

Selective functionalization of furfural and its derivatives Sebastien Lubin Dylan Curpanen

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Sebastien Lubin Dylan Curpanen. Selective functionalization of furfural and its derivatives. Organic chemistry. Sorbonne Université, 2021. English. NNT: 2021SORUS369 . tel-03688548

HAL Id: tel-03688548 https://theses.hal.science/tel-03688548

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Sorbonne Université

Ecole Doctorale de Chimie Moléculaire de Paris Centre – ED 406 Institut Parisien de Chimie Moléculaire / Equipe ROCS

Fonctionnalisation sélective du furfural et de ses dérivés

Par Sebastien Lubin Dylan CURPANEN

Thèse de Doctorat de Chimie

Dirigée par le Dr. Alejandro PEREZ-LUNA et co-encadrée par le Dr. Julie OBLE

Présentée et soutenue publiquement le 3 décembre 2021

Devant un jury composé du :

Prof. Florence POPOWYCZ	Université de Lyon	Rapporteur
Dr. Morgan DONNARD	Université de Strasbourg	Rapporteur
Prof. Florian MONNIER	ENS de Chimie de Montpellier	Examinateur
Prof. Louis FENSTERBANK	Sorbonne Université	Président du jury
Dr. Julie OBLE	Sorbonne Université	Examinateur
Dr. Alejandro PEREZ-LUNA	Sorbonne Université	Examinateur







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Dr. Alejandro PEREZ-LUNA	Sorbonne Université	Examinateur

Dedicated

To my loved ones

And

The ones who left too soon

Acknowledgements

This PhD work has been undergone at the Institut Parisien de Chimie Moléculaire directed by Prof. Louis Fensterbank.

Firstly, wish to thank the members of the jury; Prof. Florence Popowycz, Dr. Morgan Donnard, Prof. Florian Monnier and Prof. Louis Fensterbank for accepting to judge my PhD work.

I am really grateful towards best duos of PhD advisors, Julie Oble and Alejandro Perez-Luna, without whom this adventure will not be possible. Firstly, for trusting me to work on this great project, which is quite challenging indeed, which makes more interesting to me Starting this project, I could not imagine at all, that you would be so friendly, so open towards me, which I really appreciate. I really learnt a lot from you; with 2 complementary styles of working, but at the same time being on the same wavelength. I know it has been difficult at some point, especially during the recent days, for the writing of the thesis, but you helped me a lot. Thank you again the Brook's team...

Giovanni Poli, thank you for the fruitful advices you gave to me during the course of the PhD and also now, as well as for contacting some of people in relation to a post-doc. Fabrice Chemla, with his very nice discussions and reflections, which led to broaden my mind and way of thinking. Along with Olivier Jackowski, Myriam Roy, Alexandre Pradal and Franck Fereira, thank you for the nice discussions and advices, especially at lunch time or during the coffee break.

A special thanks to Louis Fensterbank, with whom I started my Parisian adventure in the lab at MACO, with Gilles Lemière and Fabrizio Medici, and now in my jury.

Per, who was my only internship student during the course of PhD, and who also contributed a lot in this work. My lab mates, with whom I had some great moments, Yang my favorite Chinese guy (sorry Tingting), Karen with whom I shared the lab for almost 2 years, it was fun, with all the reggaeton and dances, Roberto (half- a man) and Joao, Greta my pizza partner. Federica, one of the best Italians here. Jenny, Hichem, Baptiste, Amal despite a short period, it was nice.

Now the new ROCS... Tingting sorry for scaring you every day but I enjoyed it. Ruben, we were a good team with great music. Gredy, I should forget to mention your name because you're always late, but you're a great little man, who was born raised and grown, (not too much) in the IPCM. You're still the

same after 5 years here. All the best for you as well as the new arrivals Marco, Federico, Mikael and Alessia (you got the best supervisors and a great project believe me).

I would also like to thank the analysis staff, first the NMR girls, Claire and Aurélie who was here and now Régina, you're doing a fantastic job. Cédric and the ones in charge of the HRMS service. And my friend Omar, with whom, always great to have a football guy in the institute. Marc, Anthony and Cassandre, for the use of the glovebox.

I also met some great people, Kelly (arrete de passer dans notre couloir), Jana (et la Kiz) and Kajetan (le BG). And Nicolas who I know for more than 5 years now.

And finally, my friends from CIUP with whom I stayed during lockdown. Rutger, Kostas, Clara, Ikenna, Kiko, Sofi, Lina, Erika, Sabrine, Christopher, Cindy... Thank you for being here during the difficult times.

Jean-Louis Roule, ancien CEO de CIDP qui m'a grandement aidé et encouragé pour faire ce séjour en France depuis le Master

Un grand merci à tante Huguette et Muloud, de m'avoir aidé permis de venir en France et tante Marceline de m'avoir aussi bien accueilli chez elle. Je serais éternellement reconnaissant envers vous.

Angélique et Stève...les mots ne suffisent pas je pense pour exprimer tout ce que je ressens. Merci beaucoup de m'avoir accueilli, et tout ce qui va avec. Vous m'avez énormément aidé durant ces 5 ans et vous le faites toujours. Mon petit frère, Joris et ma petite sœur Julia, vous me redonnez le sourire, la joie quand les choses ne vont pas bien... Vous êtes ma famille.

« Pa » mo dédié en parti sa doctorat la pu twa. Mo ti touzour dir toi mo pu fer ene manière gagn sa titre docter la mais ester la to népli la parmi nou. Mo espéré mo fer toi fier la cot to été. To ti fer boucou sacrifis ek zefor, to pane tro rode montré to soufrans, malérézema maladie ine pran toi. « Ma » mo coné sa ti compliké kan mone kite moris pu vine isi, zefort ki tone fer pu nou moi ek Alexandre pou avoy nou lekol, travay couma bef to abitié dir. Pou tou sa bane sacrifis ki tone fer pou nou 2. Sa bane dernier l'ané la mone laisse twa tousel ek tou sa bane fardo la Alexandre. Noune perdi boucou dimoune Christopher, Chenne, Titoine... tone bizin pran relev sans moi. Mais mo espéré ki ester ki tou pou pass bien. « Mami », Alexandre ek «matante » merci pou tou ceki zot ine fer pu mwa, tout le temps pé motiv mwa, encouraz mwa,... nou zwen biento. To all people that I did not mention...A big thank you

Finally, I have to say that I really enjoyed the last 3 years working here.

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Abbreviations

5-HMF	5-hydroxymethyl furfural
BCF	Tris(pentafluorophenyl)borane
Bnep	5,5-dimethyl-1,3,2-dioxaborolane
CMD	Coordination-Metalation-Deprotonation
CMF	5-(chloromethyl)furfural
COD	1,5-Cyclooctadiene
COE	Cyclooctene
dba	dibenzylidene acetone
DESI-MS	Desorption Electrospray Ionisation- Mass Spectrometry
DFF	2,5-diformylfuran
DFT	Density Functional Theory
DIPEA	Diisopropylethylamine
dipphen	2,9-diisopropyl-1,10-phenanthroline
DMF [#]	2,5-dimethylfuran
DMPU	<i>N</i> , <i>N</i> ′-Dimethylpropyleneurea
dppe	1,2-Bis(diphenylphosphino)ethane
dtbpy	4,4'-Di- <i>tert</i> -butyl-2,2'-dipyridyl
FDCA	2,5-furandicarboxylic acid
FFA	Furfuryl alcohol
GVL	Gamma-valerolactone
HFIP	Hexafluoropropan-2-ol
HMPA	Hexamethylphosphoramide
HOMSi	[2-(hydroxymethyl)phenyl] dimethylsilyl
IPr	1,3-bis(2',6'-di <i>iso</i> propylphenyl)imidazol-2-ylidene
LUMO	Lowest Unoccupied Molecular Orbital
Me-THF	2-methyltetrahydrofuran
MF	2-methylfuran
NaBArF ₄	Tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
NFPT	N-fluoropyridinium triflate
NMP	<i>N</i> -Methyl-2-pyrrolidone
NXS	<i>N</i> -halosuccinimide
phen	1,10-phenanthroline
PMP	<i>p</i> -methoxyphenyl
Ру	Pyridine
TBAT	Tetrabutylammonium difluorotriphenyl silicate
tfa	trifluoroacetic acid

GENERAL INTRODUCTION

Despite depletion of fossil resources, products derived from the petroleum industries still remain the main source of carbon, whether for fuel or for fine chemicals. Therefore, the transformation of biomass derivatives, especially those coming from agricultural wastes, such as furfural and 5-(hydroxymethyl)furfural (HMF), are of particular interest as renewable sought-after raw materials for the sustainable production of value-added compounds. In particular, the direct functionalization of furfural and derivatives by selective C–H activation is an emerging field that is attracting considerable attention.

Classical methods for achieving C–H functionalization often generate non-negligible amount of wastes (salts) or require high temperatures or harsh conditions. Catalytic C–H activation has been considered as a pinnacle of success by organic chemists, for their atom economy and the possibility to employ non-activated substrates. More importantly, selective C–H bond transformations represent a big challenge in unlocking a direct access to new molecules by controlling the regioselectivity of transformations.

Catalytic C-H activation



In this perspective, the formation of new bonds through direct transition metal (TM) catalyzed C–H activation process on furfural derivatives is an extremely attractive eco-compatible strategy and especially without prior modification of the redox state of the aldehyde function in C2 position. In particular, most of the reported examples address the functionalization at C5 of the furan ring, which is the richest site of the ring. In contrast, C3–H functionalization at the formyl-furan unit *via* directing groups, such as an imine functions, that bypass the natural C5 preference has been much less studied and remains a challenge (Figure 1).



Figure 1. Directed C3-H activation of furfurylimines: the first objective

Arylsilanes have long been used, and still receive considerable attention, by the organic chemist community. These heteroarylsilanes represent robust carbanion surrogates endowed with a number of features such as ready availability, relatively low cost, low toxicity and excellent functional-group tolerance. These attributes make them highly attractive building blocks in the context of sustainable chemical synthesis and many efforts have been devoted to develop methods for the construction of $C(sp^2)$ –Si bonds from various starting materials.



In this context, in order to access versatile platforms derived from furfurals that could undergo numerous post-functionalizations, the C3 selective TM-catalyzed C–H-to-C–Si bond transformation was envisaged during this PhD. Special attention was then given to the activation of these silyl-furfural synthons for the subsequent formation of C–C bonds and C–X bonds, where X is a heteroatom, and thus the synthesis of an even broader range of polyfunctionalized furanic synthons (Scheme 1).



Scheme 1. Post-functionalizations of C3-silyl-furfurals: the second objective

The manuscript will be divided in four chapters. The first chapter will be devoted to the state of the art regarding the functionalization of each of the three aromatic C–H bonds of furfural and derivatives *via* diverse methods. Then, the silylation methods by catalytic C–H activation will be reported, and some of them will be applied to the selective silylation at C3 of furfurylimine derivatives. Once the silylated platform has been created, the activation of the silyl moiety will be studied in two ways in order to set up different post-transformations. In chapter 3, the functionalization of the $C(sp^2)$ –Si bond through intramolecular activation of furfuryl alkoxides will be presented. Then, chapter 4 will be devoted to fluoride-mediated activation strategies. The latter will be divided into two subchapters dedicated respectively to the functionalization of C3-silylated furfuryl alcohols and C3-silylated furfural derivatives.

CHAPTER I: Furfural and Derivatives

Biomass valorization: furfural and 5-hydroxymethylfurfural

Despite advances in research, fossil resources are still the main source of (petroleum-based) raw materials, fuel and carbon. With the increase in global consumption, along with environmental and political related problems, there is an urgent need to reduce our dependency on these exhaustible resources. One of the alternatives to overcome this issue is the use of renewable biomass, constituted abundantly of carbohydrates, which are ideal precursors for the production of inexpensive and ecological chemicals.

Such prospect raises nevertheless issues associated to a negative impact on food production, as it might deviate food crops towards other uses. In this aspect, lignocellulosic materials (cellulose, hemicellulose and lignin), being non-edible, do not suffer from the above-mentioned drawbacks. More interestingly, they also represent the most abundant plant dry matter on earth which can be used as carbon source in biorefinery,^[1] and is often present in high quantity in agricultural wastes, namely corn cobs, wood chips, oat hulls, bagasse and many more. Several useful molecules can be obtained by the hydrolysis and degradation of lignocellulose. Specifically, furfural (1) and 5-hydroxymethyl furfural (5-HMF, 2) are produced in large quantities from these food crop residues and wastes from wood industry (Figure 2).



Figure 2. Furfural and 5-hydroxymethyl furfural (5-HMF)

Furfural can be obtained in 18–84% yields from acid-catalyzed dehydration reaction of hemicellulose-rich materials, especially the arabinoxylane **3** polysaccharides. Cyclodehydration of the resulting pentose sugars, such as D-xylose (**4a**) and L-arabinose (**4c**), provides furfural (Scheme 2).^[2] Currently, China is the biggest producer of furfural, representing 90% of the global world capacity (200 kt/year).^[3,4]



Scheme 2. Acid-catalyzed degradation of hemicellulose into furfural

In addition, the acidic degradation of biomass containing hexoses leads in a very similar way to 5-HMF. Different substrates can be used: the hexoses themselves such as D-fructose **5** (Scheme 3), oligoand polysaccharides, as well as industrial waste.^[5]



Scheme 3. Conversion of D-fructose into 5-HMF

The US Department of Energy classified furfural and 5-HMF among the "Top 10" value added chemicals from biomass.^{[6],[7]} It especially implies the use of these platform molecules^[4] for the sustainable production of furan-based molecules which can be of key relevance for the manufacturing of industrial solvents (furan-based), biofuels (Me-THF), as monomer for plastics, or even in the pharmaceutical industry.^{[8],[9]} The most important compounds obtained from furfural or 5-HMF are shown in Figure 3.

(a) Products derived from furfural (1) and their uses



*RCC: Reinforced Carbon-Carbon

Figure 3. Main industrially relevant compounds obtained from furfural and 5-HMF

Among the principal issues for moving towards biomass development is the production cost, implementation of new industrial technologies and logistics. Of the world production of furfural (1), 60–70% is converted to furfuryl alcohol, which is the main ingredient for furan resins employed in metal casting. The remaining part is used as: (a) extractant for aromatics and other polar compounds from lubricant oils and petroleum; (b) purification solvent for C4 and C5 hydrocarbons; (c) reactive solvent and wetting agents for phenolic resins; (d) nematode control agents for crops; (e) chemical feedstock for numerous derivatives, particularly for furan-containing compounds.^[10] Hence, despite an obvious interest and competitiveness for the transformation of furfural, there are still limited applications as biomass-based material for added value chemicals. Towards this end, achieving selective functionalization of the heteroaromatic ring appears a key endeavor to access a larger array of potentially useful compounds and thereby valorize the furfural biomass-based materials.

Selective functionalization of furfural derivatives

With the emergence of the concept of green chemistry, sustainable development and the need to increase atom economy in processes, transition-metal-catalyzed C–H bond activation reactions have gained paramount importance. This technique allows to decrease the number of steps generally necessary for the introduction and removal of functional groups, and thus to form C–C or C–X bonds by direct C–H bond functionalization. Accordingly, the functionalization and transformation of furfural derivatives by C–H bond activation is currently a competitive area of research, providing access to new

functionalized building blocks of interest to the pharmaceutical and agrochemical industries. As C–H bonds are strong and poorly polarized, their activation represents a challenge for the chemist.

Furfural is composed of a heteroaromatic ring, an aldehyde function and three different aromatic C– H bonds (Figure 4). Only few methods allowing the transformation of these C–H bonds have been so far reported. In the following section, the different approaches implemented for the functionalization of each position of the furan ring will be discussed.



Figure 4. Furfural

2.1 C5-functionalization

It is well established that in furanic cores the C–H bonds α to the oxygen atom are the more reactive ones. Thus, not surprisingly, in the case of furfural, the strategies for C5-functionalization have so far attracted most of the attention.

2.1.1 Arylation

One of the most common ways to functionalize furfural at C5 is the catalytic arylation reaction, which was been achieved with several transition-metal catalysts. The first example of C5-direct arylation applied to furfural **1** was developed by McClure and co-workers in 2001.^[11] The reaction was carried out with PdCl₂ as pre-catalyst, in the presence of aryl iodide, KOAc, Bu₄NBr and in DMF at 110 °C (Scheme 4). In this case, the selectivity is driven by the innate reactivity preference of the substrate for the C5 position. The yields are high, but a large excess of furfural is necessary, and this was attributed to competitive homocoupling of furfural.



Scheme 4. McClure's procedure for Pd(0)-catalyzed arylation at C5-H of an excess of furfural

In 2009, an improved protocol for direct C5-arylation was also developed by Fagnou with a stoichiometric amount of furfural **1** and aryl bromide in the presence of Pd(OAc)₂, Cy₃P•HBF₄ and K₂CO₃ as a base (Scheme 5a).^{[12][13]} Substoichiometric amounts of pivalic acid are also mandatory to increase reactivity which can be attributed to a concerted-metalation-deprotonation (CMD) mechanistic pathway for C–H activation, wherein, the pivalate serves as a soluble proton transfer agent from the arene and palladium catalyst to the insoluble carbonate base. Under similar conditions, Soos and co-workers also performed the arylation reaction with a preformed Pd(0) catalyst having (3,5-bis(trifluoromethyl))triphenyl phosphine as ligand (Scheme 5b),^[14] while an aerobic version was performed from bulky α -hydroxyimine palladium complexes as pre-catalyst (Scheme 5c).^[15]



Scheme 5. Pd(0)-catalyzed arylation at C5–H of furfural as limiting reagent

Another method for the arylation of an aromatic ring is the decarboxylative coupling from an aromatic carboxylic acid. Su and co-workers reported in 2014 the sole example of this reaction on furfurals (Scheme 6).^[16] The reaction, selective for the C5 position, is catalyzed by Pd(tfa)₂, which performs the C–H activation on the furan, in the presence of Ag₂CO₃, which promotes the decarboxylation of the carboxylic acid. Transmetalation between Pd-furyl and Ag-aryl species, followed by reductive elimination, affords the cross-coupling product.



Scheme 6. C5 decarboxylative coupling of furfural with aromatic carboxylic acids

On a rarer basis, dual C–H activations of furfural **1** and simple arenes was achieved through Pdcatalyzed oxidative aromatic coupling. Most of the cases involve the use of an excess of the furfural and the use of a stoichiometric amounts of an oxidant. The examples in Scheme 7 show the use of furfural **1** as the limiting agent with NFPT (*N*-fluoropyridinium triflate) as oxidant^[17] (Scheme 7a), and copper(II) acetate as oxidant in the second case (Scheme 7b).^[18] These reactions are proposed to proceed through a Pd(II)-Pd(IV) catalytic cycle, wherein the substrates are activated by an electrophilic palladation mechanism. This pathway would prefer the C-5 over the C-4 position because of the resonance stability of the cation resulting from S_EAr and the higher acidity of the C–H at C5 than that at the C4 position.



Scheme 7. Pd(II)-catalyzed C5 oxidative arylation of furfural with simple arenes

C5-arylation was also achieved under copper-catalysis. You and co-workers reported a copper(I)iodide catalyzed cross-coupling involving *p*-iodomethoxybenzene and two equivalents of furfural **1** (Scheme 8). The reaction yielded 72% of the arylated product.^[19]



Scheme 8. Copper-catalyzed arylation at C5-H of furfural

2.1.2 Alkenylation

As early as the 1980s, direct alkenylation of an excess furfural with diphenylacetylenes as the reactive partner was reported under rhodium catalysis (Scheme 9).^[20] Harsh conditions, such as a high pressure of carbon monoxide and high temperatures were involved in this reaction to obtain the C5-alkenylated product in 41% yield (based on the alkyne) as a mixture of Z:*E* isomers in 59:41 ratio. Regarding the alkyne, the reaction is a hydroarylation since a C–H bond of the substrate is activated by the metal, and then addition on the unsaturated reaction partner (in this case, the acetylene) occurs.



Scheme 9. Rh-catalyzed C5-alkenylation of furfural with diphenylacetylene

Later, C5-alkenylation of C2- and C3-substituted furan substrates was performed under palladium(0)-catalysis through a similar alkenylation reaction using a Pd(dba)₂/PCy₃ catalytic system with a carboxylic acid additive (Scheme 10). Here, after coordination of the alkyne to the Pd(0) complex, the carboxylic acid reacts to generate an alkenylpalladium amylate complex. The regioselectivity is probably derived from the steric repulsion between bulky substituents on the alkynyl carbon and the palladium center. Then, a C–H activation of **1** (*via* the CMD pathway) takes place to give the corresponding single and double alkenylated products.^[21] Reductive elimination of the alkenyl-palladium-aryl complex leads to a syn-addition product. It should be noted that the reactive aldehyde group remains intact during this reaction.



Scheme 10. Palladium/carboxylic acid-catalyzed alkenylation of furfural with alkynes

Interestingly, when a competitive reaction between furfural (2-furancarboxaldehyde) and 3-furancarboxaldehyde was carried out under the same conditions (Scheme 11), C–H alkenylation occurred predominantly on the 3-furancarboxaldehyde regioisomer (at C2). This result suggests that an electron-deficient directing group enhances the reactivity of the C2–H bond in spite of a higher steric hindrance.



Scheme 11. Competition experiments between 3-furancarboxaldehyde and furfural

C5-fluorosulfonylvinylation of furfural **1** was carried out under oxidative conditions with silver(I) acetate as oxidant, $Pd(OAc)_2$ and a pyridine-based ligand (**L1**) in HFIP to yield a β -heteroarylethenesulfonyl fluoride in moderate yield (Scheme 12).^[22] The electron-deficient 2-pyridone ligand is crucial for this transformation in accelerating the C–H cleavage step as an inner base and stabilizing the active palladium catalyst. Similar Fujiwara-Moritani-type processes were also reported by Itahara from electron-poor alkenes, but in the presence of a stoichiometric amount of $Pd(OAc)_2$.^[23,24]



Scheme 12. Pd-catalyzed C5 oxidative alkenylation of furfural with vinyl sulfonyl fluorides

2.1.3 Alkynylation

The alkynylation of furfural **1** with phenylacetylene was also developed. Using $Pd_2(dba)_3$ as precatalyst and an Ag(I)-based oxidation system, C5-alkynylated furfural was produced in 45% yield (Scheme 13). The reaction proceeds through the formation of an alkynyl-Ag(I) species,^[25] which then transmetalates with a Pd(II) species (or Ar–[Pd(II)] generated through a CMD mechanism) from which reductive elimination produces the final product; thus, Ag(I) is implied not only as oxidant of Pd(0) to Pd(II), but also takes part in the formation of the reactive alkynyl intermediate.



Scheme 13. C5-alkynylation of furfural with phenylacetylene

2.1.4 Alkylation

Besides these catalytic C–H activation processes, functionalization at C5 was also achieved through stoichiometric metalation. In 1985, Chadwick reported the C5-regioselective metalation of furfural following protection of the aldehyde unit as an imidazolidine derivative (**6**) and treatment with *n*-BuLi. (Scheme 14).^[26] The C5-lithiated intermediate **7** undergoes electrophilic substitution with an array of electrophiles, delivering C5-functionalized furfural derivatives following acidic work-up (which also induces aldehyde deprotection).



Scheme 14. Synthesis of C5-subtituted furfurals via a metallo-imidazolidine intermediate

A few years after, Roschanger showed that a similar strategy could be implemented on treatment of furfural with lithium *N*,*O*-dimethylhydroxylamide. No directing effect was observed and deprotonation with *n*-BuLi occurred regioselectively at C5 (Scheme 15).^[27] Trapping with iodomethane and deprotection led to C5-methylfurfural. Later, Killpack demonstrated that using lithium N-methyl piperazide (instead of lithium *N*,*O*-dimethylhydroxylamide) also allowed to achieve C5-metalation regioselectively.^[28]



Scheme 15. Use of lithium N,O-dimethylhydroxylamide as an in situ protecting agent for the aldehyde

Finally, Zhou and co-workers reported one example of the alkylation of furfural **1** with alkyl iodides under Pd(0) catalysis.^[29] The reaction with cyclohexyl iodide in the presence of Pd(PPh₃)₄/dppp as catalytic system and Cs₂CO₃ as base, afforded predominantly the C5-alkylated product with only minor amounts of the C3-alkylated isomer in 80% combined yield (Scheme 16). Mechanistically, the authors propose a radical pathway with the formation of an alkyl radical and a Pd(I) intermediate.



Scheme 16. C5-alkylation of furfural with cyclohexyl iodide

Using FeCl₂, a radical approach has also been developed by Nishikata to carry out the selective functionalization of furfural derivatives at the C5 position (Scheme 17).^[30] The alkylation was performed in the presence of a tertiary alkyl bromide and diisopropylethylamine. It was proposed that the alkyl radical generated by single electron transfer (SET) adds to the C5 position. The resulting radical is then oxidized by Fe(III) and the cation trapped by bromide. The presence of base was proposed to be essential for the re-aromatization of the heteroaromatic ring.



Scheme 17. Iron-catalyzed radical C-H alkylation

2.2 C4-functionnalization

In contrast with the C5-position, direct selective C4-functionalization has received little attention. The C4-functionalized products are often achieved by the C2-formylation reaction of C4-substituted furans through the Vilsmeier-Haack reaction.^[31] In addition, they are sometimes obtained as a side product from C5-arylation under acidic media. For instance, Itahara and co-workers reported that under harsh conditions : Pd(OAc)₂ (1 equiv.), furfural and benzene (in large excess) as coupling partners, in acetic acid under reflux, a mixture of the C4- and C5-arylated product was obtained, with a slight preference for the C4-position (Scheme 18).^[24] It is nonetheless important to highlight the absence of the C3-H activation was evidenced, which showed that it is a hardly accessible position. Under similar conditions in acetonitrile, it was noted that biphenyls and furfural dimer were obtained as side products of the reaction.^[23]



Scheme 18. Pd(OAc)₂-mediated oxidative aromatic coupling of furfural and benzene

Later, Doucet reported the selective Pd(0)-catalyzed C4-arylation of 5-methylfurfural using electrondeficient aryl bromides. This cross-coupling was performed under low catalyst loading of dimeric (allyl)palladium chloride with KOAc as base (Scheme 19).^[32] Here, the C5 position of the substrates tested is always substituted so that competition can only occur between C4- and C3-functionalization, and reaction at C4 is favored. Note however that such innate selectivity depends on the base used. Indeed, in the presence of bases other than KOAc (e.g. K₂CO₃, Cs₂CO₃, or K₃PO₄) arylation at C3 was observed leading to C3-arylated or C3,C4-diarylated compounds. The authors rationalized this behavior in terms of a preferred S_EAr mechanism when KOAc is used (which involves a cationic palladium complex), as opposed to an insertion mechanism (Mizoroki-Heck type), favored in the presence of the other bases. However, the yields of 5-methyl furan 2-carboxaldehyde products are significantly lower than the ketone counterpart. This behaviour can relate to the use of an excess of furan substrate, because furfural is known to undergo decarbonylative processes under certain conditions unlike the ketone derivative.^[33]



Scheme 19. Pd(0)-catalyzed arylation at C4-H of furfural

While the above-discussed results establish that C4-functionalization may be achieved through Friedel-Crafts-type^[34] reactivity, only a very limited amount of work has been accomplished towards this goal, which leaves much room for future work on this direction.

2.3 C3-functionnalization

Functionalization of the C–H bond at C3 of furfural derivatives has attracted considerable attention. Given that innate selectivity is rarely in favor of this position, selective functionalization relies mostly on directed activation strategies that take advantage from the carbonyl substituent at C2.

2.3.1 Directed metalation

In 1985, Chadwick and co-workers developed methodologies for the selective functionalization of five-membered heteroarenes through directed metalation using amides as directing groups, and implemented this strategy for the C3-functionalization of the furan ring.^[35] They noticed that poor yields were obtained with tertiary carboximido groups, while with secondary amides, better yields and selectivity were obtained. It was suggested that following deprotonation of the amide with one equivalent of *s*-BuLi, the resulting lithiated intermediate **8** directed the second deprotonation towards the C3–H, delivering **9**. Subsequently, trapping of **9** with electrophiles, allowed to obtain various C3-substitued furanamides (Scheme 20).



Scheme 20. Directed-metalation of 2-carboxamide-furan

In another approach, Guo and co-workers,^[36] and later Knochel,^[37] considered the use of esters as directing groups for C3-metallation. It is known in the literature that the C5–H is the most acidic proton for this type of heteroaromatic ring, and the group of Knochel calculated pKa values through computational calculations of the different protons for the C2-carboxylate thiophene derivative as shown in Figure 5.



Figure 5. pKa of C-H bonds for the C2-substituted thiophene derivative

From these data, two different protocols were proposed by Knochel to perform the C5 or the C3 functionalization selectively.^[37] In order to perform C5-metalation, TMPMgCl•LiCl was used. Metalation at this position is thermodynamically favoured, since H5 is the most acidic hydrogen atom. By contrast, deprotonation with TMPLi in the presence of either ZnCl₂•2LiCl or CuCN•2LiCl allowed for directed metalation at C3 and subsequent functionalization through metal-catalyzed electrophilic substitution (Scheme 21). The later procedure allowed for direct C3-arylation (Scheme 21, left) and allylation reactions (Scheme 21, right).



Scheme 21. Selective C3 metalation of 2-carboxylate furans

In addition to the previous reports, it should also be mentioned that similar examples of C3 metalation exist with symmetrical substrates bearing ester substituents at the C2 and C5 positions (Scheme 22).^[38] Here, TMPMgCl•LiCl promoted the deprotonation at the C3 position (only one regioisomer can be produced), and the organometallic intermediate was trapped by an acyl chloride in the presence of CuCN•LiCl. This method is compatible with a number of functional groups, including bromide, cyano, silyl, and thiol.



Scheme 22. Preparation of 2,3,5-trisubstituted furans

2.3.2 Directed catalytic functionalization

a. Arylation

Directed catalytic C3–H arylations of 2-acylfurans are quite rare. In an isolated example within a study not devoted to furan functionalization, DeBoef and coworkers reported that 2-acetyl-5-methyl

furan could be arylated at C3–H *via* iron-catalysis (Scheme 23).^[39] Although the value of the transformation is clear, the generality of the method is still to be established, along with deeper knowledge of the reaction mechanism as well as the role of each additive and the need for excess of Grignard reagent.



Scheme 23. Iron-catalyzed C3–H arylation of a 2-acylfuran

Another approach for catalytic C3-directed arylation relies on the Ru(II)-catalyzed cross-coupling reactions of 2-carboxamide furans. Here, the presence of a tertiary amide allows the coordination (through the oxygen atom) to the metal, and thus favoring regioselectivity at the C3-position. Two strategies were developed by Szostak and co-workers (Scheme 24). The first strategy involves a Suzuki-Miyaura-like reaction^[40] between the furanamide and phenyl boronic acid as coupling partner, in the presence of [RuCl₂(*p*-cymene)]₂, AgSbF₆, Ag₂O as mild base and Cu(OTf)₂ under oxidizing conditions (conditions a); the arylated product was obtained in 91% yield. The second strategy involves a Hiyama-Denmark-like reaction^[41] between the amide and phenyl trimethoxysilane, in the presence of the same catalyst, AgSbF₆ and copper(II) fluoride, which is required for the activation of the aryl silane (conditions b); The desired C3-arylated product was obtained in 78% yield.



Scheme 24. Ru(II)-catalyzed C3-arylation of furan-2carboxamides
Very recently, Ananikov reported the Pd(0)-catalyzed vicinal arylation of 2,5-diformylfuran in the presence of aryl iodides (Scheme 25).^[42] No Pd-ligand is necessary and copper(I)-oxide is proposed by the authors to serve as halogen scavenger. These arylations work satisfactorily on the diformylated furan ring, but much less efficiently for analogous 2-formylfuran substrates substituted at C5 or non-substituted, for which lower yields and low regioselectivity was observed. Supported by DFT studies, the authors propose a mechanism involving *syn*-insertion of the arylpalladium(II) complex into the double bond of the furan core, followed by *syn*-dehydropalladation. The latter step appears to be favored only in the case of the presence of a formyl function (as opposed to a carbomethoxy function), as it allows an energetically favored equilibration of the palladium complex *via* enolization, thus favoring an easy *syn*-dehydropalladation.



Scheme 25. Formyl group-promoted catalytic C-H arylation of 2,5-diformylfuran

b. Alkylation

In the 1990s, Murai and co-workers showed that 2-acetylfuran undergoes selective alkylation at C3 in the presence of catalytic $RuH_2(CO)(PPh_3)_3$ and vinyl triethoxysilane, on heating at 135 °C in toluene (Scheme 26).^[43,44] The mechanism of this reaction has been studied both experimentally and computationally. Coordination of the metal to the ketone function, followed by C3–H activation *via* an oxidative addition, leads to a metallacycle which permits regioselective functionalization. The subsequent insertion of the vinyl silane into the Ru–H bond, followed by a reductive elimination, gives the C3-alkylated product.^[45,46]



Scheme 26. Murai reaction on 2-acetylfuran

It was later reported that under similar conditions, aromatic aldehydes undergo decarbonylation,^[33] thus thwarting directed alkylation. Murai proposed two different strategies to overcome this limitation: first, the introduction of a bulky group *ortho* to the aldehyde group; second,^[47] the protection of the aldehyde as aldimine with Ru₃CO₁₂ as catalyst. The nature of the imine was very important here, as it proved to be inefficient towards sterically hindered imines and provided low yields with monodentate imines. While they proved efficient with several aromatic aldehydes, neither of these two approaches was considered with furfural derivatives.

In this context, our group recently reported the Ru(0)-catalyzed C3–H alkylation of furfural *via* the Murai reaction (Scheme 27).^[48] Although (non-surprisingly) direct alkylation of furfural was not possible, only the temporary conversion of the formyl function into a bidentate amino-imine, which acts as directing group, enabled the desired coupling using catalytic Ru₃(CO)₁₂ in presence of vinyl silanes or styrenes. Interestingly, removal of the directing group took place during the purification step, delivering directly C3-alkylated furfural derivatives.



Scheme 27. Murai reaction of furfurylimines catalyzed by ruthenium

Following on this work, a carbonylative version of the alkylation reaction was achieved by working under CO atmosphere (1 bar) (Scheme 28).^[49] Once again, the process is highly dependent on the nature of the imine directing group. While no reaction occurred with bidentate amino-imines or sterically demanding imines, the use of aromatic electron rich monodentate *p*-methoxyphenyl imine (PMP-imine) led to the formation of the C3-acylated products of furfural and other C5-substituted furfural derivatives. The latter could be obtained after column chromatography on silica-gel without hydrolysis of the PMP-imines (which are more robust than the bidentate alkyl imines previously employed), and the aldehyde function could be recovered by subsequent hydrolysis. Following theoretical studies, it was proposed that the presence of CO in the reaction medium leads to the formation of mononuclear Ru(CO)₃, which is the active catalytic species upon complexation with the monodentate imine.



Scheme 28. C3-acylation of furfural and derivatives with aromatic imines

More recently, our group also developed the directed Ru(0)-catalyzed C3–H alkenylation of furfuryl imines using electron poor alkenes as vinyl partners. Interestingly, this unprecedented dehydrogenative coupling does not need the presence of an additional sacrificial oxidizing agent (Scheme 29).^[50]



Scheme 29. Acceptorless Ru(0)-catalyzed C3–H alkenylation of furfuryl imines.

This C3 transformation was extended to arylation and alkenylation through a Ru(0)-catalyzed directed C–H activation using aryl/alkenyl boronic esters.^[51] The reaction was proposed to proceed in a similar fashion on electron-rich aromatic imines, except a sacrificial hydride acceptor such as benzylidene acetone was added, in order to trap the hydride coming from the C–H activation step (Scheme 30). This reaction provides access, after imine hydrolysis, to C3–arylated or vinylated furfural derivatives.



Scheme 30. C3-arylation of alkenylation of furfural and derivatives with aromatic imines

This methodology was then applied in collaboration between our team and that of Prof. C. Afonso. In this study, a chemoselective sequence including enzymatic desymmetrization by flow chemistry in the presence of Candida Antarctica Lipase B (CAL B), followed by arylation through Ru(0)-catalyzed C–H activation was developed to obtain differently trisubstituted furans from esters derived from 2,5-furan dicarboxylic acid (FDCA) (Scheme 31).^[52] Despite the presence of two functional groups: ester and amide, the reaction proceeded with a good regioselectivity controlled by the amide group in presence of RuH₂(CO)(PPh₃)₃ as pre-catalyst.



Scheme 31. Chemoselective sequence: enzymatic monoamidation by flow chemistry/C3-arylation in flask of FDC-derived esters

Objectives

Due to the significance of furfural and 5-HMF as potential building blocks for industrially relevant compounds, it is highly desirable to achieve their functionalization through the selective formation of new bonds. Within a broad project directed towards the sustainable functionalization of bio-sourced furfurals, the selective formation of new bonds through direct transition metal catalyzed C–H activation process, without prior modification of the redox state of the aldehyde function, has become one of our emerging areas of research.

As demonstrated by our literature survey, direct selective functionalization of the C3 position is not well-established and remains less common than functionalization at the C5 position. In this context, it should first be underscored that the directed C3–H metalation reactions using lithium, magnesium or zinc amides was only implemented on acylfurans bearing ester^[37] or amide^[35] units, i.e., on substrates having a higher oxidation state than the parent aldehyde. Importantly, we also established that the directed metalation strategy is inefficient when directly applied to furfural derivatives, due to the degradation of the elusive C3-lithiated furan.^[53]

Hence, our efforts to achieve the functionalization of furfurals focused on TM-catalyzed C–H activation process. Following a thorough exploration that considered several hypotheses, it is believed that C3–H activation is more probable to be achieved by nucleophilic transition metal catalysts that can undergo an oxidative addition step. On the contrary, electrophilic TM-complexes that elicit S_EAr or concerted-metalation-deprotonation mechanisms are less favorable. So far, methods for selective C3-alkylation, arylation and alkenylation have been developed in the group, but there is still much room for improvement in the valorization of furfural.

Now, still with the idea of developing new methods of functionalization of furfural derivatives, and more particularly to lead to platforms that can allow us to introduce a variety of functions, we envisage a particularly attractive strategy involving the synthesis of C3-silyl furfural derivatives and the subsequent functionalization of the $C(sp^2)$ –SiR₃ bonds formed (Scheme 32). It is known that organosilicon reagents are a powerful tool for chemists to perform a number of synthetically useful transformations. In this aspect such a C3-silylated-furfural platform could allow through C–Si bond functionalization approaches to access a number of original transformations involving C–C or C–heteroatom bond-formations.



Scheme 32. Objective: synthesis of C3-silyl furfural derivatives and the subsequent functionalization of the C-SiR3 bonds

In the next chapter, direct silulation methods will be briefly reviewed, as well as their applicability on furfural derivatives.

CHAPTER II: Silylation of C(sp²)–H Bonds

Introduction

Alkenyl-, aryl-, and heteroarylsilanes are robust carbanion surrogates endowed with a number of features such as ready availability, low toxicity and excellent functional-group tolerance. These attributes make them highly attractive building blocks in the context of sustainable chemical synthesis and many efforts have been devoted to develop methods for the construction of $C(sp^2)$ –Si bonds. In this section, we will discuss the different methods of silylation of aryl- and heteroaryl derivatives using directing and non-directing groups. Given the wealth of reports on such $C(sp^2)$ –Si bond-formation reactions, only the most relevant examples in the context of our work will be presented.

Arylsilanes have long been known and prepared traditionally by reaction of organometallic reagents (organolithium or Grignard reagents) with chlorosilanes^{[54][55]} (Scheme 33). However, this approach can meet limitations associated with low functional group compatibility of the preparation of the arylmetal. The latter is achieved through reductive metalation of haloarenes or deprotonation of arenes.



Scheme 33. Traditional methods for the preparation of arylsilanes from aryl-metal

Other methods for the preparation of (hetero)arylsilanes rely on cross-coupling reactions between hydrosilanes or disilanes and aryl halides (Scheme 34). These coupling reactions have been achieved using organometallic catalysts such as Rh(I) and Pd(0). Implementation of such approach requires nevertheless the pre-functionalization of the corresponding arene to its halide counterpart.^[56–60]



Scheme 34. Cross-coupling of aryl halides with hydrosilanes or disilanes

Lately, dehydrogenative silylation systems involving the cross-coupling reaction of (hetero)arenes and hydrosilanes or disilanes have attracted a lot of interest as a more step- and atom-economic alternative to the two previous methods (Scheme 35).^[61] Achieving control of the regio- and chemoselectivity during these transformations, and also preventing competitive protodesilylation of the substrate,^[62] are the main issues that need to be solved to obtain a synthetically useful methodology. Many parameters have to be taken into account for this purpose, such as: i) the nature of the silicon moiety, which includes the number of the substituents and their corresponding natures (trialkyl, triaryl or trialkoxy silane), ii) its functional group tolerance and iii) the nature of the arene (and its directing group, if applicable). We will now address recent advances concerning the dehydrogenative silylation of non-activated C–H bonds.



Scheme 35. Catalytic dehydrogenative silylation of C-H bonds

Overview of dehydrogenative silylation methods

Non-directed dehydrogenative silvlation of arenes has been achieved so far according to three main types of reactions, namely: (a) electrophilic substitution reactions, (b) free-radical silvlation, and (c) transition-metal (TM) catalyzed reactions (Scheme 36). The site-selectivity in some cases is innate to the substrate, while in other cases, modulation reaction parameters, such as the ligand could bring about a preferential regioselectivity.

a) C(sp²)–H silylation via aromatic electrophilic substitution:





c) C(sp²)–H and C(sp³)–H silylation via transition-metal (TM) catalyzed Si–H/ C–H activation:



Scheme 36. Non-directed dehydrogenative silylation

2.1 Electrophilic substitution

Sila-Friedel-Crafts reactions were developed from hydrosilanes. Different ways of activation of the Si–H bond have been envisaged in such cases. For example, in 2010 Kawashima reported the use of trityl cation for the hydride abstraction of a dialkylaryl hydrosilane providing a silylium ion which is prone to perform an intramolecular sila-Friedel-Crafts reaction with a tethered arene, in the presence of 2,6-lutidine (Scheme 37a).^[63] The intermolecular version of the reaction was also possible under similar conditions: triphenyl silane was converted into tetraphenyl silane (Scheme 37b), even though in this case, the silylated arene (benzene) was used as solvent.



Scheme 37. Sila-Friedel–Crafts reaction

The Oestreich group developed the regioselective intermolecular electrophilic C–H silylation of nitrogen-containing electron-rich arenes such as indoline or aniline derivatives, under iron Lewis-acid catalysis (Scheme 38).^[64] The use of FeCl₂ in combination with NaBAr^F₄ (also referred as $[Na]^+[B(C_6F_5)_4]^-$) showed a co-operative effect for the electrophilic aromatic substitution (S_EAr), under base free conditions. It was suggested that the potential formation of "[FeCl]+[BAr^F₄]" allows the generation of a stabilized silylium cation, which allows for a Friedel-Crafts-type of reaction. The site-selectivity is innate and favors the substitution *para* to the nitrogen atom. Note that dehydrogenative Si–N silylation was observed when arenes having free NH groups were used. Similar reactivity was observed with cationic Ru–S complexes, to afford the C3-silylated indole derivatives.^[65]



Scheme 38. Electrophile C-H silylation of electron-rich arenes

The use of Lewis acids such as $B(C_6F_5)_3$ has also gained considerable interest for the Si–H bond activation.^[66–68] Indeed, this is a Lewis acid of choice, combining considerable electrophilicity with sufficient size to "frustrate" the formation of Lewis adducts. $B(C_6F_5)_3$ thus activates R_3Si –H via a frustrated Lewis pair, leading to the generation of R_3Si^+ . This silylium ion is transferred to the heteroarene leading to the formation of an arenium ion (C) and a borohydride. Finally, in the re-

aromatization step with the $[HB(C_6F_5)_3]^-$ anion, H₂ and the boron catalyst are (re)generated. After this step, in order to avoid a competing pathway leading to the reduction of arenes with H₂, the addition of the pyridine base in catalytic amount provided better results. This reaction is also highly substrate dependent, for example, with 2-*tert*-butyl thiophene, a higher yield of silylated product could be obtained compared to the 2-methyl thiophene due to a catalytic hydrogenation of 2-*tert*-butyl-thiophene retarded by coordination of 2-*tert*-butyl-tetrahydrothiophene to B(C₆F₅)₃. In addition, the Brønsted basicity of the heteroarene also plays an important part in H₂ activation, and therefore the competitive reduction. As a consequence, a higher proportion of reduced *N*-TIPS indole was obtained compared to the 2-2-*tert*-butyl-thiophene (Scheme 39).^[69]



Scheme 39. Dehydro-/hydro-silylation catalyzed by $B(C_6F_5)_3$

In 2016, Hou reported a boron-catalyzed C–H silylation of aniline under base-free conditions with hydrosilanes (Scheme 40).^[70] It was also proposed that the interaction between the $B(C_6F_5)_3$ and the hydrosilane weakens the Si–H bond. The electropositive silicon intermediate would therefore undergo a nucleophilic attack by the electron rich arene in *para* position, resulting in the intermediate ion pair. Upon rearomatization by deprotonation of the borohydride, the *p*-substituted aniline could be obtained, with the regeneration of the boron catalyst.



Scheme 40. Boron-catalyzed C-H bond silylation with hydrosilanes of anilines

2.2 Radical silylation

Recently, a cross-dehydrogenative heteroaromatic C–H functionalization with hydrosilanes catalyzed by an alkaline earth metal reagent was reported.^[71,72] The authors demonstrated that in the presence of trialkylsilanes, potassium *tert*-butoxide in catalytic amount, the C2-position of indoles was preferentially functionalized (Scheme 41). This reaction takes place in mild conditions, in the absence of hydrogen acceptors, ligands or additives, and is applicable on various N-, O- and S-containing heteroarenes. However, this silylation was found to be reversible, as when performed at higher temperatures or longer times, the regioselectivity turned out to be in favor of the thermodynamic product, C3-functionalized. Nevertheless, experimental and computational mechanistic studies did not allow the authors to decide between a radical or an ionic mechanism for these transformations.^[72]



Scheme 41. t-BuOK-catalyzed dehydrogenative silylation of indoles with hydrosilanes

Indeed, the formation of silicon-centered radicals is a useful strategy in the creation of C–Si bond through Si–H and C–H bond transformation. There are several ways of initiating such radical reactions. Peroxides have often been used as an initiator. Thermal assistance^[73–75] or copper (I/II)^{[76][77][78]} are often used for the generation of alkoxy radicals (Scheme 42). The latter can therefore perform hydrogen abstraction from hydrosilanes producing the reactive silyl radicals, which add to the aryl species. Upon oxidation of the aryl radical, and subsequent deprotonation, the silylated aryl is obtained.^[77–79]



Scheme 42. Silicon-centred radicals involved in dehydrogenative silylation

2.3 Transition-metal catalyzed silylation

Until now, most dehydrogenative silylation reactions achieved between hydrosilanes (or disilanes) and (hetero)arenes have been conducted using transition metal (TM) based-organometallic catalysts. As a general way of representing this reaction, there is the formation of a $C(sp^2)$ –Si bond and the release of H₂ gas (or a hydrosilane) as represented in Scheme 43. In a (very) schematic mechanistic view, a silicon metal species [M]–SiR₃, formed by the oxidative addition of a hydride metal intermediate to a hydrosilane (or a disilane) followed by the release of H₂ (or hydrosilane), can perform the C–H activation step of the arene. A reductive elimination step leads to an arylsilane and regenerates the hydride–metal active species. As will be discussed hereafter, a number of variations to this general mechanism exist.



Scheme 43. Transition-metal catalyzed silylation with hydrosilanes or disilanes

Based on DFT calculations for the silvlation of benzene, it has been shown that the reaction is thermodynamically unfavorable when performed with hydrosilane, by contrast to the one performed with disilane, which relates to the smaller bond dissociation energy of Si–Si bond (Scheme 44).^[80]



Scheme 44. C-H bond silylations based on bond-dissociation energies (DFT)

2.3.1 Silylation involving disilanes

Benzodisilacyclobutenes proved to be useful reagents for arene C–H silylation. A Ni(0) catalyst could perform an insertion into the strained Si–Si bond and the resulting intermediate could undergo oxidative addition into a C–H bond of an arene (Scheme 45).^[81] Succeeding reductive elimination leads to the silylated product. The remaining silicon atom acts as hydride acceptor which allows to close the catalytic cycle (Scheme 45). The effect of the different arenes according to steric considerations was put in evidence. *Meta*-substitution is favored with mono-substituted arenes (toluene, *iso*-propylbenzene) and for *m*-xylene, while for *p*-xylene *ortho*-substitution is observed.



Scheme 45. Nickel-catalyzed reactions of benzodisilacyclobutene with aromatic compounds

Under iridium(I) catalysis, the synthesis of aryl halosilanes was developed starting from 1,2-di-*tert*butyl-1,1,2,2-tetrafluorodisilane $(t-BuF_2Si)_2$ and an excess of the arene partner in presence of a bipyridine ligand (Scheme 46).^[82] The regio-selectivity was again governed by steric factors, with C– Si bond-formation occurring predominantly in *meta* position. A lower regio-selectivity was obtained with OMe and Cl substituents.



Scheme 46. Ir(I)/dtbpy-catalyzed aromatic C–H silylation by disilanes

Following on this work, Miyaura screened different bipyridine ligands in order to improve the regioselectivity of these reactions.^[83] Optimized conditions permited the reaction between arenes (in lower excess; 10 equiv.) and 1,2-di-*sec*-butyl-1,1,2,2-tetrafluorodisilane (*s*-BuF₂Si)₂ as silylating agent and 2,9-diisopropyl-1,10-phenanthroline (dipphen), with a very good regioselectivity (Scheme 47). The reaction was also independent on the electronic nature of the substituents on the arene.



Scheme 47. Ir(I)/dipphen-catalyzed aromatic C-H silylation by disilanes

Chatani and co-workers reported the rhodium-catalyzed silylation of 2-arylpyridines with hexamethyldisilane.^[84] The first step is an oxidative addition of rhodium(I) species into the Si–Si bond giving a [Rh]–SiR₃ intermediate. Coordination of the pyridine part enhances the activation of an *ortho* C–H bond of the 2-arylpyridine, which is followed by a reductive elimination giving the corresponding silylated aryl-pyridine compounds (Scheme 48).^[85] In addition, the C3 substitution on the pyridine ring provided a better selectivity for the monosilylated product with respect to the di-silylated product, which is related to the unfavorable conformation due to steric repulsion following the first silylation of the ring. Disilanes such as (*t*-BuMe₂Si)₂ and (Et₃Si)₂ did not give satisfying results, which could be related either to the C–H activation or the reductive elimination steps. Moreover, when other directing groups such as amide, imidazole and oxazoline were involved, low or poor results were obtained, which showed the substrate dependence of such reactions.



Scheme 48. Rh-catalyzed silylation of 2-arylpyridines with disilane

In 1995, was reported one of the first imine-directed arene silylations *vi*a platinum-catalyzed C–H activation.^[86] Pt–P(OCH₂)₃CEt was used to catalyze this silylation using disilanes. It was known that [Pt(0)] could perform oxidative addition onto Si–Si bonds.^[87,88] The *N*-benzylidenealkylimines directing group permitted the formation of *ortho*-silylated products, mono- and bis-silylated. However, the reaction was still dependent on other parameters such as the ratio of aryl imine to disilane. For

example, an excess of imine compared to disilane (4:1 ratio) led to 82% yield in monosilylated product and 9% yield in disilylated product. Conversely, when this ratio is reversed, 23% yield in monosilylated and 52% yield in disilylated product was obtained (Scheme 49).



Scheme 49. Pt-catalyzed ortho-silylation of benzylidenealkylimines

2.3.2 Dehydrogenative silvlation involving hydrosilanes

The use of hydrosilanes as silicon donor has been considered. Non-directed silylation of arenes, as well as directed *ortho*-silylations with a number of directing groups such as amides, esters, oxazolines, alcohols, imines and others will be discussed in this section.^[89] Among the group 8 and 9 catalysts such as ruthenium, rhodium and mainly iridium have been the most extensively studied and will be detailed in the next sections. Platinum^[90–92] and iron^[93]-catalyzed silylation, despite showing some potential, often require very high temperature (Pt catalysis) or have not been reported to catalyze directed silylations.

a Effect of the hydrogen by-product

A key difference between systems relying on hydrosilanes as silicon donor and those relying on disilanes, is the requirement for removal or trapping with sacrificial hydride acceptors of released molecular dihydrogen to provide a driving force for the dehydrogenative silylation reaction. This point was well evidenced in a study by Hartwig and co-workers.^[94] For example, the silylation of *o*-xylene, with an [Ir(cod)OMe] and 2,9-Me₂Phen catalytic system in a closed vial with a hydrosilane led to 18% yield of the silylated compound, while in an opened system with a nitrogen inlet a much higher yield (77%) was obtained (Scheme 50). The nitrogen flow in this case, prevented the catalyst inhibition through the removal of H₂ gas. The presence of hydrogen atmosphere as well seemed to significantly reduce the catalytic activity.



Scheme 50. Ir-catalyzed silylation of arenes with hydrosilanes: effect of N2 flow

The authors also reported the use of hydrogen acceptors for this purpose in a closed vessel, in comparison with an opened-system.^[94] Although no real correlation could be established for the silylation yields, the reaction carried in a closed vessel with hydrogen acceptor was considered to be more convenient on a practical aspect, as well as to occur at a faster rate than with a nitrogen stream (Scheme 51). Some commonly used sacrificial hydrogen acceptors are: cyclohexene, norbornene (nbe), cyclooctadiene (cod), dimethyl-2-butene^[62] and 3,3-dimethyl-1-butene (tbe). Several factors might be taken into consideration for the choice of the sacrificial hydrogen acceptor. For example, the steric bulk or the ring strain of the alkene, this might lower the rate of hydrosilylation of such molecules, whilst being prone to accept metal hydrides or molecular hydrogen.



Scheme 51. Ir-catalyzed silylation of (hetero)arenes with hydrosilanes: effect of hydrogen acceptors

b Ruthenium-catalyzed silylation

Initial studies involving ruthenium(II) catalysts were carried out by Berry in 1998, and showed the feasibility of dehydrogenative silylation of trifluoromethylbenzene in the presence of the as sacrificial hydrogen acceptor.^[95] (η^6 -C₆Me₆)Ru(H)₂(SiEt₃)₂ and [(η^6 -C₆Me₆)RuCl₂]₂ showed the best selectivity in favor of the formation of the aryl silane, compared to carbosilane formation by dimerization of triethylsilane or hydrosilylation of the (Scheme 52). Silylation yielded both the *meta*- and *para*-silylated

isomers in a 2:1 ratio; the *ortho* isomer was not detected. The absence of electron-withdrawing substituents was deleterious, leading to poorer results in the case of o- and m-xylene, or to the absence of reactivity in the case of p-xylene and mesitylene.



Scheme 52. Ru-catalyzed silylation of trifluoromethylbenzene with hydrosilanes

Following their previous report for the silylation of heteroarenes using vinyl silanes,^[96] Murai and co-workers developed a new strategy for the silylation with hydrosilanes of arenes bearing an oxazoline directing group.^[97] The *ortho*-directing effect arises from the chelation of a ruthenium(0) catalyst, such as Ru₃(CO)₁₂, to the oxazoline moiety, promoting the C–H activation step through insertion into the C–H bond. As mentioned above, in the absence of the sacrificial hydrogen acceptor (here tbe), a very poor yield (7%) of product was obtained. Thus, equimolar quantities of hydrosilane and the were systematically added, and a 5-fold excess with respect to the arene proved optimal, yielding 93% of desired product, when the reaction was performed with triethylsilane (Scheme 53). The reaction was however quite dependent on the steric bulk and the nature of the silane, because a lower yield (16%) was observed with *tert*-butyldimethylsilane, and it failed with tri-*iso*-propylsilane, triethoxysilane and ethoxydimethylsilane respectively. While this reaction proceeded smoothly with *ortho*- and *para*-subtituted arenes, *meta*-substitution of such systems was quite problematic. Therefore, that study was pursued with these afore-mentioned substituted arenes using RuH₂(CO)(PPh₃)₃ as catalyst, which led to improved results in most cases, to the exception of, electron-withdrawing substituents which lowered the reaction yields.



Scheme 53. Ru(0)-catalyzed silylation of aryloxazolines with hydrosilanes

Ruthenium(0) catalyzed *ortho*-silylation is in fact applicable with a broad scope of nitrogen containing-directing groups, such as imines, amides and nitrogen containing heterocycles (Scheme

54).^[98,99] Furthermore, *ortho*-silylation was also extended to non π -conjugated assistance chelation, with an amine as directing group. While the reaction proved to be efficient with *N*,*N*-dimethylbenzylamine; benzylpyridine, phenyl pyridyl ether and azole derivatives led to the formation of significant amounts of bis-silylation products. One major drawback is the regiocontrol of this reaction. In some cases, such as for 2-phenyl pyridine, the disilylated compound is obtained in considerable amounts, but in others, such as for 3-methyl-2-phenyl pyridine in which there is a proximal methyl group on the pyridine ring providing steric repulsion,^[99,100] the amount is lower.



Scheme 54. Ru(0)-catalyzed ortho-silylation with various nitrogen containing-directing groups

An acceptorless version of dehydrogenative silvlation^[101] exists with similar substrates using $[RuCl_2(p-cymene)]_2$ (1 mol%) as catalyst. The protocol was found to be efficient with Et₃SiH, (Me₃SiO)Me₂SiH and (Me₃SiO)₂MeSiH, but inefficient with HSi(OEt)₃. Nonetheless, high temperatures (200 °C) are necessary to achieve the silvlation.

Quite recently, a strategy involving removable directing groups, known as boron-masking strategy, was developed to obtain the *ortho*-silylation of arylboronic acids. Protection as pyrazolylaniline (pza) boronic esters (Scheme 55, eq. 1)^[102] or anthranilamide (aam) boronic esters (eq. 2)^[103] allowed for efficient *ortho*-silylation with triethylsilane of the parent aryl boronic acids using RuH₂(CO)(PPh₃)₃ as catalyst in the presence of norbornene. The steric bulk of the silane and its respective nature has an influence on the reaction since lower yields are obtained in the case of HSiMe₂*t*-Bu, while the reaction failed with tri-isoproylsilane and triethoxysilane.



Scheme 55. Ortho-C–H silylation of arylboronic acids via removable directing group

Interestingly, a one-pot preparation / C2-silylation of 3-thiopheneboronic acids was performed, through the protection of the boronic acid with pyrazolylaniline followed by the C2 silylation following the previously mentioned procedure.^[102]

c Rhodium-catalyzed silylation

Silylation of arenes using hydrosilanes (or disilanes) under rhodium catalysis has long been reported, in presence of RhCl(CO)(PMe₃)₂ catalyst, triethylsilane and a large excess of the corresponding arene under irradiation.^[104] It has been shown during benzene silylation that a too low Si/Rh ratio (0.1 mol% of catalyst) leads in majority to the biphenyl by-product, whereas with 1 mol% catalyst, triethylphenylsilane becomes the main product (Scheme 56). In terms of mechanism, the original proposal involving a triethylsilyl radical intermediate was later excluded on the basis of the behavior of toluene which undergoes silylation at the aromatic ring (at the *meta* and *para* positions) and not at the methyl group which would be expected in the case of a radical mechanism. The authors also proposed that using RhCl(CO)PMe₃, under irradiation promotes C–H bond activation, at room temperature.



Scheme 56. Rh-catalyzed arene silylation under irradiation

In 1998, Berry investigated the synthesis of aryl silanes from mono-, di- and tri-substituted arenes, using $[Cp*RhCl_2]_2$ as catalyst, triethylsilane as silicon donor and the as hydrogen acceptor.^[95] A competitive reaction between mono-substituted arenes and benzene evidenced a faster reaction rate for electron-poor arenes, which could be related to the C–H activation step being less energetically demanding. Owing to steric congestion, no noticeable *ortho*-silylation could be evidenced with substituted arenes, except with fluorobenzene, for which the formation of the three regioisomers was noted. Mono-substituted arenes led to the formation of mixtures of *meta*- and *para*-silylated isomers in a statistical distribution (Scheme 57). *p*-Xylene and mesitylene did not yield any arylsilane.



Scheme 57. Influence of substituent on silvlation of arenes catalyzed by [Cp*RhCl2]2

In these early studies, arenes are used in high excess and/or as solvent, despite being often the most valuable coupling partner. Other strategies using arenes as limiting reagent were developed next.

As discussed here above, undirected silulation of functionalized arenes gives a statistical distribution of regioisomers. Hence, the use of specific ligands to enhance the regioselectivity in such reactions was contemplated. In 2014, Hartwig developed a strategy which allowed for better regiocontrol based of the

steric congestion of the substituents.^[105] This reaction between a stoichiometric amount of an arene and $HSiMe(OSiMe_3)_2$, using cyclohexene as sacrificial hydrogen acceptor, was catalyzed by $[Rh(coe)_2OH]_2$ in the presence of a bulky bidentate phosphine ligand (L2) (Scheme 58). The silylation of 1,2-disubstituted arenes occurred with good regioselectivity (>80% of major regioisomer) in favor of the isomer having the silicon moiety further away from the bulkiest substituent, and 1,3-disubstituted arenes gave rise only to one regioisomer. Nevertheless, electronic effects had also an impact on the regioselectivity of the reaction. For example, the electron-donating NMe₂ group favored silylation in *para*-position, while electron-withdrawing CF₃ favored silylation at the *meta*-position (to some extent). The reaction scope was also extended to 1,4-disubstituted arenes, which were obtained in good yield and regioselectivity, as well as heteroarenes such as indoles and benzofurans.



Scheme 58. Rhodium-catalyzed intermolecular C-H silylation of arenes with high steric and electronic control

The nature of the ligand plays a crucial role to favor arene C–H silylation over competitive alkene hydrosilylation, as illustrated with the example depicted in Scheme 59. Electron-rich ligand L2 enhances the electron-density of the metal center, which improves the capacity of the Rh–Si intermediate to perform C–H bond oxidative addition, thus leading ultimately to arylsilane formation. Conversely, with electron-deficient ligand L3 the oxidative addition to the arene C–H bond is less favorable and the alkene hydrosilylation pathway becomes predominant.



Scheme 59. Effect of ligand electronic properties on arene vs alkene silylation

An intramolecular version of the Rh-catalyzed arene C–H silylation in "acceptorless" conditions was disclosed by Takai for the preparation of silafluorenes from biarylhydrosilanes using RhCl(PPh₃)₃ as catalyst (Scheme 60).^[106] Though not mandatory, the presence of the improved nevertheless both the yields and rate of the reaction in some cases. As discussed previously, the silylation step is highly dependent on steric effects and thus regiocontrol was achieved in most cases through the inhibition by the R group at the *ortho*-position in the previous examples. The bulkiness of the substituents of the arene undergoing silylation is another important factor influencing the formation of the silacycle. For example, biphenylhydrosilanes bearing two bulky isopropyl groups led to the formation of the corresponding fluorene only in a very poor yield (12%). In terms of mechanism, it could be established in this work through deuterium labelling experiments that the C–H activation step is the rate-determining step of the silafluorene-formation reaction.



Scheme 60. Rhodium-catalyzed intramolecular C-H silylation of arenes

More recently, Shi reported a directed version of dehydrogenative silvlation catalyzed by a Rh(II) catalyst. As illustrated in Scheme 61, phosphine-substituted biaryl derivatives undergo regioselective C–H silvlation with a large variety of hydrosilanes using $Rh_2(OAc)_4$ as catalyst in the presence of norbornene. ^[107] In this case, the regioselectivity is controlled by the complexation of the phosphine moiety to rhodium, which directs the C–H activation event. In addition to the biaryl core, phosphines

having other motifs, including, *N*-aryl pyrrole, ferrocene- and binaphthalene were found to be suitable substrates.



Scheme 61. Rhodium-catalyzed silylation of biaryl-type monophosphines with hydrosilanes

Although rhodium catalyzes intermolecular dehydrogenative silylation of aryl C–H bonds at relatively low temperatures, there still resides some major shortcomings. Firstly, a limited amount of functional groups are tolerated by the current catalytic systems. For instance, heavy halides and carbonyls lead to reduced products, while some nitrogen-based heteroarenes as well as nitrile groups poison the catalyst. In addition, some of the frequently used ligands, such as **L2**, are chiral and are quite costly.

d Iridium catalyzed silylation

Iridium is one of the most commonly used metals when it concerns dehydrogenative silulation, and both undirected and directed silulations have been disclosed.

Undirected iridium-catalyzed intermolecular silylations

The group of Hartwig reported a related Ir(I)-catalyzed protocol for the silylation of (hetero)arenes using HSiMe(OSiMe₃)₂ as silylating agent. Here, substituted phenanthroline ligand L4 is used, under a flow of N₂ or norbornene as hydrogen acceptor (unless specified), and the arene is the limiting reagent.^[94] This protocol was applied to various electron-rich, electron-neutral and electron-poor arenes, as well as C2-substituted (hetero)arenes (whenever applicable), showing the robustness of this catalytic system (Scheme 62).^[94] Experimental studies involving kinetic isotope effects and isolation of the intermediates as well as computational studies have allowed to determine the key steps of this reaction. C–H bond cleavage is rate-limiting for electron-rich arenes, while the C–Si bond formation is considered to be rate limiting in the case of electron-poor and electron-neutral arenes.^[108]



(*) yield when carried in the presence of norbornene (1 equiv.) instead of N₂ flow [*Si*]= SiMe(OSiMe₃)₂



In addition, the selective silvlation of azole derivatives was achieved in high yields in the presence of norbornene as hydrogen acceptor (Scheme 63). The regioselectivity was again governed by the steric constraints of the molecule rather than by electronic effects, which favored silvlation at the sterically less hindered position.



Scheme 63. Ir-catalyzed silylation of azoles

The same group reported also showcased the functional-group tolerance of this silylation procedure. This time, the reaction was run with (hetero)arenes as limiting agent, in the presence of cyclohexene as hydrogen acceptor an [Ir]/L5 catalyst. This was applied to highly functionalized substrates bearing nitrile, ester, ketone and heavy halogen (only trace amounts of the reduction products were observed form iodoarenes) functions, as well as to a variety of sulfur-, oxygen- or nitrogen heteroarenes (Scheme 64). Reaction of five-membered heteroarenes proceeded with high levels of regioselectivity for functionalization of the C–H bonds α to the heteroatoms. Silylation of heteroarenes in which the α -positions are substituted or sterically hindered because of a large substituent on the nitrogen occurred at the β -positions. This includes also C–H silylation of pharmaceutical precursors (Ketotifen, Clopidogrel, Clonidine,...) offering opportunities for late-stage functionalization.



[Si]= SiMe(OSiMe₃)₂

Scheme 64. Undirected iridium-catalyzed silylation of highly functional (hetero)-arenes

Very recently, a silvlation strategy involving chiral bidentate nitrogen-based ligand **L6** was developed, which was found to be highly efficient for the C-5 silvlation of C-3 functionalized heteroarenes, including furans, thiophenes and pyrroles, with cyclohexene as hydrogen acceptor.^[110] This method could by-pass the natural selectivity of the substrate for the C2 position (Scheme 65).



^aCO₂Me instead of CO₂Et

Scheme 65. Ir-catalyzed silylation of 5-membered heteroarenes: High sterically derived selectivity from a pyridylimidazoline ligand

It is known from the literature that 2-methyl phenanthroline could catalyze dehydrogenative silylation processes of norbornene,^[111] while Me₄Phen results in the hydrogenation process to norbornane. This is why, in 2019, the same group investigated the ligand dependence of the silylation of unactivated arenes. Unlike what was previously reported,^[109] the rate of the reaction was investigated with phenanthroline ligands for the silylation of benzene. As previously reported, **L5** showed a higher activity after 27 h of reaction time.^[109] However, for the initial reaction rates (less than 5000 s), the rate of silylation was 5-fold lower with **L5** than with 2,9-Me₂Phen (**L4**), a feature that had remained hidden by the significant drop in the latter's catalytic activity over time. The author attributed it to the catalyst poisoning by H_2 .^[112] Based on the results of the different phenanthroline ligands, the C2 and C9 substitution on the phenanthroline have seemingly a high influence on the initial silylation rate, while substitution on the other positions did not contribute to changes in the silylation rates (Scheme 66).



Scheme 66. Evaluation of phenanthroline ligand for the silylation of unactivated arenes

The high catalytic activity was ascribed to a thermodynamically favorable oxidative addition of C– H bond. This step seems to be reversible taking into account experiments carried out with deuterated arenes. The active catalyst is the square pyramidal iridium (III) hydride complex (G)^[109] obtained by reaction between [Ir(cod)(OMe)]₂, 2,9-Me₂phen, and excess heptamethyltrisiloxane, and characterized by NMR and mass spectroscopies. The presence of substituents in C2 and C9 position of phenanthroline ligand showed high steric strain between the methyl group (pink ball) and X (H and/or SiMe(OSiMe₃)₂). Oxidative addition into the aryl C–H bond resulted in a mono-capped trigonal prism geometry (H), creating a steric relief between the methyl and X (Scheme 67). In general, the stability of the pentavalent iridium (III) complex was dependent on the number of silane coordinated to the iridium.^[108] Usually, L7IrSi₃ is more stable than L7IrSi₂H and L7IrSiH₂, but, due to steric interactions, such is not the case for (2,9-Me₂Phen)Ir(Si)₃ and instead (2,9-Me₂Phen)IrSi₂H is the most probable intermediate. On the other side, disilyl hydride complexes undergo faster oxidative addition to arene C–H bonds than trisilyl iridium complexes due to important steric congestion which disfavors the approach of the arene.



Scheme 67. Steric relief upon oxidative addition

In 2008, Falck reported the silvlation of a wide variety of N-, S-, and O-heteroarenes with [Ir]/dtbpy catalytic system and HSiEt₃ as silicon source.^[113] This method featured a high level of regioselectivity for S- and O-heteroarenes ((benzo)-thiophene or -furan), with in rare cases to disilvlation of those species. In the case of the indoles, electron-donating groups on the nitrogen enhance the reactivity

towards triethylsilane. While the initial idea for the mechanism was proposed by the authors to be by chelation assisted C–H activation by the heteroatom (nitrogen, oxygen or sulfur)), the C3 silylation of N-tosyl pyrrole led to suggest either a change in the mechanism, or a metal migration from C2 to C3 (Scheme 68).



Scheme 68. Efficient Ir-catalyzed C-H silylation of N-, S-, and O-heteroarenes

The nature and/or the size of the silane is another important factor governing the regioselectivity of the silylation.^[105] For example, when silylation of tri*iso*propyl(*o*-tolyloxy)silane is carried out in the presence of triethylsilane, *meta*-functionalization to the OTIPS group, which is the less-electron rich position, takes place. However, with HSiMe(OSiMe₃)₂, *para*-substitution is ascribed by the authors to minimize the steric clash with the bulky OTIPS group (Scheme 69).



Scheme 69. Influence of the size of the silane in regards to the regioselectivity

Ishiyama and Miyaura disclosed the silylation of arenes with hydrosilatranes with the aim to install a silicon unit offering opportunities to perform post-functional transformations (Scheme 70).^[114] The

catalytic system developed involved a combination of $[Ir(cod)OMe]_2$ with a phenanthroline (dmphen) ligand. 1-Hydrosilatrane being a rather costly silane, it was used as limiting reagent, while arene was used in large excess in solventless conditions. The reaction was operated under a flow of nitrogen gas allowing for discharge of released H₂, and in the presence of hydrogen scavengers the desired products did not form. The regioselectivity of the reaction was again governed by steric effects, with the most accessible C–H bond being the preferred silvlation site.



Scheme 70. Aromatic C-H silylation of arenes with 1-hydrosilatrane catalyzed by iridium(1)/dmphen

All these considerations coupled with some computational studies led the Hartwig group to propose a mechanism^[108] for the silylation of electron-rich, electron-neutral, and electron-poor C–H bonds. These mechanisms occur through the same intermediate iridium complexes, but differ in the ratelimiting step (RLS) and the resting state of the catalyst (Scheme 71). On the other hand, for reactions of electron-poor or electron-neutral arenes, the resting state of the catalyst is the 5-coordinate iridium disilyl hydride complex (I). The coordination of complex I, by the arene, leads to complex J, which by reversible oxidative addition of the C–H bond leads to complex K. This oxidative addition step is considered to be the rate-limiting step for electron-rich arenes. The heptavalent Ir(V) complex, K, is poised for reductive elimination, releasing the arylsilane and complex L. The reductive elimination of the arylsilane represents the rate-limiting step for electron-poor arenes. In the presence of another hydrosilane molecule, the latter can coordinate to complex L, to form M, followed by an oxidative addition and a subsequent reductive elimination, upon the release of H₂, to generate the catalyst's resting state I.



Scheme 71. Proposed catalytic cycles for the silylation of electron-rich or -poor aromatic C-H Bonds

Iridium-catalyzed intramolecular dehydrogenative silylation

Silylation of arenes could also be performed in an intramolecular fashion. A one-pot procedure was described by Gevorgyan for the synthesis of fused heteroaromatic dihydrosiloles starting from styrene derivatives (Scheme 72).^[115] The first step involves the hydrosilylation of the double bond with diphenylsilane in the presence of a Ni(0) catalyst. The second step then involves a dehydrogenative Si–H/C–H cyclisation in *ortho*-position catalyzed by an [Ir]/Phen catalytic system in the presence of norbornene, and leads to the corresponding dihydrosiloles. This method grants access to a number of highly valuable building blocks consisting of different heteroarenes. C–Si bond could be formed during the cyclisation into different positions of the pyridine, except in the C2 position, while the other heteroarenes, such as furan, thiophene and pyrrole, could be functionalized in the C4-, C3- and C3-positions respectively.


Scheme 72. Synthesis of fused heteroaromatic dihydrosiloles

Similar strategies were also applied to aryl- and heteroaryl carbonyl derivatives as well as benzylic alcohols. Hydrosilylation of C=O bonds and dehydrosilylation of alcohols by reaction with diethylsilane, delivering the corresponding silyl ethers, were achieved first using an iridium catalyst.^[116] Then, with an [Ir]/Phen catalytic system in the presence of norbornene at 100 °C, intramolecular C–H silylation was accomplished at the *ortho* position of the directing group (Scheme 73).^[117,118] The oxasilole intermediates thus produced are relevant synthetic intermediates for which the C(sp²)–Si bond can be easily activated under basic conditions to promote Hiyama-type cross-coupling reactions or Tamao-Fleming oxidations.



Scheme 73. Iridium-catalyzed arene ortho-silylation by formal hydroxyl-directed C-H activation

Later, the synthesis of azasilolane under similar conditions was reported from secondary benzylamines (Scheme 74).^[119]



Scheme 74. Synthesis of azasilolane

Directed Iridium-catalyzed intermolecular dehydrogenative silylation

In addition to intramolecular dehydrogenative silulation with tethered silulations, *ortho*-directed silulation of arenes can also be achieved directly under iridium catalysis using directing groups.

In a first example, the 2-pyridyl moiety promoted regioselective *ortho*-silylation in 2arylpyridines.^[120] The key element here is the use of Lewis acidic HSiFPh₂ which coordinates to the nitrogen atom to give intermediate **N** (identified by ²⁹Si NMR). Formation of such complex weakens the Si–H bond and makes that the Ir–Si intermediate (**O**) responsible for C–H activation through oxidative addition is generated in close vicinity of the *ortho* C–H bond. A 6-membered iridacycle (**P**) is generated, and evolves to the final product after a reductive elimination step (Scheme 75). It is noteworthy to mention that this silylation reaction did not proceed with HSiPh₃, HSiEt₃ and H₂SiPh₂. Accordingly, the authors suggested that the presence of the highly electronegative fluorine atom on the silyl group renders it more Lewis acidic.



Scheme 75. Ir-catalyzed ortho-selective C–H silylation of aromatic compounds directed towards the synthesis of π conjugated molecules with Lewis acid–base interaction

In 2017, Wang disclosed another system using HSiMe(OSiMe₃)₂ as silane and involving milder operating conditions (80 °C) (Scheme 76).^[121] Here, [IrCl(COD)]₂ in combination with di*iso*propylethylamine (DIPEA) was used as catalytic system, in the presence of the. The regioselective *ortho* C–H silylation of arenes bearing functional groups such as aldehydes and ketones was achieved following their transformation to imines. Imines have proven-efficiency for the *ortho*-direction and as such the silylation were first performed on these related imines. Accordingly, the reaction was also performed with directing groups such as, pyridine, amide, oxazoline, oxime ether, hydrazone and amine. It has to be pointed out, that the 2-phenyl pyridine, underwent directed silylation using HSiMe(OSiMe₃)₂ as silicon donor. Importantly, the approach was also applicable to heteroarenes, including the C3-silylation of furfural.



Scheme 76. Iridium-catalyzed intermolecular directed dehydrogenative ortho C-H silylation

3 C3-silylation of furfural derivatives: results and discussion

With the outermost aim of valorizing furfural derivatives through C–H activation and in order to have a highly functionalizable platform, we focused on the development of a method for C3-directed silylation.

However, it is worth to remember that the C5-position of the furfural is the most reactive position to perform the C–H activation. Therefore, in the absence of *ortho*-directing group, the functionalization is driven towards the C5-position. Thus, silylation conditions tested on acetal **10**, obtained by simple

acetalization of furfural in the presence of trimethyl orthoformate,^[122] led to 27% of the C5-silylated product **11** (Scheme 77).



Scheme 77. C5-silylation of 2-(dimethoxymethyl)furan

In addition, we have verified that this silulation reaction cannot be performed using the aldehyde as the directing group, due to its degradation by decarbonylation processes. ^[33,123–125] However, hydrosilulation of the aldehyde function is known to occur at room temperature (Scheme 78).



Scheme 78. Hydrosilylation of furfural at room temperature

As mentioned in chapter I, ruthenium(0)-catalyzed reactions have recently been developed in the team for the C3–H functionalization of furfural derivatives, *via* the formation of imines acting as directing groups for the C–H activation step. Therefore, the installation of this type of easily accessible temporary groups was investigated for this study.

3.1 Preparation of furfurylimines

Various imines were accessed through a simple condensation reaction between the furfural derivatives and a primary amine in the presence of MgSO₄ as drying agent (Scheme 79). This general procedure provided high or quantitative yields for a variety of imines. Furthermore, as discussed in Chapter 1, the related C–H transformations based on furfurylimines are dependent on the nature of the imine. Therefore, the preparation of a variety of imines, such as electron-enriched (**14a-c**, **f**) and electron-deficient aromatic imines (**14d** and **14e**), as well as mono- (**14g**) and bidentate-aliphatic imines (**14h-l**) has been essential for the proper understanding and screening of the silylation reaction.



Scheme 79. Preparation of furfurylimines

3.2 Ruthenium(0)-catalyzed silylation

Initial tests were performed on furfurylimines with $Ru_3(CO)_{12}$ as catalyst in the presence of trisubstituted hydrosilanes and a sacrificial hydride acceptor. Inspired by conditions reported in the literature, several optimizations of the different parameters that can influence this reaction were performed.

3.2.1 Variation of the imine directing group

Different furfurylimines were reacted with triethylsilane in the presence of 5 mol% $Ru_3(CO)_{12}$ and 2.0 equivalents of the, in toluene at 120 °C (Table 1). In the case of aromatic imines derived from electron-poor anilines **14d** and **14e** (entries 4–5) and of alkylamine **14i** (entry 6) only imine reduction to the corresponding furfurylamines **18x-Si-a**_h was observed. Conversely, C3-silylated furfurylimines **18x-Si-a** were formed when electron-rich **14a** and **14b** or -neutral imines **14c** were considered (entries 1–3), but large amounts of reduced products were still detected.





^aRatio of 18x-Si-a to 18x-Si-a_h. (*) ¹H NMR yield using 3,4,5-trimethoxybenzaldehyde as internal standard

3.2.2 Variation of the operating conditions

Using the PMP-imine (14a), the influence of the operating parameters was investigated briefly (Table 2). Performing the reaction at 80 °C instead of 120 °C delivered the imine reduction product almost exclusively (entry 2), while operating at 140 °C led to the decomposition of the starting material

^{α} The numbering the imines are described as **14x**: where **x** represents the R group of the imine. And in the final product, *Si*-**a**, represents the SiEt₃. For example **18a**-*Si*-**a**, corresponds to product coming from substrate **14a**, with *Si*-**a**, functionalized with a SiEt₃. **18x**-*Si*-**a**_h, here represents the product of hydrosilylation of imine **14x**.

(entry 4). At 120 °C, reducing the reaction time from 19 h to 7 h had no impact on the yield in silylation and reduction products (entry 3), in spite of a lower conversion rate. This suggests that substrate or product degradation occurs over time. Due to the poor solubility of the ruthenium catalyst in toluene, the reaction was also performed in a mixture of *n*-hexane and CH_2Cl_2 (9/1) (entry 5), but in this solvent mixture imine reduction became clearly predominant.



O N O O Me 14a		—OMe	Ru ₃ (CO) ₁₂ (5 mol%) HSiEt ₃ (1.5 equiv.) t_{Bu} (2 equiv.) Solvent (0.5 M), T (°C) t (h), Ar Screwcapped tube	SiEt ₃ N-OMe +	Et ₃ Si 18a- <i>Si</i> -a _h	
Entry	t (h)	T (•C) Solvent	Conversion (%)	18a-Si-a (%)	18a-Si-a _h (%)
1	19	120	Toluene	100	23	14
2	19	80	Toluene	>95	traces	58
3	7	120	Toluene	70	22	14
4	19	140	Toluene	100	a	
5	19	120	<i>n</i> -hexane/ CH ₂ Cl ₂ (9/1) 96	<5	90

¹*H* NMR yield calculated using 3,4,5-trimethoxybenzaldehyde as internal standard. ^aA complex mixture was obtained.

3.2.3 Variation of the sacrificial H-acceptor

Careful analysis by ¹H NMR of the crude reaction mixtures of the first trials showed that a significant amount of *trans*-3,3-dimethyl-1-(triethylsilyl)-l-butene (**21**) was being formed during the process. Furthermore, it was demonstrated that **21** was produced in quantitative yield if no furfurylimine was present in the reaction medium (Scheme 80).



Scheme 80. Silylation of 3,3-dimethylprop-1-ene

A plausible mechanism for the formation of this side-product^[126,127] involves oxidative addition of the Si–H bond to the Ru(0) catalyst, generating a Si–[Ru]–H intermediate, followed by migratory insertion of the alkene that might occur either into the [Ru]–H or the [Ru]–Si bond (Scheme 81). If the latter occurs, vinylsilane **21** can be generated following a subsequent β -H elimination. Note that the first pathway would lead to the formation of alkene hydrosilylation product (**22a**), which is not observed in our case.



Scheme 81. Possible mechanism for the silylation of 3,3-dimethylprop-1-ene

These considerations thus tend to indicate that in our furfurylimine silylation attempts, the rate of insertion of the into the Ru–*Si* bond is faster than that of oxidative addition to the furyl C–H bond, which consumes the hydrosilane reagent and precludes arene C–H functionalization. In order to avoid losing the silane partner through its reaction with the sacrificial hydrogen acceptor, two other commonly used derivatives, namely, benzylidene acetone and norbornene were contemplated. The reaction of the PMP-imine **14a** in the presence of benzylidene acetone only led to product degradation and the conversion was not complete (Table 3, entry 2). Full conversion was observed using norbornene, but here as well a complex mixture was obtained (entry 3). Hence, the was the only hydrogen acceptor with which the C3-silylated furfurylimine **18a-Si-a** was obtained (entry 1).



Table 3. Ru(0)-catalyzed silylation: H-acceptor investigations

¹H NMR yield calculated using 3,4,5-trimethoxybenzaldehyde as internal standard

3.2.4 Variation of the silicon donor

Then, other silanes were screened. Silylation with $HSiMe(OSiMe_3)_2$ occurred with a similar (low) yield as with $HSiEt_3$ (Table 4, compare entries 1 and 2), while using Ph_3SiH (entry 3) a complex mixture of products which we were unable to identify was recovered. The use of hexamethyldisilane (in the absence of tbe) was next contemplated, but no reaction was observed and the starting imine was recovered intact (entry 4).





Entry	Silane	Conversion (%)	18a-Si-y (%)
1	HSiEt ₃	100	23
2	HSiMe(OSiMe ₃) ₂	100	20
3	HSiPh ₃	100	a
4^b	Me ₃ Si–SiMe ₃	0	_

¹*H* NMR yield calculated using 3,4,5-trimethoxybenzaldehyde as internal standard. ^aA complex mixture was obtained. ^bNo tbe added.

^{β} For the numbering of silvlated furfuryl imine, *Si*-y represent the silane. For example, **14a** functionalized with HSiMe(OSiMe₃)₃ (*Si*-b), corresponds to product **18a**-*Si*-b.

In the light of these disappointing results for the Ru(0)-catalyzed approach for the C3-silylation of furfurylimines, we turned our attention towards rhodium and iridium catalysis.

3.3 Iridium(I)-catalyzed C3-silylation

3.3.1 Screening of catalysts

In our model reaction involving PMP-furfurylimine **14a**, Et₃SiH and the as hydrogen acceptor, we first tested the performance of rhodium catalysts [RhCl(COD)]₂ (Table 5, entry 1) and RhCl(PPh₃)₃ (entry 2), and found that only imine reduction occurred. We thus focused on iridium catalysis building on the (unique) precedent for furfurylimine C3–H silylation reported by Li.^[121] Using 2 mol% [IrCl(COD)]₂ and 20 mol% of (*i*-Pr)₂NEt, in hexane at 120 °C in a screwcapped tube under argon, the C3-silylated product **18a-Si-a** was obtained in 65% yield with almost no imine reduction (entry 3). However, C3,C5-bis-silylated product **18a-Si-a**_b was also formed in 20% yield. By contrast, cationic Ir(I) catalyst [Ir(COD)(PPh₂Me)]PF₆ (entry 4) was found to be ineffective and all the starting material was recovered intact. This could be related to the formation of a stable 18-electron iridium complex after coordination of the imine, thwarting the catalytic activity. An Ir(II) approach involving [IrCl(Cp*)]₂ (entry 5) was also investigated, but again very low conversion was noted. Following these results, we decided to optimize the catalytic system based on [IrCl(COD)]₂.

Table 5. Ir-catalyzed silylation: catalyst investigations⁸



2	[RhCl(COD)] ₂	100	_	_	100 ^a
3	[IrCl(COD)] ₂	100	65	20	_
4	[Ir(COD)(PPh ₂ Me)]PF ₆	_	_	_	_
5	$[IrCl(Cp^*)]_2$	7	7	_	_

¹H NMR yield calculated using 3,4,5-trimethoxybenzaldehyde as internal standard. ^aOnly the ratio of the products observed were reported.

3.3.2 Influence of reaction time

1

Knowing that the C5-position is the most reactive position, it was initially thought that the bissilylated product $18a-Si-a_b$ could result from an over-silylation of the C3-silylated product (18a-Si-a). To get better insight into the origin of the bis-silvlated product, **18a-Si-a**_b, the progress over time of our model reaction was monitored (Table 6). A reaction time of 2 h was insufficient to have a complete conversion of the imine and a relatively low yield was obtained for the C3-silylated product **18a-Si-a**, with still bis-silylated product $(18a-Si-a_b)$ (entry 1). When the reaction was carried out over 4 h, an improvement in yield was evidenced (entry 2), while the addition of hydrosilane and 3,3-dimethylbut-1-ene to a preheated solution comprising the imine, the iridium catalyst and the base, did not influence the ratio of **18a-Si-a** and **18a-Si-a** (entry 3). However, over longer time periods (entries 4-5), the yield of 18a-Si-a dropped, while the yield of 18a-Si- a_b seemed to be quite stable over time, which would assert that **18a-Si-a**_b is produced at the beginning of the reaction. But the origin of this product is still

^δ The numbering of silvlated furfuryl imines, **18a-Si-a**, corresponds to product coming from substrate **14a**, functionalized with SiEt₃, which corresponds to silane Si-a. 18a-Si-a_b, where b represents the 3,5-bis-silylated product of 14a with silane Si-a. 18a-Si-ah, here represents the product of hydrosilylation of imine 14a.

unclear. It should also be noted that in none of these cases, the C5-monosilylated product was evidenced.



Table 6. Ir-catalyzed silylation: time optimization

¹*H* NMR yield calculated using 3,4,5-trimethoxybenzaldehyde as internal standard. ^aAddition of [IrCl(COD)]₂ (2 mol%), (i-Pr₂)NEt (20 mol%) in hexane (0.2 M) to imine **14a** (0.4 mmol), heated 120 °C, 20 min in a microwave vial, closed by a septum. Then, the (2 equiv.), followed by the HSiEt₃ (2.5 equiv.) were added and the mixture was, heated for another 4.5 h.

3.3.3 Optimization of the amount of hydrosilane

In the event of reducing the amount of $18a-Si-a_b$, the amount of hydrosilane was modulated. In Table 7 can be evidenced that the best result was obtained with 1.5 equivalents of HSiEt₃ (entry 2) leading to a lower amount of $18a-Si-a_b$ in relation to the desired product, 18a-Si-a, while lower quantity of hydrosilane (entry 3), led to similar results as entry 1. However, when HSiEt₃ and the were employed in large excess (entry 4), only the bis-silylated product was obtained, but the latter was obtained in relatively low yields.

Table 7. Ir-catalyzed silylation: optimization of equivalence of silane

$14a PMP = PMP = PMP \left[\frac{[IrCl(COD)]_2 (2 \text{ mol}\%)}{(t \cdot Pr)_2 \text{NEt } (20 \text{ mol}\%)} \right]$		$[IrCl(COD)]_{2} (2 mol\%)$ $HSiEt_{3} (x equiv.)$ $(i-Pr)_{2}NEt (20 mol\%)$ $n-hexane (0.25 M)$ $120 °C, 4 h, Ar$ Screwcapped tube $18a$ $PMP= OMe$	NPMP + Et ₃ Si O NPMP + Si-a 18a-	NPMP +	N−PMP × 18a- <i>Si</i> -a _h K= H or SiEt ₃
Entry	x	Conversion (%)	18a-Si-a (%)	18a-Si-a _b (%)	18a-Si-a _h (%)
1	2.5	100	75	10	_
2	1.5	100	82	5	_
3	1.1	100	73	12	_
4^a	4.0	100	_	33	_

¹*H* NMR yield calculated using 3,4,5-trimethoxybenzaldehyde as internal standard. ^atbe (4 equiv.) was added.

3.3.4 Variation of the directing group

The next stage of our method development involved screening different furfurylimines in the new optimized conditions, *i.e.*: $[IrCl(COD)]_2(2 \text{ mol}\%)$, (*i*-Pr₂)NEt (20 mol%), triethylsilane (1.5 equiv.), and 3,3-dimethylprop-1-ene (2 equiv.) in hexane at 120 °C in a screwcapped tube under argon atmosphere during 4 h (Table 8). Imines derived from anilines having electron-donating substituents provided the best results with relatively good silylation yields and no trace of the reduction product **18x**-*Si*-**a**_h (entries 1,2). As noted before, very good selectivity for the C3-silylation over disilylation had been obtained with PMP-imine **14a** (entry 1). On the one hand, 2,4-dimethoxyphenylimine **14f** showed an even better selectivity, where only the C3-silylated product was detected. The 2-methoxy substituent could contribute to a better chelation of the metal, limiting the C5–H activation (entry 3). Nevertheless, the yield obtained for the C3-silylated imine **18f**-*Si*-**a** is lower than that obtained with PMP-imine (**18a**-*Si*-**a**). On the other hand, the use of phenylimine **14c** (entry 4) led to a significant degradation of the products, while the imines derived from anilines with electron-withdrawing substituents **14e** were shown to be more prone to competing hydrosilylation (entry 5).

Table 8. Ir-catalyzed silylation: optimization of imine function

14x	[IrCl(COD)] ₂ (2 mol% HSiEt ₃ (1.5 equiv.) (<i>i</i> -Pr) ₂ NEt (20 mol% <i>i</i> -Bu (2 equiv.) <i>i</i> -hexane (0.25 M) 120 °C, 4 h, Ar Screwcapped tube	$\stackrel{()}{\longrightarrow} \qquad \stackrel{O}{\underset{\text{SiEt}_{3}}{}} NR$ $18x-Si-a$	+ Et ₃ Si	O NR + SiEt₃ - <i>Si</i> -a _b	N-R X 18x- <i>Si</i> -a _h X= H or SiEt ₃
Entry	R	Conversion (%)	18x-Si-a (%)	18x-Si-b (%)	18x-Si-c (%)
1	OMe 14a	100	82 (46)	5	_
2	NMe ₂	100	74	12	-
3	MeO OMe	100	56	_	-
4	14c	79	13	_	25
5	CF ₃	100	54	16	19
6	14σ	100	56	14	_
7	NMe ₂	8	Traces	_	_
8	NEt ₂ 14i	90	80 (55)	-	-
9	14j	35	26	-	_
10	NMe ₂	100	85 (46)	_	_
11	NEt ₂	100	79	8	-

¹*H* NMR yield calculated using 3,4,5-trimethoxybenzaldehyde as internal standard. (*) shows the isolated yield after (acid or silica gel) hydrolysis of the imine.

For aliphatic imines, monodentate imine **14g**, derived from butylamine gave C3-silylated and disilylated products in 56% and 14% yield, respectively (entry 6). In order to see if the use of bidentate directing groups could improve the selectivity of this reaction, different bidentate aliphatic imines were synthesized and tested. The first tests were performed with *N*,*N*'-amino-imines bearing two carbons between the two nitrogen atoms. While imines with a terminal *N*,*N*'-dimethylamine group (**14h**, entry 7) or a piperidyl group (**14j**, entry 9) led to poor conversion, the one having a *N*,*N*'-diethylethane group **14i** (entry 8) gave the C3-silylated aldehyde in 55% yield after purification on silica gel. In the same fashion, bidentate imine possessing three carbon spacing displayed better yields (entry 10) compared to the two carbon spacing ones, which is in sharp contrast to the case of ruthenium catalyzed Murai reaction.^[48] Furthermore, amino-imine **14l** showed comparable yield to amino-imine **14i** (compare entries 8 and 11). Two possible factors might be responsible for this difference. It might be intrinsic to the iridium catalyst, which accommodates better a 6-membered metallacycle, or related to a looser complexation of the second amine, which prevents the catalyst poisoning. Furthermore, **14k** proved to be very selective, where only one product was obtained with high yield (entry 10), whereby **14l** was formed in slightly lesser yield, but the di-silylated product was obtained (entry 11). The bidentate directing groups, in most of the cases, gave rise to C3-silylated product **18k-Si-a** only.

Based on these results, PMP-imine **14a** and amino-imines **14i** and **14k** provided the best yields. We decided to pursue this silylation study with these imines, where **14a** proved to be robust, while **14i** and **14k** provided excellent selectivity and yields.

3.3.5 Solvent dependence

Several solvents were then tested with these three imines, mainly apolar ones given that typically for directed C–H activation, non-coordinating solvents often favor *ortho*-substitution (Table 9). Initial attempts with toluene (entry 2) showed slightly lesser yields, with **18x**-*Si*-**a**_h product also obtained, while the reaction in xylene (entry 3) met limitations in terms of incomplete conversion, and the presence of non-negligible amounts of side-product **18x**-*Si*-**a**_h. However, toluene showed some promising results with 64% and 68% yield with the PMP-imine **14a** and bidentate imine **14i** respectively (entry 2). As previously reported, when performed in *n*-hexane, the directed C3-silylation was achieved smoothly with the imines tested, with yields above 80% (entry 1). The boiling point of *n*-hexane being 69 °C, which is well below the reaction's temperature, might influence other reaction parameters, such as the pressure in the reaction vessel. Therefore, other aliphatic solvents such as cyclohexane (b.p 81 °C) and heptane (b.p 98 °C) were evaluated, but unsatisfactory yields were obtained (entries 4-5). Acetonitrile (entry 6), was a poorly efficient solvent in the C–H activation of the furan ring, and was mainly responsible for reduction products.

Table 9. Ir-catalyzed silylation: solvent investigation

0 14x	[IrCl(COD)] ₂ (HSiEt ₃ (1.5 er (<i>i</i> -Pr) ₂ NEt (20 <i>t</i> -Bu (2) Solvent (0.25 120 °C, 4 h, A Screwcapped	2 mol%) quiv.) mol%) equiv.) M) Ar I tube	O SiEt ₃ 18x- <i>Si</i> -a	O SiEt₃ 18x- <i>Si</i> -a _b X	$ \begin{array}{c} O \\ N-R \\ X \\ 18x-Si-a_h \\ = H \text{ or SiEt}_3 \end{array} $	(a) OMe NEt ₂ (i)
Entry	Solvent	Imine	Conversion (%)	18x-Si-a (%)	18x-Si-a _b (%)	18x-Si-a _h (%)
		14a	100	82	5	_
1	<i>n</i> -hexane	14i	90	80	_	_
		14k	100	85	_	-
2	taluana	14a	100	64	9	11
2	toluelle	14i	100	68	_	6
2	uulana	14a	71	29	_	35
3	xylene	14i	20	13	_	8
4	cyclohexane	14i	79	44	_	_
5	h t	14a	100	38	10	27
	neptane	14k	85	53	_	4
6	a aatonituil-	14a	41	10	_	49
6	acetonitrile	14k	32	_	_	15

¹*H* NMR yields are calculated using 3,4,5-trimethoxybenzaldehyde as internal standard.

3.3.6 Temperature dependence

Typically, high temperatures are often required for the C–H activation of arenes. In the case of a simple furan ring, the bond dissociation energy of the C3–H is around 494 kJmol^{-1,[128]} while the Si–H activation of a typical trialkylsilane approximates 400 kJmol⁻¹. Therefore, energy could be provided to achieve this silylation reaction. Temperature screening is crucial for the optimization of this reaction. A temperature of 50 °C was not found to be sufficient for the silylation of furfurylimine (Table 10, entry 2). It is important to note that the selected imines can withstand the hydrosilylation reaction at this temperature, unlike carbonyls, alcohols and amines.^[117] Increasing the temperature to 80 °C (entry 3) favors the conversion of PMP-imine to **14a**, but at this temperature, longer reaction might be required. On the other hand, the transformation of bidentate imines (**14i** and **14k**) was quite low for temperatures below 120 °C (entries 2-4). Thus, 120 °C seemed to be the optimal temperature in

performing this transformation using these imines (entry 1), but at 140 °C, the silvlated imines **18a**-*Si*-**a**, has a tendency to perform a second silvlation step with the product **18a**-*Si*-**a**_b rising to 17% (entry 5).



Table 10. Ir-catalyzed silylation: temperature investigation

¹*H* NMR yields are calculated using 3,4,5-trimethoxybenzaldehyde as internal standard.

This result is in contrast with previously reported conditions by $\text{Li}_{,}^{[121]}$ where the silylation of **14a** with HSiMe(OSiMe₃)₂ was carried out at 80 °C with the conditions reported, which gave rise to 62% of isolated product after hydrolysis. In our trial, under these conditions, a mixture of C3-mono-silylated furfuryl imine **18a**-*Si*-**e** was obtained with 37% yield, along with the 3,5-bisilylated furfuryl imine **18a**-*Si*-**e**_b in 23% yield.

3.3.7 Amount of catalyst and sacrificial H-acceptor

In a way to minimize the amount of heavy metal used in this reaction, the reaction was performed at 1 mol% of the catalyst with **14k** under the optimized conditions. Only 62% conversion was observed, with a yield of 41% (entry 2). Interestingly, when performed with 5 mol% [IrCl(COD)]₂, the reaction reached full conversion, but 52% yield was observed as well as 9% of the bis-silylated product (entry 3). These results were significantly less good at higher catalytic loadings, probably due to the conversion of the C3-silylated product to the bis-silylated one.

As discussed at the beginning of this chapter, the use of a sacrificial hydrogen acceptor is necessary and/or more convenient for the reaction to proceed smoothly. Under the optimized conditions, the reaction was performed in the absence of 3,3-dimethylbut-1-ene, as well as with 1 equiv. and 2 equiv. In the absence of the hydrogen acceptor, only 5% yield of **18k**-*Si*-**a** was obtained (entry 4), while a low (69%) conversion of the furfurylimine was evidenced with 1 equivalent of 3,3-dimethylbut-1-ene, yielding 54% of **18k**-*Si*-**a**. This yield is significantly lower than the one obtained previously with 2 equivalents of hydrogen acceptor (entry 1).

Table 11. Effect of the amount of hydrogen acceptor



Entry	x (mol%)	y (equiv.)	Conversion (%)	18k-Si-a (%)	18k-Si-a _b (%)	18k-Si-a _h (%)
1	2	2	100	85	_	_
2	1	2	62	41	_	_
3	5	2	100	52	9	_
4	2	0	36	5	_	_
5	2	1	69	54	_	-

¹H NMR yield calculated using 3,4,5-trimethoxybenzaldehyde as internal standard.

3.3.8 Influence of tertiary amine

Finally, we wanted to assess the importance of $(i-Pr)_2NEt$, for this iridium-catalyzed silylation. Based on the reported results with PMP-imine, better yield was obtained with 20 mol% of $(i-Pr)_2NEt$ (Table 12, entry 1) in comparison with triethylamine (entry 2) and without additives (entry 3). In addition, triethylamine seemed to favor more the di-silylated product.

A significant difference in the yield was evidenced with and without $(i-Pr)_2NEt$, 86% and 53% respectively, in the case of amino-imine **14k** (entry 3). In addition, full conversion was not achieved without this additive, which might account for a faster reaction rate.



Table 12. Importance of (*i-Pr*)₂*NEt*

¹H NMR yields are calculated using 3,4,5-trimethoxybenzaldehyde as internal standard. ^aNEt₃ used instead of (*i*-Pr)₂NEt

3.3.9 Silylation scope

With all these data and parameters in hand, a silylation scope was developed on furfural (1), 5methyl furfural (13) and (TBDMS)-protected 5-HMF (2a), via the formation of PMP-imines (14a, 15a, 16a) and bidentate imines (14k, 15k and 16k) as directing groups. The optimized conditions, i.e.: $[IrCl(COD)]_2$ (2 mol%), (*i*-Pr₂)NEt (20 mol%), HSiR₃ (1.5 equiv), and 3,3-dimethylprop-1-ene (2 equiv.) in hexane at 120 °C in a screwcapped tube under argon atmosphere during 4 h, were investigated with various hydrosilanes. Due to the relative volatility of the C3-silylated furfuraldehydes, after concentration under reduced pressure of the volatiles, the crude was analyzed by ¹H NMR in order to quantify the amount of obtained C3-silylated furfurylimines using 3,4,5-trimethoxybenzaldehyde as internal standard. Then, the crudes were subjected to hydrolysis and isolated by silica-gel column chromatography.

The silulation scope was first performed of PMP-imines (a), then applied to the bidentate amino imines (b).

a. PMP-imine silylation scope

The silylation of these imines was performed under the above-mentioned optimized conditions (Scheme 82). After the analysis and quantification of the C3-silylated furfurylimines by ¹H NMR, the crude mixture was subjected to hydrolysis prior to its purification. Due to their robustness, these imines were subjected to acid hydrolysis by treatment with HCl (1 M) in Et₂O for 1 h at room temperature to recover to corresponding furfuraldehyde containing mixture. The latter was then purified by silica-gel column chromatography.

The silylation process was initially intended to develop mainly tri-alkyl(aryl)silanes and so, were applied HSiEt₃, HSi(*i*-Pr)₃, HSiMe₂Bn, and HSiMe₂t-Bu (final compounds **18**-*Si*-**a to 18**-*Si*-**d**). However, the silylation can also be performed with HSiMe(OSiMe₃)₂ as silicon donor, which afforded decent yield (final compounds **18**- to **20**-*Si*-**e**). As previously commented, based on the ¹H NMR yield, moderate to good yields were obtained, but the isolation of the C3-silylated aldehydes proved to be difficult for **18**-*Si*-**a** to **18**-*Si*-**d**. These silylated products were seemingly less volatile when substituted at the C5-position, as ¹H NMR yields based on the imine are consistent with the isolated yields. It has to be mentioned that in general the C3-silylation performed with (TBDMS)-protected 5-HMF derivatives was less efficient compared to its 5-methyl analogue. In addition, HSiMe₂t-Bu displayed lower silylation yields compared to the other trialkylsilanes, probably due to the steric dependence of this reaction.



(*) NMR yield was calculated using 3,4,5-trimethoxybenzaldehyde as internal standard based on the imine. ^aYields for the 3,5-bis-silylated product.

^bYields for the reduction products.

Scheme 82. Silylation scope of furfurylimines owing PMP-based imines[®]

b. Bidentate amino-imine silylation scope

The C3-silylation of these furfurylimines was carried out following the above-optimized procedure (Scheme 83). Owing to the results obtained in section 0, these imines are expected to offer excellent selectivity for this reaction so the silylation was carried out with the same array of hydrosilanes previously used with PMP-imines.

Bidentate amino-imines are easily hydrolyzed. Thus, here, the crude mixture resulting from the silylation reaction was allowed to stir in a solution of Et₂O, to which silica and water were added. The

 $[\]varepsilon$ The numbering of silvlated furfuraldehydes, for example, hydrolysis of imine 18<u>x</u>-*Si*-a leads to aldehyde 18-*Si*-a.

mixture was then concentrated, and purified by silica-gel column chromatography to afford the corresponding C3-silylated furfuraldehyde.

As a general trend, the C3-silylation provided relatively good yields with SiEt₃ (**18-** to **20-Si-a**) and SiMe₂Bn (**18-** to **20-Si-d**), but seemed to be extremely dependent on the steric bulk of the silane. For example, sterically more hindered silanes, such as Si(n-Pr)₃ granted their corresponding products (**18-** to **20-Si-b**) in low yields, while SiMe₂t-Bu, did not afford their respective C3-silylated product (**18-** to **20-Si-c**). In addition, this imine was also poorly efficient with HSiMe(OSiMe₃)₂ as silylating agent.

In this aspect the bidentate amino-imines showed some limitations due to the steric constraints of the silanes.



(*) NMR yield was calculated using 3,4,5-trimethoxybenzaldehyde as internal standard based on the imine. ^aYields for the 3,5-bis-silylated product.

^bYields for the reduction products.

Scheme 83. Silylation scope of furfurylimines owing bidentate amino-imines

c. Failed attempts

Apart from trialkylsilanes, silylation of PMP-imine **14–16a** with other trisubstituted hydrosilanes was attempted (Scheme 84). For instance, using HSiMe₂Ph and HSiMePh₂ resulted in their corresponding products **18-Si-g** and **18-Si-f**, respectively in very low yields.

In order to get more evidence about the steric dependence of this reaction, the reaction was performed with more sterically demanding hydrosilanes, such as $HSi(n-Bu)_3$, $HSi(SiMe_3)_3$ and $HSiPh_3$, but none of these led to the corresponding product.

In the advent of performing this dehydrogenative silulation in the absence of an external hydrogen acceptor, the use of vinyldimethylsilane or diphenylallyl silane was envisaged to fulfil both the role of silicon source and sacrificial hydrogen acceptor. However, no C3-functionalized product could be evidenced and relatively poor conversion could be noticed.

In addition, the nature of the hydrosilane has a very important role. For example, alkoxysilanes, led to degradation and/ or reduction of the furfurylimines, as well as dihydrosilanes, which are known to be good reducing agents.



(*) NMR yield was calculated using 3,4,5-trimethoxybenzaldehyde as internal standard based on the imine. ^aYield for 3,5-bis-silylated product.

Scheme 84. Failed C3-silylation attempts

d. Ortho-directed dehydrogenative silulation applied to other hetero(arenes)

This approach was extended to the *ortho*-silylation of other (hetero)arenes. For example, the *ortho*-silylation of *N*-PMP-tolylmethanimine **22** was carried out with HSiEt₃ as silicon source (Scheme 85). However, with our general protocol, 50% conversion of the substrate was noticed, and 32% of the product **23-***Si***-a**. Therefore, the reaction was allowed to stir over a longer time period (16 h), but the yield and conversion only improved slightly, 39% and 63% respectively.



Scheme 85. Iridium-catalyzed ortho-silylation of N-PMP-tolylmethanimine

Finally, pyrrole 2-carboxaldehyde was considered as a suitable starting substrate, given its direct availability from furfural via the Paal-Knorr synthesis,^[130] or via a three-step sequence (carbonyl reduction / Achmatowicz rearrangement / Maillard condensation).^[131] This substrate can thus be considered as a biomass-derived building block, too.^[132,133] So, we decided to investigate about the *ortho*-silylation of **17a** with HSiEt₃, under the classical conditions, but again 46% conversion was evidenced after 16 h reaction, with 25% yield. By extension, an increase in catalytic loading [IrCl(COD)]₂ (5 mol%), increase in temperature from 120 °C to 140 °C improved the yield to 49% (Scheme 86).



Scheme 86. Iridium-catalyzed ortho-silylation of PMP-based pyrrole

3.3.10Proposed mechanism

In the light of our own observations, along with the mechanistic studies for the iridium-catalyzed dehydrogenative silulation performed by Hartwig and co-workers, we therefore propose a mechanism for this *ortho*-directed silulation of furfurylimines (Scheme 87).

Starting from the pre-catalyst, we propose the formation of a mono-nuclear complex in the presence of $(i-Pr)_2NEt$. The formation of an iridium(III) intermediate results from the reaction with the

hydrosilane by oxidative addition into the Si–H bond. This step is followed by a reductive elimination, releasing HCl and the active-catalytic species, X1. The role of the amine is crucial, as it can trap resulting acid, forming the ammonium salt.

In the presence of HSiR₃, the probable resting state of the catalyst is generated through the oxidative addition of **X1** into the H–Si bond. The resulting iridium (III) disilyl hydride complex **X2** is therefore coordinated to the furfurylimine. The pre-coordination of the [Ir(III)] complex **X3**, provides *ortho*-direction *via* the imine to perform oxidative addition into the arene C3–H bond, giving an hexacoordinated iridacycle **X4**, which leads to the formation of the intermediate **X5**, after reductive elimination. In the presence of the, the C3-silylated furfurylimine is released and the latter, coordinated to the iridium (III) dihydride silyl complex **X6**. Successive migratory insertion of the alkene into the [Ir]–H bond gives **X7**, which is followed by reductive elimination, liberating 3,3-dimethylbutane and the active catalytic species **X1**, is recovered.

For now, the formation of 3,5-bissilylated furfurylimine is unclear, but hydrosilylation of aldimines have been described using cationic [Ir(I)] complex in the presence of HSiEt₃.^[134] The generation of an iridium (III) silyl hydride was considered to be responsible of the reduction of imines.



Scheme 87. Proposed mechanism for directed C3-silylation of furfurylimine

4 Conclusion

In summary, we have developed a strategy for the selective C3-silylation of furfural derivatives. This relatively simple, and quite robust process is catalyzed by [IrCl(COD)]₂, in the presence of a bulky tertiary amine additive ((*i*-Pr)₂NEt) and the as sacrificial hydrogen acceptor. The installation of an imine temporary directing group serves both for the *ortho*-directing effect, as well as protecting group towards side reactions such as hydrosilylation and decarbonylation processes of the aldehyde function. Furthermore, this synthetic strategy is highly dependent on the nature of the imine. For example, bidentate amino-imines are highly selective with trialkylsilanes for the C3-silylation, but inefficient towards sterically hindered silanes, and show some limitations towards hydrosilylation processes. Moreover, the PMP-imines, though slightly less selective, are more robust towards hydrosilylation, and thus can be applied generally to a wide range of silanes. While aryltrialkylsilanes are known to be very

stable, there are limited synthetic methods for the post-transformations, such as the Brook rearrangement and these require specific conditions. The preparations of synthetically useful motifs such as aryl-heptamethyltrisiloxane, or aryl siloxane are also quite interesting, as they are known to allow post-transformations, through Hiyama cross-coupling reactions.

Therefore, this methodology provided a silulation platform based on furfural derivatives which are derived from biomass. This platform is highly valuable as it allows a number of post-transformations when properly activated. The activation of these arylsilanes will be developed in the next two chapters.

CHAPTER III:

Carbon-to-Oxygen silyl migration

1 C(sp²)–Si bond functionalization through intramolecular activation by alkoxides

This bibliographic section has been published as a review in Eur. J. Org. Chem. **2021**, 1055-1071. Sebastien Curpanen made the literature search and wrote the first draft of this review during the first lockdown of 2020, as well as the front cover picture of the issue.

Abstract. Organosilicon reagents are invaluable tools in the hands of the modern chemist that allow accomplishing a number of synthetically useful transformations. While some are standard reactions, other are more complex transformations, such as the Brook rearrangement and its variants. This carbon-to-oxygen silyl migration represents a privileged method to generate transient carbanionic species well suited to undergo functionalization upon electrophilic substitution in the presence of an electrophile. This minireview focuses on recent advances in $C(sp^2)$ –Si bond functionalization through intramolecular activation by alkoxides. The key elements of reactivity will be highlighted in the introduction to allow the proper understanding of the migration process. Then, an overview of the reactivity of substrates incorporating the $C(sp^2)$ –Si motif and their synthetic applications will be provided.

1.1 Introduction

Alkenyl-, aryl-, and heteroarylsilanes can be used as robust carbanion surrogates endowed with a number of features such as ready availability, low toxicity and excellent functional-group tolerance. These attributes make them highly attractive building blocks in the context of sustainable chemical synthesis and many efforts have been devoted to develop methods for the construction of $C(sp^2)$ –Si bonds. Yet, the counterpart to the assets related to the stability of these reagents is that their use as carbon nucleophiles is the need of specific strategies to activate the $C(sp^2)$ –Si bond. Intramolecular carbon-to-oxygen (C→O) silyl migrations offer the possibility to generate with high selectivity carbanionic species from C–Si bonds. Whereas this approach has been massively applied for the functionalization of $C(sp^3)$ –Si bonds, related $C(sp^2)$ –Si bond-functionalizations are comparatively rather scarce. This notwithstanding, a number of elegant methodologies has been gradually developed over the years. The aim of this minireview is to illustrate the high synthetic potential of this rapidly growing field of chemistry. Following some general considerations on intramolecular C→O silyl migrations, the most relevant strategies applied in the context of $C(sp^2)$ –Si bond functionalization will be devoted to the related field of $C(sp^2)$ –Si cross-coupling through intramolecular activation with alkoxides.

1.1.1 Background and general reactivity trends

In the early 1950s, Gilman discovered that whereas the reaction of triphenylsilylpotassium with formaldehyde^[135] (or aliphatic ketones)^[136] provided the "normal" addition product (*i.e.* **25**), the reaction with benzophenone yielded alkoxysilane **26** (Scheme 88, top).^[137] The same outcome was observed by Brook for the addition of other triphenylsilylmetal reagents on benzophenone,^[138,139] and also upon deprotonation with active metals, organometallic species or organic bases of α -silylcarbinols **28** (Scheme 88, bottom).^[140,141] It was then established by Brook,^[138,139,142,143] that the formation of silyl ethers in these reactions was the result of the [1,2]-C-to-O migration of the triorganosilyl group in α -triorganosilyl alkoxides **27a–c**. This type of rearrangement reaction was popularized as the "Brook rearrangement" and proved to be much more general-in-scope, allowing for 1,2-, 1,3-, 1,4- and 1,5-migrations.



Scheme 88. Seminal reports on $C \rightarrow 0$ triorganosilyl migrations (Brook rearrangement) from a-triorganosilyl alkoxides

1.1.2 Mechanistic considerations

The main mechanistic features underpinning these rearrangements were established at an early stage.^[143] The migration is in fact a reversible process passing through a pentavalent silicon intermediate **30** (Scheme 89). The observed high negative entropy is consistent with the formation of such a silacycle.^[143] Once this intermediate is formed from an alkoxide **29**, it can evolve through C–Si bond cleavage to give carbanion **31** and thereby complete a 1,2-, 1,3-, 1,4- or 1,5-C-to-O migration (Brook rearrangement). However, the reversibility of the process also makes possible to produce an alkoxide **29** from a carbanion **31** through O-to-C migration (retro-Brook rearrangement). Both processes are useful in synthetic organic chemistry and have notably been beautifully combined in the Anion Relay

Chemistry concept developed by Smith,^[144] wherein site-selective synthetic elaboration is achieved upon the transfer of a negative charge from one place to another.



Scheme 89. The Brook and the retro-Brook rearrangements

The triorganosilyl migration being reversible, the relative stabilities of the starting and final product play a key role to determine the issue of the rearrangement. The driving force behind the C \rightarrow O migration is often attributed to the high affinity of silicon for oxygen (BDE Si–O is 191.3 kcal/mol compared to 106.9 kcal/mol for the Si–C).^[129] However, it also depends on the relative stability of the carbanion compared to that of the alkoxy anion generated. The thermodynamic considerations are in line with the difference in rate of the silyl migration (kinetics) in α -silylcarbinols bearing different substituents (R², R³) on the carbon atom bonded to oxygen (Table 13). Electron-withdrawing groups promote the formation of the carbanionic species, whereas electron-donating groups destabilize this species, so a lower rate for the rearrangement is observed. The nature of the migrating triorganosilyl group also influences the kinetics of the rearrangement. With electron-withdrawing R¹ groups, the rearrangement rate is increased, likely as the result of increased stabilization of the cyclic pentacoordinate silicon intermediate.^[140,143,145–147]

$\mathbf{R}^{1}_{3}\mathbf{S}_{\mathbf{i}}, \mathbf{v}^{\mathbf{O}}_{\mathbf{R}^{2}} \mathbf{R}^{3} \longleftrightarrow \begin{bmatrix} \mathbf{R}^{1}_{3}\mathbf{S}_{\mathbf{i}}, \mathbf{v}^{\mathbf{O}}_{\mathbf{O}} \\ \mathbf{R}^{2}\mathbf{R}^{3} \end{bmatrix} \mathbf{M}^{\oplus} =$	$\xrightarrow{\mathbf{R}^{1}_{3}\mathbf{S}_{i}}_{\mathbf{M}} \xrightarrow{\mathbf{R}^{2}}_{\substack{\Theta \\ \Theta \\ \mathbf{R}^{3}}}$
Carbinol	$k_2 (M^{-1}s^{-1})$
9-Triphenylsilyl-9-hydroxyfluorene	1.18
Ph ₃ SiCPh ₂ OH	6.10×10^{-3}
Ph ₂ MeSiCPh ₂ OH	$0.98 imes 10^{-3}$
PhMe ₂ SiCPh ₂ OH	1.50×10^{-4}
Me ₃ SiCPh ₂ OH	2.50×10^{-5}
Ph ₃ SiCPhMeOH	4.30×10^{-6}
Ph ₃ SiCMe ₂ OH	Too slow

Table 13. Rates for $C \rightarrow O$ migration in selected α -triorganosilylcarbinols

The ease of C \rightarrow O silyl migration also depends on the nature of the metal counter-cation. With coordinating or oxophilic metal cations such as lithium, the migration is less favorable, and therefore, adjustments of some experimental parameters become essential. For example, the use of polar solvents and/or additives with high dielectric constant is a common tactic to trigger this rearrangement^[143,148] by promoting ion pair dissociation.^[149,150] Furthermore, while C \rightarrow O silyl migrations are usually performed at low temperatures, high temperatures may be needed to achieve formation of the pentacoordinate silicon intermediate in unfavorable cases.

Furthermore, independently of the intrinsic position of the equilibrium of the rearrangement step, the silyl migration may require the presence of an appropriate electrophile to occur. In this case, the aptitude of the carbanionic species to undergo electrophilic substitution becomes crucial, and operating under Barbier-type conditions mandatory. In these frequent situations, although the rearrangement equilibrium is not in favor of the O-silyl carbanionic species, the latter undergoes an irreversible electrophilic substitution more promptly than the C-silyl metal alkoxide. The reaction outcome is governed by the Curtin-Hammett principle: equilibration is fast compared with possible competing O-or C-functionalization, and the rate of formation of **33** is much higher than that of **32** ($k_c \gg k_0$) (Scheme 90). Consequently, only the Brook-product (**33**) is formed. Note that in this process the "electrophile" can be not only the stoichiometric reagent delivering the desired functionalization, but also the metal salt in the case of transition-metal catalyzed cross-coupling reactions. Finally, to be thorough, it should also be mentioned that there are also related cases (not shown in the scheme) wherein C-functionalization is quantitatively achieved due to the reversibility of the O-functionalization.



Scheme 90. Shifting of the silyl-migration equilibrium allowing for C-Si bond functionalization

The Brook rearrangement has attracted considerable interest and found many applications in organic synthesis. Some reviews and book chapters exist, describing applications, asymmetric transformations and mechanistic details.^[144,147,152–157] An inspiring personal account on anion relay chemistry was published by Smith during the preparation of the present review.^[154] However, synthetic methods relying on $C(sp^2)$ –Si bond functionalization upon activation through Brook rearrangements and related intramolecular activations by alkoxides, which are the focus of this minireview, have not been specifically surveyed previously.

We have organized this review in two parts, according to the nature of the bond cleavage. In the first part (Brook rearrangement), $C(sp^2)$ –Si bond functionalization is achieved through "endocyclic" cleavage (Scheme 91, top). In this case the silyl ether moiety remains in the target compound. Usually, a trialkylsilane is used as the migrating group, and thus the selectivity of C–Si bond cleavage from the silacyclic intermediate is not an issue, as the formation of a more stable $C(sp^2)$ –Si bond undergoes $C(sp^2)$ –Si over $C(sp^3)$ –Si bond-cleavage. In the second part, the reacting $C(sp^2)$ –Si bond undergoes "exocyclic" cleavage. In this case, no silyl migration occurs and the alkoxy unit "only" serves as intramolecular trigger (Scheme 91, bottom). Most of the tethers developed for this purpose so far involve a $C(sp^2)$ –Si linkage, and thus, here, the selectivity of the $C(sp^2)$ –Si bond cleavage from the cyclic hypervalent silicon intermediate can be an issue.^[158]

C(sp²)–Si Bond functionalization through endocyclic cleavage



Scheme 91. General approaches for $C(sp^2)$ -Si bond functionalization through intramolecular activation by alkoxides

1.2 C(sp²)–Si bond functionalization through endocyclic cleavage

Selective functionalization of alkenes and aromatic rings bearing other functional groups is often rather problematic. In this context, $C(sp^2)$ –Si bond functionalization of alkenyl- or (hetero)aryl-silanes through the Brook rearrangement represents a useful alternative to metalation chemistry and offers specific opportunities for regio- and stereocontrol.

1.2.1 C(sp²)–Si bond functionalization of alkenylsilanes

In 2001, the Takeda group developed a strategy for the stereoselective allylation of (*Z*)- γ -trimethylsilyl allylic alcohols **34**.^[159] Successive treatment with copper(I) *tert*-butoxide and allyl halides in DMF, followed by the TBAF-assisted hydrolysis, yielded dienyl alcohols **35** with complete retention of configuration of the double bond (Scheme 92). The mechanism involves firstly the formation of a copper alkoxide that then rearranges by [1,4]-C(sp²) \rightarrow O trimethylsilyl migration to give a vinylcopper species, which is then trapped by the corresponding allyl halide. In agreement with the intramolecular character of the rearrangement, formation of the *E* isomers (*e.g.* (*E*)-**35e**) was not observed from the parent (*E*)- γ -trimethylsilyl allylic alcohols. It is noteworthy that this activation method was also suitable to perform palladium-catalyzed cross-coupling reactions.



Scheme 92. Copper(I) tert-butoxide-promoted [1,4]- $C(sp2) \rightarrow O$ silyl migration of (Z)- γ -trimethylsilyl allylic alcohols

The synthetic value of this method triggered a number of synthetic applications that exploited trapping of the vinylcopper intermediate with a number of electrophiles. In a total synthesis of dolabelide D, vinylsilane **36** was methylated to yield **37** (Scheme 93).^[160] In this case, the trimethylsilyl group served not only as platform for functionalization, but also as alcohol protecting group for subsequent transformations.



Scheme 93. A key step for a total synthesis of dolabelide D

The same alkenyl anion generation strategy was followed in a (formal) total synthesis of strychnine, wherein allylic alcohol **38** was transformed into the pentacyclic product **40** (Scheme 94). Following deprotonation of the hydroxy function of **38** with NaHMDS, a [1,4]-C(sp²) \rightarrow O trimethylsilyl migration was triggered by the addition of a copper(I) salt in presence of NMP or DMPU. At room temperature,
the transient vinylcopper anion **39** led only to the protodemetalated product **38-H**. By contrast, at 65 °C, intramolecular 1,4-addition on the α , β -unsaturated aldehyde occurred, yielding 5–10% of the cyclized product **40** that could not be accessed by other means.^[161]



Scheme 94. A key step for a formal total synthesis of strychnine

This approach was later applied with γ, γ' -bis(trimethylsilyl) allylic alcohols **41**.^[162,163] Specifically, CuCN/ lithium *tert*-butoxide in DMF/ THF triggered the [1,4]-Brook rearrangement, and trapping with an array of electrophiles led fully stereoselectively to trisubstituted vinylsilanes such as **42** (Scheme 95). The key point of this reaction is that only the triethylsilyl group *cis* to the hydroxy undergoes the $C(sp^2) \rightarrow O$ migration, as the triethylsilyl group *trans* to the alkoxy anion cannot take part in the formation of a cyclic hypervalent pentacoordinate silicon complex. Interestingly, in the formation of **42d** and **42e**, [1,4]-silyl migration fully overrides a possible alternative [1,7]-silyl migration.



Scheme 95. Stereoselective [1,4]-Brook rearrangement/alkylation of geminal y, y'-bis-silyl allylic alcohols

The *gem* bis(triethylsilyl) alkene system was also used to study the competition between [1,4]- and $[1,5]-C(sp^2)-Si\rightarrow O$ migration in the Brook rearrangement. Specifically, deprotonation with butyllithium of the 1,2-diol **43**^[164] followed by CuCN / DMF addition (to promote the silyl migration), and trapping with allylchloride gave only the [1,4]-silyl migration product **44** (Scheme 96).



Scheme 96. Regioselective [1,4]-Brook rearrangement of geminal bis-silyl allylic 1,2-diol

The [1,4]-Brook rearrangement of (*Z*)- γ -trimethylsilyl allylic alcohols has also been embedded in multi-step sequences involving a preceding alkoxide-forming reaction. For instance, the 1,2-addition of an organolithium reagent to aldehyde **45** generates an alkoxy anion, which, activated in the presence of CuI and HMPA, undergoes the Brook rearrangement. The resulting organocopper intermediate can be trapped by an allyl bromide giving products such as **46a** or **46b**. Alternatively, in the presence of aryl or vinyl halides and of a palladium(0) catalyst, the corresponding arylated or alkenylated products (i.e. **46c** or **46d**) can be obtained (Scheme 97).^[165]



Scheme 97. Three-component anion relay couplings from an aldehyde/ vinyl silane linchpin

The strategy was also implemented with geminal bis(triethylsilyl) enals **47**.^[166] Upon 1,2-addition of organolithium reagents, the lithium alkoxides produced were treated with CuCN and an electrophile in DMF, to obtain trisubstituted vinylsilanes **48** in excellent yields and stereoselectivities (Scheme 98).



Scheme 98. Three-component reaction to synthesize trisubstituted vinylsilanes from geminal bis(silyl)enals

Another example involves a more complex sequence including a preceding anion relay step (Scheme 99). Geminal bis(triethylsilyl) allyl silyl ether **49** was metalated at the allylic position and then opposed to aldehydes to generate the corresponding alkoxides **50**. This triggered a [1,4]-O \rightarrow O silyl migration followed by a [1,4]-C(sp²) \rightarrow O silyl migration, and the alkenylcopper reagents then generated were

trapped in the presence of electrophiles to yield adducts **51**. Finally, treatment with PPTS in MeOH led to diols **52**.^[167]



Scheme 99. Sequential [1,4]-O-to-O / [1,4]-C(sp²)-to-O silyl migrations

A related [1,4]-Brook rearrangement is also at the origin of the strategy developed by Shindo and co-workers to achieve the cross-coupling of the (*Z*)- β -(trialkylsilyl)acrylic acids. The presence of a β located carboxylic acid function provides a smooth way to activate the C–Si bond of vinyl silanes **53** (Scheme 100).^[168] Indeed, intramolecular carboxylic acid-triggered silane activation can be smoothly obtained with cesium carbonate. The resulting transient cyclic hypervalent silicon intermediates **54** can then be treated with aryl iodides in the presence of an appropriate Pd catalyst, to yield the corresponding (*Z*)- β -(aryl)acrylic acids **55**.



Scheme 100. Cross-coupling of (Z)- β -(trialkylsilyl)acrylic acids via intramolecularly activation of vinyl silane

In 2015, Takeda reported on the C(sp²)–Si functionalization of enantiopure γ -(trimethylsilyl) homoallylic alcohols **56** giving products **57** upon [1,4]-C(sp²) \rightarrow O trimethylsilyl migration followed by electrophilic substitution of the alkenyl carbanion (Scheme 101).^[169] Allylation and alkylation reactions, such as those yielding **57a–b**, were performed by treatment with *t*-BuOCu in the presence of alkyl- or allyl-halides. Vinylation or arylation reactions, such as those yielding **57c–d**, were also feasible using vinyl or aryl halides as electrophiles, albeit only in the presence of an additional palladium-catalyst. These reactions have been shown to occur without variation in the diasteromeric ratio, which means that this method is well-suited in the context of stereoselective synthesis as it does not promote the epimerization of carbon stereocenters.



Scheme 101. Stereoselective synthesis of β , γ -disubstituted tert-homoallylic alcohols

As for the previous [1,4]-Brook rearrangement of (*Z*)- γ -trimethylsilyl allylic alcohols, the rearrangement of γ -(trimethylsilyl) homoallylic alcohols can also be included into multicomponent systems (most commonly, three-component systems), with the key step being the generation of an alkoxide ion. This includes bifunctional silylated linchpins bearing carbonyl and/or epoxide functions.^[165] For instance, the alkoxide resulting from the nucleophilic addition of lithium dibutyl cuprate to epoxide **58** can be activated in the presence of copper(I) iodide in HMPA, triggering a [1,4]-silyl migration (Scheme 102). The subsequent organocopper reagent can be trapped by an allyl bromide, leading to compounds **59a** and **59b**, or, in the presence of palladium(0) catalyst, be arylated to yield compounds **59c** or **59d** via cross-coupling reactions.^[165]



Scheme 102. Three-component anion relay coupling from epoxide vinyl silane linchpin

In a study performed by Smith in 2017, the requirements to achieve [1,4]- and [1,5]-C(sp²) \rightarrow O silyl migrations from copper(I) alkoxides were investigated by a combination of experimental results and computations.^[170] The [1,4]-C(sp²) \rightarrow O silyl migrations on alkenyl systems most often involve internal alkenes, while terminal alkenes are less described. In line with these observations, theoretical studies using the DFT method (M06 with solvation) showed that the terminal alkene **61** is coordinated more strongly to copper(I) iodide than the internal one **60** (Figure 6 and Figure 7, compare the blue profiles). This leads to a striking silyl migration activation barrier difference between **61** and **60**, the latter being 13.8 kcal/mol easier due to its higher strain.

The requirement established in earlier experimental work for two equivalents of alkyl lithium to achieve efficient [1,4]-Brook rearrangement was also analyzed. It was proposed that the first equivalent serves to achieve alkoxide generation (through hydroxide deprotonation or nucleophilic addition to aldehydes), while the second generates an alkylcopper reagent. For the latter (*e.g.* MeCu), owing to a higher LUMO level resulting in a less strong coordination of the copper atom to the alkene, the

activation barrier for silyl migration is lower than for CuI. In the case of vinylsilane **61** bearing a terminal alkyne, silyl migration with CuMe (E_{A2}) was computed to have an activation barrier lower by 4.0 kcal/mol than with CuI (E_{A1}) (Figure 7, compare blue and orange profiles). While these theoretical studies provide valuable insight to shed light on the influence of the nature of the copper species on the Brook-rearrangement, they should be taken with caution as the reacting copper species certainly differ in many other aspects (*e.g.* aggregation state, electronic nature).



Figure 6. [1,4]-Vinyl Brook rearrangements involving an internal double bond and CuI



Figure 7. [1,4]-Vinyl Brook rearrangements involving a terminal double bond and CuI or CuMe.

[1,5]-C(sp²) \rightarrow O silyl migration is more difficult than the corresponding [1,4] one, as demonstrated in the same study by Smith,^[170] and has been somewhat less described in the literature. The rearrangement of the silyl alkoxide **62**, bearing one carbon atom more than **61** between the alkoxide and the alkene functions, requires a silyl migration activation barrier that is 3.7 kcal/mol higher than from **61** (Figure 7 and Figure 8, compare the orange profiles). This can be ascribed to a larger conformational change between the intermediate and the transition state for the [1,5]-rearrangement (15.3°) than for the [1,4]-counterpart.



Figure 8. [1,5]-Vinyl Brook rearrangements involving a terminal double bond and CuMe

The influence of conformational constraints in the substrates was further analyzed by considering the [1,5]-C(sp²) \rightarrow O silyl migrations in conformationally rigid molecules with different tethers such as phenyl (63), *cis*-cyclohexyl (64) and *trans*-cyclohexyl (65) (Scheme 103). A number of electrophiles, including alkyl, benzyl and allyl halides, can be used to trap the anion arising from the Brook rearrangement and deliver 1,1-disubstituted alkenes. Arylation and alkenylation are also possible for these compounds, provided a palladium-catalyst is added.^[170]



Scheme 103. [1,5]-C \rightarrow O silyl migrations in conformationally rigid molecules

The calculated activation barrier for **63-TS**, **64-TS** and **65-TS**, which are close models, increases from 23.3 kcal/mol to 25.6 kcal/mol and 29.7 kcal/mol, respectively (Table 14). These values are consistent with the experimental temperatures required to observe the rearrangement: room temperature

for **63** (giving **66**), 60°C for **64** (producing **67**), and 100 °C under micro-wave irradiation for **65** (yielding **68**) (Scheme 103). In addition, the calculations demonstrated a good correlation between the extent of the required conformational change of the tether and the barrier for the [1,5]-Brook rearrangement. For instance, the rigidity of **63**, combined with a minimum required conformational change, accounts for the low energy barrier to the rearrangement in this case. Furthermore, the difference between the ease of migration of cis-cyclohexyl **64** with respect to trans-cyclohexyl **65** can be rationalized on the grounds of differential dihedral angle (OC-C-C-CSi) distortion $\Delta\phi$. Indeed, the latter substrate is associated to a much energy demanding $\Delta\phi$ (from 6.1° to 13.5°). The key points in terms of conformational changes, intermediates and transition states for this rearrangement, are represented in Table 14.





 $\Delta\phi$ was calculated C₁-C₂-C₃-C₄ and $\Delta\phi$ is the difference between ϕ (intermediate) and ϕ (TS).

 $C(sp^2)$ –Si bond functionalization of vinylsilanes through [1,3]-Brook rearrangements are much less common than [1,4]- and [1,5]-migrations. Nevertheless, Tsubouchi and Takeda exploited such a rearrangement to develop a strategy for the preparation of substituted silyl enol ethers starting from α silyl α , β -unsaturated ketones **69** (Scheme 104).^[171] 1,4-Addition of organocopper reagents to these substrates leads to the formation of the corresponding copper enolates as an equilibrating mixture of two diastereoisomers (*Z* and *E*). Following addition of DMF and at higher temperature, [1,3]-C(sp²) \rightarrow O triphenylsilyl migration becomes possible, but only for the *Z* isomer, which is the only one for which formation of a cyclic pentavalent silicon intermediate is feasible. Hence, the stereoselective formation of alkenylcopper intermediates is obtained, and their functionalization, with retention of the doublebond geometry, can be performed through electrophilic substitution. This method provides direct access to tetrasubstituted silyl enol ethers **70**, which are particularly useful reagents for the construction of quaternary stereogenic centres.^[172]



Scheme 104. Synthesis of substituted silvl enol ethers from a-silvl a, β-unsaturated ketones

1.2.2 C(sp²)–Si bond functionalization of arylsilanes

The [1,4]-C(sp²) \rightarrow O migration has also been used for the activation of arylsilane derivatives. In 2004, Takeda demonstrated that *o*-(1-hydroxyalkyl)arylsilanes **71** could undergo cross-coupling with organic halides by treatment with copper(I) *tert*-butoxide, in DMF in the presence of an electrophile to

afford compounds **72** (Scheme 105).^[173] This is among the first examples of Brook rearrangement on aryl silanes.



Scheme 105. t-BuOCu-promoted coupling of o-(1-hydroxyalkyl)arylsilanes with organic halides

A related [1,4]-C(sp²) \rightarrow O migration is also involved in the substitution of a robust *tert*butyldimethylsilyl (TBDMS) group by aryl groups in Hiyama-type cross-coupling reactions.^[174] For instance, the coupling of 8-TBDMS-1-naphthol **73** occurs in the presence of cesium carbonate in DME. The mechanism is expected to involve the formation of cyclic hypercoordinate silicon intermediate **73**', which then undergoes transmetalation with the aryl palladium iodide species in turn generated by oxidative addition of the aryl iodide to Pd(0). A reductive elimination then leads to the corresponding product **74** (Scheme 106).



Scheme 106. Hiyama-type cross-coupling reactions of 8-TBDMS-1-naphthols

As for some of the above discussed reactions with alkenylsilanes, the silyl-migration step can be combined with a preceding alkoxide-generating reaction. For instance, the nucleophilic addition of organolithium reagents to carbonyl derivative **75** was combined with subsequent Cu(I)-mediated [1,4]-silyl migration, which allows for the selective functionalization of the aromatic ring in the *ortho* position to give alcohols **76** (Scheme 107).^[165,175] It is important to note that the use of a Pd(0) catalyst in addition to copper is necessary for electrophilic substitutions with aryl- or vinyl-halides yielding products **76d**–**f**.



Scheme 107. [1,4]-silyl migration from ortho-TMS benzaldehyde

Similarly, a combined 1,2-addition/directed $C(sp^2)$ –Si functionalization was achieved in the threecomponent reaction between silylated benzaldehyde **77**, lithiated bis(triethylsilyl) allyl silyl ether **78** and electrophiles in the presence of *t*-BuLi. Alkoxide **79** arising from the 1,2-addition has the possibility to engage in silyl migrations both with the alkenyl- and the aryl-silane moieties. Only migration leading to an aryl anion was observed, and subsequent alkylation with allyl bromide resulted in the formation of compound **80** (Scheme 108). The exact origin of this selectivity in the migration was not determined, but it could be related to the higher stability of an aryl anion relative to an alkenyl anion, to more favorable kinetics for trimethylsilyl versus triethylsilyl migration, to a preference for [1,4]-migration over [1,5]-migration or, likely, to a combination of all the three reasons.^[164]



Scheme 108. Selective C(sp2)–Si migration of an aryl-silane versus of an alkenylsilane

Such Brook-promoted $C(sp^2)$ -Si activation reactions were also combined with anion relay processes. The example shown in Scheme 109 is based on initiation through the opening of an epoxide. Ring-opening of epoxide **81** with dimethyl cuprate gives rise to alkoxide **82**. The addition of copper iodide in the presence of HMPA triggers a first [1,5]-O→O silyl migration (involving the TBDMS group) which provides copper alkoxide **83**. Following a second [1,4]-C(sp²)→O silyl migration, the aryl anion (**84**) generated, is in turn trapped by an electrophile, leading to the final compound **85**.^[176]



Scheme 109. Multiple transfer of silyl groups through sequential $1,5-0 \rightarrow 0/1,4-C \rightarrow 0$ migrations

On a green chemistry perspective, one-pot multicomponent or sequential transformations are considered more environmentally friendly as they involve fewer purification steps, thus less product loss, and also, from an economic point of view, they are less expensive.^[144]

In this context, recently, a procedure for the one-pot bidirectional difunctionalization through two consecutive Brook rearrangements of benzylic alcohol 62 bearing two *ortho*-trimethylsilyl groups was developed (Scheme 110). In these processes, following deprotonation with *t*-BuOLi, a first [1,4]- $C(sp^2)\rightarrow O$ trimethylsilyl migration occurs in the presence of DMF, copper(I) iodide and phenanthroline ligand L9. The aryl carbanion is then trapped by a first electrophile E^1X^1 , leading to silyl ether 87, which can be converted in situ into alkoxide 87' by addition of a fluoride source and lithium *tert*-butoxide. The alkoxide thus formed is engaged in a second [1,4]- $C(sp^2)\rightarrow O$ trimethylsilyl migration, which gives the difunctionalized compounds 88 by reaction with E^2X^2 . This method can also be combined with palladium cross-coupling reactions to perform arylation and vinylation reactions.^[177]



Scheme 110. Sequential [1,4]- $C(sp^2) \rightarrow O$ silyl migrations of 2,6-di(trimethylsilyl) benzyl alcohol

The same strategy and similar operating conditions were also successfully applied to achieve the bifunctionalization of bis-*ortho*-trimethylsilyl benzhydrol derivative **89** leading to unsymmetrical diarylmethanols **90** (Scheme 111).^[178]



Scheme 111. Sequential [1,4]- $C(sp^2) \rightarrow O$ silyl migrations of bis-ortho-trimethylsilyl benzhydrol

Alkoxides arising from the addition of organolithium reagents to tricarbonyl(η^{6} -2-TMSbenzaldehyde)chromium **91** undergo quantitative [1,4]-C(sp²) \rightarrow O trimethylsilyl migration because the anion produced benefits from stabilization by the Cr(CO)₃ moiety. Subsequent trapping with electrophiles is possible even in the absence of polar additives or Cu(I) salts.^[179] This feature was nicely exploited to develop a Brook-based [3+2]-annulation reaction upon (stereoselective) addition of an ester enolate to **91** (Scheme 112).^[180] Here, the transiently generated aryl anion undergoes a final intramolecular acylation to deliver **92**. The chromium tricarbonyl can easily be detached after the transformation by simple exposure to air and sunlight.



Scheme 112. Brook rearrangement in silylarene chromium tricarbonyl complexes

1.2.3 C(sp²)–Si bond functionalization of heteroarylsilanes

Heteroarenes are ubiquitous units in organic compounds, and their regioselective functionalization is a fundamental endeavor for synthetic chemists.^[110] In this context, the Brook rearrangement is a useful tool for this purpose, as shown by the several studies on intramolecular [1,4]-C(sp²) \rightarrow O silyl migrations of silylated furans and thiophenes.

Implementation of this tactic received particular attention for the preparation of (2,3)-disubstituted furans and thiophenes. Initial studies on the [1,4]-C(sp²) \rightarrow O silyl migration in furan **93** and thiophene **94**, having a TBDMS group on position C2 and a hydroxymethyl group on position C3, showed that the reactions were highly solvent and counterion dependent (Table 15).^[181] Whereas the Brook rearrangement leading to silyl ethers **95** and **96** proceeded smoothly using sodium or potassium hydride, as well as sodium hydroxide in DMF or THF (entries 1-2, 4-6), lithium or magnesium bases failed to promote the migration in THF (entries 7-8). The lack of reactivity of these Li and Mg derivatives was possibly due to the high oxophilic nature of these metal cations, resulting in a stronger coordination to oxygen.^[181–183] This limitation represented a significant flaw for synthetic applications, as the carbanion formed by the migration promoted with the sodium or potassium bases could not be trapped with electrophiles other than protons.

	Solver OH 2. Hydrol	nt, rt ysis	² —H ─O SiMe₂t-I	Bu
	93 (X= O) 94 (X=S)	9 9	95 (X= O) 96 (X=S)	
Entry	Base	Solvent	t	Yield (%)
1	NaH (5 equiv.)	DMF	5 min	88
2	NaH (5 equiv.)	THF	16 h	80
3	NaH (5 equiv.)	Et ₂ O	7 d	_
4	NaH (1 mol%)	DMF	15 min	92
5	KH (5 equiv.)	THF	2 d	61
6	NaOH (5 equiv.)	DMF	1 h	64
7	CH ₂ =CHMgBr (1 equiv.)	THF	1 d	_
8	n-BuLi (1 equiv.)	THF	1 d	_

Table 15. [1,4]- $C(sp^2) \rightarrow O$ silyl migrations 2-TBDMS-3-hydroxymethyl furan and thiophene derivatives.

Some years after, a similar behavior was observed for the base-promoted rearrangement of 3hydroxyalkyl-2-silylthiophenes 97a-c (Scheme 113).^[184] After screening different additives, it was found that $[1,4]-C(sp^2)\rightarrow O$ silyl migration can be obtained by treatment with *t*-BuLi in THF, in the presence of DMPU. Other common additives such as HMPA or 12-crown-4 ether lead to very poor results. The optimized experimental conditions are also appropriate for the silyl migration of different trialkylsilyl moieties and, most importantly, can be combined with the trapping of the anion produced with different electrophiles, including methyl iodide (98aa, 98ab), benzaldehyde (98ba, 98bb, 98bc) and benzophenone (98cc), leading to 2,3-difunctionalized thiophenes, while, with allyl bromide, a moderate yield is obtained for 98db.



Scheme 113. Silyl migration/alkylation of 3-hydroxyalkyl-2-silylthiophenes.

Additionally, this reaction can be carried out in a sequential one-pot reaction starting from bromothiophenes **99a–c** (Scheme 114).^[184] The first step involves a Br–Li exchange upon addition of *tert*-butyl lithium. The thus formed organolithium reagent is then trapped by an aldehyde to provide alkoxides **100a–c**, which, under polar conditions and in the presence of an electrophile (alkyl halides, benzaldehyde or benzophenone), undergoes the silyl migration, leading to the final compounds **98**. The yield of the one pot reaction from **99a–c** to **98** is in concordance with the previous formation of **98** in two steps (Scheme 113).



Scheme 114. One-Pot synthesis of 2,3-disubstituted thiophenes

Following a related three-component strategy, the 2,3-disubstituted thiophenes **103** and furans **104** have been obtained from the 3-formyl heterocyclic precursors **101** and **102** (Scheme 115).^[151] Addition

of the alkyllithium reagents to the aldehydes generates the corresponding alkoxides, which undergo the Brook rearrangement. This crucial step is again carried out in a THF/DMPU (4/1) mixture, and the resulting carbanion can be trapped by benzaldehyde, for example. However, in the case of the furan derivative **104**, the Brook rearrangement requires the use of an $Et_2O/HMPA^{[185]}$ (1/1) mixture (Scheme 115).



Scheme 115. Synthesis of 2,3-disubstituted thiophenes and furans from 3-formyl heterocycles.

The work reported so far demonstrates the utility of $C(sp^2) \rightarrow O$ silyl migration in the field of heteroarene functionalization. Though, only a limited number of substrate-types has been studied, and the topic is far from being at a mature stage.

1.2.4 Synthesis of arynes from arylsilane

Arynes are important reactive intermediates in organic synthesis,^[186] and the Brook rearrangement provides a useful alternative to existing methods^[187,188] for the generation of these intermediates under mild conditions and without the need of fluoride salts.

Indeed, arynes can be generated from (*ortho*-silyl)phenyl triflates following intramolecular by [1,3]or [1,4]-silyl migrations. For example, after deprotonation of 3-hydroxy-2-(trialkylsilyl)aryl triflates with a mild base such as potassium carbonate or potassium *tert*-butoxide, the phenoxide anion formed undergoes a [1,3]-Brook rearrangement that generates a phenyl carbanion. The subsequent E1cb triflate elimination at the *ortho* position releases the corresponding aryne, which can undergo in situ trapping by a number of reaction partners (Scheme 116).^[189]



Base= KHMDS, MeLi, NaH, K₂CO₃...

Scheme 116. Arynes generation from 3-hydroxy-2-(trialkylsilyl)aryl triflates

The thus generated 3-trialkylsiloxybenzynes can, for example, be regioselectively trapped by aniline, as shown with the formation of compound **106**, or undergo a [4+2] cycloaddition reaction with 2,5-dimethylfuran, leading to the bridged tricyclic product **108** (Scheme 117).^[190] These examples showcase the power of this chemistry, which found many applications in synthesis.^[191]



Scheme 117. Some reactions of 3-trialkylsiloxybenzynes

Another tactic to produce arynes involves the addition of an appropriate carbanion to 2-silyl-3-OTf aromatic carbonyl compounds, such as **109**. The alkoxide **110** thus produced rearranges through [1,4]- $C(sp^2) \rightarrow O$ silyl migration to give carbanion **111**. Analogously to the previous example, β -elimination of the subsequent triflate yields the corresponding aryne **112**, which can undergo a wide variety of interor intramolecular [2+2], [3+2], and [4+2] cycloaddition reactions (Scheme 118).^[191]



Scheme 118. Aryne generation from (3-carbonyl)-2-(trialkylsilyl)aryl triflates

1.3 C(sp²)–Si bond functionalization through exocyclic cleavage

The palladium-catalyzed Hiyama–Denmark cross-coupling reaction occupies a prominent position in the rich chemistry of organosilanes, and represents an important tool in organic synthesis, especially for the construction of $C(sp^2)-C(sp^2)$ bonds from $C(sp^2)$ –Si bonds. Activation of the $C(sp^2)$ –Si bond towards transmetalation is a key requirement in this cross-coupling chemistry, and intramolecular alkoxide-promoted activation has been elegantly exploited as a mean to trigger the cross-coupling reaction of aryl- and alkenylsilanes under fluoride-free conditions.

As discussed in the introduction, intramolecular C–Si bond activation by alkoxides generates a hypervalent silicon intermediate embedded in a siloxycycle. In particular, the cleavage of a C–Si bond that is not part of this cycle is possible (exo-cyclic cleavage), which generates a carbanionic organometallic species along with a cyclic silyl ether byproduct. The organometallic intermediate formed is a suitable nucleophile for a number of cross-coupling reactions (Scheme 119). The selectivity of exo-cyclic *vs* endo-cyclic C–Si bond cleavage for the silacyclic intermediate is related to the stability of the resulting carbanion: typically, $C(sp^2)$ –Si bond cleavage is favored over $C(sp^3)$ –Si bond cleavage, unless the latter leads to particularly stabilized species such as benzylic or allylic organometallics.^[192,193] Where the bias is not obvious, as for example the competition between two $C(sp^2)$ –Si bond cleavages giving carbanions of similar stability, the products of exo-cyclic cleavage are usually predominant. However, the reasons for this selectivity have not been clearly established and may differ on a case-by-case basis. It has to be noticed, however, that the fundamental difference between endo- and exo-cyclic cleavage is that the former is a reversible process, while the latter is not.



Scheme 119. Alkoxide-promoted exo-cyclic cleavage of a C(sp2)-Si bond

It has been suggested that the transmetalation step in a cross-coupling reaction may proceed through two alternative pathways (Figure 9).^[194] The first one involves assistance by the alkoxide through **114**, wherein the transition metal atom directly interacts with the oxygen atom.^[195] The alternative pathway involves a compound of the type of **115**, where the silicon atom is coordinated by the counter-anion of the transition metal complex. Note that this second scenario complies with Muetterties' rule which states that the more electronegative ligands (aryl and vinyl ligands in this case) occupy an axial position in such hypervalent compounds.



Figure 9. Postulated pathways for silicon-to-transition-metal transmetalations in cross-coupling reactions of aryl- and alkenylsilanes

1.3.1 C(sp²)–Si bond functionalization of alkenylsilanes

Hiyama and Nakao developed the [2-(hydroxymethyl)phenyl] dimethylsilyl (HOMSi) unit as trigger to perform base-promoted C(sp²)–Si cross-coupling reactions.^[196] This method is highly attractive since the organosilane reagents are stable, and become reactive upon treatment with weak bases. One of the applications of this strategy was first investigated for the arylation of alkenylsilanes **116** (alkenyl–HOMSi reagents). This reaction was carried out with aryl iodides in the presence of palladium dichloride and potassium carbonate (Scheme 120).^[197] The reaction turned out to be tolerant to a wide range of aryl- or heteroaryl (**117f** and **117g**) iodides and suitable for diverse alkenylsilanes, including terminal and internal disubstituted, as well as tri-substituted. In all cases, exquisite retention of the aryli odides (such as aldehyde, ester, ether and alcohol), giving the coupling products in good to excellent yields.



Scheme 120. Arylation of alkenyl-2-(hydroxymethyl)phenyl]-dimethylsilyl derivatives

As to the mechanism of this protocol, after the intramolecular activation through the formation of a cyclic hypervalent silicon species from **116**, transmetalation by aryl-palladium(II) intermediates and subsequent reductive elimination gives the corresponding products **117**. Although this method is intrinsically not atom economical, the cyclic silyl ether byproduct **118** can be conveniently recycled and reused by treatment with organolithium or organomagnesium nucleophiles.^[194–199]

Alkenyl–HOMSi reagents **116** are also competent donors for rhodium-catalyzed 1,4-addition reactions to cyclic enones.^[200] As depicted in Scheme 121, 1,2-disubstituted- (**119a–d**), as well as 1,1,2-(**119e**) and 1,2,2-trisubstituted (**119f**) alkenylsilanes participate readily in reactions with 5-, 6-, or 7-membered cyclic enones. Again, retention of the double bond geometry of the alkenylsilanes is observed, and the mild activation conditions make the procedure highly functional-group tolerant with respect to the organosilane partner. Importantly, it has also been demonstrated that the method is amenable to enantioselective variants.



Scheme 121. Rhodium-catalyzed 1,4-addition to enones of alkenyl-2-(hydroxymethyl)phenyl]-dimethylsilyl derivatives

1.3.2 C(sp²)–Si bond functionalization of arylsilanes

Aryl–HOMSi derivatives **120** also undergo arylation reactions under palladium catalysis. By contrast with the alkenyl–HOMSi, in this case, the addition of a copper(I) salt is mandatory Despite the role of the copper(I) salt being unclear,^[194] it has been proposed that the transmetalation of the aryl group either occurs from silicon to palladium directly, or in two steps, following first silicon-to-copper transmetalation and then copper-to-palladium. Excellent yields are obtained with both electron-rich and electron-deficient aryl iodides, including heteroaryliodides (**121e**), with good tolerance of various functional groups (Scheme 122). In addition to phenylsilane (**121a,e,f**), C–Si arylation was also performed efficiently on electron poor aryl silanes (**121b**) as well as on 2-silylthiophene (**121d**), but was slightly less efficient for electron-rich aryl silanes (**121c**).^[198,201]



Scheme 122. Arylation of aryl-2-(hydroxymethyl)phenyl]dimethylsilyl derivatives

Such arylation reactions of aryl–HOMSi reagents have found relevant applications for the synthesis of extended polyarene π -systems. A first approach relies on halogenated aryl–HOMSi compounds.^[202] Owing to the fact that the HOMSi trigger relies exclusively on the presence of a free hydroxy group, halogenated arenes having THP-protected HOMSi units can participate as electrophiles in cross-coupling reactions with (unprotected) aryl–HOMSi nucleophiles without interference of the protected HOMSi moiety. Upon alcohol deprotection, the HOMSi trigger is "turned-on" and the adduct becomes a suitable nucleophilic partner for a following cross-coupling reaction. Entailing successive coupling and deprotection steps thus allows for the preparation of well-defined oligoarenes.

Bis-arylation strategies have also been considered on substrates bearing two (or more) halogenated groups,^[203] or two (or more) HOMSi units.^[199,204] For example, the double functionalization of one equivalent of bis-aryl bromide **122** was performed in the presence of two equivalents of arylsilane **123** (Scheme 123, top) to deliver **124**. Similarly, the bis-arylation product **127** was synthesized from two equivalents of bromobenzene **125** and bis-aryl silane **126** (Scheme 123, bottom).



Scheme 123. Bis-arylation strategies from (hetero)aryl-2-(hydroxymethyl) phenyl]dimethylsilyl derivatives

The strategy was also useful for the synthesis of polyarenes **128**. The formation of such species is possible by either iterative cross-coupling,^[194] or by copolymerization of dihalide-monoarenes **122** and aryl-bisHOMSi reagent **126** in equimolar quantities (Scheme 124).^[205]



Scheme 124. Synthesis of polyarenes from aryl-bis(2-(hydroxymethyl) phenyl]dimethylsilyl) derivatives

Aryl–HOMSi reagents **120** participate readily to the same rhodium-catalyzed 1,4-addition reactions to enones discussed above for alkenyl–HOMSi reagents **116** (see Scheme 121). Interestingly, in the presence of chiral diene ligands **L12** and **L13**, 1,4-adducts **129** can be obtained in high yield and excellent enantioselectivity (Scheme 125).^[200] The procedure is suitable not only for cyclic enones (**129a,b**), including nitrogen-containing derivatives (**129c,d**), but also for acyclic enones (**129e**).



Scheme 125. Enantioselective rhodium-catalyzed 1,4-addition to enones of aryl-2-(hydroxymethyl)phenyl]-dimethylsilyl derivatives

The development of another family of HOMSi silanes by Nakao and Hiyama, namely the 2-(hydroxy-methyl)cyclohexyl substituted arylsilanes **130**, allowed for the development of the first nickel-catalyzed silicon-based arylation leading to bis-aryl derivatives **131** (Scheme 126).^[206] Importantly, this cross-coupling reaction can even be performed using aryl chlorides. The electronic nature of the aryl chloride has an influence on the reaction outcome. Indeed, electron-poor aryl chlorides give better yields (**131b**) than electron-rich ones (**131a**). Conversely, no significant difference based on the electronic character of the aryl silane is observed (compare **131c** and **131d**). Interestingly, 2- and 3- aryl thiophenes can be obtained in reasonable yields (**131e** and **131f**), as well as 3-aryl pyridines (**131g**), albeit with a lower yield.



Scheme 126. Arylation of aryl-2-(hydroxy-methyl)cyclohexyl derivatives

The nickel-catalyzed arylation of aryl-HOMSI derivatives **130** can also be achieved using as coupling partners aryl tosylates, which are readily available from phenols (Scheme 127).^[206] For electron-rich aryl tosylates, PPh₃ was used as ligand, while in the case of electron-poor aryl tosylates, PPh₂Me was required. Interestingly, the same cross-coupling reaction was latter achieved with improved scope under cooperative palladium/copper catalysis.^[207]



Scheme 127. Nickel-catalyzed cross-coupling of aryl (HOMSi) with aryl tosylates

The HOMSi activation approach has also been used to achieve copper-catalyzed $C(sp^2)$ –N bondforming reactions from $C(sp^2)$ –Si bonds. The reaction between arylsilanes **119** and hydroxylamines **132**, in the presence of lithium *tert*-butoxide and a catalytic system composed of a copper(I) salt and JohnPhos (**L14**) as ligand, gives the corresponding anilines **133** (Scheme 128).^[208] The reaction is expected to involve the electrophilic amination of an aryl copper species arising from exo-cyclic $C(sp^2)$ – Si cleavage of the hypervalent silicon intermediate, in turn generated by intramolecular addition of the pendant alkoxide anion to the silicon atom.



Scheme 128. Copper-catalyzed C(sp2)-N bond-forming reactions from C(sp2)-Si bonds

A final (rare) example involving both endocyclic and exocyclic $C(sp^2)$ –Si bond cleavage has been disclosed by the group of Takeda (Scheme 129).^[209] Thus, treatment of *ortho*-silylphenones **134** with

copper *tert*-butoxide and an organic halide generates the corresponding silyl enol ethers. Interestingly, the substitution pattern of the silicon atom can be altered during the reaction.

The mechanism of this protocol implies the initial reaction of the *ortho*-silylphenones **134** with copper(I) *tert*-butoxide to produce a copper(I) enolate (**135**), followed by the formation of the corresponding silacyclic intermediate **135**'. The evolution of this intermediate differs according to the substitution of the silicon atom. On the one hand, with *t*-BuMe₂Si (pathway a), $C(sp^2)$ –Si endocyclic cleavage triggers *tert*-butyldimethylsilyl C-to-O migration, which generates the expected *ortho* substituted *tert*-butyldimethylsilyl enol ether **136** upon trapping with R²X. On the other hand, with Me₂PhSi (pathway b), bis(*tert*-butoxy)methylsilyl enol ether **137** is generated.



Scheme 129. Copper(I) tert-butoxide-promoted cross-coupling of o-silylphenyl ketones: endocyclic and exocyclic cleavage

This result has been rationalized by the authors on the basis of a first $C(sp^2)$ –Si exocyclic cleavage from **135'b**, to generate **138** and PhCu, and the subsequent addition of a first equivalent of *t*-BuOCu triggers the release of MeCu from the resulting pentavalent silicon intermediate (Scheme 130). Addition of a second equivalent of *t*-BuOCu triggers endocyclic $C(sp^2)$ –Si cleavage passing through intermediate **139**. Coupling of the thus generated arylcopper intermediate with the organic halide generates the final bis(*tert*-butoxy)methylsilyl enol ether **137**.^[209]



Scheme 130. Possible evolution of the oxasilacycle with an excess of CuOt-Bu

1.4 Conclusion

As illustrated in this minireview, carbon-to-oxygen silyl migration provides an efficient way to generate $C(sp^2)$ carbanion surrogates with perfect control of the site selectivity, and thereby the opportunity to perform a wide range of transformations under mild reaction conditions. The approach is particularly useful for the functionalization of molecules for which metalation cannot be envisaged due to low or inappropriate site-selectivity, or because of the instability of the resulting carbanion. Another attractive feature of this chemistry is that it also contributes to the evolution towards more sustainable synthetic chemistry, amid others through the possibility to perform, through the anion relay chemistry, multi-component and multi-step one-pot reactions, and by extending, through the HOMSI silane technology, the scope of cross-coupling reactions relying on organosilanes.

 $C(sp^2) \rightarrow O$ silyl migration has been chiefly implemented for arene and alkene functionalization and has reached a certain degree of maturity for this purpose. By contrast, heteroarene functionalization has received considerably less attention so far, even though some reports demonstrate the viability of the approach. We thus foresee that achieving this interesting prospect will become in the near future an important focus of research in the field.

2 Silyl-migration from C3-silylated furfural derivatives: results and discussion

2.1 Synthesis of model C3-silylated furfuryl alcohols

Since most of the existing examples for the $C(sp^2) \rightarrow O$ silyl migration involve alcohol derivatives, a model system was designed from the C3-silylated furfuryl alcohol (**140**-*Si*). Therefore, the derivatization of aldehyde **18**-*Si* to the corresponding alcohols **140a**-*Si* was first carried out in presence of *n*-butyllithium (Scheme 131). The preparation of the furyl trialkylsilanes was achieved in good yields, but not the C3-SiMe(OSiMe₃)₂ analogue, for which a complex inseparable mixture was obtained, probably due to the alkoxy groups on the silane moiety.



Scheme 131. Preparation of C3-silylated furfuryl alcohol.

2.2 t-BuOCu-promoted silyl migration of arylsilanes

Before studying the silyl migration on C3-silylated furfurylalcohol **140-***Si* following the conditions disclosed by Takeda in 2004 (Scheme 105)^[173] regarding the Cu(O*t*-Bu)-mediated silyl migration starting from o-(1-hydroxypropyl)benzyltrimethylsilane, we decided to reproduce the reported results.

The reactions between of 2-(trimethylsilyl)-, and most importantly 2-(triethylsilyl)-benzylic alcohols (**141-***Si-m* and **141-***Si-a* respectively) and allyl chloride were first reproduced in presence of CuI (0.5 equiv.), *t*-BuOLi (1.2 equiv) in DMF at 0 °C. Initial results with freshly opened bottles of CuI and *t*-BuOLi led to the desired coupling products in good yield. However, the results were not reproducible with aged reagents due to the cumbersome behavior of copper (I) *tert*-butoxide. Therefore, it was decided to store and handle CuI and *t*-BuOLi in a dry glovebox. The reactions represented in Scheme 132 evidence similar results for the two trialkylsilyl moieties in relation to the C→O silyl migration (Scheme 132(a)). However, when the reaction was performed in a mixture of THF/DMPU (12/1) instead of DMF, the main reaction product is oxasilacycle **143** (55%) and only 15% of the allylated product **142-m** (Scheme 132 (b)) was obtained.

^{ϕ} **140a**-*Si*-**x**, where **140** represents the furfuryl alcohol obtained from **18**-*Si*-**x**, **a** represents the butyl chain, from which from which results the nucleophilic addition of *n*-BuLi to the aldehyde function and *Si*-**x** represents the silane.



Scheme 132. Cu(Ot-Bu)-mediated silyl migration of 2-(trimethylsilyl)- and 2-(triethylsilyl)-benzylic alcohols

2.3 t-BuOCu-promoted silyl migration of furfurylsilanes

These conditions were then addressed to the C3-silylated furfuryl alcohol (**140a**-*Si*-**a**) (Table 16). However, under conditions similar to the previous ones (entries 1 and 2), poor conversion of the substrate was evidenced, and no $C(sp^2)$ -allyl product was observed. The formation of furfuryl alkoxide ion, instead of triggering the [1,4]-silyl migration, promotes O-allylation. The exchange of allyl chloride by allyl bromide, only improved slightly the yield of O-allylated product (entry 2).

The variation of several parameters, such as the solvent system, the temperature, the reaction time, the base, copper salt among others, was therefore undertaken. Some results following these trials are also reported in the experimental section (Table S25). Increasing the temperature or the time of the reaction mixture only improved the conversion and/or O-allylated product, but no other identifiable product was obtained (Entry 3). The influence of the base and/ metal ion was investigated. For example, the use of potassium *tert*-butoxide having a less coordinating counterion was contemplated, but did not improve the conversion (entry 4). The use of stronger bases, for example *n*-BuLi, only afforded 50 % conversion (entry 5). So, the problem, did not relate to the strength of the base. Poor conversions were in generally recorded for the Brook's rearrangement (Table 16), which led us towards other strategies.

SiEt ₃	Cul (0.5 equiv.) H <i>t</i> -BuOLi (1.2 equiv.) DMF (0.1 M) 30 °C, 2 h		Bu -SiEt ₃ + SiEt	n-Bu 	O n-Bu SiEt ₃ +	SiEt ₃
+		144a- <i>Si</i> -	a 145a	a- <i>Si</i> -a	146	147
(2 equiv)					
Entry	Solvent	Conversion	144a-Si-a (%)	145a-Si-a (%)	146 (%)	147(%)
1	DMF	43	_	12		<5
1 2^a	DMF DMF ^c	43 62	_	12 18		<5 8
$\frac{1}{2^a}$ $\frac{3^b}{3^b}$	DMF DMF ^c DMF ^b	43 62 56	-	12 18 12		<5 8
$ \frac{1}{2^a} $ $ \frac{3^b}{4^c} $	DMF DMF ^c DMF ^b DMF)	43 62 56 37		12 18 12 5		<5 8

Table 16. First trials of Cu(Ot-Bu)-mediated silyl migration of C3-silylated furfuryl alcohol 140-Si-a

¹H NMR yields were determined using dimethylsulfone was used as internal standard. ^aAllyl bromide used instead of allyl chloride. ^bThe reaction was heated from 0 °C to 60 °C. ^ct-BuOK and CuCl used instead of t-BuOLi and CuI. ^d n-BuLi (1.2 equiv.) used instead of t-BuOLi.

Alternatively, copper-free conditions with NaH as the base, based on Keay's 1989 work on 1,4-silyl migration of 3-[(triethylsilyl)oxymethyl]furan **93**,^[181] were tested on our C3-silylated furfuryl alcohol (**140a**-*Si*-**a**). However, no protodesilylated product was evidenced, and only degradation products were observed, as we had previously noticed in our C3-lithiation studies (Scheme 133).^[53]



Scheme 133. NaH triggering [1,4]-C \rightarrow O silyl migration of 140-Si-a

Another important aspect was the use of highly polar solvents or additives in attempts to favor $C(sp^2) \rightarrow O$ silyl migration. Neither the use of HMPA nor DMPU improved the conversion nor delivered the Brook's rearrangement product. For instance, on heating the reaction mixture to 80 °C in THF/HMPA (1/1), a mixture of products was obtained (Scheme 134). Four of the products could be identified and characterized. Two of these products were quite unexpected, namely **146** and dehydroxylated product **147**.



Scheme 134. Cu(Ot-Bu)-mediated silyl migration of C3-silylated furfuryl alcohol 140a-Si-a in THF/HMPA

To account for the formation of **146** and **147**, we hypothesized the following scenario: O-allylated compound **145a**-*Si*-**a** undergoes reversible deprotonation resulting in the formation of organocopper **145a**'-*Si*-**a**. The latter can undergo a [2,3]-Wittig sigmatropic rearrangement through a cyclic 6-membered transition state and give product **148** (Scheme 135).^[210,211] Nevertheless, this product **148** was not observed by ¹H NMR of the crude. Instead, **146a**-*Si*-**a** and **147a**-*Si*-**a** were observed in equimolar quantities. In the presence of copper, another 6-membered transition, **149**, was envisaged, where the alkoxide ions of **148** and **140a**'-*Si*-**a** are coordinated to copper. Hydride transfer from **140a**'-*Si*-**a** brings about product **146**, while **148** gets reduced (de-hydroxylation), to give **147**.



Scheme 135. Mechanistic hypothesis for the formations of 146 and 147

The use of other silvl units such as *tert*-butyldimethylsilyl, did not lead to any C-allylated product, despite good conversion (89%), which might relate to degradation of the substrate.
2.4 Barbier-type conditions

Attempts to perform the C(sp²)–Si functionalization reaction under "Barbier-type" conditions by adding *n*-BuLi to the C3-silylated furfuraldehyde (**18**-Si-c), followed by the addition of benzaldehyde, were unsuccessful. Instead of the envisioned C(sp²) \rightarrow O silyl migration, only alcohol **140**-Si-c was obtained (Scheme 136). Despite, the variety of aryl(trialkyl)silanes that have been reported in the literature, there are still limited applications for the transformation of the heteroarylsilane congeners.



Scheme 136. One-pot synthesis of 2,3-disubstituted furan from 18-Si-c through, nucleophilic addition to the aldehyde followed by 1,4-Brook rearrangement

2.5 Conclusion

Following these results, several hypotheses were considered, namely the stability of the aryl anion and geometrical reasons. In comparison with the previously reported benzyl alcohol **141**-*Si*, where silyl migration was feasible, furfuryl alcohols (**140**-*Si*) provide the C-allylated product only in low yields if at all. A correct geometrical arrangement is necessary for the formation of the cyclic hypervalent silicon intermediate of the Brook rearrangement. As shown in Scheme 137, angles *a* and *b* are greater in the case of 5-membered heterocycles,^[110] especially for the furan ring, than in the case of benzene. This could disfavor the formation of the cyclic pentavalent silicon intermediate, both due to the difficult approach of the alkoxide to the (het)aryl-silane and the low stability of the highly strained ring. Furthermore, other considerations such as the relatively low stability of the anion in the C3 position might also influence the migration of the silicon group. Indeed, the formation of the cyclic pentavalent silicon intermediate is reversible; the equilibrium might be poorly shifted towards the C \rightarrow O silyl migration.



Scheme 137. Geometrical considerations

Finally, one can also envisage the formation of an alkoxide intermediate upon deprotonation of the furfuryl alcohol leading to two possible conformers (Scheme 138). One, **140a'-Si-a**_{β}, which is coordinated to the lone pair of oxygen of the furan, hence providing extra-stabilization of the conformer and a second one, **140a'-Si-a**_{α} where the oxygen is in the same plane as the silicon atom. In this case, the activation through the pentavalent cyclic silicon intermediate can only arise from the least stable conformer, and this would be deleterious for the reaction to proceed. Depending on the stability of the chelating group, energy has to be provided to limit this interaction.





However, promising results were obtained for the reaction between **153a**-*Si*-**d** bearing a dimethylbenzylsilyl group, and benzaldehyde, triggered by *t*-BuOCu in THF/HMPA. Interestingly, 1,2-addition of furan to the benzaldehyde was not observed; but the nucleophilic addition of the benzyl anion to benzaldehyde was noticed, with the formation of product **156** (Scheme 139). We explain the formation of this product by a 1,4-silyl migration giving rise to a pentavalent silicon complex, from which is released a benzylcopper species. Here, exocyclic cleavage prevails over endocyclic cleavage because the benzylmetal is more stable than a putative furfurylmetal. Exocyclic cleavage also suggests the formation of an oxasilacycle **155**. However, aqueous work-up of strained cycle, **155** led to its degradation, which explain for its absence from the crude of the ¹H NMR spectrum. In addition, the product of allylation of benzyl anion was not observed previously, possibly due to its volatility.



Scheme 139. Formation of an oxasilacycle

Following this result, several trials were performed by varying the base, the addition of an external nucleophile (MeLi, LiOCH₂CH₂OH, *t*-BuOK (in excess)), as well as additives, to activate **155** towards subsequent trapping by electrophiles: they were all unsuccessful. Failure to properly trigger the C3-functionalization prompted us to think about other activation strategies, in particular using fluoride anions.

CHAPTER IV:

Fluoride-mediated transmetalation

1 Introduction

Another way to promote C(sp²)–Si bond functionalization of arylsilanes relies on activation by fluoride anions. Silicon has a high affinity for fluorine with a bond dissociation energy for Si–F of approximately 576 kJ•mol^{-1[129]} and which is comparable to that of oxygen. Fluorine anions are therefore used to selectively target the silicon unit because of its marked nucleophilic affinity for the latter to generate a pentavalent silyl group (Figure 10). The concept of hypervalence (pentavalent or hexavalent) of silicon is considered to be largely due to its d-orbitals, and was considered by Oestreich to enhance the Lewis acidic character of the silicon species, independent of its formal charge.^[212] This aspect is quite important for the proper understanding of this mode of activation (Chapter IV, section 0).

Upon formation of a silicon pentacoordinated species, the C–Si bonds of the organosilane are polarized and electrophilic substitution reactions become possible, including transmetalation reactions. The C–Si bond of the fragment associated to the more stable carbanion is the more reactive one in this context. It was rapidly recognized that heteroatom substitution on silicon giving additional polarization to the reacting C–Si bond was required to develop broad-in-scope protocols. Hence, aryl(halo)silanes, aryl(alkoxy)silanes, including trialkoxysilanes, dimethylsilanols and tetraorganosilanes that behaved as masked dimethylsilanols, and were converted into these active species on hydrolytic cleavage of labile groups such as 2-pyridyl, 2-thienyl, 3,5-bis(trifluoromethyl)phenyl, benzyl, allyl or hydrogen, have been extremely studied for this type of transformation.



Figure 10. Simplified activation of the C(sp2)–Si bond by fluoride anion

In this context, we have considered this activation strategy for the functionalization of the $C(sp^2)$ – Si bond of our furfuryl platforms along two approaches: a) functionalization of C3-SiMe₂Bn furfuryl alcohols wherein the alcohol function has the possibility to participate in the activation process (Figure 11) and b) functionalization of C3-SiMe(OSiMe₃)₂ furfuraldehydes (Figure 12).



Figure 11. Fluoride mediated-functionalization of furfuryl alcohols



Figure 12.Metal-fluoride assisted functionalization of C3-silylated furfuraldehydes

2 Fluoride-promoted cross-coupling reactions of organobenzyldimethylsilanes and cyclic siloxanes

2.1 Case of alkenyl benzyldimethylsilanes

To the best of our knowledge, no direct cross-coupling reactions of aryl benzyldimethylsilanes have been reported. By contrast, alkenyl benzyldimethylsilanes have been used profusely as carbon donors in metal-catalyzed cross-coupling reactions. Some selected examples of such reactions are discussed hereafter to highlight the potential of this chemistry.

In 2003, one of the pioneer work involving SiMe₂Bn as coupling partner, was disclosed for the palladium catalyzed cross-coupling reaction involving vinyl silanes and iodo-arenes.^[213] In a first step, the vinyl silane was pre-activated at 0 °C in the presence of TBAF, for the de-benzylation process, which is able to promote its transmetalation following the addition of [Pd₂dba₃]•CHCl₃ and a coupling partner (Scheme 140). This methodology was first applied to 1,1-disubstituted vinylsilanes, extended to trisubstituted vinylsilanes, then later to 2,2-disubstituted vinylsilanes.^[214] This strategy was also involved in the arylation step, for the synthesis of lactimidomycin analogue.^[215] However, it is not limited only to arylation but, was also efficient for the cross-coupling between vinylsilane and iodoalkenyl, where it was applied for the synthesis of carotenoids.^[216]



Scheme 140. Palladium-catalyzed cross-coupling of di- and tri-substituted vinylsilanes

Fluoride-promoted cross-coupling reactions of alkenylbenzyldimethylsilanes were also reported under copper(I) catalysis. In 2014, Takeda reported the alkylation of alkenybenzyldimethylsilanes (Scheme 141).^[217] The authors highlighted the importance of an anhydrous source of fluoride, as TBAF(t-BuOH)₄ to attenuate the formation of the proto-desilylated side product. Two equivalents of this reagent were necessary to promote the transmetalation of the hypervalent silyl group to Cu(I). The alkenyl-copper, could therefore be trapped by an alkyl- or allyl-halide to give the corresponding products. This strategy can be applied to di- and tri- substituted alkyl dimethyl silanes as well as to homoallylic alcohols, whilst also keeping a complete retention of configuration.



*DMSO/THF used instead of DMF

Scheme 141. Cu(I) promoted alkylation of alkenylbenzyldimethylsilanes

2.2 Case of cyclic siloxanes

2.2.1 Fluoride mediated cyclic siloxanes synthesis

Recently, Anderson disclosed the synthesis of cyclic alkenyl siloxanes from benzyldimethylsilanesubstituted allylic and homoallylic alcohols.^[218] Treatment of these alcohols with TBAF triggered a rapid debenzylation and the formation of the corresponding 5- and 6- membered cyclic alkenyl siloxanes- A catalytic amount of TBAF was necessary to fulfil the complete conversion of these substrate and furnish relatively good yield of the cyclic siloxane (Scheme 142).



Scheme 142. Synthesis of cyclic alkenyl dimethylsiloxanes from alkynyl benzyldimethylsilanes

Interestingly, a similar behaviour was reported for a benzyldimethylsilane-substituted allylic acetate, in the presence of TBAF, providing 99% yield of the 5-membered cyclic siloxane.^[218] Nevertheless, the homoallylic analogue gave only rise to acyclic silanol. Based on these evidences, the authors proposed a mechanism for this cyclization. On addition of the fluoride source, instantaneous debenzylation occurs and a silanol intermediate is formed. The nucleophilic hydroxyl group of the silanol, undergoes a transesterification with the proximal acetate, generating an alkoxide, which cyclizes on the acetoxysiloxane. Upon liberation of acetate, the 5-membered cyclic siloxane was obtained (Scheme 143).



Scheme 143. Possible mechanism for the de-benzylation and formation of the cyclic siloxane

Such reactions are important because cyclic siloxanes are also competent carbon-donors for crosscoupling reactions promoted by fluoride activation.

2.2.2 Fluoride-mediated cross-coupling of cyclic siloxanes

The arylation and alkenylation of the 5-, 6-, 7-membered siloxanes has been described using Pd(dba)₂ or [allylPdCl]₂ as pre-catalyst, with iodobenzene and alkenyl -bromide or -iodide as coupling partners.^[218–223] The cross-coupling was mediated by the presence of TBAF as fluoride anion source. The cleavage of the C(sp²)–Si bond prior to the transmetalation to palladium was proposed to be dependent on the stability of the cyclic siloxane. In this context, longer reaction times were necessary for the 6-membered siloxanes as compared to the 5-membered analogues. The conversion rate, is especially striking, for the alkenylation reactions, where the reaction time was 21 times higher with the 6-membered cyclic siloxane in comparison with its 5-membered analogue (Scheme 144 (a)). The actual methodology also provides a stereo-controlled cross-coupling reaction, starting from enantioenriched cyclic siloxanes for the synthesis of Fostriecin fragment, Phoslactomycin B fragment, Leukotriene B,^[218] bitungolide C^[223] and Resolvins,^[219] while it also represents an alternative to the classical Stille coupling.

This methodology is not only limited to intermolecular cross-coupling reactions, but can also be used in an intramolecular fashion. Denmark, established a strategy, based on 6-membered cyclic siloxane, for the macrocyclization to furnish a 9-membered ring. The cross-coupling between the alkenyl iodide and the oxasilacycle under [allylPdCl]₂ and TBAF, provided the desired product in 61% yield (Scheme 144 (b)).^[220,221] In this case, a high excess of TBAF was used to promote the transmetalation to palladium. In addition, longer reaction times were necessary, probably, relates the unfavorable, 9-membered ring cyclization.



Denmark et al. J. Am. Chem. Soc. 2002, 124, 15196.

Regarding the mechanism of the activation, some synthetic intermediates were characterized for the 6-membered siloxane.^[218] In fact, it seems that the cyclic siloxanes dimerize to acyclic disiloxanes and it is this intermediates that undergo fluoride activation as shown in Scheme 145 top, and that become the active transmetalating species. Such mechanism is reminiscent of the transmetalating species previously reported by Denmark^[224,225] for the palladium coupling of aryl halide and alkenyl silanol. The in-*situ* formation of alkenyl-silanolate species, granted access to an efficient transmetalation of the alkenyl group to palladium, prior for the formation of the coupling product.^[224,225] In the case of the 5-membered siloxanes, the mechanistic details still remain quite unclear because no intermediate has been isolated so far. It is suspected that acyclic disiloxanes are also formed, but that the activation towards transmetalation originates from a proximal alcohol function, as depicted in Scheme 145, bottom.

Scheme 144. Palladium-catalyzed cross-coupling reaction between alkenyl- or aryl-halide and oxasilacycle



Scheme 145. Possible mechanisms for transmetalation of cyclic siloxane-derived intermediates.

2.3 Fluoride-promoted functionalization of C3-SiMe₂Bnsubstituted furfuryl alcohols

2.3.1 Results and discussion

As described earlier, the reaction of **152-Si-d** and benzaldehyde, in the presence of in-*situ* prepared Cu(Ot-Bu) delivered in 75% yield product **155** (Scheme 139) which most likely comes from exo-cyclic cleavage of a hypervalent aryl silicon intermediate. We decided therefore to focus our attention on the functionalization of dimethylbenzyl silyl furfuryl alcohols under fluoride-activation conditions, in particular through the formation of the corresponding oxasilacycles.

a. Activation of C3-silylated furfuryl alcohols

Inspired by the above-discussed reports by Anderson and co-workers, we considered the cyclization of the furfuryl alcohol substrates on treatment with fluoride anions (Table 17). The use of a catalytic quantity of TBAF (entry 1) did not promote the formation of **155**, despite prolonged reaction times. We then observed that a stoichiometric amount of TBAF was necessary to fully activate the aryl silicon moiety (entry 2), but higher amount of TBAF did not really influence the $C(sp^2)$ –Si bond cleavage. Other sources of fluoride were considered. Neither CsF was efficient for this reaction, probably due to its poor solubility (entry 3), nor the anhydrous source of fluoride anion [Ph₃SiF₂]NBu₄ (entry 4). In addition, polystyrene-supported fluoride was not an efficient activator of **153a-Si-d** in THF at rt (entry 5), but in benzene-*d*₆ under reflux, led to the formation of the proto-desilylated product as major product along with an unidentifiable aryl–silicon species (entry 6). It is also important to mention that in addition to fluoride sources, we also considered activation by KOSiMe₃, which proved inefficient (entry 7).

	⊖H SiMe₂Bn 153a-Si-d	THF (0.2 M), rt	Si ⁺ O Si ⁺ O 155	+	
Entry	Activator	Time (h)	Conversion (%)	155 (%)	Remarks
1	TBAF•3H ₂ O (0.25 equiv.)	0.25	10 ^b	-	
2	TBAF•3H ₂ O (1.0 equiv.)	0.25	100	98	Reaction carried out in THF- <i>d</i> ₈ PhCH ₃ (86%) obtained.
3	CsF (1.0 equiv.)	24	-	_	
4	[Ph ₃ SiF ₂]NBu ₄ (1.0 equiv.)	24	44	Traces	Corresponds to reported ratios.
5	PS (1.1 equiv.)	0.25	_	_	Same result with benzene- d_6 and THF
6	(1.1 equiv.)	24	100	-	Benzene- <i>d</i> ₆ used instead of THF without stirring under reflux. Proto- desilylated product and an un-identifiable product was obtained
7	KOSiMe ₃ (1.5 equiv.)	24	20	-	No change after 2 h

Table 17. Mode of activation of C3-silylated furfuryl alcohol 153-Si-d

___*n*-Bu

н

n-Bu

Activator

The isolation of the cyclic siloxane, **155**, proved to be complicated; therefore, it was directly characterized from the crude both by NMR, and HRMS. Our attempt to isolate this product through silica gel chromatography led, to a mixture of several products. Similar results were obtained, for the washing of the crude organic extract with water, or aqueous HCl (1 M) solution (Figure 13, dark blue). But the washing of the crude extract with KOH (6 M) solution, led to the selective formation of disiloxane, which was later characterized by NMR and HRMS techniques (Figure 13, red), and corresponds to the disiloxanes.

¹*H NMR yields were determined using 3,4,5-trimethoxybenzaldehyde.*



Figure 13. Degradation of 155 (black) in acidic (dark blue) and basic medium (red)

These cyclic siloxanes are of particular interest, because, they are easily activated using an organometallic reagent or a fluorine source. But, due to the difficult isolation of **155**, the use of organometallic reagents mainly resulted in the deprotonation of acidic protons from ammonium ions and therefore, made their selective activation difficult. On this basis, because of the sensitive nature of these cyclic siloxanes, there is a need to develop of a one-pot procedure, involving both the activation of the C3-silylated furfuryl alcohol in the presence of TBAF, as well as its functionalization.

b. Arylation of furfuryl alcohols

Following reported procedures by Anderson,^[218] our initial attempt involved a one-pot sequential procedure starting from **140**-*Si*-**d**, in which following the addition of TBAF, in THF, $Pd(dba)_2$ and iodobenzene were added to perform the arylation (Scheme 146(a)). However, the proto-desilylated product was the only one observed.

It is known in the literature, that palladium cross-coupling reactions between aryl silanes and aryl halide often require copper (I) salt to proceed. It was proposed that silicon-to-copper transmetalation of

the aryl–silicon derivative occurs first, which allows then transmetalation to palladium which is responsible for the C–C bond-formation event. Adapting procedures for the arylation of alkenyl silanes, with copper(I) co-catalysts, on pre-activation of **153a**-*Si*-**d** by TBAF, in the presence of iodobenzene, CuI and Pd₂dba₃, the arylated product, **157aa** was obtained in 70% yield (Scheme 146(b)). The arylation process performed reasonably well with (electron-rich) 4-iodoanisole as coupling partner, delivering **157ab** in 57% yield. Conversely, no arylation was observed with (electron-deficient) 1-iodo-4-nitrobenzene.



Scheme 146. Palladium-catalyzed arylation of 153a-Si-dⁿ

Finally, an attempt to perform the alkenylation of **152-Si-d** with β -bromostyrene, using the same procedure, did not provide any alkenylated product. No in-depth investigation of this type of functionalization was performed, which, leaves room for further optimization. Notably, the use of iodoalkenes for which the oxidative addition into the alkenyl–halide bond would be easier is sought to be considered.

In our following studies, we rather focused on transformations allowing for $C(sp^2)-C(sp^3)$ bond formation.

^{η} The numbering of **157ab** represents the product obtained from **153a**-*Si*-**d**, where **a** represents the butyl chain and **b** the aryl. **140a**-**H**, where **H** represents the protodesilylated product of **140a**-*Si*-**d**.

c. Allylation and alkylation of furfuryl alcohols

In literature, few cases of allylation or alkylation of the furan ring have been reported; and most of this concerns the C5- and the C2-functionalization of these heteroaromatic rings. Selective C3-transformations are quite challenging and often require an excess of the furfuryl derivatives, which would not be appropriate in our case because we envisage to use the furan substrates as the limiting reagents.

As discussed previously, treatment with 1 equivalent of TBAF (Figure 14, top) leads to the cyclized structure, **158**. The same compound is observed when 3 equivalents of TBAF are added, along with another compound, probably a silanol, which could not be characterized (Figure 14, middle). We contemplated the possibility to perform electrophilic substitution of this activated intermediates in the presence of added electrophiles. However, this activation was not sufficient to promote direct allylation in the presence of allylchloride (Scheme 147, Figure 14, bottom) which demonstrated the requirement for metal catalysts to achieve such transformations.



Scheme 147. Direct allylation test of 140a-Si-d in the presence of allylchloride



Figure 14: Activation of C3-silylated furfuryl alcohol for functionalization (Calibration of the ¹H NMR was based on the ammonium salt)

c1. Method development

Takeda and co-workers reported that, for the fluoride-promoted alkylation and allylation of alkenyl benzyldimethylsilanes with Cu(I) catalysts, the choice of the appropriate TBAF reagent plays a crucial role. We thus considered the optimization of this parameter. Therefore, the reaction between **153a**-*Si*-**d** and methallyl chloride was optimized taking as working conditions 1.5 equivalents of CuI and P(OEt)₃ as ligand in DMF. This reaction was strictly carried out under argon to prevent any side reactions to occur. The first trial with TBAF in solution in THF (Table 18, entry 1), provided the methallylated product **159aa** in 30% yield, but a non-negligible amount of proto-desilylated product (**153a-H**) was evidenced, which could relate the presence of protic sources in the reaction medium. The solvent being anhydrous and freshly opened, along with the substrates and electrophile, freshly prepared and distilled respectively. The TBAF solutions of TBAF are reckoned to be highly hygroscopic. The use of molecular sieves as additive, appeared to be beneficial for the reaction, and a higher ratio of **159aa** to **153a-H** was obtained (entry 2). We then shifted to TBAF(*t*-BuOH)₄^[226] as an anhydrous fluoride anion source, and these conditions provided **159aa** in good yield with quite low amounts of the proto-

desilylated product (entry 3). Lastly, it should be noted that the number of equivalents of fluoride ions is crucial for efficient Si \rightarrow Cu transmetalation as 32% of the proto-desilylated product was formed when 1.2 equivalents were used instead of 2.4 equivalents (compare entries 3 and 4).



Table 18. Optimization of fluoride reagent⁹

¹H NMR yields were calculated using Me_2SO_2 as internal standard. ^aMS 4Å was used as additive.

We then went on to optimize other reaction parameters (Table 19). It was found that the reaction was over after only 2 h and those identical yields were obtained as for the reaction during 24 h (entries 1 and 2). Furthermore, as previously evidenced for the activation of the aryl–silane, low temperature (0 °C) largely influences the activation of these silyl moiety, resulting in poor conversion of this species. Therefore, all the reactions were performed at temperature above 0 °C and mostly at 30 °C.

The presence of a ligand for copper proved beneficial for the reaction outcome. In its absence, poor reaction yield was evidenced, along with a higher proportion of proto-desilylated product **153a-H** (entry 3). One plausible explanation is related to the stability of the aryl–Cu species generated which could be increased by the ligand. Alternatively, the reactivity of the aryl–Cu towards the electrophile could be increased, making the electrophilic substitution step more efficient. No difference in yield was noted using pre-formed CuI•P(OEt)₃ instead of CuI and free P(OEt)₃ (entry 4). The presence of P(OEt)₃ was nevertheless problematic because pure product isolation without contamination by the phosphite was barely possible. Thus, the reaction was carried out with PPh₃ as ligand. The yield was significantly improved to 80 % in presence of over-stoichiometric amounts of CuI and PPh₃ (entry 5) and no loss of efficiency was observed using 20 mol% of the same catalytic system (entry 6). In addition, with these reaction conditions, the isolation of pure methallylated product **159aa** was straightforward. With a

^{γ} The numbering of **159aa** represents the product obtained from **153a-Si-d**, where the first **a** represents the butyl chain and **a** methallyl electrophile. **153a-H**, where **H** represents the protodesilylated product of **153a-Si-d**.

lower loading (10 mol%) longer reaction times were necessary to achieve good levels of conversion and in that case the amount of protodesilylation increased significantly (entries 7 and 8). Here, starting from pre-formed CuI•PPh₃ slightly improved the reaction yield under catalytic-in-copper conditions (entries 9 and 10).

Finally, the use of THF as solvent was considered. In these conditions the amount of protodesilylation was higher and thus the yield in allylation compound dropped. It could be that as DMF has a higher dielectric constant than THF, the nucleophilicity of the aryl–copper is and thus electrophilic trapping more favorable (entry 11).



Table 19. Optimization of catalytic system and operating conditions

¹H NMR yields are calculated using dimethyl sulfone as internal standard, except entry 2, 1,4-dinitrobenzene where was used. ^aTHF used as solvent instead of DMF

c2. Reaction scope

With these optimized conditions in hand, application of the methodology was considered for a range of furfuryl alcohols. Different classes of these alcohol derivatives were prepared by 1,2-nucleophilic addition of alkyl, vinyl and phenyl- lithium or Grignard reagents to furfurals (Scheme 148). In order to access a large scope of C3-functionalized synthetically useful intermediates, different functionalization reactions were contemplated.



Scheme 148. Transformation of C3-silylated furfural to alcohols[®]

Firstly, methallylation and allylation reactions were studied. The dual activation by fluoride ion coupled with the intramolecular assistance of the alcohol function led to the C3-functionalized products in moderate to good yields (Scheme 149). Methallylation of the 5-methyl furfuryl alcohol derivatives was achieved in 65–84% yields and the nature of the substituent α to the alcohol had little influence on the C3-functionalization efficiency. Nevertheless, in the case of phenyl-substituted **19**-*Si*-**d**, O-allylation also took place, leading to 25% of side-product **159ba**_a. We surmise that O-alkylation occurs during the reaction basic work-up (6 M aqueous KOH). Allylation was achieved in slightly lower yields (both with allyl chloride and allyl bromide) as demonstrated with the formation of **159ab**.

A drop in the yields was noticed when the reactions were performed on C3-silylated furfuryl alcohols, **140a-Si-d** and **140b-Si-d**. For example, the methallylation of α -butyl furfuryl alcohol yielded the desired **160aa** in 42% along with 28% of the proto-desilylated product **140a-H**, and both products could not be separated. In the case of α -phenyl furfuryl alcohol, **140b-Si-d**, the methallylated product, **160ba** was formed in 54% yield, but here the process was hampered by the formation of **161** (10%), the origin of which still remains unclear.

^{ϕ} For the numbering of **140**<u>z</u>-Si-d, z represents the α -substituent of the alcohol.



*Isolated in a mixture

Scheme 149. Scope of allylation and metallylation of furfuryl alcohols

c3. C3-alkylation reactions

Alkylation of the silylated furfuryl alcohols was considered next (Scheme 150). Methylation of the C3-position proceeded in quite good yield using methyl iodide as electrophile and either a stoichiometric or a catalytic amount of CuI•PPh₃. It is interesting to note that a non-negligible decrease in the yield was noted when stoichiometric amounts of the copper complex were used (Scheme 150 (a)). By contrast, functionalization of **153a**-*Si*-**d** using iodoethane as electrophile was unsuccessful and led only to the formation of the proto-desilylated product **153a**-**H** (Scheme 150 (b)), both running the reaction at 30 °C or at 50 °C.

Furthermore, using benzylbromide as electrophile, C3-benzylation of **153a**-*Si*-**d** was also achieved using CuI/P(OEt)₃. But the reaction had to be run at 50 °C to afford the product **159ae**_e with a relatively low yield. As previously mentioned, the use of P(OEt)₃ made difficult the isolation of the coupling products, which led us later to CuI-PPh₃. Furthermore, additional O-benzylation could not be prevented and only product **159ae**_e was isolated, and no proto-desilylated product could be identified from the crude, nevertheless, its formation cannot be excluded. As previously, it is likely that O-benzylation occurs during the basic reaction work-up (Scheme 150 (c)).



Scheme 150. Cu(I) catalyzed C3-alkylation of furfuryl alcohol

c4. Mechanistic considerations

Following the ¹H NMR analysis of the crude mixture of the reaction in Scheme 150 (a), a multiplet was evidenced in the aromatic region, which corresponds to the phosphine. Based on these observations, ³¹P NMR analysis was later carried out to investigate about the identity of this species. It is well known that PPh₃ affords the corresponding phosphonium salts on nucleophilic displacement of the halide of alkyl halides. To gain insight on the impact of this process in our reaction conditions we analysed by ³¹P NMR the reaction media composed of **153a**-*Si*-**d**, CuI•PPh₃ (1.2 equiv.) and TBAF in THF-*d*₈ and observed the formation of CH₃PPh₃⁺ (21.5 ppm) along with a peak at –8.6 ppm that increased over time. This peak could be that of the ylide CH₂PPh₃ produced by deprotonation of CH₃PPh₃⁺ (Figure 15). If such is the case, the base responsible for the deprotonation is likely to be the C3 metalated furyl–copper

organometallic and this process could be responsible (at least to some extent) for the formation of protodesilylation products.



Figure 15. ³¹P studies for the consumption of ligand or reagent

On the basis of our experimental results and previously reported ones, a plausible mechanism scenario accounting for our C3–Si functionalization method is proposed in Scheme 151. The first step involves the activation of the furylsilane by fluoride ions. The formation of intermediate **155** was evidenced upon addition of one equivalent of fluoride anion to **153a**-*Si*-**d**. The addition of excess TBAF, does not promote the cleavage of the C–Si bond unless a copper(I) salt is present. In that case, Si \rightarrow Cu transmetalation occurs, delivering a C3-furyl–Cu species that can then undergo electrophilic substitution reactions giving **165**.

Lower yields and conversion were noted when only one equivalent of TBAF was used instead of two, which can be ascribed to a poorly inefficient transmetalation from the pentavalent silicon intermediate **162**. The improved results obtained with two equivalents of TBAF suggest that the formation of a hexavalent silicon species **163** might be plausible, and increases the efficiency of the transmetalation to copper.

Lastly, we have demonstrated that, when PPh_3 is used, the proto-desilylated product **153a-H** can be produced from the deprotonation of an in-*situ* generated phosphonium ion by **164**. This deprotonation

is in competition with the nucleophilic reactions of the furyl-copper organometallic with electrophiles and hampers the C–Si bond functionalization. The extent of this process with $P(OEt)_3$ and in the case of allylation and methallylation reactions still remains to be clarified.



Scheme 151. Plausible reaction mechanism and side-reactions

2.3.2 Conclusion and outlook

The hereby presented results provide a straightforward method for the functionalization of furfural and 5- methyl furfural derived alcohols at the C3-position with several electrophiles. Following the selective activation of the silicon moiety by both fluoride ions and the tethered alcohol function, C3- arylation, allylation and alkylation of furfuryl alcohols in good to excellent yields was achieved.

The establishment of a catalytic-in-copper version of the cross-coupling reduces the load of necessary transition metal significantly, improving atom economy as well as sustainability.

An enantioselective version for the preparation of the secondary furfuryl alcohols can also be envisaged, in the presence of a chiral additive or ligand, which aims at targeting molecules bearing biological activities.

Furthermore, the interest in this kind of multi-functionalized furfural alcohols remains unwavering, in particular due to their ability to undergo further transformations, including ring-closing metathesis of allylated or vinylated products, reactions as well as Piancatelli or Achmatowicz rearrangements (Scheme 152). The variety and applicability of this type of post-functionalization protocols grant access to a wide range of possibilities in regards to the synthesis of demanding molecule structures.



Scheme 152. Perspectives for these furfuryl alcohols transformations

2.4 Functionalization of C3-SiMe₂Bn furfurylimines and related derivatives

Having demonstrated the feasibility to promote with fluoride anions silicon-to-copper transmetalation from C3-SiMe₂Bn units, and thereby further C3-elaboration, we then envisaged to transpose the methods developed for furylalcohols to furfurylimine derivatives. Indeed, an important goal at the outset of our work was to achieve the C3-functionalization of furfural and its derivatives without modifying the redox state of the aldehyde. We quickly learned that direct functionalization of C3- SiMe₂Bn furfural was not possible under TBAF-activation because it led to notable degradation (Scheme 153); no silanol nor siloxane derivatives could be detected by ¹H NMR analysis of crude, nor the presence of an aldehyde function. We thus reasoned that working with the more robust PMP-imines could represent a valuable solution. In a qualitative analysis, the treatment of imine **19a-Si-d** with TBAF•3H₂O did not lead to substrate decomposition, but unfortunately only resulted in the formation of proto-desilylated imine **15a**.



Scheme 153. Stability of 19a-Si-d and 19-Si-d towards TBAF•3H₂O

We also contemplated the direct arylation procedure we previously optimized for the furfuryl alcohols. The reaction between **19a**-*Si*-**d** and iodobenzene was carried out in the presence of TBAF (1 M THF solution) using Pd₂dba₃ and CuI as catalysts (Table 20). Only proto-desilylated product, **15a** resulted from this reaction. This could be rationalized by the impossibility to form a stable cyclic siloxane which would conduct to fast proto-desilylation following debenzylation. The same reaction, when performed with TBAF(*t*-BuOH)₄ (2.4 equiv.) instead of TBAF in THF solution, gave **166/15a** in 1:3 ratio (entry 2), and a better **166/15a** = 1:2 ratio was achieved when TBAF(*t*-BuOH)₄ (1.2 equiv.) was employed (entry 3).



Table 20. Attempted aryl cross-coupling with C3-SiMe₂Bn furfurylimine 19a-Si-d

Following the disappointing results with imines, but still with the aim to achieve functionalization while maintaining the same redox state as the aldehyde function, we contemplated the transformation of the aldehyde to an isolable hemiaminal. Using a reported protocol by Dixon,^[227] lithium pyrrolate was prepared by reaction of *n*-BuLi with pyrrole in toluene, and added to aldehydes **18**-*Si*-**d** and **19**-*Si*-**d** to obtain **167** and **168** respectively (Scheme 154).



Scheme 154. Preparation of furyl-pyrrole alcohol

By forming such hemiaminals, we reasoned that a similar behaviour to the furfuryl alcohols could be obtained, with the possible formation of a cyclic siloxane from the hydroxyl group of the hemiaminal upon debenzylation of the SiMe₂Bn unit following treatment with TBAF•3H₂O. The expected activation process was studied by ¹H NMR in a reaction performed in THF-*d*8. In this experiment, the formation of cyclic- (or even acyclic) siloxanes was not detected, and instead furfural, pyrrole and toluene were produced (Scheme 155).

Our rationalization of this result is as following. According to the proposed mechanism for the activation of the benzyldimethylsilane (Chapter III, section 0), we assume that debenzylation of **167** occurs first, liberating the benzyl anion. The latter is responsible for the deprotonation of the hemiaminal, which triggers elimination of the pyrrole with formation of C3-silylated furfural. This reversibility is in line with the reported observation by Dixon on these type of pyrrole carbinol.^[228] In the absence of additional stabilization through cyclic siloxane formation, the C3-silylated furfural undergoes protodesilylation.



Scheme 155. Mechanism for the formation of furfuraldehyde from furyl-pyrrole alcohol, 167

In spite of these results, we decided nevertheless to attempt a Hiyama-Denmark-like cross-coupling on the hemiacetal derivative **168** using our reported procedure (Scheme 156). The reaction with iodobenzene, carried in the presence of catalytic amounts of Pd_2dba_3 and CuI, resulted unsurprisingly only in degradation of the starting material.



Scheme 156. Attempted arylation to C3-silylated furyl-pyrrole alcohol

Failing to properly activate the C3-SiMe₂Bn furfuraldehydes without decomposition or protodesilylation led us to consider alternative silicon units.

3 Functionalization of C3-SiMe(OSiMe₃)₂ furfuraldehydes

3.1 C3-halogenation of furfuraldehydes

It is classically known that aryltrialkyl silanes are susceptible to undergo halodesilylation by reaction with electrophilic halogen sources without the requirement of specific C–Si bond activation. In the

1970s, Eaborn reported the first examples of such reactions for the incorporation of an iodine atom (or Hg(OAc)).^[229,230] The mechanism involves an ipso-substitution by the electrophile, which is made possible by the β -effect of the silvl group which is responsible for the stabilization of carbocations at the *ortho* position (Scheme 157).



Scheme 157. Ipso-substitution of aryl silane

We attempted to apply this chemistry on our substrates, starting from 5-methyl-3-silylated furan carboxaldehydes as model substrates. In initial trials, was considered the reaction of substrate **18**-*Si*-**a** having an SiEt₃ unit with ICl as electrophilic iodine source. The reaction was performed at 0 °C, 25 °C and under reflux following reported protocols,^[231] but only the starting material was recovered. A similar behavior was noted with **18**-*Si*-**e** having an SiMe(OSiMe₃)₂ unit, which had also been reported to be competent for such transformation (Scheme 158).^[232]



Scheme 158. Attempt for iodination of 19-Si-a and 19-Si-e in the presence of ICl

Hartwig recently showed the feasibility of the halodesilylation reaction of aryl-SiMe(OSiMe₃)₂ derivatives by reaction with *N*-halosuccinimides in the presence of AgF to activate the C–Si bond.^[110] This method was therefore considered for the bromodesilylation of C3-silylated furfuraldehyde **18**-*Si*-**e** and promising results were obtained since C3-brominated furfuraldehyde **169b** was obtained in a moderate 43% yield (Scheme 159).



Scheme 159. Bromination of 18-Si-e with NBS in the presence of AgF

Following on this result, iododesilylation reactions were considered (Table 21). However, under the reported protocols involving *N*-iodosuccinmide (NIS), only 27% of **170c** was recovered along with 29% of the protodesilylated **13** (entry 1). Thus, further optimization of the halodesilylation procedures was undertaken. The use of undistilled acetonitrile, led to significant amount of protodesilylated product, **13**, and relatively poor yields were obtained with both NIS and I₂ (entries 2-3). When I₂ was used as electrophilic iodine source, longer reaction times only increased slightly the yield (entry 4). The best result was obtained with two equivalents of NIS, which resulted in 68% isolated yield of **170c** (entry 5). Again, in the absence of AgF, no noticeable product was observed, and only the starting material was recovered (entry 6). The role of AgF is not clear: it might induce the formation of a hypervalent silicon species that could be more reactive in an electrophilic aromatic substitution process or lead to the formation of a furyl-silver species. Furthermore, the addition of a CuI additive resulted in a poor conversion of the substrate (entry 7), which can also relate to the formation of a precipitate, obtained from the mixture AgF and CuI. The replacement of CuI by CuCN improved the conversion, but a lower yield, was still obtained in contrast to the reaction without copper (I) additives (entry 8).



	SiMe(OSiMe ₃)	+ I-N	AgF (2 equiv.) CH ₃ CN (0.10 M) 50 °C, dark	+	H H	C
	19- <i>Si</i> -e			170c	13	
Entry	'' I +'' souce	Additives	Remarks	t (h)	170c (%)	13 (%)
1	NIS (1 equiv)			6	27	29
2	NIS (1 equiv)		CH ₃ CN (not distilled)	6	11	20
3	I ₂ (1 equiv.)		CH ₃ CN (not distilled)	6	6	6
4	I ₂ (1 equiv.)			Overnight	14	36
5	NIS (2 equiv)			Overnight	68%	_
6	NIS (1 equiv)		Absence of AgF Only 19-Si-e	Overnight	-	-
7 ^a	NIS (2 equiv)	CuI (1 equiv.)	Ratio 19-<i>Si</i>-e 67%	Overnight	33	_
8	NIS (2 equiv)	CuCN (1 equiv.)	76% conversion	Overnight	41	_

¹*HNMR* yields calculated using Me₂SO₂ as internal standard. ^aOnly the ratio **19-Si-e**/**170c** was reported.

With these optimized conditions in hand, a scope for the C3-halodesilylation of furfural related products was developed. The halogenation reactions were carried out with recrystallized *N*-halosuccinmide (NXS) (2 equiv.), the corresponding C3-silylated furfuraldehyde (1 equiv.) and AgF (2 equiv.) as activating agent, in freshly distilled CH₃CN at 50 °C (Scheme 160).

The reaction between **18**-*Si*-**e** and *N*-halosuccinimides provided their respective C3-halogenated products in reasonable to good yields. Conversely, relatively lower yields were obtained with the 5-methyl-3-silylated furfuraldehyde (**19**-*Si*-**e**), especially for the bromination. It should be noted that the reaction was carried out almost always with equimolar amounts of AgF and NXS. In the case of **20**-*Si*-**e**, four equivalents of NXS and AgF were used to carry out the reaction, in order to ensure full activation of the C(sp²)–Si bond, due to the presence of a *tert*-butyldimethylsilyl protecting group. Relatively good yield was obtained for the chlorination (**171a**), while a relatively low yield was obtained for iodination (**171c**). Quite surprisingly, no brominated product (**171b**) was obtained when the reaction was carried out with NBS. In fact, as a general trend, it was observed that poorer yields were obtained with NBS, especially in the case of the C5-substituted furfuraldehydes. It was surmised that radical bromination of the methyl group on furfural could be a competitive side reaction.



Scheme 160. C3-halogenation of furfuraldehydes

In addition to C–Cl, C–Br and C–I bond formation, experiments were ran to achieve C–F bondformation from 5-methyl-3-silylated-furfuraldehydes (**19-***Si***-***e*) using N-fluoropyridinium tetrafluoroborate or F-TEDA (SelectFluorTM) as electrophilic fluoride source,^[233] but no fluorinecontaining product could be evidenced (Scheme 161).



Scheme 161. Attempted fluorination of 19-Si-e

In order to perform this transformation, it might be of particular relevance to carry out this reaction with *N*-fluorobenzenesulfonimide as electrophile. As an alternative, fluorination of aryl–SiMe(OSiMe₃)₂, has also been reported using KHF₂ (6 equiv.) as fluoride source, Cu(OTf)₂ in acetonitirile at 60 °C to afford the fluorinated arenes.

In spite of this limitation, encouraged by the success in the activation by AgF of the C3– SiMe(OSiMe₃)₂ bond of the furfural derivatives, and inspired by Hartwig's reports on cross-coupling reactions involving aryl–SiMe(OSiMe₃)₂ nucleophiles, we considered applying the same activation strategy to achieve other types of C3-functionalizations.

3.2 C3-alkenylation and -arylation of furfuraldehydes

Cross-coupling reactions with sp² electrophiles were considered first. Most of these cross-couplings have been applied to alkenyl- or aryl- trialkoxysilanes or the corresponding disiloxanes.^[235–237]

Ferreira reported the palladium cross-coupling reaction between vinyl silane, bearing an allylic alcohol function and ethyl-4-iodobenzoate.^[238] This reaction with feasible in the presence of TBAF and Pd₂dba₃ as catalyst (Scheme 162 (a)). Similar strategy was adopted for the arylation of esters bearing vinyl silane or their ynamide analogue, where Pd(PPh₃)₄ was employed as catalyst, with KHF₂ acting as a mild fluoride source (Scheme 162 (b)).^[239] Ag₂O has shown to have a crucial role in this reaction, because in its absence, relatively lower yields were obtained. Two hypotheses were proposed: the first one, being the generation of an organosilver species which could participate in the transmetalation step with palladium; while, the second hypothesis involve the ionization of the Pd–X bond of pre-formed Ar–Pd–X after oxidative addition into aryl halide, which would result in efficient transmetalation of the hypervalent aryl–silicon to palladium. This was later was supported by the absence of coupling product, when aryl triflate was used as coupling partner.



Scheme 162. Palladium-catalyzed aryl cross-coupling reaction with vinyl silanes, bearing allylic alcohol and ester

Under Pd(OAc)₂/DCPE catalytic system, the cross-coupling between electron-poor arylsilane and electron-rich aryl iodide, could also provide the bis-aryl product (Scheme 163).^[105] In this case, KOSiMe₃, was used as activating agent, to promote transmetalation to the aryl–palladium species.



Scheme 163. Palladium catalysed bis-arylation formation from arylsilanes catalyzed by KOSiMe3

Murata reported the palladium catalyzed cross-coupling between 3-phenyl-heptamethyltrisiloxane and 4-bromobenzotrifluoride as limiting reagent. In the presence of TBAF and PdCl₂(PCy₃)₂ in a mixture of THF/H₂O (5/1), afforded the coupling product in excellent yield (Scheme 164).^[240]



Scheme 164. PdCl₂(PCy₃)₃-catalyzed cross-coupling between 3-phenyl-heptamethyltrisiloxane and 4bromobenzotrifluoride

Later, the group of Hartwig established new protocols to perform cross-coupling between heteroaryl silanes and aryl-halide with the former mentioned used as limiting reagent. Two synthetic strategies were developed.^[110] The first one was applied to the C2-silylated furan or thiophene derivatives for the the cross-coupling reaction with *m*-iodochlorobenzene. This reaction was performed in the presence of AgF as fluoride source and catalyzed by $Pd(t-Bu_3)_2$ to provide respectively 68% and 76% for the furan and thiophene derivatives (Scheme 165 (a)). In addition, variations in the procedure were done in order to perform this coupling with silyl azole. Here, the use of CsF was necessary along with Pd_2dba_3 •CHCl₃/BINAP catalyst, to provide the arylated product (Scheme 165 (b)).



Scheme 165. Palladium-catalyzed arylation of silylated heteroarenes

Following on theses literature precedents, the reaction between **19**-*Si*-**e** and iodobenzene was carried out using a Pd₂dba₃•CHCl₃/BINAP catalytic system in the presence of AgF, and an excellent 81% yield of arylated product **173a** was obtained, along with 16% of **13** (Scheme 166). Interestingly, the same reaction in the presence of CsF only led to the formation of the protodesilylated product **13**, a result that underscores the importance of using AgF as fluoride source.



Scheme 166. Choice of fluoride source for the aryl cross-coupling

The same conditions were next adopted for other arylation and alkenylation reactions (Scheme 167). Arylation of **18**-*Si*-**e** and **19**-*Si*-**e** with iodobenzene proceeded in reasonably good yield (48–81%) while in the case of **20**-*Si*-**e** a significant drop was noted. The preparation of similar motifs have previously been reported by Oble and Poli, for the ruthenium catalyzed arylation of furfurylimines.^[51] Alkenylation
of 5-methylfurfuraldehyde was performed with β -bromostyrene to deliver **173b** in 45% yield, as well as with 2-bromo-propene to deliver **173c**, albeit in poor yield.



(*) ¹H NMR yields were calculated using Me₂SO₂ as internal standard

*The product was not isolated

**The product 173c was obtained in a mixture with the protodesilylated product (15%: 39%) and not isolated

Scheme 167. Arylation and alkenylation of C3-silylated furfuraldehydes

3.3 C3-alkynylation of furfuraldehydes

Hiyama-Denmark-type cross-coupling reactions, devoted to the $C(sp^2)-C(sp)$ bond formation between alkynyl halides (or terminal alkynes) and aryl silanes have received far less attention as Sonogashira-type reactions between aryl halides and alkynylmetals remain the preferred approach for the preparation of aryl-substituted alkynes.^[241–243]

In 2014, Guo reported the first alkynylation protocol for aryl trialkoxysilanes by reaction with alkynyl halides, catalyzed by Pd(dba)₂ in the presence AgF and KHCO₃.^[244] This reaction was carried out under aerobic conditions and this cross-coupling could also be performed with terminal alkynes instead of the halide analogues (Scheme 168).



Scheme 168. First reported alkynylation of aryl trialkoxysilane

Later, was disclosed a decarboxylatative version of the reaction between alkynyl carboxylic acids and arylsiloxanes, where instead of AgF and KHCO₃, AgF₂ was used to play both the role of fluoride additive and oxidant.^[245] Such coupling was also achieved with Ni(acac)₂/Phen as catalytic system using a combination of CsF as fluoride source for the siloxane activation and CuF₂ as oxidant.^[246,247]

So far, all the reported protocols for arylsiloxane alkynylation require the use of the organosilicon donor in excess. Furthermore, no procedure starting from aryl–SiMe(OSiMe₃)₂ derivatives was disclosed (nor starting from aryltrialkylsilanes). Having in mind these challenges and inspired by Guo's protocols, the reaction between alkynyl bromide and **19-Si-e** as limiting reagent, was carried out in the presence of Pd₂dba₃•CHCl₃, AgF and KHCO₃, under aerobic conditions (Scheme 169 (a)). Alkynylation delivering **175** was indeed observed, but only in relatively poor yield. Performing the cross-coupling reaction under anaerobic and base-free conditions (Scheme 169 (b)) led to similar yields.



Scheme 169. Palladium-catalyzed alkynylation of 19-Si-e

While modest, these results remain promising and leave room for improvement. The use of oxidants such as CuF_2 or AgF_2 might be investigated.

3.4 C3-allylation and alkylation of furfuraldehydes

We then went on to consider the creation of $C(sp^2)-C(sp^3)$ bonds, which represents one of the most challenging transformation, when it concerns selective functionalization of heteroarenes. With the lack of allylation or alkylation processes based on alkenyl- or aryl- SiMe(OSiMe₃)₂, we got inspired by the reaction diversity of alkoxysilanes proposed. So far, there are limited existing examples for the alkylation of these motifs, most of these C(sp²)–Si transformations have been implemented for the allylation reaction.

In 2014, Riant developed an efficient catalytic method to functionalize di- and tri-substituted vinyl siloxanes by allylation with allyl bromides (Scheme 170). This fluoride-mediated transformation involves the use of TBAT (tetrabutylammonium difluorotriphenyl silicate) as anhydrous fluoride source in stoichiometric amount and copper(I) iodide in catalytic quantities. The allylation occurred with perfect retention of the double bond geometry and the strategy was tolerant towards a wide range of functional groups.



Scheme 170. Cu(I) catalyzed allylation of alkenyl trialkoxysilane

Alternatively, the authors also disclosed a benzylation protocol for these vinylsiloxanes, in the presence of TBAT as fluoride activator, $[Cu(CH_3CN)_4]PF_6$ as catalyst and benzylbromide as electrophile (Scheme 171).^[248] As for the allylation reaction, full retention of the alkenylsiloxane's configuration was observed.



Scheme 171. Cu(I)-catalyzed benzylation of Z- alkenyl trialkoxysilane

Ball developed another strategy to achieve the allylation of aryl triethoxysilanes. Given that Cu(I)– F complexes are often reported to be quite unstable with respect to disproportionation, he considered the preparation of a stable copper (I) fluoride complex: (IPr)CuF (IPr= 1,3-bis(2',6'diisopropylphenyl)imidazol-2-ylidene).^[249] It was demonstrated that this reagent permits an efficient activation of the $C(sp^2)$ –Si bonds of aryl triethoxysilanes and induces silicon-to-copper transmetalation to deliver an aryl–Cu(I)(IPr) complex. The latter can be isolated, in relatively good yields both with electron-rich and electron-deficient arenes. Alternatively, on treatment of these complexes with allyl bromide, the allylation product is obtained in good yield (Scheme 172).



Scheme 172. (IPr)CuF-catalyzed allylation of allyl- and aryl- trialkoxysilane

Due to the limited reactivity of the aforementioned complex ((NHC)Cu–aryl), other (NHC)CuF complexes were prepared to perform additional allylic substitution reactions. For instance, the cross-coupling with vinyl-epoxides was achieved in quite good yields,^[250] and could be applied to heteroarenes, as depicted in Scheme 173.



Scheme 173. (CySI)-CuF catalyzed cross-coupling between vinylepoxides aryl- trialkoxysilane

One of the rare examples focused on the alkylation reaction have been performed on vinyldisiloxanes was catalysed by [(allyl)PdCl]₂.^[251] The activation of disiloxanes with TBAF, generate silanolates, which promotes the transmetalation to the alkyl–palladium species. This TBAF-assisted cross-coupling was subjected to benzylation reaction, with (primary and secondary) benzylic and allylic bromides, chlorides, tosylates and mesylates, but did not afford the alkylation with tertiary alkyl halides. In addition, allylation of these substrates can also be achieved using this protocol (Scheme 174).



Scheme 174. Palladium-catalyzed alkylation and allylation of vinyldisiloxanes

3.4.1 Allylation reactions

In continuation of our thorough investigation of the allylation of C3-silylated furfuraldehydes, we attempted to achieve the same transformation by reaction of **19**-*Si*-**e** with AgF (2 equiv.) in the presence of allyl bromide, according to the activation strategy we had previously applied successfully for the halodesilylation reaction (*vide infra* Table 22, entry 1). However, only the starting material was recovered under these conditions. The failure to promote the allylation with AgF made us turn back to consider copper-based strategies. In an ideal situation, the reaction with Cu–F complexes would allow the generation of an hypervalent silicon species and thereby to trigger the silicon-to-copper transmetalation.

a. Preparation of Cu–F complexes

We thus engaged in the preparation of such Cu–F complexes. Some of them are air-sensitive and their preparation can require expensive ligands,^[249,250] but we instead focused on easily accessible and air-stable complexes. Following a reported procedures,^[252] complex **176** was prepared by the reaction of PPh₃ and CuF₂ in methanol under reflux (Scheme 175). Placing **176** under high vacuum at 90 °C delivered **177**. Attempts to prepare analogue complexes from CuF₂, with dppe or phenanthroline/PPh₃ (1/1), failed. Also, PPh₃-ligand displacement from CuF(PPh₃) by either dppe and phenanthroline for the same purpose did not give the desired complexes.



Scheme 175. Preparation of CuF(PPh₃)₃ complex

b. Optimization of the allylation conditions

With complexes **176** and **177** in hands, we tested the allylation reaction of **19**-*Si*-**e** with allyl bromide in DMF (Table 22). After two hours reaction in the presence of 1.2 equiv (PPh₃)₃CuF•2MeOH, the desired product **178a** was indeed obtained, but with a relatively poor yield and along with protodesilylated product **13** (entry 2). The reaction was also incomplete after four hours (entry 3), which led to consider running it overnight (entry 4). Under these conditions, 58% yield of **178a** was obtained, which was quite satisfying. The possibility to use (PPh₃)₃CuF•2MeOH in a substoichiometric amount was investigated, with 50 mol% of the latter (entry 5), which resulted in a poor conversion of the substrate. Contrarily, an increased quantity of the fluoride source led to a slightly improved yield (entry 6). Interestingly, using (PPh₃)₃CuF without the methanol molecules in the complex, no proto-desilylated **13** was noticed, which resulted in a slightly better yield in **178a** (entry 7).

Optimization of the solvent was also investigated, but it should be noted that this study was mostly carried out using CuF(PPh₃)•2MeOH. The reaction was performed in THF, but lower reaction yield was obtained (entry 8). It is known from literature,^[149,150] that polar solvents or additives having higher dielectric constants favor ion-pair dissociation and lead to increased nucleophilicity of carbanion. Thus, the solvent system THF/HMPA was considered, but an even lower yield was obtained, which we attributed to degradation of the product (entry 9). Finally, the temperature (entry 10) did not seem to greatly influence the reaction.



Table 22. Optimization of allylation process

¹H NMR yields are calculated using Me₂SO₂ as internal standard.

c. Reaction scope

Following the series of optimizations with the bench-stable Cu–F complex **177**, the functionalization of 5-methyl furfuraldehyde derivative (**19-Si-e**) by reaction with other allylic bromides was considered (Scheme 176). The reaction with methallyl bromide led to the corresponding product of allylic substitution in quite good yield (67%). When performed with cinnamyl bromide, however, a moderate yield was obtained, where an inseparable mixture, containing **178c** and **13** (1.0/0.10) respectively. Surprisingly, methyl 4-bromocrotonate, did not provide any product.

The scope was then extended to furfuraldehyde derivatives (**18**-*Si*-**e**), which afforded the allylated and methallylated products **179a** and **179b** in reasonably good yields. Unfortunately, **179a** was not isolated and was probably lost during the *vacuo* concentration process due to its high volatility.



(*) NMR yield using Me₂SO₂ as standard

Scheme 176. Allylation scope of C3-silylated furfuraldehyde

This allylation procedure was transposed to the related C3-silylated furfurylimine (**19a-***Si***-e**). Unfortunately, only 20% of the C3-allylation product (**178b**) was obtained upon hydrolysis, but instead, the *N*-bis-allylated product (**180**) was obtained as the major product (Scheme 177). Further analyses have to be performed to explain the formation of product **180**.



Scheme 177. Attempt to perform the allylation of C3-silylated PMP-furfurylimine

3.4.2 Alkylation reactions

Alkylation processes were then studied. Methyl iodide and benzyl bromide were respectively used as electrophiles, as they have commonly been used for alkylation strategies.

The reaction between **19**-*Si*-**e** and iodomethane or benzyl bromide was performed in the presence of $CuF(PPh_3)_3$ (1.2 equiv.), in DMF at 60 °C (Scheme 178). In the case of the former mentioned (Scheme 178 (a)), a relatively low isolated yield of **181** was observed along with 10% of the protodesilylated product. Notwithstanding, because of the low molar mass of the product and side-product(s), the yield might be under-estimated. In the case of benzyl bromide (Scheme 178 (b)), an even lower yield of the coupling product could be evidenced. Another side-product, **183**, which corresponds to the product coming from a Wittig reaction, was rather formed in considerable amounts. **183** was obtained in an E/Z = 1:1 ratio.



Scheme 178. Attempt to perform methylation (a) and benzylation of C3-silylated furfuraldehyde

Our explanation for the presence of **183** is as follows (Scheme 179). It is known from literature,^[252] that at room temperature, one or two phosphines of $(Ph_3P)_3Cu$ –F are in their free-form (not coordinated to Cu(I)). They can thus react with benzyl bromide to generate the phosphonium salt, **184**.

The aryl-copper (I) species formed from the transmetallation step (185), acts as base for the deprotonation of the phosphonium salt. This gives protodesilylated 5-methyl furfuraldehyde (13) and the reactive ylide 186 which is responsible for the formation of 183, *via* a Wittig reaction (Scheme 179). This result is fully consistent with our observations discussed in Chapter IV, section 2.3.1 (c4. Mechanistic considerations).

De-complexation of PPh₃ (Ph₃P)₃Cu-F (Ph₃P)₂Cu (Ph₃P)Cu-2 PPh₃ Mechanism of formation of XX Br⊖ ⊕ PPh₃ PPh_3 ò Cu] 185 184 186 13 Wittig reaction 183

Scheme 179. Proposed mechanism of formation of 183

To try to circumvent this limitation for the benzylation reactions promoted by CuF(PPh₃)₃, we first considered the use of catalytic amounts of the copper complex (Table 23, entry 1). However, as observed previously, this transmetalation did not fully proceed in these conditions and the addition of fluoride additives in stoichiometric amounts appears necessary to promote the alkylation at the C3-position. The use of NEt₃•HF for this purpose did not provide full conversion, and only protodesilylated product was obtained (entry 2). A similar behaviour was evidenced for TBAF(*t*-BuOH)₄ (entry 3). Furthermore, the implication of CsF in this reaction, led to a non-negligible amount of **183** (entry 4), comparable to entry 1. Interestingly, AgF, afforded 40% of product **182**, and no **183** was observed (entry 5). The pre-mixing of CuF(PPh₃)₃ with the benzyl bromide, provided 35% of product **183**, while no other product could be observed (entry 6). This result could be related to the initial formation of the phosphonium, which promotes the formation of **183**. But the in-*situ* preparation of other Cu–F sources in the presence of AgF as additive, did not result in the C3-benzylated product **182**, but instead provided the protodesilylated product and degradation respectively (entries 7-8).

• • • • • • • • • • • • • • • • • • •		$\begin{array}{c} CuF(PPh_3)_3 (0.2 \text{ equiv.}) \\ \hline \text{"F"" additives} \\ \hline DMF (0.1 \text{ M}) \\ 60 \ ^\circ\text{C}, \text{ overnight} \end{array} \qquad $			Ph
		182	13	18	3
Entry.	"F-" additives	Remarks	182 (%)	13 (%)	183 (%)
1	CuF(PPh ₃) ₃ (1.2 equiv.)		4	_	54
2	NEt ₃ •3HF (0.4 equiv.)	Incomplete conversion. Only ratio of 19 - <i>Si</i> - e to 13 reported (45:55).	_	55	_
3	TBAF(t-BuOH) ₄ (2 equiv.)		_	20	_
4	CsF (2 equiv.)		_	12	38
5	AgF (2 equiv.)		40	20	
6	AgF (2 equiv.)	CuF(PPh ₃) ₃ (20 mol%) was stirred with Bn- Br (1 equiv.)in DMF for 1 h at rt, before 19 - <i>Si</i> -e, AgF and Bn-Br (2 equiv.) were added.	_	_	35
7	AgF (2 equiv.)	CuF ₂ (2 mol%) IPr•HCl (2 mol%), NaOt-Bu (12 mol%) used instead of CuF(PPh ₃) ₃ . Incomplete conversion with a ratio of 19-Si - e : 13 (17:83).	_	83	-
8	AgF (2 equiv.)	(Ph ₃ P)CuI (20 mol%) and AgF (2equiv.) were stirred for 30 min at rt, before 19-Si-e and Bn-Br were added.	_	_	_

Table 23. Optimization for the benzylation of C3-silylated furfuraldehyde (19-Si-a)

¹HNMR yields were calculated using Me₂SO₂ as internal standard.

Under the same conditions, methylation by reaction with methyl iodide was also achieved in a 35% yield, with only 10% of the protodesilylated product **13** (Scheme 180).



Scheme 180. Alkylation of C3-silylated furfuraldehyde

3.5 C3-trifluoromethylation of furfuraldehyde

Recently, the trifluoromethyl group has gained lot of attention in medicinal chemistry due to C–F bond stability compared to C–H bonds. It also improves the lipophilicity of molecules due to its strong electron-withdrawing character.^[253] We thus reasoned that the development of methodologies for the trifluoromethylation of the C3-silylated furfuraldehydes could certainly provide some added-value to the development of our synthetic platform around the furan carboxaldehyde derivatives.

Trifluoromethylating reagents show different reactivities (Scheme 181): for example, some commonly reported electrophilic "CF₃" sources include the Togni's reagent^[254] and Umemoto reagent,^[255] while nucleophilic sources, include the Rupperts' reagent,^[256] Langlois' reagent^[257] and Chen's reagent.^[258] Other "CF₃" sources showed yet different behaviours. For example, (phen)CuCF₃ can act as a radical "CF₃" donor, but also as a "CF₃" source or "CF₃+" source depending on copper's oxidation state. The choice of the appropriate "CF₃" reagent is thus decisive.



Scheme 181. Common trifluoromethylating agent.

In 2016, Hartwig disclosed the first example of trifluoromethylation applied to arylsilanes.^[259] The reaction between aryl–SiMe(OSiMe₃)₂ and (phen)CuCF₃ was carried out in the presence of AgF as fluoride source in DMF. The use of benzoquinone as co-oxidant in open air provided best yields for this reaction (Scheme 182).



Scheme 182. Trifluoromethylation of 2,5-dimethyl 3-silylated furan

This protocol for trifluoromethylation was thus applied to **19**-*Si*-**e** in a one-pot procedure.^[260] The air-sensistive reagents CuCl, *t*-BuOK and phenanthroline were used from the glovebox and pre-mixed, after which TMS–CF₃ was added, to generate in-*situ* the (phen)CuCF₃ complex. **19**-*Si*-**e**, AgF and benzoquinone were then added under aerobic conditions. In our case, the reaction did not work. Despite multiple additional attempts, where the reaction was carried out without co-oxidant or in the presence of molecular oxygen, no trifluoromethylated product was noticed (Scheme 183).



Scheme 183. Attempt for trifluoromethylation of C3-silylated furfuraldehyde using (phen)CuCF₃

So, we decided to use an electrophilic trifluoromethylating agent, such as the Umemoto's reagent, in combination with activation by AgF. No furyl product could be evidenced, and only the dibenzothiophene was identified (Scheme 184).



Scheme 184. Trifluoromethylation attempt with Umemoto's reagent

In a final attempt for this reaction, (phen)Cu(CF₃)₃ was prepared and isolated according to Zhang's protocols.^[261] The reaction was performed under similar conditions, with AgF as the activating agent under oxygen atmosphere, and the desired trifluoromethylated product **187** was obtained in satisfactory yield (Scheme 185).



Scheme 185. Trifluoromethylation of C3-silylated furfuraldehyde using (phen)Cu(CF₃)₃ reagent

It has to be noted that the reaction mixture was thoroughly degassed before being back-filled with O_2 . The volume of the container used, was taken into account, and relates to the volume of oxygen at atmospheric pressure (in mmol) required to re-oxidise the copper species.

On a mechanistic point of view, we consider a scenario similar to the one reported for the trifluoromethylation of arylboronic acids with (phen)Cu(CF₃)₃. It has been proposed that (phen)CuCF₃

would first undergo an oxidation to Cu(III) which would allow the transmetalation of the pentavalent silicon species to copper, which releases a "CF₃-". The presence of a pre-existing Cu(III) species, when performed with (phen)Cu(CF₃)₃, could probably provide an ease for transmetalation. After transmetalation, reductive elimination gives the desired product (Scheme 186). In order to sustain the process, oxidation of (phen)Cu(CF₃ or (phen)Cu(CF₃)₂ is necessary.



Scheme 186. Trifluoromethylation of C3-silylated furfuraldehyde

3.6C3-amination of furfuraldehydes

Arene C–N bond formation has lately been achieved using aryltrialkoxysilanes. Amination procedures have been reported in the literature both through electrophilic amination processes,^[262] where a tertiary amine bearing a good leaving group and through nucleophilic amination procedures, which can be carried out with primary and secondary amines.^[263] Yet, nucleophilic amination procedures have more extensively been explored with aryl halides for the Buchwald-Hartwig amination^[264,265] under palladium-catalyzed reactions, and with aryl boronic acids (or boronic esters), for the Chan-Lam amination.^[266,267]

Lam and co-workers, developed a variant of the amination reaction of arylsilanes.^[268] The generation of a hypervalent siloxane species with TBAF, is key for the efficient arylation of N–H containing compounds. Similar to conditions with arylboronic acids, the use of Cu(OAc)₂ was necessary for the transmetalation of the hypervalent arylsiloxane to Cu(II). The authors also proposed a similar mechanism to the ones with aryl boronic acids (Scheme 187).



Scheme 187. Copper catalyzed arylation of amines, with arylsilane as limiting reagent

However, it is unclear concerning the oxidation state of the copper species from which results the reductive elimination. The aerial oxidation of **189** leads to the formation of the Cu(III) intermediate **188**, and can promote more efficient reductive elimination giving the *N*-arylated product and Cu(I) (Scheme 188). Alternatively, **189** undergo reductive elimination to give Cu(0) and *N*-arylated product.



Scheme 188. Proposed mechanism of formation of aryl-amines by copper catalyzed reaction of aryl silane and an amine

Later, Cheng described the copper-TBAF catalyzed arylation of primary and secondary amines and amides with aryl trimethoxysilane.^[269] These arylations were feasible under catalytic amounts of both TBAF and Cu(OAc)₂, and the presence of electron-withdrawing phosphine ligands, provided efficiently the C–N coupling product.

Lately, Hartwig reported the oxidative coupling of arylsilanes with nitrogen nucleophiles.^[270] This new procedure permits the arylation of the amines from aryl–SiMe(OSiMe₃)₂ used as limiting reagent. With a series of fluoride activator screened, the authors reported that the homocoupling (diaryl product), was obtained with fluoride sources less activating than CsF, NaF providing the best results. The reaction between arylsilanes and the corresponding amines was performed in DMSO, in the presence of Cu(OAc)₂, Na₂CO₃ and NaF under aerobic conditions, and led to the arylation of these amines with electron-deficient arenes in reasonably good yields (Scheme 189). Interestingly, the reaction showed

some limitations with electron-rich arenes, where lower yields were obtained. The authors proposed the use of a more activating fluoride source (KHF₂) to overcome this problem.



Scheme 189. Copper catalyzed arylation of amines, with arylsilane as limiting reagent

In regards to the amination procedures reported by Hartwig,^[270] the amination of furfuraldehyde **19**-*Si*-e with pyrrolidone was set as a model reaction, in the presence of $Cu(OAc)_2$, Na_2CO_3 as base and NaF as fluoride source (Table 24). Using their conditions, only 17% of the product **190** (entry 1). This amination is known to work under aerobic conditions. Therefore, the reaction was performed with an air-circulation (*ie* with an entry of air and an exit outlet), which led to an improvement in the ratio of in favour of **190**, but due to solvent evaporation over time, full conversion of the substrate could not be achieved (entry 2). The same reaction was carried out with a CaCl₂ trap (to allow entry of dry air), and showed similar result, where 16% of **190** was obtained (entry 3). In addition, an increase in the amount of pyrrolidone as well as Cu(OAc)₂, slightly improved the yield (entry 4), while the use of THF as solvent did not show any conversion of the substrate **19**-*Si*-e, probably due to poor solubility of NaF in THF (entry 5).

In order to allow smooth and slower transmetalation of the hypervalent silicon species to copper, NaF (1 equiv.) was used, but poor yield of **190** was evidenced (entry 6). As reported in that former paper, the high solubility of the C–N coupling product bearing a pyrrolidone moiety was considered to be water-soluble. Further optimization was performed by considering a mixture of DMSO and THF (1/1) to carry out the reaction; an improved yield of 38% of **190** was obtained (entry 7). It has to be highlighted that the first organic extract (after 3 extractions with EtOAc) contained 27% of **190**, while after a second extraction of the aqueous phase contained 12% of **190** can be recovered. AgF as fluoride additive only led to protodesilylation of **19-Si-e** (entry 8).

Table 24. Optimization of amination and of 19-Si-e in the presence of pyrrolidone



Entry	w (equiv.)	x (equiv.)	y (equiv.)	z (equiv.)	190 (%)
1	2	3	2	2	17
2^a	2	3	2	2	50 ^b
$\mathcal{3}^b$	2	3	2	2	16
4	4	4	4	2	28
5^c	4	4	4	2	_
6	4	4	4	1	7
7^d	4	4	4	1	38
8^e	2	3	2	2	

¹HNMR yields were calculated using 3,4,5-trimethoxybenzaldehyde as internal standard. ^aReaction performed under air circulation. Only ratios of **190:other product:19-Si-e** were calculated (50:20:30). ^bReaction performed under air conditions, with a CaCl₂ trap. ^cTHF used instead of DMSO. ^dTHF/DMSO (1/1) solvent mixture used. ^eAgF (2 equiv.) used instead of NaF. Only proto-desilylated product observed.

These optimized conditions were next applied with other amines, such as 2-aminopyrimidine, morpholine and pyrrole. Among these amines, only the first one provided the desired product, but in a very poor isolated yield (4%) (Scheme 190).



Scheme 190. Arylation of 2-aminopyrimidine by arylsilane

4 Derivatization of C3-functionalized furfuraldehydes

Different transformations at the C3-position of furfuraldehyde derivatives, starting from the silylation step to the post-transformation of these molecules have been performed, without alteration of the redox state of the aldehyde. One of the key assets of keeping the redox state unchanged throughout the course of these transformations, is the possibility to use the furfuraldehyde motif to access novel complex molecules. First, the aldehyde function provides a platform for the preparation of tertiary alcohols (as shown in the previous sub-chapter), but can also be subjected to Wittig reaction, Ohira-Bestmann and many more carbonyl-based reactions. Also, upon decarbonylation, a new class of C3-substituted furans should be accessible. In addition, it is known from the literature that furfural derivatives can undergo several rearrangements,^[271] including the aza-Piancatelli rearrangement^[271,272] or the generation of pyridinium zwitterion (with 5-HMF derivatives),^[273,274] that they can also be involved in Diels-Alder rearrangements^[275] or used for the preparation γ -crotonolactone,^[276] as well as engaged in the Biginelli reaction^[277] or Knoevenagel reaction to give synthetically useful motifs (Scheme 191).

Up to now, a limited amount of these transformations have been reported on C3-functionalized furfuraldehydes.



Scheme 191. Perspectives of C3-functionalized furfuraldehydes, bearing an aldehyde function

4.1 Aza-Piancatelli

The aza-Piancatelli rearrangement was performed on **18**-*Si*-**a**, according to the reported procedures, in the presence of morpholine, and catalyzed by AlCl₃ (Scheme 192).



Scheme 192. Preparation of cyclopentenone, 192 from C3-substituted furfuraldehyde 19-Si-e

Under Lewis acid catalysis (AlCl₃), the generation of 193 was made possible through the nucleophilic addition of the amine. The latter can be stabilized by the transient furan oxonium (193'),

which is subjected to a nucleophilic addition by the amine, resulting in ring-opening, to form **195**. After conrotatory electrocyclization, **195** led to the formation of **196** (Scheme 193).



Scheme 193. Mechanism for aza-Piancatelli rearrangement

It was reported that the cyclopentenone derivatives can be subjected to a 1,4-nucleophilic addition in the presence of an external nucleophile. In the case of **196**, however, it can be envisaged in the presence of a nucleophile that the 1,4-addition to **196**, promotes the 1,4-silyl migration, which can be trapped by an electrophile giving a cyclopentanone derivative.

4.2 Pyridinium zwitterion from HMF

Afonso described the direct synthesis of pyridinium ion from 5-HMF derivatives. In attempts to prepare the corresponding pyridinium zwitterion, **198** was used in the presence of butylamine and formic acid. **197** was estimated to be obtained in 61% yield (Scheme 194), but due to solubility problems, the product could not be obtained pure. Also, the latter could not be recovered after silicagel chromatography.



Scheme 194. Preparation of pyridinium zwitterion from C3-substituted HMF derivative 197

Following, the proposed mechanism by Afonso and co-workers,^[278] imine **199** was generated by an acid-catalyzed imine formation. Under acid catalysis, water could act as a nucleophile and promote the ring opening to **203**. The resulting ketone **203** is subjected to a nucleophilic addition by the nucleophilic

nitrogen, to give **205**. As a consequence of dehydration, the final pyridinium compound **198** was obtained (Scheme 195). This mechanism was consistent with the DFT results reported by the same group as well as with the isotopic labelling of oxygen ($H_2^{18}O$)



Scheme 195. Proposed mechanism for the formation of pyridinium zwitterion from C3-substituted HMF derivative 197

5 Conclusion and outlook

The development of synthetic strategies applied to furfuraldehydes allowed a wide range of transformations, including C–C to C–X bond formations from these C3-silylated furfuraldehydes. It is important to stress the fact that, these developed methodologies have consistently been used, with the furfuraldehydes as limiting reagent, and were compatible with the aldehyde functions. In addition, on a rarer basis, the creation of $C(sp^2)$ – $C(sp^3)$ bond formation with allyl and alkyl halides represent a novel way of preparing these furfural derivatives. With the C3-functionalization with this redox state of the furfuraldehyde, this opens doors to reaching new molecules, with potential utility in the pharmaceutical or chemical industries.

CONCLUSION AND PERSPECTIVES

This PhD work relates to the development of synthetic methods for achieving the selective C3-functionalization of furfural and derivatives.

The first part of this work was devoted for the creation of a silylation platform. This was made possible, by taking advantage of the aldehyde function, to introduce a temporary imine directing group. The directed dehydrogenative C–H silylation of furfurylimines under iridium catalysis, gave rise to a wide range of C3-silylated furfuraldehydes.

The compelling attributes of silicon chemistry allowed the creation of synthetic platform, to provide an array of products, ranging from the C–C to C–X bond formations (Figure 16). Despite failure in triggering, the C-to-O silyl migration on C3-silylated furfuryl motifs, fluoride-mediated cross-coupling reactions led to more promising results, where a number of post-functional transformation, such as arylation, alkenylation, alkynylation, allylation and alkylation. But the synthetic scope was not only limited to the C–C bond formation, as amination and halogenation of these heteroarenes were developed.



Figure 16. C3-silylated platform

In addition, synthetic protocols regarding the $C(sp^2)$ –Si bond transformations have therefore, been established for the valorization of these silvlated biomass derivatives, and in this regard, the latter has systematically been used as limiting reagent. Furthermore, these synthetic methods, were tolerant to

aldehyde functions. Moreover, C3-silylated furfuraldehyde was also transformed to a number of furfuryl alcohols by addition of nucleophile. The then, formed alcohol was also subjected to further functionalization, notably for the $C(sp^2)-C(sp^3)$ bond formations. Derivatization through rearrangement of C3-functionalized furfural has also been carried out, to grant access to novel classes of molecules.

With the access to the C3-synthons of the furan, across this silylated platform, the applicability of these high-added value molecules is another important aspect. Beyond applications as biofuels or biofuel additives, it remains essential to further promote eco- compatible synthetic chemistry for value-added chemical compounds, especially in the means of resource availability. This work may contribute to a much-needed larger shift in the direction of more sustainable fine chemistry research and industrial application of biomass.

Given prospects of the selective transformation of furfural, another PhD project was funded, which aims at selectively triggering the C4-position of the furfural derivatives. Two strategies can be envisaged for achieving the functionalization in this position (Scheme 196). These are:

(a) In a first step, the dehydrogenative borylation of the furfurylimine, leading to the C3-borylated product. From literature, it was shown that the boronic ester, can be readily converted in the presence of pza or aam, for the generation of $B(pza)^{[102]}$ or B(aam),^[103] which is a good directing group. This related directing group, would therefore, provide a platform to achieve the directed C4-functionalization (Scheme 196 (a)).

(b) The protection of the furfural, formyl function with a non-directing group, such as an acetal, promotes therefore, the C5-functionalization. The functionalization with dialkyl hydrosilane,^[116,117,118] or B(pza),^[102] provides an approach to further *ortho*-functionalization (Scheme 196 (b)).



Scheme 196. Future work for C4-functionalization

EXPERIMENTAL SECTION

General Information

All reactions were carried out under an argon atmosphere by standard syringe and septa techniques. Reactions were run in flasks or ace pressure tubes with magnetic stirring. Glassware was dried under vacuum or taken directly from the oven and let cool under vacuum prior to use.

Reagents and solvents were purchased from commercial sources and generally used as received. CH₂Cl₂ and Et₂O were dried on a Mbraun purification system MB SPS-800. THF from the MB SPS-800 was distilled over sodium and benzophenone under nitrogen flow prior to utilization. Acetonitrile and DMSO were distilled over calcium chloride and calcium hydride, respectively, before each use. *N*,*N*-Dimethylformamide, 99.8%, Extra Dry over Molecular Sieve, AcroSeal®, was purchased from ACROS; HMPA from Sigma Aldrich and DMPU from TCI Europe. Copper (I) salts were purchased from Sigma Aldrich and lithium *tert*-butoxide from Alfa Aesar; both of which were stored in a glovebox.

NMR spectra (¹H, ¹³C, ¹⁹F, ³¹P) were recorded on a Bruker AM 300 MHz or a Bruker AVANCE 400 MHz spectrometer. NMR experiments were carried out at room temperature in CDCl₃. Chemical shifts are given in parts per million (ppm) using the CDCl₃ residual non-deuterated signals as reference (δ ¹H = 7.26 ppm; δ ¹³C = 77.16 ppm). The terms m, s, d, t and q represent multiplet, singlet, doublet, triplet and quartet, respectively. The term (br.) is used when the peak is broad, and the correct multiplicity cannot be assigned unambigously. Coupling constants (*J*) are given in Hertz (Hz). For previously unknown compounds, a combination of ¹H, ¹³C and 2D experiments (COSY, HSQC, HMBC) was used to complete assignment of ¹H and ¹³C signals.

IR spectra were recorded with a Tensor 27 (ATR diamond) Bruker spectrometer, and reported as characteristic bands (cm⁻¹). High-resolution mass spectra (ESI–MS or APCI–MS) were acquired using an LTQ-Orbitrap XL from Thermo Scientific (Thermo Fisher Scientific, Courtaboeuf, France) operated in positive ionization mode. Melting points were measured in capillary tubes on Stuart Scientific SMP3 apparatus and are uncorrected.

TLC were performed on Merck 60 F254 silica gel and revealed with either a ultra-violet lamp ($\lambda = 254$ nm) or a specific color reagent (potassium permanganate, *p*-anisaldehyde, etc.). A silica gel Merck Geduran® SI 60 (40-63 µm) was used for flash column chromatography. Preparative thin layer chromatography was realized with PLC silica gel 60 F254 (1 mm, 20x20 cm).

S1. Synthesis of the OTBDMS-protected HMF derivative

2a



5-(((tert-butyldimethylsilyl)oxy)methyl)furan-2-carbaldehyde

Following a reported procedure,^[279] 5-(hydroxymethyl)furan-2carbaldehyde (HMF) **2** (2.52 g, 20 mmol, 1 equiv.) was dissolved CH₂Cl₂ (100 mL). Imidazole (1.50 g, 22 mmol, 1.1 equiv.) was added at room temperature, and the mixture was stirred 15 min before the addition of *tert*-butyldimethylsilylchloride (2.33 g, 21.4 mmol, 1.07 equiv.). The mixture was allowed to stir overnight at room temperature. Water was then added to the organic phase, the aqueous phase was extracted thrice with CH₂Cl₂ and the organic phase dried over MgSO₄. The solution was filtered and concentrated under reduced pressure, giving 3.65 g of **2a** (76% yield). ¹**H NMR** (300 MHz, CDCl₃) δ 9.59 (s, 1H-1), 7.20 (d, *J* = 3.6 Hz, 1H-3), 6.46 (d, *J* = 3.6 Hz, 1H-4), 4.74 (s, 2H-6), 0.92 (s, 9H-9), 0.11 (s, 6H-7). These data are in good agreement with those reported in literature.^[279]

S2. Synthesis of the dimethylacetal of furfural

10



Chemical Formula: $C_7H_{10}O_3$ Molecular Weight: 142.1540

2-(dimethoxymethyl)furan

Following a reported procedure, a MeOH (20 mL) solution of furfural (1) (961 mg, 10 mmol, 1.0 equiv.) were added trimethyl orthoformate (4.25 g, 40 mmol) and *p*-TsOH•H₂O (19 mg, 0.11 mmol). The mixture was stirred at 50 °C overnight. After the starting material was totally consumed (TLC monitoring, using cyclohexane/EtOAc 9/1 as eluent) the reaction was quenched with saturated aqueous NaHCO₃, and extracted with Et₂O. The organic phases were dried over MgSO₄, filtered and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (cyclohexane/EtOAc 85/15 as eluent) to obtain 1 g of **10** as a pale-yellow liquid (71% yield). ¹H NMR (300 MHz, CDCl₃) δ 7.41 (dd, *J* = 1.8, 0.9 Hz, 1H-5), 6.42 (dt, *J* = 3.3, 0.8 Hz, 1H-4), 6.36 (dd, *J* = 3.3, 1.8 Hz, 1H-3), 5.43 (d, *J* = 0.8 Hz, 1H-1), 3.35 (s, 6H-6). ¹³C NMR (75 MHz, CDCl₃) δ 151.1 (C-2), 142.6 (C-5), 110.2 (C-

4), 108.6 (C-3), 98.2 (C-1), 53.0 (C-6). These data are in good agreement with those reported in literature.^[280]

S3. Preparation of imine derivatives



General procedure GP1: In a 50 mL round bottom flask was introduced the appropriate furfural derivative (10 mmol, 1 equiv.) followed by the corresponding amine (10 mmol, 1 equiv.) and MgSO₄ (2.41 g, 20 mmol). Anhydrous CH_2Cl_2 (20 mL) was added and the reaction mixture was placed under argon and left to stir overnight. The resulting mixture was then filtered, concentrated and analyzed by NMR.

14a



Chemical Formula: C₁₂H₁₁NO₂ Molecular Weight: 201.2250





Chemical Formula: C₁₃H₁₄N₂O Molecular Weight: 214.2680

14c

1-(furan-2-yl)-N-(4-methoxyphenyl)methanimine

Prepared according to **GP1**: the reaction of furfural (**1**) (0.961 g, 10 mmol) with *p*-anisidine (1.232 g, 10 mmol) in the presence of MgSO₄ (2.41 g, 20 mmol) in CH₂Cl₂ gave 2.053 g of **14a** as a brown solid (quantitative yield). ¹**H NMR** (400 MHz, CDCl₃) δ 8.33 (s, 1H-1), 7.62 (d, *J* = 1.5 Hz, 1H-5), 7.32 – 7.25 (m, 2H-7), 6.97 – 6.92 (m, 3H-3, 8), 6.57 (dd, *J* = 3.4, 1.8 Hz, 1H-4), 3.85 (s, 3H-10). These data are in good agreement with those reported in literature.^[48]

4-((furan-2-ylmethylene)amino)-N,N-dimethylaniline

Prepared according to **GP1**: the reaction of furfural (**1**) (0.961 g, 10 mmol) with *N*,*N*-dimethylbenzene-1,4-diamine (1.362 g, 10 mmol) in the presence of MgSO₄ (2.41 g, 20 mmol) in CH₂Cl₂ gave 2.034 g of **14b** as a brown solid (95% yield). ¹**H NMR** (400 MHz, CDCl₃) δ 8.35 (s, 1H-1), 7.58 (d, *J* = 1.8 Hz, 1H-5), 7.33 – 7.26 (m, 2H-7), 6.86 (dd, *J* = 3.4, 0.8 Hz, 1H-3), 6.79 – 6.71 (m, 2H-8), 6.53 (dd, *J* = 3.4, 1.8 Hz, 1H-4), 2.99 (s, 6H-10). These data are in good agreement with those reported in literature.^[51]

(E)-1-(furan-2-yl)-N-phenylmethanimine



Chemical Formula: C₁₁H₉NO Molecular Weight: 171.1990





Chemical Formula: C₁₁H₈FNO Molecular Weight: 189.1894





Chemical Formula: C₁₂H₈F₃NO Molecular Weight: 239.1972





Chemical Formula: C₁₃H₁₃NO₃ Molecular Weight: 231.2510

Prepared according to **GP1**: the reaction of furfural (1) (0.961 g, 10 mmol) with aniline (0.931 g, 10 mmol) in the presence of MgSO₄ (2.41 g, 20 mmol) in CH₂Cl₂ gave 1.754 g of **14c** as a brown oil (quantitative yield). ¹**H NMR** (300 MHz, CDCl₃) δ 8.32 (s, 1H-1), 7.65 (d, *J* = 1.7 Hz, 1H-5), 7.42 (dd, *J* = 8.4, 7.0 Hz, 2H-7), 7.26 (br. S, 3H-8, 9), 6.99 (d, *J* = 3.5 Hz, 1H-3), 6.59 (dd, *J* = 3.5, 1.7 Hz, 1H-4). These data are in good agreement with those reported in literature.^[281]

N-(4-fluorophenyl)-1-(furan-2-yl)methanimine

Prepared according to **GP1**: the reaction of furfural (**1**) (0.961 g, 10 mmol) with 4-fluoroaniline (1.111 g, 10 mmol) in the presence of MgSO₄ (2.41 g, 20 mmol) in CH₂Cl₂ gave 1.89 g of **14d** as a brown oil (quantitative yield). ¹**H NMR** (300 MHz, CDCl₃) δ 8.28 (s, 1H-1), 7.63 (br. s, 1H-5), 7.36 – 7.19 (m, 2H-7), 7.17 – 7.03 (m, 2H-8), 6.97 (d, *J* = 3.2 Hz, 1H-5), 6.70 – 6.52 (m, 1H-4). These data are in good agreement with those reported in literature.^[282]

(E)-1-(furan-2-yl)-N-(4-(trifluoromethyl)phenyl)methanimine

Prepared according to **GP1**: the reaction of furfural (1) (308 mg, 3.21 mmol) with 4-(trifluoromethyl)aniline (517 mg, 3.21 mmol) in the presence of MgSO₄ (750 mg, 6.22 mmol) in CH₂Cl₂ gave 735 mg. The latter was recrystallized from hot *n*-hexane to give pure **14e** as a brown solid (75% yield). ¹**H NMR** (400 MHz, CDCl₃) δ 8.26 (s, 1H-1), 7.63 (m, 3H-5, 7), 7.30 – 7.27 (m, 2H-8), 7.02 (dd, *J* = 3.5, 0.8 Hz, 1H-3), 6.59 (dd, *J* = 3.5, 1.8 Hz, 1H-4). These data are in good agreement with those reported in literature.^[283]

(E)-N-(2,4-dimethoxyphenyl)-1-(furan-2-yl)methanimine

Prepared according to a reported procedure.^[49] Furfural **1** (480 mg, 5 mmol, 1.0 equiv.) was dissolved in anhydrous Et₂O (50 mL) and 2,4-dimethoxyaniline (0.8 g, 5 mmol, 1 equiv.) was added dropwise followed by the addition of molecular sieves (4 Å, 10 g) and *p*-TsOH•H₂O (10 mg, 0.05 mmol, 0.01 equiv.). The reaction mixture was let to stir overnight at room temperature. The molecular sieves were subsequently filtered and the filtrate concentrated under

reduced pressure to give 1.0 g (87% yield) of pure product **14f** as brown oil. ¹**H NMR** (400 MHz, CDCl₃) δ 8.38 (s, 1H-1), 7.57 (d, *J* = 1.7 Hz, 1H-5), 7.05 (d, *J* = 8.6 Hz, 1H-12), 6.91 (dd, *J* = 3.4, 0.7 Hz, 1H-4), 6.56 – 6.45 (m, 3H-3, 8, 13), 3.87 (s, 3H-11), 3.82 (s, 3H-10). These data are in good agreement with those reported in literature.^[49,284]

N-Butylfurfurylimine

Prepared according to **GP1**: the reaction of furfural (**1**) (480 mg, 5.0 mmol) with *N*-butylamine (366 mg, 5.0 mmol) in the presence of MgSO₄ (1.2. g, 10 mmol) in CH₂Cl₂ gave 0.755 g of **14g** as a brown oil (quantitative yield). ¹**H NMR** (300 MHz, CDCl₃) δ 8.07 (d, *J* = 1.6 Hz, 1H-1), 7.49 (d, *J* = 1.8 Hz, 1H-5), 6.70 (d, *J* = 3.4 Hz, 1H-3), 6.45 (dd, *J* = 3.4, 1.8 Hz, 1H-4), 3.57 (td, *J* = 7.0, 1.3 Hz, 2H-6), 1.69 (p, *J* = 7.1 Hz, 2H-7), 1.45 – 1.26 (m, 2H-8), 0.93 (t, *J* = 7.3 Hz, 3H-9). These data are in good agreement with those reported in literature.^[285]

N, N^{I} -dimethyl- N^{2} -(furan-2-ylmethylene)ethane-1,2-diamine

Prepared according to **GP1**: the reaction of furfural (1) (961 mg, 10 mmol) with N^{l} , N^{l} -dimethylethane-1,2-diamine (882 mg, 10 mmol) in the presence of MgSO₄ (2.41 g, 20 mmol) in CH₂Cl₂ gave 1.66 g of **14h** as a yellow oil (quantitative yield). ¹**H NMR** (300 MHz, CDCl₃) δ 8.05 (d, J = 1.6 Hz, 1H-1), 7.43 (d, J = 1.8 Hz, 1H-5), 6.72 – 6.59 (d, J = 3.4 Hz, 1H-3), 6.39 (dt, J = 3.4, 1.7 Hz, 1H-4), 3.71 – 3.59 (td, J = 6.9, 1.6 Hz, 2H-6), 2.59 (td, J = 7.0, 1.6 Hz, 2H-7), 2.22 (d, J = 1.9 Hz, 6H-8). These data are in good agreement with those reported in literature.^[48]

N^{1} , N^{1} -diethyl- N^{2} -(furan-2-ylmethylene)ethane-1, 2-diamine

Prepared according to **GP1**: the reaction of furfural (1) (0.961 g, 10 mmol) with N^{I} , N^{I} -diethylethane-1,2-diamine (1.162 g, 10 mmol) in the presence of MgSO₄ (2.41 g, 20 mmol) in CH₂Cl₂ gave 1.941 g of **14i** as a yellow oil (quantitative yield). ¹**H NMR** (400 MHz, CDCl₃) δ 8.09 (t, J = 1.3 Hz, 1H-1), 7.49 (d, J = 0.7 Hz, 1H-5), 6.71 (dd, J = 3.4, 0.8 Hz, 1H-4), 6.45 (dd, J = 3.4, 1.8 Hz, 1H-3), 3.70 –





Chemical Formula: C₉H₁₃NO Molecular Weight: 151.2090





Chemical Formula: C₉H₁₄N₂O Molecular Weight: 166.2240

14i



Chemical Formula: C₁₁H₁₈N₂O Molecular Weight: 194.2780

3.64 (m, 2H-6), 2.80 – 2.74 (m, 2H-7), 2.58 (q, J = 7.1 Hz, 4H-8), 1.03 (t, J = 7.1 Hz, 6H-9). These data are in good agreement with those reported in literature.^[48]

N-(furan-2-ylmethylene)-2-(piperidin-1-yl)ethanamine

Prepared according to **GP1:** the reaction of furfural (1) (0.961 g, 10 mmol) with 2-(pyperidin-1-yl)ethanamine (1.282 g, 10 mmol) in the presence of MgSO₄ (2.41 g, 20 mmol) in CH₂Cl₂ gave 1.89 g of **14j** as a brown oil (92% yield). ¹**H NMR** (300 MHz, CDCl₃) δ 8.09 (d, J = 1.4 Hz, 1H-1), 7.49 (d, J = 1.8 Hz, 1H-5), 6.71 (d, J = 3.4 Hz, 1H-3), 6.45 (dd, J = 3.4, 1.8 Hz, 1H-4), 3.72 (td, J = 7.3, 1.3 Hz, 2H-6), 2.72 – 2.60 (m, 2H-7), 2.54 – 2.36 (m, 4H-8), 1.57 (p, J = 5.6 Hz, 4H-9), 1.42 (qd, J = 6.4, 4.1 Hz, 2H-10). These data are in good agreement with those reported in literature.^[48]

N-(furan-2-ylmethylene)- N^3 , N^3 -dimethylpropan-1,3-diamine

Prepared according to **GP1**: the reaction of furfural (1) (480 mg, 5 mmol) with N^{I} , N^{I} -dimethylpropan-1,3-diamine (511 mg, 5 mmol) in the presence of MgSO₄ (1.20 g, 10 mmol) in CH₂Cl₂ gave 824 mg of **14k** as a brown oil (91% yield). ¹**H NMR** (300 MHz, CDCl₃) δ 8.09 (d, J = 1.4 Hz, 1H-1), 7.49 (d, J = 1.8 Hz, 1H-5), 6.71 (d, J = 3.4 Hz, 1H-3), 6.46 (dd, J = 3.4, 1.8 Hz, 1H-4), 3.60 (td, J = 7.1, 1.4 Hz, 2H-6), 2.37 – 2.26 (m, 2H-8), 2.22 (s, 6H-9), 1.89 (q, J = 7.2 Hz, 2H-7). These data are in good agreement with those reported in literature.^[48]

N-(furan-2-ylmethylene)-*N*³,*N*³-diethylpropan-1,3-diamine

Prepared according to **GP1**: the reaction of furfural (**1**) (480 mg, 5 mmol) with N^{I} , N^{I} -diethylpropan-1,3-diamine (511 mg, 5 mmol) in the presence of MgSO₄ (1.20 g, 10 mmol) in CH₂Cl₂ gave 1.012 g of **14l** as a brown oil (97% yield). ¹**H NMR** (300 MHz, CDCl₃) δ 8.09 (d, J = 1.4 Hz, 1H-1), 7.49 (d, J = 1.7 Hz, 1H-5), 6.71 (d, J = 3.4 Hz, 1H-3), 6.46 (dd, J = 3.4, 1.8 Hz, 1H-4), 3.59 (td, J = 7.1, 1.3 Hz, 2H-6), 2.60 – 2.42 (m, 6H-8, 9), 1.85 (p, J = 7.1 Hz, 2H-7), 1.00 (t, J = 7.1 Hz, 6H-10). No ¹³C NMR, HRMS and IR were recorded.

4-methoxy-*N*-((*E*)-(5-methylfuran-2-yl)methylidene)aniline



Chemical Formula: C₁₂H₁₈N₂O Molecular Weight: 206.2890



14i



Chemical Formula: C₁₀H₁₆N₂O Molecular Weight: 180.2510

141



Chemical Formula: C₁₂H₂₀N₂O Molecular Weight: 208.3050



Molecular Weight: 215.2520





Chemical Formula: C₁₁H₁₈N₂O Molecular Weight: 194.2780

16a



Chemical Formula: C₁₉H₂₇NO₃Si Molecular Weight: 345.5140

Prepared according to **GP1**: the reaction of 5-methyl-2-furaldehyde (**13**) (1.10 g, 10 mmol) with *p*-anisidine (1.23 g, 10 mmol) in the presence of MgSO₄ (2.41 g, 20 mmol) in CH₂Cl₂ gave, after recrystallisation in hot pentane, 2.15 g of **15a** as a brown solid (quantitative yield). ¹**H NMR** (400 MHz, CDCl₃) δ 8.21 (s, 1H-1), 7.28 – 7.22 (m, 2H-7), 6.97 – 6.89 (m, 2H-8), 6.81 (d, *J* = 3.3 Hz, 1H-3), 6.17 (dq, *J* = 3.1, 1.0 Hz, 1H-4), 3.84 (s, 3H-10), 2.45 (s, 3H-11). These data are in good agreement with those reported in literature.^[286]

N-(5-methylfuran-2-ylmethylene)- N^3 , N^3 -dimethylpropan-1,3-diamine

Prepared according to **GP1**: the reaction of 5-methyl-2-furaldehyde (**13**) (2.202 g, 20 mmol) with N^{1} , N^{1} -dimethylpropan-1,3-diamine (2.044 g, 20 mmol) in the presence of MgSO₄ (4.815 g, 40 mmol) in CH₂Cl₂ gave 4.05 g of **15k** as a brown oil (quantitative yield). ¹**H NMR** (400 MHz, CDCl₃) δ 7.98 (d, J = 1.4 Hz, 1H-1), 6.58 (d, J = 3.3 Hz, 1H-3), 6.06 (d, J = 2.9 Hz, 1H-4), 3.58 (t, J = 7.1, 2H-6), 2.36 (s, 3H-10), 2.32 (t, J = 7.4 Hz, 2H-8), 2.22 (s, 6H-9), 1.87 (p, J = 7.2 Hz, 2H-7). ¹³**C NMR** (101 MHz, CDCl₃) δ 155.57(C-5), 150.32 (C-2), 149.71 (C-1), 115.99 (C-3), 108.06 (C-4), 59.96 (C-6), 57.68 (C-8), 45.62 (C-9), 29.05 (C-7), 14.03 (C-10). **HRMS**: m/z calculated for C₁₁H₁₈N₂OH [M+H]⁺ 195.1492, found 195.1492. **IR**: v (cm⁻¹) 2923, 2851, 2116, 1647, 1472, 1016, 502.

(*E*)-1-(5-(((tert-butyldimethylsilyl)oxy)methyl)furan-2-yl)-*N*-(4-methoxy phenyl)methanimine

Prepared according to **GP1**: the reaction of 5-(((*tert*-butyldimethylsilyl)oxy)methyl)furan-2-carbaldehyde (**2a**) (2.0 g, 8.32 mmol) with *p*-anisidine (1.02 g, 8.32 mmol) in the presence of MgSO₄ (2.05 g, 17 mmol) in CH₂Cl₂ gave 2.86 g of **16a** as a yellow oil (quantitative yield). ¹**H NMR** (300 MHz, CDCl₃) δ 8.25 (s, 1H-1), 7.26 – 7.19 (m, 2H-7), 6.91 (m, 3H-3, 8), 6.40 (dd, *J* = 3.4, 0.9 Hz, 1H-4), 4.76 (s, 2H-11), 3.82 (d, *J* = 0.8 Hz, 3H-10), 0.93 (d, *J* = 0.9 Hz, 9H-14), 0.11 (d, *J* = 0.9 Hz, 6H-12). These data are in good agreement with those reported in literature.^[49]


Chemical Formula: C₁₇H₃₂N₂O₂Si Molecular Weight: 324.5400

17a



Chemical Formula: C₁₉H₁₈N₂O Molecular Weight: 290.3660

5-(((tert-butyldimethylsilyl)oxy)methyl)-*N*-(5-methylfuran-2ylmethylene)-*N*³,*N*³-dimethylpropan-1,3-diamine

Prepared according to **GP1**: the reaction of 5-(((*tert*-butyldimethylsilyl)oxy)methyl)furan-2-carbaldehyde (**2a**) (3.65 g, 15.2 mmol) with N^{I} , N^{I} -dimethylpropan-1,3-diamine (1.55 g, 15.2 mmol) in the presence of MgSO₄ (3.66 g, 30.4 mmol) in CH₂Cl₂ gave 4.64 g of **16k** as a brown oil (94% yield). ¹**H NMR** (300 MHz, CDCl₃) δ 8.04 (t, J = 1.2 Hz, 1H-1), 6.68 (d, J = 3.4 Hz, 1H-3), 6.32 (d, J = 3.4 Hz, 1H-4), 4.71 (s, 2H-6), 3.59 (td, J = 7.1, 1.3 Hz, 2H-10), 2.38 – 2.28 (m, 2H-12), 2.22 (s, 6H-13), 1.92 – 1.78 (m, 2H-11), 0.91 (s, 9H-9), 0.08 (s, 6H-7). ¹³**C NMR** (101 MHz, CDCl₃) δ 157.5 (C-1), 150.9 (C-5), 150.0 (C-2), 114.8 (C-3), 108.6 (C-4), 59.9 (C-10), 58.7 (C-6), 57.6 (C-12), 45.5 (C-13), 28.9 (C-11), 25.9 (C-9), 18.5 (C-8), -5.2 (C-7). **HRMS**: m/z calculated for C₁₇H₃₂N₂O₂SiH [M+H]⁺ 325.2306, found 325.2304. **IR**: v (cm⁻¹) 2930, 2857, 2096, 1645, 1464, 1257, 1079, 837, 777.

(*E*)-1-(1-benzyl-1*H*-pyrrol-2-yl)-*N*-(4-methoxyphenyl)methanimine

Following a reported procedure,^[51] in a round-bottom flask equipped with a magnetic stirrer, 1-benzyl-1*H*-pyrrole-2carbaldehyde (926 mg, 5 mmol, 1 equiv.) was introduced and dissolved in anhydrous Et₂O (50 mL). *p*-Anisidine (615 mg, 5 mmol, 1 equiv.) was added dropwise followed by molecular sieves (4 Å, 10 g) and PTSA (10 mg, 0.05 mmol, 0.01 equiv.). The reaction mixture was stirred at room temperature overnight. The reaction course was followed by ¹H-NMR spectroscopy: if the reaction was not complete, one of the reagents was added, and the reaction mixture was let stir until completion. The molecular sieves were removed by filtration, and the solvent was removed by evaporation at reduced pressure to give 1.49 g of the corresponding imine (quantitative yield) as a yellow solid. **M.p.**: 93-94 °C. ¹**H**-**NMR** (300 MHz, CDCl₃): δ 8.32 (s, 1H-1), 7.37-7.23 (m, 3H-14, 15), 7.23-7.17 (m, 2H-7), 7.08 (d, *J* = 9.1 Hz, 2H-13), 6.93-6.86 (m, 3H-5,8), 6.73 (dd, J = 3.9, 1.7 Hz, 1H-3), 6.29 (dd, J = 3.9, 2.7 Hz, 1H-4), 5.80 (s, 2H-11), 3.83 (s, 3H-10). These data are in good agreement with those reported in literature.^[51]

S4. Silylation of furfural derivatives

S4.1 Silylation using [Ir] catalyst



General procedure GP2: 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. Then, the reaction mixture was allowed to cool to room temperature and transferred to a round bottom flask containing a known amount of 3,4,5-trimethoxy benzaldehyde which was used as a standard for the NMR quantification. The solvent was removed under reduced pressure and the crude mixture was analyzed by ¹H NMR in CDCl₃.

Purification and hydrolysis of the imines:

PMP-imines: When possible, silylated PMP-imines were purified by rapid silica gel chromatography. However, due to a partial hydrolysis on silica, usually they were directly hydrolyzed in aqueous acidic medium.

The C3-silylated furfuryl PMP-imine was hydrolyzed using 2 mL of 1 M HCl solution in 2 mL Et₂O. The mixture was stirred for 30 min, then a brine solution was added to it prior for extraction with Et₂O. The aqueous layer was extracted 3 times with Et₂O, and the combined organic layers were dried over MgSO₄ or Na₂SO₄, filtered and carefully concentrated under low reduced pressure (*Note: Silylated furfural derivatives are quite volatile*). The hydrolyzed crude was purified by silica gel chromatography, was concentrated under vacuum at 40 °C, 600 mbar for around 10-20 min.

Bidentate imines: as bidentate imines are unstable on silica, they are directly hydrolyzed to aldehyde during chromatography purification.

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.

18a-Si-a

(*E*)-*N*-(4-methoxyphenyl)-1-(3-(triethylsilyl)furan-2-yl) methanimine



Chemical Formula: C₁₈H₂₅NO₂S Molecular Weight: 315.4880





Chemical Formula: C₂₄H₃₉NO₂Si₂ Molecular Weight: 429.7510



(*E*)-1-(3,5-bis(triethylsilyl)furan-2-yl)-*N*-(4-methoxyphenyl) methanimine

¹**H NMR** (400 MHz, CDCl₃) δ 8.36 (d, J = 0.7 Hz, 1H-1), 7.25 – 7.17 (m, 2H-7), 6.97 – 6.88 (m, 2H-8), 6.70 (d, J = 0.7 Hz, 1H-4), 3.83 (s, 3H-10), 1.06 – 0.90 (m, 18H-12,14), 0.85 (m, 12H-11,13). ¹³**C NMR** (101 MHz, CDCl₃) δ 161.4 (C2 or 5), 160.7 (C2 or 5), 158.3 (C-9), 147.6 (C-1), 145.3 (C-6), 128.6 (C-4), 122.3 (C-7), 122.3 (C-3), 114.5 (C-8), 55.6 (C-10), 7.6 (C-14/12), 7.5 (C-14/12), 4.2 (C-11/13), 3.4 (C-11/13). **HRMS**: *m*/*z* calculated for C₂₄H₃₉NO₂Si₂Na [M+Na]⁺ 452.2410, found 452.2412. **IR**: v (cm⁻¹) 2953, 2875, 1621, 1504, 1246, 1007, 725

18-*Si*-a

3-(triethylsilyl)furan-2-carbaldehyde



Chemical Formula: C₁₁H₁₈O₂Si Molecular Weight: 210.3480

Prepared according to **GP2** from the reaction of PMP-imine **14a** (81 mg, 0.40 mmol) and HSiEt₃ (100 μL, 0.60 mmol) at 120 °C for 4.5 h. The crude mixture was quantified by ¹H NMR, providing 82% NMR yield of the C3-silylated PMP-imine **18a**-*Si*-**a** and 5% of the bis-silylated imine **18a**-*Si*-**a**_b. The crude was hydrolyzed following the detailed procedure and purified by silica-gel chromatography [eluent (99/1) to (95/5) pentane/Et₂O]. 39 mg of the silylated aldehyde **18**-*Si*-**a** (46% yield) was isolated as a yellow oil, and in a second fraction 2 mg of the bis-silylated aldehyde **18a**-*Si*-**a**_b (2% yield) as a yellow solid. The same yields were obtained from 2 mmol of imine. ¹H NMR (400 MHz, CDCl₃) δ 9.69 (s, 1H-1), 7.68 (d, *J* = 1.5 Hz, 1H-5), 6.56 (d, *J* = 1.6 Hz, 1H-4), 0.98 – 0.90 (m, 9H-7), 0.88 – 0.79 (m, 6H-6). ¹³C NMR (101 MHz, CDCl₃) δ 178.9 (C-1), 156.8 (C-2), 147.3 (C-5), 130.6 (C-3), 118.3 (C-4), 7.3 (C-6), 3.9 (C-7). **HRMS**: *m*/*z* calculated for C₁₁H₁₈O₂SiNa [M+Na]⁺ 233.0968, found 233.0969. **IR**: v (cm⁻¹) 2955, 2875, 1685, 1463, 1247, 765, 725.

<u>Note</u>: This compound was also obtained according to **GP2** from bidentate imine **18a-Si-k** (361 mg, 2 mmol). In this case, after purification by silica-gel column chromatography, 250 mg of product **18**-*Si*-**a** (59% yield) was isolated

3,5-bis(triethylsilyl)furan-2-carbaldehyde



¹**H** NMR (400 MHz, CDCl₃) δ 9.74 (s, 1H-1), 6.71 (s, 1H-4), 1.06 – 0.89 (m, 18H-7/7'), 0.89 – 0.79 (m, 12H-8/8'). ¹³**C** NMR (101 MHz, CDCl₃) δ 179.2 (C-1), 165.5 (C-5), 160.6 (C-2), 129.5 (C-3), 128.5 (C-4), 7.5 (C-7/7'), 7.4 (C-7/7'), 4.0 (C-6/6'), 3.2 (C-6/6') HRMS: *m/z* calculated for $C_{17}H_{32}O_2Si_2Na_1$ [M+Na]⁺ 387.1833, found 387.1833. IR: v (cm⁻¹) 2953, 2875, 1621–1504, 1246, 1007, 821, 724

Chemical Formula: $C_{17}H_{32}O_2Si_2 \ \ 1621, \ 1504, \ 1246, \ 1007, \ 831, \ 724.$ Molecular Weight: 324.6110

19-*Si*-a

18-Si-a_b

5-methyl-3-(triethylsilyl)furan-2-carbaldehyde

Prepared according to **GP2** from the reaction of PMP-imine **15a** (87 mg, 0.40 mmol) and HSiEt₃ (100 μ L, 0.60 mmol) at 120 °C for 4.5 h. The crude mixture was quantified by ¹H NMR, providing 70% NMR yield of the C3-silylated PMP-imine **19a-Si-a**. The crude was hydrolyzed following the detailed procedure and purified by silica-gel column



Chemical Formula: C₁₂H₂₀O₂Si Molecular Weight: 224.3750 chromatography [eluent (99/1) to (95/5) pentane/Et₂O], to afford 69 mg of the silylated aldehyde **19-Si-a** (77% yield) as a yellow oil (72% yield was obtained at a 1.2 mmol of imine scale). ¹H NMR (400 MHz, CDCl₃) δ 9.55 (s, 1H-1), 6.20 (d, *J* = 1.0 Hz, 1H-4), 2.40 (d, *J* = 0.8 Hz, 3H-8), 0.96 (t, *J* = 7.7 Hz, 9H-7), 0.89 – 0.75 (m, 7H-6). ¹³C NMR (101 MHz, CDCl₃) δ 177.9 (C-1), 158.9 (C-5), 155.9 (C-2), 133.9 (C-3), 115.4 (C-4), 13.8 (C-8), 7.4 (C-6), 4.1 (C-7). HRMS: *m*/*z* calculated for C₁₂H₂₀O₂SiNa [M+Na]⁺ 247.1125, found 247.1125. **IR**: v (cm⁻¹) 2954, 2876, 1678, 1502, 1220, 973, 802, 779, 725

Note: This compound was also obtained according to **GP2** from bidentate imine **15k** (77 mg, 0.40 mmol). In this case, after purification by column chromatography on silica-gel, 49 mg of product **19-Si-a** (55% yield) was isolated.

5-(((tert-butyldimethylsilyl)oxy)methyl)-3-(triethylsilyl)furan-2carbaldehyde



20-Si-a

Chemical Formula: C₁₈H₃₄O₃Si₂ Molecular Weight: 354.6370

Prepared according to **GP2** from the reaction of PMP-imine **16a** (137 mg, 0.40 mmol) and HSiEt₃ (100 µL, 0.60 mmol) at 120 °C for 4.5 h. The crude mixture was quantified by ¹H NMR, providing 62% NMR yield of the C3-silylated PMP-imine **20a**-*Si*-**a**. The crude was hydrolyzed following the detailed procedure and purified over a silica-gel chromatography [eluent (99/1) to (95/5) pentane/Et₂O], to afford 75 mg of the silylated aldehyde **20**-*Si*-**a** (53% yield) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 9.63 (s, 1H-1), 6.43 (t, *J* = 0.8 Hz, 1H-4), 4.74 (d, *J* = 0.9 Hz, 2H-8), 0.99 – 0.93 (m, 9H-7), 0.92 (d, *J* = 0.6 Hz, 9H-10), 0.87 – 0.80 (m, 6H-6), 0.10 (d, *J* = 0.6 Hz, 6H-9). ¹³C NMR (101 MHz, CDCl₃) δ 178.7 (C-1), 160.5 (C-5), 156.0 (C-2), 132.3 (C-3), 115.3 (C-4), 58.7 (C-8), 25.9 (C-10), 18.3 (C-11), 7.4 (C-7), 4.0 (C-6), -5.2 (C-9). HRMS: *m*/*z* calculated for C₁₈H₃₄O₃Si₂Na [M+Na]⁺ 377.1940, found 377.1939. **IR**: v (cm⁻¹) 2954, 2857, 1682, 1504, 1252, 1090, 837, 778, 725, 701.

3-(tripropylsilyl)furan-2-carbaldehyde



Chemical Formula: C₁₄H₂₄O₂Si Molecular Weight: 252.4290

Prepared according to **GP2** from the reaction of PMP-imine **14a** (81 mg, 0.40 mmol) and HSi(*n*-Pr)₃ (100 µL, 0.60 mmol) at 120 °C for 4.5 h. The crude mixture was quantified by ¹H NMR, providing 82% NMR yield of the C3-silylated PMP-imine **18a**-*Si*-**b**. The crude was hydrolyzed following the detailed procedure and purified by silica-gel column chromatography [eluent (99/1) to (95/5) pentane/Et₂O]. 29 mg of the silylated aldehyde **18**-*Si*-**b** (30% yield) was isolated as a yellow oil. ¹H **NMR** (400 MHz, CDCl₃) δ 9.71 (s, 1H-1), 7.69 (dd, *J* = 7.2, 1.5 Hz, 1H-5), 6.57 (dd, *J* = 7.2, 1.5 Hz, 1H-4), 1.33 (m, 6H-7), 0.96 (m, 9H-8), 0.90 – 0.80 (m, 6H-6). ¹³C NMR (101 MHz, CDCl₃) δ 179.0 (C-1), 156.5 (C-2),147.2 (C-5), 130.4 (C-3), 118.2 (C-4), 18.5 (C-8), 17.5 (C-7), 15.8 (C-6), 7.4 (C-8), 4.0 (C-6). **HRMS**: *m*/*z* calculated for C₁₄H₂₄NaO₂Si [M+Na]⁺ 275.1438, found 275.1438. **IR**: v (cm⁻¹) 2954, 2871, 1683, 1462, 1183, 894, 763, 726, 701.

<u>Note</u>: This compound was also obtained according to **GP2** from bidentate imine **14k** (72 mg, 0.40 mmol). In this case, after purification by column chromatography on silica gel, 18 mg of product **18-Si-b** (23% yield) was isolated.

5-methyl-3-(tripropylsilyl)furan-2-carbaldehyde

19-*Si*-b



Chemical Formula: C₁₅H₂₆O₂Si Molecular Weight: 266.4560 Prepared according to **GP2** from the reaction of PMP-imine **15a** (138 mg, 0.40 mmol) and HSi(*n*-Pr)₃ (100 µL, 0.60 mmol) at 120 °C for 4.5 h. The crude mixture was quantified by ¹H NMR, providing 87% NMR yield of the C3-silylated PMP-imine **19a**-*Si*-**b**. The crude was hydrolyzed following the detailed procedure and purified by silica-gel column chromatography [eluent (99/1) to (95/5) pentane/Et₂O], to afford 73 mg of the silylated aldehyde **19**-*Si*-**b** (68% yield) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 9.55 (s, 1H-1), 6.18 (d, *J* = 1.0 Hz, 1H-4), 2.40 (d, *J* = 0.9 Hz, 3H-9), 1.40 – 1.28 (m, 6H-7), 0.96 (t, *J* = 7.2 Hz, 9H-8), 0.84 – 0.77 (m, 6H-6). ¹³C NMR (101 MHz, CDCl₃) δ 177.9 (C-1), 158.9 (C-5), 155.7 (C-2), 134.7 (C-3), 115.3 (C-4), 18.5 (C-8), 17.5 (C-7), 15.9 (C-6), 13.9 (C-9). HRMS: *m*/*z* calculated for C₁₅H₂₆O₂SiNa [M+Na]⁺ 289.1594, found 289.1594. **IR**: v (cm⁻¹) 2954, 2868,1678, 1501, 1197, 1063, 1003, 775, 706.

5-(((tert-butyldimethylsilyl)oxy)methyl)-3-(tripropylsilyl)furan-2carbaldehyde



20-Si-b

Chemical Formula: C₂₁H₄₀O₃Si₂ Molecular Weight: 396.7180

Prepared according to **GP2** from the reaction of PMP-imine **16a** (138 mg, 0.40 mmol) and HSi(*n*-Pr)₃ (100 µL, 0.60 mmol) at 120 °C for 4.5 h. The crude mixture was quantified by ¹H NMR, providing 68% NMR yield of the C3-silylated PMP-imine **20a**-*Si*-**b**. The crude was hydrolyzed following the detailed procedure and purified by silica-gel column chromatography [eluent (99/1) to (95/5) pentane/Et₂O], to afford 96 mg of the silylated aldehyde **20**-*Si*-**b** (63% yield) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 9.63 (s, 1H-1), 6.42 (d, *J* = 0.8 Hz, 1H-4), 4.74 (d, *J* = 0.8 Hz, 2H-9), 1.40 – 1.29 (m, 6H-7), 0.96 (t, *J* = 7.2 Hz, 9H-8), 0.92 (s, 9H-12), 0.86 – 0.78 (m, 6H-6), 0.10 (s, 6H-10). ¹³C NMR (101 MHz, CDCl₃) δ 178.7 (C-1), 160.5 (C-5), 155.9 (C-2), 133.2 (C-3), 115.2 (C-4), 58.7 (C-9), 25.9 (C-12), 18.5 (C-11), 18.5 (C-8), 17.5 (C-7), 15.8 (C-6), -5.2 (C-10). HRMS: *m*/*z* calculated for C₂₁H₄₀O₃Si₂Na [M+Na]⁺ 419.2408, found 419.2408. **IR**: v (cm⁻¹) 2954, 2866, 1683, 1504, 1254, 1090, 1005, 836, 777.

18-Si-d

5 0 0 4 3 1 3 6 7 8 9 10 11

Prepared according to **GP2** from the reaction of bidentate imine **14k** (72 mg, 0.40 mmol) and HSiMe₂Bn (100 µL, 0.60 mmol) at 120 °C for 4.5 h. The crude mixture was quantified by ¹H NMR, providing 45% NMR yield of the C3-silylated PMP-imine **18k**-*Si*-**d** and 5% of the bis-silylated imine **18k**-*Si*-**d**_b. The crude was purified by silica-gel column chromatography [eluent (99/1) to (95/5) pentane/Et₂O]. 42 mg of the silylated aldehyde **18**-*Si*-**d** (43% yield) was isolated as a yellow oil, and in a second fraction 3 mg of the bis-silylated aldehyde **18**-*Si*-**d**_b (3% yield) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 9.52 (s, 1H-1), 7.67 (d, *J* = 1.5 Hz, 1H-5), 7.19 (dd, *J* = 8.1, 6.6 Hz, 2H-10), 7.11 – 7.04 (m, 1H-11), 6.97 – 6.91 (m, 2H-9), 6.51 (d, *J* = 1.5 Hz, 1H-4), 2.38 (s, 2H-7), 0.32 (s, 6H-6).

3-(benzyldimethylsilyl)furan-2-carbaldehyde

Chemical Formula: C₁₄H₁₆O₂Si Molecular Weight: 244.3650

¹³**C NMR** (101 MHz, CDCl₃) δ 179.3 (C-1), 156.7 (C-2), 147.1 (C-5), 138.9 (C-8), 131.0 (C-3), 128.4 (C-9/10), 128.4 (C-9/10), 124.6 (C-11), 117.9 (C-4), 115.1 (C-8), 25.6 (C-7), -2.7 (C-6). **HRMS**: *m/z* calculated for C₁₄H₁₆O₂SiNa [M+Na]⁺ 267.0812, found 267.0812. **IR**: v (cm⁻¹) 3024, 1679, 1461, 1382, 1249, 1185, 1057, 821, 760.

<u>Note</u>: This compound was also obtained according to **GP2** from PMPimine **14a** (805 g, 4.0 mmol). In this case, after purification by column chromatography on silica-gel, 553 mg of product **18-Si-d** (57% yield) was isolated.

3,5-bis(benzyldimethylsilyl)furan-2-carbaldehyde

¹**H** NMR (400 MHz, CDCl₃) δ 9.63 (s, 1H-1), 7.23 (m, 4H-10/10'), 7.12 (dtt, *J* = 7.4, 5.2, 2.9 Hz, 2H-11/11'), 6.98 (dt, *J* = 7.9, 1.6 Hz, 4H-9/9'), 6.59 (s, 1H-4), 2.41 (d, *J* = 1.4 Hz, 4H-7/7'), 0.33 (s, 6H-6/6'), 0.32 (s, 6H-6/6'). ¹³**C** NMR (101 MHz, CDCl₃) δ 179.6 (C-1), 165.1 (C-5), 160.5 (C-4), 139.0 (C-8/8'), 138.5 (C-8/8'), 129.5 (C-3), 128.4 (C-9/9'), 128.3 (C-10/10'), 128.0 (C-2), 124.6 (C-11/11'), 124.5 (C-11/11'), 25.6 (C-7/7'), 25.0 (C-7/7'), -2.7 (C-6/6'), -3.8 (C-6/6'). **HRMS**: *m/z* calculated for C₂₃H₂₈O₂Si₂Na [M+Na]⁺ 415.1520, found 415.1519.

19a-*Si-*d

(E)-1-(3-(benzyldimethylsilyl)-5-methylfuran-2-yl)-N-(4-methoxy phenyl)methanimine



Chemical Formula: C₂₂H₂₅NO₂S Molecular Weight: 363.5320

Prepared according to **GP2** from the reaction of PMP-imine **15a** (138 mg, 0.40 mmol) and HSiMe₂Bn (100 µL, 0.60 mmol) at 120 °C for 4.5 h. The crude mixture was purified by (fast) silica-gel column chromatography [eluent (95/5) pentane/Et₂O] to afford the C3-silylated PMP-imine **19a-Si-d** as an oil. ¹H **NMR** (400 MHz, CDCl₃) δ 7.89 (s, 1H-1), 7.15 (t, *J* = 7.5 Hz, 2H-10), 7.11 (d, *J* = 8.6 Hz, 2H-14), 7.00 (t, *J* = 7.4 Hz, 1H-11), 6.95 (d, *J* = 7.6 Hz, 2H-9), 6.89 (d, *J* = 8.6 Hz, 2H-13), 6.09 (s, 1H-4), 3.83 (s, 3H-16), 2.41 (s, 3H-17), 2.34 (s, 2H-7), 0.30 (s, 6H-6). ¹³C **NMR** (101 MHz, CDCl₃) δ 158.4 (C-15), 155.6 (C-5), 155.3 (C-2), 146.6 (C-1), 144.9 (C-12), 139.2 (C-8), 128.5 (C-9/10), 128.4 (C-9/10), 126.8 (C-3), 124.5 (C-11), 122.4 (C-14), 114.4 (C-13), 113.8 (C-

18a-*Si-*d_b



Chemical Formula: C₂₃H₂₈O₂Si₂ Molecular Weight: 392.6450 4), 55.6 (C-16), 26.5 (C-7), 13.8 (C-17), -2.0 (C-6). **IR**: ν (cm⁻¹) 3060, 2957, 1674, 1501, 1250, 1127, 828, 772.

19-Si-d





Molecular Weight: 258.3920

Prepared according to **GP2** from the reaction of PMP-imine **15a** (86 mg, 0.40 mmol) and HSiMe₂Bn (100 µL, 0.60 mmol) at 120 °C for 4.5 h. The crude mixture was quantified by ¹H NMR, providing 84% NMR yield of the C3-silylated PMP-imine **19a-Si-d**. The crude was hydrolyzed following the detailed procedure and purified by silica-gel column chromatography [eluent (99/1) to (95/5) pentane/Et₂O], to afford 76 mg of the silylated aldehyde **19-Si-d** (74% yield) as a yellow oil. ¹H **NMR** (300 MHz, CDCl₃) δ 9.33 (s, 1H-1), 7.19 (d, *J* = 7.0 Hz, 2H-10), 7.09 (t, *J* = 7.0 Hz, 1H-11), 6.94 (d, *J* = 7.0 Hz, 2H-9), 6.15 (d, *J* = 1.0 Hz, 1H-4), 2.39 (d, *J* = 0.9 Hz, 3H-12), 2.36 (s, 2H-7), 0.29 (s, 6H-6). ¹³C **NMR** (75 MHz, CDCl₃) δ 178.2 (C-1), 158.7 (C-5), 155.7 (C-2), 138.8 (C-8), 133.5 (C-3), 128.4 (C-10), 128.4 (C-9), 124.6 (C-11), 115.0 (C-4), 25.8 (C-7), 13.8 (C-12), -2.5 (C-6). **HRMS**: *m/z* calculated for C₁₅H₁₈O₂SiNa [M+Na]⁺ 281.0968, found 281.0969. **IR**: v (cm⁻¹) 3024, 2957, 1674, 1501, 1251, 828, 772, 699.

<u>Note</u>: This compound was also obtained according to **GP2** from bidentate imine **15k** (78 mg, 0.40 mmol). In this case, after purification by column chromatography on silica-gel, 58 mg of product **19-Si-d** (56% yield) was isolated.

5-(((tert-butyldimethylsilyl)oxy)methyl)-3-(benzyldimethylsilyl)

furan-2-carbaldehyde

20-Si-d



Chemical Formula: C₂₁H₃₂O₃Si₂ Molecular Weight: 388.6540 Prepared according to **GP2** from the reaction of PMP-imine **16a** (138 mg, 0.40 mmol) and HSiMe₂Bn (100 μ L, 0.60 mmol) at 120 °C for 4.5 h. The crude mixture was quantified by ¹H NMR, providing 74% NMR yield of the C3-silylated PMP-imine **20a**-*Si*-d. The crude was hydrolyzed following the detailed procedure and purified by silica-gel column chromatography [eluent (99/1) to (95/5) pentane/Et₂O], to afford 100 mg of the silylated aldehyde **20**-*Si*-d (64% yield) as a yellow oil. ¹H NMR

(300 MHz, CDCl₃) δ 9.44 (s, 1H-1), 7.19 (dd, *J* = 8.1, 6.6 Hz, 2H-10), 7.09 (t, *J* = 7.3 Hz, 1H-11), 6.94 (d, *J* = 7.1 Hz, 2H-9), 6.38 (d, *J* = 1.1 Hz, 1H-4), 4.72 (d, *J* = 0.8 Hz, 2H-12), 2.38 (s, 2H-7), 0.93 (s, 9H-15), 0.30 (s, 6H-6), 0.12 (s, 6H-13). ¹³C NMR (75 MHz, CDCl₃) δ 179.0 (C-1), 160.2 (C-5), 156.0 (C-2), 138.8 (C-8), 132.4 (C-3)*, 128.4 (C-9/10), 128.4 (C-9/10), 124.6 (C-11), 114.9 (C-4), 58.6 (C-12), 26.0 (C-15), 25.6 (C-7), 18.5 (C-14), -2.6 (C-6), -5.2 (C-13). **13C 132.38 ppm correlation observed by HMBC for C3 position.* **HRMS**: *m*/*z* calculated for C₂₁H₃₂O₃Si₂Na [M+Na]⁺ 411.1782, found 411.1783. **IR**: v (cm⁻¹) 2955, 2857, 1680, 1505, 1251, 1189, 828, 773, 696.

18-Si-c



Chemical Formula: C₁₁H₁₈O₂Si Molecular Weight: 210.3480

3-(tert-butyldimethylsilyl)furan-2-carbaldehyde

Prepared according to **GP2** from the reaction of the PMP-imine **14a** (81 mg, 0.40 mmol) and HSiMe₂*t*Bu (100 µL, 0.60 mmol) at 120 °C for 4.5 h. The crude was hydrolyzed following the detailed procedure and purified by silica-gel column chromatography [eluent (99/1) to (95/5) pentane/Et₂O], to afford 35 mg of the silylated aldehyde **18**-*Si*-**c** (41% yield) as a yellow oil. ¹**H NMR** (400 MHz, CDCl₃) δ 9.70 (d, *J* = 0.8 Hz, 1H-1), 7.70 (dd, *J* = 1.6, 0.8 Hz, 1H-5), 6.58 (d, *J* = 1.6 Hz, 1H-4), 0.91 (s, 9H-8), 0.34 (s, 6H-6). ¹³**C NMR** (101 MHz, CDCl₃) δ 178.9 (C-1), 156.9 (C-2), 147.1 (C-5), 131.8 (C-3), 118.6 (C-4), 29.8 (C-7), 26.4 (C-8), -4.5 (C-6). **HRMS**: *m*/*z* calculated for C₁₁H₁₈O₂SiNa [M+Na]⁺ 233.0967, found 233.0968. **IR**: v (cm⁻¹) 2928, 2856, 1682, 1464, 1361, 810, 680.

19-Si-c



Chemical Formula: C₁₂H₂₀O₂Si Molecular Weight: 224.3750

3-(tert-butyldimethylsilyl)furan-2-carbaldehyde

Prepared according to **GP2** from the reaction of PMP-imine **15a** (86 mg, 0.40 mmol) and HSiMe₂*t*-Bu (100 μ L, 0.60 mmol) at 120 °C for 4.5 h. The crude mixture was quantified by ¹H NMR, providing 59% NMR yield of the C3-silylated PMP-imine **19a-***Si***-c**. The crude was hydrolyzed following the detailed procedure and purified by silica-gel column chromatography [eluent (99/1) to (95/5) pentane/Et₂O], to afford 50 mg of the silylated aldehyde **19-***Si***-c** (55% yield) as a yellow oil. ¹H NMR

(400 MHz, CDCl₃) δ 9.55 (s, 1H-1), 6.20 (q, *J* = 1.0 Hz, 1H-4), 2.40 (d, *J* = 1.0 Hz, 3H-9), 0.91 (s, 9H-8), 0.31 (s, 6H-6). ¹³C NMR (101 MHz, CDCl₃) δ 177.9 (C-1), 158.6 (C-5), 155.9 (C-2), 134.7 (C-3), 115.7 (C-4), 26.4 (C-8), 16.9 (C-7), 13.8 (C-9), -4.4 (C-6). HRMS: *m/z* calculated for C₁₂H₂₀O₂SiNa [M+Na]⁺ 247.1124, found 247.1125. **IR**: v (cm⁻¹) 3345, 2929, 2857, 1753, 1513, 1252, 839, 824.

5-(((tert-butyldimethylsilyl)oxy)methyl)-3-(tert-butyldimethylsilyl) furan-2-carbaldehyde

Prepared according to **GP2** from the reaction of PMP-imine **20a**-*Si*-**c** (138 mg, 0.40 mmol) and HSiMe₂*t*Bu (100 µL, 0.60 mmol) at 120 °C for 4.5 h. The crude mixture was quantified by ¹H NMR, providing 75% NMR yield of the C3-silylated PMP-imine **20a**-*Si*-**c**. The crude was hydrolyzed following the detailed procedure and purified by silica-gel column chromatography [eluent (99/1) to (95/5) pentane/Et₂O], to afford 62 mg of the silylated aldehyde **20**-*Si*-**d** (44% yield) as a yellow oil. ¹H **NMR** (400 MHz, CDCl₃) δ 9.63 (s, 1H-1), 6.43 (d, *J* = 1.0 Hz, 1H-4), 4.74 (d, *J* = 0.9 Hz, 2H-9), 0.92 (s, 9H-8/12), 0.91 (s, 9H-8/12), 0.33 (s, 6H-6), 0.10 (s, 6H-10). ¹³C NMR (101 MHz, CDCl₃) δ 178.6 (C-1), 160.3 (C-5), 156.1 (C-2), 133.5 (C-3), 115.5 (C-4), 58.7 (C-9), 26.5 (C-8/12), 25.9 (C-8/12), 18.5 (C-11), 17.1 (C-7), -4.5 (C-6), -5.2 (C-10). **HRMS**: *m*/*z* calculated for C₁₈H₃₄O₃Si₂Na [M+Na]⁺ 377.1938, found 377.1939. **IR**: v (cm⁻¹) 3346, 2954, 2885, 1743, 1683, 1505, 1253, 813.

18-Si-е



Chemical Formula: C₁₂H₂₄O₄Si₃ Molecular Weight: 316.5750

$\label{eq:2.1} 3-(1,1,1,3,5,5,5-heptamethyltrisiloxan-3-yl) fur an -2-carbaldehyde$

Prepared according to **GP2** from the reaction of the PMP-imine **14a** (81 mg, 0.40 mmol) and HSiMe(OTMS)₂ (100 μ L, 0.60 mmol) at 120 °C for 4.5 h. The crude mixture was quantified by ¹H NMR, providing 54% NMR yield of the C3-silylated PMP-imine **18a**-*Si*-**e** and 23% of the bis-silylated imine **18a**-*Si*-**e**_b. The crude was hydrolyzed following the detailed procedure and purified by silica-gel column chromatography [eluent (99/1) to (95/5) pentane/Et₂O], to afford 65 mg of the silylated aldehyde **18**-*Si*-**e** (51% yield) as a yellow liquid. ¹H NMR (300 MHz,



20-Si-c

Chemical Formula: C₁₈H₃₄O₃Si₂ Molecular Weight: 354.6370 CDCl₃) δ 9.79 (d, J = 0.8 Hz, 1H-1), 7.66 (dd, J = 1.5, 0.8 Hz, 1H-5), 6.57 (d, J = 1.5 Hz, 1H-4), 0.34 (s, 3H-6), 0.13 (s, 18H-7). These data are in good agreement with those reported in literature.^[121]

¹H NMR (300 MHz, CDCl₃) δ 9.82 (s, 1H-1), 6.78 (s, 1H-4), 0.33 (s,

3H-6/6'), 0.32 (s, 3H-6/6'), 0.12 (d, *J* = 1.4 Hz, 36H-7).

18-Si-е



Chemical Formula: C₁₉H₄₄O₆Si₆ Molecular Weight: 537.0650

19-Si-е

5-methyl,3-(1,1,1,3,5,5,5-heptamethyltrisiloxan-3-yl)furan-2carbaldehyde



Chemical Formula: C₁₃H₂₆O₄Si₃ Molecular Weight: 330.6020

Prepared according to **GP2** from the reaction of PMP-imine **15a** (86 mg, 0.40 mmol) and HSiMe(OTMS)₂ (100 µL, 0.60 mmol) at 120 °C for 4.5 h. The crude mixture was quantified by ¹H NMR, providing 84% NMR yield of the C3-silylated PMP-imine **19a**-*Si*-e. The crude was hydrolyzed following the detailed procedure and purified by silica-gel column chromatography [eluent (99/1) to (95/5) pentane/Et₂O], to afford 111 mg of the silylated aldehyde **19**-*Si*-e (83% yield) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 9.65 (s, 1H-1), 6.18 (q, *J* = 1.0 Hz, 1H-4), 2.40 (d, *J* = 1.0 Hz, 3H-8), 0.31 (s, 3H-6), 0.13 (s, 3H-7), 0.12 (s, 15H-7). ¹³C NMR (101 MHz, CDCl₃) δ 178.3 (C-1), 158.7 (C-5), 155.3 (C-2), 135.1 (C-3), 114.2 (C-4), 13.8 (C-8), 2.0 (C-7), 1.9 (C-7), 1.5 (C-6). HRMS: *m/z* calculated for C₁₃H₂₆O₄Si₃Na [M+Na]⁺ 353.1031, found 353.1032. IR: v (cm⁻¹) 2958, 1682, 1509, 1251, 1221, 836, 753.

5-methyl,3-(1,1,1,3,5,5,5-heptamethyltrisiloxan-3-yl)furan-2carbaldehyde

20-Si-e



Chemical Formula: C₁₉H₄₀O₅Si₄ Molecular Weight: 460.8640

18-Si-f



Chemical Formula: C₁₈H₁₆O₂Si Molecular Weight: 292,4090 Prepared according to **GP2** from the reaction of PMP-imine **16a** (138 mg, 0.40 mmol) and HSiMe(OTMS)₂ (100 µL, 0.60 mmol) at 120 °C for 4.5 h. The crude mixture was quantified by ¹H NMR, providing 64% NMR yield of the C3-silylated PMP-imine **20a**-*Si*-e. The crude was hydrolyzed following the detailed procedure and purified by silica-gel column chromatography [eluent (99/1) to (95/5) pentane/Et₂O], to afford 105 mg of the silylated aldehyde **20**-*Si*-e (57% yield) as a yellow liquid. ¹H NMR (400 MHz, CDCl₃) δ 9.71 (d, *J* = 3.3 Hz, 1H-1), 6.44 (t, *J* = 0.9 Hz, 1H-4), 4.74 (t, *J* = 2.0 Hz, 2H-8), 0.92 (s, 9H-11), 0.32 (s, 3H-6), 0.12 (m, 18H-7), 0.11 (s, 6H-9). ¹³C NMR (101 MHz, CDCl₃) δ 178.8 (C-1), 160.5 (C-5), 155.5 (C-2), 133.9 (C-3), 114.1 (C-4), 58.7 (C-8), 25.9 (C-11), 18.5 (C-10), 1.9 (C-7), 1.5 (C-6), -5.2 (C-9). HRMS: *m*/z calculated for C₁9H₄₀Na₁O₅Si₄ [M+Na]⁺ 483.1846, found 483.1845.

3-(methyldiphenylsilyl)furan-2-carbaldehyde

Prepared according to GP2 from the reaction of PMP-imine 14a (138 mg, 0.40 mmol) and HSiMePh₂ (100 µL, 0.60 mmol) at 120 °C for 4.5 h. The crude mixture was quantified by ¹H NMR, providing 35% NMR yield of the C3-silylated PMP-imine 18a-Si-f. The crude was hydrolyzed following the detailed procedure and purified by silica-gel column chromatography [eluent (99/1) to (95/5) pentane/Et₂O], to afford 8 mg of the silvlated aldehyde 18-Si-f (7% yield) as a yellow liquid, and in a second fraction 11 mg of the bis-silvlated aldehyde **18-Si-f**_b (6% yield) as a yellow solid ¹H NMR (400 MHz, CDCl₃) δ 9.35 (s, 1H-1), 7.76 – 7.67 (m, 1H-5), 7.55 – 7.50 (m, 5H-Ar), 7.44 – 7.41 (m, 2H-8), 7.41 – 7.37 (m, 5H-Ar), 6.50 (d, J = 1.6 Hz, 1H-4), 0.90 (s, 4H-6). ¹³C NMR (101 MHz, CDCl₃) δ 178.9 (C-1), 156.9 (C-2), 147.2 (C-5), 135.0 (C-8), 134.7 (C-7), 130.4 (C-3), 130.2 (C-10), 128.4 (C-9), 119.0 (C-4), -2.5 (C-6). **HRMS**: m/z calculated for C₁₈H₁₆O₂SiNa [M+Na]⁺ 315.0812, found 315.0812. **IR**: v (cm⁻¹) 3069, 2955, 2925, 1428, 1304, 1026, 763, 699.

5,3-bis(methyldiphenylsilyl)furan-2-carbaldehyde



¹**H** NMR (400 MHz, CDCl₃) δ 9.42 (s, 1H-1), 7.60 – 7.48 (m, 10H-Ar), 7.43 – 7.32 (m, 10H-Ar), 6.74 (s, 1H-4), 0.86 (s, 6H-6,6'). δ **HRMS**: m/z calculated for C₃₁H₂₈O₂Si₂Na, [M+Na]⁺ 511.1520, found 511.1522. **IR**: v (cm⁻¹) 2926, 2854, 1680, 1429, 1264, 1112, 941, 793, 732.

Chemical Formula: C₃₁H₂₈O₂Si₂ Molecular Weight: 488.7330



18-Si-g_b



Chemical Formula: C₁₃H₁₄O₂Si Molecular Weight: 230.3380

3-(dimethyl(phenyl)silyl)furan-2-carbaldehyde

Prepared according to GP2 from the reaction of PMP-imine 14a (81mg, 0.40 mmol) and HSiMe₂Ph (100 µL, 0.60 mmol) at 120 °C for 4.5 h. The crude mixture was quantified by ¹H NMR, providing 14% NMR yield of the C3-silylated PMP-imine 18-Si-g; the amount of bis-silylated imine 18-Si-g_b could not be determined due to signal overlapping. The crude was hydrolyzed following the detailed procedure and purified by silicagel column chromatography [eluent (99/1) to (95/5) pentane/Et₂O]. 7 mg of the silvlated aldehyde 18-Si-g (9% yield) was isolated as a yellow liquid, and in a second fraction 13 mg of the bis-silvlated aldehyde 18-Si-g_b (12% yield) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 9.58 (s, 1H-1), 7.67 (d, J = 1.5 Hz, 1H-5), 7.59 – 7.51 (m, 2H-8), 7.39 (m, 3H-9/10), 6.51 (d, J = 1.6 Hz, 1H-4), 0.62 (s, 6H-6). ¹³C NMR (101 MHz, CDCl₃) δ 179.1 (C-1), 156.6 (C-2), 147.1 (C-5), 136.7 (C-7), 134.0 (C-8), 131.5 (C-3), 129.8 (C-10), 128.2 (C-9), 118.4 (C-4), -1.8 (C-6). **HRMS**: m/z calculated for C₁₃H₁₄O₂SiNa [M+Na]⁺ 253.0654, found 253.0655. **IR**: v (cm⁻¹) 2922, 2852, 2192, 2139, 1971, 1686, 1634, 1540, 1377, 1251, 1112, 810.

5,3-bis(dimethyl(phenyl)silyl)furan-2-carbaldehyde



Chemical Formula: C₂₁H₂₄O₂Si₂ Molecular Weight: 364.5910

¹**H** NMR (400 MHz, CDCl₃) δ 9.62 (s, 1H-1), 7.56 (td, J = 7.5, 2.0 Hz, 4H-8/13), 7.46 – 7.34 (m, 6H-Ar), 6.68 (s, 1H-4), 0.59 (s, 6H-6 or 11), 0.59 (s, 6H-6 or 11). ¹³**C** NMR (101 MHz, CDCl₃) δ 179.4 (C-1), 134.0 (C-8/13), 133.9 (C-8/13), 129.8(C-9/10/14/15), 129.5(C-9/10/14/15), 128.4 (C-4), 128.04 (C-9/10/14/15), 128.0 (C-9/10/14/15), -2.0 (C-6/11), -3.1 (C-6/11). *13C 164.90, 160.50 and 130.49 ppm correlation observed by HMBC for C5, C2 and C3 position respectively and correlation at 137.00 ppm corresponding to C7 and C12. HRMS: m/z calculated for C₂₁H₂₄O₂Si₂Na [M+Na]⁺387.1207, found 387.1209. IR: v (cm⁻¹) 2926, 2853, 1682, 1536, 1453, 1318, 1250, 1111, 943, 835, 810.

(5-(dimethoxymethyl)furan-2-yl)triethylsilane

Prepared according to GP2 from the reaction of acetal 10 (137 mg, 0.40 mmol) and HSiEt₃ (100 µL, 0.60 mmol) at 120 °C for 8 h. The reaction mixture was allowed to cool to room temperature, aqueous HCl (1 mL, 1 M) was added and it was then stirred for 1 h. The layers were separated and the aqueous one was extracted 3 times with Et₂O. The combined organics were washed with brine, dried over MgSO₄ and concentrated under reduced pressure (600 mbar, 40 °C for 10-20 min). The residue was purified by silica-gel column chromatography [eluent (95/5) pentane/ether then to (90/10) pentane/Et₂O; solvent evaporation at 40 °C under 600 mbar for around 10-20 min], to afford 29mg of 11 as a yellow oil (27% yield). ¹**H NMR** (400 MHz, CDCl₃) δ 6.59 (d, J = 3.2 Hz, 1H-4), 6.40 (dd, J = 3.2, 0.8 Hz, 1H-3), 5.46 (d, J = 0.8 Hz, 1H-1), 3.33 (s, 6H-8), 1.03 - 0.91 (t, J = 7.7 Hz, 9H-7), 0.76 (qd, J = 7.8, 1.1 Hz, 6H-6). ¹³C NMR (101 MHz, CDCl₃) δ 158.6 (C-5), 155.3(C-2), 121.2 (C-4), 108.4 (C-3), 98.4 (C-1), 52.8 (C-8), 7.4 (C-7), 3.3 (C-6). HRMS: m/z calculated for C₁₃H₂₄O₃SiNa [M+Na]⁺ 279.1387, found 279.1387. IR: v (cm⁻¹) 2949, 2837, 1653, 1419; 1110.

1-benzyl-3-(triethylsilyl)-1H-pyrrole-2-carbaldehyde

11

24-Si-a



Chemical Formula: C₁₃H₂₄O₃Si Molecular Weight: 256.4170



Chemical Formula: C₁₈H₂₅NOSi Molecular Weight: 299.4890

Prepared according to GP2 from the reaction of PMP-imine 17a (138 mg, 0.40 mmol) and HSiEt₃ (100 µL, 0.60 mmol) at 120 °C for 24 h. The reaction mixture was allowed to cool to room temperature, aqueous HCl (2 mL, 1 M) was added, and the mixture was stirred for 1 h. The layers were separated and the aqueous phase was extracted 3 times with Et₂O. The combined organics were washed with brine, dried over MgSO₄ and concentrated (600 mbar, 40 °C for 20 min). The crude was purified by silica-gel column chromatography [eluent (95/5) pentane/ether then to (90/10) pentane/Et₂O; solvent evaporation at 40 °C under 600 mbar for around 10-20 min], to afford 292 mg of 22-Si-a as a yellow oil (49% yield). ¹**H NMR** (400 MHz, CDCl₃) δ 9.70 (d, J = 1.1 Hz, 1H-1), 7.34 – 7.23 (m, 3H-11/12), 7.16 – 7.10 (m, 2H-10), 7.00 (dd, J = 2.4, 1.0 Hz, 1H-5), 6.36 (d, J = 2.4 Hz, 1H-4), 5.62 (s, 2H-8), 1.02 - 0.94 (m, 9H-7), 0.88 - 0.78 (m, 6H-6). ¹³C NMR (101 MHz, CDCl₃) δ 180.5 (C-1), 137.9 (C-9), 135.8 (C-2), 133.3 (C-3), 131.6 (C-5), 128.8 (C-11/12), 127.7 (C-11/12), 127.3 (C-10), 117.7 (C-4), 52.4 (C-8), 7.6 (C-7), 5.0 (C-6). IR: v (cm⁻¹) 2952 2910, 2874, 1655, 1618, 1395, 1171, 1004, 716.

(E)- 3,3-dimethyl-1-(triethylsilyl) but-1-ene



21

Chemical Formula: C₁₂H₂₆Si Molecular Weight: 198.4250 Prepared from the reaction of the 3,3-dimethyl propene (130 µL, 1.0 mmol) and HSiEt₃ (120 µL, 0.75 mmol) at 120 °C in the presence of Ru₃(CO)₁₂ (17.3 mg, 0.025 mmol) in toluene (1.0 mL) for 7 h. The crude mixture was concentrated and analyzed by ¹H NMR and the colorless liquid, seemed to contain 150.4 mg (99% yield) of the product **21**. ¹H **NMR** (400 MHz, CDCl₃) δ 6.04 (d, J = 19.1 Hz, 1H-1), 5.42 (d, J = 19.1 Hz, 1H-2), 1.00 (s, 9H-5), 0.96 – 0.88 (m, 9H-4), 0.55 (m, 6H-3). These data are in good agreement with those reported in literature.^[126]

S4.2 Silylation through directed metalation

23-Si-m

2-(trimethylsilyl)benzaldehyde



Chemical Formula: C₁₀H₁₄OSi Molecular Weight: 178.3060

According to reported procedures,^[28] *N*,*N*,*N*-trimethylethylene diamine (0.467 mL, 3.6 mmol, 1.2 equiv.) was placed in a flame-dried round bottom flask under argon in THF (12 mL) at -78 °C. n-BuLi (1.56 mL, 3.6 mmol, 1.2 equiv.) was added dropwise at this temperature and the mixture was allowed to stir for 15 min. Freshly distilled benzaldehyde (319 mg, 3.0 mmol, 1 equiv.) was then added at -78 °C. The mixture was stirred for 15 min and then n-BuLi (5.77 mL, 9.0 mmol, 3 equiv.) was added at -23 °C. The reaction mixture was kept at this temperature for 3 h, then cooled again to -78 °C prior to the addition of TMSCI (2.3 mL, 18 mmol, 6 equiv.). The mixture was then allowed to reach room temperature over 30 min. The subsequent reaction mixture was poured onto brine (20 mL) and stirred vigorously before being extracted with Et₂O (x 3), dried over MgSO₄ and concentrated under reduced pressure. Purification by silica-gel column chromatography (99/ 1 pentane/ Et₂O) afforded 400 mg of 23-Si-m (75% yield) as a yellow liquid. ¹H NMR (300 MHz, CDCl₃) δ 10.17 (s, 1H-1), 7.93 – 7.87 (m, 1H-Ar), 7.75 – 7.68 (m, 1H-Ar), 7.61 – 7.51 (m, 2H-Ar), 0.36 (s, 9H-8). These data are in good agreement with those reported in literature.^[287]

23-Si-a

2-(triethylsilyl)benzaldehyde

According to reported procedures,^[28] *N*,*N*,*N*-trimethylethylene diamine (0.467 mL, 3.6 mmol, 1.2 equiv.) was placed in a flame-dried round bottom flask under argon in THF (12 mL) at -78 °C. *n*-BuLi (1.56 mL, 3.6 mmol, 1.2 equiv.) was added dropwise at this temperature and the mixture was allowed to stir for 15 min. Freshly distilled benzaldehyde (319 mg, 3.0 mmol, 1 equiv.) was then added at -78 °C. The mixture was stirred for 15 min and then *n*-BuLi (5.77 mL, 9.0 mmol, 3 equiv.) was added at -23 °C. The reaction mixture was kept at this temperature for 3 h, then cooled again at -78 °C prior to the addition of TESCI (3.0 mL, 18 mmol, 6 equiv.). The mixture was then allowed to reach room temperature over 30 min. The subsequent reaction mixture was stirred vigorously with 20 mL brine and extracted with three times with diethyl ether, dried over MgSO₄ and concentrated under reduced pressure. Purification by silica-gel column chromatography (99/ 1 pentane/ Et₂O)



Chemical Formula: C₁₃H₂₀OSi Molecular Weight: 220.3870

afforded 471 mg of **23-***Si***-m** (71% yield-as a yellow liquid. ¹**H NMR** (300 MHz, CDCl₃) δ 10.21 (s, 1H-1), 7.96 – 7.91 (m, 1H-7), 7.70 – 7.65 (m, 1H-4), 7.55 (m, 2H-5,6), 0.93 (m, 15H-8,9). These data are in good agreement with those reported in literature.^[288]

S5. Preparation of furfuryl alcohols

S5.1 Furyl-alkyl alcohols

General procedure GP3: In a flame-dried round bottom flask under argon, was placed the appropriate C3-silylated furfuraldehyde and dissolved in freshly distilled THF (0.3 M). The solution was cooled to -78 °C and then *n*-BuLi (1.2 equiv.) was added dropwise. The reaction mixture was allowed to stir at -78 °C for 30 min and then quenched with an aqueous sat NH₄Cl/NH₃ = 2:1 solution. The mixture was diluted with Et₂O and the aqueous phase was extracted three times. The combined organics were washed with brine, dried over MgSO₄, filtered, concentrated under reduced pressure and purified by silica-gel column chromatography.

140a-Si-a



Chemical Formula: C₁₅H₂₈O₂Si Molecular Weight: 268.4720

1-(3-(triethylsilyl)furan-2-yl)pentan-1-ol

Prepared according to **GP3** from C3-silylated aldehyde **18**-*Si*-**a** (367 mg, 1.75 mmol). Purification by silica-gel column chromatography yielded 461 mg of **140a**-*Si*-**a** (98% yield) as a yellow liquid. ¹H NMR (400 MHz, CDCl₃) δ 7.42 (d, *J* = 1.7 Hz, 1H-5), 6.28 (d, *J* = 1.7 Hz, 1H-4), 4.62 (t, *J* = 7.1 Hz, 1H-1), 1.99 – 1.78 (m, 2H-6), 1.71 (s, 1H-OH), 1.42 – 1.11 (m, 4H-7, 8), 1.01 – 0.93 (m, 9H-11), 0.89 (t, *J* = 7.2 Hz, 3H-9), 0.82 – 0.68 (m, 6H-10). ¹³C NMR (101 MHz, CDCl₃) δ 160.9 (C-2), 141.7 (C-5), 115.2 (C-4), 111.9 (C-3), 68.5 (C-1), 36.1 (C-6), 28.2 (C-7), 22.6 (C-8), 14.1 (C-9), 7.5 (C-11), 4.3 (C-10). HRMS: *m/z* calculated for C₁₅H₂₈O₂SiNa [M+Na]⁺ 291.1751, found 291.1751. IR: v (cm⁻¹) 3350, 2955, 2875, 1756, 1678, 1416, 1127, 1016, 724.

140a-Si-c

1-(3-(tert-butyldimethylsilyl)furan-2-yl)pentan-1-ol



Chemical Formula: C₁₅H₂₈O₂Si Molecular Weight: 268.4720 Prepared according to **GP3** from C3-silylated aldehyde **18**-*Si*-**c** (209 mg, 0.992 mmol). Purification by silica-gel column chromatography, yielded 176 mg of **140a**-*Si*-**c** (66% yield) as a yellow oil. ¹**H NMR** (400 MHz, CDCl₃) δ 7.41 (d, *J* = 1.7 Hz, 1H-5), 6.29 (d, *J* = 1.8 Hz, 1H-4), 4.65 (dd, *J* = 7.7, 6.4 Hz, 1H-1), 2.00 – 1.78 (m, 2H-6), 1.34 (m, 4H-7, 8), 0.89 (s, 12H-12, 9), 0.25 (s, 3H-10), 0.22 (s, 3H-10). ¹³**C NMR** (101 MHz, CDCl₃) δ 161.0 (C-2), 141.4 (C-5), 115.5 (C-4), 112.5 (C-3), 68.3 (C-1), 36.1 (C-6), 28.2 (C-7), 26.5 (C-12), 22.6 (C-8), 17.1 (C-11), 14.1 (C-9), -4.4 (C-10), -4.7 (C-10). **HRMS**: *m/z* calculated for C₁₅H₂₈O₂SiNa [M+Na]⁺ 291.1751, found 291.1751. **IR**: v (cm⁻¹) 3401, 2955, 2929, 2857, 1662, 1510, 1464, 1390, 1250, 1133, 832.

140a-Si-d

153a-Si-d



Chemical Formula: C₁₈H₂₆O₂Si Molecular Weight: 302.4890 Prepared according to **GP3** from C3-silylated aldehyde **18**-*Si*-**d** (256 mg, 0.992 mmol). Purification by silica-gel column chromatography, yielded 200 mg of **140a**-*Si*-**d** (61% yield) as a yellow oil. ¹**H NMR** (400 MHz, CDCl₃) δ 7.41 (d, *J* = 1.8 Hz, 1H-5), 7.24 – 7.15 (m, 2H-13/14), 7.12 – 7.05 (m, 1H-15), 6.98 – 6.91 (m, 2H-13/14), 6.27 (d, *J* = 1.7 Hz, 1H-4), 4.39 (t, *J* = 7.0 Hz, 1H-1), 2.26 (d, *J* = 2.0 Hz, 2H-11), 1.89 – 1.66 (m, 2H-6), 1.37 (s, 1H-OH), 1.34 – 1.23 (m, 3H-7, 8), 1.12 (tdd, *J* = 13.2, 6.5, 4.5 Hz, 1H-7), 0.88 (t, *J* = 7.1 Hz, 3H-9), 0.28 (s, 3H-10), 0.25 (s, 3H-10). ¹³C **NMR** (101 MHz, CDCl₃) δ 161.3 (C-2), 141.7 (C-5), 139.8 (C-12), 128.4 (C-13/14), 128.3 (C-13/14), 124.5 (C-15), 114.6 (C-4), 112.8 (C-3), 68.3 (C-1), 35.7 (C-6), 28.1 (C-7), 27.0 (C-11), 22.7 (C-8), 14.1 (C-9), -2.0 (C-10), -2.0 (C-10). **HRMS**: *m/z* calculated for C₁₈H₂₆O₂SiNa [M+Na]⁺ 325.1595, found 325.1594. **IR**: v (cm⁻¹) 3367, 2929, 2861, 1684, 1575, 1494, 1453, 1377, 1251, 1186, 1109, 1033, 964, 890, 824, 795, 763, 699, 630, 558, 479, 413.

1-(3-(benzyldimethylsilyl)-5-methylfuran-2-yl)pentan-1-ol

1-(3-(benzyldimethylsilyl)furan-2-yl)pentan-1-ol



Chemical Formula: C₁₉H₂₈O₂Si Molecular Weight: 316.5160 Prepared according to **GP3** from C3-silylated aldehyde **19**-*Si*-**d** (1.121 g, 4.33 mmol). Purification by silica-gel column chromatography, yielded 1.03 g of **153a**-*Si*-**d** (75% yield) as a yellow oil. ¹**H NMR** (400 MHz, CDCl₃) δ 7.20 – 6.92 (m, 5H-Ph), 6.20 (s, 1H-4), 4.40 (t, *J* = 6.6 Hz, 1H-1), 2.29 (s, 3H-6), 2.26 (s, 2H-12), 1.86 – 1.67 (m, 2H-7), 1.36 – 1.11 (m, 4H-8, 9), 0.88 (t, *J* = 7.2 Hz, 3H-10), 0.25 (d, *J* = 8.5 Hz, 6H, H-11). ¹³**C NMR** (101 MHz, CDCl₃) δ 159,6 (C-5), 151,4 (C-2), 139.9 (C-13), 128.4 (C-14/15), 128.3 (C-14/15), 124.4 (C-16), 119.8 (C-3), 110.5 (C-4), 68.6 (C-1), 35.5 (C-7), 28.1 (C-8), 27.0 (C-12), 22.6 (C-9), 14.1 (C-10), 13.3 (C-6), -2.1 (C-11). **HRMS**: *m*/*z* calculated for C₁₉H₂₈O₂SiNa [M+Na]+: 339.1751, found 339.1752. **IR**: v (cm⁻¹) 3409, 3024, 2956, 1678, 1250, 994, 699, 479.

141-Si-m



Chemical Formula: C₁₄H₂₄OSi Molecular Weight: 236.4300

141-*Si*-a



Chemical Formula: C₁₇H₃₀OSi Molecular Weight: 278.5110 Prepared according to **GP3** from C3-silylated aldehyde **23**-*Si*-**m** (0.171 g, 0.96 mmol). Purification by silica-gel column chromatography, yielded 80 mg of **141**-*Si*-**m** (35% yield) as a colourless oil. ¹**H NMR** (300 MHz, CDCl₃) δ 7.55 (d, *J* = 7.7 Hz, 1H), 7.49 (dd, *J* = 7.4, 1.5 Hz, 1H), 7.41 (td, *J* = 7.6, 1.5 Hz, 1H), 7.26 (s, 4H), 4.90 (dd, *J* = 8.8, 4.1 Hz, 1H-1), 1.92 – 1.47 (m, 4H-9,10), 1.44 – 1.23 (m, 5H-11, OH), 0.91 (t, *J* = 7.1 Hz, 4H-12), 0.35 (s, 9H-8).

1-(3-(triethylsilyl)benzyl-2-yl)pentan-1-ol

11-(3-(trimethylsilyl)benzyl-2-yl)pentan-1-ol

Prepared according to **GP3** from C3-silylated aldehyde **23**-*Si*-**a** (0.471 g, 2.14 mmol). Purification by silica-gel column chromatography, yielded 1.03 g of **141**-*Si*-**a** (59% yield) as a colourless oil. ¹**H NMR** (300 MHz, CDCl₃) δ 7.59 – 7.53 (m, 1H-7), 7.48 – 7.37 (m, 2H-5,6), 7.30 – 7.22 (m, 1H-4), 4.84 (dt, *J* = 9.2, 3.4 Hz, 1H-1), 1.90 – 1.76 (m, 1H-10), 1.63 (dd, *J* = 12.5, 3.2 Hz, 2H-OH, 10), 1.44 – 1.27 (m, 4H-11,12), 1.01 – 0.81 (m, 18H-8,9,13).

140H-Si-a

(3-(triethylsilyl)furan-2-yl)methanol



Chemical Formula: C₁₁H₂₀O₂Si Molecular Weight: 212.3640

140iPr-Si-a



Chemical Formula: C₁₄H₂₆O₂Si Molecular Weight: 254.4450 Following a reported procedure,^[211] a solution of the silylated aldehyde **18**-*Si*-**a** (54 mg, 0.256 mmol, 1 equiv.) in methanol (1.0 mL,) was cooled to 0 °C. NaBH₄ (10 mg, 0.26 mmol, 1 equiv.) was added and the mixture was allowed to stir at this temperature for 4 h. The reaction mixture was concentrated and then partitioned in Et₂O / water. The aqueous phase was extracted 3 times with Et₂O, and the combined organics were dried over MgSO₄ and concentrated under reduced pressure. The crude was purified by silica-gel column chromatography [eluent (90/ 10) pentane/ Et₂O] to afford 15 mg of **140H-***Si***-a** (28% yield) as a yellow oil. ¹**H NMR** (400 MHz, CDCl₃) δ 7.44 (d, *J* = 1.7 Hz, 1H-5), 6.32 (d, *J* = 1.8 Hz, 1H-4), 4.60 (d, *J* = 5.9 Hz, 2H-1), 1.64 (t, *J* = 6.0 Hz, 1H-OH), 0.96 (t, *J* = 7.8 Hz, 9H-7), 0.76 (qd, *J* = 7.7, 1.1 Hz, 6H-6). ¹³**C NMR** (101 MHz, CDCl₃) δ 158.7 (C-2), 142.2 (C-5), 115.5 (C-4), 113.1 (C-3), 58.1 (C-1), 7.5 (C-7), 4.2 (C-6).

2-methyl-1-(3-(triethylsilyl)furan-2-yl)propan-1-ol

To an Et₂O (2.0 mL) solution of the silylated aldehyde **18**-*Si*-**a** (100 mg, 0.475 mmol) at -30 °C, was added dropwise *i*-PrMgCl (0.26 mL, 0.52 mmol, 1.0 M). The reaction mixture was stirred at this temperature for 5 h, then quenched with a aqueous saturated NH₄Cl. The aqueous phase was extracted 3 times with Et₂O; the combined organics were dried over MgSO₄ and concentrated under reduced pressure. The crude was purified by silica-gel column chromatography [eluent (90/ 10) pentane/ Et₂O] to afford 32 mg of **140***i***Pr-***Si***-a** (27% yield) as a yellow oil. ¹**H NMR** (400 MHz, CDCl₃) δ 7.41 (d, *J* = 1.7 Hz, 1H-5), 6.28 (d, *J* = 1.7 Hz, 1H-4), 4.22 (dd, *J* = 8.7, 5.0 Hz, 1H-1), 2.23 – 2.13 (m, 1H-8), 1.76 (d, *J* = 5.7 Hz, 1H-OH), 1.10 (d, *J* = 6.6 Hz, 3H-9/9'), 0.96 (td, *J* = 7.8, 2.5 Hz, 9H-7), 0.81 – 0.69 (m, 9H-6, 9/9'). ¹³C NMR (101 MHz, CDCl₃) δ 160.4 (C-2), 141.6 (C-5), 115.1 (C-4), 112.7 (C-3), 74.2 (C-1), 33.9 (C-8), 19.4 (C-9/9'), 19.3 (C-9/9'), 7.5 (C-7), 4.3 (C-6).

S5.2 Furyl-aryl alcohols

General procedure GP4: In a flame-dried round bottom flask under argon, was placed the appropriate C3-silylated furfuraldehyde (**18-Si-d and 19-Si-d**) and dissolved in freshly distilled THF (0.2 M solution). The solution was cooled to 0 °C, then PhMgBr (1.3 equiv.) was added dropwise (the rate of

addition was equal or lower than 0.125 mL/min). The mixture was allowed to stir at 0 °C for 1 h, then allowed to reach room temperature for another 2 h. The reaction mixture was quenched with a solution of saturated NH_4Cl , CH_2Cl_2 was added and the aqueous phase was extracted three times with CH_2Cl_2 . The combined organics were dried over Na_2SO_4 , filtered, concentrated under reduced pressure and purified by silica-gel column chromatography.

140b-Si-d



Chemical Formula: C₂₀H₂₂O₂Si Molecular Weight: 322.4790

(3-(benzyldimethylsilyl)furan-2-yl)(phenyl)methanol

Prepared according to **GP4** from C3-silylated aldehyde **18**-*Si*-**d** (244 mg, 1.00 mmol). Purificationby silica-gel column chromatography [eluent (5/1 to 1/1) cyclohexane/ethyl acetate] yielded 268 mg of **140b**-*Si*-**d** (80% yield) as a yellow oil. ¹**H NMR** (400 MHz, CDCl₃) δ 7.26 (d, J = 1.8 Hz, 1H-5), 7.21 – 7.09 (m, 5H-Ph), 7.06 (td, J = 7.7, 1.8 Hz, 2H-Ph), 6.95 (dd, J = 8.3, 6.4 Hz, 1H-Ph), 6.84 – 6.78 (m, 2H-Ph), 6.15 (d, J = 1.8 Hz, 1H-4), 5.45 (d, J = 5.0 Hz, 1H-1), 2.15 (d, J = 3.2 Hz, 2H-7), 1.79 (dd, J = 5.3, 1.7 Hz, 1H-OH), 0.15 (d, J = 4.4 Hz, 6H-6). ¹³**C NMR** (101 MHz, CDCl₃) δ 159.7 (C-2), 142.4 (C-5), 141.2 (C-8/12), 139.7 (C-8/12), 128.5 (CH-Ph), 128.4 (CH-Ph), 127.8 (CH-Ph), 126.5 (CH-Ph), 124.5 (CH-Ph), 114.8(C-4), 113.9 (C-3), 70.1 (C-1), 27.0 (C-7), -1.9 (C-6), -2.0 (C-6). **HRMS**: *m*/z calculated for C₂₀H₂₂O₂SiH [M+H]⁺: 323.1462, found 323.1465. **IR**: v (cm⁻¹) 3377, 3025, 2956, 1599, 1493, 1451, 1250, 1206, 1154, 1129, 1017, 895. 820, 792, 751, 696, 629, 557, 479, 418.

153b-Si-d



Chemical Formula: C₂₁H₂₄O₂Si Molecular Weight: 336.5060

(3-(benzyldimethylsilyl)-5-methylfuran -2-yl)(phenyl)methanol

Prepared according to **GP4** from C3-silylated aldehyde **19**-*Si*-**d** (78 mg, 0.30 mmol). Purificationby silica-gel column chromatography [eluent (5/1 to 1/1) cyclohexane/ethyl acetate] yielded 96 mg of **153b**-*Si*-**d** (71% yield) as a light-yellow oil. ¹**H NMR** (400 MHz, CDCl₃) δ 7.26 – 7.23 (m, 4H-Ph), 7.24 – 7.17 (m, 2H-Ph), 7.16 (s, 1H-Ph), 7.06 – 7.00 (m, 1H-Ph), 6.93 – 6.88 (m, 2H-Ph), 5.82 (q, *J* = 1.0 Hz, 1H-4), 5.47 (d, *J* = 5.1 Hz, 1H-1), 2.21 (d, *J* = 2.6 Hz, 2H-8), 2.18 (d, *J* = 1.0 Hz, 3H-6), 1.91 (d, *J* = 5.1 Hz, 1H-OH), 0.20 (d, *J* = 3.8 Hz, 6H-7). ¹³**C NMR** (101 MHz, CDCl₃) δ 158.0 (C-2), 152.2 (C-5), 141.5 (C-13), 139.8 (C-9),

128.5 (CH-Ph), 128.4 (CH-Ph), 128.4 (CH-Ph), 127.6 (CH-Ph), 126.6 (CH-Ph), 124.6 (CH-Ph), 115.1 (C-3), 110.7 (C-4), 70.1 (C-1), 26.9 (C-8), 13.4 (C-6), -1.9 (C-7), -2.0 (C-7). **HRMS** *m*/*z* calculated for $C_{21}H_{24}O_2SiH$ [M+H]⁺ 337.1618, found 337.1620. **IR**: v (cm⁻¹) 3377, 3025, 2956, 1599, 1493, 1250, 895, 751, 557, 479.

S5.3 Furyl-allyl alcohol

153c-Si-d



Chemical Formula: C₁₈H₂₄O₂Si Molecular Weight: 300.4730

1-(3-(benzyldimethylsilyl)furan-2-yl)but-3-en-1-ol

In a flame-dried round bottom flask under argon, was placed C3silvlated furfuraldehyde **19-Si-d**, (258 mg, 1.0 mmol) and freshly distilled THF (10 mL, 0.1 M solution). The solution was cooled to 0 °C, then allyl magnesium bromide (4.28 mL, 1.30 mmol, 0.7 M) was added dropwise. The mixture was allowed to stir at 0 °C for 1 h and then allowed to reach room temperature for another 20 h. The reaction mixture was quenched with a saturated solution of NH₄Cl and then diluted with CH₂Cl₂. The aqueous phase was extracted three times with 30 mL CH₂Cl₂. The combined organics were dried over MgSO₄, filtered, and concentrated under reduced pressure. Purification of the residue by silica-gel column chromatography [eluent (80/ 20) cyclohexane/ethyl acetate] afforded 300 mg of 153c-Si-d (70% yield) as a light-yellow oil. ¹**H NMR** (400 MHz, CDCl₃) δ 7.20 (t, J = 7.4 Hz, 2H-11), 7.08 (t, J =7.4 Hz, 1H-12), 6.95 (d, J = 7.4 Hz, 2H-10), 5.85 (q, J = 1.0 Hz, 1H-4), 5.67 (m, 1H-14), 5.13 - 5.04 (m, 2H-15), 4.36 (ddd, J = 7.8, 6.0, 4.5 Hz)1H-1), 2.61 – 2.42 (m, 2H-13), 2.28 (d, J = 1.0 Hz, 3H-6), 2.24 (s, 2H-8), 1.55 (d, J = 4.5 Hz, 1H-OH), 0.23 (s, 3H-7), 0.21 (s, 3H-7). ¹³C NMR (101 MHz, CDCl₃) δ 158.8 (C-2), 151.7 (C-5), 139.9 (C-9), 134.4 (C-14), 128.5 (C-10/11), 128.3 (C-10/11), 124.4 (C-12), 118.1 (C-15), 114.4 (C-3), 110.6 (C-4), 67.6 (C-1), 40.6 (C-13), 27.0 (C-8), 13.4 (C-6), -2.0 (C-7), -2.0 (C-7). **HRMS** m/z calculated for C₁₈H₂₄O₂SiH $[M+H]^+$ 301.1618, found 301.1618. **IR**: v (cm⁻¹) 3424, 3080, 2954, 1642, 1493, 1337, 1250, 994, 828, 558, 479.

S5.4 Furyl-pyrrol alcohol

168



Chemical Formula: C₁₉H₂₃NO₂Si Molecular Weight: 325.4830





Chemical Formula: C₁₈H₂₁NO₂Si Molecular Weight: 311.4560

(3-(benzyldimethylsilyl)-5-methylfuran-2-yl)(1H-pyrrol-1yl)methanol

Following a reported procedure,^[227] in a flame-dried Schlenk tube was placed pyrrole (7 µL, 0.10 mmol) in freshly distilled toluene (1 mL) at 0 °C. n-BuLi (60 µL, 0.095 mmol) was slowly added at 0 °C, then allowed to reach room temperature for 5 min. The solution was cooled to -78 °C prior to the addition of the silvlated aldehyde 19-Si-d (26 mg, 0.10 mmol) dissolved in toluene (0.2 mL) and allowed to stir 30 min at this temperature. The reaction mixture was then quenched with a solution of acetic acid (1 M in THF) at -78 °C, then allowed to reach room temperature for 30 min, filtered over a silica-gel pad (20 mm) and eluted with ethyl acetate. The mixture was concentrated under reduced pressure and the residue purified by silica-gel column chromatography [eluent pentane/Et₂O (80/ 20)] to afford 21 mg of 168 (66% yield) as a yellow oil. ¹**H NMR** (400 MHz, CDCl₃) δ 7.20 (t, J = 7.5 Hz, 2H-10/9), 7.09 (t, J = 7.4 Hz, 1H-11), 6.94 (d, J = 7.4 Hz, 2H-10/9), 6.74 (t, J = 2.1 Hz, 2H-13), 6.16 (m, 3H-1,14), 5.92 (s, 1H-4), 3.00 (d, J = 6.8 Hz, 1H-OH), 2.31 (s, 3H-12), 2.23 (s, 2H-7), 0.21 (s, 3H-6), 0.16 (s, 3H-6). ¹³C NMR (101 MHz, CDCl₃) δ 153.4 (C-2), 152.3 (C-5), 139.5 (C-8), 128.5 (C-9), 128.4 (C-10), 124.5 (C-11), 119.2 (C-13), 116.3 (C-3,) 111.3 (C-4), 109.2 (C-14), 77.6 (C-1), 26.5 (C-7), 13.4 (C-12), -2.4 (C-6), -2.2 (C-6).

(3- (benzyldimethylsilyl)-furan-2-yl)(1H-pyrrol-1-yl) methanol

Prepared according to the same procedure as **168** from C3-silylated aldehyde **18**-*Si*-**d** (74 mg, 0.30 mmol). Purification by silica-gel column chromatography [eluent cyclohexane/ EtOAc (90/10)] afforded 28 mg of **167** (30% yield) as a yellow oil. ¹**H NMR** (400 MHz, CDCl₃) δ 7.47 (s, 1H-5), 7.20 (t, *J* = 7.4 Hz, 2H-10), 7.09 (t, *J* = 7.3 Hz, 1H-11), 6.93 (d, J = 7.5 Hz, 2H-9), 6.72 (q, J = 2.0 Hz, 2H-12), 6.33 (s, 1H-4), 6.17 (d, J = 2.3 Hz, 2H-13), 2.95 (d, *J* = 6.9 Hz, 1H-OH), 2.25 (s, 2H-7), 0.25 (d, J = 3.8 Hz, 3H-6), 0.19 (s, 3H-6). **HRMS**:

m/z calculated for $C_{18}H_{21}NO_2SiNa$ [M+Na]⁺ 334.1234, found 334.2352. **IR**: v (cm⁻¹) 3356, 3024, 2957, 2924, 2854, 1754, 1678, 1600, 1378, 1251, 826, 700.

S6. Attempts for silvl migration: Brook rearrangement

Brook rearrangement on benzylic alcohol

142

1-(2-allylphenyl)pentan-1-ol

To a dry microwave vial in the glovebox, was placed the corresponding CuI (29 mg, 0.15 mmol) and *t*-BuOLi (29 mg, 0.36 mmol). The vial was sealed, then removed from the glovebox. Previously degassed DMF (1.0 mL), was added and allowed to stir 10 min at 0 °C, after which **141**-*Si*-**a** (92 mg, 0.33 mmol) in DMF (2.0 mL) was degassed by freeze-pump thaw (3 times), and cannulated under argon followed by the addition of allyl chloride (29 μ L, 0.36 mmol). The mixture was stirred at 30 °C for 2 h. Then, was quenched with aqueous NH₃ (10 mol%), extracted with Et₂O, 3 times, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude was analyzed and quantified by ¹H NMR using Me₂SO₂ as internal standard (72% NMR yield). The mixture was washed twice with HCl (1 M), then NaCl to afford then the product **142-a**.

The same protocol was applied to **142-Si-m** on a (63 mg, 0.27 mmol) scale to afford **142-m** with 71% NMR yield.

¹**H NMR** (400 MHz, CDCl₃) δ 7.43 (dd, J = 7.5, 1.7 Hz, 1H-9), 7.22 – 7.14 (m, 2H-8, 7), 7.14 – 7.06 (m, 1H-6), 5.92 (ddt, J = 16.5, 10.1, 6.2 Hz, 1H-4), 5.01 (dq, J = 10.1, 1.6 Hz, 1H-5), 4.93 (dq, J = 17.1, 1.8 Hz, 1H-5), 4.88 (dd, J = 8.1, 5.0 Hz, 1H-10), 3.46 – 3.31 (m, 2H-3), 1.76 – 1.57 (m, 2H-11), 1.47 – 1.36 (m, 1H-12), 1.35-1.23 (m, 3H-12/13), 1.21 (s, 1H-OH) 0.83 (t, J = 7.1 Hz 3H-14). ¹³C **NMR** (101 MHz, CDCl₃) δ 143.0 (C-1), 137.7 (C-4), 136.4 (C-2), 129.9 (C-6), 127.4 (C-7/8), 126.9 (C-7/8) 125.8 (C-9), 115.9 (C-5), 70.3 (C-10), 38.2 (C-11), 36.8 (C-3), 28.4 (C-12), 22.7 (C-13), 14.1 (C-14).





Chemical Formula: C14H20O

Molecular Weight: 204.3130

Mixture of products A/B/C/D



To a dry microwave vial in the glovebox, was placed the corresponding CuI (51 mg, 0.27 mmol) and t-BuOLi (22 mg, 0.27 mmol). The vial was sealed, then removed from the glovebox. Previously degassed THF (1.0 mL), was added and allowed to stir 10 min at 30 °C, after which 140-Sia (43 mg, 0.16 mmol) in THF (1.0 mL) was degassed by freeze-pump thaw (3 times), and cannulated under argon and allowed to stir 10 min. Previously degassed HMPA (1.5 mL) was added, and stir 10 min, afterwhich, allyl chloride (0.37 mL, 0.45 mmol) was added and let to stir at 80 °C overnight. The reaction mixture was quenched with aqueous NH₃ (10 mol%), extracted with Et₂O, 3 times, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude was analyzed and quantified by ¹H NMR using Me₂SO₂ as internal standard. 70% conversion of the substrate 140-Si-a was observed, as well as A (11%), **B** (4%), **C** (4%) and **D** (6%) The crude was attempted for purification by silica-gel chromatography [eluent pentane/Et₂O (99/ 1) to (98/2)] to afford 24 mg of a fraction containing all A, B, C and D.



Chemical Formula: C₁₈H₃₂O₂Si Molecular Weight: 308.5370

Characteristic peak for the compound A (145a-*Si*-a): ¹H NMR (400 MHz, CDCl₃) δ 7.45 (d, J = 1.7 Hz, 1H-5), 6.28 (d, J = 1.8 Hz, 1H-4), 5.86 (m, 1H-11), 5.23 (dq, J = 17.3, 1.7 Hz, 1H-12), 5.13 (dq, J = 10.4, 1.5 Hz, 1H-12), 4.33 (t, J = 7.0 Hz, 1H-1), 3.90 – 3.76 (m, 2H-10), 2.07 – 1.90 (m, 1H-6), 1.82 – 1.64 (m, 1H-6). ¹³C NMR (101 MHz, CDCl₃) δ . 159.2 (C-2), 141.9 (C-5), 135.2 (C-11), 116.5 (C-12), 114.9 (C-4), 75.2 (C-1), 69.1 (C-10), 33.9 (C-6).



B Chemical Formula: C₁₅H₂₆O₂Si Molecular Weight: 266.4560



C Chemical Formula: C₁₈H₃₂OSi Molecular Weight: 292.5380



Chemical Formula: C₁₈H₃₂O₂Si Molecular Weight: 308.5370

Characteristic peak for the compound B (146): ¹H NMR (400 MHz, CDCl₃) δ 7.53 (d, *J* = 1.6 Hz, 1H-5), 6.53 (d, *J* = 1.6 Hz, 1H-4), 2.94 – 2.86 (t, *J*= 7.4 Hz, 2H-6), 2.07 – 2.01 (q, *J* = 6.0 Hz, 1H-7). ¹³C NMR (101 MHz, CDCl₃) δ 194.3 (C-1).

Characteristic peak for the compound C (147): ¹H NMR (400 MHz, CDCl₃) δ 7.55 (d, J = 1.6 Hz, 1H-5), 6.55 (d, J = 1.6 Hz, 1H-4), 5.73 (m, 1H-11), 5.03 – 4.88 (m, 2H-12), 3.52 (tt, J = 8.0, 5.8 Hz, 1H-1), 2.46 (m, 1H-10), 2.31 – 2.20 (m, 1H-10). ¹³C NMR (101 MHz, CDCl₃) δ 144.6 (C-5), 136.1 (C-11), 118.8 (C-4), 116.5 (C-12), 46.3 (C-1).

Characteristic peak for the compound D (144a-*Si*-a): ¹H NMR (400 MHz, CDCl₃) δ 7.27 (s, 1H-5), 6.18 (s, 1H-4), 5.86 (m, 1H-11), 5.28 – 5.12 (m, 2H-12), 4.66 (t, *J* = 7.1 Hz, 1H-1), 3.18 (d, 6.3 Hz, 2H-10), 0.51 (q, *J* = 7.9 Hz, 6H-13). ¹³C NMR (101 MHz, CDCl₃) δ 151.8 (C-2), 140.8 (C-5), 136.9 (C-11), 117.9 (C-3), 115.5 (C-12), 111.8 (C-4), 66.8 (C-1), 37.1 (C-6), 29.2 (C-10), 7.48 (C-14), 4.78 (C-13).



Figure S17. 1H NMR of the crude reaction mixture



Figure S18. 13C NMR of the crude reaction mixture

HRMS B: m/z calculated for C₁₅H₂₂O₂Si₁Na₁ [M+Na]⁺289.1600, found 289.1595

HRMS A and D: calculated for $C_{18}H_{32}O_2Si_1Na_1$ [M+Na]⁺ 331.2064, found 331.2063.

1-(3-allylfuran-2-yl)pentan-1-ol

The fraction containing a mixture of A, B, C and D was treated with TBAF in THF (0.2 mL, 0.2 mmol, 1 M) and allowed to stir 2 h at room temperature. The reaction mixture was diluted with 1 mL H₂O, then extracted 3 times with Et_2O , and the combined organic phase was dried over MgSO₄, filtered and concentrated under reduced pressure.

Characteristic peak for the compound: ¹**H NMR** (400 MHz, CDCl₃) δ 7.30 (s, 1H-1), 6.21 (s, 1H-2), 5.90 (ddt, J = 16.6, 10.8, 6.3 Hz, 1H-11), 5.09 – 5.00 (m, 2H-12), 4.75 – 4.68 (m, 1H-5), 3.19 (d, J = 6.3 Hz, 2H-10). ¹³**C NMR** (101 MHz, CDCl₃) δ 151.4 (C-4), 141.4 (C-1), 137.1 (C-11), 119.1 (C-3), 115.7 (C-12), 112.3 (C-2), 68.5 (C-5), 29.2 (C-10). Purification by silica-gel column chromatography [eluent pentane/ Et₂O (98/2)] afforded 11 mg of **159ab** (estimated to 8% yield, contaminated with pentane and silyl residuals) as a yellow oil.

Other attempts of Brook rearrangement on furfurylic alcohol

To a dry microwave vial in the glovebox, was placed the corresponding CuX and *t*-BuOM salt. The vial was sealed, then removed from the glovebox. Previously degassed solvent was added and allowed to stir 10 min at 0 °C, after which **140a**-*Si*-**a** in the corresponding solvent was degassed by freeze-pump thaw (3 times), and cannulated under argon. Allyl chloride, was then added, and stirred at the respective temperature for 2 h. The reaction mixture was quenched with aqueous NH₃ (10 mol%), extracted with Et₂O, 3 times, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude was analyzed and quantified by ¹H NMR using Me₂SO₂ as internal standard.



159ab

Chemical Formula: C₁₂H₁₈O₂ Molecular Weight: 194.2740

Table S25. Other trials for Brook's rearrangement



144.

145-

Entry	x (equiv.)	m (equiv.)	n (equiv.)	Т (•С)	Solvent	Additives	Conversion (%)	Si-a (%)	Si-a (%)	146 (%)	147 (%)
1	1.2	1.2	1.2	30	THF/ HMPA (1.5/1. 5)	-	20%		_	-	-
2	2	2	2	30	THF/ DMPU (12/1)		29%		9	_	_
3	1.2	1.2 (<i>n</i> -BuLi)	0.5	30	DMF/ THF (3 mL/ 0.6 mL)	LiCl (1.2 equiv)	53%	_	traces	-	-
4	1.2	1.2	0.5	30	DMF	LiCl (1.2 equiv)	48%		5%	traces	traces
5	1.2	1.2 (<i>t</i> -BuOK)	0.5 (CuCl)	30	DMF (3.0 mL)	-	37%	-	5%	10%	
6	1.6	1.2	1.2	60	DMF		23%	_			
7	2	2	2	30	THF/ DMPU (12/1)		29%	-	_	_	-

S7. Fluoride mediated cross-coupling of furfuryl alcohols

S7.1 Preparation of TBAF(t-BuOH)₄

TBAF(*t*-**BuOH**)4According to a reported procedure, [226] a commercially available
anhydrous THF solution of TBAF (1M, 10 mL, 10 mmol) was
concentrated. Then *t*BuOH (30 mL) was added, followed by *n*-hexane
(6 mL). The mixture was stirred for 30 min at 90 °C, cooled to room
temperature, and concentrated to ~half of the solution upon which the
formation of a white crystalline solid was observed. The solid was
filtered using a Büchner funnel and washed with *t*-BuOH rapidly. The



Chemical Formula: C₃₂H₇₆FNO₄ Molecular Weight: 557.9614

solid was kept under vacuum for 15–20 min and recovered. 5.3 g of TBAF(*t*-BuOH)₄ (95% yield) was obtained as white crystals. ¹**H NMR** (400 MHz, CDCl₃) δ 3.49 ppm (t, *J* = 9.0 Hz, 8H-1), 1.67- 1.71 (m, 8H-2), 1.44-1.48 (m, 8H-3), 1.27 (s, 36H-6), 1.01 (t, *J* =9.0 Hz, 12H-4). ¹⁹**F NMR** (376 MHz, CDCl₃) δ 109.08. These data are in good agreement with those reported in literature.^[226]

S7.2 Preparation of CuI•P(OEt)3

CuI•P(OEt)₃



According to a reported procedure,^[289] Triethyl phosphite (92 µL, 0.535 mmol, 1.05 equiv.) and copper(I) iodide (99 mg, 0.519 mmol, 1.0 equiv.) were added to benzene (10 mL) at room temperature and let stir overnight. The solvent was removed in vacuum and the residue was washed with benzene (10 mL) over a Büchner funnel. 142 mg of CuI•P(OEt)₃ (77% yield) were obtained as a white crystalline powder ¹H NMR (400 MHz, CDCl₃) δ 4.12 (q, *J* = 7.2 Hz, 6H-1), 1.29 (t, *J* = 7.2 Hz, 9H-2). These data are in good agreement with those reported in literature.^[289]

S7.3 Preparation of CuI•PPh₃

CuI•PPh₃

Chemical Formula: $C_{18}H_{15}CuPh$

Molecular Weight: 452.7422

According to a reported procedure,^[290] triphenylphosphine (161 mg, 0.525 mmol) was dissolved in acetonitrile (2.0 mL) at 35 °C and added to a solution of copper(I) iodide (100 mg, 0.525 mmol) in acetonitrile (10.0 mL) at the same temperature. After a few seconds the iodo(triphenylphosphine)copper complex started to precipitate. The mixture was stirred for 1 h. The solid was filtered over a Büchner funnel, washed with acetonitrile (20.0 mL), and vacuum-dried. 231 mg of CuI•PPh₃ (97% yield) were obtained as a white crystalline powder.³¹P-NMR (161 MHz, CDCl₃) δ -49.46. These data are in good agreement with those reported in literature.^[290]

S7.4 Hiyama-type cross-coupling allylation and alkylation reactions S7.4.1 Activation of silylated furfuryl alcohols

158



Chemical Formula: C₁₁H₁₈O₂Si Molecular Weight: 210.3480

3-butyl-1,1-dimethyl-1,3-dihydrofuro[3,2-c][1,2]oxasilole

To a THF solution (0.2 M) of furfuryl alcohol **140a**-*Si*-**d** (32 mg, 0.104 mmol) was added TBAF•3H₂O (35 mg, 0.11 mmol) and the mixture was stirred under argon overnight. It was then concentrated and analyzed by NMR. ¹**H NMR** (400 MHz, CDCl₃) δ 7.26 (s, 1H-5), 6.22 (s, 1H-4), 4.81 (t, *J* = 7.2 Hz, 1H-1), 1.83 (m, 2H-7) 1.29 (m, 3H-8/9), 1.14 (m, 1H-9), 0.85 (t, *J* = 6.9 Hz, 3H-10), 0.26 (s, 3H-6), 0.22 (s, 3H-6). ¹³C NMR (101 MHz, CDCl₃) δ 164.3 (C-2), 139.8 (C-5), 115.3 (C-3), 114.3 (C-4), 66.7 (C-1), 35.0 (C-7), 28.3 (C-8), 22.9 (C-9), 13.8 (C-10), 2.3 (C-6). **HRMS**: *m*/*z* calculated for C₁₁H₁₉O₂Si [M+H]⁺ 211.1149, found 211.1147.

3-butyl-1,1,5-trimethyl-1,3-dihydrofuro[3,2-c][1,2]oxasilole

To a THF- d_8 (0.5 mL) solution of **153a**-*Si*-**d** (32 mg, 0.10 mmol) was added TBAF•3H₂O (35 mg, 0.11 mmol) and the mixture was stirred under argon overnight. The mixture was analyzed by ¹H NMR what evidenced the formation of 89% of oxasilole **155** and 85% of toluene. ¹H NMR (400 MHz, THF- d_8) δ 5.80 (s, 1H-4), 4.77 (t, *J* = 7.0 Hz, 1H-1), 2.24 (s, 3H-11), 1.83 (q, *J* = 7.2 Hz, 2H-7), 1.41 – 1.16 (m, 4H-8/9), 0.93 (t, *J* = 7.0 Hz, 3H-10), 0.23 (s, 3H-6), 0.17 (s, 3H-6). ¹³C NMR (101 MHz, THF- d_8) δ 164.3 (C-2), 149.3 (C-5), 117.2 (C-3), 111.1 (C-4), 67.6 (C-1), 36.3 (C-7), 29.5 (C-8/9), 23.9 (C-8/9), 14.8 (C-10), 13.5 (C-11), 2.9 (C-6), 2.3 (C-6). IR: v (cm⁻¹) 3727, 2963, 2877, 2360, 2341, 1653, 912, 735.



Chemical Formula: C₁₂H₂₀O₂Si Molecular Weight: 224.3750

S7.4.2 Copper-mediated cross-coupling allylation and alkylation reactions



General procedure GP5: CuI•PPh₃ (20 mol% or 120 mol%) was introduced in a flame-dried microwave vial which was then placed under argon atmosphere and sealed. In a Schlenk-tube, the appropriate C3-silylated furfuryl alcohol (1 equiv.) was dissolved in CH_2Cl_2 (1 mL), concentrated under reduced pressure and placed under argon. DMF (0.1 M) was added and the solution was degassed by doing 3 freeze-pump thaw cycles. TBAF(*t*-BuOH)₄ was then added along with the corresponding electrophile, E–X (3 equiv.). The mixture was stirred for 2–3 min at room temperature, then cannulated into the vial containing the copper complex. The mixture was stirred for 2 h at 30 °C, then quenched with aqueous KOH (6 M, 1 mL). The mixture was extracted with cyclohexane/CH₂Cl₂ (9/1) (4 ×10 mL), the combined organics were washed with water (10 mL), dried over MgSO₄ and concentrated under reduced pressure. The residue was first analyzed by 1H NMR spectroscopy using Me₂SO₂ as internal standard and then purified by silica-gel column chromatography.

159aa

1-(5-methyl-3-(2-methylallyl)furan-2-yl)pentan-1-ol



Chemical Formula: C₁₄H₂₂O₂ Molecular Weight: 222.3280 Prepared according to **GP5** from C3-silylated alcohol **153a**-*Si*-**d** (95 mg, 0.30 mmol) and methallyl chloride (88 mL, 0.90 mmol) using CuI•PPh₃ (27 mg, 0.060 mmol). The crude was analyzed by ¹H NMR and the product quantified using dimethyl sulfone as internal standard providing 84% NMR yield of **159aa** and 1% of proto-desilylated product **153a**-H. The crude was purified by silica-gel column chromatography [eluent (90/10) pentane/Et₂O] to afford 52 mg of **159** (78% yield), as a pale-yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 5.78 (s, 1H-4), 4.73 (m, 2H-1), 4.61 (m, 1H-12), 3.06 (s, 2H-10), 2.24 (s, 3H-14), 1.95 – 1.77 (m, 2H-6), 1.71 (br. s, 4H-13, OH), 1.39 – 1.15 (m, 4H-8/7), 0.88 (d, *J* = 7.2 Hz, 3H-9). ¹³C NMR (101 MHz, CDCl₃) δ 150.8 (C-5), 150.0 (C-2), 145.0 (C-11), 119.8 (C-3), 111.2 (C-12), 108.4 (C-4), 66.1 (C-1), 35.5 (C-6), 33.5 (C-10), 28.1 (C-7), 22.6 (C-8), 22.4 (C-13), 14.1 (C-9), 13.7 (C-14). HRMS *m*/*z* calculated for C₁₄H₂₂O₂H [M+H]⁺: 223.1693, found 223.1693. **IR**: v (cm⁻¹) 3360, 3076, 1642, 1575, 1251, 993, 914, 416.

<u>Note</u>: The compound **159aa**, was also obtained according to **GP5**, from **153a**-*Si*-**d** (95 mg, 0.30 mmol). In this case, CuI•PPh₃ (204 mg, 0.45 mmol), it afforded 79% NMR yield and 43 mg (65% yield) of **159aa** upon purification was obtained.

1-(3-(2-methylallyl)furan-2-yl)pentan-1-ol

Prepared according to **GP5** from C3-silylated alcohol **140a**-*Si*-**d** (91 mg, 0.30 mmol) and methallyl chloride (88 mL, 0.90 mmol) using CuI•PPh₃ (27 mg, 0.060 mmol). Purification by silica-gel column chromatography [eluent (90/10) pentane/Et₂O] afforded an inseparable mixture of products containing **160aa** (42% NMR yield quantified with dimethyl sulfone as internal standard) and the protodesilylated product (28% NMR yield quantified with dimethyl sulfone as internal standard). NMR characterization of **160aa** and **140a**-H was possible from this mixture:

160aa: ¹**H NMR** (400 MHz, CDCl₃) δ 7.30 (d, J = 1.8 Hz, 1H-5), 6.20 (d, J = 1.8 Hz, 1H-4), 4.78 (s, 1H-12), 4.70 (s, 1H-12), 4.66 (q, J = 4.4 Hz, 1H-1), 3.12 (s, 2H-10), 1.96 – 1.81 (m, 2H-6), 1.79 (d, J = 4.9 Hz, 1H-OH), 1.71 (t, J = 1.1 Hz, 3H-13), 1.47 – 1.12 (m, 4H-7, 8), 0.89 (dt, J = 9.3, 7.1 Hz, 3H-9). ¹³**C NMR** (101 MHz, CDCl₃) δ 151.8 (C-2), 144.8 (C-11), 141.2 (C-5), 119.0 (C-3), 112.5 (C-12), 111.4 (C-4), 66.2 (C-1), 35.5 (C-10), 33.3 (C-6), 28.0 (C-7), 22.4 (C-8), 14.1 (C-9). **HRMS** m/z calculated for C₁₃H₂₀O₂H [M+H]⁺: 209.1536, found 209.1535. **IR**: v (cm⁻¹) 3340, 2932, 1653, 1509, 1145, 997, 735.

1-(furan-2-yl)pentan-1-ol (140a-H): ¹H NMR (400 MHz, CDCl₃) δ 7.37 (dd, J = 1.9, 0.8 Hz, 1H-5), 6.32 (dd, J = 3.3, 1.8 Hz, 1H-4), 6.22 (d, J = 3.2 Hz, 1H-3), 4.67 (m, 1H-1), 1.97 – 1.81 (m, 2H-6), 1.47 – 1.13 (m, 4H-7, 8), 0.89 (m, 3H-9). These data are in good agreement with those reported in literature.^[291]

1-(5-methyl-3-(2-methylallyl)furan-2-yl)but-3-en-1-ol

160aa



Chemical Formula: C₁₃H₂₀O₂ Molecular Weight: 208.3010

and

140a-H



Chemical Formula: C₉H₁₄O₂ Molecular Weight: 154.2090

159ca



Chemical Formula: C₁₃H₁₈O₂ Molecular Weight: 206.2850 Prepared according to GP5 from C3-silylated alcohol 153c-Si-d (91 mg, 0.30 mmol) and methallyl chloride (88 mL, 0.90 mmol) using CuI•PPh₃ (163 mg, 0.36 mmol). The crude was analyzed by ¹H NMR and the product quantified using dimethyl sulfone as internal standard providing 72% NMR yield of 159ca and 5% of proto-desilvlated product 153a-H The crude was purified by silica-gel column chromatography [eluent (90/10) pentane/Et₂O] to afford 40 mg of **159ca** (65% yield) as a paleyellow oil. ¹**H NMR** (400 MHz, CDCl₃) δ 5.86 – 5.70 (m, 2H-4, 12), 5.24 - 5.06 (m, 2H-13), 4.76 (s, 1H-9), 4.70 (s, 1H-9), 4.69 - 4.62 (m, 1H-1), 3.06 (s, 2H-7), 2.72 – 2.50 (m, 2H-11), 2.25 (d, J = 1.1 Hz, 3H-6), 1.89 (d, J = 4.5 Hz, 1H-OH), 1.70 (s, 3H-10). ¹³C NMR (101 MHz, CDCl₃) & 151.0 (C-5), 149.2 (C-2), 144.9 (C-8), 134.4 (C-13), 120.1 (C-3), 118.2 (C-13), 111.3 (C-9), 108.5 (C-4), 65.3 (C-1), 40.4 (C-11), 33.4 (C-7), 22.4 (C-10), 13.7 (C-6). **HRMS** m/z calculated for C₁₃H₁₈O₂H [M+H]⁺: 207.1380, found 207.1380. **IR**: v (cm⁻¹) 3424, 2954, 1642, 1493, 1155, 915, 762, 699, 629, 558, 479.

159ba



Chemical Formula: C₁₆H₁₈O₂ Molecular Weight: 242.3180

(5-methyl-3-(2-methylallyl)furan-2-yl)(phenyl)methanol

Prepared according to **GP5** from C3-silylated alcohol **153b**-*Si*-**d** (101 mg, 0.30 mmol) and methallyl chloride (88 mL, 0.90 mmol) and using CuI-PPh₃ (27 mg, 0.060 mmol). The crude was purified by silica-gel column chromatography [eluent (90/ 10) pentane/Et₂O] to afford 40 mg of **159ba** (56% yield) as a yellow liquid and 22 mg of **159ba**_a (25% yield) as a yellow oil.

159ba: ¹**H NMR** (400 MHz, CDCl₃) δ 7.25 (d, J = 7.4 Hz, 2H-12), 7.17 (t, J = 7.5 Hz, 2H-13), 7.13 – 7.07 (m, 1H-14), 5.63 (d, J = 3.7 Hz, 2H-1, 4), 4.62 – 4.51 (m, 2H-9), 2.87 (s, 2H-7), 2.17 (s, 1H-OH), 2.04 (s, 3H-6), 1.51 (s, 3H-10). ¹³**C NMR** (101 MHz, CDCl₃) δ 151.5 (C-5), 148.8 (C-2), 144.8 (C-8), 141.6 (C-11), 128.4 (C-13), 127.6 (C-14), 126.5 (C-12), 120.6 (C-3), 111.4 (C-9), 108.7 (C-4), 68.2 (C-1), 33.5 (C-7), 22.4 (C-10), 13.7 (C-6). **HRMS** *m*/*z* calculated for C₁₆H₁₈O₂H

[M+H]⁺: 243.1380, found 243.1380. **IR**: v (cm⁻¹) 3391, 2995, 1600, 1493, 1145, 888, 732, 479.



Chemical Formula: C₂₀H₂₄O₂ Molecular Weight: 296.4100

159ba_a: ¹**H NMR** (400 MHz, CDCl₃) δ 7.30 – 7.21 (m, 5H-12,13,14), 5.73 (s, 1H-4), 5.34 (s, 1H-1), 4.91 (s, 1H-9), 4.85 (s, 1H-9), 4.71 (s, 1H-17), 4.65 (s, 1H-17), 3.83 (s, 2H-15), 3.02 (s, 2H-7), 2.14 (s, 3H-6), 1.69 (s, 3H-18), 1.62 (s, 3H-10). ¹³**C NMR** (101 MHz, CDCl₃) δ 151.7 (C-5), 147.1 (C-2), 144.6 (C-8), 142.3 (C-16), 140.2 (C-11), 128.8 – 127.1 (C-12,13,14), 121.0 (C-3), 112.6 (C-9), 111.6 (C-17), 108.3 (C-4), 73.5 (C-1), 72.3 (C-15), 33.5 (C-7), 22.4 (C-10), 19.8 (C-18), 13.8 (C-6).

160ba



Chemical Formula: C₁₅H₁₆O₂ Molecular Weight: 228.2910

(3-(2-methylallyl)furan-2-yl)(phenyl)methanol

Prepared according to GP5 from C3-silylated alcohol 140b-Si-a (97 mg, 0.30 mmol) and methallyl chloride (88 mL, 0.90 mmol) using CuI-PPh₃ (27 mg, 0.060 mmol). The crude was analyzed by ¹H NMR and the product quantified using dimethyl sulfone as internal standard (45% NMR yield, 10% 161 and 1% protodesilylated product, 140b-H). The crude was purified by silica-gel column chromatography [eluent (90/10) pentane/Et₂O] to afford 40 mg of 160ba (40% yield), as a yellow oil and 5 mg of **161** (10%) as a yellow oil. ¹**H NMR** (400 MHz, CDCl₃) δ 7.39 -7.17 (m, 6H-5,11, 12, 13), 6.15 (d, J = 1.8 Hz, 1H-4), 5.80 (d, J = 4.4Hz, 1H-1), 4.72 (s, 1H-8), 4.64 (s, 1H-8), 3.05 (s, 2H-7), 2.26 (d, J = 5.1Hz, 1H-OH), 1.62 (s, 3H-9). ¹³C NMR (101 MHz, CDCl₃) δ 150.7 (C-2), 144.6 (C-6), 141.8 (C-5), 141.3 (C-10), 128.5 (CH-Ar), 127.8 (CH-Ar), 126.5 (CH-Ar), 119.7 (C-3), 112.7 (C-4), 111.7 (C-8), 68.3 (C-1), 33.4 (C-7), 22.4 (C-9). **HRMS** m/z calculated for C₁₅H₁₆O₂H [M+H]⁺: 229.1223, found 229.1224. **IR**: v (cm⁻¹) 3359, 2915, 1652, 1493, 1177, 891, 699, 418.

furan-2-yl(phenyl)methanone


Chemical Formula: C₁₁H₈O₂ Molecular Weight: 172.1830

159ab

159ac



Chemical Formula: C₁₃H₂₀O₂ Molecular Weight: 208.3010

¹**H** NMR (300 MHz, CDCl₃) δ 7.98 (d, J = 7.2 Hz, 2H-7), 7.71 (dd, J = 1.8, 0.8 Hz, 1H-5), 7.65 – 7.55 (m, 1H-9), 7.50 (tt, J = 6.8, 1.6 Hz, 2H-8), 7.24 (dd, J = 3.6, 0.8 Hz, 1H-4), 6.60 (dd, J = 3.6, 1.7 Hz, 1H-3). These data are in good agreement with those reported in literature.^[292]

1-(3-allyl-5-methylfuran-2-yl)pentan-1-ol

Prepared according to **GP5** from C3-silylated alcohol **153a**-*Si*-**d** (95 mg, 0.30 mmol) and allyl chloride (73 mL, 0.90 mmol) using CuI+PPh₃ (163 mg, 0.36 mmol). The crude was analyzed by ¹H NMR and the product quantified using dimethyl sulfone as internal standard (58% NMR yield) and 12% of proto-desilylated product **153a-H**. The crude was purified by silica-gel column chromatography [eluent (90/10) pentane/Et₂O] to afford 40 mg of **159ab** (64% yield) as a pale-yellow liquid. ¹H NMR (300 MHz, CDCl₃) δ 5.97 – 5.72 (m, 2H-4, 11), 5.12 – 4.87 (m, 2H-12), 4.59 (q, *J* = 7.0 Hz, 1H-1), 3.11 (dd, *J* = 6.3, 1.8 Hz, 2H-10), 2.22 (d, *J* = 2.8 Hz, 3H-13), 1.95 – 1.71 (m, 2H-6), 1.30, (m, 4H-7/8), 0.94 – 0.75 (m, 3H-9). ¹³C NMR (75 MHz, CDCl₃) δ 150.8 (C-2), 149.5 (C-5), 137.2 (C-11), 119.6 (C-3), 115.3 (C-12), 108.1 (C-4), 66.1 (C-1), 35.5 (C-6), 29.2 (C-10), 28.1 (C-7), 22.5 (C-8), 14.1 (C-9), 13.6 (C-13). HRMS *m*/z calculated for C₁₃H₂₀O₂H [M+H]⁺: 209.1536, found 209.1536. **IR**: v (cm⁻¹) 3356, 3079, 2956, 1640, 1574, 1036, 993, 785.

Note: The compound **159ab**, was also obtained according to **GP5**, from **153a**-*Si*-**d** (95 mg, 0.30 mmol). In this case, allyl bromide (78 μ L, 0.90 mmol) was used, which afforded **159ab** (61% NMR yield) and protodesilylated product **153a**-**H** (16%).

The compound **159ab**, was also obtained according to **GP5**, from **153a**-*Si*-**d** (95 mg, 0.30 mmol). In this case, CuI•PPh₃ (27 mg, 0.06 mmol) and allyl bromide (78 μ L, 0.90 mmol) were used, which afforded **159ab** (41% NMR yield).

1-(3,5-dimethylfuran-2-yl)pentan-1-ol



Chemical Formula: C₁₁H₁₈O₂ Molecular Weight: 182.2630 Prepared according to **GP5** from C3-silylated alcohol **153a**-*Si*-**d** (95 mg, 0.30 mmol) and iodomethane (56 mL, 0.90 mmol) using CuI-PPh₃ (27 mg, 0.06 mmol). The crude was analyzed by ¹H NMR and the product **159ac** was quantified using dimethyl sulfone as internal standard (61% NMR yield) and 10% proto-desilylated product **153a**-**H**. The crude was purified by silica-gel column chromatography [eluent (90/10) pentane/Et₂O] to afford 40 mg of **159ac** (64% yield) as a pale-yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 5.77 (s, 1H-4), 4.62 (td, *J* = 7.2, 3.9 Hz, 1H-1), 2.23 (s, 3H-10/11), 1.97 (s, 3H-10/11), 1.95 – 1.76 (m, 2H-6), 1.69 (d, *J* = 4.6 Hz, 1H-OH), 1.41 – 1.12 (m, 4H-7,8), 0.89 (t, *J* = 7.0 Hz, 3H-9). ¹³C NMR (101 MHz, CDCl₃) δ 150.6 (C-2/5), 149.2 (C-2/5), 147.2 (C-3), 109.2 (C-4), 66.2 (C-1), 35.6 (C-6), 28.1 (C-7), 22.6 (C-8), 14.1 (C-4), 13.6 (C-10/11), 9.8 (C-10/11). HRMS *m*/*z* calculated for C₁₁H₁₈O₂H [M+H]⁺: 183.1380, found 183.1379. IR: v (cm⁻¹) 3356, 2956, 1640, 1574, 1036, 993, 736, 698.

<u>Note</u>: The compound **159ac**, was also obtained according to **GP5**, from **153a**-*Si*-**d** (95 mg, 0.30 mmol). In this case, CuI-PPh₃ (163 mg, 0.36 mmol) was used, which afforded **159ac** (51% NMR yield) and protodesilylated product **153a**-**H** (7%). The crude was purified by silica-gel column chromatography [eluent (90/10) pentane/Et₂O] to afford 27 mg of **159ac** (50% yield) as a pale-yellow oil.

159ae_e



Chemical Formula: C₂₄H₂₈O₂ Molecular Weight: 348.4860

3-benzyl-2-(1-(benzyloxy)pentyl)-5-methylfuran

A microwave vial was charged with CuI (71 mg, 0.375 mmol) and TBAF(*t*-BuOH)₄ (334 mg, 0.60 mmol), sealed and flushed with argon. In a Schlenk tube was placed furfuryl alcohol **153a**-*Si*-**d** (79 mg, 0.25 mmol), which was previously dissolved and concentrated in CH₂Cl₂ under inert atmosphere, P(OEt)₃ (64 μ L, 0.375 mmol) and DMF (3.0 mL). The solution was degassed by freeze-pump-thaw and transferred via cannula to the microwave vial under inert conditions and. Freshly distilled benzyl bromide (89 μ L, 0.75 mmol) was added at room temperature and the reaction mixture was allowed to stir at 30 °C for 2 h. It was then quenched with aqueous KOH (6 M, 1 mL) and extracted with cyclohexane/CH₂Cl₂ (9/1), (4 ×10 mL). The combined organics

were washed with water (10 mL), dried over MgSO₄ and concentrated under reduced pressure. The crude was purified by silica-gel column chromatography [eluent (100/1) cyclohexane/EtOAc] to afford 22 mg of **159ae**_e (25% yield) as a pale-yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.36 – 7.12 (m, 10H-Ph), 5.77 (s, 1H-4), 4.49 (d, *J* = 12.1 Hz, 1H-16), 4.36 (t, *J* = 7.3 Hz, 1H-1), 4.28 (d, *J* = 12.1 Hz, 1H-16), 3.75 – 3.61 (m, 2H-10), 2.26 (s, 3H-15), 2.08 – 1.94 (m, 1H-6), 1.91 – 1.78 (m, 1H-6), 1.30 (m, 3H-7, 8), 1.23 – 1.07 (m, 1H-7), 0.87 (t, *J* = 7.1 Hz, 3H-9). ¹³C NMR (101 MHz, CDCl₃) δ 151.5 (C-5), 147.6 (C-2), 140.9 (C-11), 138.9 (C-17), 128.6 (CH-Ph), 128.5 (CH-Ph), 128.4 (CH-Ph), 127.8 (CH-Ph), 127.5 (CH-Ph), 126.2 (CH-Ph), 122.6 (C-3), 108.1 (C-4), 72.4 (C-1), 70.0 (C-16), 34.1 (C-6), 30.9 (C-10), 28.2 (C-7), 22.6 (C-8), 14.1 (C-9), 13.8 (C-15). HRMS *m*/z calculated for C₂₄H₂₈O₂Na [M+Na]⁺: 371.1982, found 371.1982. **IR**: v (cm⁻¹) 2952, 2842, 1266, 1551, 1407, 1112, 1014.

S7.4.3 Pd-catalyzed Hiyama-type arylation of furfuryl alcohols



General procedure GP6: A flame-dried Schlenk tube was charged with CuI (20 mol%) and Pd₂dba₃ (2.5 mol%) and heated gently under vacuum by means of a heat gun. In another Schlenk tube, the appropriate iodoarene (1.7 equiv.) and silylated furfuryl alcohol (1 equiv.) were dissolved in freshly distilled THF. The solution was degassed by 3 cycles of freeze-pump thaw 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 room temperature, then concentrated and filtered through a short pad of silica-gel. Purification of the crude was achieved by silica-gel column chromatography using (90/10) cyclohexane/ethyl acetate as eluent.

156aa 1-(5-methyl-3-phenylfuran-2-yl)pentan-1-ol



Chemical Formula: C₁₆H₂₀O₂ Molecular Weight: 244.3340

Prepared according to **GP6** from C3-silylated alcohol **142-Si-b** (60 mg, 0.19 mmol) and iodobenzene (32 µL, 0.28 mmol). Purification by silicagel column chromatography yielded 34 mg of **156aa** (74% yield) as a yellow oil. ¹**H NMR** (400 MHz, CDCl₃) δ 7.31 – 7.27 (m, 4H-11/12), 7.18 (ddt, *J* = 9.0, 6.5, 3.4 Hz, 1H-13), 6.01 (s, 1H-2), 4.65 (t, *J* = 7.2 Hz, 1H-5), 2.23 (s, 3H-14), 1.95 – 1.71 (m, 3H-6/ O-H), 1.35 – 1.04 (m, 4H-7/8), 0.78 (t, *J* = 7.0 Hz, 3H-9). ¹³**C NMR** (101 MHz, CDCl₃) δ 151.3 (C-1), 149.5 (C-4), 133.8 (C-10), 128.7 (C-11/12), 128.3 (C-11/12), 126.9 (C-13), 124.4 (C-3), 107.7 (C-2), 66.5 (C-5), 35.5 (C-6), 28.2 (C-7), 22.6 (C-8), 14.1 (C-9), 13.6 (C-14). **HRMS** *m*/*z* calculated for C₁₆H₂₀O₂H [M+H]⁺: 245.1535, found 245.1536. **IR**: v (cm⁻¹) 2955, 2857, 1575, 1456, 1289, 1246, 1108, 1015.





Chemical Formula: C₁₇H₂₂O₃ Molecular Weight: 274.3600

1-(3-(4-methoxyphenyl)-5-methylfuran-2-yl)pentan-1-ol

Prepared according to **GP6** from C3-silylated alcohol **142-***Si***-b** (37 mg, 0.12 mmol) and 4-iodoanisole (41 mL, 0.18 mmol). Purification by silica-gel column chromatography yielded 18 mg of **156ab** (57% yield) as a yellow liquid. ¹**H NMR** (400 MHz, CDCl₃) δ 7.31 (d, *J* = 8.3 Hz, 2H-11), 6.93 (d, *J* = 8.4 Hz, 2H-12), 6.07 (s, 1H-4), 4.72 (t, *J* = 7.3 Hz, 1H-1), 3.83 (s, 3H-15), 2.31 (s, 3H-14), 2.06 – 1.77 (m, 2H-6), 1.83 (s, 1H-OH), 1.46 – 1.19 (m, 4H-8,7), 0.88 (t, *J* = 7.0 Hz, 3H-9). ¹³**C NMR** (101 MHz, CDCl₃) δ 158.8 (C-13), 151.1 (C-5), 149.0 (C-2), 129.3 (C-11), 126.3 (C-10), 124.0 (C-3), 114.2 (C-12), 107.8 (C-4), 66.5 (C-1), 55.4 (C-15), 35.5 (C-6), 28.2 (C-7), 22.6 (C-8), 14.1 (C-9), 13.7 (C-14). **HRMS** *m*/*z* calculated for C₁₇H₂₂O₃Na [M+Na]⁺: 297.1461, found 297.1460. **IR**: v (cm⁻¹) 2955, 2857, 2138, 1575, 1456, 1289, 1108, 1015.

S8. Functionalization of C3-silylated furfuraldehydes

S8.1 Halogenation



General procedure GP7: 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 CH₂Cl₂, concentrated, and then NXS (2 equiv.) was added (unless specified). 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. The mixture was stirred at 50 °C overnight (otherwise mentioned). The reaction mixture was filtered through a short pad of silica-gel, which was washed with Et₂O. The filtrate was concentrated under reduced pressure and the residue was purified by silica-gel column chromatography with (90/10) pentane /Et₂O as eluent.

170a



Chemical Formula: C₆H₅ClO₂ Molecular Weight: 144.5540

170b

170c



Chemical Formula: C₆H₅BrO₂ Molecular Weight: 189.0080

3-chloro-5-methylfuran-2-carbaldehyde

Prepared according to **GP7** from C3-silylated furfural **19**-*Si*-**e** (33 mg, 0.10 mmol), *N*-chlorosuccinimide (27 mg, 0.20 mmol) and AgF (25 mg, 0.20 mmol). Purification afforded 2 mg of product **170a** (11% yield) as a yellow oil. ¹**H NMR** (400 MHz, CDCl₃) δ 9.65 (s, 1H-1), 6.24 (d, *J* = 1.1 Hz, 1H-4), 2.40 (d, *J* = 0.8 Hz, 3H-6). ¹³C **NMR** (101 MHz, CDCl₃) δ 174.7 (C-1), 159.7 (C-5), 146.0 (C-2), 129.0 (C-3), 111.2 (C-4), 14.4 (C-6). These data are in good agreement with those reported in literature.^[27]

3-bromo-5-methylfuran-2-carbaldehyde

Prepared according to **GP7** from C3-silylated furfural **19-Si-e** (99 mg, 0.30 mmol), *N*-bromosuccinimide (107 mg, 0.60 mmol) and AgF (76 mg, 0.60 mmol). Purification afforded 18 mg of product **170b** (32% yield) as a yellow oil. ¹**H NMR** (400 MHz, CDCl₃) δ 9.51 (s, 1H-1), 7.18 (s, 1H-4), 2.41 (s, 3H-6). ¹³**C NMR** (101 MHz, CDCl₃) δ 176.7 (C-1), 156.9 (C-5), 151.0 (C-2), 124.4 (C-4), 99.8 (C-3), 12.6 (C-6).These data are in good agreement with those reported in literature.^[293]

3-iodo-5-methylfuran-2-carbaldehyde



Chemical Formula: C₆H₅IO₂ Molecular Weight: 236.0085

169a



Chemical Formula: $C_5H_3CIO_2$ Molecular Weight: 130.5270





Chemical Formula: C₅H₃BrO₂ Molecular Weight: 174.9810 Prepared according to **GP7** from C3-silylated furfural **19-Si-e** (33 mg, 0.10 mmol), *N*-iodosuccinimide (45 mg, 0.20 mmol) and AgF (25 mg, 0.20 mmol). Purification afforded 16 mg of product **170c** (68% yield) as a yellow oil. ¹**H NMR** (400 MHz, CDCl₃) δ 9.51 (s, 1H-1), 6.40 (s, 1H-4), 2.41 (s, 3H-6). ¹³**C NMR** (101 MHz, CDCl₃) δ 176.8 (C-1), 160.5 (C-5), 149.4 (C-2), 117.8 (C-4), 81.2 (C-3), 14.1 (C-6). These data are in good agreement with those reported in literature.^[293]

3-chloro-furan-2-carbaldehyde

Prepared according to **GP7** from C3-silylated furfural **18**-*Si*-**e** (95 mg, 0.30 mmol), *N*-chlorosuccinimide (27 mg, 0.60 mmol) and AgF (76 mg, 0.60 mmol). Purification afforded 31 mg of product **169a** (78% yield) as a yellow oil. ¹**H NMR** (400 MHz, CDCl₃) δ 9.76 (s, 1H-1), 7.67 – 7.59 (m, 1H-5), 6.59 (d, *J* = 1.9 Hz, 1H-4). ¹³**C NMR** (101 MHz, CDCl₃) δ 175.6 (C-1), 147.6 (C-5), 147.1 (C-2), 127.7 (C-3), 114.5 (C-4). **HRMS**: *m/z* calculated for C₅H₃ClO₂H [M+H]⁺ 130.9894, found 130.9892. **IR**: v (cm⁻¹) 3151, 2926, 2855, 1678, 1562,1399, 1275, 1150, 1009, 768.

3-bromo-furan-2-carbaldehyde

Prepared according to **GP7** from C3-silylated furfural **18**-*Si*-**e** (32 mg, 0.10 mmol), *N*-bromosuccinimide (20 mg, 0.10 mmol) and AgF (25 mg, 0.20 mmol) and allowed to stir at 50 °C for 1 h. The crude reaction mixture was purified by PTLC (80/20) pentane/Et₂O to afford 7 mg of product **169b** (40% yield) as a yellow oil. ¹**H NMR** (400 MHz, CDCl₃) δ 9.73 (s, 1H-1), 7.63 (s, 1H-5), 6.66 (t, *J* = 1.5 Hz, 1H-4). ¹³**C NMR** (101 MHz, CDCl₃) δ 176.4 (C-1), 148.3 (C-2), 148.0 (C-5), 116.7 (C-4), 112.6 (C-3). These data are in good agreement with those reported in literature.^[294]

3-iodo-furan-2-carbaldehyde

169c



Chemical Formula: C₅H₃IO₂ Molecular Weight: 221.9815

Prepared according to GP7 from C3-silvlated furfural 18-Si-e (95 mg, 0.30 mmol), N-iodosuccinimide (135 mg, 0.60 mmol) and AgF (76 mg, 0.60 mmol) and allowed to stir at 50 °C for 2 h. Purification afforded 55 mg of product 169c (82% yield) as yellow oil, contaminated with traces of protodesilylated product. ¹H NMR (400 MHz, CDCl₃) δ 9.65 (s, 1H-1), 7.63 (d, J = 1.7 Hz, 1H-5), 6.75 (d, J = 1.7 Hz, 1H-4). ¹³C NMR (101 MHz, CDCl₃) δ 177.5 (C-1), 150.3 (C-2), 148.7 (C-5), 121.1 (C-4), 78.2 (C-3). **HRMS**: m/z calculated for C₅H₃IO₂H [M+H]⁺ 222.9251. found 222.9250. These data are in good agreement with those reported in literature.^[294]

171a



Chemical Formula: C12H19CIO3Si Molecular Weight: 274.8160

171c



Chemical Formula: C₁₂H₁₉IO₃Si Molecular Weight: 366 2705

5-(((tert-butyldimethylsilyl)oxy)methyl)-3-chlorofuran-2carbaldehyde

Prepared according to GP7 from C3-silvlated furfural 20-Si-e (46 mg, 0.10 mmol), N-chlorosuccinimide (53 mg, 0.20 mmol) and AgF (51 mg, 0.40 mmol). The crude reaction mixture was purified by silica-gel column chromatography (80/20 pentane/Et₂O) to afford 22 mg of product **171a** (79% yield) as a yellow oil. ¹H NMR (400 MHz, CDCl3) δ 9.70 (s, 1H-1), 6.47 (t, J = 1.0 Hz, 1H-4), 4.69 (d, J = 1.0 Hz, 2H-6), 0.92 (s, 9H-9), 0.11 (s, 6H-7). ¹³C NMR (101 MHz, CDCl₃) δ 175.3 (C-1), 161.3 (C-5), 146.2 (C-2), 128.9 (C-3), 111.0 (C-4), 58.8 (C-6), 25.9 (C-9), 18.4 (C-8), -5.3 (C-7). HRMS *m/z*: [M+H]⁺ Calculated for C₁₂H₁₉ClO₃SiH 275.0865. Found 275.0866. **IR**: v (cm⁻¹) 2924, 2854, 2167, 2012, 1729, 1684, 1581, 1462, 1257, 1131, 837, 779.

5-(((tert-butyldimethylsilyl)oxy)methyl)-3-iodofuran-2carbaldehyde

Prepared according to GP7 from C3-silvlated furfural 20-Si-e (46 mg, 0.10 mmol), N-iodosuccinimide (78 mg, 0.35 mmol) and AgF (51 mg, 0.40 mmol). Purification afforded 6 mg of product **171c** (16% yield) as a yellow oil. ¹**H NMR** (400 MHz, CDCl₃) δ 9.59 (s, 1H-1), 6.62 (d, J = 1.0 Hz, 1H-4), 4.72 (d, J = 1.0 Hz, 2H-6), 0.92 (s, 9H-9), 0.11 (s, 6H-7). ¹³C NMR (101 MHz, CDCl₃) δ 177.3 (C-1), 162.3 (C-5), 149.5 (C-

2), 117.6 (C-4), 80.0 (C-3), 58.6 (C-6), 25.9 (C-9), 18.4 (C-8), -5.3 (C-7). **HRMS** m/z: [M+H]+ Calculated for C₁₂H₁₉IO₃SiH 367.0221. Found 367.0221. **IR**: v (cm⁻¹) 2925, 2854, 2152, 1980, 1683, 1513, 1463, 1377, 1131, 1100, 781, 444.

S8.2 Arylation / Alkenylation



General procedure GP8: A flame-dried microwave vial was charged with Pd_2dba_3 •CHCl3 (3 mol%) and BINAP (6 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 CH₂Cl₂ 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/Et₂O; solvent evaporation at 40 °C, 500 mbar].

173a



Chemical Formula: C₁₂H₁₀O₂ Molecular Weight: 186.2100

5-methyl-3-phenylfuran-2-carbaldehyde

Prepared according to **GP8** from C3-silylated furfural **19**-*Si*-**e** (95 mg, 0.30 mmol) and iodobenzene (98 mg, 0.45 mmol). The crude was analyzed by ¹H NMR and quantified using dimethyl sulfone as internal standard (83% NMR yield) and 16% of proto-desilylated product **13**. Purification afforded 45 mg of **173a** (81% yield) as a yellow oil. ¹H **NMR** (400 MHz, CDCl₃) δ 9.61 (s, 1H-1), 7.55 – 7.50 (m, 2H-Ph), 7.49 – 7.38 (m, 3H-Ph), 6.37 (s, 1H-4), 2.45 (s, 3H-6). ¹³C NMR (101 MHz, CDCl₃) δ 177.2 (C-1), 159.2 (C-5), 146.9 (C-2), 141.1 (C-3), 131.0 (C-7), 129.2 (CH-Ph), 129.1 (CH-Ph), 129.1 (CH-Ph), 110.7 (C-4), 14.2 (C-6). These data are in good agreement with those reported in literature.^[51]

3-phenylfuran-2-carbaldehyde



Chemical Formula: C₁₁H₈O₂ Molecular Weight: 172.1830 Prepared according to **GP8** from C3-silylated furfural **18**-*Si*-**e** (95 mg, 0.30 mmol) and iodobenzene (98 mg, 0.45 mmol). The crude was analyzed by ¹H NMR and quantified using dimethyl sulfone as internal standard (46% NMR yield). The product was purified by silica-gel column chromatography [eluent pentane/Et₂O (90/10)] to afford 25 mg of **172a** (48% yield) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 9.72 (d, *J* = 0.8 Hz, 1H-1), 7.68 (dd, *J* = 1.8, 0.8 Hz, 1H-5), 7.57 – 7.52 (m, 2H-Ph), 7.49 – 7.41 (m, 3H-Ph), 6.72 (d, *J* = 1.8 Hz, 1H-4). These data are in good agreement with those reported in literature.^{[51],[31]}

5-{[(tert-Butyldimethylsilyl)oxy]methyl}-3-phenylfuran-2carbaldehyde



Chemical Formula: C₁₈H₂₄O₃Si Molecular Weight: 316.4720



174a



Chemical Formula: C₁₄H₁₂O₂ Molecular Weight: 212.2480

Prepared according to **GP8** from C3-silylated furfural **20**-*Si*-**e** (138 mg, 0.30 mmol) and iodobenzene (98.1 mg, 0.45 mmol). The crude was analyzed by ¹H NMR and quantified using dimethyl sulfone as internal standard (27% NMR yield). ¹H NMR (300 MHz, CDCl₃) δ 9.68 (s, 1H-1), 7.62 – 7.52 (m, 2H-Ph), 7.46 (m, 3H-Ph), 6.61 (s, 1H-4), 4.78 (s, 2H-6), 0.95 (s, 9H-13), 0.14 (s, 6H-11). These data are in good agreement with those reported in literature.^[51]

(E)-5-methyl-3-styrylfuran-2-carbaldehyde

Prepared according to **GP8** from C3-silylated furfural **19**-*Si*-**e** (99 mg, 0.30 mmol) and cinnamyl bromide (E/Z=87/13) (58 mg, 0.45 mmol). The product was purified by silica-gel column chromatography [eluent pentane/ Et₂O (90/ 10)] to afford 29 mg of **173b** (45% yield) as a yellow oil. ¹**H NMR** (400 MHz, CDCl₃) δ 9.81 (s, 1H-1), 7.53 (d, J = 7.2 Hz, 3H-Ph,), 7.37 (t, J = 7.5 Hz, 3H-Ph, H7), 7.32 (d, J = 7.4 Hz, 1H-Ph), 7.08 (d, J = 16.2 Hz, 1H-8), 6.49 (s, 1H-4), 2.40 (s, 3H-6). ¹³**C NMR** (101 MHz, CDCl₃) δ 188.9 (C-1), 159.1 (C-5), 147.3 (C-2), 136.4 (C-3), 135.1 (C-8), 134.9 (C-9), 128.9 (CH-Ph), 128.5 (CH-Ph), 127.1 (CH-Ph), 116.8 (C-7), 106.7 (C-4), 14.2 (C-6). These data are in good agreement with those reported in literature.^[51]

172a

(E)-5-methyl-3-styrylfuran-2-carbaldehyde



Prepared according to **GP8** from C3-silylated furfural **19-Si-e** (99 mg, 0.30 mmol) and 2-bromo propene (54 mg, 0.45 mmol). The crude was analyzed by ¹H NMR and quantified using dimethyl sulfone as internal standard (15% NMR yield and 39% of proto-desilylated product, **13**). The product was purified by silica-gel chromatography [eluent pentane/ Et₂O (90/ 10)] to afford 19.3 mg of **173c** of the unseparable mixture was obtained. ¹H NMR (300 MHz, CDCl₃) δ 9.64 (s, 1H-1), 6.21 (s, 1H-4), 5.32 (s, 1H-8), 5.29 (m, 1H-8), 2.38 (s, 3H-6/9), 2.11 (s, 3H-6/9). No further analysis was performed on product to confirm its structure.

S8.3 Alkynylation

175



5-methyl-3-(phenylethynyl)furan-2-carbaldehyde

A microwave vial was charged with AgF (76 mg, 0.60 mmol), Pd₂dba₃•CHCl₃ (5 mg, 0.0045 mmol) and phenylalkynyl bromide (82 mg, 0.45 mmol). The C3-silylated furfuraldehyde 19-Si-e (99 mg, 0.30 mmol) was placed in a Schlenk tube and freshly distilled acetonitrile (3 mL) was added under Ar atmosphere. The mixture was degassed by three freeze-pump-thaw cycles, and transferred via cannula to the microwave vial. The reaction mixture was kept under vigorous stirring overnight at 60 °C. It was then cooled to room temperature, filtered through a silicagel pad, concentrated and analyzed by NMR. Purification by silica-gel column chromatography [eluent, pentane/diethyl ether (90/10)] afforded 14 mg of product 175 (21% yield), containing traces of dba. ¹H NMR (400 MHz, CDCl₃) δ 9.60 (s, 1H-1), 7.31 – 7.15 (m, 5H-Ph), 6.16 (s, 1H-4), 2.27 (s, 4H-6). ¹³C NMR (101 MHz, CDCl₃) δ 175.4 (C-1), 159.3 (C-5), 152.0 (C-2), 134.8 (C-Ph), 131.92-128.53-Ph, 122.1 (C-3), 112.0 (C-4), 97.2 (C-8), 78.7 (C-7), 14.1 (C-6). HRMS: m/z calculated for C₁₄H₁₀O₂Na [M+Na]⁺ 233.0573, found 233.0572. IR: v (cm⁻¹) 3344, 2949, 2839, 2150, 1412, 1160.

173c

S8.4 Allylation

Preparation of CuF(PPh₃)₃: Following a reported procedure, CuF(PPh₃)₃ was prepared.^[252] To a round bottom flask containing CuF₂•2H₂O (2.76 g, 20 mmol), was placed 200 mL methanol. PPh₃ (18.4 g, 70 mmol) was added, then, heated under reflux for 2 h. The mixture was cooled, and half of the solvent was removed under reduced pressure. The solution was cooled to 0 °C and allowed to crystallize overnight. The suspension was filtered, and the solid washed with cold methanol and filtered under vacuum to afford CuF(PPh₃)•2MeOH. The white solid was then placed under reduced vacuum at 90 °C for 2 h, which led to 3.21 g of CuF(PPh₃)₃, **177** (19% over 2 steps). ¹H NMR (300 MHz, CDCl₃) δ 7.41 – 7.28 (m, 15H), 7.27 – 7.14 (m, 9H). ³¹P NMR (162 MHz, CDCl₃) δ 29.02, -3.65. ¹⁹F NMR (376 MHz, CDCl₃) δ -183.81.

<u>Note</u>: The synthesis of CuF(PPh₃)₃•2MeOH (**176**) was performed on a 5 mmol scale, to give 0.789 g (17% yield). ¹**H NMR** (400 MHz,CDCl₃) δ 7.29 (dd, J = 10.6, 6.6 Hz, 15H), 7.18 (t, J = 7.1 Hz, 9H), 3.48 (s, 1H). ³¹**P NMR** (162 MHz, CDCl₃) δ 29.04, -3.22. ¹⁹**F NMR** (376 MHz, CDCl₃) δ -183.99.



R= H, CH₃, CH₂OTBDMS

General procedure GP9: 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 CH₂Cl₂. 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 them 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 Et₂O, and the combined organics were washed with water and dried over Na₂SO₄.

178a 3-allyl-5-methylfuran-2-carbaldehyde



Chemical Formula: C₉H₁₀O₂ Molecular Weight: 150.1770 Prepared according to **GP9** from C3-silylated furfural **19**-*Si*-**e** (99 mg, 0.30 mmol), allyl bromide (78 µL, 0.90 mmol) and CuF(PPh₃)₃ (313 mg, 0.36 mmol). The crude reaction mixture was purified by silica-gel column chromatography (90/10 pentane/Et₂O) to afford 28 mg of product **178a** (62% yield) as a yellow oil. ¹**H NMR** (400 MHz, CDCl₃) δ 9.54 (s, 1H-1), 6.01 (s, 1H-4), 5.82 (ddt, *J* = 16.7, 10.1, 6.5 Hz, 1H-8), 5.09 – 4.97 (m, 2H-9), 3.41 (dt, *J* = 6.5, 1.6 Hz, 2H-7), 2.27 (s, 3H-6). ¹³**C NMR** (101 MHz, CDCl₃) δ 176.8 (C-1), 59.0 (C-5), 147.6 (C-2), 138.2 (C-3), 135.0 (C-8), 117.0 (C-9), 111.5 (C-4), 29.3 (C-7), 14.2 (C-6). **HRMS**: *m*/*z* calculated for C₉H₁₀O₂H [M+H]⁺ 151.0754, found 151.0751. **IR**: v (cm⁻¹).2924, 2852, 1665, 1525, 1414, 1373, 1290, 1199, 993, 839.

5-methyl-3-(2-methylallyl)furan-2-carbaldehyde



178b

178c

Chemical Formula: $C_{10}H_{12}O_2$ Molecular Weight: 164.2040 Prepared according to **GP9** from C3-silylated furfural **19-Si-e** (99 mg, 0.30 mmol), methallyl bromide (91 µL, 0.90 mmol) and CuF(PPh₃)₃ (313 mg, 0.36 mmol). The crude reaction mixture was purified by silica-gel column chromatography (90/10 pentane/Et₂O) to afford 33 mg of product **178b** (67% yield) as a yellow oil. ¹H **NMR** (400 MHz, CDCl₃) δ 9.64 (s, 1H-1), 6.09 (s, 1H-4), 4.84 (s, 1H-9), 4.77 (s, 1H-9), 3.44 (s, 2H-7), 2.37 (s, 3H-6), 1.73 (s, 3H-10). ¹³C **NMR** (101 MHz, CDCl₃) δ 159.0 (C-5), 148.1 (C-2), 143.0 (C-8), 138.1 (C-3), 112.8 (C-9), 111.8 (C-4), 33.4 (C-7), 22.3 (C-10), 14.2 (C-6). **HRMS**: *m/z* calculated for C₁₀H₁₂O₂H [M+H]⁺ 165.0910, found 165.0908. **IR**: v (cm⁻¹) 2925, 2855, 1670, 1530, 1441, 1187, 1078, 810, 760, 655, 606, 420.

3-cinnamyl-5-methylfuran-2-carbaldehyde



Chemical Formula: C₁₅H₁₄O₂ Molecular Weight: 226.2750

179a



Chemical Formula: C₈H₈O₂ Molecular Weight: 136.1500 Prepared according to **GP9** from C3-silylated furfural **19**-*Si*-**e** (99 mg, 0.30 mmol), cinnamyl bromide (177 mg, 0.90 mmol) and CuF(PPh₃)₃ (313 mg, 0.36 mmol). The crude reaction mixture was purified by silicagel column chromatography (90/10 pentane/Et₂O) affording 36 mg of product **178c** (53% yield) as a yellow oil contaminated with traces of protodesilylated product **13**. ¹**H NMR** (400 MHz, CDCl₃) δ 9.67 – 9.56 (m, 1H-1), 7.21 (m, 5H-Ph), 6.41 (dd, *J* = 16.0, 4.9 Hz, 1H-9), 6.19 (m, 1H-8), 6.08 (d, *J* = 5.0 Hz, 1H-4), 3.59 (t, *J* = 5.6 Hz, 2H-7), 2.30 (d, *J* = 3.6 Hz, 3H-6). ¹³**C NMR** (101 MHz, CDCl₃) δ 177.0 (C-1), 159.1 (C-5), 147.6 (C-2), 138.1 (C-3)*, 137.1 (C-10), 134.0 (CH-Ph), 133.8 (CH-Ph), 132.2 (C-9), 128.7 (CH-Ph), 127.6 (CH-Ph), 126.5 (C-8), 126.3 (CH-Ph), 111.5 (C-4), 28.5 (C-7), 14.2 (C-6). **13C 138.15 ppm correlation observed by HMBC for C3 position*. **HRMS**: *m*/*z* calculated for C₁₅H₁₄O₂H [M+H]⁺ 227.1067, found 227.1063. **IR**: v (cm⁻¹) 2923, 2853, 2152, 1669, 1527, 1375, 1293, 1072, 970, 823.

3-allyl-furan-2-carbaldehyde

Prepared according to **GP9** from C3-silylated furfural **18-Si-e** (95 mg, 0.30 mmol), allyl bromide (78 µL, 0.90 mmol) and CuF(PPh₃)₃ (313 mg, 0.36 mmol). A 51% yield was determined by ¹H NMR analysis of the crude with dimethylsulfone as internal standard. The crude reaction mixture was purified by silica-gel column chromatography (90/10 pentane/Et₂O) to afford 8 mg of product **179a** (24% yield) as a yellow oil which was volatile and no further analysis could be performed. ¹H NMR (400 MHz, CDCl₃) δ 9.78 (s, 1H-1), 7.64 – 7.52 (s, 1H-5), 6.51 – 6.43 (s, 1H-4), 5.93 (ddt, *J* = 16.7, 10.2, 6.5 Hz, 1H-7), 5.20 – 5.08 (m, 2H-8), 3.58 (d, *J* = 6.4 Hz, 2H-6). No ¹³C NMR, HRMS and IR data were recorded.

3-(2-methylallyl)furan-2-carbaldehyde



Chemical Formula: $C_9H_{10}O_2$ Molecular Weight: 150.1770

Prepared according to **GP9** from C3-silylated furfural **18**-*Si*-**e** (95 mg, 0.30 mmol), methallyl bromide (91 µL, 0.90 mmol) and CuF(PPh₃)₃ (313 mg, 0.36 mmol). A 93% yield was determined by ¹H NMR analysis of the crude with dimethylsulfone as internal standard. The crude reaction mixture was purified by silica-gel column chromatography (90/10 pentane/Et₂O) to afford 29 mg of product **179b** (64% yield) as a yellow oil. ¹H **NMR** (400 MHz, CDCl₃) δ 9.76 (s, 1H-1), 7.56 (d, *J* = 1.7 Hz, 1H-5), 6.44 (d, *J* = 1.7 Hz, 1H-4), 4.84 (s, 1H-8), 4.75 (s, 1H-8'), 3.50 (s, 2H-6), 1.72 (t, *J* = 1.1 Hz, 3H-9). ¹³C **NMR** (101 MHz, CDCl₃) δ 178.0 (C-1), 148.9 (C-5), 147.3 (C-2), 142.8 (C-7), 135.7 (C-3), 114.8 (C-4), 112.8 (C-8), 33.3 (C-6), 22.3 (C-9). **HRMS** *m/z*: [M+H]⁺ calculated for C₉H₁₀O₂H 151.0754. Found 151.0752. **IR**: v (cm⁻¹) 2925, 2855, 1670, 1599, 1530, 1376, 1251, 1187, 1078, 977, 760.

S8.5 Alkylation

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Chemical Formula: C₇H₈O₂ Molecular Weight: 124.1390

A microwave vial was charged with CuF(PPh₃)₃ (52 mg, 0.060 mmol) and AgF (76 mg, 0.60 mmol), sealed and placed under argon atmosphere. In a Schlenk tube was placed C3-silylated furfural 19-Si-e (99 mg, 0.30 mmol) previously dissolved in CH₂Cl₂ and concentrated under inert atmosphere. Then, DMF (3 mL) was added and the solution was degassed by three freeze-pump-thaw cycles. The solution was transferred via cannula to the microwave vial and iodomethane (56 µL, 0.90 mmol) was added. The reaction mixture was heated at 60 °C overnight. It was then cooled, guenched with aqueous HCl (2 M), and extracted three times with Et₂O. The combined organics were washed with water, and dried over Na₂SO₄. The crude was analyzed by ¹H NMR and quantified using dimethyl sulfone as internal standard (35% NMR yield). The product was purified by silica-gel column chromatography [eluent pentane/ Et₂O (90/ 10)] to afford 7 mg of 181 (19% yield) as a yellow oil which was very volatile. ¹**H NMR** (400 MHz, CDCl₃) δ 9.63 (s, 1H-1), 6.06 (s, 1H-4), 2.35 (s, 3H-6/7), 2.33 (s, 3H-6/7). ¹³C NMR (101 MHz, CDCl₃) δ 158.9 (C-5), 148.0 (C-2), 136.2 (C-3), 112.6 (C-4), 14.1 (C-6/7), 10.5 (C-6/7)

3,5-dimethylfuran-2-carbaldehyde

(*note: aldehyde peak missing*). **HRMS** m/z: $[M+H]^+$ calculated for C₇H₈O₂H 125.0597. Found 125.0597.

3-benzyl-5-methylfuran-2-carbaldehyde

A microwave vial was charged with CuF(PPh₃)₃ (52 mg, 0.060 mmol) and AgF (76 mg, 0.60 mmol), sealed and placed under argon atmosphere. In a Schlenk tube, was placed **19-Si-e** (99 mg, 0.30 mmol) previously dissolved in CH₂Cl₂ and concentrated under inert atmosphere. Then, DMF (3 mL) was added and the mixture was degassed with three freezepump-thaw cycles. The solution was transferred via cannula to the microwave vial containing copper, and benzyl bromide (107 µL, 0.90 mmol) was added. The reaction mixture was heated to 60 °C overnight. It was then cooled, guenched with aqueous HCl (2 M), and extracted three times with Et₂O. The combined organics were washed with water and dried over Na₂SO₄. The crude was analyzed by ¹H NMR and quantified using dimethyl sulfone as internal standard (40% NMR yield and 20% of protodesilylated product). The product was purified by silicagel column chromatography [eluent pentane/ Et₂O (90/ 10)] to afford 17 mg of **182** (29% yield) as a yellow oil).¹**H** NMR (400 MHz, CDCl₃) δ 9.69 (s, 1H-1), 7.38 - 7.12 (m, 5H-Ph), 6.01 (s, 1H-4), 4.10 (s, 2H-7), 2.34 (s, 3H-6). **HRMS**: m/z calculated for C₁₃H₁₂O₂H [M+H]⁺ 201.0910, found 201.0909. **IR**: v (cm⁻¹) 2923, 2853, 2072, 1659, 1528, 1445, 1376, 1259, 976, 842.

2-methyl-5-styrylfuran

A microwave vial was charged with $CuF(PPh_3)_3$ (313 mg, 0.36 mmol), sealed and placed under argon atmosphere. In a Schlenk tube, was placed **19-Si-e** (99 mg, 0.30 mmol) previously dissolved in CH₂Cl₂ and concentrated under inert atmosphere. Then, DMF (3 mL) was added and the mixture was thoroughly degassed with three freeze-pump-thaw cycles. The solution was transferred via cannula to the microwave vial containing copper, and benzyl bromide (107 µL, 0.90 mmol) was added. The reaction mixture was heated to 60 °C overnight. It was then cooled, quenched with aqueous HCl (2 M), and extracted three times with Et₂O.

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 $\begin{array}{l} Chemical \ Formula: \ C_{13}H_{12}O_2\\ Molecular \ Weight: \ 200.2370 \end{array}$



Chemical Formula: C₁₃H₁₂O Molecular Weight: 184.2380 The combined organics were washed with water and dried over Na₂SO₄. The product was purified by silica-gel column chromatography [eluent pentane/ Et₂O (90/ 10)] to afford 47 mg of **183** (53% estimated yield, the product was not fully concentrated) as a yellow oil, the product was not fully concentrated) as a yellow oil, the product **182** (4% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.57 – 7.15 (m, 10H-Ph), 6.97 (d, J = 16.2 Hz, 1H-1*E*), 6.84 (d, J = 16.2 Hz, 1H-7*E*), 6.39 (d, J = 12.7 Hz, 1H-1*Z*), 6.31 (d, J = 12.6 Hz, 1H-7*Z*), 6.25 (d, J = 3.3 Hz, 1H-4*E*), 6.16 (d, J = 3.3 Hz, 1H-4*Z*), 6.02 (d, J = 3.2 Hz, 1H-3*E*), 5.92 (d, J = 3.2 Hz, 1H-3*Z*), 2.36 (s, 3H-6*E*), 2.26 (s, 3H-6*Z*). **HRMS**: *m*/*z* calculated for C₁₃H₁₂O₁H [M+H]⁺ 185.0961, found 185.0960. These data are in good agreement with those reported in literature. ^[296]

S8.6 Trifluoromethylation

Preparation of trifluoromethylating agent

(phen)Cu(CF₃)₃



Chemical Formula: C₁₅H₈CuF₉N₂ Molecular Weight: 450.7746 Following a reported procedure for the one-pot synthesis of (phen)Cu(CF₃)₃,^[261] in the glove box, CuI (380 mg, 2 mmol), AgF (1.16 g, 8 mmol) and 1,10-phenanthroline (360 mg, 2 mmol) were introduced in a 50 mL Schlenk tube which was then closed by a septum. DMF (6 mL) was thoroughly degassed by three freeze-pumpthaw cycles in another Schlenk tube, and then transferred via cannula to the tube containing the catalytic mixture. The mixture was kept away from light exposure using aluminium foil. After stirring 30 min at room temperature, TMS-CF₃ (1.77 mL, 12 mmol) was added dropwise under continuous stirring and the mixture was allowed to stir overnight at room temperature. The crude was diluted with 20 mL DCM, filtered and the residue washed with 10 mL DCM. The organic layer was washed once with 10 mL H₂O, then concentrated with silica gel prior to purification by column chromatography using cyclohexane/ethyl acetate (2/1) as eluent. The product was washed again with water to remove traces of DMF, and afforded 244 mg of (phen)Cu(CF₃)₃ (27% yield) as a yellow solid. ¹H NMR (300 MHz, CD_2Cl_2) δ 9.43 (dd, J = 4.9, 1.5 Hz, 2H), 8.63 (dd, J = 8.2, 1.4 Hz, 2H), 8.06 (s, 2H), 8.01 (dd, J = 8.2, 4.9 Hz, 2H). ¹⁹F NMR (282 MHz,

CD₂Cl₂) δ -24.40 (d, *J* = 11.2 Hz), -37.40 (q, *J* = 9.6 Hz). These data are in good agreement with those reported in literature.^[261]

Trifluoromethylating using (phen)Cu(CF₃)₃

187





Chemical Formula: C₇H₅F₃O₂ Molecular Weight: 178.1102

In a 25 mL Schlenk tube equipped with a stirring bar was introduced the C3-silylated furfuraldehyde 19-Si-e (33 mg, 0.10 mmol) and DMF (1 mL), previously degassed by three freeze-pump-thaw cycles and backfilled with dry O₂. (phen)Cu(CF₃)₃ (54 mg, 0.12 mmol) and AgF (0.025 g, 0.20 mmol) were respectively added under oxygen atmosphere. The Schlenk was then closed with a glass stopper and heated to 50 °C, whilst under vigorous stirring. The reaction mixture was kept at 50 °C overnight. It was then diluted with diethyl ether and filtered over celite. The latter was then washed twice with 50 mL water, dried over Na₂SO₄ and concentrated at 500 mbar, 40 °C. The product was purified by PTLC (80/20 pentane/ Et₂O) to obtain 8 mg of **187** (44% yield) as a pale-yellow oil (. ¹**H NMR** (300 MHz, CDCl₃) δ 9.8 (s, 1H-1), 6.4 (s, 1H-4), 2.4 (s, 3H-6). ¹⁹F NMR (282 MHz, CDCl₃) δ -56.70. ¹³C NMR (101 MHz, CDCl₃) δ 176.0 (C-1), 159.2 (C-5), 147.8 (q, ³*J* = 3.0 Hz, C-2), 126.8 (q, $^{2}J = 39.2$ Hz, C-3), 121.5 (q, $^{1}J = 268.7$ Hz,-7), 107.6 (q, $^{3}J = 3.0$ Hz, C-4), 14.1 (C-6). **HRMS** *m*/*z*: [M+H]⁺ calculated for C₇H₅F₃O₂H 179.0314, found 179.0315. **IR**: v (cm⁻¹) 2924, 2854, 1686, 1554, 1464, 1141, 1034, 972, 907, 731.

S8.7 Nucleophilic amination of aryl silane

190





Chemical Formula: C₁₀H₁₁NO₃ Molecular Weight: 193.2020 Following a modified procedure,^[270] was introduced in an oven-dried screwcapped tube, Cu(OAc)₂ (218 mg, 1.20 mmol), Na₂CO₃ (127 mg, 1.20 mmol), pyrrolidone (91 μ L, 1.20 mmol) and THF (1 mL). The mixture was stirred for 15 min at room temperature and C3-silylated furfuraldehyde **19-Si-e** (99 mg, 0.30 mmol) and NaF (13 mg, 0.30 mmol) were added under air atmosphere, followed by freshly distilled DMSO

(1 mL). The tube was closed by means of a screw cap and heated at 80 °C for 16 h. The reaction mixture was cooled to room temperature, 5 mL H₂O were added and the mixture was extracted thrice with 4 mL ethyl acetate. The organic layer was washed twice with brine and dried over Na₂SO₄. The latter was concentrated and purified by silica-gel column chromatography [eluent (cyclohexane/ethyl acetate 1/1)] to afford 21 mg of **19** (38% yield) as a yellow liquid. ¹H NMR (400 MHz, CDCl₃) δ 9.75 (s, 1H-1), 6.81 (s, 1H-4), 3.95 (t, *J* = 7.1 Hz, 2H-7), 2.59 (t, *J* = 8.1 Hz, 2H-9), 2.38 (s, 3H-6), 2.23 (p, *J* = 7.6 Hz, 2H-8). ¹³C NMR (101 MHz, CDCl₃) δ 176.8 (C-1), 174.8 (C-10), 159.0 (C-5), 140.9 (C-2), 135.4 (C-3), 105.2 (C-4), 50.7 (C-7), 31.5 (C-9), 18.9 (C-8), 14.5 (C-6). HRMS (ESI) *m*/*z*: [M+Na]⁺ calculated for C₁₀H₁₁NO₃Na 216.0631, found 216.0632. **IR**: v (cm⁻¹) 2922, 2853, 2075, 1714, 1642, 1596, 1534, 1456, 1369, 1202, 1090, 989, 842.

5-methyl-3-(pyrimidin-2-ylamino)furan-2-carbaldehyde

Following reported procedures,^[270] an oven dried screwcapped tube was charged with Cu(OAc)₂ (218 mg, 1.20 mmol), Na₂CO₃ (127 mg, 1.20 mmol) and 2-aminopyrimidine (114 mg, 1.20 mmol). THF (1 mL) was added and the mixture was stirred for 15 min at room temperature. The C3-silylated furfuraldehyde 19-Si-e (99 mg, 0.30 mmol) and NaF (0.0126 g, 0.30 mmol) were added under air atmosphere followed by 1 mL of freshly distilled DMSO. The tube was closed by means of a screw cap and heated at 80 °C for 16 h. The reaction mixture was cooled, 5 mL H₂O added and the mixture was extracted thrice with 4 mL ethyl acetate. The organic layer was washed twice with brine, dried over Na₂SO₄, and concentrated. Purification by silica-gel column chromatography [eluent (cyclohexane/ethyl acetate 1/1)] afforded 2 mg of **191** (4% yield) as a yellow liquid. ¹**H NMR** (400 MHz, CDCl₃) δ 9.67 (d, *J* = 0.8 Hz, 1H-1), 9.50 (s, 1H-NH), 8.49 (d, J = 4.8 Hz, 2H-9), 7.32 (S, 1H-4), 6.83 (t, J = 4.8 Hz, 1H-10), 2.40 (d, J = 0.9 Hz, 3H-6). ¹³C NMR (101 MHz, CDCl₃) δ 178.1 (C-1), 159.8 (C-5), 159.3 (C-8), 158.3 (C-9), 139.7 (C-2/3), 138.8 (C-2/3), 114.2 (C-10), 104.4 (C-4), 29.8 (C-6). HRMS m/z:

191



Chemical Formula: C₁₀H₉N₃O₂ Molecular Weight: 203.2010

 $[M+H]^+$ calculated for C₁₀H₉N₃O₂H 204.0768, found 204.0768. **IR**: ν (cm⁻¹) 2923, 2853, 1641,1492, 1396, 1263, 1065, 845, 740.

S9. Post-functionalization/ Derivatization

S9.1 Aza-Piancatelli rearrangement

192





Chemical Formula: C₁₉H₃₄N₂O₃Si Molecular Weight: 366.5770

Following a reported procedure,^[76] a MeOH (1.20 mL, 0.25 M) solution of C3-silylated furfuraldehyde 18-Si-a (63 mg, 0.30 mmol) and morpholine (52 mg, 0.60 mmol) was added to a dry flask containing AlCl₃ (4 mg, 0.030 mmol) and 4Å molecular sieves (60 mg) at room temperature. The mixture was vigorously stirred overnight at room temperature. The reaction was quenched with a buffered solution of AcOH/NaOAc at pH 5 (1 mL), then filtered through a short celite pad. The aqueous phase was extracted thrice with 3 mL CH₂Cl₂; the combined organics were washed twice with 2 mL water, dried over MgSO4 and concentrated under reduced pressure. Purification by silica-gel column chromatography with eluent (95/5 CH₂Cl₂/EtOH) afforded 71 mg of 192 (65% yield) as a yellow oil. ¹**H NMR** (400 MHz, CDCl₃) δ 7.65 (d, J = 2.1 Hz, 1H-2), 3.76 (dd, J = 3.4, 2.1 Hz, 1H-3), 3.72 (t, J = 4.86 Hz, 4H-9), 3.67 (t, J = 4.86 Hz, 4H-11), 3.26 (d, J = 3.3 Hz, 1H-4), 2.83 (dt, J = 10.1, 4.6 Hz, 2H-10), 2.72 – 2.52 (m, 6H-8,10'), 1.01 – 0.78 (m, 9H-7), 0.77 – 0.63 (m, 6H-6). ¹³C NMR (101 MHz, CDCl₃) δ 209.5 (C-5), 168.9 (C-2), 147.5 (C-1), 68.8 (C-4), 68.2 (C-3), 67.5 (C-11), 67.3 (C-9), 50.3 (C-10), 50.0 (C-8), 7.5 (C-7), 2.8 (C-6). **HRMS** m/z: $[M+H]^+$ Calculated for C₁₉H₃₄N₂O₃SiH 367.2411. Found 367.242. **IR**: v (cm⁻¹) 2954, 2926, 2874, 1696, 1513, 1413, 1377, 1251, 1116, 1007, 898, 736.

S9.2 Pyridinium salt from 5-HMF derivatives

1-butyl-6-(hydroxymethyl)-5-phenylpyridin-1-ium-3-olate



C3-functionalized HMF **197**, (13 mg, 0.06 mmol) was introduced in a microwave vial, followed by freshly distilled butylamine (5 mg, 0.07 mmol), formic acid (4 μ L, 0.019 mmol), EtOH (0.40 mL) and water (0.40 mL). The tube was sealed and heated at 80 °C for 3 days. The reaction was monitored by TLC (3/7 EtOAc/ MeOH). On completion, the mixture was diluted with 5 mL H₂O, activated charcoal was added and it was filtered through a celite pad. The reaction mixture was concentrated under high vacuum at 60 °C, which afforded 10 mg of a brown-yellow solid (61% estimated yield) along with some starting material **198**. The product was poorly soluble in CDCl₃, partly soluble in CD₃OD, D₂O and acetone-d₆ which led to poorly resolved NMR. ¹H **NMR** (300 MHz, CDCl₃) δ 8.14 (s, 1H-1), 7.41 (q, *J* = 7.3 Hz, 5H-Ph), 6.52 (s, 1H-3), 4.70 (s, 2H-5), 3.58 (t, *J* = 7.2 Hz, 2H-7), 1.68 (q, *J* = 7.6 Hz, 2H-8), 1.44 – 1.19 (m, 2H-9), 0.93 (t, *J* = 7.3 Hz, 3H-10).

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Fonctionnalisation sélective du furfural et de ses dérivés

Afin de se tourner vers une chimie synthétique plus écocompatible, il est nécessaire de synthétiser des intermédiaires et des produits à forte valeur ajoutée à partir de substrats provenant de la biomasse plutôt que ceux de ressources fossiles. Le furfural et le 5-(hydroxymethyl)furfural (HMF) sont répertoriés comme étant parmi les plus prometteurs. Ils sont obtenus à travers la déshydratation de la lignocellulose de la biomasse provenant des déchets agricoles. Ces molécules ont un grand potentiel en tant que plateformes renouvelables pour la production durable de chimie fine. Notamment, la fonctionnalisation directe du furfural, sans modification au préalable de l'état redox de la fonction aldéhyde par activation C-H sélective, est un domaine émergent qui suscite un intérêt considérable. Nous rapportons ainsi une C3–H silvlation dirigée des dérivés du furfural par catalyse à l'iridium à travers des imines furfuryliques avec des triorganosilanes ou organodisilyloxysilanes en présence d'un piégeur d'hydrogène. Cette transformation donne accès à des plateformes encore plus polyvalentes, pouvant donner lieu à une diversité de molécules. Les post-fonctionnalisations – via des réactions de couplages croisés catalysées par des métaux de transitions (TM) et des réarrangements de type Brook – sont étudiées ; en particulier par l'activation aux fluorures. La deuxième stratégie permet un éventail de transformations postfonctionnelles à partir des furfuraldéhydes silvlés pour la création des liaisons C-C et C-X, ce qui est assez prometteur. Une nouvelle plateforme de fonctionnalisation C3 a également été établie sur la base de furfuryl alcools dérivés de furfuraldéhydes silvlés correspondant pour fournir une nouvelle classe de molécules, qui donnent suite à la formation de liaisons C-C en position C3. Par conséquent, la plateforme de silvlation représente un outil puissant pour accéder à des produits hautement fonctionnalisés et ainsi, ouvre des portes pour l'obtention de produits à haute valeur ajoutée à partir de substrats provenant de la biomasse.

Mots clés : Furfural, biomasse, silvlation, réarrangement de Brook, cuivre, couplage-croisé

Selective functionalization of furfural and its derivatives

In order to develop an ever more eco-compatible synthetic chemistry, it is nowadays essential to synthesize intermediates and added-value chemical compounds starting from substrates derived from biomass rather than those from fossil resources. Furfural and 5-(hydroxymethyl)furfural (HMF) are among the most promising bio-based molecules. Obtained by dehydrating lignocellulosic biomass from agricultural residues and dedicated crops, these molecules have great potential as renewable platforms for the sustainable production of fine chemicals. In particular, the direct functionalization of furfural, without prior modification of the redox state of the aldehyde function, by selective C-H activation is an emerging field that is attracting considerable interest. Herein, we disclose a directed C3–H silvlation of furfural derivatives under iridium catalysis. In the presence of a hydride scavenger, C3-silylation of the furfuryl imines can be achieved with triorganosilanes or organodisilyloxysilanes as silicon donor. This transformation gives access to even more versatile platforms that can be further functionalized using the $C(sp^2)$ -Si bond as handle. Post-functionalization through TM-catalyzed cross-coupling reactions or Brook-type rearrangements are investigated; especially through fluoride anion activation. The second mentioned strategy, permits a wide range of post-functional transformations based of the silvlated furfuraldehyde from the creation of C-C bonds to the creation of C-X bonds, which is quite promising. A new C3-functionalization platform also established based on C3-silylated furfuryl alcohols derived from the corresponding furfuraldehydes to provide a novel class of molecules via the formation of C-C bonds in the C3 position. Therefore, the silvlation platform represents a powerful tool to access highly functionalized products and open doors to achieve high-added value products from biomass-based substrates.

Keywords: Furfural, biomass, silvlation, Brook rearrangement, copper, cross-coupling