r** : 25
5	 **3d**	**4dA**: 54	**5dA**: 16	**3d^r** : 19
6	 **3e**	**4eA**: 80 (55)[c]	-	-
7	 **3f**	**4fA**: traces	-	-
8	 **3g**	**4gA**: 26	-	-
9	 **3h**	**4hA**: 79	-	-
10	 **3i**	**4iA**: 85 (46)[c]	-	-

[a] Yield calculated by ^{1}H NMR using 3,4,5-trimethoxybenzaldehyde as internal standard. [b] With Et_3SiH (2.5 equiv.) for 6 h. [c] Isolated yield.

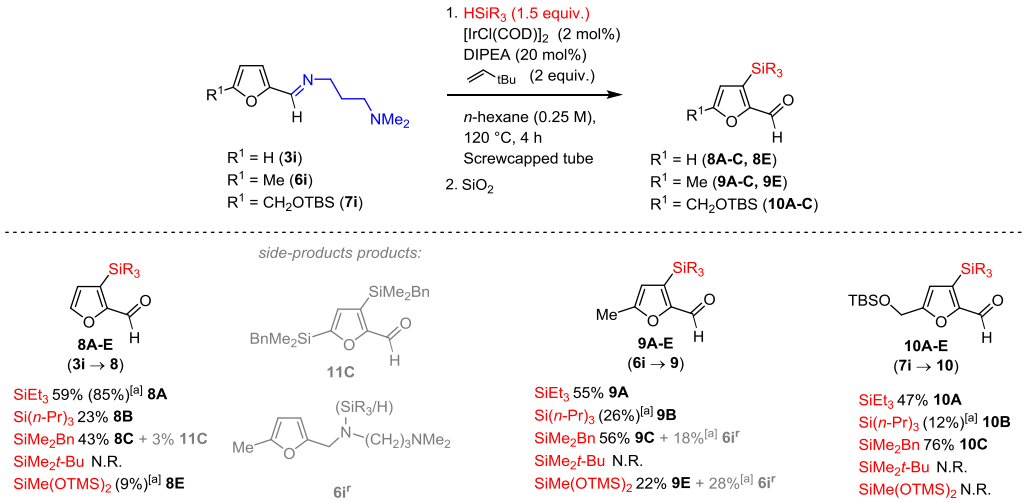
The reaction crudes were subjected to imine hydrolysis, either by HCl treatment (for PMP-imines), or directly by silica gel chromatography (for bidentate amino-imines). Due to the high volatility of the C3-silylated furfurals (in particular of the C5 unsubstituted ones), the ^{1}H-NMR-yields of the crude silylated furfurylimines were also measured in some cases (see SI).

The silylation step was carried out conveniently using trialkylsilanes such as $HSiEt_3$, $HSi(i\text{-}Pr)_3$, $HSiMe_2Bn$, and $HSiMe_2t\text{-}Bu$ (final compounds **8A-D**, **9A-D** and **10A-D**). Using $HSiMePh_2$ and $HSiMe_2Ph$, the corresponding products **8F-8G** were also formed, albeit in very low yields. The use of more sterically demanding hydrosilanes such as $HSi(n\text{-}Bu)_3$, $HSi(SiMe_3)_3$ and $HSiPh_3$ 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 $HSi(i\text{-}Pr)_3$ and $HSiMe_2t$-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.

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 vinyldimethylsilane 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).

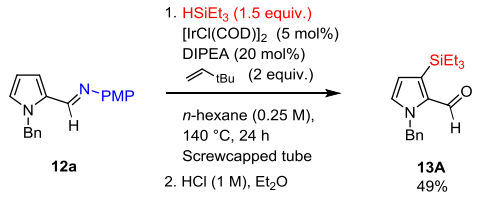


Scheme 3. Scope of the C3-silylation of PMP-furfurylimines (**3a**, **6a**, **7a**). [a] ^{1}H-NMR yield prior to imine-hydrolysis calculated with 3,4,5-trimethoxybenzaldehyde as internal standard. [b] 2 mmol scale



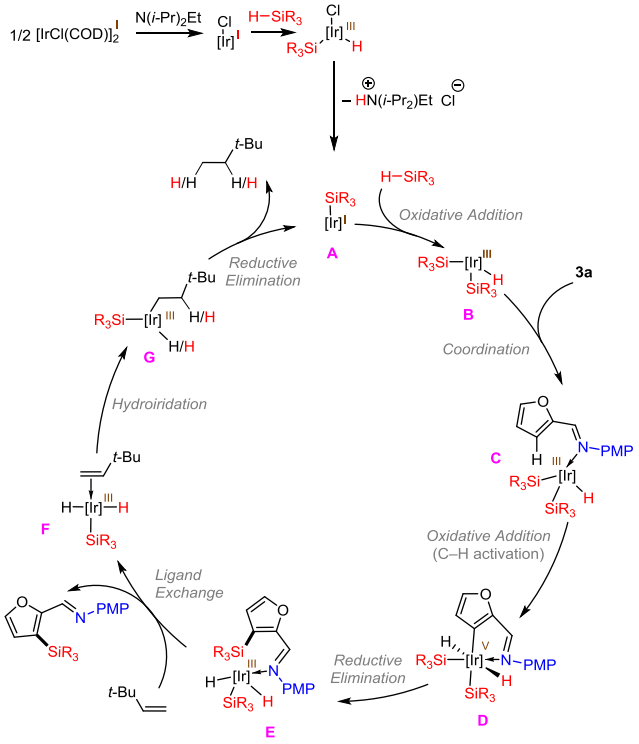
Scheme 4. Scope of the C3-silylation of *N*,*N*'-dimethylpropane-furfurylimines (**3i**, **6i**, **7i**). [a] ^{1}H-NMR yield prior to imine-hydrolysis calculated with 3,4,5-trimethoxybenzaldehyde as internal standard.

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 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,[47] we propose the following mechanism for this C3-directed silylation of furfurylimines (Scheme 6). Starting from the pre-catalyst, the formation of a mono-nuclear complex in the presence of (*i*-Pr_2)NEt 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 3,5-bis-silylated furfurylimine is unclear. On the other hand, hydrosilylation of aldimines have been previously been described with cationic [Ir(I)] complex in the presence of $HSiEt_3$.[48] The generation of an Ir(III) silyl hydride was considered to be responsible of the reduction of imines.

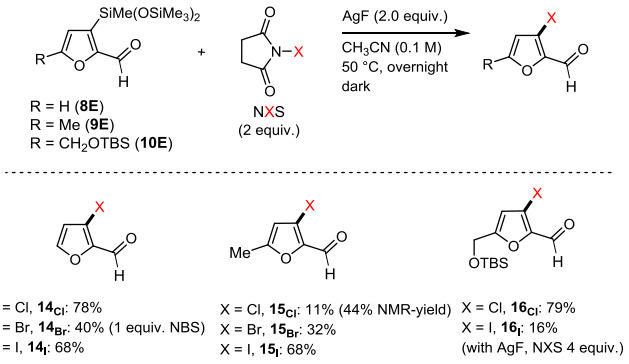


Scheme 6. Proposed mechanism for directed C3-silylation of *p*-methoxyphenyl-furfurylimine **3a**.

With the C3-silylated furfurals in hand, we then sought to exploit the C(sp^2)–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-($SiMe_2Bn$) substituted substrate **8C**, we soon discovered that

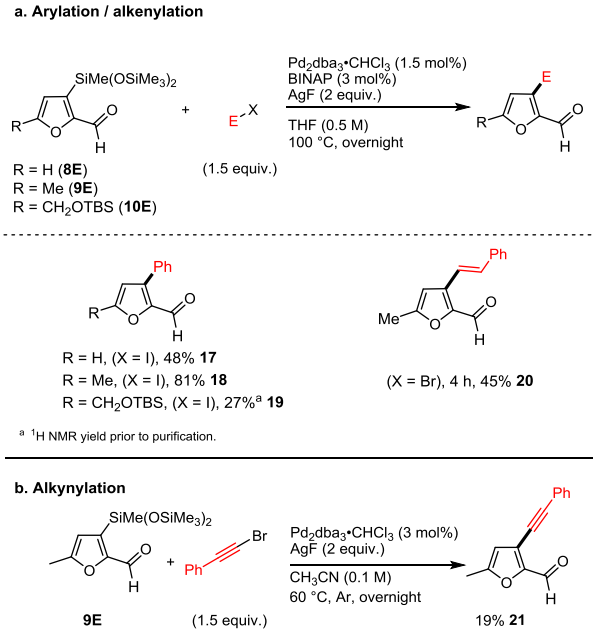
the C3–SiMe(OSiMe$_3$)$_2$[49] substituted derivatives **8E**, **9E** and **10E** were optimal platforms for such challenging C3-functionalizations.

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$_{Cl}$**), brominated (**14-15$_{Br}$**) and iodinated (**14-16$_{I}$**) 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® as electrophilic fluoride sources,[50] but proved unsuccessful.



Scheme 7. C3-halogenation of C3-silylated furfurals.

The above AgF activation was subsequently applied to achieve cross-coupling reactions with C(sp^2)-electrophiles. Accordingly, by adapting literature protocols,[51] 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,[52] treatment of **9E** with phenylethynyl bromide gave the expected alkynylated product **21**, albeit in a poor 19% yield (Scheme 8b).

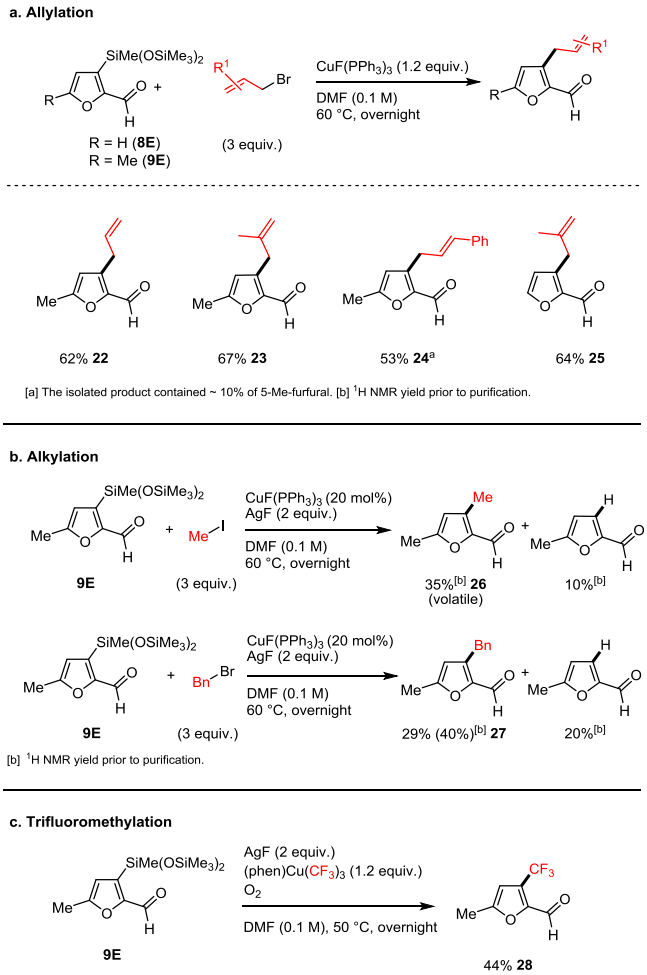


Scheme 8. Arylation, alkenylation and alkynylation of C3-silylated furfurals.

We then passed to tackle [C3(sp^2)–Si]-to-[C3(sp^2)–C(sp^3)] cross-coupling reactions. As no reaction was observed reacting **9E** with allyl bromide under Pd(0) catalysis in the presence of AgF, we directed our attention to copper-based strategies,[53,54] and particularly to the use of Cu–F complexes, known to be able to trigger silicon-to-copper transmetalation. For this purpose, bench-stable (PPh$_3$)$_3$Cu–F was prepared by the reaction of PPh$_3$ and CuF$_2$.[55] With this promoter, cross-coupling of silylated 5-methyl furfural **9E** 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 (PPh$_3$)$_3$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, (phen)Cu(CF$_3$)$_3$ was prepared and isolated according to a literature protocol.[56] Then, the reaction between **9E** 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).



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

Conclusion

In summary, we have developed an efficient protocol towards novel scaffolds arising from the biomass-derived furfurals, by selective iridium-catalyzed C3-H silylation of furfurylmimines. This transformation involves the C3–H activation of the furan ring by the transient participation of a monodentate arylimine, or bidentate amino-imine 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 $SiMe(OSiMe_3)_2$ unit. Using fluoride-mediated activation strategies (with AgF or CuF reagents), these C3–$SiMe(OSiMe_3)_2$ furfural derivatives were converted into the corresponding furfurals decorated at C3 with halogen, aryl, alkenyl, alkynyl, methyl, benzyl and CF_3 groups. Such transformations could be achieved in high yields in the case of arylation, allylation and halogenation reactions, and in more modest yields for alkenylation, alkylation, trifluoromethylation or alkynylation reactions. This work is expected to further raise the value of the biobased furanic platform molecules.

Experimental Section

Further optimizations, all the experimental procedures and compound characterizations are in the supporting information.

General procedure Ir-catalyzed silylation. In a dried screw-capped tube equipped with a stirring bar, were added successively the appropriate furfuryl imine (1.0 equiv.), $[IrCl(COD)]_2$ (2 mol%), DIPEA (20 mol%), the corresponding hydrosilane (1.5 equiv.), 3,3-dimethyl propene (2.0 equiv.) and *n*-hexane (to reach 0.25 M). The resulting solution was stirred at 120 °C for 4–6 h in an oil bath. The solvent was removed under reduced.

Purification and hydrolysis of the C3-silylated imines. *PMP-imines***:** C3-silylated furfuryl PMP-imines were hydrolyzed using 2 mL of 1 M HCl solution in 2 mL Et_2O. The mixture was stirred for 30 min, then brine was added. The aqueous layer was extracted 3 times with Et_2O, and the combined organic layers were dried over $MgSO_4$ or Na_2SO_4, filtered and carefully concentrated under low reduced pressure. The hydrolyzed crude was purified by silica gel chromatography, was concentrated under vacuum at 40 °C, 600 mbar for around 10-20 min (silylated furfural derivatives are quite volatile). *Amino-imines***:** To a solution of C3-silylated bidentate imine in Et_2O was added a spatula of silica. The mixture was stirred then dried under vacuum at 40 °C, 600 mbar. The product was purified by silica gel chromatography, concentrated under vacuum at 40 °C, 600 mbar for around 10-20 min.

C3-halogenation of furfuraldehyde. In a glovebox, a microwave vial fitted with a stir-bar was charged with AgF (2 equiv.) and sealed. The corresponding furfural derivatives was placed in a Schlenk tube, dissolved in CH_2Cl_2, concentrated, and then NXS (2 equiv.) was added. Freshly distilled acetonitrile (0.1 M) was added under argon and the mixture was degassed by 3 freeze-pump-thaw cycles. It was then transferred via cannula to the microwave vial containing AgF. The mixture was stirred at 50 °C overnight (unless otherwise mentioned). The reaction mixture was filtered through a short pad of silica-gel, which was washed with Et_2O. The filtrate was concentrated under reduced pressure and the residue was purified by silica-gel column chromatography with (90/10) pentane /Et_2O as eluent.

Arylation and alkenylation of C3-silylated furfuraldehydes. A flame-dried microwave vial was charged with Pd_2dba_3•$CHCl_3$ (1.5 mol%) and BINAP (3 mol%). The vial was flushed with argon three times, then placed in a glovebox where, AgF (2 equiv.) was introduced. The vial was sealed. In a dry Schlenk tube was placed the C3-silylated furfuraldehyde dissolved in CH_2Cl_2 and concentrated under argon. Then the appropriate iodoarene (1.5 equiv.) and THF were added. The solution was degassed by three freeze-pump-thaw cycles, after which, it was transferred via cannula to the microwave vial containing the palladium catalytic system. The mixture was heated to 100 °C overnight. The mixture was allowed to cool down to room temperature and then filtered through a pad of silica-gel, eluting with diethyl ether. The crude was concentrated at 40 °C, 500 mbar. The product was purified by silica-gel column chromatography [eluent (99/1) pentane/ether then to (90/10) pentane/Et_2O; solvent evaporation at 40 °C, 500 mbar].

Allylation of C3-silylated furfuraldehydes.A dry microwave vial was charged with $(PPh_3)_3$-Cu-F (1.2 equiv.) and placed under argon. The vial was sealed by means of a cap, and underwent 3 vacuum/argon cycles. In a Schlenk tube was placed the corresponding C3-silylated furan-2-carboxaldehyde (1.0 equiv.) and dissolved in CH_2Cl_2. The latter was

concentrated under argon and then DMF (0.1 M) was added. The solution was degassed three times (vacuum/argon cycles) and then transferred via cannula to the microwave vial. Allyl bromide (3-6 equiv.) was then added and the mixture was allowed to stir at 60 °C overnight. It was then cooled and quenched with aqueous HCl (2 M). The mixture was extracted three times with Et_2O, and the combined organics were washed with water and dried over Na_2SO_4.

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