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Copper-catalysed transformations of acylsilanes

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Abbreviations

[O]	Oxidative conditions
18-C-6	1,4,7,10,13,16-hexaoxacyclooctadecane
2,2-DMP	2,2-Dimethoxypropane
Å	Ångström
Ac	Acetyl
AIBN	Azobisisobutyronitrile
Alk	Alkyl
Ar	Aryl
Bn	Benzyl
Bu	Butyl
Cy	Cyclohexyl
d.r.	Diastereoisomeric ratio
DBM	Dibenzoylmethane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DMF	Dimethylformamide
DMS	Dimethyl sulfide
DMSO	Dimethyl sulfoxide
E^+	Electrophilic compound
ee	Enantiomeric excess
eq.	Equivalents
Et	Ethyl

EWG	Electron withdrawing group
Fmoc	Fluorenylmethyloxycarbonyl
h	Hour(s)
HPLC	High-Performance Liquid Chromatography
*I*Mes	1,3-Dimesitylimidazol-2-ylidene
*i*Pr	*iso*-propyl
*I*Pr	1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene
IR	Infra-Red
KHMDS	Potassium bis(trimethylsilyl)amide
LDA	Lithium diisopropylamide
LG	Leaving group
LiHMDS	Lithium bis(trimethylsilyl)amide
*m*CPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
MeCN	Acetonitrile
MVPO	Meerwein-Ponndorf-Verley-Oppenauer
n.d.	Not determined
n.r.	No reaction
NBS	N-Bromosuccinimide
NCS	N-Chlorosuccinimide
NMR	Nuclear magnetic resonance
Ph	Phenyl
Pin	Pinacol
Piv	Pivaloyl
pm	Picometer
ppm	Parts per million
PTSA	*para*-Toluenesulfonic acid

Py	Pyridyl
r	Radius
RT	Room Temperature
SiX_3	Any silyl group
T	Temperature
TBAB	Tetrabutylammonium bromide
TBAF	Tetrabutylammonium fluoride
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TfO	Triflate
THF	Tetrahydrofuran
THP	Tetrahydropyranyl
TIPS	Triisopropylsilyl
TMAF	Tetramethylammonium fluoride
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
Tol	Tolyl
UV	Ultra-violet
X	Electronegativity
XRD	X-ray diffraction

Abstract

Acylsilanes are an intriguing class of organic compounds that display unique reactivity modes. For several years, innovative methodologies have been developed using their key features for the synthesis of valuable organic molecules. Yet, the copper chemistry of acylsilanes is underdeveloped in the literature. Furthermore, when this PhD work was initiated, no copper-catalysed reaction of acylsilane had been reported.

Our research groups being active in the fields of copper chemistry and silicon chemistry, it was decided to take a look in the copper chemistry of acylsilanes with the goal of discovering copper-catalysed transformations.

The first project was devoted to the development of a copper-catalysed domino reaction with acylsilanes as electrophilic partners. These investigations led us to work on various subprojects related to copper-catalysis, acylsilanes and silicon chemistry.

The second project led us to the discovery of an intriguing copper-catalysed 1,2-selective hydroborylation reaction of acylsilanes. The resulting α-hydroxysilanes are obtained with great typical yield, enantioselectivity and regioselectivity. These optically active products were further derivatised with excellent chiral transfer.

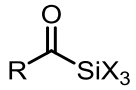
Finally, every section of this thesis is concluded with a summary of the developed reactions, their advantages and limitations. Additionally, suggestions of new related research topics are given.

Table of contents

Chapter I General introduction on acylsilanes

1 General properties

Acylsilanes are an intriguing class of organic compounds in which a silicon atom is directly bonded to the sp^2 carbon of an acyl moiety (Scheme I-1).

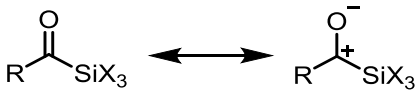


Scheme I-1 General structure of acylsilanes.

After their first report in 1957 by the group of Brook[1], investigations were initially conducted on their spectral and structural properties.[2] Indeed, the neighbouring position of the silyl group to the carbonyl function has a great impact on those particular features. In infrared and ultra-violet spectroscopy, acylsilanes show maximum absorbance at higher wavelengths than their ketone analogues.[3] Silicon being relatively large (r_{Si} = 111 pm; r_C = 76 pm)[4] and electropositive (X_{Si} = 1.9, X_C = 2.5)[4], it has a marked inductive releasing ability towards the carbonyl group. This inductive effect is responsible for the easier polarisability of the C=O bond resulting in its weakening and explaining the bathochromic shifts observed in IR and UV spectra. ^{13}C NMR spectra of acylsilanes also exhibit characteristic peaks as the carbonyl carbon's signal is usually observed at very high ppm values. This downfield shift is again explained by the presence of the silicon atom and its inductive effect which weakens the shielding of the carbon.[5] Furthermore, the anisotropic effect and the difference in electronegativity influence the ^1H NMR spectra as well, as the protons attached to the α carbon of the carbonyl appear to be deshielded. However this effect is less pronounced than in the ^{13}C NMR spectra.[2] In addition to spectroscopic observations, single crystal diffraction

revealed an unusually long Si-C(=O) bond length of 1.926 Å in comparison with other Si-C bond lengths, e.g. 1.864 Å for Si-C(Ph) and 1.870 Å for Si-C(CH_3).[6]

Those peculiarities are consistent with the unusual reactivity modes of acylsilanes, i.e. the reactivity of the carbonyl group, the activation of the Si-C bond and their photochemical behaviour. Based on this, the resonance structure of acylsilanes is believed to have a more significant contribution to their reactivity than that of simple ketones (Scheme I-2).



Scheme I-2 Resonance structure of acylsilanes.

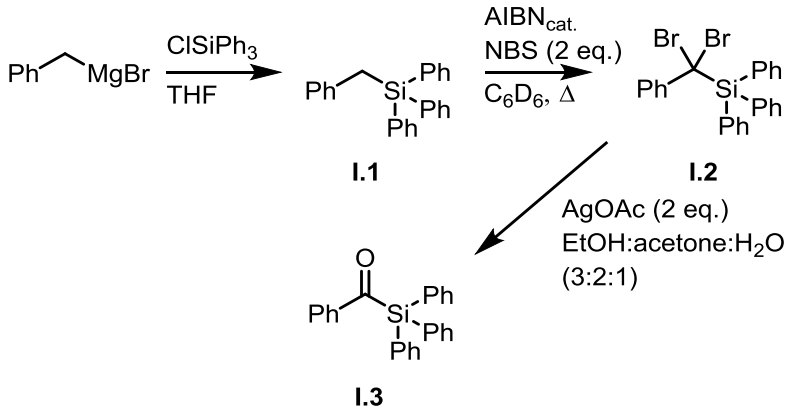
In addition to its electronic properties, the bulky trisubstituted silicon atom also presents interesting steric effects. The combination of the electronic and steric effects of silicon have proven to deeply impact the regio- and diastereochemical outcome of the synthetic applications of acylsilanes.[7]

2 Synthesis of acylsilanes

Acylsilanes have attracted the attention of organic chemists for several decades due to their fascinating reactivity modes. As a result, the number of synthetic methods leading to those molecules is tremendous. Many good reviews summarise all those known methods.[7-8] This section focuses on the main existing methods and on those that were used for the purpose of this thesis.

2.1 Acylsilanes from benzylsilanes

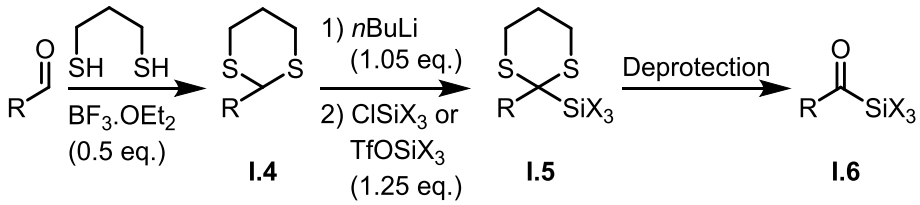
The first successful access to acylsilanes was achieved following a three step procedure (Scheme I-3). After nucleophilic addition of a benzyl Grignard reagent to triphenylchlorosilane, the resulting benzylic silane **I.1** is oxydised by N-bromosuccinimide. Finally the *gem*-dibromo intermediate **I.2** is hydrolysed in the presence of silver(I) acetate yielding the corresponding triphenylsilyl acylsilane **I.3**.[1] This method is rather efficient to access aromatic acylsilanes. However, this method is best avoided due to the need for large amounts of silver salt during the hydrolysis step.



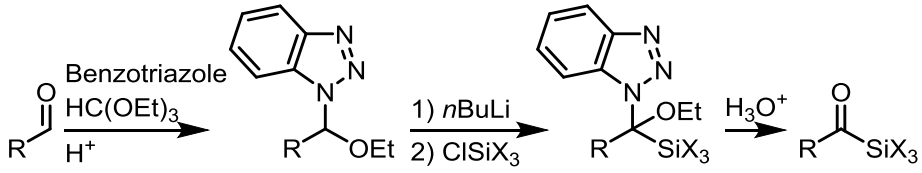
Scheme I-3 First known synthesis of acylsilanes.

2.2 Acylsilanes from masked aldehydes

The Corey-Brook strategy is the most widely used strategy towards the desired acylsilanes. This methods relies on the protection of an aldehyde through formation of a 1,3-dithiane **I.4** followed by subsequent deprotonation and quenching of the resulting organolithium species by a silylchloride or silyltriflate. The silylated dithiane **I.5** is then hydrolysed yielding the desired product **I.6** (**Erreur ! Source du renvoi introuvable.**).[9] While the two first steps usually operate with quantitative yields and do not require purification, the final hydrolysis has proven challenging and is substrate dependent. The first reports made use of mercury salts given the affinity of sulfur for mercury, but additionally to the toxicity issues of mercury salts, over-oxidation of the weak Si-C bond could lead to product loss. Therefore other oxidative conditions have been reported for the removal of the thioketal protecting group including chloramine-T/methanol,[10] electrochemical hydrolysis,[11] $AgNO_3$/NCS,[12] $CuCl_2$/CuO[13] or I_2/$CaCO_3$.[14] The present strategy gives efficient access to aromatic, aliphatic and substituted acylsilanes. Some reports reveal that alkenyl acylsilanes are available using the same strategy however with dramatically reduced yields and functional group tolerance.[15]



In the nineties' the group of Katritzki developed a similar methodology based on the transformation of aldehydes to benzotriazole derivatives **I.7** (Scheme I-4). After deprotonation and silylation, the final deprotection is conducted under acidic, non-oxidative conditions avoiding over-oxidation to the carboxylic acid.[16]



I.7

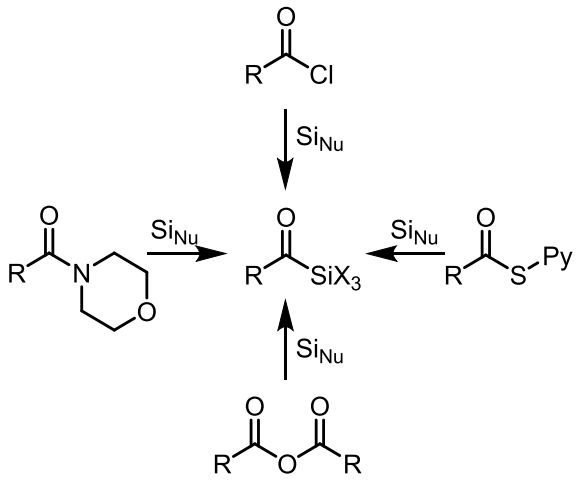
Scheme I-4 Katritzki's acylsilane synthesis.

2.3 Acylsilanes from carboxylic acid derivatives

Addition of nucleophilic silicon species to carboxylic acid derivatives is a straightforward synthetic approach to acylsilanes. Indeed the protection/deprotection sequence is suppressed (Scheme I-5).

The first reports in this category make use of copper salts to promote the addition of Li-Si and Al-Si reagents to acid chlorides, anhydrides or S-2-pyridyl esters.[17] Later silyl-zinc cyanocuprate $(Me_2PhSi)_2Cu(CN)(ZnCl)_2$ was developed by Bonini *et al.* in order to synthesise acylsilanes under milder conditions by addition to acid chlorides.[18] Morpholinamides showed to be suitable electrophiles in the direct reaction with silyl lithium reagents as no over-addition to the acylsilane was observed unlike with esters.[19] Palladium catalysis has also been used for the synthesis of acylsilanes using di-silicon[20] or silicon-tin[21] reagents as silyl source and acid chlorides as electrophiles. These latter palladium-catalysed methods provide access to the desired products with a higher degree of selectivity and a

better functional group tolerance leading to widely substituted acylsilanes. Finally the copper-catalysed addition of the Suginome's reagent to acid anhydrides was reported by Cirriez *et al.*[22] Unfortunately, most of these methods are restricted to aromatic and aliphatic acylsilanes and access to α,β-unsaturated acylsilanes therefore remains scarce.

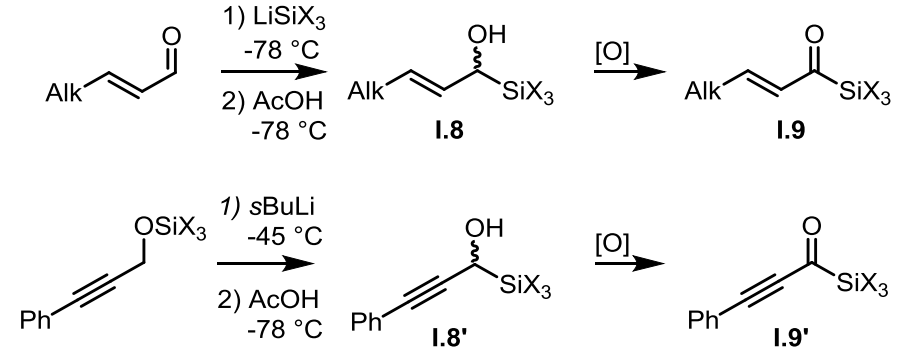


Scheme I-5 Suitable carboxylic acid derivatives for acylsilane synthesis.

2.4 Acylsilanes from α-hydroxysilanes

Access to racemic α-hydroxysilanes **I.8** and **I.8'** is an easy task as they can be accessed by direct addition of silyl lithium reagents to aldehydes[23] or by the retro-Brook rearrangement of the corresponding silylethers.[24] Subsequent oxidation of the alcohol under appropriate conditions affords the corresponding acylsilanes with good yields. Several oxidation protocols are known to be applicable however the most convenient option is the Swern oxidation. Notably, unlike the previously cited reactions, the oxidation of α-hydroxysilanes grants access to aromatic, aliphatic and also α,β-

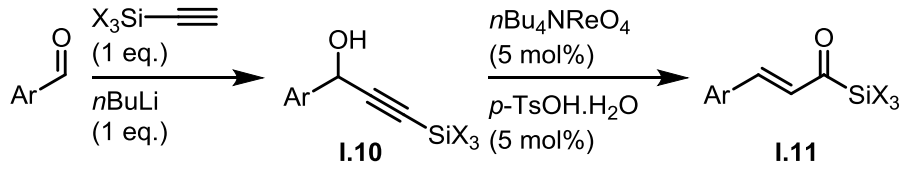
unsaturated acylsilanes among which alkenyl- and alkynyl-acylsilanes **I.9** and **I.9'** respectively (Scheme I-6).



Scheme I-6 Oxidation of α-hydroxysilanes to acylsilanes.

2.5 α,β-unsaturated acylsilanes from propargylic alcohols

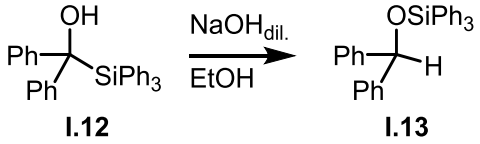
Despite the fact that α,β-unsaturated acylsilanes are an appealing class of molecules their synthesis most often requires manipulation of highly volatile intermediates, harsh multi-step conditions or malodorous reagents. Recently, Nikolaev *et al.* reported that silylated propargylic alcohols **I.10** could undergo a perrhenate-catalysed Meyer-Schuster rearrangement leading to a variety of (*E*)-β-aryl substituted α,β-unsaturated acylsilanes **I.11** with good yields (Scheme I-7). Remarkably the method tolerates an array of functional groups on the aromatic ring and is compatible with different silyl groups.[25]



Scheme I-7 Meyer-Schuster rearrangement of propargylic alcohols.

3 The Brook rearrangement of acylsilanes

Discovered and reported by A. G. Brook in 1958,[26] the base-mediated anionic migration of a silyl group from a carbon atom to an oxygen atom is known as the Brook rearrangement.[27] The first observation of this reaction was a 1,2-silyl shift from the silyl carbinol **I.12** to form silylether **I.13** in the presence of diluted sodium hydroxide (Scheme I-8).



I.12 **I.13**

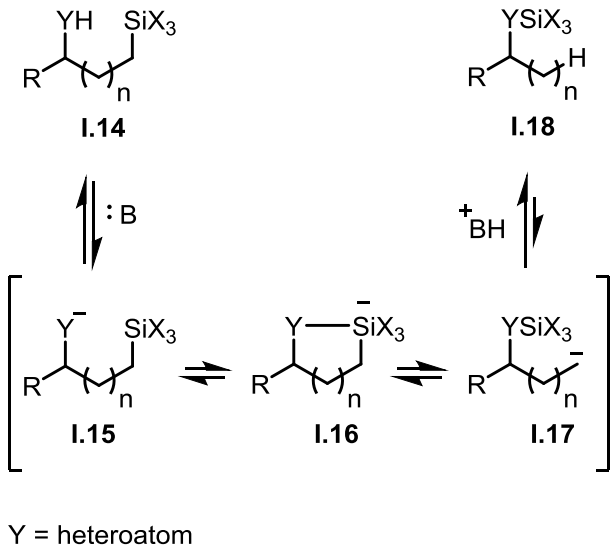
Scheme I-8 First observed Brook rearrangement.

With time, this silyl shift proved to be more general than its 1,2 version and 1,n silyl migrations were reported, breaking a record with the 1,6-Brook rearrangements.[28] The reverse rearrangement is also frequently encountered.[29] First observed by Speier,[29a] involving the shift of a silyl group from oxygen to carbon, it is commonly called the retro-Brook rearrangement. Furthermore, similar processes were discovered in which oxygen is replaced by other heteroatoms as nitrogen, sulfur or phosphorus. Those reactions are called aza-, thia-, and phospha-Brook rearrangements respectively.[30]

Over the years, the Brook and the retro-Brook rearrangements have found widespread applications in organic synthesis.[31] In addition, they were successfully applied to tandem bond formation reactions with migration of the silicon atom before or/and after other bond formations.[27a]

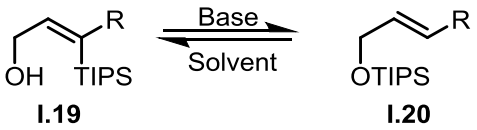
3.1 Mechanistic considerations

Factors determining the equilibrium's position are essential to control in order to develop highly selective methodologies based on the Brook rearrangement. The activation energy for the 1,2-silyl shift from carbon to oxygen has been evaluated to be quite low by Antoniotti *et al.*, i.e. 12 – 15 kcal.mol^{-1}.[32] Therefore thermal equilibrium, depending on the relative stability of both species, can usually be assumed in solution (Scheme I-9). Hence, when the reaction is conducted in a protic medium or launched by a catalytic amount of base, the relative energies of the protonated species **I.14** and **I.18** determine the equilibrium constant. In this case, the formation of a strong Si-O bond (120 – 130 kcal.mol^{-1}) at the expense of a weaker Si-C bond (75 – 85 kcal.mol^{-1}) usually drives the equilibrium towards the formation of a silylether **I.18** after protonation of the carbanionic intermediate **I.17**. On the other hand, when no spontaneous quenching of the reaction medium is possible, the position of the equilibrium is determined by the energies of the alkoxide **I.15** and the carbanion **I.17**. In the latter case, the basicities of the anions, the kind of counter-ions and the choice of the solvent system have an important impact on this equilibrium.[27a]



Scheme I-9 Competing species in solution during the Brook Rearrangement.

Lautens *et al.* reported a study on the effects of these reaction parameters on the 1,4-Brook rearrangement of vinylsilane allylic alcohol **I.19** (Scheme I-10). Lithiated bases did not trigger the silyl shift because of the strong coordination of the alkoxide to the lithium ion. The use of a larger cation such as sodium or potassium in the more coordinating DMF displaced the reaction to the formation of the allyl silyl ether **I.20**. Alternatively, it was shown that an electron withdrawing group in α position to the silicon to be transferred would help stabilising the negative charge and favor the rearrangement even in the presence of a lithiated base.[33]



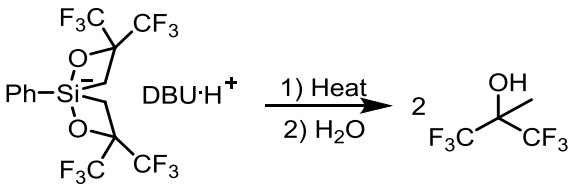
I.19 **I.20**

R = TMS or Ph

Base	Solvent	R	Product
MeLi	THF	TMS	**I.19**
NaH	DMF	TMS	**I.20**
*t*BuLi	THF	Ph	**I.20**

Scheme I-10 Effects of reaction parameters on the Brook rearrangement.

Concerning the mechanism, the Brook rearrangement has been shown to proceed through a pentacoordinate silicate intermediate. To this end, several well defined silicates were synthesised, characterised and shown to form the Brook-reaction product upon thermolysis (Scheme I-11).[34]

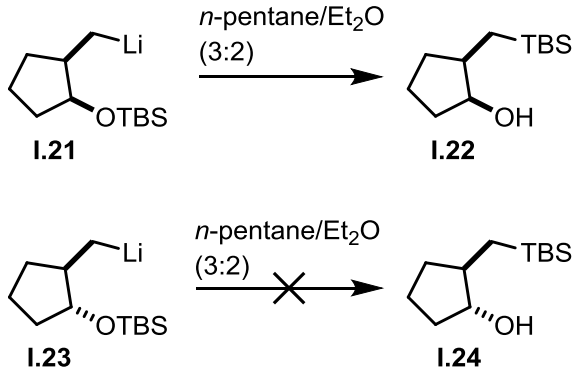


Stable below
room temperature

Scheme I-11 Thermolysis of a pentacoordinate silicate species to an alcohol.

Furthermore a number of studies ruled out the possibility of an intermolecular rearrangement by conducting cross experiments[33, 35] and by subjecting structurally stranded molecules to the retro-rearrangement conditions. For example, *cis*-silylether **I.21** smoothly rearranged, yielding alcohol **I.22**. On the contrary, *trans*-silylether **I.23** was not able to undergo 1,4-silyl shift. This result was used as

evidence by Jiang and co-workers to support the intramolecular nature of the Brook rearrangement. Indeed, while for **I.21** the formation of a silicate is conformationally allowed, the conformational strain in **I.23** is not favourable to the formation of the cyclic pentacoordinated silicon intermediate. If an intermolecular mechanism would have been possible, alcohol **I.24** should have been obtained from **I.23** (Scheme I-12).[36]

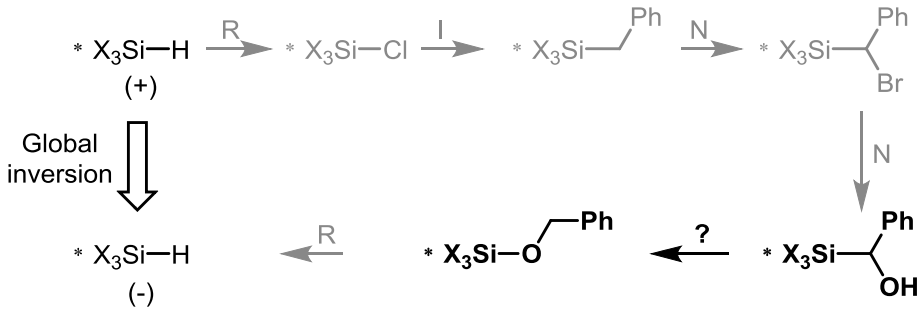


Scheme I-12 Cross experiments unravelling the intramolecular nature of the Brook rearrangement.

The stereochemistry of the Brook and retro-Brook rearrangements has been the topic of many publications. Attention was given to the stereochemical fate of both the silicon atom and the carbon atom.

Optically active silyl groups were found to undergo the Brook reaction and the reverse process with full retention of stereochemistry. Early indirect evidence was brought by subjecting an asymmetric silane of known configuration to a multistep cyclic reaction sequence involving one Brook rearrangement, the stereochemistry for all mechanisms being well-known except for the Brook reaction. Stereochemical comparison of the starting silane with the final silane indicated that the Brook rearrangement had to be a conservative process at the silicon center (Scheme I-13).[37] More recently, the retro-Brook

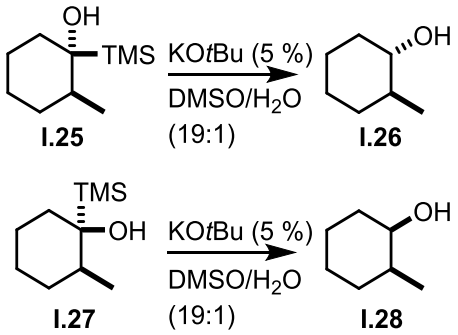
rearrangement has been shown to be a stereospecific process and to proceed with retention at the silicon. This was achieved by direct observations based on HPLC and XRD analysis.[38]



R= retention
I= inversion
N= no effect on Si*

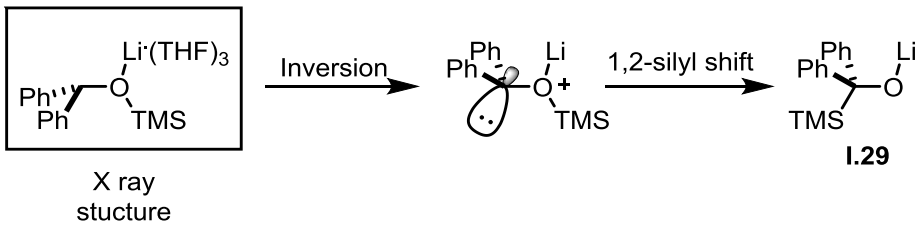
Scheme I-13 Reaction sequence with global inversion at the silicon center.

Studies concerning the stereochemistry at the carbon center throughout the Brook rearrangement are numerous. Most often they rely on the synthesis of well-defined hydroxysilanes or silyl ethers which are subsequently submitted to the rearrangement conditions. Comparison of the rearranged product's stereochemistry with that of the starting material reveals the stereochemical course of the investigated reaction. From these studies, it is commonly accepted that the Brook rearrangement of molecules bearing alkyl substituents on the carbanionic site proceed with retention of the stereochemistry at the carbon. For example, the *trans*-alcohol **I.25** is converted to the corresponding *trans*-alcohol **I.26** in the presence of potassium *tert*-butanolate and the *cis*-alcohol **I.27** follows the same path to form **I.28** with retention (Scheme I-14).[35b, 39] This is usually explained by the high conformational stability of the carbanion against epimerisation.[35b]



Scheme I-14 Retention of stereochemistry of alkyl substituted silylcarbinols upon Brook rearrangement.

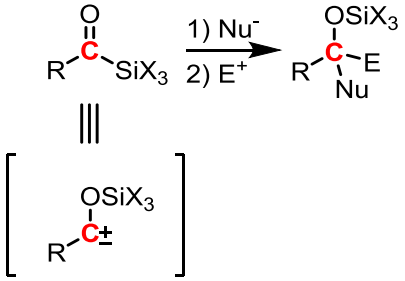
On the other hand, substrates bearing stabilising groups on the carbanion's position seem to proceed through inversion at the carbon. Reasons for inversion are not fully clear although some reports provide pieces of answer explaining this reactivity. While Antoniotti and co-workers[32] and Wang and co-workers[40] used calculations to propose transition state structures compatible with the observed inversions, Boche *et al.* were able to obtain a crystal structure for the carbanionic intermediate.[41] In their structure, the lithium cation is bonded to the coordinating oxygen rather than to the carbanion due to the stabilisation of the negative charge by two phenyl groups. Subsequent inversion at the carbon and suprafacial migration of the silyl group yielded the rearranged compound **I.29** with inversion at the carbon atom (Scheme I-15).



Scheme I-15 Crystal structure of the anionic intermediate of the retro-Brook rearrangement and inversion of its stereochemistry.

3.2 Synthetic applications of the Brook rearrangement

In the following section, the focus will be set on the 1,2-Brook rearrangement of acylsilanes. The 1,2-C-to-O silyl shift is commonly expected to arise from reactions involving acylsilanes. Therefore, many methodologies based on the Brook reaction of acylsilanes were developed. Furthermore, this unique reactivity of acylsilanes makes them highly desirable candidates in tandem bond formation reactions as their carbonyl carbon behave as a 1,1-dipole and can react in turn with nucleophiles and electrophiles (Scheme I-16).



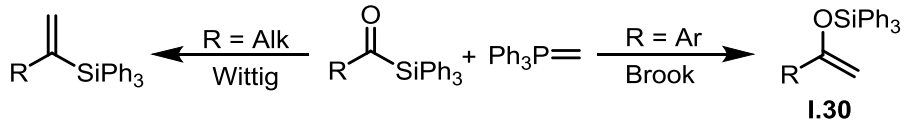
Scheme I-16 Acylsilanes as a 1,1-dipoles.

Addition of a nucleophilic species on an acylsilane gives rise to an equilibrium between the resulting alkoxide and the corresponding carbanion. Pulling the balance towards the carbanionic species is essential for the success of tandem bond forming reactions. To do so, chemists have identified several tricks which will be covered here. For the sake of clarity, the following methodologies will be categorised according to the strategy used to balance the equilibrium.

3.2.1 Leaving groups

Brook was the first to note that acylsilanes reacted in an unusual manner when treated with nucleophiles bearing an α-leaving group. Reaction of diazomethane or Wittig reagents with benzoylsilanes resulted in the formation of silyl enol ethers **I.30** after 1,2-silyl

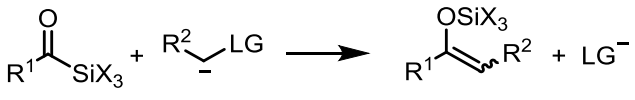
migration. The outcome of the reaction was however closely bonded to the charge stabilising ability of the acylsilane's aromatic substituent. Indeed, aliphatic acylsilanes underwent normal reaction in the presence of those reagents (Scheme I-17). With these initial observations, Brook paved the way for the discoveries that followed.[42]



I.30

Scheme I-17 Reaction of acylsilanes with a Wittig reagent.

Based on Brook's findings, the group of Reich became highly involved in the use of acylsilanes as silyl enol ether precursors. The competing reactions observed in the early reports of Brook were efficiently suppressed by using nucelophiles and α-leaving groups that do not trigger other reactions. As a result, aliphatic acylsilanes turned into effective electrophilic candidates for those transformations. These investigations found sulfones, sulfoxides, sulphides or nitriles to be successful leaving groups (Scheme I-18). Notably it was shown that the leaving groups could be placed on the nucleophiles as on the acylsilanes with the same efficiency.[10, 43]

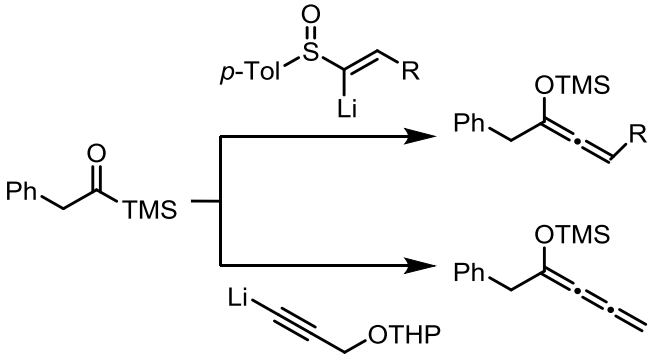


LG = SO_2Ar, SOAr, SAr, CN

Scheme I-18 Synthesis of silyl enol ethers by the reaction of acylsilanes with nucleophiles bearing α-leaving groups.

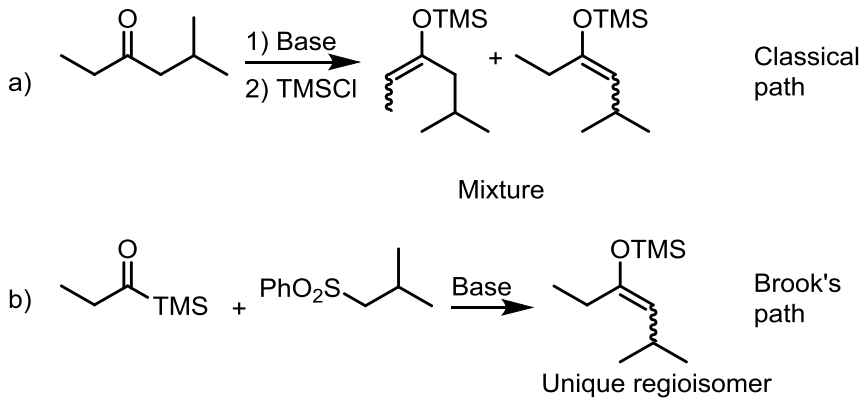
Additional studies granted access to siloxyallenes[44] and siloxypentatrienes[45] from acylsilanes by addition of lithiated

vinylsulfoxides and lithiated propargylic ethers respectively (Scheme I-19).



Scheme I-19 Synthesis of siloxyallenes and siloxypentatrienes by the Brook rearrangement.

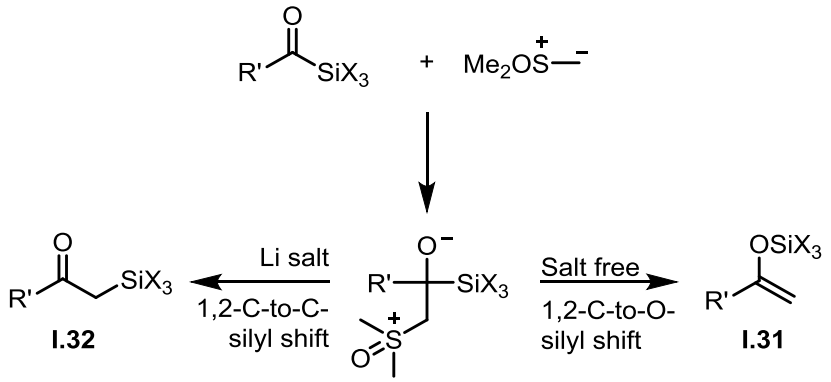
Interestingly, this synthetic method has the powerful advantage of providing silyl enol ethers with complete regioselectivity. Indeed careful choice of the reaction partners determines the regiochemical identity of the product. On the opposite, classical methods for the synthesis of silyl enol ethers (i.e. ketone enolisation/silyl chloride capture sequence) usually provide mixtures of regioisomers, particularly when the ketone is substituted by two sterically and electronically similar groups (Scheme I-20). Therefore the present concept provides an attractive alternative and was used in the synthesis of several natural products, such as sesquiterpenes by Reich,[46] the tetracyclic marine sesterterpene scalarenedial[47] and the pentacyclic triterpenoid serratenediol[48] by Corey's group and, more recently, representative fragments of natural macrolides by Grée's group.[49]



Scheme I-20 Regioselective access to silyl enol ethers via the Brook rearrangement of acylsilanes.

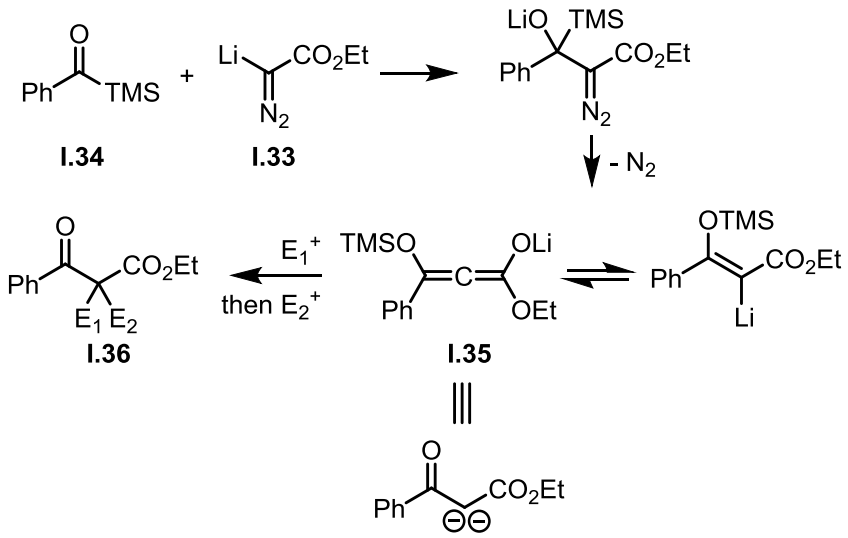
Following a similar approach, additions of sulfur ylides to acylsilanes were carefully investigated by Nakajima and co-workers.[50] Similarly to Brook's observations, the addition adducts were found to undergo two distinct rearrangement pathways. It is however worth specifying that no epoxysilane was detected under these conditions. On one hand silyl enol ethers **I.31** were obtained after the expected Brook rearrangement/β-sulfide elimination sequence. On the other hand anionotropic silyl migration afforded β-silyl ketones **I.32** as the sulphide was expelled. Meticulous examination revealed that the selectivity of the reaction could be guided by the presence or the absence of lithium salts. Indeed in the presence of lithium ions coming from the ylide solution, the main product was the β-silyl ketones **I.32**. On the opposite, getting rid of the lithium afforded the silyl enol ether **I.31** with up to 99 % selectivity. These results were explained by the formation of a tight ion pair of the lithium ion with the alkoxide preventing the Brook rearrangement and thereby favouring the alternative route (Scheme I-21). More recently, another competition has been reported in the addition of tetrazolosulfones to acylsilanes

although in this case the Smiles rearrangement prevailed on the Brook rearrangement and vinylsilanes were formed as the major products.[51]



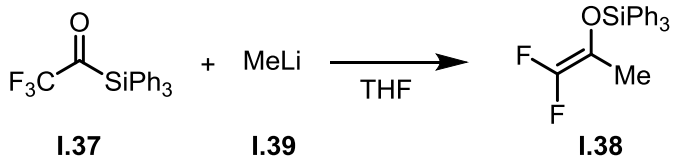
Scheme I-21 Effect of lithium salts on the outcome of the reaction of acylsilanes with sulfur ylides.

Another remarkable example is the addition of diazo esters to acylsilanes as the rearrangement adduct is a *gem*-dianion equivalent. After deprotonation by LDA, the lithiated diazo ester **I.33** is added onto the acylsilane **I.34**. After rearrangement and loss of nitrogen, a β-siloxyallenoate **I.35** is generated which can trap one or two equivalents of an electrophile. After work-up highly substituted β-keto esters **I.36** are isolated with good to excellent yields.[52]



Scheme I-22 Siloxyallenoates as a gem-dianion equivalent.

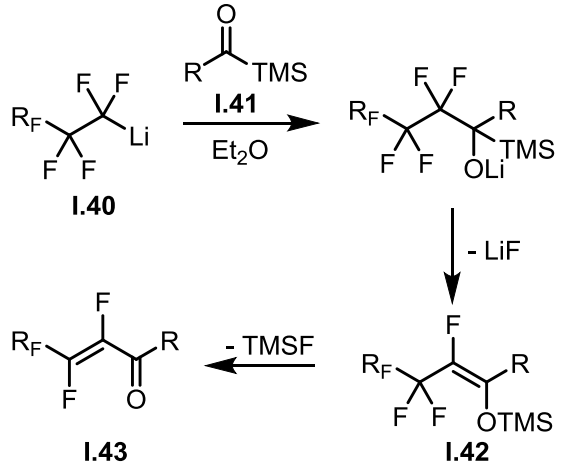
Finally, the leaving group ability of the fluorine atom was observed by Jin *et al.*, as trifluoromethylated acylsilane **I.37** yielded 2,2-difluoro enol silyl ether **I.38** upon addition of organolithium reagent **I.39** (Scheme I-23).[53] From this starting point, the Brook rearrangement-triggered synthesis of perfluorinated silyl enol ethers and their derivatives was broadly studied.



Scheme I-23 Brook rearrangement of trifluoromethylated acylsilanes.

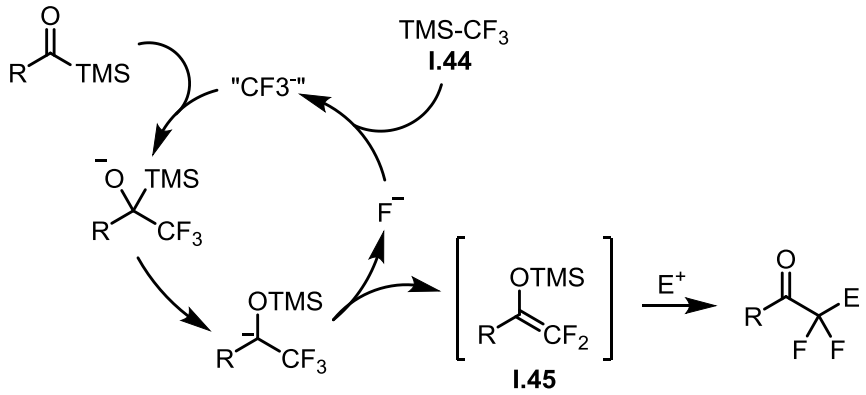
One of the main techniques to reach this goal is the addition of perfluoro lithium reagents to acylsilanes. The nucleophiles **I.40** are obtained by transmetallation of iodoperfluoroalkanes with methyl lithium. Subsequent addition to the acylsilane **I.41** and Brook rearrangement afford the perfluorinated silyl enol ethers **I.42**. The latter compounds being ratter labile readily decompose to the

corresponding perfluoroenones **I.43** with complete (*E*) selectivity (Scheme I-24).[54] This method has also been applied to the synthesis of perfluorinated homo-C-nucleoside analogs.[55]



Scheme I-24 Perfluoroenone synthesis via the Brook rearrangement.

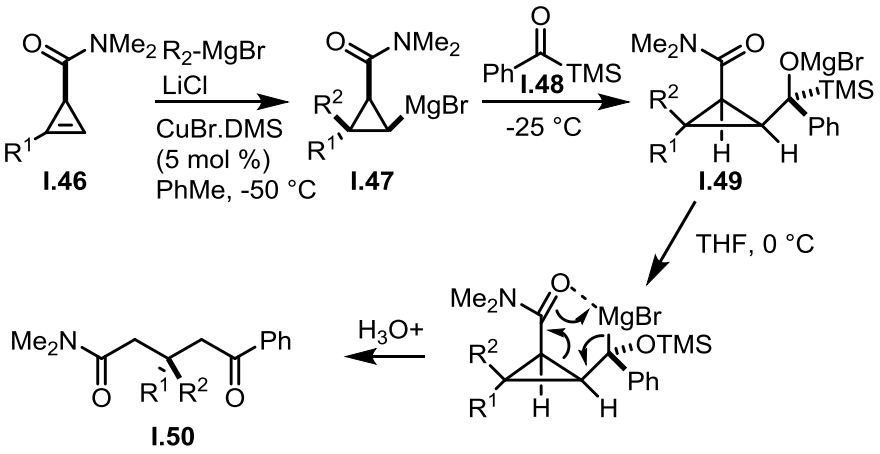
An elegant method leading to fluorinated silyl enol ethers *via* the Brook rearrangement is the fluoride-catalysed addition of the Ruppert-Prakash reagent to acylsilanes (Scheme I-25).[56] After activation of the Ruppert-Prakash reagent **I.44** by fluoride, the trifluoromethyl moiety is transferred on the acylsilane, triggering a Brook rearrangement. A 2,2-difluoro enol silyl ether **I.45** is released along with a fluoride ion which further serves as a catalyst. The difluoroenoxysilane **I.45** was not isolated but rather reacted with a variety of electrophiles as aldehydes, enones, allylic esters, halides or imines *in situ*. This catalytic method has been applied to the synthesis of various fluorinated analogs of naturally occurring organic molecules by Portella and co-workers.[56a]



Scheme I-25 Fluoride-catalysed addition of the Ruppert-Prakash reagent to acylsilanes.

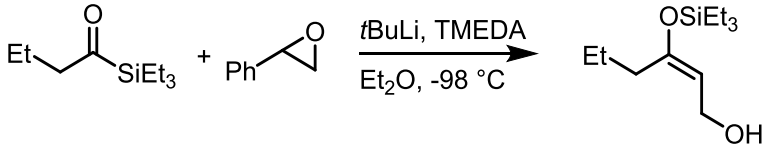
3.2.2 Ring opening

It was found that opening of cyclopropyl rings was compatible with the Brook rearrangement. However, in the same study, it was clear that cyclopropane opening could not be used as sole driving force to favour the aforementioned rearrangement. Indeed, ring opening was only observed if anion-stabilising groups were already present in the system to drive the Brook reaction.[57] In this context, Zhang *et al.* very recently reported a one-pot strategy to access acyclic systems bearing an optically active quaternary center through the Brook rearrangement-triggered β-fragmentation of strained cyclopropyl rings (Scheme I-26). In this reaction, copper-catalysed carbomagnesiation of an enantiomerically pure cyclopropene species **I.46** occurs regio- and diastereoselectively. The resulting cyclopropylmagnesium moiety **I.47** traps an acylsilane **I.48** affording the corresponding α-alkoxysilane **I.49** with high diastereoselectivity. Upon addition of THF to the reaction mixture, the Brook rearrangement induces opening of the cyclic system leading to δ-ketoamides **I.50** bearing a quaternary carbon center after acidic hydrolysis.[58]



Scheme I-26 Brook rearrangement-mediated opening of cyclopropyl rings.

Yet, oxygenated ring systems seem to overcome the previous limitations and their opening is an effective driving force for the Brook rearrangement. In this context, furyllithium reagents efficiently led to bis-silyl enol ethers after addition to acylsilanes, 1,2-silyl shift and furyl ring opening.[59] In the same way, oxiranyl anions readily open their epoxide ring upon addition to acylsilanes affording silyl enol ethers with high stereoselectivity (Scheme I-27).[60]

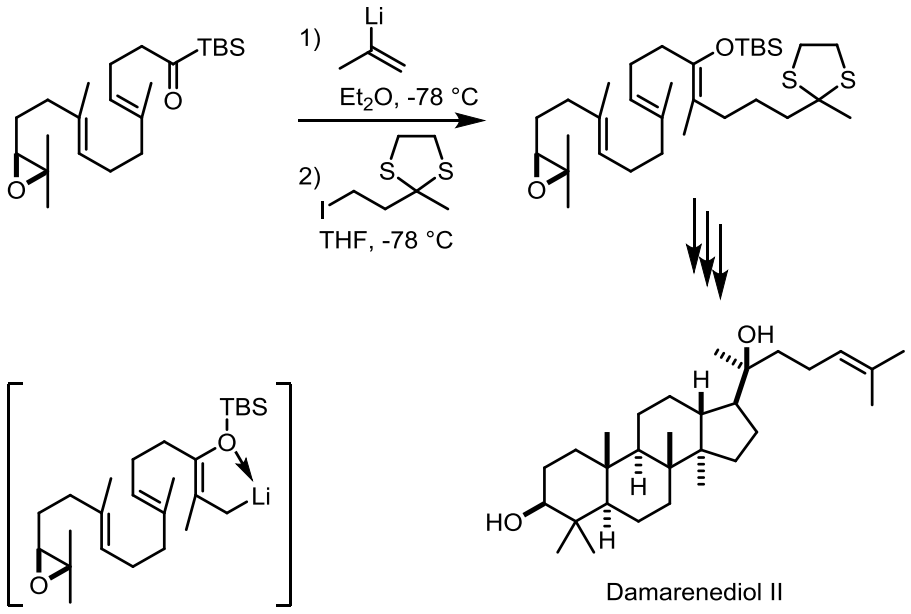


Scheme I-27 Addition of oxiranyl anions to acylsilanes.

3.2.3 Anion-stabilising groups

Besides exploiting leaving groups or ring strain release, an important means to drive the equilibrium in the Brook reaction of acylsilanes is based on the use of carbanion-stabilising groups. This strategy broadens the scope of the Brook rearrangement of acylsilanes as it does not limit its use to the synthesis of silyl enol ethers anymore.

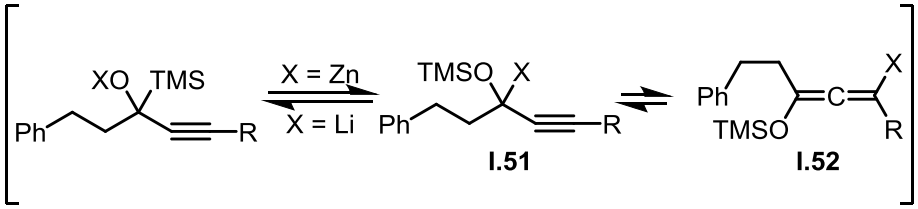
First examples of the use of such carbanion-stabilising groups were reported by the group of Reich.[43b, 61] In their case, simple vinyllithium or acetylenic lithium reagents were added on aliphatic acylsilanes. The Brook rearrangement was driven by delocalisation of the negative charge through the unsaturation. Vinyl lithium addition was particularly attractive as following allylic transposition of the anion, coordination of the lithium to the oxygen favoured highly selective formation of the (*Z*) silyl enol ethers upon capture with electrophiles. This system was efficiently used by Corey and Lin in the first synthesis of Dammarenediol II, a naturally occurring antiviral agent (Scheme I-28).[62]



Scheme I-28 Highly (Z)-selective silyl enol ether synthesis through intramolecular coordination of the allyllithium intermediate and application to the synthesis of Dammarenediol II.

Initially, alkynyl groups were not as efficient at pulling the balance. Indeed, products arising from allylic transposition of the anion were

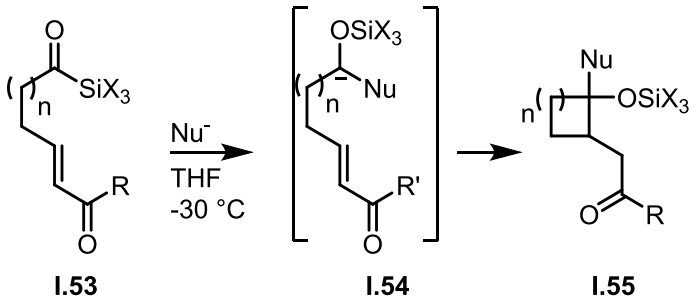
only obtained upon reaction with soft electrophiles. Quenching the reaction media with water resulted in the isolation of the addition adduct, i.e. the α-hydroxyalkynylsilane. This inconvenience was solved by the use of organozinc reagents rather than organolithium nucleophiles (Scheme I-29). Evidence was provided that, unlike lithium propargylic alkoxide, zinc propargylic alkoxide was readily transformed to the Zn-Brook adduct **I.51** which was in synthetically useful equilibrium with its allenylzinc equivalent **I.52**. Stabilising interactions of zinc's filled *d* orbitals with the π-antibonding C-C orbitals, and weak O-Zn bond energy stand for explanations of this reverse behaviour. This strategy was employed for the highly stereoselective synthesis of five membered carbocycles and linear compounds *via* a Zn-ene-allene reaction of the Zn-allene intermediates.[63]



Scheme I-29 Effect of zinc salts on the Brook rearrangement of propargylic α-alkoxysilanes.

Similarly, Takeda developed a tandem Brook rearrangement/intramolecular Michael addition by adding phenyl lithium or the heteroatomic nucleophile lithium dimethylphosphite to acylsilanes linked to Michael acceptors **I.53**. The negative charge formed during the rearrangement in **I.54** is efficiently stabilised by the anion-stabilising ability of the nucleophiles and then adds on the

Michael acceptor in a 1,4-intramolecular fashion leading to cyclic compounds **I.55** (Scheme I-30).[64]



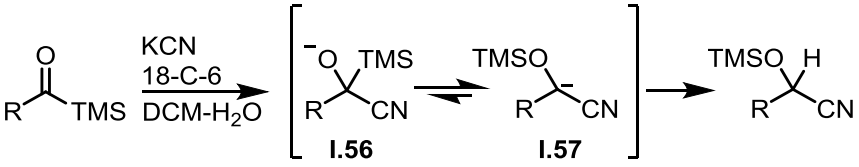
I.53 **I.54** **I.55**

Nu^- = PhLi, $(MeO)_2OPLi$

Scheme I-30 Intramolecular Michael addition of the nucleophile-stabilised α-siloxycarbanion.

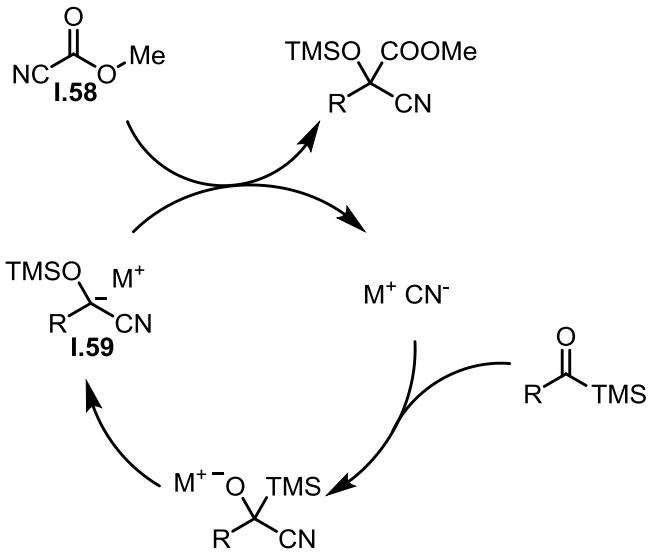
The cyanide ion revealed to be a useful nucleophile with a great anion-stabilising ability. Therefore it was used in several bond formation strategies with acylsilanes. Potassium cyanide was found to be efficiently added to acylsilanes, however a phase transfer catalyst or a crown ether was often needed to deal with its poor solubility. The resulting α-alkoxysilanes **I.56** were found to undergo efficient Brook reaction rather that protonation to the corresponding α-hydroxysilanes, even in biphasic medium. This result is consistent with the strong carbanion-stabilisation effect of the nitrile group (Scheme I-31). Analogous reactions were developed in anhydrous medium with the aim of using the silyl-protected cyanohydrin carbanion **I.57** to trap organic electrophiles instead of water. In this context, cyanation-triggered Brook rearrangement was carried out on α,β-unsaturated acylsilanes in the presence of methyl iodide,[65] on δ-silyl-γ,δ-epoxy-α,β-unsaturated acylsilanes in the presence of

cyanoformates[66] and on γ-bromo-α,β,γ,δ-unsaturated acylsilanes with ejection of the bromide leaving group.[67]



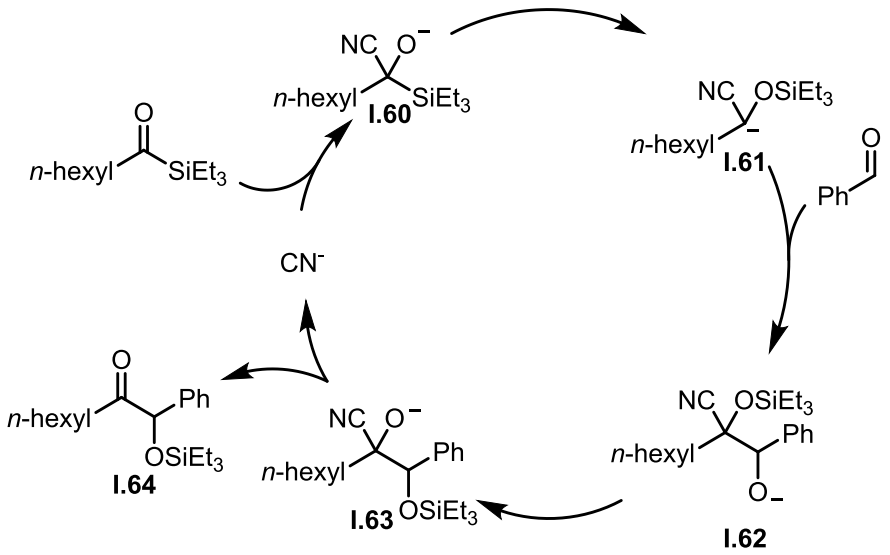
Scheme I-31 Cyanide-promoted Brook rearrangement in biphasic medium.

Interestingly, potassium cyanide could be used as a catalyst to promote the rearrangement of aromatic and aliphatic acylsilanes (Scheme I-32). Subsequent trapping of cyanoformates **I.58** resulted in the acylation of the cyanohydrin anion **I.59** along with the release of a cyanide ion equivalent.[68] The process was further improved by replacing the potassium ion by a chiral aluminium-salen complex. This organometallic complex efficiently promoted the enantioselective version of the reaction although no example with aliphatic acylsilanes appears in this report.[69]



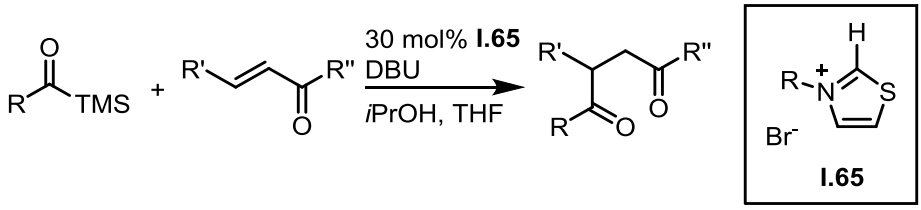
Scheme I-32 Cyanide-catalysed acylation of acylsilanes.

Based on the fact that anion-stabilising nucleophiles readily drive the Brook rearrangement of acylsilane in a synthetically useful manner, sila-benzoin condensation reactions of acylsilanes were developed. The classical bezoin condensation is the cyanide-catalysed umpolung addition of an aldehyde to another aldehyde leading to α-hydroxyketones. To this end, the catalyst is required to behave at different stages of the mechanism as a nucleophile, as an anion-stabilising group and as a leaving group. Potassium cyanide[70] and chiral metallophosphite complexes[71] were found to act as efficient catalysts in this reaction and granted access to the cross benzoin products with high selectivity and no by-product formation as it is often the case in the classical benzoin condensation. In a typical reaction, the cyanide catalyst adds on the acylsilane, triggering the Brook rearrangement of the α-alkoxysilane **I.60** to the corresponding cyanohydrin carbanion **I.61**. Benzaldehyde is subsequently captured by **I.61** leading to alkoxide **I.62** which undergoes 1,4-silyl migration to alkoxide **I.63**. Finally, the catalyst is released with the formation of the α-siloxyketone **I.64** (Scheme I-33).



Scheme I-33 Cyanide-catalysed sila-benzoin coupling of acylsilanes.

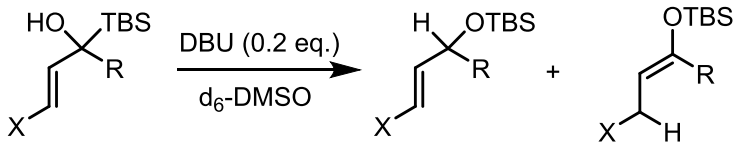
In the same way, a thiazolium salt **I.65** was used as catalyst in the sila-Stetter reaction of acylsilanes, i.e. the umpolung Michael addition of acylsilanes to α,β-unsaturated electrophiles. Similarly to the cyanide-catalyzed sila-benzoin coupling, the catalyst **I.65** activates the acylsilane and catalyses its addition to the Michael acceptor prior to being released in the reaction medium (Scheme I-34).[72]



Scheme I-34 Sila-Stetter reaction of acylsilanes.

Kei Takeda and his group played a crucial role in the chemistry of the Brook rearrangement as they discovered that well positioned heteroatomic groups on the acylsilanes help to properly stabilise negative charges and thereby facilitate the rearrangement process. The stabilising abilities of the mainly employed heteroatomic substituents

were assessed by NMR measurement of α-hydroxyallylsilanes' half-lives during their DBU-catalysed Brook rearrangement (Scheme I-35).[73] Sulfoxide, thiophenyl and phenyl appeared to be very good at stabilising the negative charge of the carbanion and at promoting the reaction. Trimethylsilyl was considerably less stabilising as the starting material **I.66** had a half-life of 30 minutes and a mixture of Brook adduct **I.67** and allyl Brook adduct **I.68** was obtained. Finally halogens showed the weakest stabilising ability as **I.66** was mainly recovered after more than 24 hours and no **I.68** was observed.



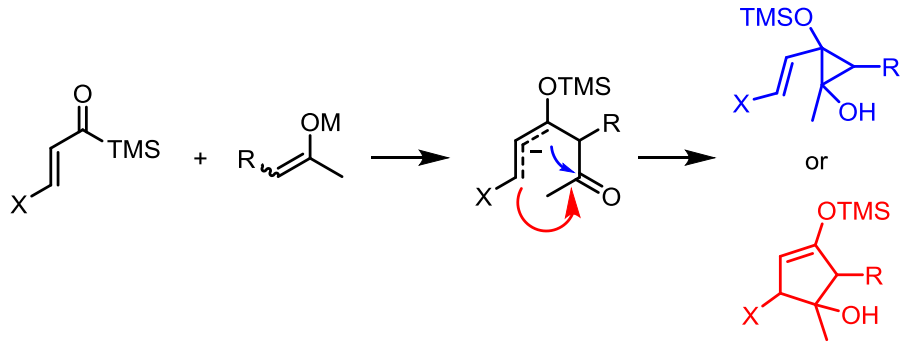
I.66 **I.67** **I.68**

X	Product	$t_{1/2}$ (min)
SPh	**I.68**	3.2
TMS	**I.67** : **I.68** (2:1)	27.5
Ph	**I.68**	5.5
S(O)Ph	**I.68**	<1.0
Cl	**I.67**	**I.66** : **I.67** (2.2 : 1) (25h)
Br	**I.67**	**I.66** : **I.67** (4.5 : 1) (43h)

Scheme I-35 Assessment of the stabilising abilities of the mainly employed heteroatomic substituents.

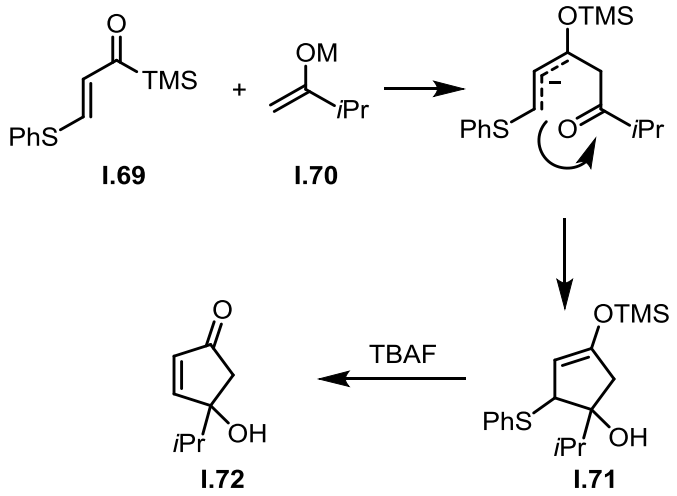
Takeda's group made extensive use of these findings to stabilise carbanions generated from the addition of enolates to α,β-unsaturated acylsilanes. Enolates proved to be extremely fruitful nucleophiles as they allowed innovative cyclisation chemistry by the incorporation of an electrophilic site in the Brook reaction system. Hence, carbanions stabilised by heteroatomic substituents were suited for cyclisation

through intramolecular capture of the newly introduced electrophiles. In addition, this intramolecular trapping further balances the equilibrium towards the Brook rearrangement (Scheme I-36).



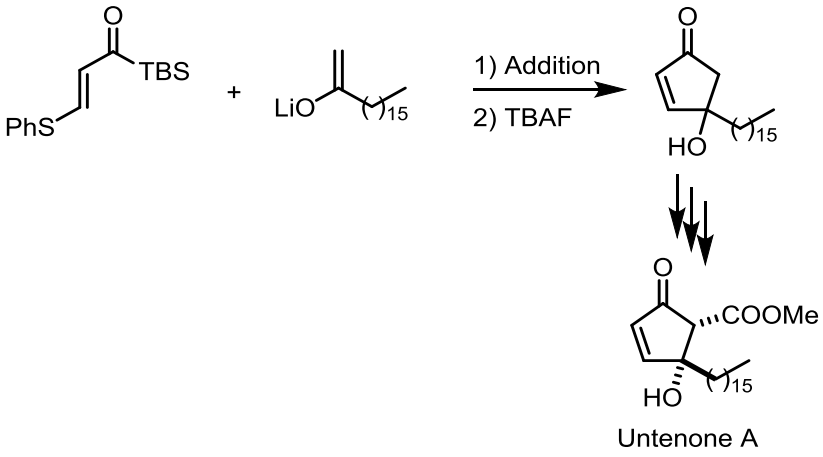
Scheme I-36 Enolate addition to α,β-unsaturated acylsilanes followed by 5-exo-trig or 3-exo-trig cyclisations.

The first contribution to this domain was the [3+2] annulation strategy (Scheme I-37). In this reaction, the three-carbon partner is a β-heteroatom α,β-unsaturated acylsilane **I.69** while the two-carbon partner is a lithium enolate **I.70** generated from the deprotonation of a ketone by LDA. The thiophenyl group was found to be a stabilising group of choice as it permitted the complete conversion to the five-membered cyclic silyl enol ether **I.71** with good yields.[74] Improvement of the method was achieved using β-stabilising groups which had a leaving group character. This modification favoured spontaneous elimination of the stabilising group by the silyl enol ether while the removal of the thioether moiety previously required an additional step, e.g. the treatment of **I.71** with TBAF affording cyclopentenone **I.72**.[75]



Scheme I-37 [3+2] cyclisation strategy based on the addition of enolates to α,β-unsaturated acylsilanes.

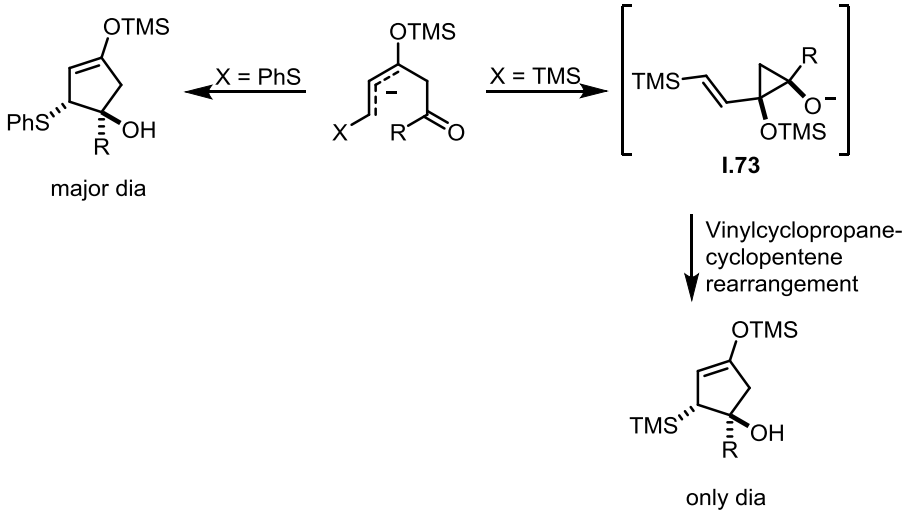
This powerful [3+2] cyclisation strategy was employed for the synthesis of the cyclopentenone core of natural products such as chromomoric acid DII,[74] calvulones[76] and untenone A (Scheme I-38).[77]



Scheme I-38 Application of the [3+2] cyclisation startegy to the total synthesis of Untenone A.

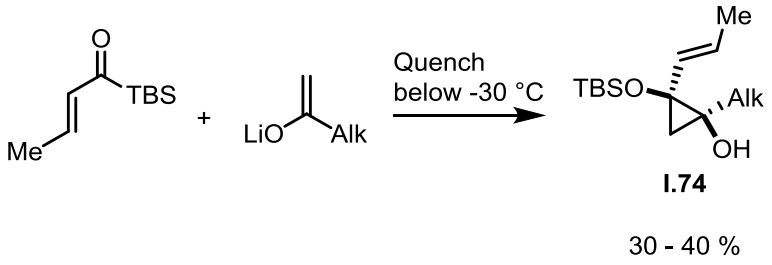
Mechanistically, the good anion-stabilising ability of the thiophenyl group has shown to efficiently delocalise the negative charge

generated by the Brook rearrangement. This effect results in an effective 5-exo-trig type cyclisation. On the other hand, the less stabilising trimethylsilyl group is not as effective in delocalising the carbanion. Therefore, the five membered ring is formed indirectly. A cyclopropanolate **I.73**, resulting of the trapping of the ketone by the α-siloxy anion, is initially formed and then undergoes a vinylcyclopropane-cyclopentene rearrangement. Isolation of the vinylcyclopropanol intermediates by low temperature quenching supports this hypothesis (Scheme I-39).[78]



Scheme I-39 Effect of the anion-stabilising groups on the cyclisation's mechanism.

As mentioned above, cyclopropanation is possible through the Brook rearrangement of acylsilanes. Use of non-delocalising stabilising groups on the acylsilane, in combination with nucleophilic enolates yielded cyclopropanediols **I.74** with low yields, though without further rearrangement to five-membered rings (Scheme I-40).[79]



I.74

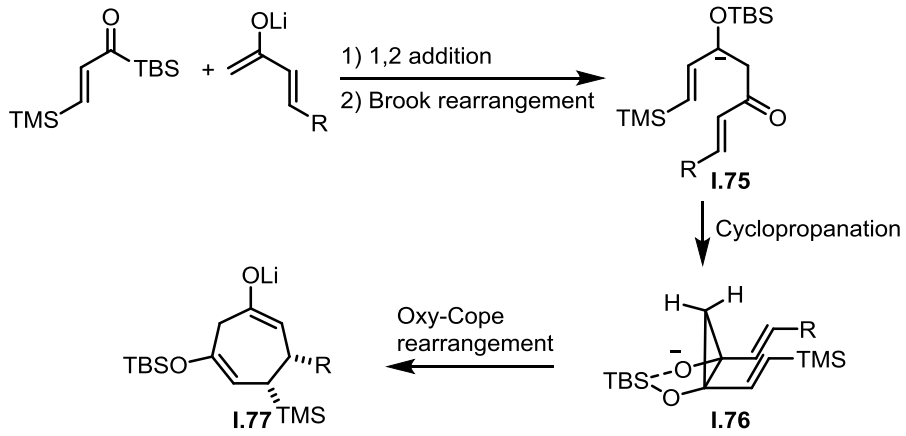
30 - 40 %

Scheme I-40 Formation of cyclopropanols through the addition of enolates to α,β-unsaturated acylsilanes.

Use of enone enolates instead of unconjugated enolates broadened the scope of the cyclisation strategy introducing [3+4] annulations. The stabilised carbanion would be used in a Michael addition to form seven membered rings.[80] This new method was applied to the synthesis of the 5-6-7 tricyclic skeleton of biologically active cyathins.[81]

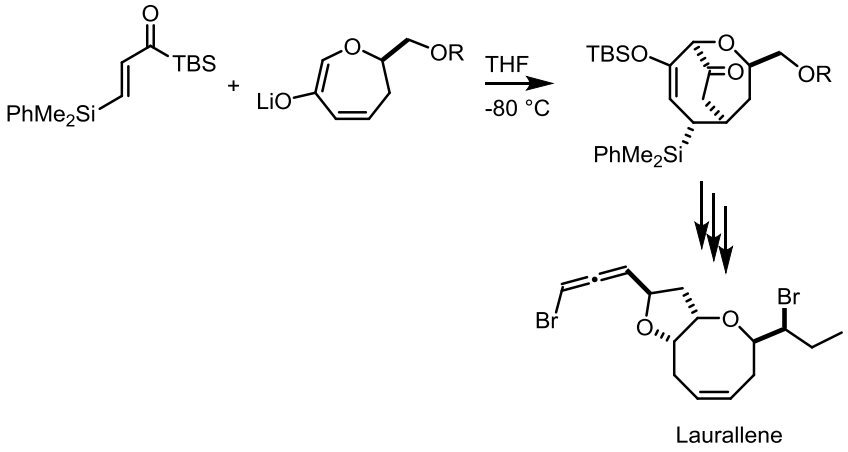
In contrast with the [3+2] strategy, the less stabilising trimethylsilyl and tributylstannyl β groups were the best to promote the desired [3+4] annulation while the β-phenylthioacylsilane afforded the vinyl cyclopentenone derived from the corresponding [3+2] cyclisation process. Intriguingly, the stereochemistry of the formed product was unlikely to be obtained from a Brook reaction/allylic anion stabilisation/Michael addition sequence. Mechanistic insight was again provided by isolation of cyclopropanol intermediates after low temperature quenching of the reaction medium. On this basis, a more likely pathway, consistent with the final stereochemistry, was proposed (Scheme I-41). After enolate addition to the acylsilane, weak β-stabilising groups would favour the Brook rearrangement and stabilise the α-siloxycarbanion **I.75** without allylic transposition. The carbanion **I.75** would be engaged in a 3-exo-trig type

cyclopropanation with high stereoselectivity resulting from the O-Si coordination in the transition state. The resulting *cis*-divinylcyclopropanolate **I.76** would then undergo a stereospecific oxy-Cope rearrangement leading to the seven-membered ring **I.77** with the right stereochemical configuration. From these experiments, it is clear that the strong thiophenyl stabilising group hinders the formation of the key cyclopropanolate intermediate **I.76** by efficient allylic delocalisation of the negative charge. The resulting carbanion then engages in a 5-exo-trig cyclisation rather than in a less favoured 7-endo-trig cyclisation explaining the intriguing formation of five membered rings in the presence of strong stabilising groups.[82]



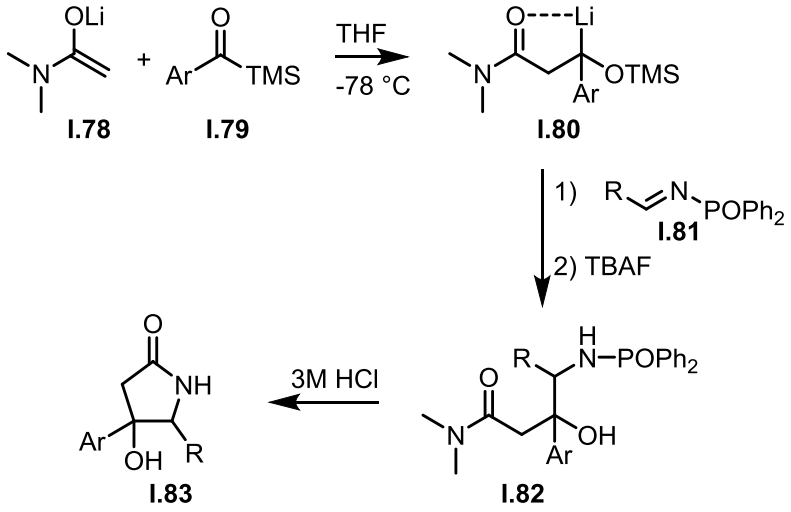
Scheme I-41 Proposed mechanism for the [3+4] cyclisation reaction of enone enolates and α,β-unsaturated acylsilanes.

Fine-tuning of the structural and electronic properties of the reaction partners allowed to further apply this [3+4] annulation strategy to the synthesis of fused polycyclic systems[80b, 83] and to eight membered rings[84] of synthetic interest as demonstrated by the synthesis of the natural products prelaureatin[85] and laurallene (Scheme I-42).[85-86]



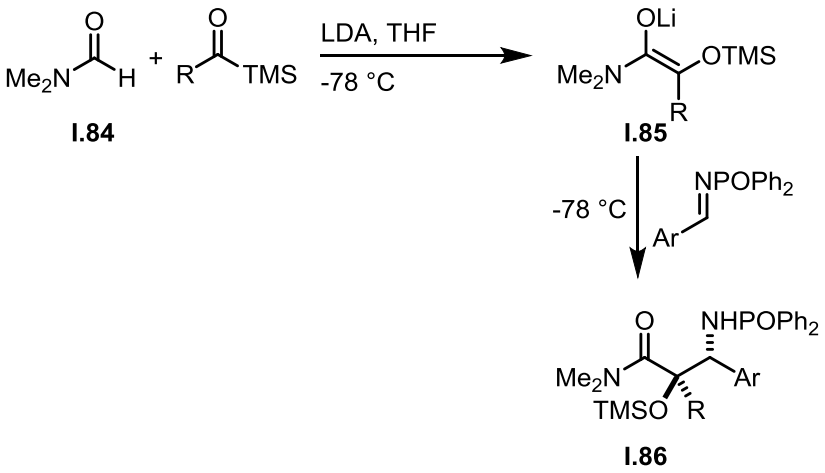
Scheme I-42 Application of the [3+4] cyclisation strategy of Takeda to the synthesis of eight-membered natural product Laurallene.

Lettan *et al.* discovered that addition of amide enolates **I.78** to aromatic acylsilane **I.79** was an efficient way to access β-siloxy homoenolate nucleophiles **I.80**. Unlike in the methods of Takeda, the amide homoenolates are not prone to cyclisation due to the lower electrophilicity of the amide carbonyl function. Therefore electrophilic trapping is possible in an intermolecular fashion, effective electrophilic partners being various alkyl halides, benzaldehyde, acetone and phosphoryl imines **I.81**. The latter electrophiles are particularly appealing as the resulting γ-amino-β-hydroxy amides **I.82** are readily converted to γ-lactams **I.83** by treatment with hydrochloric acid (Scheme I-43). Additionally, stereoselective conditions were found, further improving the value of the method.[31d, 87]



Scheme I-43 Addition of amide homoenolates to N-phosphoryl imines and application the synthesis of γ-lactams.

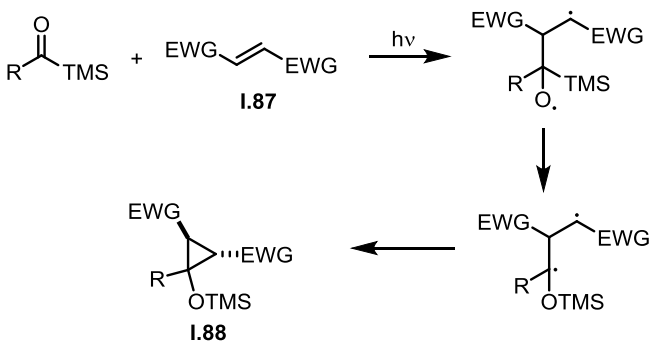
Addition of carbamoyl anions **I.84** to acylsilanes by Lin *et al.* provided the corresponding α-siloxy enolates **I.85** which reacted with phosphoryl imines in a similar way as the homoenolates of Lettan and co-workers. Again, the resulting β-amino-α-hydroxy amides **I.86** were obtained with high diastereoselection (Scheme I-44).[88]



Scheme I-44 Synthesis of β-amino-α-hydroxy amides from the reaction of acylsilanes with carbamoyl anions.

3.2.4 Radical Brook rearrangement

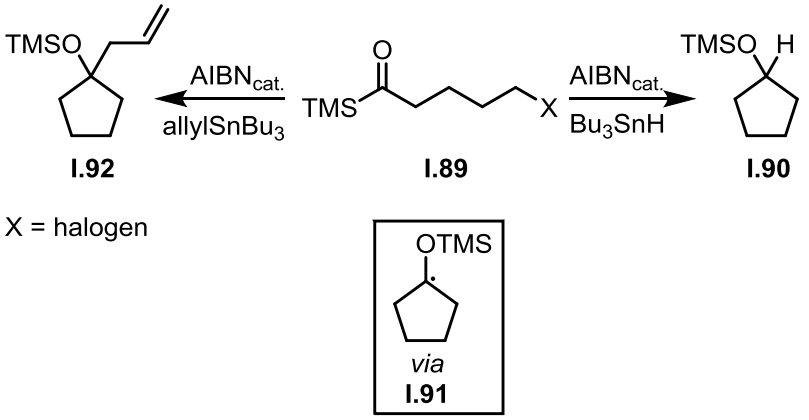
Besides the classical anionic Brook rearrangement, the radical Brook rearrangement exists as well. Unlike its ionic version, the radical Brook rearrangement is not reversible. Therefore no specific effort is needed to balance the equilibrium to one side or the other. However, the radical Brook rearrangement of acylsilanes has been less studied than its anionic counterpart. The possibility of a radical Brook rearrangement was first hypothesised in the photochemical reaction of acylsilanes with electron poor alkenes **I.87** leading to cyclopropane rings **I.88** (Scheme I-45).[89]



Scheme I-45 Radical Brook rearrangement of acylsilanes.

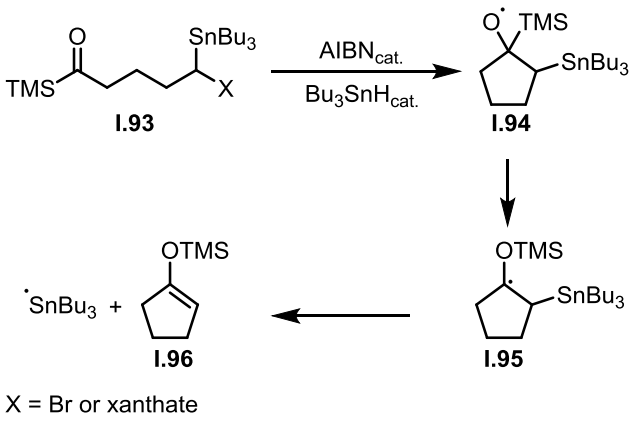
From there on, it has been used to develop several cyclisation reactions. In this perspective, acylsilanes are regarded as geminal radical acceptor/radical donor synthons. δ-haloalkyl acylsilanes **I.89** have been shown to be effective candidates for cyclisation in the presence of a radical initiator. While 5-exo-trig cyclisations lead to silyl protected cyclopentanols **I.90** upon capture of tributyltin hydride,[90] the siloxycarbinyl radical **I.91** intermediate can also be used to capture allylstannanes in tandem bond formation reactions leading to homoallylic silyl ether **I.92** (Scheme I-46).[91] The initial radical of the sequence can be generated as an alkyl, vinyl or aryl

radical with satisfying results in every case. The radical 6-exo-trig annulation is more challenging because a competing 1,5-hydrogen transfer is giving rise to by-products.[92] These cyclisation reactions have been used to synthesise the cyclic core of some natural products.[93]



Scheme I-46 Radical Brook rearrangement/cyclisation sequences.

Modification of the starting acylsilanes allowed the formation of silyl enol ethers from the intramolecular trapping of the carbinyl radical. Indeed, in the presence of a radical initiator δ,δ-bromo,tin-acylsilanes **I.93** cyclised in a 5-exo-trig fashion. The subsequent alkoxy radical **I.94** rearranged leading to the α-tin siloxy carbinyl radical **I.95** which upon fragmentation resulted in a silyl cyclopentenol ether **I.96** along with the tributylstannyl radical (Scheme I-47).[94]



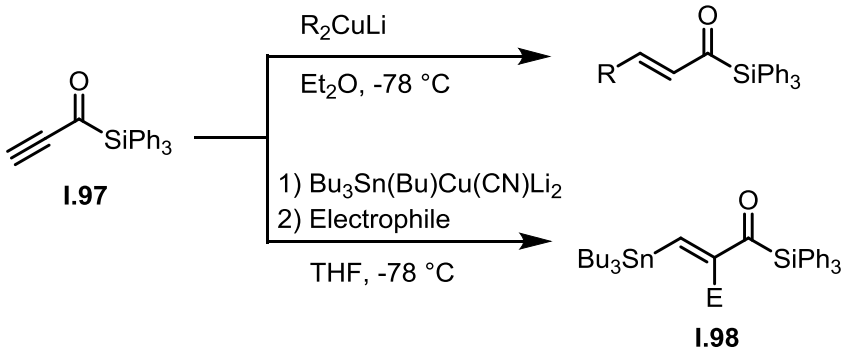
Scheme I-47 Silyl enol ether formation via the radical Brook rearrangement.

This method was generalised to five and six membered silyl enol ethers by placing the final radical acceptor in α position to the acylsilane rather than on the δ position. This fine-tuning hindered competing 1,5-hydrogen abstraction by destabilising the potential resulting radical and allowed efficient 6-exo annulation.[95]

4 Acylsilanes in copper chemistry

While the copper chemistry of carbonylated molecules, e.g. aldehydes, ketones or amides, is well developed, copper mediated transformations of the related acylsilanes are critically underdeveloped.

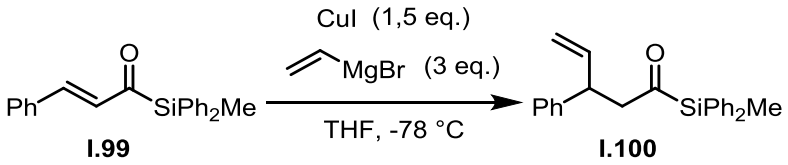
In 1983, Reich mentioned that cuprates add in a typical 1,4-fashion to propenoylsilane but no example of this reaction was given at that time.[43c] Latter, Degl'Innocenti *et al.* reported the 1,4-addition of alkyl, aryl and alkenyl groups to the acetylenic acylsilane **I.97** through the use of cuprates as nucleophiles.[96] The same group extended this methodology to the 1,4-stannylcupration of the same acylsilane **I.97**. The stannylcuprated acylsilane was efficiently trapped by various organic electrophiles or by protons during work-up. Additionally, the resulting β-stannyl-α,β-unsaturated acylsilanes **I.98** were successful candidates for subsequent palladium-catalysed cross-coupling reactions, thereby broadening the reach of this reaction (Scheme I-48).[97]



Scheme I-48 Cuprate conjugated additions to etynylacylsilane.

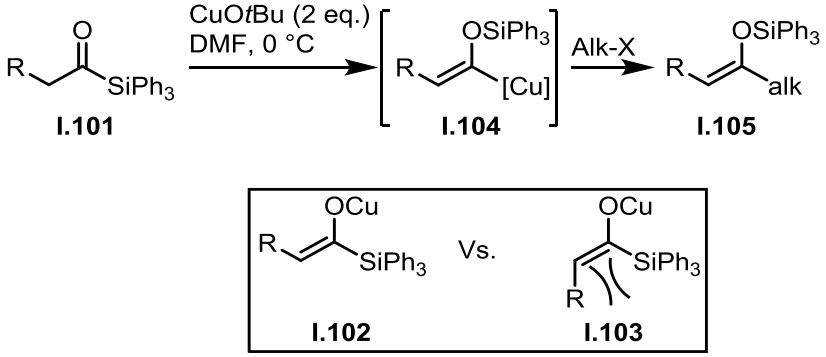
Struggling with regioselectivity issues in the addition of vinylcuprates to cinnamaldehyde, Tsai and co-workers developed the 1,4-addition of

vinylcuprates to the corresponding α,β-unsaturated acylsilane **I.99** (Scheme I-49). After desilylation of the addition product **I.100**, this strategy afforded the desired aldehyde without regioselectivity issues.[98]



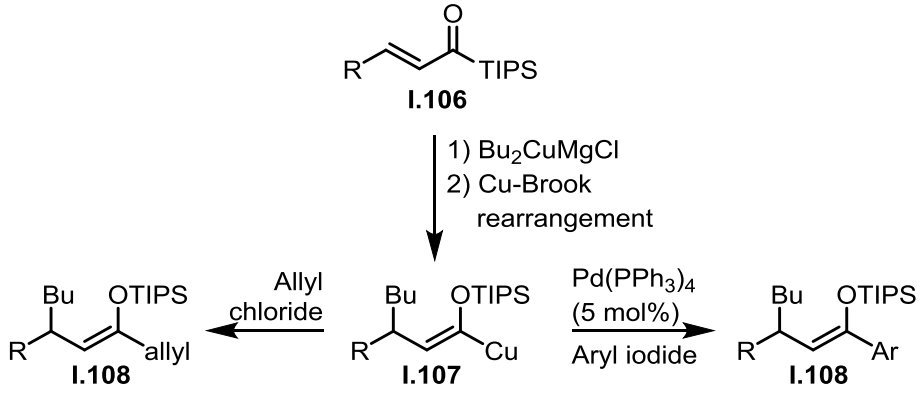
Scheme I-49 Conjugated addition of vinylcuprate to cinnamoylsilane.

During prolific investigation on the copper-mediated Brook rearrangement, Takeda's group discovered that treatment of aliphatic acylsilanes **I.101** with copper *tert*-butanolate in DMF led to the copper enolate **I.102** which readily underwent 1,2-C^{sp2}-to-O-silyl shift. The resulting vinylcopper intermediate **I.104** was used to trap alkyl halides and as nucleophilic partner in palladium-catalysed coupling reactions. In every case, the product was a silyl enol ether **I.105** with complete (*Z*) stereochemistry due to the selective formation of (*Z*) enolate **I.102** avoiding steric clash of the alkyl chain with the large triphenylsilyl group in the (*E*) enolate **I.103** (Scheme I-50).[99]



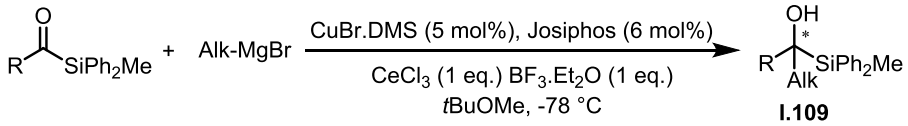
Scheme I-50 Copper-Brook rearrangement of acylsilanes leading to silyl enol ethers.

In the same way, a tandem bond formation methodology was developed. The key vinylcopper intermediate **I.107** was obtained after conjugated cuprate addition to α,β-unsaturated acylsilanes **I.106** and Brook rearrangement of the subsequent copper enolate. Similarly to the previous report, the vinylcopper species **I.107** was obtained with high stereoselectivity and was efficiently trapped by allylic halides or used in cross-coupling reactions affording tri-substituted silyl enol ethers **I.108** (Scheme I-51).[100]



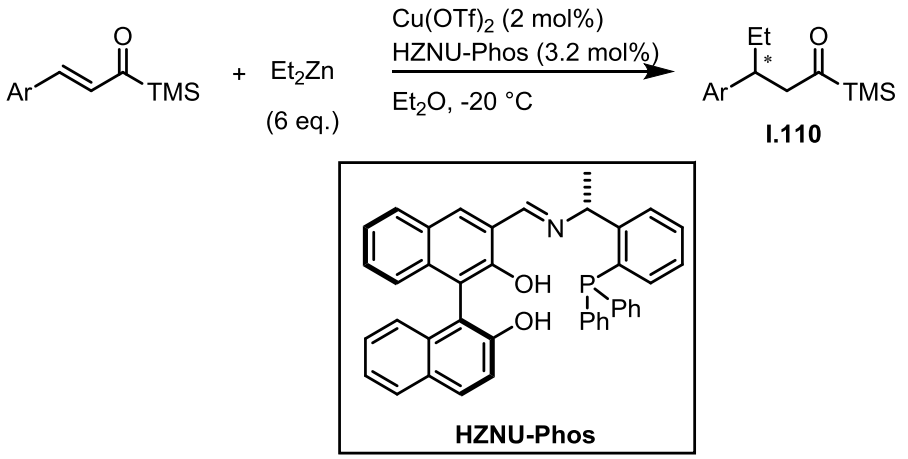
Scheme I-51 Access to vinylcopper intermediates through cuprate conjugated addition to α,β-unsaturated acylsilanes and subsequent synthesis of silyl enol ethers.

More recently, the first copper-catalysed reaction of acylsilanes was reported. It involves the enantioselective 1,2-addition of Grignard reagents to aromatic and α-methyl-α,β-unsaturated acylsilanes giving access to optically active tertiary α-hydroxysilanes **I.109**. In this reaction, the main drawback, i.e. a competing uncatalysed MVPO reduction, was circumvented by the use of a cocktail of Lewis acids, preventing the coordination of the organomagnesium reagents to the carbonyl of the substrate.[101]



Scheme I-52 Copper-catalysed addition of Grignard reagents to acylsilanes.

To date, the most recent report concerning copper and acylsilanes is an enantioselective copper-catalysed addition of diethylzinc to α,β-unsaturated acylsilanes. Hence the method leads to β-ethyl substituted acylsilanes **I.110**. In this reaction, the use of the HZNU-Phos ligand leads to fair enantiomeric excess along with moderate yields. Unfortunately, no other nucleophilic partner than diethylzinc was compatible under the optimised conditions (Scheme I-53).[102]



Scheme I-53 Copper-catalysed addition of diethyl zinc to α,β-unsaturated acylsilanes.

5 Main objectives and outline of the thesis

In this chapter, the use of acylsilanes in tandem bond formation reactions has been underlined. It was shown that they can be transformed in useful and versatile building blocks, e.g. silyl enol ethers and their derivatives, in pharmaceutically relevant compounds, e.g. γ-lactams, but also in complex synthetic intermediates of natural products. The majority of these methods however rely on the use of strong bases and/or strong nucleophiles among which organolithium compounds often appear. As a result, special care must be taken in order to avoid functional group incompatibility or low chemoselectivity.

For decades, catalysis has been one typical solution to those major issues. Indeed, mild and selective catalysts can in several cases replace harsh stoichiometric reagents and therefore improve reaction yields or increase the functional tolerance of the process. When it comes to reactions involving acylsilanes, there is a clear lack of catalytic transformations in comparison with the analogous carbonyl compounds, e.g. ketones, aldehydes, imines, … A few organocatalytic methods have been presented in the previous pages but they each suffer from evident limitations. Organometallic catalytic transformations of acylsilanes also exist but they remain anecdotic.[7]

Cuprous catalysis gathers several desirable assets. Notably, copper(I) catalysts are able to transfer pronucleophiles, e.g. hydrides, boryl groups or silyl groups, under extraordinarily mild conditions. Under similar conditions, nucleophilic copper-carbon reagents can be generated and used to trap electrophiles. In combination with its relatively low cost, the previous features make cuprous catalysis a

strong field of chemical research. Yet, the copper chemistry of acylsilanes remains underdeveloped.

Uses of acylsilanes being mainly limited to classical organic chemistry, it is envisioned that developing new copper(I) catalytic transformations would offer new opportunities to acylsilane chemistry by broadening its scope and making new innovative perspectives available.

In chapter 2, the development of a copper-catalysed domino silylative aldol reaction with acylsilanes is aimed. First, diastereoselective conditions for Reich's silyl enol ether synthesis are developed. The drawbacks of non-catalytic methods are highlighted by the low substrate scope of this method. Finally, the initial goal is partly reached using acrylates as Michael acceptors, giving an entry to complex tertiary α-hydroxysilanes.

Chapter 3 is devoted to a 1,2-selective copper-catalysed hydrofunctionalisation of α,β-unsaturated acylsilanes. After developing asymmetric addition conditions, the substrate scope is broadened to aromatic and aliphatic acylsilanes. A short hypothesis explaining the unusual 1,2-selectivity of the reaction is proposed. The reaction products are finally applied in a reductive copper-catalysed Claisen rearrangement with excellent diastereoselectivity and transfer of chirality.

Chapter 4 concludes this thesis and chapter 5 contains all required experimental data.

6 References

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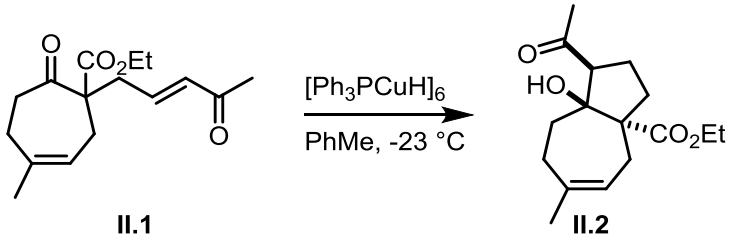
Chapter II Towards copper-catalysed domino reactions of acylsilanes

1 Introduction

Domino reactions are a class of organic reactions in which multiple chemical bonds are created in a single step without isolation of reaction intermediates, changing the reaction conditions or adding new chemicals to the reaction mixture. This type of reaction is extremely desirable because high molecular complexity can be achieved with little waste of time and material.[1]

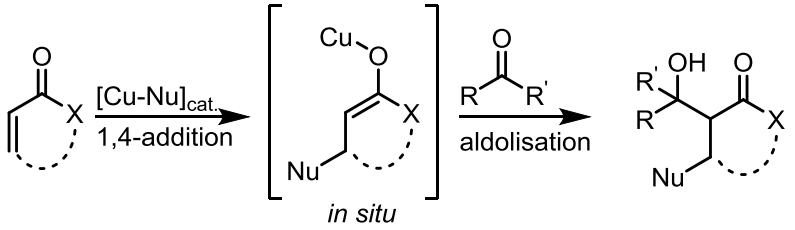
During their investigation on the synthesis of pseudolaric acid A, Chiu and co-workers discovered Stryker's reagent, i.e. a hexameric stable triphenylphosphine-copper hydride reagent, to be an efficient reagent to promote intramolecular domino reduction/aldolisation reactions. In their approach, Stryker's reagent was used as a copper hydride source for the synthesis of a key bicyclic intermediate of their target. Conjugated reduction of the enone **II.1** provided the corresponding copper-enolate *in situ*. This intermediate was subsequently involved in an intramolecular aldol reaction with the ketone affording the desired synthetic intermediate **II.2** (Scheme II-1**)**.[2]



Scheme II-1 Stryker's reagent promoted domino reduction/aldolisation.

1.1 Riant's contribution to copper-catalysed domino reactions

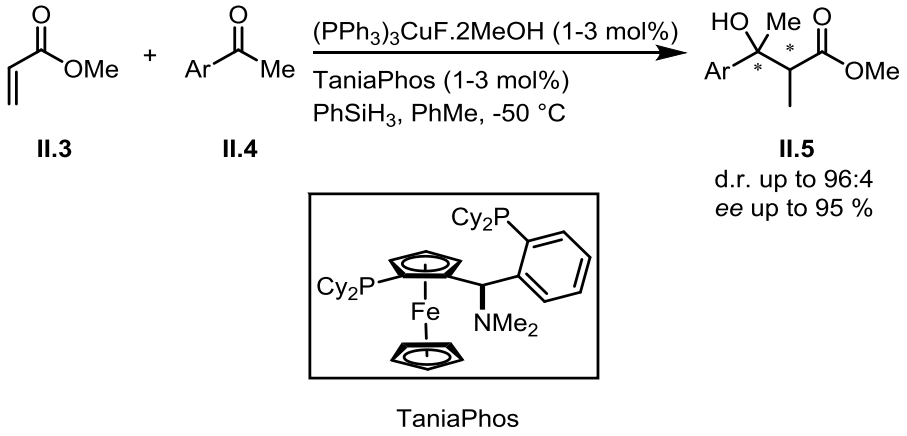
Based on the initial findings of Chiu, our group became interested in the discovery of copper-catalysed domino conjugated addition/aldolisation reactions (Scheme II-2).



Scheme II-2 General strategy of the copper-catalysed domino conjugated addition/aldolisation reactions.

1.1.1 Domino reductive aldol reactions

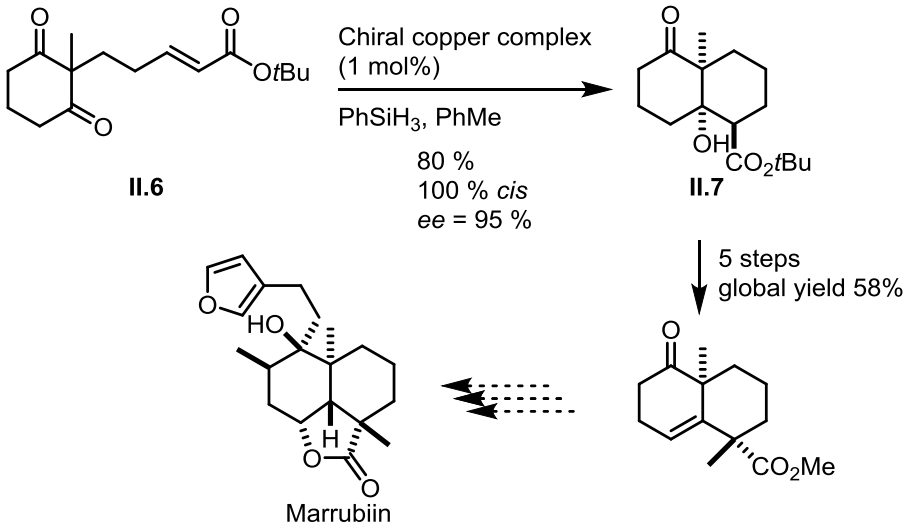
Deschamp *et al.* reported that copper(I) diphosphine complexes can be used in catalytic amounts in combination with phenylsilane to trigger the conjugated reduction of methyl acrylate **II.3** followed by the capture of the resulting enolate by aromatic ketones **II.4**. This domino reaction resulted in the formation of tertiary alcohols **II.5** with good yields while the direct reduction of the ketones by the copper hydride species was mostly insignificant. The use of a chiral TaniaPhos ligand allowed high diastereoselectivity and enantioselectivity during the formation of the products (Scheme II-3).[3]



Scheme II-3 Copper-catalysed domino conjugated reduction/aldolisation.

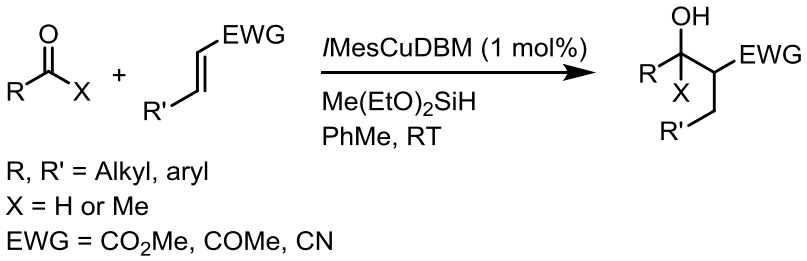
This method was further expanded to the intermolecular capture of aromatic and aliphatic aldehydes by methyl acrylate-derived enolates. The resulting β-hydroxyesters were obtained with fair enantiomeric excesses although moderate diastereoselectivity.[4]

A domino conjugated reduction/intramolecular aldolisation reaction catalysed by chiral copper diphosphine complexes leading to fused bicyclic compounds was next developed. The bulkiness of the ester moiety was found to have a great impact on the diastereomeric outcome of the reaction. Indeed, while methyl carboxylate resulted in a moderate diastereomeric ratio (*cis*:*trans* = 72:28), the corresponding *tert*-butyl carboxylate **II.6** led to complete *cis* selectivity of the bicyclic product **II.7** which was obtained with good enantiomeric excess (Scheme II-4).[5] This intramolecular cyclisation methodology was applied to the synthesis of a key synthetic intermediate of the natural diterpene Marrubiin.[6]



Scheme II-4 Application of the copper-catalysed domino reaction to the synthesis of a key intermediate towards Marrubiin.

Notably, (NHC)copper complexes have also been used as catalysts in this type of reactions and efficiently catalysed the reduction/aldolisation of various Michael acceptors such as acrylates, acrylonitriles and enones (Scheme II-5).[7]

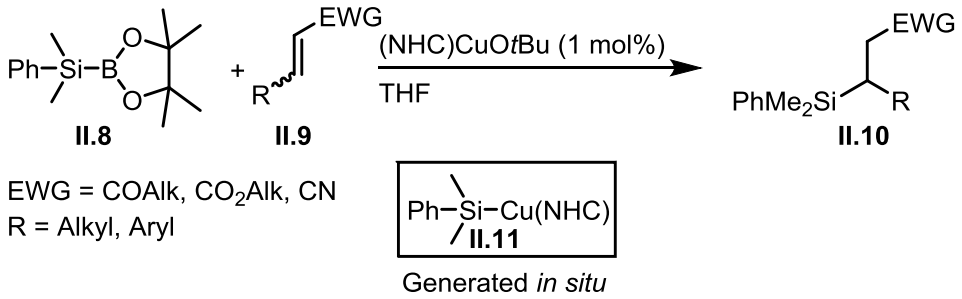


Scheme II-5 (NHC)copper complexes as catalyst for domino reductive aldol reactions.

1.1.2 Domino silylative aldol reactions

Conjugated addition of heteroatoms instead of hydrides would lead to even higher molecular complexity through domino addition/aldol reactions. Early 2010, Lee and Hoveyda reported that Suginome's reagent **II.8** reacted well with chiral NHC copper alkoxides to

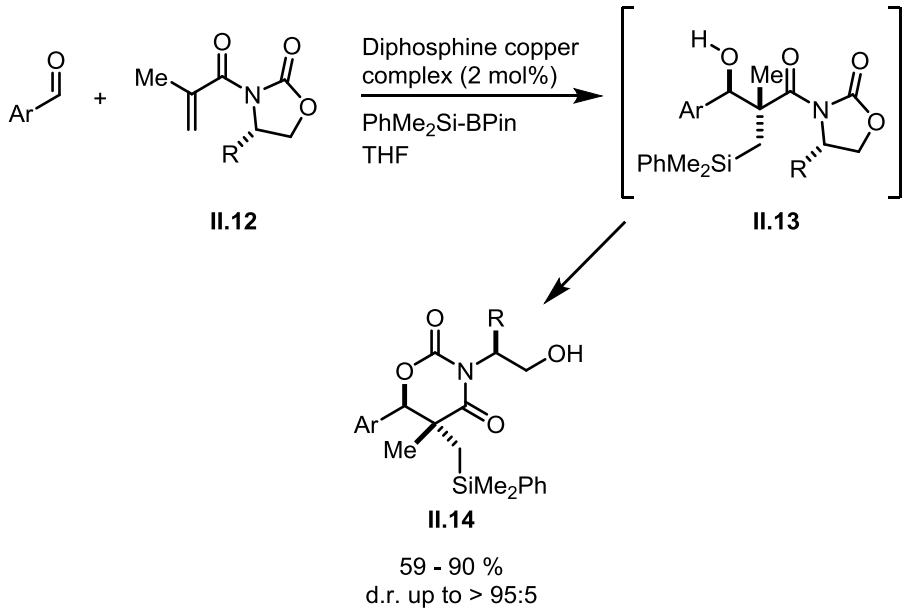
generate copper-silicon complexes **II.11**. Catalytic formation of these silylcopper reagents led to efficient asymmetric conjugated addition to a range of α,β-unsaturated electrophiles **II.9** yielding β-silylated products **II.10** (Scheme II-6). In their report, a preliminary experiment shows that the intermediate enolate can trap benzaldehyde to yield a domino adduct.[8]



Scheme II-6 Copper-catalysed conjugated addition of Suginome's reagent to Michael acceptors.

The same year, our group reported the copper-diphosphine catalysed domino conjugated silylation/intermolecular aldolisation of Michael acceptors. In this reaction, the use of methyl methacrylate as enolate precursor leads to the aldol product bearing a quaternary carbon centre while the use of acetophenone as final electrophile yields tertiary alcohols, yet under standard conditions no diastereoselectivity was observed. Replacing the methacrylates by Michael acceptors bearing chiral oxazolidinone auxiliaries however resulted in a highly diastereoselective reaction. Hence, under these conditions α-methyl enoyloxazolidinones **II.12** granted access to quaternary carbon atoms with high diastereoselective control. It should be noted that the domino adduct **II.13** spontaneously underwent ring-opening-

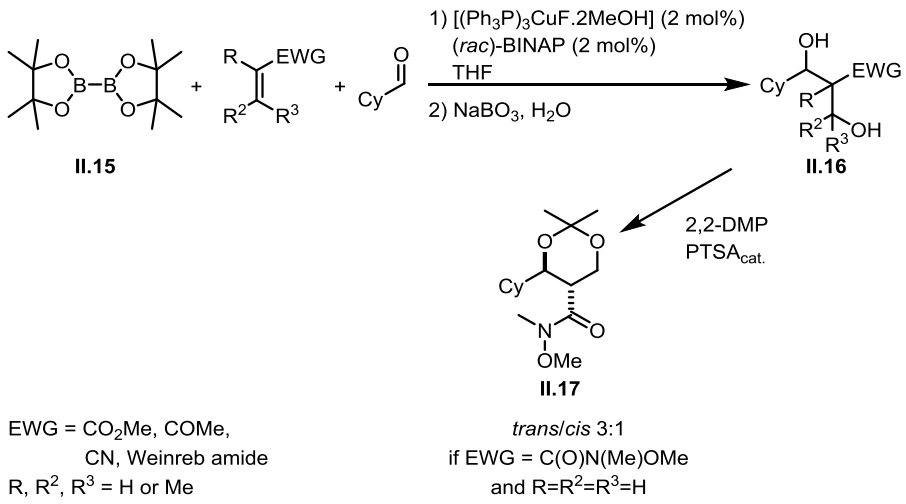
cyclisation rearrangement to the six-membered product **II.14** (Scheme II-7).[9]



Scheme II-7 Diastereoselective domino silylative aldol reaction with enoyloxazolidinones.

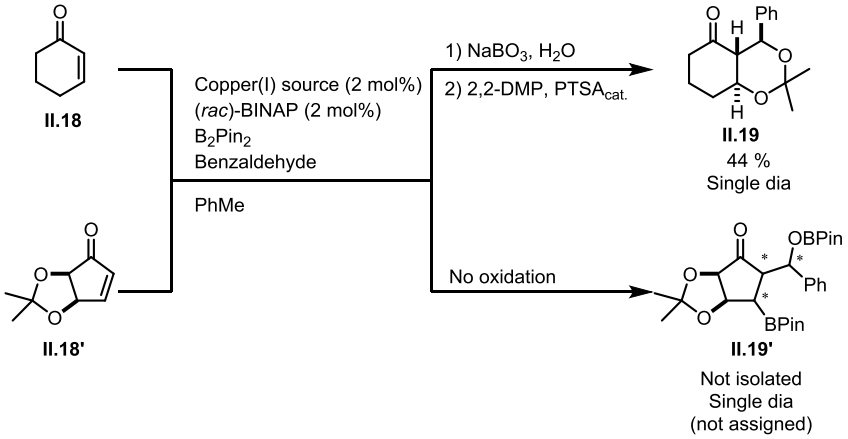
1.1.3 Domino borylative aldol reactions

Similarly to Suginome's reagents, bispinacolatodiboron **II.15** can also be used as an efficient pronucleophile in copper catalysis to transfer a boron moiety to electrophiles. In the context of domino conjugated addition/aldol reactions, this reagent's potential was investigated. Under similar conditions as for the reductive and silylative domino reactions, **II.15** was efficiently transferred to several Michael acceptors in 1,4-fashion followed by the capture of aldehydes by the resulting copper enolates. Even tough good yields of the final diols **II.16** were obtained after oxidation of the borylated domino adducts, the diastereoselectivities were disappointingly limited to a 3:1 *trans*:*cis* ratio at best, as determined after cyclisation of **II.16** to ketal **II.17** (Scheme II-8).



Scheme II-8 Copper-catalysed borylative aldol reaction.

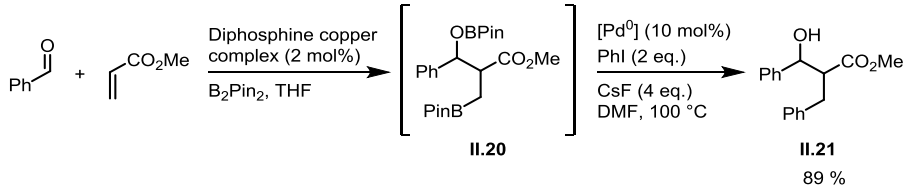
This issue was efficiently tackled by using cyclic enones **II.18** and **II.18'** and the domino adducts **II.19** and **II.19'** were obtained as single diastereoisomers in both investigated cases (Scheme II-9).



Scheme II-9 Stereoselective borylative aldol reactions with cyclic enones.

Finally, the borylated domino adducts **II.20** were used as nucleophilic partners without further oxidation or purification in a palladium-catalysed Suzuki type coupling with phenyl iodide. The product **II.21** was obtained with an excellent yield of 89% from the methacrylate (Scheme II-10). This final derivatisation shows the potent of the

domino borylative aldol reaction as it gives access to many post-functionalisation opportunities *via* palladium catalysis.



Scheme II-10 One-pot domino borylative-aldol reaction/Suzuki coupling.

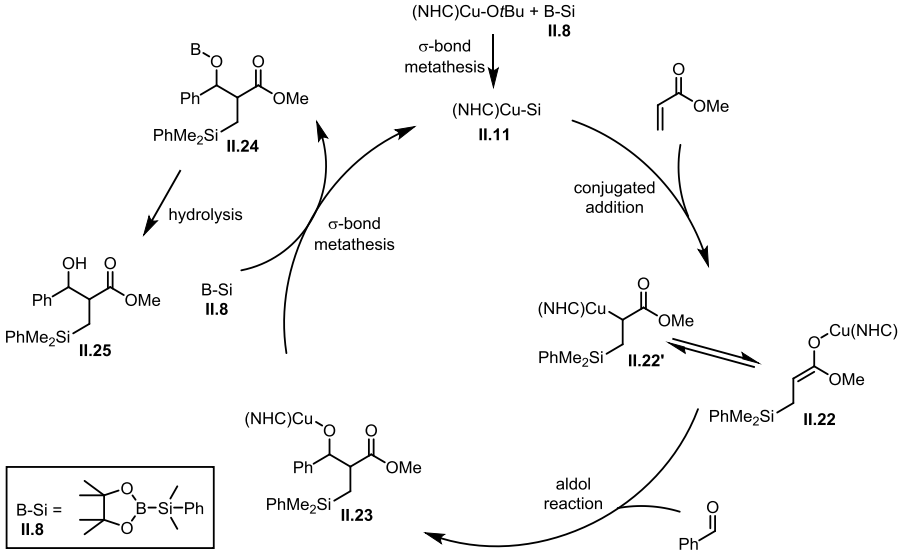
1.1.4 General mechanism of the Riant's domino reactions

All the previously described domino reactions from our group obey to the same catalytic system which deserves to be detailed for the sake of this thesis.

Previously, diphosphine copper complexes were mainly employed to catalyse the domino reactions but NHC ligands showed to allow similar reactivity to the catalyst and avoid problems linked with the complexation/decomplexation equilibrium often observed with phosphine ligands. Hence, for the sake of clarity, the catalytic cycle will be explained based on robust (NHC)copper complexes. However the following statements remain applicable to diphosphine copper complexes. Furthermore, it was chosen to explain the catalytic cycle for the conjugated silylation reaction. Again, a similar pathway is expected for the corresponding reductive and borylative reactions.

A key step in the catalytic cycle is the formation of the copper-nucleophile species. The (NHC)copper *tert*-butoxide undergoes a σ-bond metathesis with the pronucleophile, i.e. the borosilane **II.8**, leading to the silyl-copper complex **II.11**. This complex is then involved in a conjugated addition to a Michael acceptor. The resulting copper enolate is in equilibrium between two forms, i.e. the O-enolate **II.22** and the C-enolate **II.22'**. Subsequent reaction with a

carbonylated electrophile, e.g. benzaldehyde, will lead to the copper alkoxide **II.23**. Then, the latter copper intermediate **II.23** reacts with an equivalent of the pronucleophile **II.8** leading to the regeneration of the catalytically active silyl-copper species **II.11**. Simultaneously, the boryl-protected aldol adduct **II.24** is released. Upon hydrolysis under suitable conditions, the unprotected aldol product **II.25** is obtained (Scheme II-11).

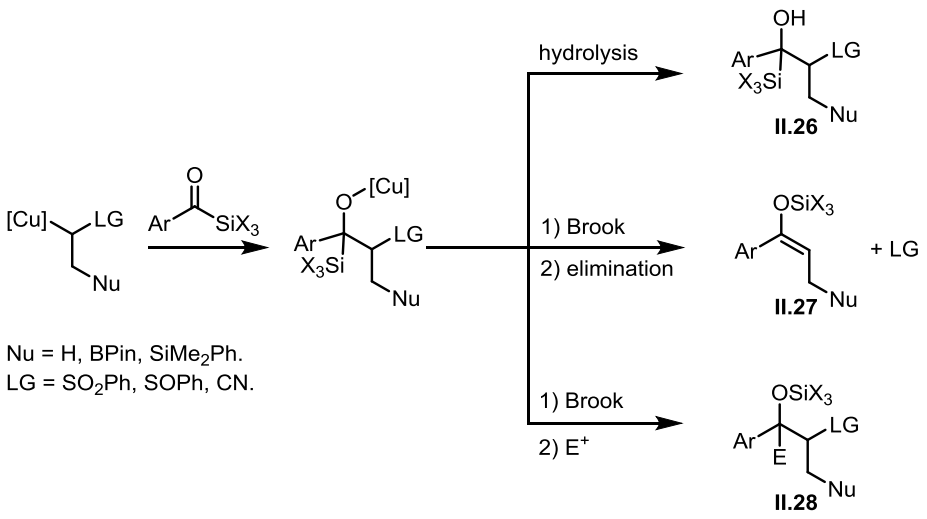


Scheme II-11 General mechanism of the copper-catalysed domino conjugated addition/aldolisation reactions.

2 Aim

As pointed out in the general introduction, acylsilanes are an intriguing class of organic compounds which arise the curiosity of organic chemists. Acylsilanes were extensively used for the synthesis of regio-defined silyl enol ethers. The methodology relies on a nucleophilic addition to an acylsilane, followed by a Brook rearrangement leading to the formation of a siloxycarbanion and to the final ejection of an α-leaving group.

Since a synthetic strategy towards acylsilanes was recently developed in our group,[10] we envisioned that our knowledge in the field of copper-catalysed domino addition/aldol reactions could be coupled with acylsilane chemistry. Indeed, enolates generated from the copper-catalysed conjugated addition of pronucleophiles to Michael acceptors could be used to trap acylsilanes. After capture, the process could be interrupted leading to functionalised α-hydroxysilanes **II.26**. However, subsequent Brook rearrangement could lead to the ejection of a leaving group or to the capture of an electrophile affording silyl enol ether **II.27** or silyl ethers **II.28** respectively (Scheme II-12). Such a methodology would be one of the first copper-catalysed transformations of acylsilanes and to our knowledge no copper-catalysed Brook rearrangement has been reported in the literature so far.

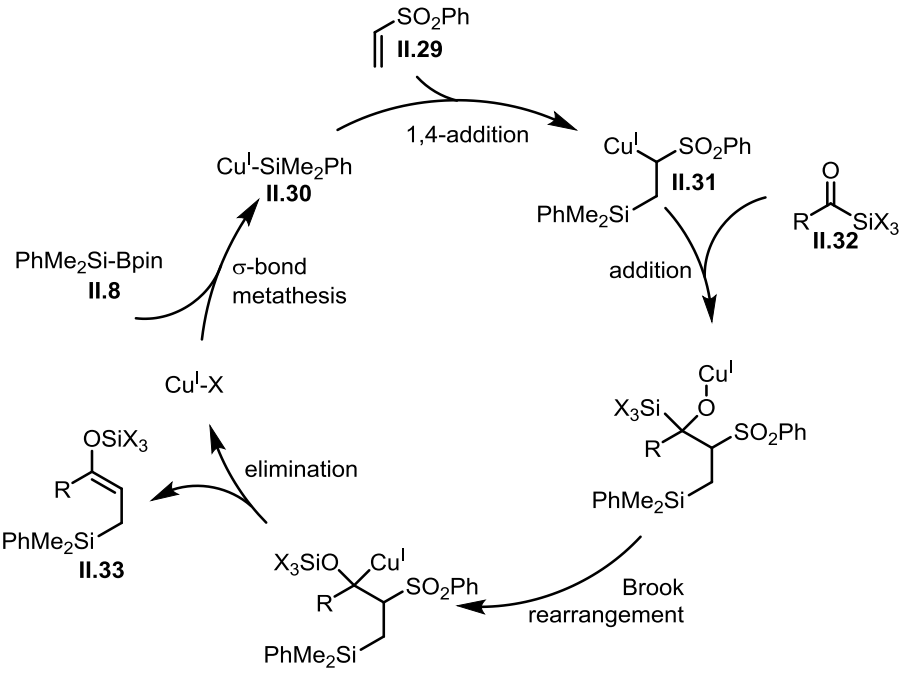


Scheme II-12 Copper-catalysed additions to acylsilanes via domino strategies.

To this end, a study of the copper-catalysed domino conjugated addition/aldolisation/Brook rearrangement reaction was undertaken.

3 Results and discussion

In our quest to the domino conjugated addition/aldolisation/Brook rearrangement sequence, it was first decided to investigate the copper-catalysed conjugated silylative aldol/Brook rearrangement of vinylsulfones. In this reaction, Suginome's reagent **II.8** would serve as pronucleophile, the vinylsulfone **II.29** would play the role of the Michael acceptor undergoing β-functionalisation by a silyl-copper nucleophilic species **II.30**. The α-cupro-sulfone intermediate **II.31** would then trap an acylsilane **II.32**. Subsequent Brook rearrangement and elimination of the sulfonyl leaving group would lead to the regio-defined silyl enol ethers **II.33** (Scheme II-13).



Scheme II-13 Targeted domino silylative/addition/Brook rearrangement/elimination sequence.

As domino reactions involve several bond formations in one single process, it was decided to study these successive elementary steps independently to avoid competitions and unproductive interactions between the different reagents.

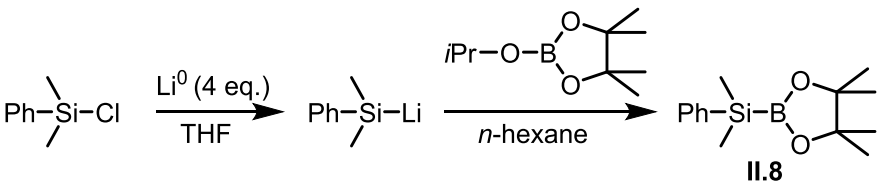
3.1 Copper-catalysed β-silylation of vinylsulfones

The first elementary step involved in the targeted domino transformation is the copper(I)-catalysed conjugated addition of Suginome's reagent to the vinylsulfone. Although some reports on the copper-catalysed β-silylation of α,β-unsaturated sulfones exist,[11] no example of the conjugated copper(I)-catalysed silylation of vinylsulfone with borosilane reagents is known. However, the conditions reported by Moure *et al.* for the catalytic asymmetric conjugate borylation of α,β-unsaturated sulfones with bisboronate[12] might be compatible with Suginome's reagent to conduct the desired β-silylation reaction. Based on this report, the exploration was initiated.

3.1.1 Synthesis of the substrates

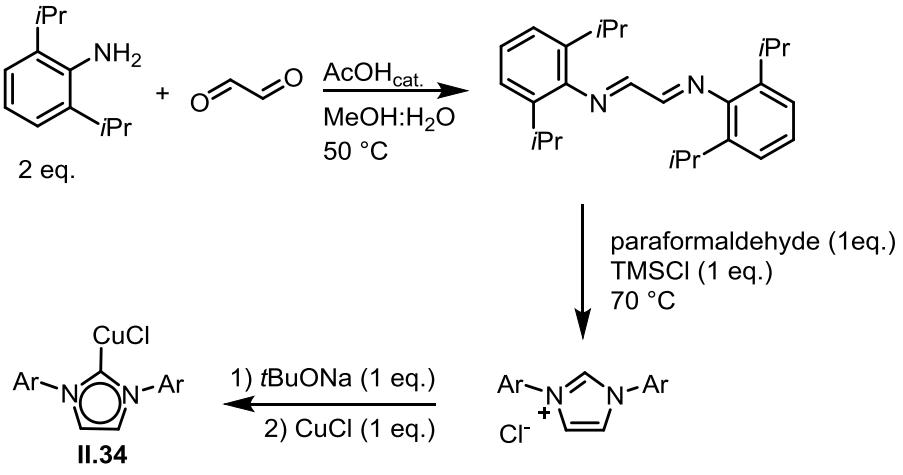
While the simple vinylsufone needed for the initial tests is commercially available, Suginome's reagent and the catalyst need to be synthesised.

Suginome's reagent was synthesised according to a procedure of the literature.[13] Dimethylphenylchlorosilane was first treated with an excess of metallic lithium affording the corresponding silyllithium species. The latter was reacted with 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane to yield the final product **II.8** as a colourless sensitive oil after distillation (Scheme II-14).



Scheme II-14 Synthesis of Suginome's reagent.

In the role of the copper(I) source, *I*PrCuCl was chosen as a model candidate because of its robustness, easy synthesis and bench stability. It was synthesised in three steps following the literature.[14] An aqueous solution of glyoxal was reacted at 50 °C with two equivalents of 2,6-diisopropylaniline in the presence of a catalytic amount of acetic acid leading to the formation of the corresponding diimine as yellow crystals. The diimine was then treated with paraformaldehyde and trimethylsilylchloride affording the imidazolium salt *I*Pr.HCl. Subsequent deprotonation by sodium *tert*-butanolate and complexation with copper(I) chloride led to the bench-stable (NHC)copper complex **II.34** as an off-white powder with an overall yield of 64% over three steps (Scheme II-15).



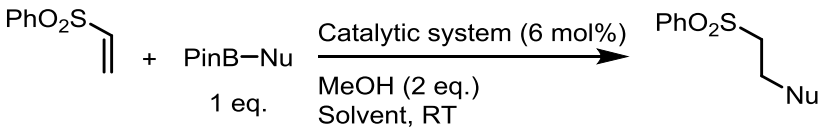
Scheme II-15 Synthesis of IPrCuCl.

3.1.2 Catalytic tests and optimisation

The system described by Moure et al. makes use of copper(I) chloride in combination with sodium tert-butoxide as copper source and methanol as final proton source. Although it is a commonly used catalytic system, it was preferred to work with IPrCuCl in order to avoid using highly air-sensitive copper(I) chloride which requires glovebox manipulation (Table II-1).

The (NHC)copper precatalyst **II.34** was efficiently activated by sodium *tert*-butoxide affording the active catalytic species *I*PrCuO*t*Bu *in situ*. This catalytic cocktail satisfyingly substituted the copper diphosphine system used by Moure *et al.* in their β-borylation reaction (entry 1 vs. entry 2). Next, the ability of the (NHC)copper complex to transfer Suginome's reagent to the vinylsufone was studied. In THF with a catalytic loading of 6 mol%, the vinylsulfone was β-silylated with 79% yield (entry 3). Running the reaction in toluene improved the yield to 89% (entry 4) while using DCM (entry 5) or acetonitrile (entry 6) resulted in uncomplete conversions after overnight stirring.

Table II-1 Short optimisation of the IPrCuCl-catalysed conjugated silylation of vinylsulfone.



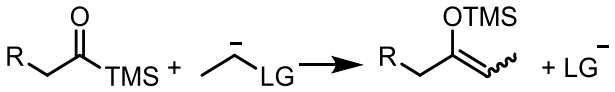
Entry	Catalytic system	Nu	Solvent	$\frac{P}{P+SM}$ ratio[a] (yield[b])
1	CuCl/*t*BuONa/BINAP	BPin	THF	100% (n.d.)
2	*I*PrCuCl/*t*BuONa	BPin	THF	100% (n.d.)
3	*I*PrCuCl/*t*BuONa	$SiMe_2Ph$	THF	100% (79%)
4	*I*PrCuCl/*t*BuONa	$SiMe_2Ph$	PhMe	100% (89%)
5	*I*PrCuCl/*t*BuONa	$SiMe_2Ph$	DCM	73% (n.d.)
6	*I*PrCuCl/*t*BuONa	$SiMe_2Ph$	MeCN	29% (n.d.)

[a] P = Desired Product; SM = Limiting Starting Material. The ratios were determined from the crude ^1H NMR spectra which mainly displayed P and SM with > 80% purity. [b] Isolated yields.

The copper-catalysed conjugated silylation of the model vinylsulfone in toluene was considered to be satisfactory, hence, no additional optimisation was carried out.

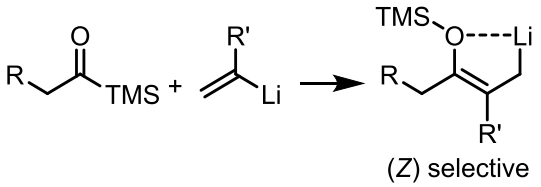
3.2 Regio- and stereoselective silyl enol ether formation

Simultaneously to the investigations on the copper-catalysed conjugated silylation of vinylsulfone, stereoselective conditions for the silyl enol ether synthesis of Reich and co-workers were sought. As explained in the general introduction, addition of a nucleophile bearing an α-leaving group to acylsilanes results in the formation of silyl enol ethers after elimination of the leaving group.[15] This method gives access to products with total regioselectivity (Scheme II-16).



Scheme II-16 Reich's regioselective synthesis of silyl enol ethers via the Brook rearrangement.

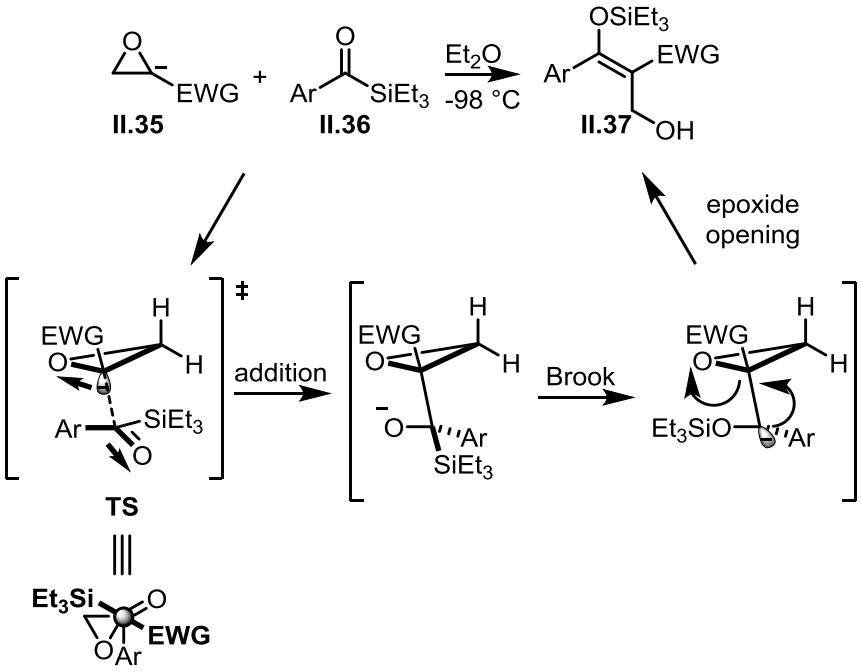
Although the method has been extensively studied and used in synthesis, the only stereoselective conditions are based on the intramolecular coordination of the delocalised allylic carbanion resulting of the Brook rearrangement.[16] Therefore, high stereoselective control during the formation of the products is only possible when allylic carbanionic transposition is possible (Scheme II-17).



Scheme II-17 Stereoselective version of Reich's silyl enol ether synthesis by allylic transposition of the anion.

More recently, a similar strategy based on the addition of oxiranyl anions **II.35** to acylsilanes was reported by Song and co-workers.[17] In their approach, the Brook rearrangement initiated by the initial addition to the acylsilane **II.36** triggered the opening of the epoxide ring leading to the formation of tetrasubstituted silyl enol ethers **II.37** with good yields and excellent stereoselectivity. The high stereoselectivity is proposed to be due to a preferred transition state **TS** during the addition step in which the bulky electron withdrawing group and the silyl group are distant from each other, and the oxygen atoms are positioned to minimise the dipolar moment. The subsequent Brook rearrangement/ring opening cascade then leads to the product

II.37 in which the silyl ether and the electron withdrawing group are in *syn* position to each other (Scheme II-18).



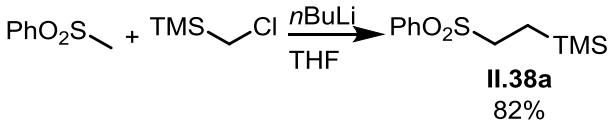
Scheme II-18 Stereoselective silyl enol ether synthesis by addition of oxiranyl anions to acylsilanes.

Given that the stereoselectivity of both previously cited methods is highly substrate dependent, they do not allow access to every pattern of silyl enol ethers. Therefore Reich's methodology was inspected with the hope of finding conditions giving access to any stereoisomer of a large array of structurally diverse silyl enol ethers.

3.2.1 Model reaction

This investigation was carried out with the goal of collecting a maximum information to be later applied to the copper-catalysed domino reaction. In this context, it was chosen to work with a β-silylsulfone nucleophile that would react similarly to the α-cupro-sulfone intermediate **II.31** obtained after the silylcupration of vinylsulfones.

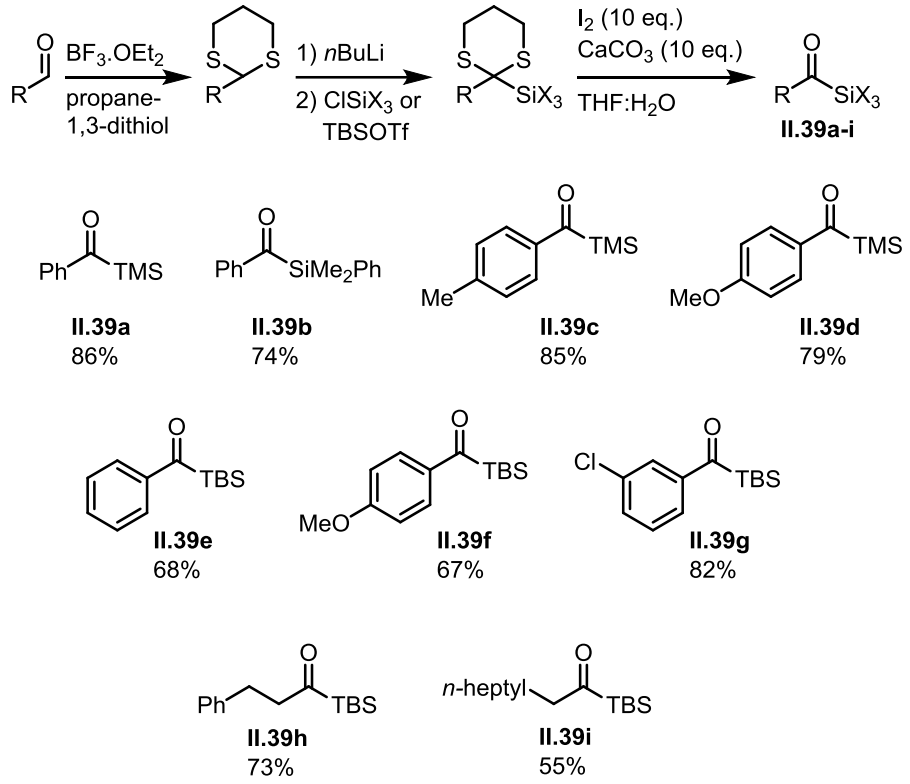
The model sulfone was synthesised in one step from methyl phenyl sulfone.[18] Deprotonation by *n*BuLi followed by addition of (chloromethyl)trimethysilane afforded the β-silylsulfone **II.38a** with 82% yield as a white solid (Scheme II-19).



Scheme II-19 Synthesis of a β-silylsulfone from methyl phenyl sulfone.

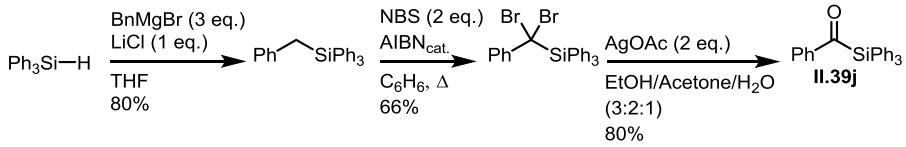
Simple aromatic acylsilanes were chosen as model electrophiles given that aromatic substitution is known to favour the Brook rearrangement by stabilisation of the α-siloxycarbanion. The dithiane route gave access to aromatic substituted acylsilanes in three steps.[19] Benzaldehyde derivatives were condensed with propane-1,3-dithiol in the presence of boron trifluoride etherate leading to the corresponding dithianes as smelly white solids with full conversion. Dithianes were deprotonated by *n*BuLi in THF. The resulting carbanions were used to capture silylchlorides to afford silylated dithianes. *Tert*-butyldimethylchlorosilane being a hygroscopic solid, it was replaced by its triflate analog for practical reasons. The silyldithianes were finally deprotected in THF:H_2O (4:1) in the presence of a large excess

of iodine and calcium carbonate. The acylsilanes **II.39a-i** were isolated as bright yellow oils or solids with good overall isolated yields over three steps (Scheme II-20).



Scheme II-20 Corey-Brook strategy for the synthesis of acylsilanes from aldehydes.

The latter methodology was inefficient for the synthesis of acylsilanes bearing bulkier silyl groups. Therefore, triphenylsilylacylsilane **II.39j** was synthesised according to Brook's original procedure.[20] Benzyltriphenylsilane was obtained from the reaction of benzylmagnesium bromide with triphenylsilane in THF in the presence of LiCl.[21] Subsequent oxidation by NBS led to the *gem*-dibromo adduct which was hydrolysed in the presence of silver acetate and water. The triphenylsilyl acylsilane **II.39j** was obtained as a bright yellow solid with 42% yield over three steps (Scheme II-21).



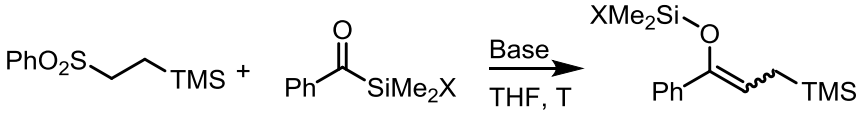
Scheme II-21 Brook's synthesis of acylsilanes.

3.2.2 Optimisation

3.2.2.1 (*Z*) Selective conditions

With the substrates in hand, stereoselective conditions for Reich's silyl enol ether synthesis were sought (Table II-2). Initial screening reactions were performed in THF at room temperature. Deprotonation of the model sulfone **II.38a** by *n*BuLi followed by addition of the acylsilane **II.39b** to the reaction mixture led to the complete conversion of the reagents to the corresponding silyl enol ether **II.40ab** with a slight preference for the (*E*) isomer (entry 1). Replacing *n*BuLi by KHMDS caused a spectacular inversion of the reaction's stereoselectivity to the (*Z*) isomer with 90% selectivity (entry 2). Cooling the reaction medium to -78 °C improved the selectivity to a 97:3 *Z*:*E* ratio (entry 3). Finally, the less hindered acylsilane **II.39a** allowed a perfect (*Z*) selectivity for the investigated transformation (entry 4).

Table II-2 Optimisation of (Z) selective silyl enol ether formation conditions.



II.38a **II.39a-b** **II.40aa-ab**

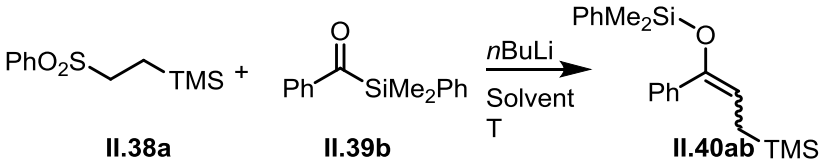
Entry[a]	X	Base	T (°C)	*Z:E* ratio[b]
1	Ph	*n*BuLi	20	40:60
2	Ph	KHMDS	20	90:10
3	Ph	KHMDS	-78	97:3
4	Me	KHMDS	-78	99:1

[a] $\left(\frac{P}{P+SM}\right).100 = 100\%$ in every case. P = Desired Product; SM = Limiting Starting Material. The ratios were determined from the crude ^{1}H NMR spectra which mainly displayed P and SM with > 80% purity. The products were not isolated. [b] *E*:*Z* ratios were determined by ^{1}H NMR and stereoisomers were assigned by NOESY experiments.

3.2.2.2 (*E*) Selective conditions

As observed previously, the counter-anion effect has a strong impact on the selectivity of the reaction. Large cations seems to favour (*Z*) selectivity hence it was decided to use lithiated bases for the opposite (*E*) optimisation (Table II-3). As reported earlier, *n*BuLi slightly favours the formation of the (*E*) silyl enol ether in THF (entry 1). Besides the choice of the base, the main parameter to modify is the solvent. Surprisingly, triethylamine proved to be a suitable solvent and the product was obtained with a satisfying 75% (*E*) selectivity (entry 2). Similarly to the (*Z*) selective conditions, cooling the reaction mixture to -78 °C enhanced the reaction's selectivity (entry 3). The intriguing effect of triethylamine was attributed to its low dipolar moment. Consequently, the effect of several more usual solvents with low dipolar moments were examined. While diethyl ether resulted in a slightly lower selectivity (entry 4), the use of *n*-hexane essentially allowed a selectivity similar to triethylamine (entry 5).

Table II-3 Initial optimisation of (E) selective silyl enol ether formation conditions.

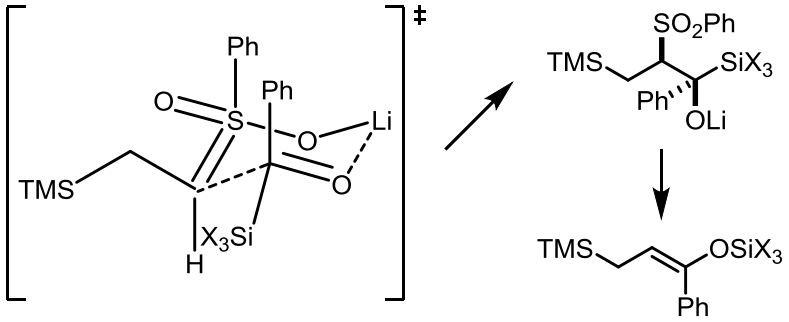


II.38a **II.39b** **II.40ab**

Entry[a]	Solvent	T (°C)	Dielectric constant[22]	*E*:*Z*[b]
1	THF	20	7.5	60:40
2	Et_3N	20	2.4	75:25
3	Et_3N	-78	2.4	81:19
4	Et_2O	-78	4.3	73:27
5	*n*-hexane	-78	1.9	78:22

[a] $\left(\frac{P}{P+SM}\right).100 = 100\%$ in every case. P = Desired Product; SM = Limiting Starting Material. The ratios were determined from the crude ^{1}H NMR spectra which mainly displayed P and SM with > 80% purity. The products were not isolated. [b] *E*:*Z* ratios were determined by ^{1}H NMR and stereoisomers were assigned by NOESY experiments.

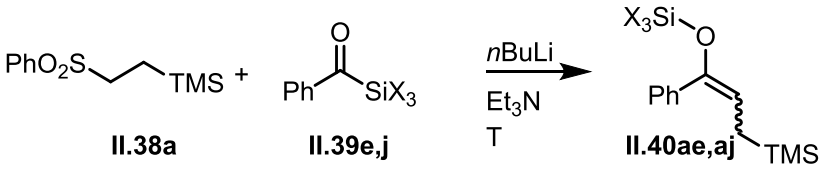
From the earlier results on the (*Z*) selective optimisation, it appeared that the steric bulk of the silyl group of the acylsilane had an influence on the stereochemical outcome of the reaction. Together with the fact that small cations and solvents with low dipolar moments favour (*E*) selectivity, a transition state for the addition of the sulfone on the acylsilane was hypothesised. In this context, a parallel was drawn with the Julia-Kocienski olefination in which apolar solvents and small cations lead to a closed transition state (Scheme II-22).[23] In this transition state configuration, the main degree of freedom is the acylsilane's orientation. As the pseudoequatorial position of the silyl group results in the formation of the (*E*) product, it was envisioned that bulkier acylsilanes would enhance the selectivity of the reaction by blocking the acylsilane in the right position in the transition state.



Scheme II-22 Closed transition state model for the (E)-selective silyl enol ether synthesis.

To verify this hypothesis, the bulky triphenylsilyl acylsilane **II.39j** was synthesised and tested in the reaction (Table II-4). Indeed, at room temperature, addition of the model sulfone **II.38a** to **II.39j** resulted in the formation of the desired compound with a satisfying 86:14 *E*/*Z* ratio (entry 1). The more easily accessible TBS acylsilane **II.39e** also gave good (*E*) selectivity although slightly lower (entry 2). Finally, running the reaction at -78 °C resulted in better *E*:*Z* ratios in both cases, i.e. 89:11 (entry 3) and 95:15 (entry 4).

Table II-4 Effect of silicon's steric bulk on the E:Z ratio.



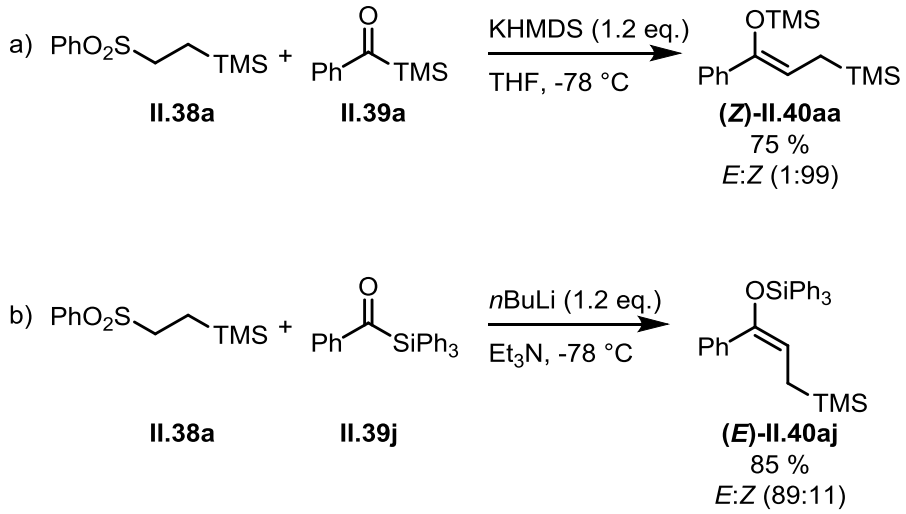
II.38a **II.39e,j** **II.40ae,aj**

Entry	SiX_3	T (°C)	*E*:*Z*
1	$SiPh_3$	20	86:14
2	TBS	20	79:21
3	$SiPh_3$	-78	89:11
4	TBS	-78	85:15

[a] $\left(\frac{P}{P+SM}\right).100 = 100\%$ in every case. P = Desired Product; SM = Limiting Starting Material. The ratios were determined from the crude ^{1}H NMR spectra which mainly displayed P and SM with > 80% purity. The products were not isolated. [b] *E*:*Z* ratios were determined by ^{1}H NMR and stereoisomers were assigned by NOESY experiments.

3.2.2.3 Optimal conditions

After screening of the reaction conditions, it was shown that simple modifications could lead selectively to both isomer of the final silyl enol ethers following Reich's model. The optimal conditions were repeated with isolation of the silyl enol ethers. While deprotonation of the model sulfone **II.38a** by KHMDS in a polar solvent afforded **(*Z*)-II.40aa** with great selectivity and 75% yield, use of *n*BuLi as a base in weakly polar solvents with bulky acylsilanes affords **(*E*)-II.40aj** with great selectivity and 85% yield (Scheme II-23). It should be noted that silyl enol ethers bearing small silyl groups suffer from easier hydrolysis explaining the lower yields after flash column chromatography over silica gel.



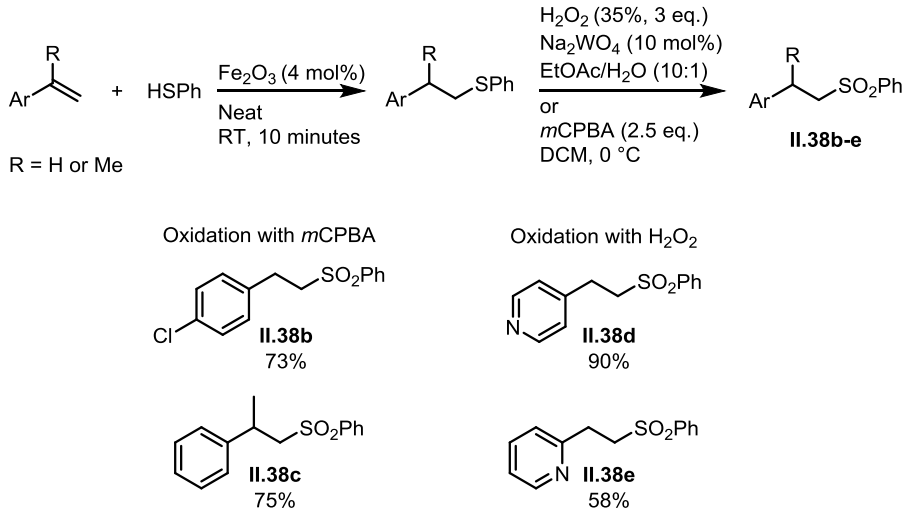
Scheme II-23 Optimal stereoselective conditions for Reich's silyl enol ether synthesis.

3.2.3 Scope of the reaction

3.2.3.1 Synthesis of the sulfones

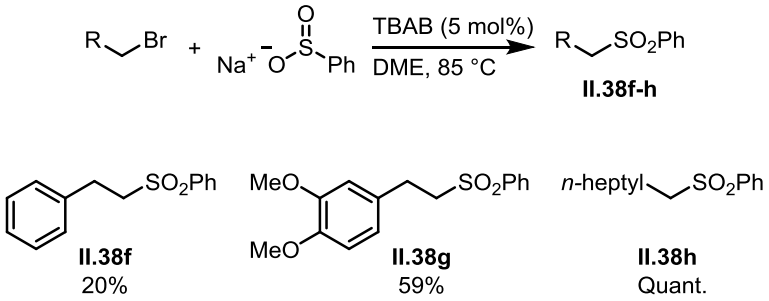
In order to study the scope of the stereoselective silyl enol ether synthesis, several sulfones were synthesised following different procedures from the literature.

Most of the sulfones were prepared in two steps starting from styrene derivatives (Scheme II-24).[24] After an iron(III)-catalysed radical hydrothiolation of styrenes,[24a] the crude sulfides were oxidised to the corresponding sulfones **II.38b-e** with good yields. The oxidation was carried out with hydrogen peroxide in the presence of sodium tungstate as a catalyst[24b] or with *m*CPBA.[24c]



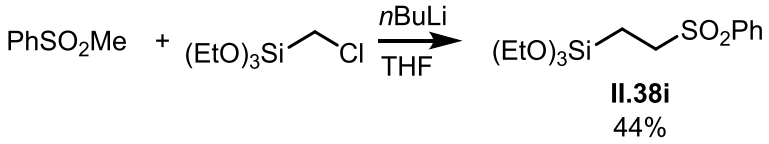
Scheme II-24 Synthesis of sulfones from styrene derivatives.

Sulfones **II.38f-h** were alternatively synthesised by the addition of sodium benzenesulfinate to alkyl bromides under phase-transfer catalysis conditions.[25] The resulting sulfones were isolated with low to quantitative yields (Scheme II-25).



Scheme II-25 Phase-transfer catalysed synthesis of sulfones from sodium benzenesulfinate.

Finally, a new β-silylsulfone **II.38i** was prepared with 44% yield following the same methodology as for **II.38a** (Scheme II-26).



Scheme II-26 β-(triethoxysilyl)sulfone syntesis from methyl phenyl sulfone.

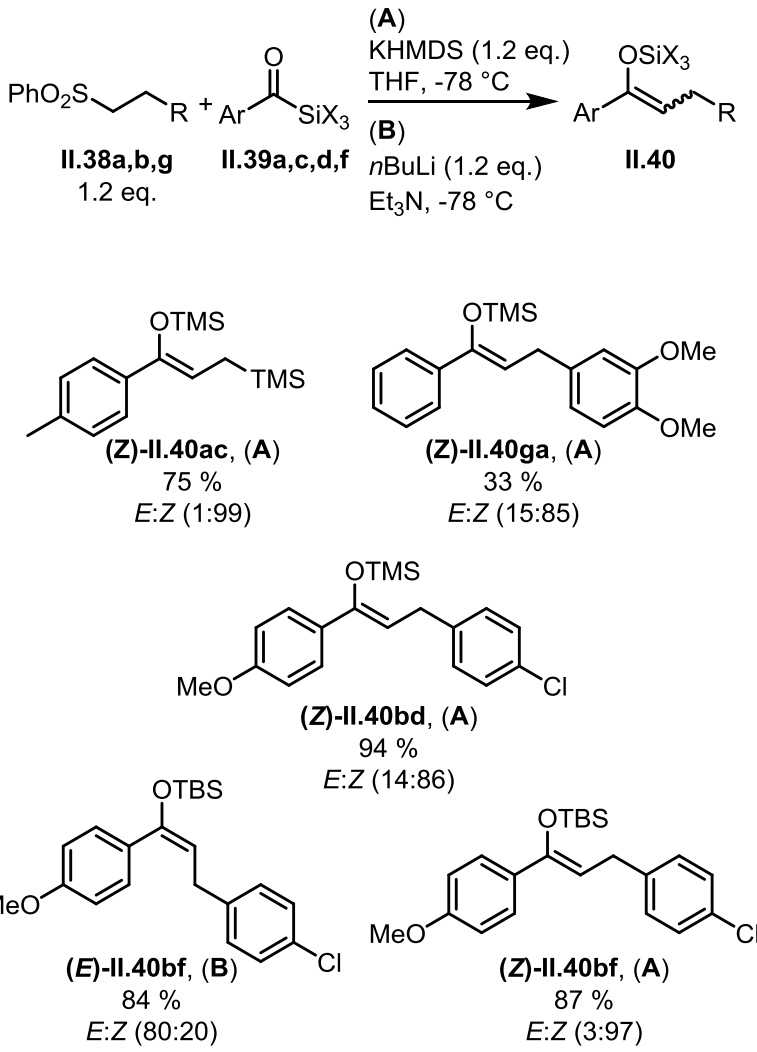
3.2.3.2 Exemplification

With the optimal conditions and the substrates in hand, the scope of the reaction was studied. Several sulfones **II.38a-i** and acylsilanes **II.39a-j** were applied to the (*Z*)-selective conditions (**A**) and to the (*E*)-selective conditions (**B**). It should be noted that even though the triphenylsilyl group led to the highest (*E*) selectivity, the use of TBS acylsilanes was preferred due to their easier synthesis.

3.2.3.2.1 Cross-experiments and stereochemical model for the (*Z*)-selective conditions

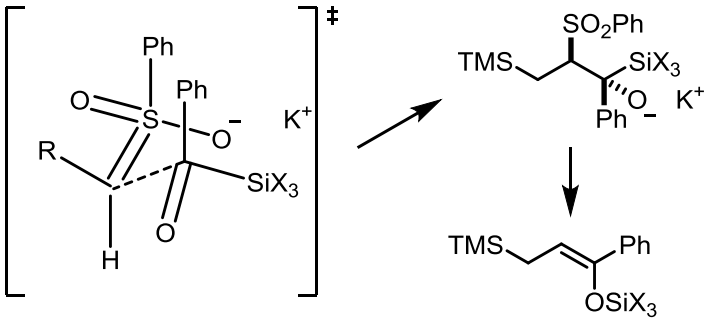
Initially, several cross-experiments were conducted with simultaneous variation of the sulfones and the acylsilanes. Aromatic acylsilanes were first evaluated (Scheme II-27). The *p*-tolyl substituted acylsilane **II.39c** combined with **II.38a** led to the corresponding (*Z*) silyl enol ether **(*Z*)-II.40ac** with 99% selectivity and 75% yield. Replacing the

trimethylsilyl group from the sulfone by an aromatic group resulted in a substantial loss in selectivity as **(*Z*)-II.40ga** was obtained with a 15:85 *E*:*Z* ratio. Similarly, **(*Z*)-II.40bd** was obtained with 94% yield and 86% selectivity. Under (*E*)-selective conditions, **(*E*)-II.40bf** was obtained with 80% selectivity and very good yield. Unexpectedly, the use of the bulky TBS acylsilane **II.39f** under (*Z*)-selective conditions led to **(*Z*)-II.40bf** with an excellent selectivity of 97%.



Scheme II-27 Cross-experiments with various sulfones and acylsilanes under (E) and (Z)-selective conditions.

To explain this high stereoselectivity compared to the formation of the analogous **(*Z*)-II.40bd** under the same conditions with the TMS acylsilane **II.39d**, a comparison was again made with the Julia-Kocienski reaction (Scheme II-28).[23] Under (*Z*)-selective conditions, a rather polar solvent is used in combination with large potassium cation and an open transition state becomes possible. In the hypothesised open transition state, the carbonyl function of the acylsilane is oriented *anti* to the sulfonyl function. The two substituents of the acylsilane, i.e. the silyl group and the aromatic substituent, are competing for the sterically less demanding position facing the proton of the sulfone. Hence, the larger the silyl group the higher the probability that it will occupy this position in the open transition state leading to the *syn*-adduct and thus the (*Z*) silyl enol ether.



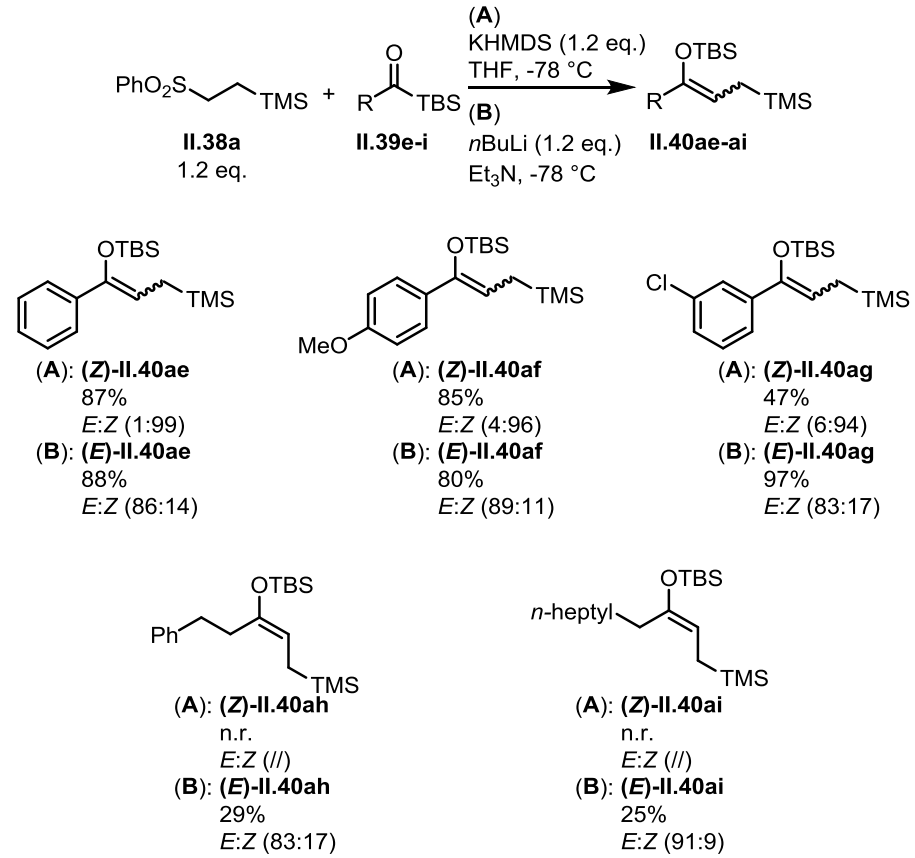
Scheme II-28 Open transition state model for the (Z)-selective conditions.

3.2.3.2.2 Scope of the acylsilanes

With the stereochemical model helping to understand the beneficial effect of bulky silyl groups on both (*E*)- and (*Z*)-selective conditions, the addition of the model sulfone **II.38a** to TBS acylsilanes **II.39e-i** was investigated (Scheme II-29). The aromatic acylsilanes **II.39e-g** reacted well and gave the corresponding silyl enol ethers **II.40ae-ag** in

excellent yields in most cases. In terms of stereochemistry, the (*Z*) isomers were obtained with an impressive level of selectivity. Minor drops in selectivity are however observed with substituted aromatic rings and are more likely due to steric than to electronic effects. The corresponding (*E*) isomers **(*E*)-II.40ae-ag** were obtained with slightly lower, yet pretty high, selectivities and great yields.

Next, aliphatic acylsilanes **II.39h,i** were studied in this reaction. No reaction was observed under (*Z*)-selective conditions and the reagents were recovered. In terms of pKa, there is a likely equilibrium in solution between the potassium bis(trimethylsilyl)amide species and the sulfonyl potassium nucleophile. This equilibrium is displaced towards KHMDS. The α-proton of the acylsilanes being the most acidic, it is probably deprotonated by KHMDS before nucleophilic attack of the sulfone. The resulting potassium enolate is finally hydrolysed after reaction leading to the recovery of the sulfone and the acylsilane. When running the reaction with aromatic acylsilanes, such a side-reaction is not possible and the minor nucleophilic sulfone will add to the acylsilane, pulling the equilibrium to the completion of the deprotonation reaction. Under (*E*)-selective conditions, a similar problem was encountered. However, since *n*BuLi is a stronger base than KHMDS, the acid-base reaction is irreversible and the sulfonyl lithium species is by far the major component of the mixture. Consequently, upon addition of the acylsilanes to the nucleophile, a similar side-reaction occurs between the α-lithio-sulfone and the acylsilanes but nucleophilic addition of the sulfone is observed to some point. As a result, **(*E*)-II.40ah,ai** were isolated with low yields but with perfect regioselectivity and appreciable stereoselectivities.

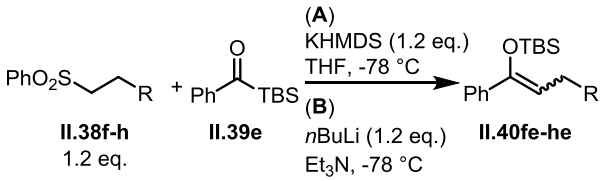


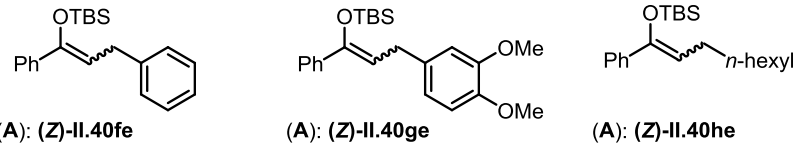
Scheme II-29 Scope of the acylsilanes in the stereoselective Reich's silyl enol ether synthesis.

3.2.3.2.3 Scope of the sulfones

Next, several sulfones **II.38f-h** were submitted to the (*E*)- and (*Z*)-selective reaction conditions with the simple phenyl-substituted TBS acylsilane **II.39e** (Scheme II-30). Again (*Z*)-selective conditions gave very satisfying results with both excellent yields and stereoselectivity. It should however be noted that octyl phenyl sulfone **II.38h** gave **(*Z*)-II.40he** with significantly lower selectivity which is attributed to the absence of a β-phenyl substituent on the aliphatic chain of **II.38h**. Concerning the (*E*)-selective silyl enol ether formation, a major problem was encountered since triethylamine proved to poorly

solubilise the sulfones or their α-lithiated equivalents. Despite this drawback, the (*E*) isomers of **II.40fe** and **II.40he** were obtained with good selectivity yet with diminished yields. Sulfone **II.38g** proved completely insoluble in triethylamine. Therefore, no deprotonation occurred in the presence of *n*BuLi and nucleophilic addition of the base to the acylsilane **II.39e** was observed.





(**A**): **(*Z*)-II.40fe**
95%
E:*Z* (7:93)
(**B**): **(*E*)-II.40fe**
47%
E:*Z* (86:14)

(**A**): **(*Z*)-II.40ge**
92%
E:*Z* (8:92)
(**B**): **(*E*)-II.40ge**
0%
E:*Z* (//)

(**A**): **(*Z*)-II.40he**
Quant.
E:*Z* (29:71)
(**B**): **(*E*)-II.40he**
58%
E:*Z* (86:14)

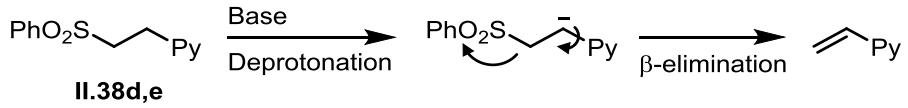
Scheme II-30 Scope of the sulfones in the stereoselective Reich's silyl enol ether synthesis.

3.2.3.2.4 Reaction's limitations

It was covered earlier that aliphatic acylsilanes bearing acidic α-protons are really challenging substrates in this reaction since deprotonation/enolisation of the acylsilanes by the nucleophile is a major issue. The use of a strong base however resulted in the conversion of the substrates to the desired silyl enol ethers in low yields.

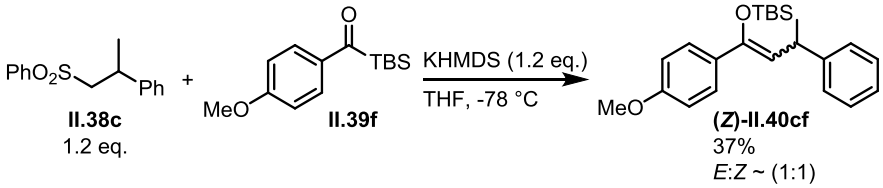
Another limitation to take into account is the β substituent of the sulfone. Indeed, some of the synthesised sulfones were not suited to the reaction due to the presence of better electron withdrawing groups in β position. As a result, deprotonation occurred in β position to the

sulfone, followed by the β-elimination of the sulfone rather than addition to the acylsilanes. This reaction was observed with β-pyridylsulfones **II.38d,e** (Scheme II-31).



Scheme II-31 Base-promoted β-sulfone elimination of β-pyridylsulfones.

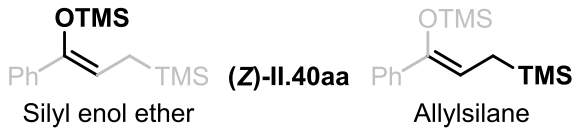
Moreover, the β-substituent of the sulfone showed great influence on the selectivity of the reaction. Indeed, rather large β substituents of sulfones **II.38a,f,g** provided the corresponding silyl enol ethers with very good selectivity while the aliphatic **II.38h** suffered from a loss in selectivity upon reaction. Finally, β,β-disubstituted sulfone **II.38c** led to **II.40cf** without selectivity under (*Z*)-selective conditions (Scheme II-32).



Scheme II-32 Unselective silyl enol ether formation with β,β-disubstituted sulfones.

3.2.4 Applications of β-silylated silyl enol ethers

Among the products obtained from the addition of sulfones to acylsilanes, the model sulfone **II.38a** afforded products **II.40ac, ae-ai** that have an ambivalent nucleophilic nature. Indeed, the products possess a silyl enol ether function and an allylsilane function involving the same carbon-carbon double bond (Scheme II-33). Consequently, it was decided to look for selective conditions to trigger their reaction in the Mukaiyama aldol-type reaction and in the Hosomi-Sakurai allylation-type reaction.

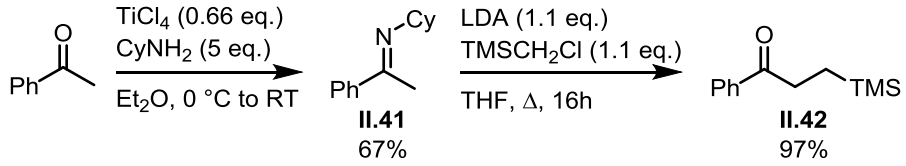


Scheme II-33 Ambivalent character of β-silylated silyl enol ethers.

3.2.4.1 Synthesis of the silyl enol ethers

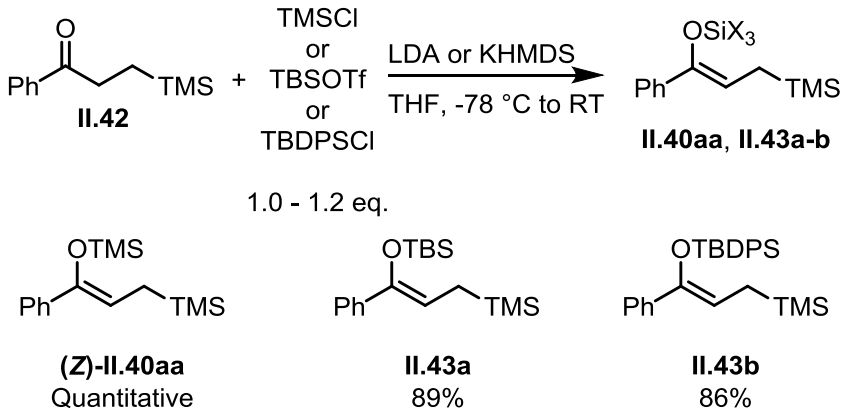
The silyl ether moiety might play a crucial role in the reactivity of the molecule. Yet, following Reich's methodology, i.e. the synthesis of silyl enol ethers *via* the Brook rearrangement of acylsilanes, the silyl group is set at an early stage of the synthesis. Therefore, using this strategy to prepare a variety of silyl enol ethers might reveal highly time consuming. Consequently, another route allowing late stage silylation was preferred.

Acetophenone was condensed with cyclohexylamine in the presence of titanium chloride affording imine **II.41**.[26] The corresponding enamine was formed by reaction with LDA and used to trap chloromethyltrimethylsilane in THF under reflux affording the β-silyl ketone **II.42** after hydrolysis (Scheme II-34).[27]



Scheme II-34 Synthesis of the β-silyl ketone.

The β-silyl ketone **II.42** was then used in classical enolisation/O-silylation reactions to yield the desired (*Z*) silyl enol ethers **(*Z*)-II.40aa**, **II.43a** and **II.43b** with late stage silylation (Scheme II-35).[28]



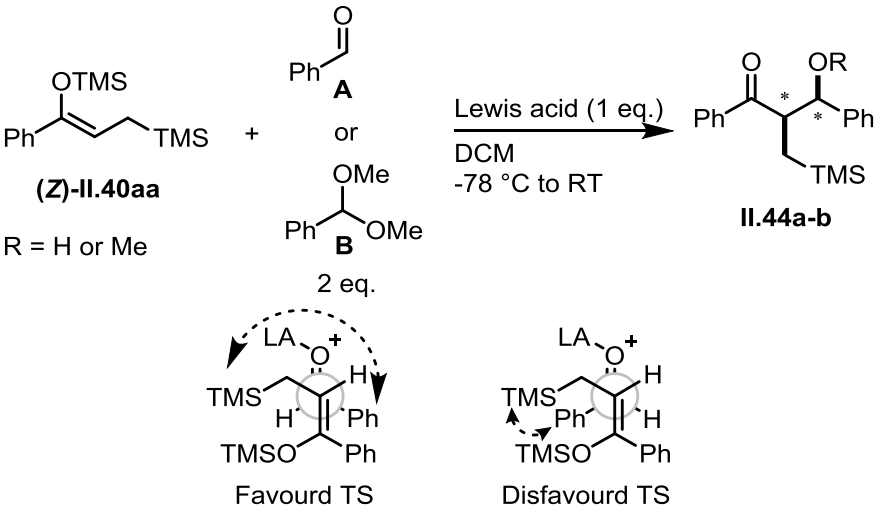
Scheme II-35 Late-stage silylation of II.42.

3.2.4.2 Investigations of the β-silylated silyl enol ethers' reactivity

With a late stage silylation method in hand for the synthesis of the substrates, the investigation was initiated (Table II-5). This screening started with the model reagent **(*Z*)-II.40aa** and benzaldehyde **A** in the presence of titanium tetrachloride as a Lewis acid. After overnight stirring from -78 °C to room temperature, the aldol adduct **II.44a** was obtained with 76% conversion from **(*Z*)-II.40aa** and with a diastereoisomeric ratio of 62:38 (entry 1). Under the same conditions, trimethylsilyltriflate promoted the formation of the aldol compound **II.44a** with similar conversion and diastereoselectivity (entry 2). Use of benzaldehyde dimethyl acetal **B** as electrophilic partner in the

presence of strong Lewis acids afforded the aldol product **II.44b** with full conversion of **(*Z*)-II.40aa** with higher diastereoisomeric ratios (entries 3 and 4). Pure **II.44b** was isolated with 91% yield and d.r. of 83:27 (entry 4). The diastereoselectivities being moderate, no additional effort was devoted to the determination of the major diastereoisomer. Yet, based on the commonly accepted open-transition state model for the Mukaiyama aldol reaction,[29] the major diastereoisomer should be the *cis* product resulting from the favoured transition state in which steric interactions are minimised.

*Table II-5 Mukaiyama aldol reaction of β-silylated silyl enol ether **(Z)-II.40aa**.*

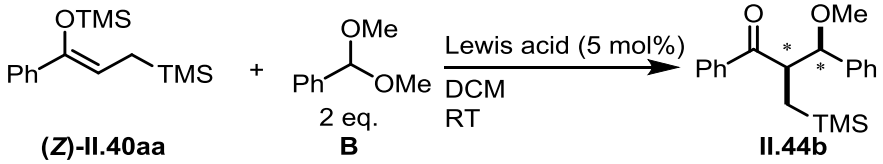


Entry	Lewis acid	Electrophile	$\frac{P}{P+SM}$ ratio (Yield)[a]	d.r.[b]
1	$TiCl_4$	**A**	76% (n.d.)	62:38
2	TMSOTf	**A**	80% (n.d.)	63:37
3	$TiCl_4$	**B**	100% (n.d.)	74:26
4	TMSOTf	**B**	100% (91%)	83:17

[a] P = Desired Product; SM = Limiting Starting Material. The ratios were determined from the crude ^{1}H NMR spectra which mainly displayed P and SM with > 80% purity and isolated yield is given after flash column chromatography. [b] Determined from the crude ^{1}H NMR spectra.

Dimethylacetal **B** being a better electrophilic candidate to reach complete conversion, it was used as coupling partner in catalytic Mukaiyama aldol reactions (Table II-6). Several transition metal salts were tested in this transformation with catalytic loadings of 5 mol%. Every tested catalyst afforded the aldol compound selectively with full conversion and moderate diastereoselectivity. Additionally, using soft Lewis acids allowed working at room temperature.

Table II-6 Soft Lewis acid-catalysed Mukaiyama aldol reactions.

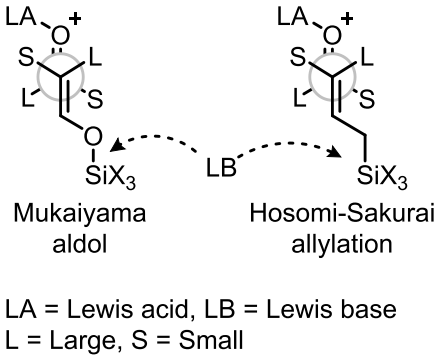


(*Z*)-II.40aa **B** **II.44b**

Entry	Lewis acid	$\frac{P}{P+SM}$ ratio[a]	d.r.[b]
1	$Zn(OTf)_2$	100%	71:29
2	$Cu(OTf)_2$	100%	73:27
4	$La(OTf)_3$	100%	65:35
5	CuOTf.Tol	100%	73:27

[a] P = Desired Product; SM = Limiting Starting Material. The ratios were determined from the crude ^{1}H NMR spectra which mainly displayed P and SM with > 80% purity. [b] Determined from the crude ^{1}H NMR spectra.

So far, it was verified that β-silylated silyl enol ether **(*Z*)-II.40aa** can serve as nucleophilic partners in the Mukaiyama aldol reaction. Unfortunately, none of the reaction conditions tested so far led to the other desired product, i.e. the allylation product **II.45**. The Hosomi-Sakurai[30] and the Mukaiyama aldol[29] reactions following similar mechanistic pathways and activation patterns, it is difficult to invert the preferred reactivity of a given substrate. Indeed, both reactions proceed through an acyclic transition state and are usually triggered *via* activation of the carbonylated derivative by a Lewis acid or activation of the silylated nucleophile by a Lewis base (Scheme II-36).

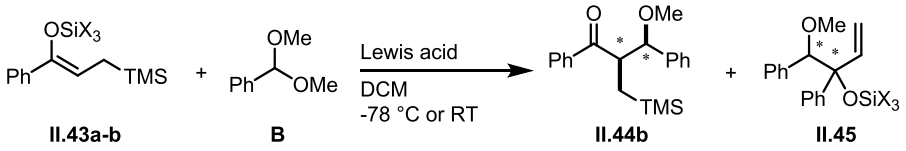


Scheme II-36 Acyclic transition state models for the Lewis acid/base-mediated Mukaiyama and Hosomi-Sakurai reactions.

Until now, the tested Lewis acids activated the aldehyde **A** and the dimethyl acetal **B** without real influence on the nucleophilic partner **(*Z*)-II.40aa**. Consequently, the activated electrophiles were attacked by the most nucleophilic function of **(*Z*)-II.40aa**. The silyl enol ether functionality of the molecule tend to be more nucleophilic than the allylsilane function. Therefore, the aldol adducts **II.44a-b** were obtained, no matter the employed Lewis acid. In order to favour the allylating behaviour of **(*Z*)-II.40aa** over its aldol behaviour, it was attempted to attenuate the reactivity of the silyl enol ether moiety. Counter anions of the Lewis acids might play a role as Lewis base promotor for the activation of the silyl groups. To avoid nucleophilic attack at the silyl ether site, highly hindered silyl enol ethers **II.43a-b** were synthesised and their reactivity tested (Table II-7). In the presence of soft copper(II) triflate, the aldol reactivity of nucleophile **II.43a-b** was effectively blocked by the steric hindrance of the large silyl groups and yet no allylation product **II.45** was observed (entries 1 and 2). In these two cases, the β-silyl ketone **II.42** resulting of the hydrolysis of **II.43a-b** was recovered. Alternatively, strong Lewis acids did not promote the Sakurai-type allylation reaction either but

the aldol adduct **II.44b** was effectively formed as sole product (entries 3 and 4).

Table II-7 Use of bulky silyl groups on the silyl ether moiety.



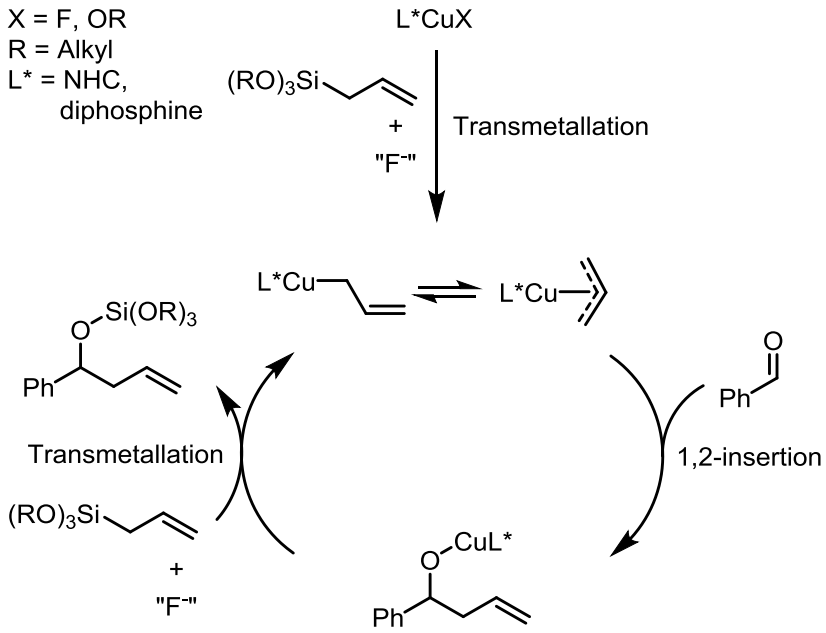
II.43a-b **B** **II.44b** **II.45**

Entry	Lewis acid	SiX_3	**II.44b** : **II.45**[c]
1	$Cu(OTf)_2$ (5 mol%)[a]	TBS	0:0
2	$Cu(OTf)_2$ (5 mol%)[a]	TBDPS	0:0
3	TMSOTf, $TiCl_4$ or $BF_3.OEt_2$ (1 eq.)[b]	TBS	1:0
4	TMSOTf, $TiCl_4$ or $BF_3.OEt_2$ (1 eq.)[b]	TBDPS	1:0

[a] Reaction at room temperature. [b] Reaction at -78 °C. [c] Determined from the crude ^1H NMR spectra. Diastereomeric ratios are not given.

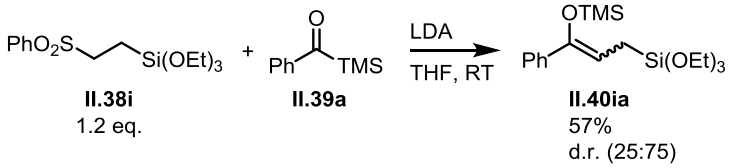
Lewis acids being unable to promote the allylation reaction selectively, the copper(I) catalysed allylation of aldehyde[31] was considered since its mechanism is completely different. In this reaction, a copper(I) fluoride or alkoxide precatalyst is used to form *in situ* an allyl copper complex *via* transmetallation with a trialkoxyallylsilane. This step may require the presence of a fluoride source as activator of the organoallylsilane. The allylcopper intermediate has been prepared, purified and characterised. In the solid state, it is observed in the η^1 coordination mode while it equilibrates quickly between the η^1 and η^3 mode in solution.[32] The cuprous complex then transfers its allyl moiety to an aldehyde affording a homoallylic copper alkoxide. Upon transmetallation with

another equivalent of the allylsiloxane, the catalytically active allylcopper complex is regenerated and the homoallylic silylether is released with good yields (Scheme II-37).



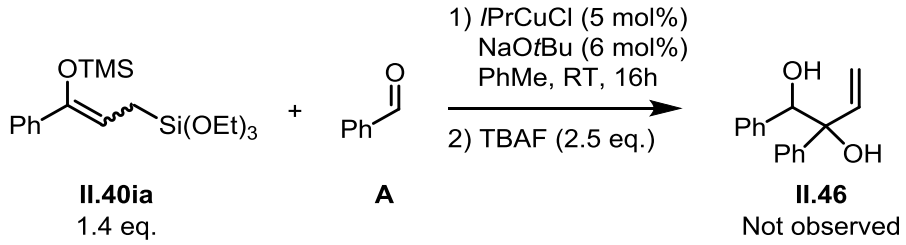
Scheme II-37 Mechanism for the copper(I)-catalysed allylation of aldehydes with allylsilanes.

In this ultimate attempt, the model substrate **II.40aa** was engaged with benzaldehyde **A** in the presence of *I*PrCuCl and *t*BuONa. After overnight stirring in toluene, the hydrolysis product **II.42** arising from the substrate was recovered along with the aldehyde **A**. As reported in the literature, alkoxide substituents on the silicon atom are crucial for good transmetallation behaviour.[31, 33] Therefore, the analogous more activated allyl(triethoxysilyl) **II.40ia** was synthesised following Reich's method. Sulfone **II.38i** was deprotonated by LDA and added to acylsilane **II.39a** at room temperature affording the product with moderate yield and selectivity (Scheme II-38).



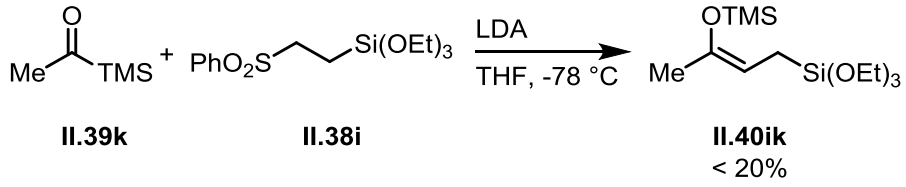
Scheme II-38 Synthesis of an allyl(triethoxysilyl) species.

Consequently, **II.40ia** was engaged in the copper-catalysed allylation reaction with benzaldehyde **A**. Nevertheless, the experiment resulted in a messy mixture and the product of interest **II.46** was not observed (Scheme II-39).



*Scheme II-39 Attempted copper-catalysed allylation of benzaldehyde with **II.40ia**.*

The latter attempt revealing unsuccessful, using a fluoride source as activator might be the solution to the problem. Care should however be taken since the silyl enol ether function is highly sensitive to such hard nucleophiles. An additional likely issue is the highly substituted architecture of the allylic carbon of **II.40ia**. In order to assess the importance of the steric factor in this reaction, the synthesis of a less congested triethoxyallylsilane **II.40ik** was envisioned. The synthesis of the aliphatic **II.40ik** following Reich's methodology followed an unexpected pathway and **II.40ik** was only obtained as a minor product (Scheme II-40).

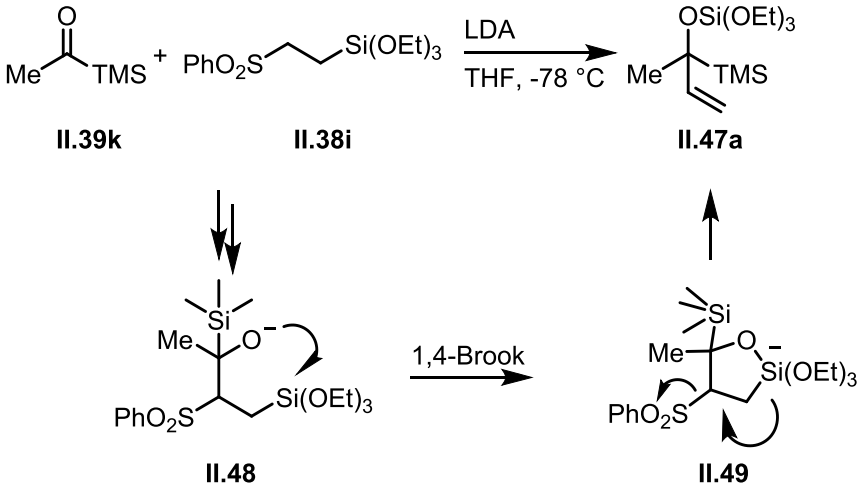


II.39k **II.38i** **II.40ik**
< 20%

Scheme II-40 Synthesis of II.40ik according to Reich's method.

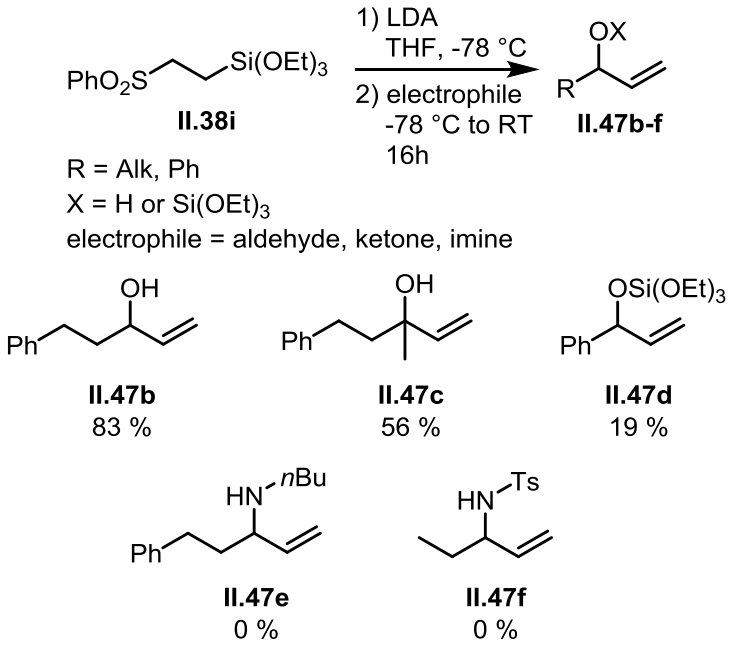
3.2.4.3 β-(triethoxysilyl)sulfone as vinyl anion equivalent

While trying to achieve the copper-catalysed allylation of benzaldehyde with allylsilanes obtained from the stereoselective Reich's silyl enol ether synthesis, the synthesis of a particular substrate **II.40ik** was attempted. To this end, the β-(triethoxysilyl)sulfone **II.38i** was added to the commercially available aliphatic acylsilane **II.39k**. Surprisingly, the reaction did not only follow the expected addition/1,2-Brook rearrangement sequence leading to silyl enol ethers. The formation of an allylic alcohol derivative **II.47a** was alternatively observed to be the major product of the reaction. This product is suspected to arise from a 1,4-Brook rearrangement/sulfone elimination subsequent to the addition of **II.38i** to the acylsilane **II.39k**. This reactivity is a result of the absence of a stabilising group, i.e. the presence of a methyl group instead of a phenyl group on the acylsilane, thereby disfavouring the α-siloxycarbanion resulting of the 1,2-Brook rearrangement. Furthermore, the triethoxysilyl group is highly activated by the inductive withdrawing effect of the ethoxy groups.[33] This activation facilitates the formation of the pentacoordinated silicate intermediate **II.49** by addition of the alkoxide **II.48** to the silicon atom (Scheme II-41).



Scheme II-41 1,4-Brook rearrangement leading to allylic alcohol derivatives.

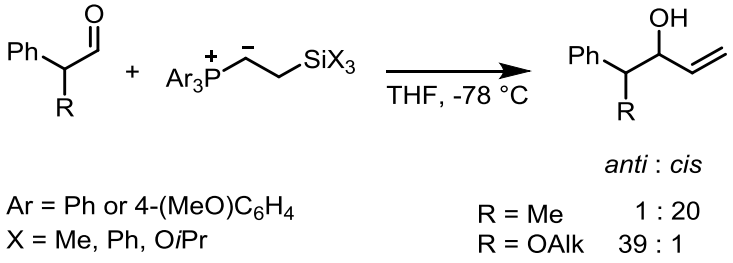
As a result, β-(triethoxysilyl)sulfone **II.38i** behaves as a vinyl anion equivalent when added to aliphatic acylsilanes even though acylsilanes are not expected to be the only suitable electrophiles. This reactivity was briefly inspected and **II.38i** was added to several carbonyl electrophiles (Scheme II-42). Addition to dihydrocinnamaldehyde, benzylacetone and benzaldehyde afforded in all cases the corresponding allylic alcohols **II.47b-d** with great to low conversions. Aliphatic dihydrocinnamaldehyde is a perfect electrophile leading to the allylalcohol **II.47b** with high conversion while the more hindered aliphatic ketone is converted to the tertiary alcohol **II.47c** with substantially lower conversion. The aromatic benzaldehyde was converted to the allylic silyl ether derivative **II.47d** yet with low conversion. Contrastingly, addition to imines did not lead to the allylic amines **II.47e,f**. The N-butyl imine was considered to be insufficiently electrophilic to undergo addition of **II.38i** however N-tosyl imine did not react either and the sulfone **II.38i** was recovered.



Scheme II-42 Use of β-(triethoxysilyl)sulfone as a vinyl anion equivalent with several carbonylated electrophiles.

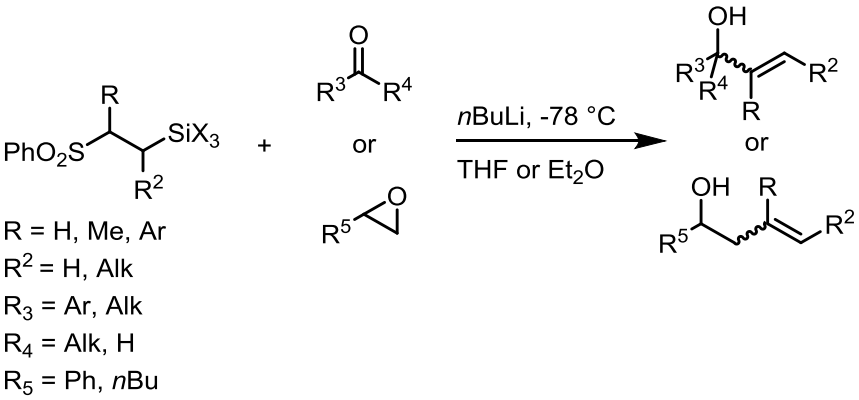
A quick review of the literature revealed that similar reactivities had been discovered and reported earlier. The group of Tokoroyama reported the addition of β-silyl phosphorous ylides to various α-chiral aldehydes leading to vinylated and propenylated products.[34] In terms of reactivity, they observed that electron rich aromatic substituents on the phosphorous atom[34a] and introduction of electronegative substituents on the silicon[34b] favour the reaction. In terms of diastereoselectivity, addition of β-silyl phosphorous ylides following the Felkin-Ahn model gave better results than the analogous vinyl Grignard reagents (Scheme II-43). Additionally a β-silyl phosphorous ylide reagent bearing a chiral ferrocenyl moiety on the phosphorous was developed and added to aromatic and aliphatic aldehyde yielding the allylic alcohols with up to 92% enantiomeric excess. The

ferrocenyl phosphine could be recycled to prepare the chiral nucleophile.[35]



Scheme II-43 Use of β-silyl phosphorous ylides as vinyl anion equivalent.

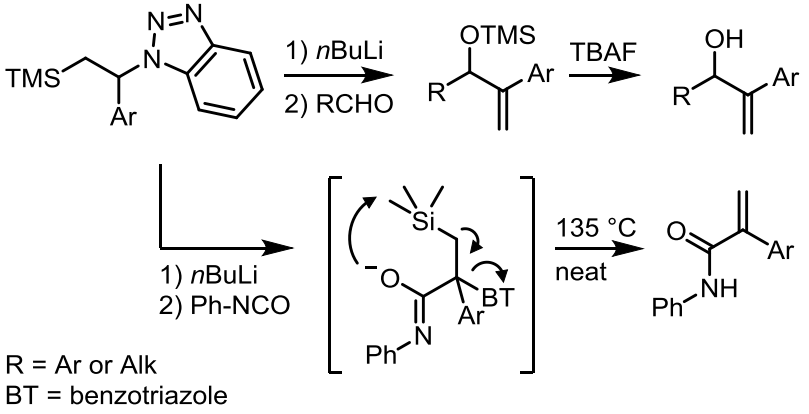
Similar chemistry was also developed with sulfones instead of phosphines as leaving groups.[36] Again, electronegative substituents on the silicon atom favoured the reaction.[36a] Although the diastereoselectivities were not as high as with phosphorous ylides, the β-silylsulfones were efficiently added to aldehydes but also ketones[36b] and epoxides[36c] leading to tertiary and homoallylic alcohol derivatives respectively (Scheme II-44).



Scheme II-44 β-silylsulfones as vinyl anion equivalent.

Finally, Katritzky and co-workers developed a related reagent with a benzotriazole leaving group. Katritzky's β-silyl-α-aryl-benzotriazoles were successfully added to a variety of aliphatic and aromatic

aldehydes affording the corresponding allylic alcohols with good yields. Interestingly, isocyanates proved to be suitable electrophiles in the allylation reaction (Scheme II-45).[37]



Scheme II-45 Katritzky's β-silyl benzotriazoles as vinyl anion equivalents.

Globally, these kind of reagents are useful in organic synthesis as they offer an alternative to vinylmetal nucleophiles for the preparation of allylic alcohols. The obvious advantage over vinyl Grignard reagents is that greater levels of diastereoselectivity are reached and that 2-substituted allylic alcohols are made available by this methodology. Consequently, this chemistry has a potential value for the synthesis of natural product where acyclic stereocontrol is important.[34b-d, 38]

Compared to the reported literature, **II.38i** is more convenient than the corresponding phosphorous ylides since no Wittig side-reaction is expected and the reagent can be stored for years without notable degradation. Also, **II.38i** is a more activated reagent than the other β-silylsulfone reagents reported so far due to the ethoxy substituents on the silicon atom. Yet, the better activation is only a moderate advantage compared to the drawbacks brought by the ethoxy substituents. Indeed, despite full conversion of the reagents, the

synthesis of **II.38i** (see: 3.2.3.1) is low yielding because of the exchange of the triethoxysilyl group on silica gel during flash chromatography. Additionally, non-nucleophilic bases are required for the deprotonation of **II.38i** since *n*BuLi would substitute the ethoxy groups. Finally, **II.38i** is an oily compound which makes it less user-friendly than the corresponding crystalline benzotriazoles of Katritzky. For those reasons, the β-(triethoxysilyl)sulfone reagents will not be further examined in this thesis.

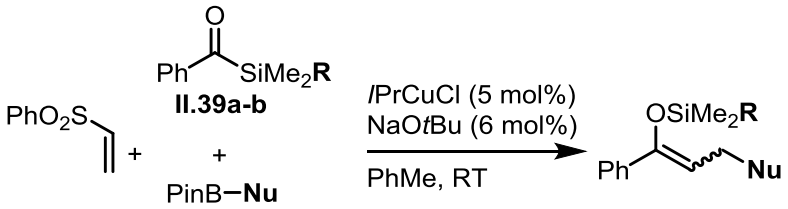
3.3 Domino reactions with acylsilanes

As the optimal conditions for the copper-catalysed conjugated silylation of vinylsulfone were rapidly unravelled, and as data about the key factors to reach high stereoselectivity during the Brook rearrangement were gathered, attention could be turned to the elaboration of the initially targeted domino addition/acylsilane capture/Brook rearrangement reaction.

3.3.1 Catalytic tests

With all the reagents in hand, the domino reaction was set up (Table II-8). Unfortunately, under the conditions earlier developed for the conjugated addition of Suginome's reagent **II.8** to vinylsulfone, no reaction occurred in the presence of the acylsilane **II.39b** (entry 1) or the less bulky acylsilane **II.39a** (entry 2). However, when bispinacolatodiboron was used as a pronucleophiles under the same conditions, the β-borylated sulfone was observed but again no acylsilane **II.39b** was consumed (entry 3).

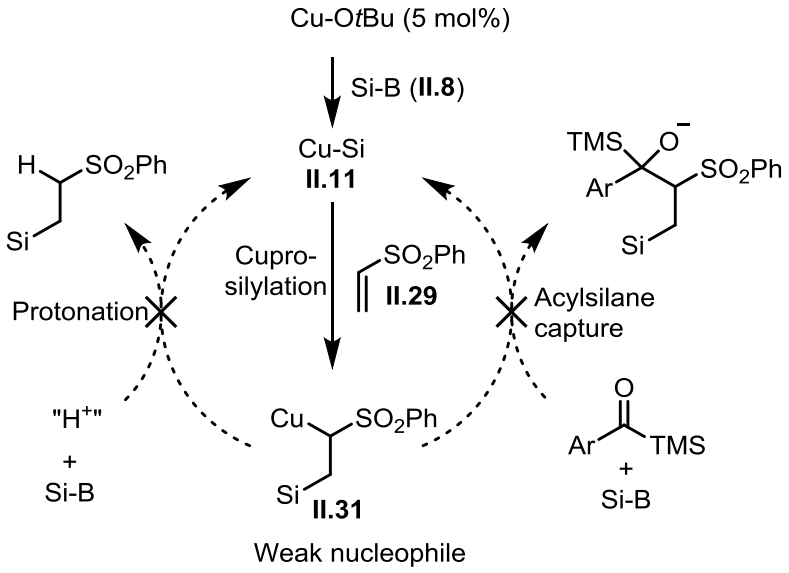
Table II-8 Exploration of the domino β-silylation/acylsilane capture/Brook rearrangement reaction.



Entry	R	Nu	Result[a]
1	Ph	$SiMe_2Ph$	No reaction
2	Me	$SiMe_2Ph$	No reaction
3	Ph	BPin	β-borylation

[a] The reactions were monitored by TLC and ^1H NMR analysis of the crude mixtures.

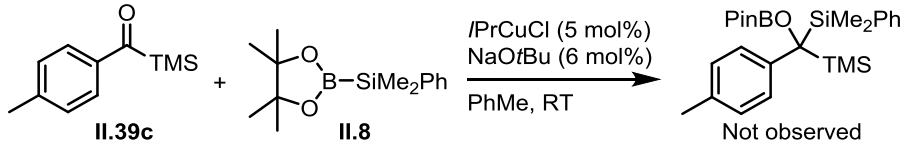
These results are quite intriguing since the reason for the absence of reactivity in the two first tests (entry 1 and 2) is unclear. A working hypothesis can however be drawn. Indeed, Suginome's reagent is likely converted into the copper-silicon species **II.11** which undergoes addition to the vinylsulfone. The resulting α-cupro-sulfone **II.31** would not be sufficiently nucleophilic to undergo addition to the acylsilane. In the absence of a suitable electrophilic species, no regeneration of the catalyst would take place until the quench of the reaction and only traces of the β-silylsulfone would be formed (Scheme II-46).



Scheme II-46 Interruption of the catalytic cycle in the absence of a suitable electrophile.

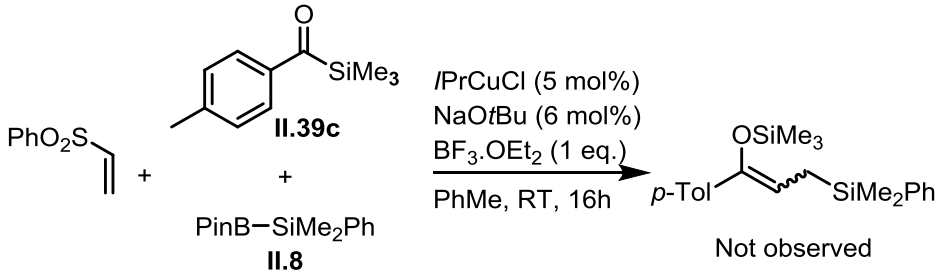
The third test however suggests efficient formation of the boryl-copper species and full conversion to the β-borylsulfone in a catalytic fashion while the acylsilane remained unconverted. This result can only be explained by the presence of an undesired proton source in the reaction medium. The analysis of those reactions being based on crude

^{1}H NMR spectra, the direct addition of Suginome's reagent to the acylsilanes cannot be excluded. Therefore, a control experiment was conducted without vinylsulfone in the reaction medium. Yet, the acylsilane **II.39c** remained untouched and was recovered with the borosilane **II.8** after overnight stirring (Scheme II-47).



Scheme II-47 Control experiment for the addition of Suginome's reagent to acylsilanes.

The use of a strong Lewis acid to enhance the electrophilic character of the acylsilane towards the α-cupro-sulfone was considered. No conversion was however observed in the presence of boron trifluoride (Scheme II-48).



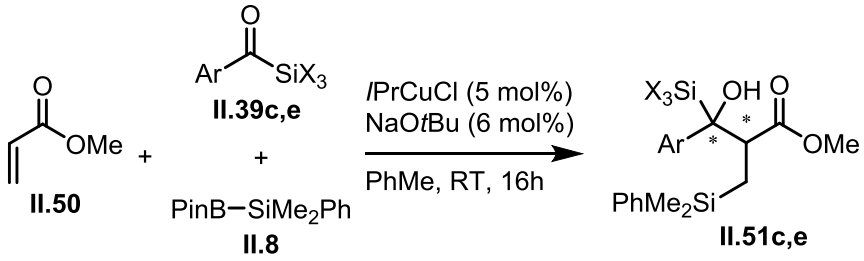
Scheme II-48 Lewis acid-mediated activation of acylsilanes.

Quickly it was found in the literature that sulfones[39] and sulfoxides[40] are known non-transferable ligands in organocuprate chemistry. Even though cuprate chemistry and cuprous catalysis are not alike, the investigations on the challenging capture of acylsilane by the weakly nucleophilic α-cupro-sulfone intermediate was put aside.

3.3.2 β-silylation/aldolisation of acrylates

Since the vinylsulfone pattern did not prove efficient in the expected domino reaction, another kind of Michael acceptor was considered. Acrylates are known to be efficient substrates in domino β-functionnalisation/aldolisation reactions. Therefore, a reaction was set up with the commercially available methyl acrylate **II.50** as Michael acceptor (Table II-9). Gratifyingly, after overnight stirring of acylsilane **II.39c** in the presence of Suginome's reagent **II.8** and a copper catalyst, the domino adduct **II.51c** was obtained as the major product and isolated with 84% yield and 37:63 diastereoisomeric ratio. Using a bulkier acylsilane **II.39e** resulted in a rise in the diastereoselectivity, d.r. 31:69, but a drop in the yield was observed. Notably, no Brook rearrangement was observed in either case. As a result, the domino adducts **51c,e** are tertiary α-hydroxysilanes. These interesting and highly substituted compounds are obtained in a single catalytic step from easily available reagents under smooth conditions with promising yields and diastereoisomeric excesses. The present reaction represents one of the few known copper-catalysed transformations of acylsilanes to date.

Table II-9 Copper-catalysed domino β-silylation/aldolisation reaction of methyl acrylate with acylsilanes.



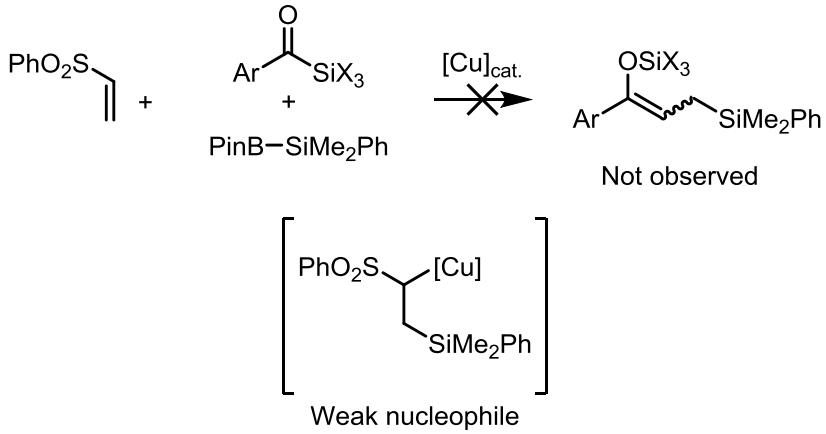
SiX_3 = TMS, TBS
Ar = Ph, *p*-Tol

Entry	Acylsilane	Product	Yield[a]	d.r.[b]
1	**II.39c**	**II.51c**	84%	37:63
2	**II.39e**	**II.51e**	67%	31:69

[a] Isolated yields after flash column chromatography over silica gel. [b] Determined from the ^{1}H NMR spectra of the pure compounds.

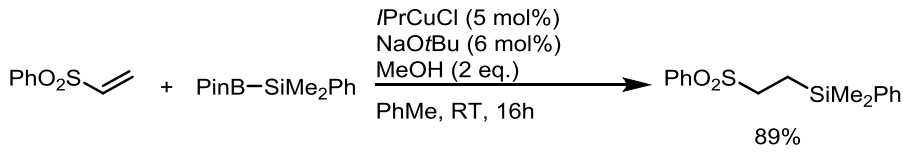
4 Conclusion and perspectives

In this chapter, the chemistry of sulfones and acylsilanes was explored. The original goal was the development of a copper-catalysed domino β-silylation/acylsilane-capture/Brook rearrangement reaction leading to silyl enol ethers. This goal was not reached given the low nucleophilic nature of the intermediate α-cuprosulfone (Scheme II-49).



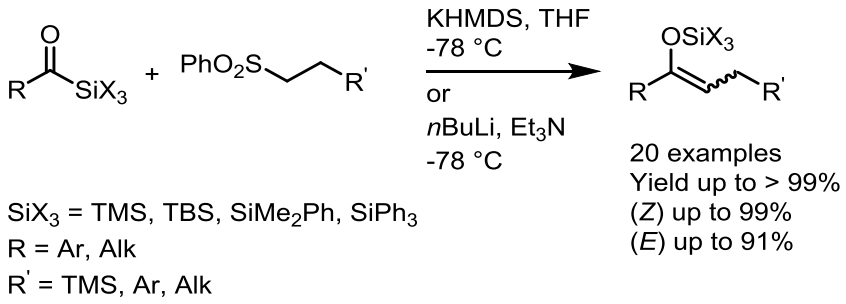
Scheme II-49 Initial goal of this chapter: the copper-catalysed domino β-silylation/acylsilane-capture/Brook rearrangement.

However, striving towards this end led to a travel through many related fields of chemistry. Consequently, the copper-catalysed β-silylation of vinylsulfone with Suginome's reagent was developed based on the known copper-catalysed β-borylation of vinylsulfones (Scheme II-50). This reaction was not further developed since it was out of the range of this thesis. However, the development of the asymmetric β-silylation of β-substituted vinylsulfones would deserve some efforts since no efficient alternative is reported.[11a, 41]



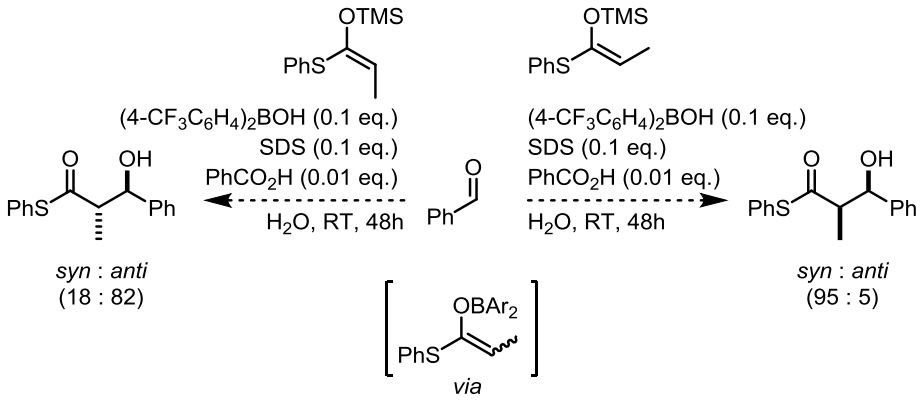
Scheme II-50 Copper-catalysed β-silylation of vinylsulfones.

Next, stereoselective conditions for Reich's silyl enol ether synthesis were developed and allowed (*E*)- and (*Z*)-selective access to silyl enol ethers from acylsilanes and sulfones. A parallel was made with the Julia-Kocienski olefination's model to explain the stereoselectivity which depends on simple modifications of the solvent and base. Hence both isomers of the same compound are easily accessible. This method was applied to the synthesis of 20 silyl enol ethers with good yields and selectivities in average (Scheme II-51).



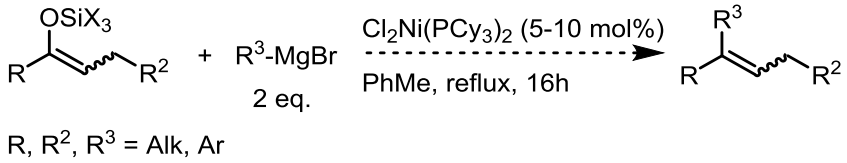
Scheme II-51 Stereoselective conditions for Reich's silyl enol ether synthesis.

Even though the double bond geometry of silyl enol ethers does not affect the diastereoselectivity of the Mukaiyama aldol reaction,[29, 42] they can be efficiently converted to the corresponding enol boranes without isomerisation of the double bond.[43] The latter reagents in turn undergo stereospecific aldolisations with aldehydes (Scheme II-52).[44] Therefore, the developed stereoselective silyl enol ether synthesis is of interest in synthesis.



Scheme II-52 Diphenylboronic acid-catalysed Mukaiyama aldol reaction of silyl enol ethers.

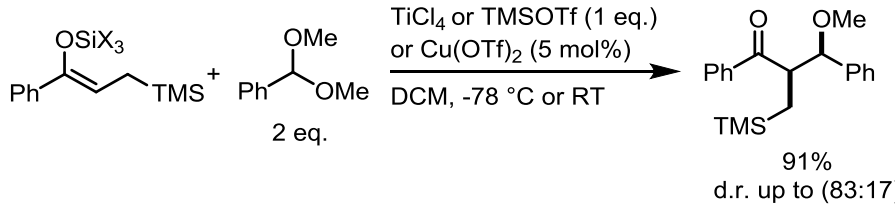
Additionally, silyl enol ethers participate in nickel-catalysed Kumada-Tamao-Corriu-type cross-coupling reactions with Grignard reagents. The silyl enol ethers enter the catalytic cycle *via* a nickel-catalysed C-O bond activation.[45] In this context, the silyl enol ethers obtained in this chapter are tri-substituted olefin equivalents (Scheme II-53). Furthermore, since the C-C double bond does not undergo isomerisation under the reaction conditions, the developed stereoselective silyl enol ether synthesis provides an entry to geometrically defined olefins of great importance in organic synthesis.



Scheme II-53 Silyl enol ethers in Kumada-Tamao-Corriu-type cross coupling reactions.

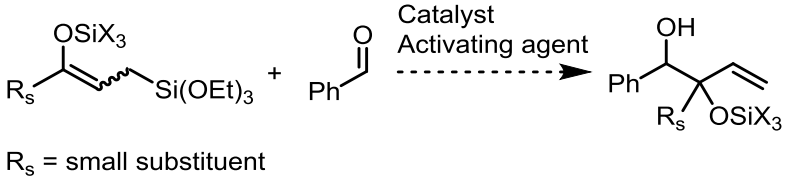
In particular cases, the silyl enol ether's double bonds were included in an allylsilane function. As a result, it was attempted to use these compounds in Mukaiyama aldol reactions and in Hosomi-Sakurai allylations. The Mukaiyama aldol reaction was easily conducted with various silyl groups in the presence of strong Lewis acids.

Furthermore, soft Lewis acids also promoted the aldol reaction and could be used in catalytic amount (Scheme II-54).



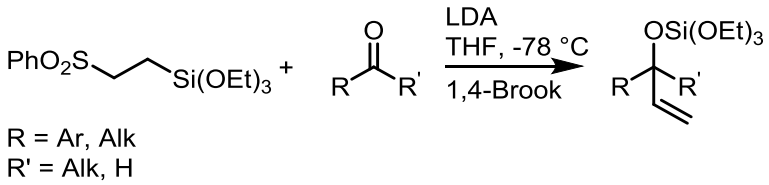
Scheme II-54 Mukaiyama aldol reaction of β-silylated silyl enol ethers.

Selective condition for the Hosomi-Sakurai-type reaction were not found. The Mukaiyama aldol reaction being largely favoured in the presence of Lewis acids, an alternative reaction pathway should be considered to carry out the allylation reaction. The copper-catalysed transmetallation pathway was considered but only two tests were carried out. It is advised to further explore this option with some modifications. The use of activators for the allylsilane species, e.g. fluoride sources, should ease the transmetallation of the silane to the copper catalyst. As pointed out in the discussion part, the examined allylsilanes are sterically demanding and may compromise the addition step. Less demanding allylsilanes should be prepared to tackle this issue. Finally, copper is not the only known element to trigger the catalytic allylation reaction with allylsilane, hence other transition metal-based catalysts should be considered (Scheme II-55).[46]



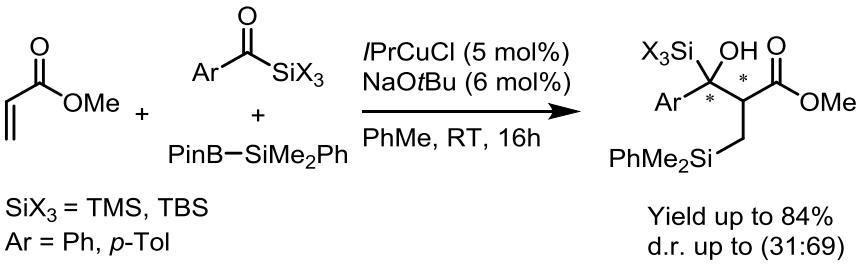
Scheme II-55 Transmetallation pathway for the allylation of aldehydes with triethoxyallylsilanes.

A β-(triethoxysilyl)sulfone was prepared and found to be a vinyl-anion equivalent when added to carbonylated electrophiles (Scheme II-56). The literature revealed that similar chemistry was already developed and reported earlier. Therefore, this topic was not developed deeper.



Scheme II-56 β-(triethoxysilyl)sulfone as vinyl anion equivalent.

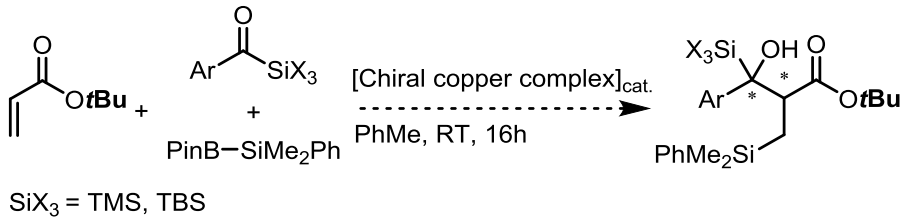
In a final attempt to observe a copper-catalysed transformation of acylsilanes, the initial goal of this chapter was adapted to the domino β-silylation/aldolisation of acrylates. Gratifyingly, methyl acrylate proved to be a suitable Michael acceptor in this reaction and acylsilanes were efficiently captured in a catalytic fashion by α-cupro-esters affording highly substituted α-hydroxysilanes with more than promising yields and diastereomeric excesses (Scheme II-57).



Scheme II-57 Copper-catalysed domino β-silylation/aldolisation of methyl acrylate with acylsilanes.

Reported domino β-addition/aldolisation chemistry of acrylates supports that *tert*-butyl acrylates induce higher diastereoselectivity.[5-6] Therefore, these reagents should be tested in this reaction. Once

satisfying diastereoselectivity will be reached, the asymmetric version of this reaction should be easily developed by screening a large array of chiral ligands (Scheme II-58). Indeed, this methodology would be of high interest in the chemistry of acylsilanes and α-hydroxysilanes.



Scheme II-58 Asymmetric and diastereoselective copper-catalysed domino β-silylation/aldolisation of tert-butyl acrylate.

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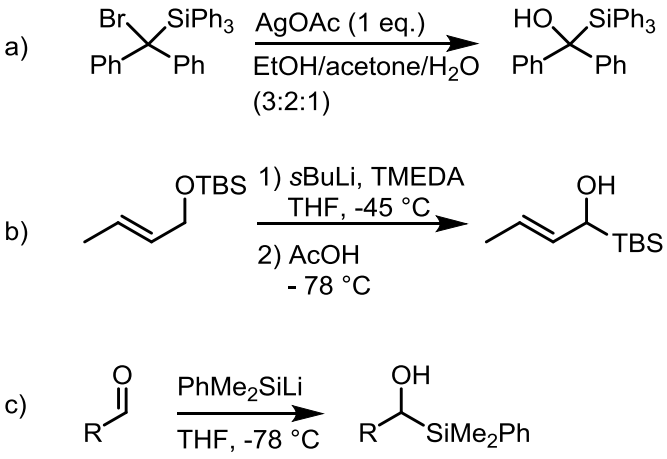
Chapter III Copper-catalysed hydrosilylation and hydroborylation of acylsilanes

1 Introduction

1.1 Racemic synthesis of α-hydroxysilanes

α-hydroxysilanes are a class of organosilicon compounds bearing a silyl group on the α-carbon of a hydroxyl group. As a result, α-hydroxysilanes often contain an asymmetric carbon centre. They are considered as a kind of chiral organometallic reagent containing a functional group. This makes them and their derivatives highly valuable building blocks in organic chemistry as they can be used in several stereocontrolled carbon-carbon bond formation reactions leading to an array of optically active organic molecules. The first methods reported to access α-hydroxysilanes rely on the silver-mediated hydrolysis of α-bromobenzylsilanes,[1] the retro-Brook rearrangement of silyl ethers[2] and the addition of silyllithium reagents to aldehydes.[3] However these methods are nowadays less desirable as they lead to racemic mixtures and have low functional group tolerance due to the harsh conditions required (Scheme III-1).

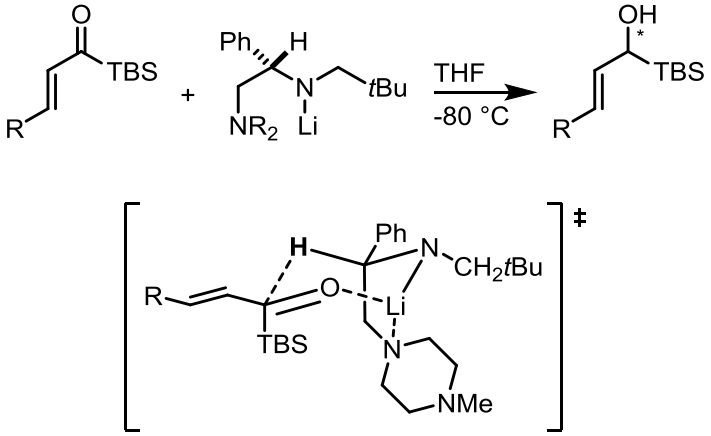


Scheme III-1 Racemic access to α-hydroxysilanes.

1.2 Enantioselective synthesis of α-hydroxysilanes

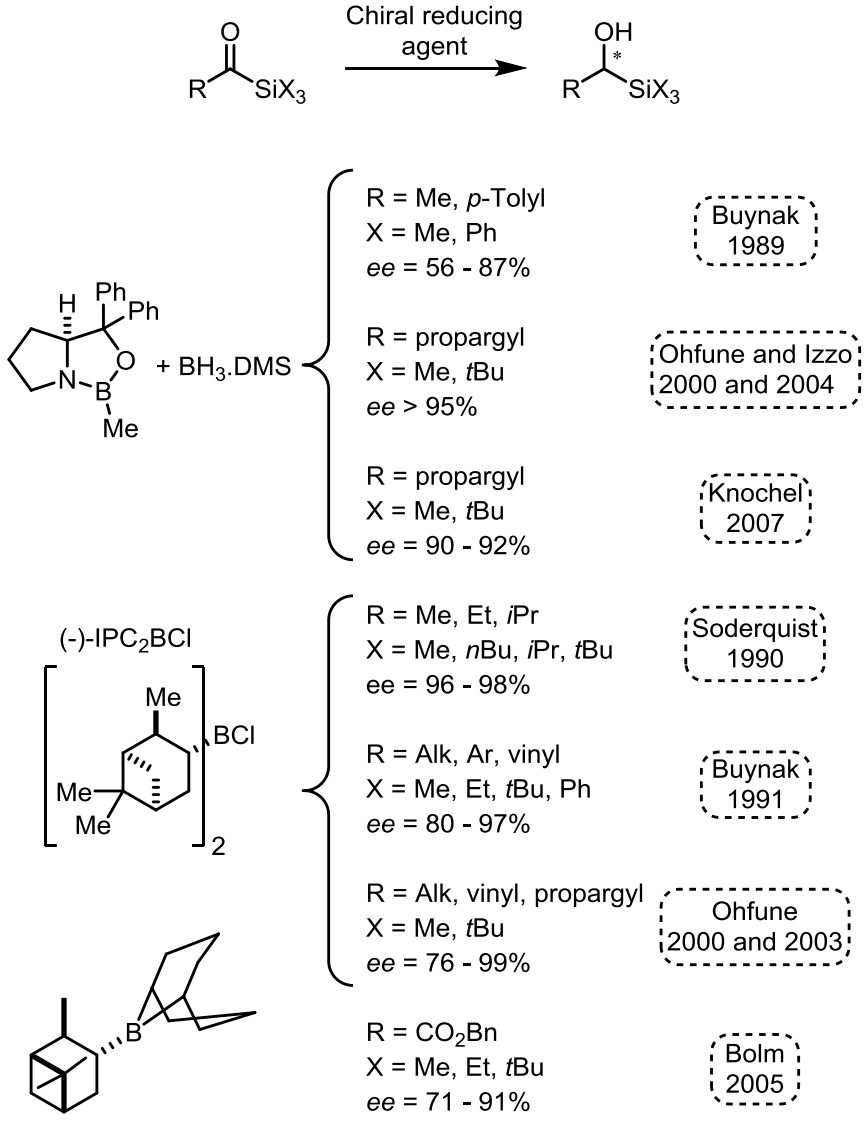
1.2.1 Stoichiometric methods

The most direct methods leading to chiral α-hydroxysilanes is the asymmetric reduction of prochiral acylsilanes. In this field, the earliest examples suffered from the requirement of stoichiometric amounts of the chiral reducing agents. In 1971, Mosher and co-workers reported a Meerwein-Pondorf-Verley type hydride transfer from a chiral organomagnesium reagent to acylsilanes with low enantiomeric excess.[4] Decades later, Takeda and co-workers accidentally observed similar hydride transfer from lithium amides. After optimisation, lithium amides of chiral secondary amines were found to be excellent hydride transfer agents to α,β-unsaturated and aromatic acylsilanes. Although conversion was not complete, the observed enantioselectivities of the 1,2-hydride transfers were superior to 99% (Scheme III-2).[5] Quite recently, this methodology has been applied to the synthesis of siloxyallenes by a tandem reduction/Brook rearrangement/protonation of alkynoyl silanes.[6]



Scheme III-2 Enantioselective reduction of α,β-unsaturated acylsilanes by chiral lithium amides.

An important class of reagents used for the reduction of acylsilanes are boron containing chiral reducing agents. Chiral organoboranes have been extensively used and are known to give great results (Scheme III-3). The first example by Buynak and co-workers was the asymmetric reduction of methyl and *p*-tolyl acylsilanes with Itsuno's reagent.[7] Chiral oxazaborolidines were then adapted to the reduction of alkynyl acylsilanes by Ohfune,[2b] Izzo[8] and Knochel[9] with great enantiomeric excesses. The most widely used chiral organoboron reducing agent is B-chlorodiisopinocampheylborane (Ipc_2BCl). After Soderquist's original report,[10] it has been employed for the enantioselective reduction of a large variety of aliphatic, aromatic, alkenyl and alkynyl acylsilanes with usually very good results.[2b, 2c, 11] Finally, Alpineborane was found to give better results for the reduction of silylglyoxylates.[12]



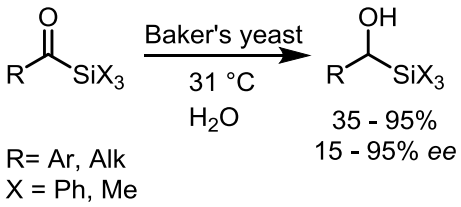
Scheme III-3 Chiral organoboranes as stoichiometric reducing agents of acylsilanes.

1.2.2 Catalytic methods

1.2.2.1 Asymmetric reductions of acylsilanes

Early catalytic and enantioselective access to α-hydroxysilanes from acylsilanes was allowed by enzymatic microbial reduction in ambient conditions with growing cells of the yeast *Kloeckera corticis*.[13]

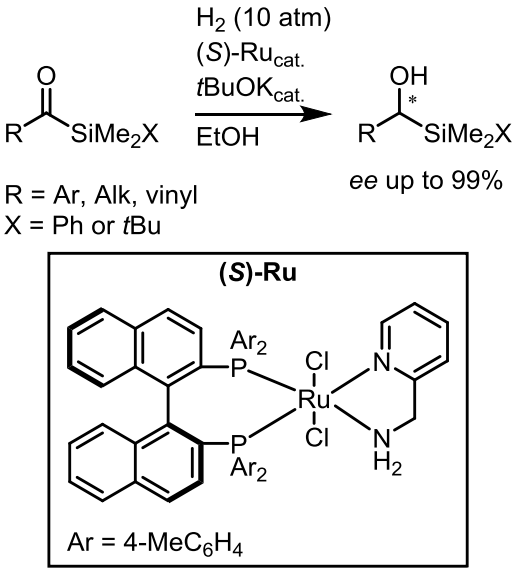
Baker's yeast was demonstrated to catalyse the reduction of a large array of acylsilanes in an asymmetric fashion by Zani (Scheme III-4).[14] These enzymatic methods suffer from extremely high substrate dependence as the smallest variations of steric or electronic properties result in dramatic decreases of reaction time, yield or enantiomeric excess.



Scheme III-4 Enzymatic asymmetric reduction of acylsilanes with Baker's yeast.

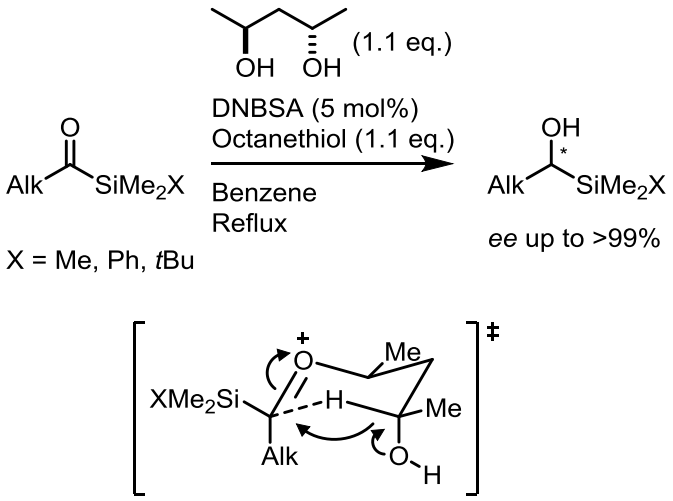
Organometallic catalysis was later found to be an efficient way to reduce acylsilanes enantioselectively. Rychnovsky and co-workers found that Noyori's system could be applied to the reduction of acylsilanes.[15] Hence, ruthenium catalysts were employed in the transfer hydrogenation of silyl ketones with isopropanol as hydride source. This system reached highest efficiency with catalyst loadings of 0.5 to 3 mol% for the reduction of aromatic acylsilane with high yields and enantioselectivities. Under these conditions however, aliphatic and α,β-unsaturated acylsilanes suffered from low conversions and *ee*'s.[16] In 2008, Arai *et al.* reported an improved Tol-binap/Pica ruthenium(II) complex that efficiently catalyses the hydrogenation of a variety of aliphatic, aromatic and α,β-unsaturated acylsilanes with excellent results both in yield and enantioselectivity. Compared to Noyori's system, this complex allows a lower catalytic loading making it suitable for preparative scale reactions (Scheme III-5).[17] Similarly, a phosphoramidite rhodium complex has been

reported to reduce silyl enolcarbamates in the presence of hydrogen gas leading to a derivative of α-hydroxysilanes.[18]



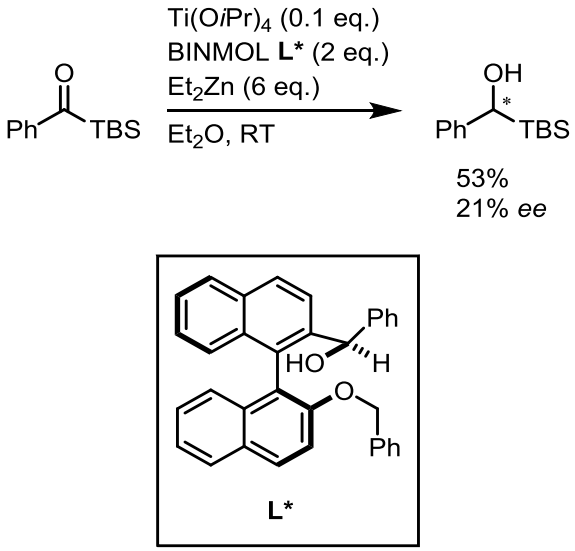
Scheme III-5 Tol-binap/Pica ruthenium(II) as a catalyst for the asymmetric hydrogenation of acylsilanes.

Undertaking investigations on the synthesis of optically active ketals in the presence of chiral diols, Matsuo and co-workers were surprised to observe enantioselective reduction of their model ketone in the presence of dinitrobenzenesulfonic acid (DNBSA) instead of the expected ketalisation. After optimisation, the reaction conditions were found to be broadly applicable to aliphatic acylsilanes giving great yields and enantiomeric excesses. The proposed reaction mechanism involves the acid catalysed formation of an oxocarbenium ion followed by intramolecular asymmetric hydride transfer from the diol moiety. The greatest drawback of this method is the need for stoichiometric amounts of the chiral diol while the catalyst is the Brønsted acid (Scheme III-6).[19]



Scheme III-6 DNBSA-catalysed reduction of aliphatic acylsilanes in the presence of a chiral diol.

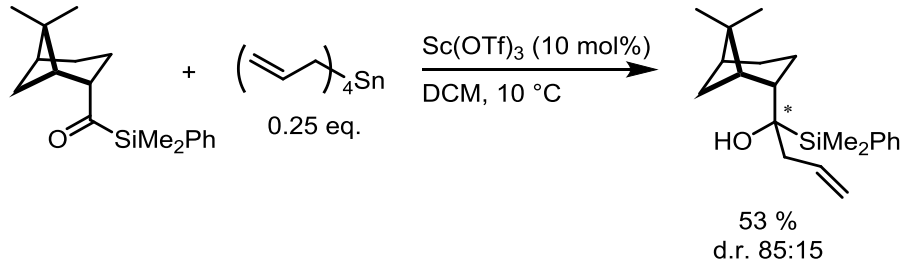
Most recently, Gao *et al.* reported the enantioselective reduction of acylsilanes by a large excess of diethylzinc in the presence of a titanium catalyst and 20 equivalents of the chiral BINMOL ligand with respect to the catalyst. Despite the excess of hydride source and ligand, only moderate yields and low enantioselectivities were obtained (Scheme III-7).[20]



Scheme III-7 Chiral titanium complex-catalysed transfer of hydrides from diethylzinc to acylsilanes.

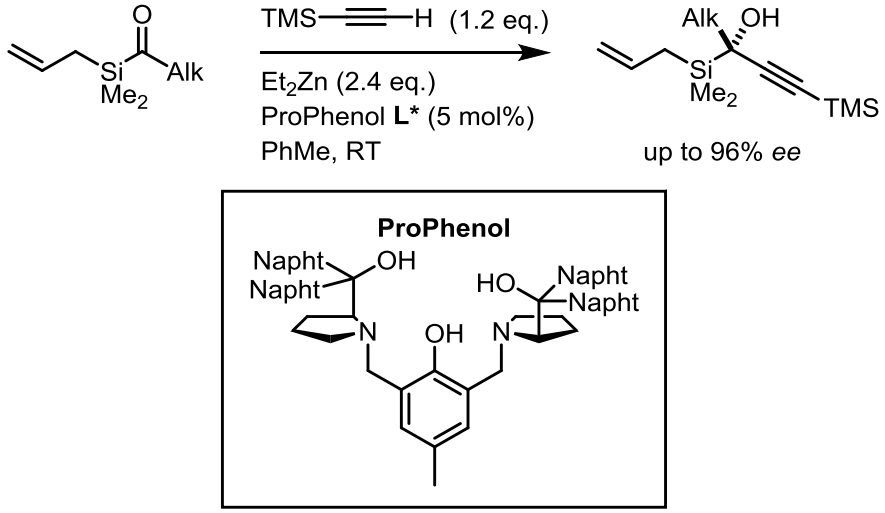
1.2.2.2 Asymmetric additions to acylsilanes

Apart from reduction reactions, addition reactions to acylsilanes are highly desirable as they lead to tertiary α-hydroxysilanes. In 1998, Ricci and co-workers described the scandium triflate catalysed allylation of acylsilanes by tetraallylstannane. Although no enantioselective conditions were developed, allylation of chiral acylsilanes proceeded with good diastereoselectivity compared to the allylation of the corresponding aldehyde (Scheme III-8).[21]



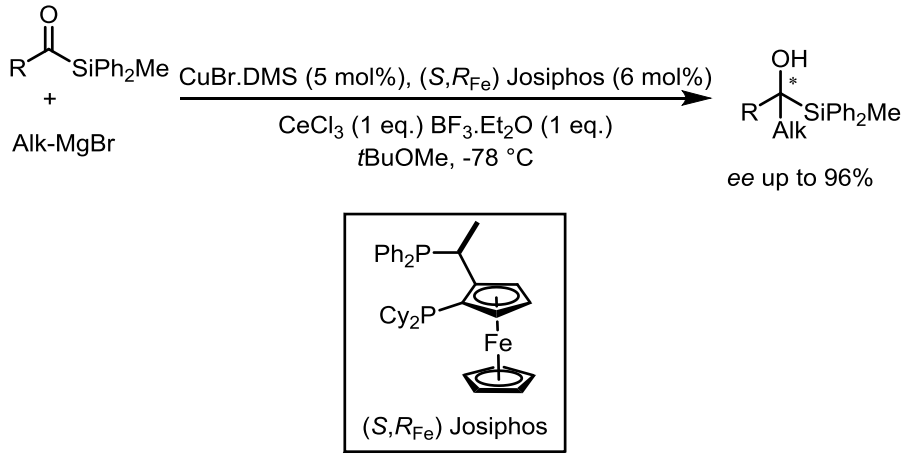
Scheme III-8 Diastereoselective addition of tetraallylstannane to a chiral acylsilane.

The groups of Chan[22] and Marek[23] simultaneously reported the highly enantioselective addition of alkynylzinc reagents to acylsilanes. Catalytic amounts of chiral Schiff bases efficiently led to enantiomeric excesses as high as 88% in the addition reaction. Marek further improved this system introducing a ProPhenol type ligand which could be used with a 5 mol% loading affording the expected product with up to 96% enantiomeric excess (Scheme III-9).[24]



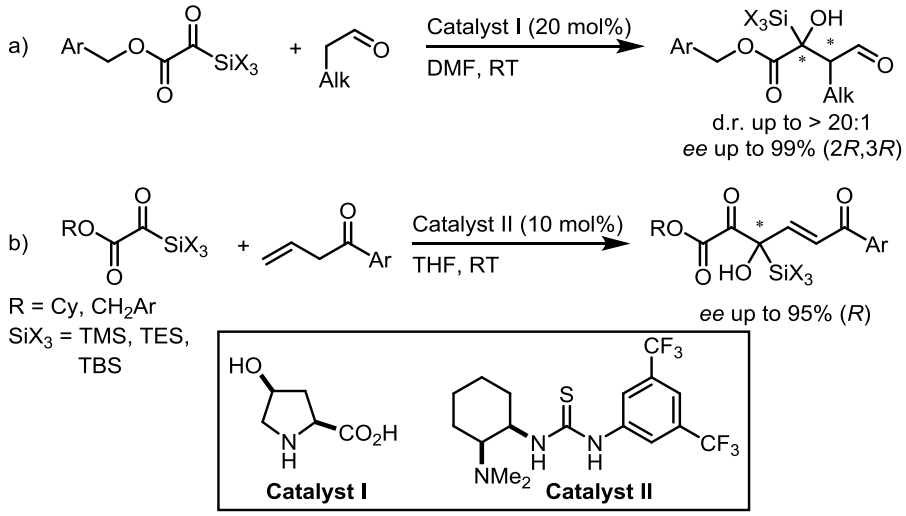
Scheme III-9 Marek's enantioselective addition of alkynylzinc reagents to acylsilanes with a ProPhenol ligand.

Despite quick evolution of the asymmetric addition reactions to acylsilanes, the previous methods suffer from the use of stoichiometric amounts of transition metal reagents. In 2015, Rong *et al.* reported the enantioselective addition of Grignard reagents to acylsilanes catalysed by a diphosphine/copper complex affording aromatic and allylic α-hydroxysilanes (Scheme III-10).[25]



Scheme III-10 Copper-catalysed asymmetric alkylation of acylsilanes with Grignard reagents.

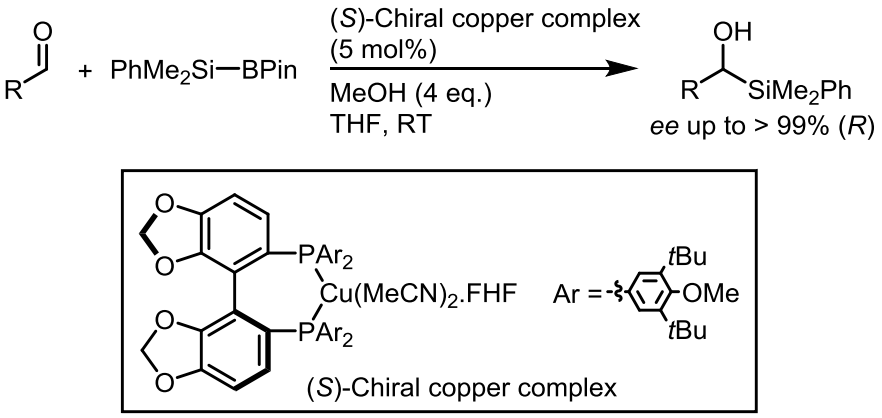
Finally, Han *et al.* became interested in the organocatalyzed aldol additions to silyl glyoxylates.[26] Asymmetric addition of aliphatic aldehydes was conducted in the presence of 20 mol% of the commercially available *cys*-L-4-hydroxyproline with impressive enantioselectivity (Scheme III-11a).[26a] Vinylogous aldol addition of aryl allyl ketone was then reported to take place in the presence of a bifunctional thiourea organocatalyst (Scheme III-11b).[26b]



Scheme III-11 Organocatalysed asymmetric aldol (a) and vinylogous aldol (b) reactions with acylsilanes.

1.2.2.3 Asymmetric additions of silicon nucleophiles to aldehydes

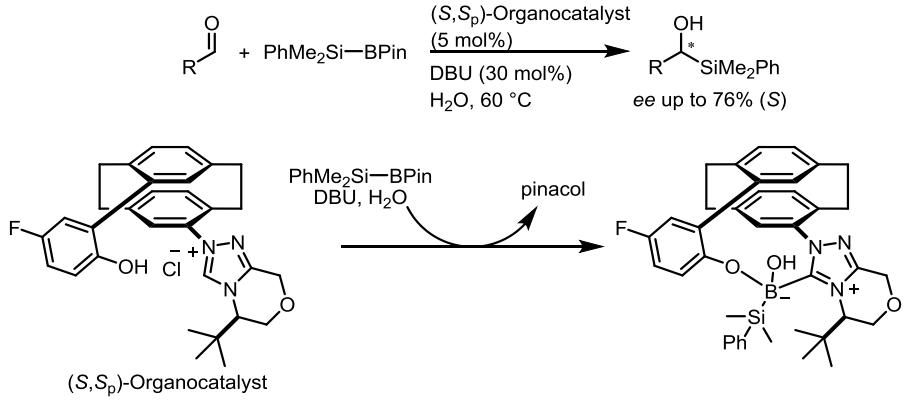
Another method to access α-hydroxysilanes is the direct addition of silyl nucleophiles to aldehydes. This scheme gives direct access to the desired compounds from commercially available aldehydes, circumventing the need for multi-step acylsilane synthesis. Despite its straightforwardness the asymmetric version of this reaction is limited to the addition of Suginome's reagent hence restricting it to the addition of the dimethylphenylsilyl group. Based on the findings by Kleeberg *et al.* that NHC-copper(I) complexes efficiently catalyse the addition of Suginome's reagent to aldehyde,[27] Cirriez *et al.* developed the enantioselective DTBMSegphos-copper(HF_2) catalysed addition of borosilane to aromatic aldehydes. The corresponding α-hydroxysilanes were obtained with an impressive average enantiomeric excess of 96% over eighteen examples (Scheme III-12).[28]



Scheme III-12 Asymmetric copper-catalysed addition of silicon nucleophiles to aldehydes.

Very recently, Ma and co-workers reported the transition metal-free addition of Suginome's reagent to various aromatic aldehydes in the presence of chiral paracyclophane-based NHC catalysts in water.[29] In

the latter case, water was found to play an important role in the reaction. It was proposed that water is involved in the hydrolysis of the pinacol moiety of the borosilane leading to a sterically less demanding boron atom which in turn engages in the complexation with the *in situ* generated carbene catalyst. The resulting carbene-borosilane complex is the actual chiral silyl transfer agent (Scheme III-13).

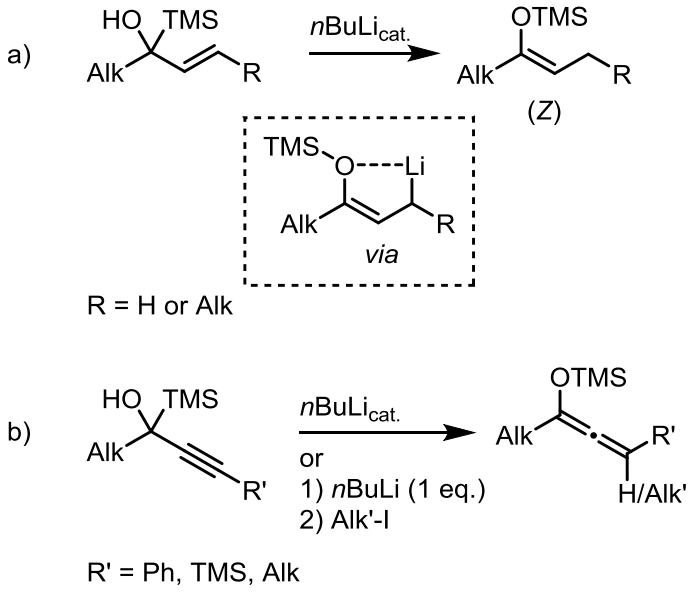


Scheme III-13 Transition metal-free addition of Suginome's reagent to aldehydes in water.

1.3 Synthetic applications of α-hydroxysilanes

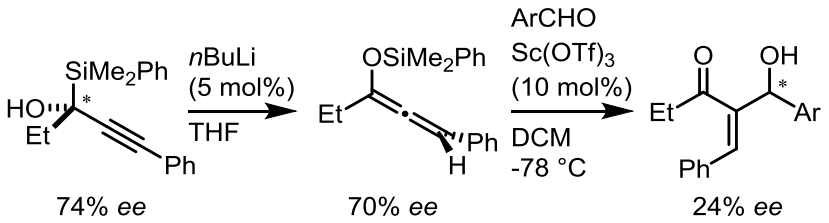
1.3.1 Brook rearrangement

In the same way as acylsilanes react upon nucleophilic attack, α-hydroxysilanes can undergo a Brook rearrangement after deprotonation by a base. The resulting α-siloxy carbanion is prone to be used in several synthetically useful transformations. In 1980, Kuwajima and co-workers reported that allylic α-hydroxysilanes are converted to silyl enol ethers with high (*Z*) selectivity by the action of catalytic amounts of *n*BuLi. The stereoselectivity of the process is attributed to the O-to-Li coordination after allylic transposition of the anion (Scheme III-14a).[30] Similarly, propargylic α-hydroxysilanes were converted to siloxyallenes after Brook rearrangement and γ-protonation or γ-electrophilic capture of methyl or butyl iodide (Scheme III-14b).[31]



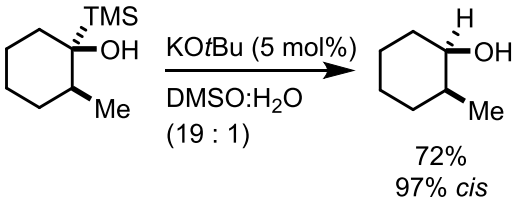
Scheme III-14 nBuLi-triggered Brook rearrangement of α-hydroxyallylsilanes (a) and α-hydroxypropargylsilanes (b).

Later, Scheidt studied the Brook rearrangement of enantioenriched propargylic α-hydroxysilanes to siloxyallenes. Even though the transfer of chirality was high during this process, the optical information was lost after subsequent aldolisation reaction and a chiral catalyst was required to obtain the product with good enantiomeric ratio (Scheme III-15).[32]



Scheme III-15 Enantiospecific conversion of propargylic α-hydroxysilanes to siloxyallenes and subsequent Mukaiyama aldol-type reaction.

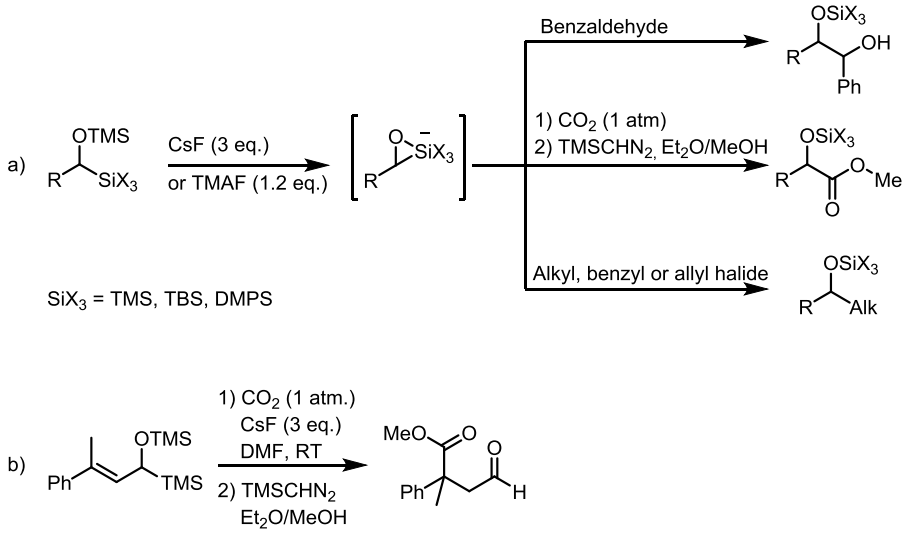
The Brook rearrangement is a known method for the stereoselective protodesilylation of α-hydroxysilanes. This transformation is highly desirable for the removal of silyl groups that have served their purpose. In a protic medium and in the presence of a catalytic amount of base, the cyclohexanol derivative of the cyclic α-hydroxysilane was obtained after a Brook rearrangement/silyl ether cleavage sequence (Scheme III-16).[33]



Scheme III-16 Potassium tert-butoxide-catalysed stereospecific protodesilylation.

Beyond the base-triggered Brook rearrangement of α-hydroxysilanes, α-siloxy carbanion equivalents were found to be accessible from α-siloxysilanes *via* fluoride-mediated cleavage of the silyl ether

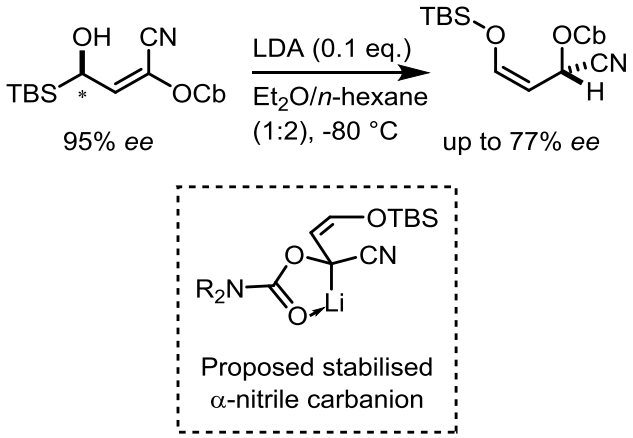
followed by Brook rearrangement.[34] This method allows access to α-siloxy carbanions without requiring strong bases. The resulting nucleophilic species are successfully quenched by a variety of alkyl halides, aldehydes[34a] or carbon dioxide (Scheme III-17a).[34b] Interestingly, when allylic α-siloxysilanes are subjected to the reaction conditions, the electrophilic species are captured in γ position provided that a phenyl ring is present on that position (Scheme III-17b).



Scheme III-17 Fluoride-promoted generation of α-siloxycarbanion equivalents from α-siloxysilanes.

Interested in the fate of allylic α-hydroxysilanes, Sasaki *et al.* investigated the chirality transfer in Brook rearrangement-mediated S_E2' solvolytic protonation of α-hydroxyallylsilanes bearing a cyano and a carbamoyl group in γ position. In this study, the conservation of optical information was attributed to the increased configurational stability of the C-chiral α-nitrile lithium species provided by the carbamoyl substituent. Indeed, the carbamoyl group is assumed to be

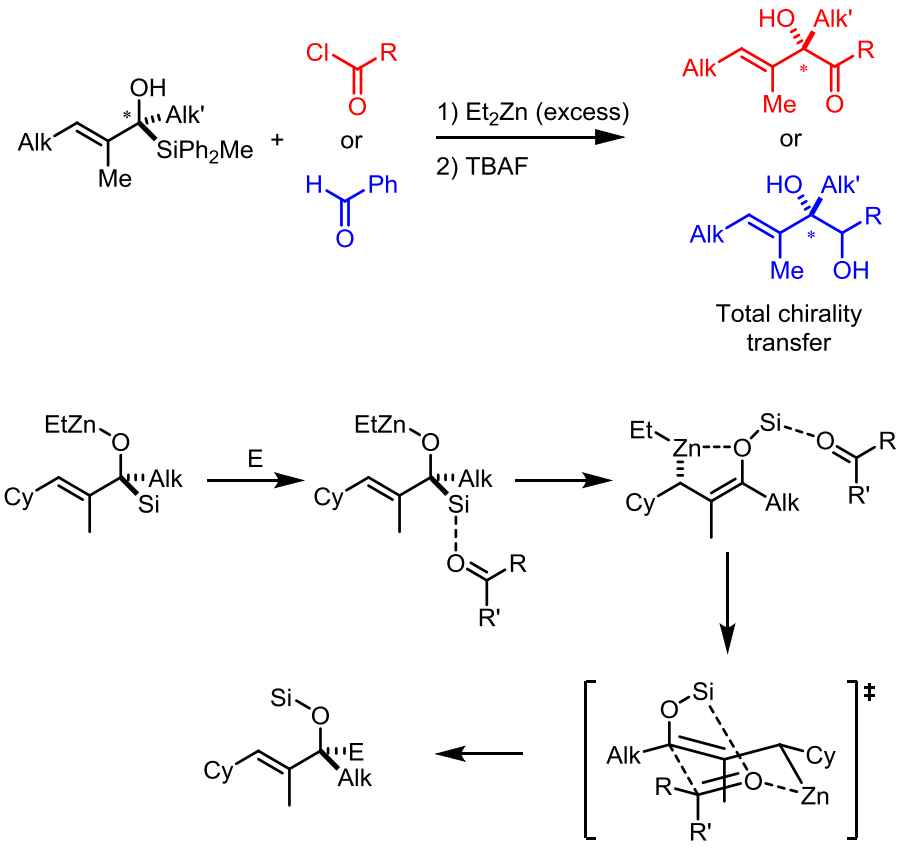
participating in a key intramolecular coordinated species involving the lithium atom (Scheme III-18).[35]



Scheme III-18 S_E2' solvolytic protonation of α-hydroxyallylsilanes with partial chirality transfer.

Simultaneously, Marek and Harutyunyan independently reported that the Brook rearrangement of optically active allylic tertiary α-hydroxysilanes could be triggered by deprotonation with diethylzinc.[36] Evidence was found that the resulting zinc alkoxide rearranged to form a configurationally stable chiral allylzinc species which upon reaction with carbonylated electrophiles yields the corresponding tertiary allylic alcohols with full chirality transfer.[36a] In these cases, no specific configurational stabilising substituents were required to ensure the conservation of optical purity. Mechanistically, it was proposed that the α-zincoxysilane resulting of the deprotonation is coordinated by the carbonyl oxygen of the electrophile at the silicon atom. This coordination is believed to actually trigger the Brook rearrangement leading to a chiral allylzinc species stabilised by intramolecular coordination with the silyl ether's oxygen. The carbonylated electrophile is subsequently trapped *via* a chair-like

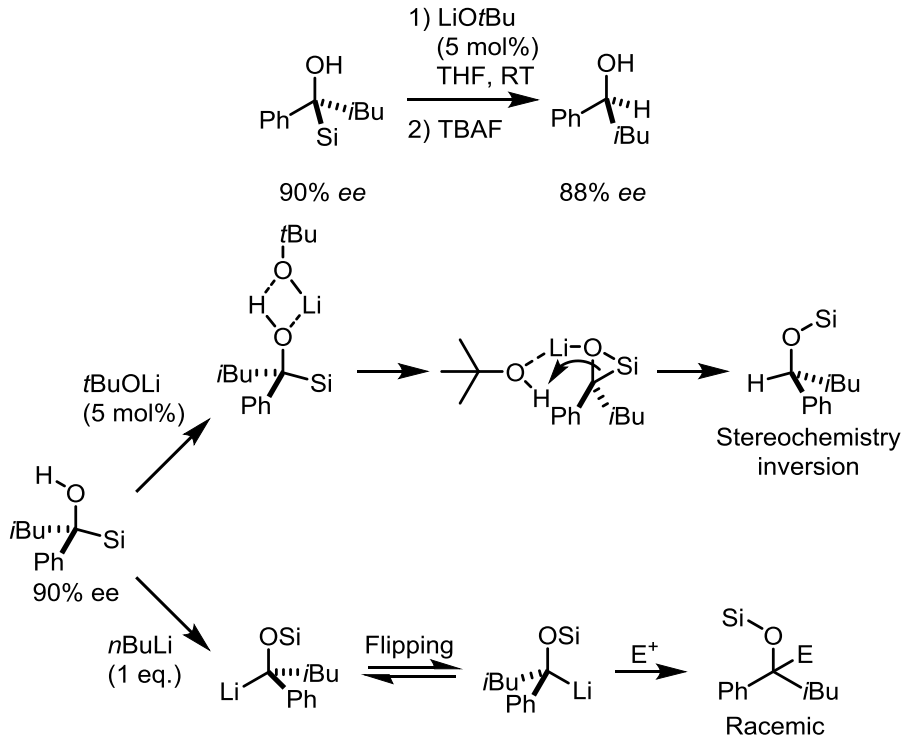
transition state leading to the desired tertiary alcohol (Scheme III-19).[36b]



Scheme III-19 Total chirality transfer in the diethylzinc-mediated Brook rearrangement of α-hydroxyallylsilanes.

Similar studies were conducted on benzylic α-hydroxysilanes.[37] However, the process was found to operate with uncomplete, yet high chirality transfer during Brook rearrangement/protonation sequences, while the corresponding Brook rearrangement/electrophile capture occurred with loss of the optical purity. The stereospecificity of the protonation process was rationalised by the coordination of the lithium *tert*-butanolate's conjugated acid to the lithium-silicate ion pair, thereby allowing fast protonation and avoiding flipping and

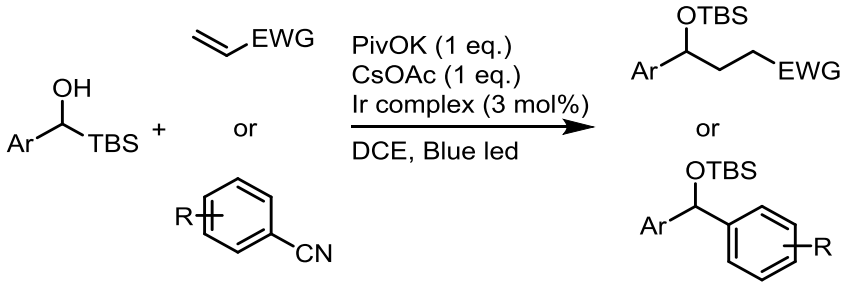
racemisation of the α-siloxy anion. Therefore, capture of carbon electrophiles results in the loss of optical information since stoichiometric amounts of stronger bases are required to avoid competing protolysis. The resulting anion lacking configurational stabilising group quickly racemises and captures the electrophiles in a racemic fashion (Scheme III-20).



Scheme III-20 Studies on the chirality transfer during the Brook rearrangement of benzilic α-hydroxysilanes.

Recently, Amos Smith III and co-workers reported that benzylic α-hydroxysilanes were suitable substrates for the oxidative visible light induced single-electron transfer triggered Brook rearrangement yielding siloxybenzylic radicals. Those radicals generated *in situ* with the help of an iridium-based photocatalyst were engaged in alkylation

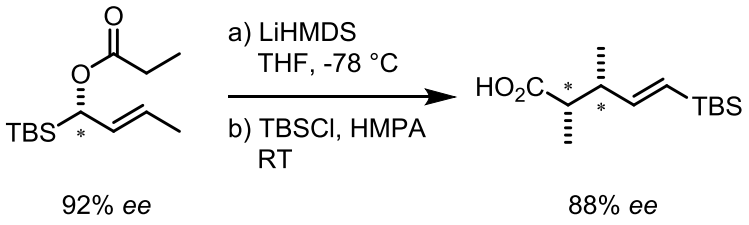
and arylation reactions with electron poor olefins and aromatic nitriles (Scheme III-21).[38]



Scheme III-21 Visible light induced single-electron transfer triggered Brook rearrangement.

1.3.2 Claisen rearrangements

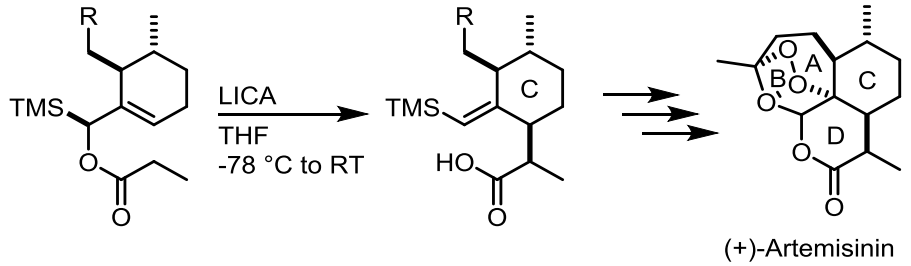
The class of allylic α-hydroxysilanes is particularly important in organic chemistry as it has found great applications in the Claisen rearrangement. Back in 1984, Ireland reported that α-hydroxyallylsilanes could serve as temporary equivalents of chiral primary allylic alcohols which upon esterification of the alcohol function became suited for the Claisen rearrangement with great stereoselectivity and transfer of chirality (Scheme III-22). This strategy was used for the synthesis of prostanoïds and the temporary silyl substituent was easily removed in the presence of tetrafluoroboric acid after reaction.[2a]



Scheme III-22 Stereoselective Claisen rearrangement of allylic α-hydroxysilane derivatives with transfer of chirality.

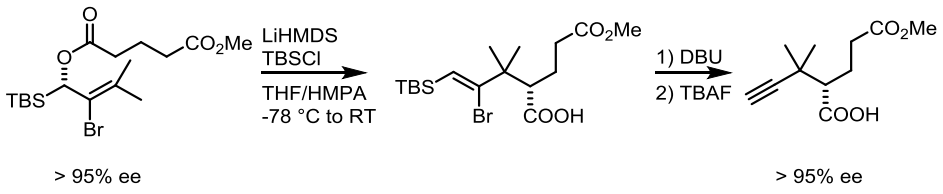
A similar strategy was used by Avery for the synthesis of the antimalarial compound (+)-Artemisinin. Upon exposure of the acetic

ester derivative of an α-hydroxyallylsilane to lithium N-isopropylcyclohexylamide (LICA), the Claisen rearrangement afforded the C ring fragment of the target compound. Further ozonolysis of the newly formed vinylsilane was used to set the D ring of the natural product (Scheme III-23).[39]



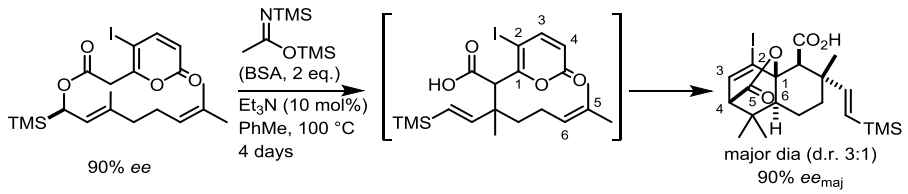
Scheme III-23 Claisen rearrangement step towards the synthesis of (+)-Artemisinin.

In 2003, Jacobi and Tassa used the ester enolate Claisen rearrangement of β-bromo-α-hydroxyallylsilanes for the synthesis of alkyne precursors of cobyric acid. Exposure of the formed vinylsilane to DBU followed by desilylation led to the formation of the desired terminal alkynes (Scheme III-24).[40]



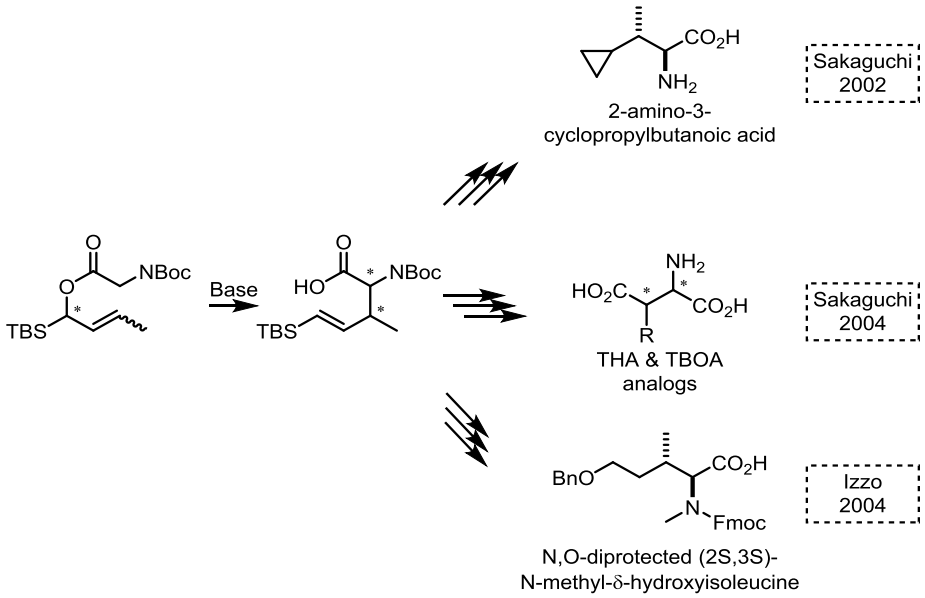
Scheme III-24 β-bromo-α-hydroxyallylsilanes in the Claisen rearrangement.

More recently, elegant work by Nelson *et al.* resulted in the total synthesis of four members of the transtaganolide family with the key step being an Ireland-Claisen rearrangement/intramolecular Diels-Alder cyclisation sequence (ICR/DA) which led to the formation of a stereochemically complex tricyclic intermediate in a single step from a simple pyrone α-hydroxyallylsilane derivative (Scheme III-25).[41]



Scheme III-25 Application of the Claisen rearrangement of α-hydroxysilanes in the synthesis of transtaganolides.

Sakaguchi and co-workers were highly active in this domain and they developed the Claisen rearrangement of α-amino acid protected allylic α-hydroxysilanes.[42] Upon exposure to LDA, these α-hydroxysilane derivatives afforded vinylsilane-bearing amino acids with excellent stereoselectivity and chirality transfer from the initial α-hydroxysilane.[42a] This method has found applications in the synthesis of 2-amino-3-cyclopropylbutanoic acid, a plant growth regulator,[42b] and in the synthesis of β-substituted aspartate analogues of THA and TBOA, inhibitors of glutamate transporters in mammalian tissues.[42c] Furthermore, Izzo used this strategy for the synthesis of N,O-diprotected (*2S,3S*)-N-methyl-δ-hydroxyisoleucine, a key intermediate towards the potent inflammatory cyclic depsipeptide Halipeptine A (Scheme III-26).[8]



Scheme III-26 The Claisen rearrangement of α-amino acid protected allylic α-hydroxysilanes as a tool in organic chemistry.

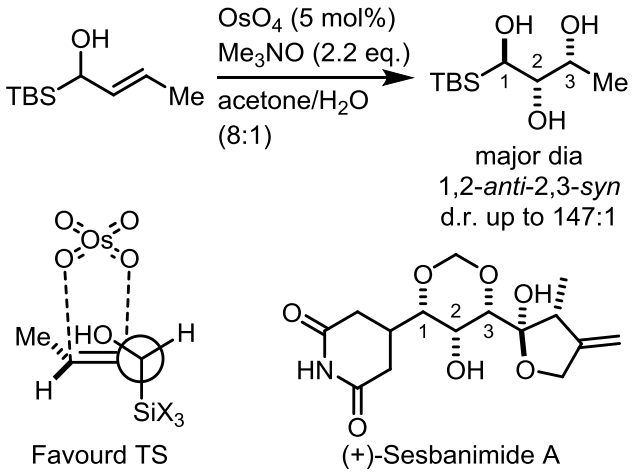
1.3.3 Miscellaneous

Besides the Brook and the Claisen rearrangements, chiral α-hydroxysilanes revealed useful in other fields of organic chemistry, mainly because great levels of chirality transfer are reached with these compounds. Some of these applications will be briefly examined in this section.

1.3.3.1 Organometallic catalysis

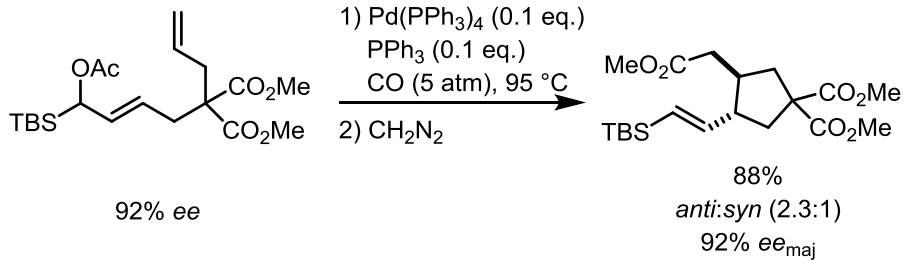
Cirillo and Panek studied the osmium tetroxide-catalysed vicinal dihydroxylation of allylic α-hydroxysilanes.[43] They found that unprecedented 1,2-*anti* diastereoselectivity could be obtained in this process. This result was attributed to the size and the σ-donating ability of the silyl group as well as to the hydroxyl group. The combined effects of those substituents largely favour a transition state in which the large silyl group is positioned antiperiplanar to the *p* orbitals of the olefin and the hydroxyl group is positioned "inside".[44]

Diastereoisomeric ratios as high as 147:1 could be obtained.[43a] These findings were subsequently applied to the synthesis of a precursor of (+)-Sesbanimide A, a potent cytotoxic agent, by installing two vicinal hydroxyl substituents of the final target (Scheme III-27).[43b] Similarly, Simmons-Smith cyclopropanation of allylic α-hydroxysilanes, although not being a catalytic process, proceeded with excellent diastereoselectivity.[11b]



Scheme III-27 Diastereoselective dihydroxylation of α-hydroxyallylsilanes, a key step in the synthesis of (+)-Sesbanimide.

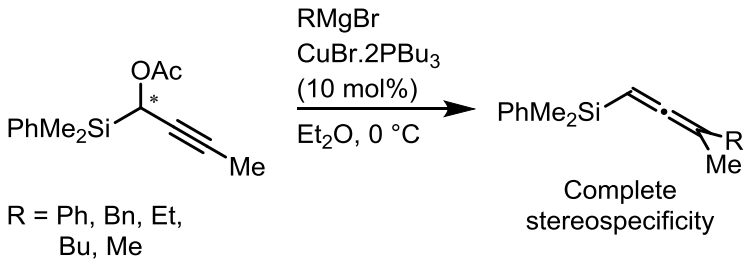
A decade later, Sakaguchi and co-workers investigated the formation of π-allyl palladium complexes from α-acetoxyallylsilanes and their capture with soft nucleophiles such as malonates. The capture operated well intra- and intermolecularly with full transfer of chirality and complete γ selectivity.[45] The methodology was then extended to the intramolecular insertion of olefins in the π-allyl palladium complex and could be combined with carbonylation under a carbon monoxide atmosphere (Scheme III-28).[46]



Scheme III-28 α-acetoxysilanes as π-allyl palladium precursors in cyclisation/carbonylation sequences.

1.3.3.2 Nucleophilic substitutions

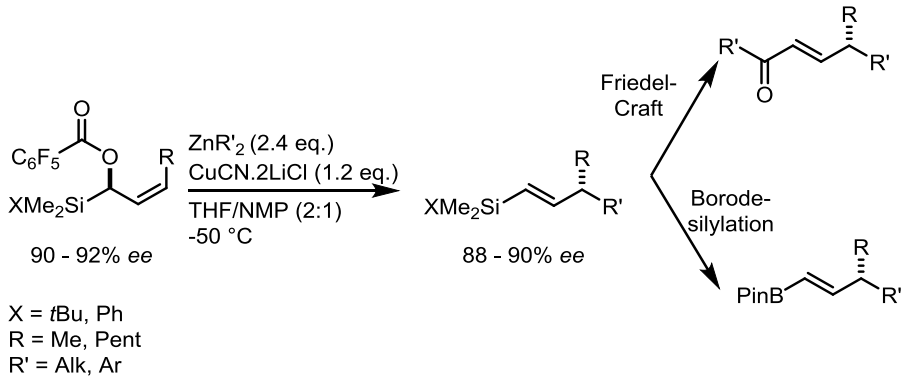
Activation of the hydroxyl substituents of β,γ-unsaturated α-hydroxysilanes made S_N2' type reactions possible.[9, 47] In 2004, Guintchin and Bienz reported the stereospecific allenylsilane synthesis from the copper-catalysed addition of Grignard reagents to optically active α-acetoxypropargylsilanes (Scheme III-29).[47a]



Scheme III-29 Stereospecific addition of Grignard reagents to propargylic α-acetoxysilanes.

Similarly, Perrone and Knochel described the copper-mediated addition of aryl- and alkylzinc reagents to enantioenriched α-hydroxyallylsilane derivatives. The resulting α-chiral vinylsilanes were obtained with excellent transfer of chirality and were efficiently converted to α,β-unsaturated-γ-chiral ketones by Friedel-Craft type acylations. Alternatively, they were derivatised to the corresponding vinylboronic esters by borodesilylation and engaged in Suzuki-type coupling reactions (Scheme III-30).[9] More recently, Sakaguchi and

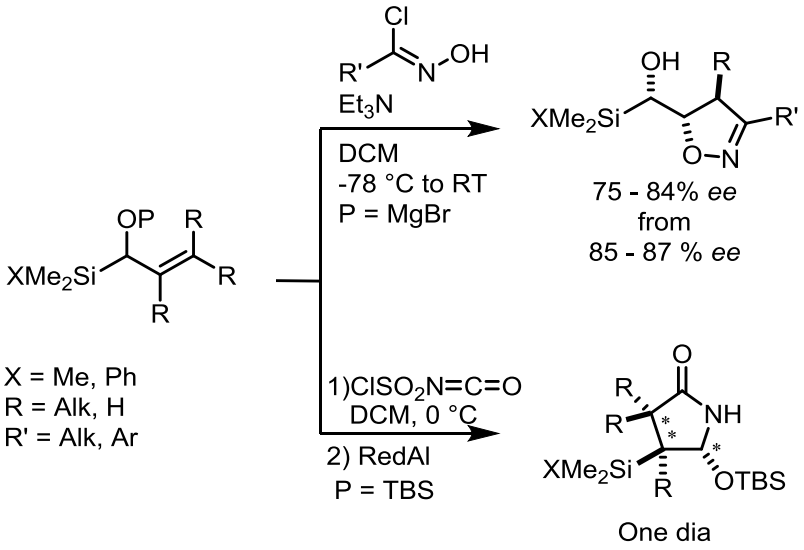
co-workers investigated the Mitsunobu reaction of α-hydroxyallylsilanes and found that the bulky silyl group favoured γ selective substitutions while the corresponding secondary allylic alcohols suffer from regioselectivity issues.[47b]



Scheme III-30 Copper-mediated addition of organozinc reagents to α-pentafluorobenzoxysilanes and derivatisation of the resulting vinylsilanes.

1.3.3.3 Cycloadditions

Allylic α-hydroxysilane derivatives were reported to undergo cycloaddition reactions when subjected to nitrile oxides in the presence of a magnesium alkoxide[48] or to N-chlorosulfonyl isocyanate.[49] As generally observed, cycloadditions with enantioenriched substrates operated with great diastereoselectivity and transfer of chirality affording the corresponding 4,5-dihydroisoxazoles and γ-lactams respectively (Scheme III-31).

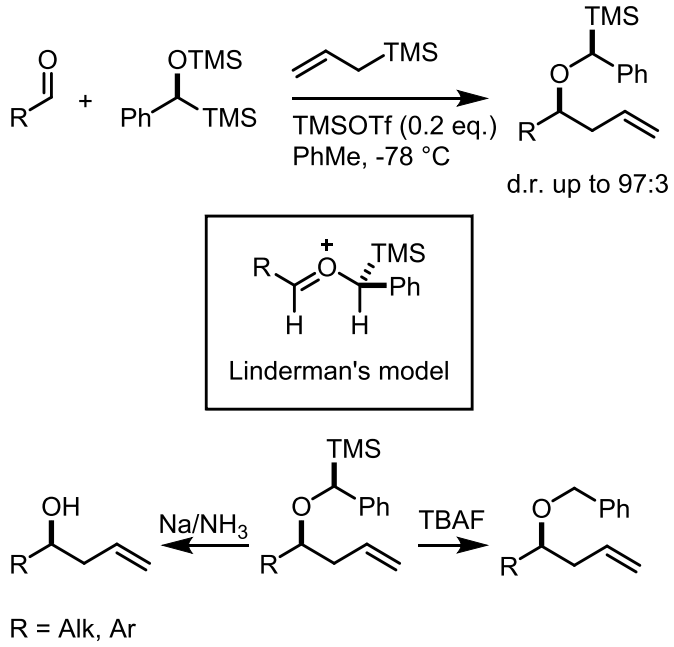


Scheme III-31 Cycloadditions of α-hydroxysilane derivatives with nitrile oxides and N-chlorosulfonyl isocyanate.

1.3.3.4 Oxocarbenium ion chemistry

Rychnovsky and co-workers took advantage of the great diastereoinductive effect of silyl groups and of their easy removal to use α-hydroxyarylsilanes as temporary chiral auxiliaries in oxocarbenium ion reactions.[15-16] Their method is based on Linderman's model according to which oxocarbenium ion derivatives of α-hydroxysilanes will have a given conformation leading to highly diastereoselective nucleophilic additions. Linderman's model states that the oxocarbenium ion will have an (*E*) geometry and that the silyl group will be positioned to reach a maximum overlap of the $\sigma_{C\text{-}Si}$ and the $\pi^*_{C=O}$ orbitals. In this conformation, nucleophiles are expected to attack selectively from the face opposite to the bulky silyl substituent. This method revealed successful and allylation of several oxocarbenium ions was achieved with great diastereomeric ratios. Finally, conversion of the chiral silyl auxiliary to a benzyl protecting

group or their complete removal afforded asymmetric secondary homoallylic alcohol derivatives with high enantiomeric excesses despite minor steric differences of their substituents (Scheme III-32).



Scheme III-32 Use of α-hydroxysilanes as chiral auxiliaries in oxocarbenium ion chemistry.

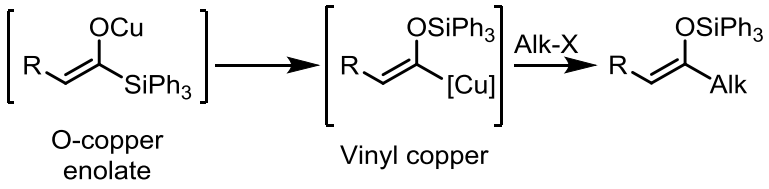
2 Aim

The very initial goal of this project found inspiration in the continuing interest in the discovery of copper-catalysed domino reactions with acylsilanes. The previous attempts having revealed unsuccessful, an alternative strategy was imagined based on Kei Takeda's reports on the copper-mediated enolisation/Brook rearrangement of acylsilanes described in a previous section.[50] However, during the initial experiments concerning this new project, an intriguing copper-catalysed 1,2-selective hydrosilylation reaction of α,β-unsaturated acylsilanes was discovered. Hence, it was decided to pursue the work on the elaboration of an enantioselective version of this copper-catalysed reaction. Furthermore, derivatives of the obtained optically active α-hydroxyallylsilanes were evaluated as substrates in a copper-catalysed Claisen reaction affording silylpentenoic acids. All the steps leading from the initial idea to the accomplishment of the final project are described in this chapter.

3 Results and discussion

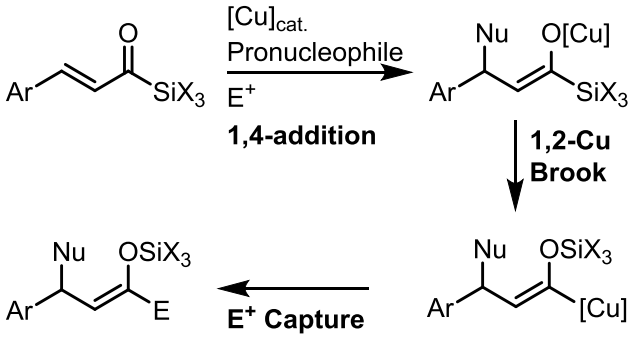
3.1 Initial strategy

The elaborated strategy was based on the work of Takeda on the copper chemistry of acylsilanes. As a reminder, copper enolates of acylsilanes efficiently underwent Brook rearrangement affording vinyl copper derivatives which were used to capture organic halides (Scheme III-33).



Scheme III-33 Copper-Brook rearrangement of O-copper enolates to vinylcopper species.

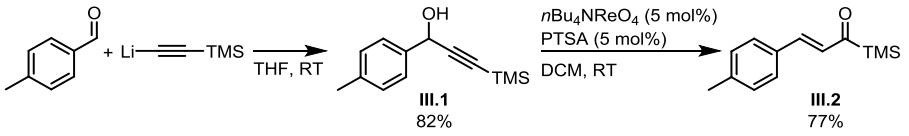
It was postulated that the same copper enolates could be accessed from α,β-unsaturated acylsilanes upon copper-catalysed conjugated additions of pronucleophilic species, e.g. Suginome's reagent, bisboronate or hydride donors. Subsequent Brook rearrangement and capture of an electrophile should lead to the formation of silyl enol ethers (Scheme III-34).



Scheme III-34 Postulated copper-catalysed conversion of α,β-unsaturated acylsilanes to silyl enol ethers.

To investigate this possibility, it was chosen the study the *I*PrCuCl catalysed silyl addition to the acylsilane equivalent of cinnamaldehyde.

The synthesis of the copper catalyst **II.34** was described in the previous chapter. The previously synthesised Suginome's reagent **II.8** was selected as silyl donor and the commercially available diethoxymethylsilane and phenylsilane were selected as hydride donor. The model α,β-unsaturated acylsilane **III.2** was synthesised according to a two-step procedure from the literature.[51] Addition of a lithium silylacetylide to *p*-tolualdehyde afforded the corresponding propargylic alcohol **III.1** with 82% yield. Subsequent perrhenate-catalysed Meyer-Schuster rearrangement afforded the model substrate **III.2** as a bright orange solid with 77% yield (Scheme III-35).



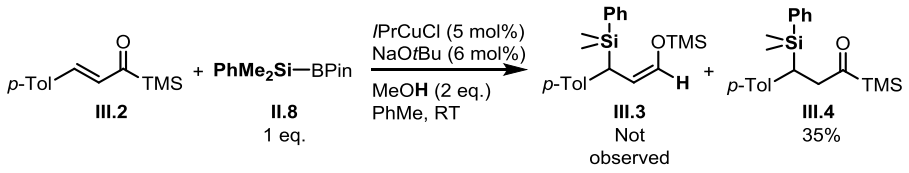
Scheme III-35 Synthesis of the model α,β-unsaturated acylsilane.

With all the reagents in hand, the initial catalytic experiments were started.

3.1.1 Addition of Suginome's reagent

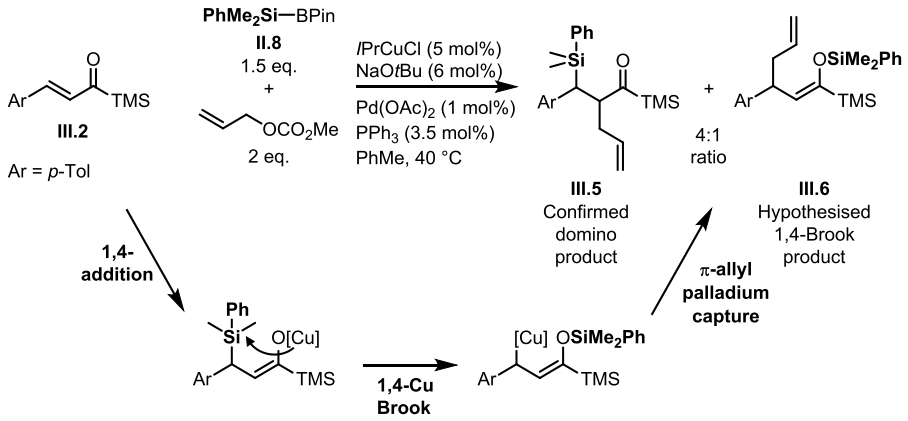
The exploration of this new project started with the addition of Suginome's reagent **II.8** to the model α,β-unsaturated acylsilane **III.2** under the conditions earlier developed for the β-silylation of vinylsulfones, with methanol as quenching electrophile. In this context the expected product was the monosubstituted silyl enol ether **III.3**. Yet, the crude NMR spectrum showed the formation of the β-silylated product **III.4** but no traces of any Brook rearrangement product were

observed. The β-disubstituted acylsilane **III.4** was isolated with 35% yield (Scheme III-36).



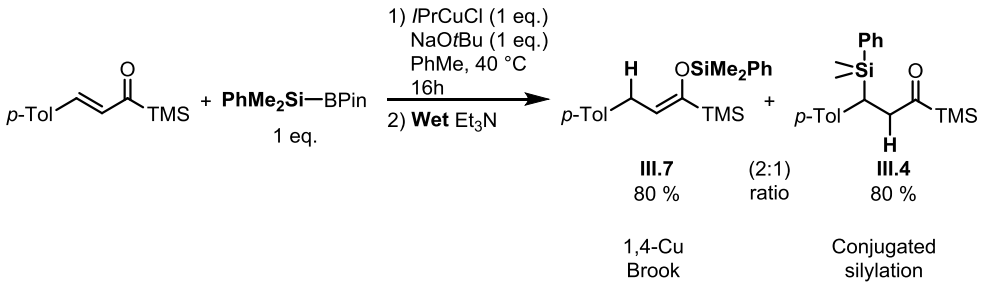
Scheme III-36 Copper-catalysed β-silylation of III.2 with Suginome's reagent.

Next, it was decided to run this β-silylation reaction with a different electrophile, i.e. a π-allyl palladium species, under conditions previously developed in our group.[52] After overnight stirring at 40 °C, the reaction yielded 79% of two isomers of a product as a 4:1 mixture. The major isomer could be isolated and was identified as the domino β-silylation/aldolisation-allylation product **III.5**. The minor isomer could not be isolated, however, it was obvious that this product was derived from the addition of the borosilane to the α,β-unsaturated acylsilane since ^{1}H NMR peaks corresponding to the dimethylphenyl group were present as well as the characteristic peak from the trimethylsilyl group. Furthermore, this compound seemed to include an allyl group and an additional unsaturation. On the basis of these observations and according to the ^{1}H NMR spectrum of the isomeric mixture, the minor product was hypothesised to be silyl enol ether **III.6**, resulting from the copper-catalysed conjugate silylation of the model substrate **III.2** followed by a 1,4-silyl migration and capture of the π-allyl palladium electrophile (Scheme III-37).



Scheme III-37 Domino copper-catalysed conjugated silylation/π-allyl palladium capture.

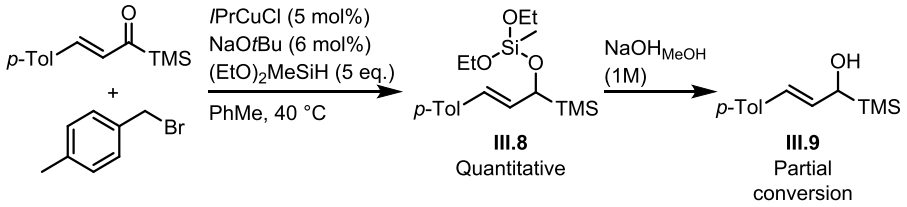
To elucidate whether the desired 1,2-copper-Brook rearrangement was possible with the acylsilane **III.2** in the presence of an (NHC)copper complex, the α,β-unsaturated acylsilane was heated to 40°C for 16 hours in the presence of Suginome's reagent **II.8** with a stoichiometric amount of copper complex **II.34** and no quenching electrophile. After quenching the reaction with wet triethylamine, two isomeric products were again obtained in a (1:2) ratio with 80% combined yield. The expected 1,2-copper-Brook rearrangement was not observed, however, this time the major product was determined to be the product from the β-silylation/1,4-Brook rearrangement **III.7** hypothesised above. The minor product could not be isolated but was identified as the β-silylated model acylsilane **III.4** (Scheme III-38).



Scheme III-38 Copper-mediated conjugated silylation/Brook rearrangement of an α,β-unsaturated acylsilane.

3.1.2 Addition of hydrides

In order to simplify the analysis of the crude ^{1}H NMR spectra and to avoid the occurrence of the 1,4-Brook rearrangement, silanes were used as pronucleophiles, i.e. hydride donors, instead of the Suginome's reagent **II.8**. A benzylic halide was used as the quenching electrophile. After overnight stirring of the reaction medium, no silyl enol ether was observed. Surprisingly, no expected conjugated hydride addition was observed either. Instead, the 1,2-hydrosilylated acylsilane **III.8** was obtained as the sole product of the reaction with full conversion. Hydrolysis of the product by a 1M methanolic sodium hydroxide solution partially afforded the corresponding allylic α-hydroxysilane **III.9** (Scheme III-39).



Scheme III-39 Unexpected copper-catalysed 1,2-hydrosilylation of αβ-unsaturated acylsilanes.

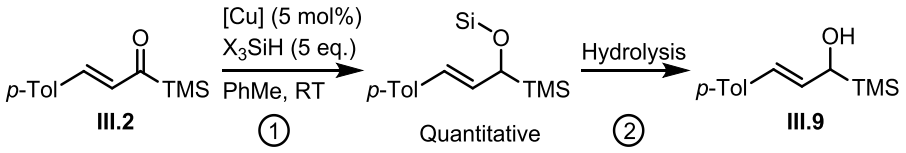
3.2 Copper-catalysed 1,2-hydride addition

Based on the excellent result obtained from the latter experiment and on a survey of the literature concerning the synthesis of α-hydroxyallylsilanes it was decided to further investigate the intriguing 1,2-selective hydrosilylation reaction of α,β-unsaturated acylsilanes and to develop enantioselective reaction conditions.

3.2.1 Initial assessment of the reaction

Investigation of the copper-catalysed 1,2-hydrosilylation of α,β-unsaturated acylsilanes was initiated with the screening of copper sources, hydride donors and hydrolysis conditions (Table III-1).

Table III-1 Screening of suitable copper sources, hydride donors and hydrolysis conditions for the copper-catalysed 1,2-hydrosilylation reaction of α,β-unsaturated acylsilanes.



Entry[a]	Copper source	X_3SiH	Hydrolysis	Conv. 2[b]
1	*I*PrCuCl/NaO*t*Bu	$Me(EtO)_2SiH$	$NaOH_{aq}$ 3M	None
2	*I*PrCuCl/NaO*t*Bu	$PhSiH_3$	$NaOH_{aq}$ 3M	Partial
3	*I*PrCuCl/NaO*t*Bu	$PhSiH_3$	HCl_{MeOH} 1M	Partial
4	*I*PrCuCl/NaO*t*Bu	$Me(EtO)_2SiH$	K_2CO_{3MeOH} Sat.	Total
5	$(PPh_3)_3CuF.2MeOH$	$Me(EtO)_2SiH$	None	/
6[c]	None	$Me(EtO)_2SiH$	/	/

[a] The copper-catalysed hydrosilylation was quantitative in all cases. [b] Conversions of the α-silyloxysilanes to free α-hydroxysilane III.9 were qualitatively determined from the crude ^1H NMR spectra. [c] No conversion of the substrate was observed for the first step.

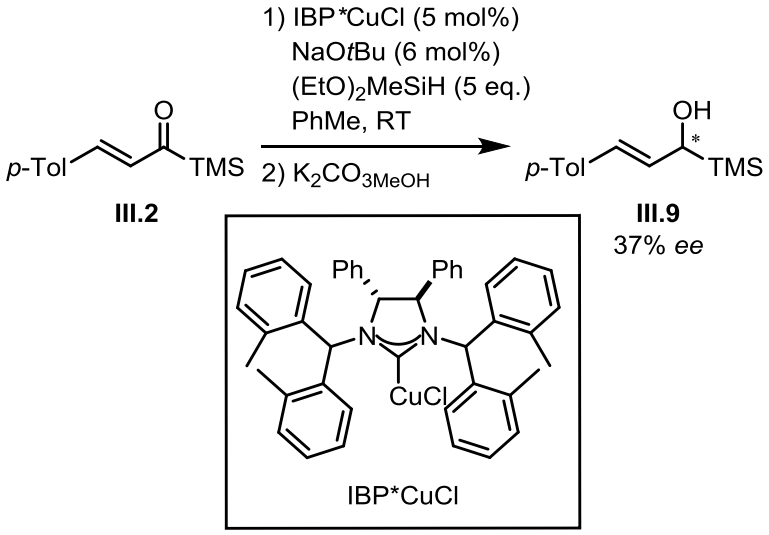
The 1,2-hydrosilylation reaction was successfully repeated at room temperature without the benzylic bromide and furnished the silylated product quantitatively. While previously, methanolic sodium hydroxide only led to partial hydrolysis of the Si-O bond, a three molar solution of aqueous sodium hydroxide did not induce any hydrolysis after 30 minutes (entry 1). Using phenylsilane instead of diethoxymethylsilane also led to total conversion of the acylsilane to the 1,2-hydrosilylated product, yet aqueous sodium hydroxide was

only suited to the partial hydrolysis of the Si-O bond (entry 2). Hydrochloric acid in methanol also led to partial hydrolysis (entry 3). After hydrosilylation with diethoxymethylsilane, a saturated methanolic solution of potassium carbonate was found to convert the totality of the α-siloxyallylsilane to the α-hydroxyallylsilane (entry 4). The opportunity to use chiral phosphine ligands to induce enantioselectivity was confirmed by successfully running the reaction with a preformed copper(I)fluoride tristriphenylphosphine complex **III.10** (entry 5).[53] Finally, a control experiment was carried in the absence of copper and demonstrated the need for a catalyst to affect this transformation under the present conditions (entry 6).

3.2.2 Enantioselective conditions

3.2.2.1 Chiral ligand screening

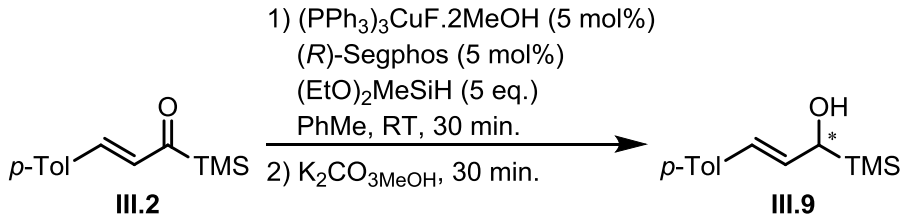
The first attempt to induce enantioselectivity in the copper-catalysed hydrosilylation reaction was performed with a chiral (NHC)copper complex, i.e. IBP*CuCl, kindly provided by Mr. Ricky B. C. Payen. After hydrosilylation and hydrolysis of the α-siloxyallylsilane, the crude α-hydroxyallylsilane was subjected to chiral HPLC analysis. The product was obtained with an encouraging enantiomeric excess of 37% (Scheme III-40).



*Scheme III-40 Enantioselective 1,2-hydrosilylation catalysed by IBP*CuCl.*

Next, it was decided to work with commercially available chiral diphosphine ligands in order to avoid the synthesis of the NHC ligands and their complexation to copper, facilitating and speeding up the screening process. This was carried out using the preformed bench stable copper(I) fluoride tristriphenylphosphine complex **III.10** (5 mol%) as copper source in toluene at room temperature (Table III-2). A first experiment was conducted with (*R*)-Segphos (6.25 mol%) as the chiral ligand. The conversion of the model substrate was complete after 30 minutes and an enantiomeric excess of 65% was measured (entry 1). In order to further improve the screening process, the reaction was repeated under ambient atmosphere and was found to effectively convert the substrate to the desired product with the same level of enantioselectivity (entry 2). Hence, the screening of chiral phosphines could be conducted in oven-dried open test tubes without requirement for drastic moisture-free conditions.

Table III-2 Effect of the atmosphere on the conversion and the enantiomeric excess.



Entry	Atmosphere	Conversion[a]	*ee*[b]
1	Argon, moisture-free	100%	65%
2	Ambient atmosphere	100%	65%

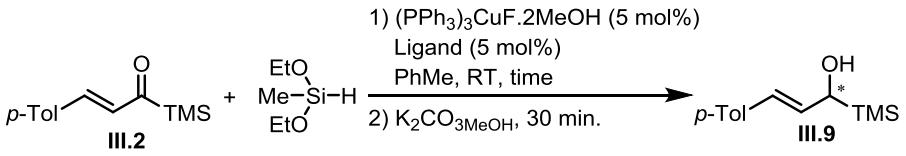
[a] Determined by TLC analysis. [b] Measured by chiral HPLC analysis.

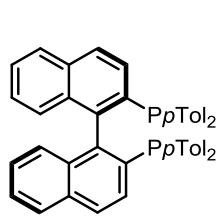
A total of 29 chiral ligands belonging to different phosphine families were tested under these conditions. The enantiomeric excesses were measured by chiral HPLC analysis of the crude α-hydroxyallylsilanes and no yields were determined. The best results are summed up below (Table III-3). The extensive results about the screening of the chiral diphosphine ligands are given in the experimental part (Chapter V).

Among the BINAP family, **III.L1** gave the α-hydroxyallylsilane with 46% enantiomeric excess (entry 1). The simple (*R*)-SEGPHOS **III.L2** used earlier was the best candidate in its family and no higher enantioselectivity than 65% was reached (entry 2). (*R*)-DTBM-Segphos **III.L3** which gave the best results in a previous study on the synthesis of α-hydroxysilanes disappointingly yielded the product in 39% enantiomeric excess (entry 3). The Josiphos family was ineffective in promoting the copper-catalysed hydride transfer in a satisfying asymmetric manner despite the seven monitored candidates (entry 4). Alternatively, the classical (*R*)-TaniaPhos **III.L5** allowed significant though insufficient enantioinduction (entry 5). Finally, the

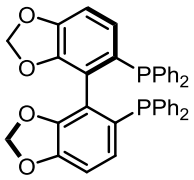
(*S*)-MeO-Biphep **III.L6** exhibited similar enantioinduction as the (*R*)-SEGPHOS **III.L2** with the added benefit of reaching complete conversion within a few seconds (entry 6).

Table III-3 Screening of the chiral diphosphine ligands.

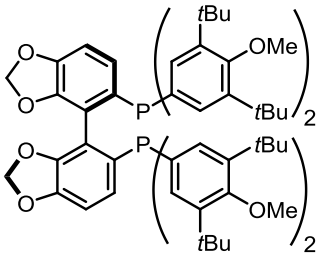




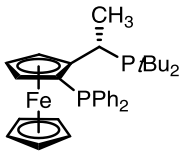
III.L1
(*R*)-*p*TolBinap



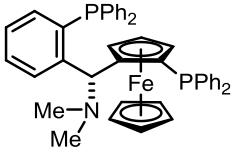
III.L2
(*R*)-Segphos



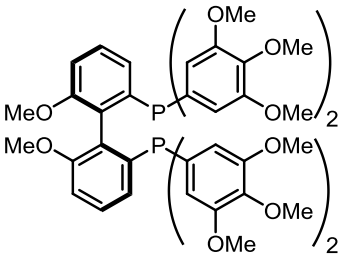
III.L3
(*R*)-DTBMSegphos



III.L4
(R,S_{Fe})-Josiphos
SL-J002-1



III.L5
(R,R_{Fe})-TaniaPhos
SL-T001-1



III.L6
(*S*)-3,4,5-trimethoxyMethoxyBiphep

Entry	Ligand	Reaction time	*ee*[a] (%)
1	(*R*)-*p*TolBinap	30 min.	46
2	(*R*)-Segphos	30 min.	65
3	(*R*)-DTBMSegphos	30 min.	39
4	(R,S_{Fe})-Josiphos SL-J002-1	30 min.	< 10
5	(R,R_{Fe})-TaniaPhos SL-T001-1	30 min.	44
6	(*S*)-3,4,5-trimethoxyMethoxyBiphep	< 1min.	65

a Enantiomeric excesses were measured by chiral HPLC analysis.

3.2.2.2 Other reaction parameters

Having established the chiral (*S*)-3,4,5-trimethoxyMethoxyBiphep as the best ligand, other reaction parameters were next studied. These optimisation reactions were carried out under a moisture-free argon atmosphere to avoid losses in yield due to the quenching of the copper-hydride by water. The copper source was found to have a great impact on the enantioselectivity of the reaction (Table III-4). Replacing the previous copper(I) source **III.10** (entry 1) by copper(II) acetate increased the enantioselectivity of the reaction to 72% (entry 2). This improvement is attributed to suppression of the competing racemic hydride transfer catalysed by the copper(I) fluoride tristriphenylphosphine complex **III.10**. In this context, the catalytically active copper(I) species is formed *in situ* by reduction of the copper(II) complex by an excess of phosphine.

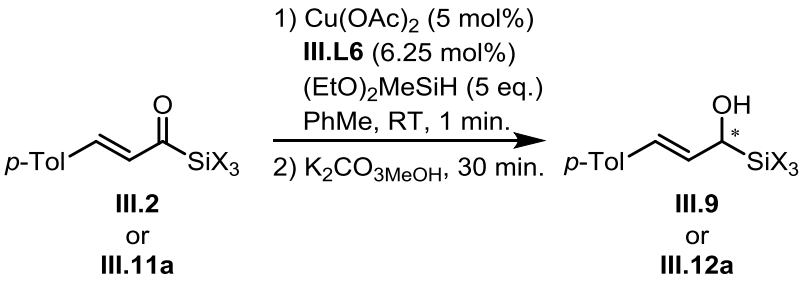
Table III-4 Effect of the copper source on the enantioselectivity.

Entry	Copper source	*ee*[a]
1	$(PPh_3)_3CuF.2MeOH$	65%
2	$Cu(OAc)_2$	72%

a Enantiomeric excesses were measured by chiral HPLC analysis.

The effect of the silyl group size on the outcome of the reaction was then investigated (Table III-5). A bulkier α,β-unsaturated acylsilane **III.11a** bearing a *tert*-butyldimethylsilyl group was synthesised with 41% global yield following the same two-step procedure as for the model substrate **III.2**.[51] Replacing the trimethylsilyl group (entry 1) by the larger *tert*-butyldimethylsilyl group caused a rise of the enantiomeric excess to 84% (entry 2). This beneficial effect is believed to arise from a better size discrimination in the chiral pocket of the complex.

Table III-5 Effect of the silyl group's size.

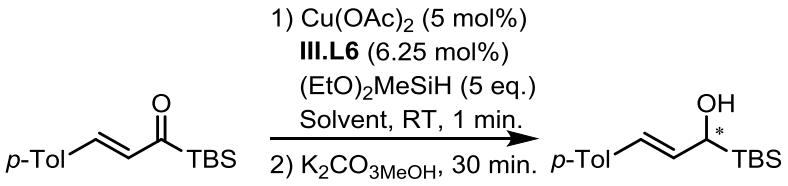


Entry	SiX_3	*ee*[a]
1	TMS (**III.2**)	72%
2	TBS (**III.11a**)	84%

a Enantiomeric excesses were measured by chiral HPLC analysis.

The effect of several solvents on the outcome of the reaction was subsequently monitored (Table III-6). While DCM (enty 2) and THF (entry 3) afforded the product with lower enantioselectivities, diethylether led to a slightly better result (entry 4) and acetonitrile gave the best result with 94% enantiomeric excess (entry 5).

Table III-6 Effect of the solvents.



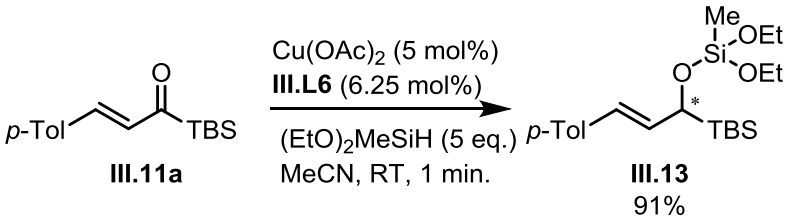
III.11a **III.12a**

Entry	Solvent	*ee*[a]
1	PhMe	84%
2	DCM	74%
3	THF	70%
4	Et_2O	86%
5	MeCN	94%

a Enantiomeric excesses were measured by chiral HPLC analysis.

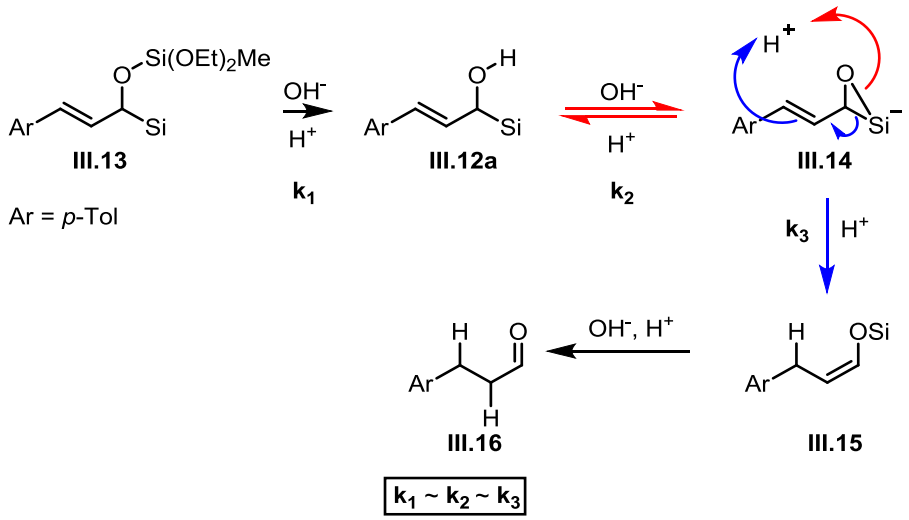
3.2.2.3 Hydrolysis

Despite high enantioselectivity, only 25% of the pure α-hydroxyallylsilane **III.12a** could be isolated. Since no purification was carried out throughout the optimisation process and since the conversion of the acylsilanes was only monitored by thin layer chromatography analysis, a control hydrosilylation experiment was run (Scheme III-41). After full conversion of the acylsilane, the α-siloxyallylsilane **III.13** was not hydrolysed but rather purified as such. Satisfyingly, after flash column chromatography on silica gel, the α-siloxyallylsilane was isolated with 91% yield. Hence, the low yield observed earlier was attributed to issues during the hydrolysis step.



Scheme III-41 Copper-catalysed 1,2-hydrosilylation of the α,β-unsaturated acylsilane and isolation of the resulting α-siloxysilane.

Better understanding of the problem was achieved by careful examination of the hydrolysis by-products. Beside the desired α-hydroxyallylsilane, the crude hydrolysis mixture contained appreciable amounts of silyl enol ether and of a dihydro-cinnamaldehyde derivative. These by-products were easily traced back from the original α-siloxyallylsilane. While the first hydrolysis affords the desired product, a further hydrolytic cascade seems likely under these basic conditions. The α-hydroxyallylsilane **III.12a** is presumably in equilibrium with its silicate form **III.14**. While reprotonation at the oxygen atom leads back to **III.12a**, S_E2' protonation at the benzylic position irreversibly affords the corresponding silyl enol ether **III.15** which upon subsequent hydrolysis in protic medium affords a dihydro-cinnamaldehyde equivalent **III.16**. In the present case, the hydrolysis rates must be similar to each other, explaining the low yield observed despite total conversion of the acylsilane to **III.12a** during the copper-catalysed step (Scheme III-42).

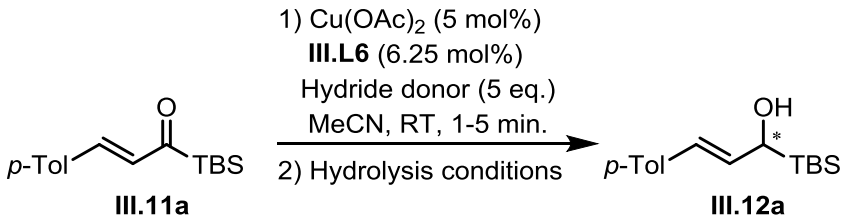


Scheme III-42 Hydrolytic cascades leading to the decomposition of III.12a.

To overcome this issue, several alternative hydrolysis conditions were evaluated,[54] however no improvement was observed (these results are not presented here). Different hydride donors were investigated in order to facilitate the hydrolysis step (Table III-7). Replacing the diethoxymethylsilane by phenylsilane led to a more labile Si-O bond which was quickly hydrolysed in biphasic medium by a saturated aqueous solution of potassium carbonate (entry 1). Notably, using pinacolborane as the hydride donor led to quantitative 1,2-hydroborylation of the α,β-unsaturated acylsilane. The resulting α-boryloxyallylsilane was hydrolysed even faster than the previous α-siloxyallylsilane and washing with a dilute solution of aqueous potassium carbonate was sufficient to complete the hydrolysis. The desired α-hydroxyallylsilane **III.12a** was obtained as a pure solid with 92% yield and 92% enantiomeric excess (entry 2). It should be specified that the copper-catalysed hydroborylation reaction is

somewhat slower than the corresponding hydrosilylation and two to five minutes were required to reach full conversion.

Table III-7 Effect of the hydride donor on the hydrolysis.



III.11a **III.12a**

Entry	Hydride donor	Hydrolysis conditions	Yield[a]	*ee*[b]
1	$PhSiH_3$	Saturated $K_2CO_{3\ aq.}$ (30 min. stirring)	86%	92%
2	PinBH	Diluted $K_2CO_{3\ aq.}$ (washing)	92%	92%

[a] Isolated yields after flash column chromatography over silica gel. [b] Enantiomeric excesses were measured by chiral HPLC analysis.

3.2.2.4 Final fine-tunings

To bring the optimisation of the reaction conditions to an end, some last modifications were considered (Table III-8).

Satisfyingly, the amount of pinacolborane could be reduced from 5 equivalents to 1.5 equivalents while the loading of copper salt and ligand were lowered from 5 mol% and 6.25 mol% to 0.1 mol% and 0.125 mol% respectively without loss of yield nor enantiomeric excess (entry 1). Further diminishing the catalytic loading resulted in a dramatic drop of both yield and enantioselectivity (entry 2). Running the reaction at lower temperatures afforded the product with moderate yield and similar enantiomeric excess (entry 3).

Table III-8 Final fine-tunings.

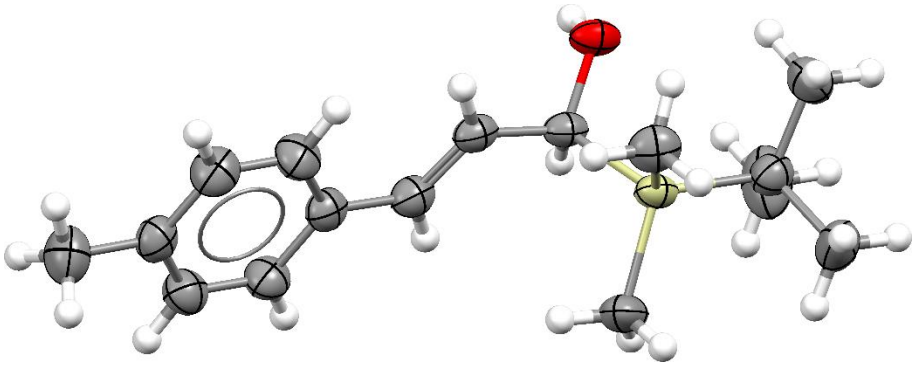
III.11a **III.12a**

Entry	X - Y	Temperature	Yield[a]	*ee*[b]
1	0.1 - 0.125	RT	92%	92%
2	0.01 - 0.0125	RT	32%	16%
3	0.1 - 0.125	-20 °C	63%	90%

[a] Isolated yields after flash column chromatography over silica gel. [b] Enantiomeric excesses were measured by chiral HPLC analysis.

These last experiments are particularly enhancing the sustainable character of the developed reaction since the amounts of hydride donor, copper source and ligand were drastically reduced without significant repercussion on the reaction's results. Notably, room temperature reactions are particularly desirable in terms of energy economy.

Having developed the optimal conditions for the asymmetric hydroborylation reaction, it was possible to obtain enantiopure crystals of the model α-hydroxyallylsilane **III.12a** by evaporation of an ethereal solution of the product. XRD analysis of those crystals revealed the absolute configuration of the α-hydroxysilane to be (*S*) (Scheme III-43).



Scheme III-43 Ortep representation of a single moiety as found in the crystal structure.

3.2.3 Scope of the reaction

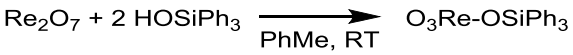
The next step of the investigation consisted in the application of the developed optimal conditions to a range of diversely substituted acylsilanes. Even though 0.1 mol% of copper salt was found to be sufficient for the studied transformation, it was decided to use 1 mol% of catalyst for the exemplification. This choice was made in order to gain sufficient precision when weighing the ligand. Indeed, the reactions are run on a 0.2 mmol scale which means that approximately 0.2 mg of ligand are required when working at a catalytic loading of 0.1 mol%.

3.2.3.1 α,β-unsaturated acylsilane

3.2.3.1.1 Synthesis of the substrates

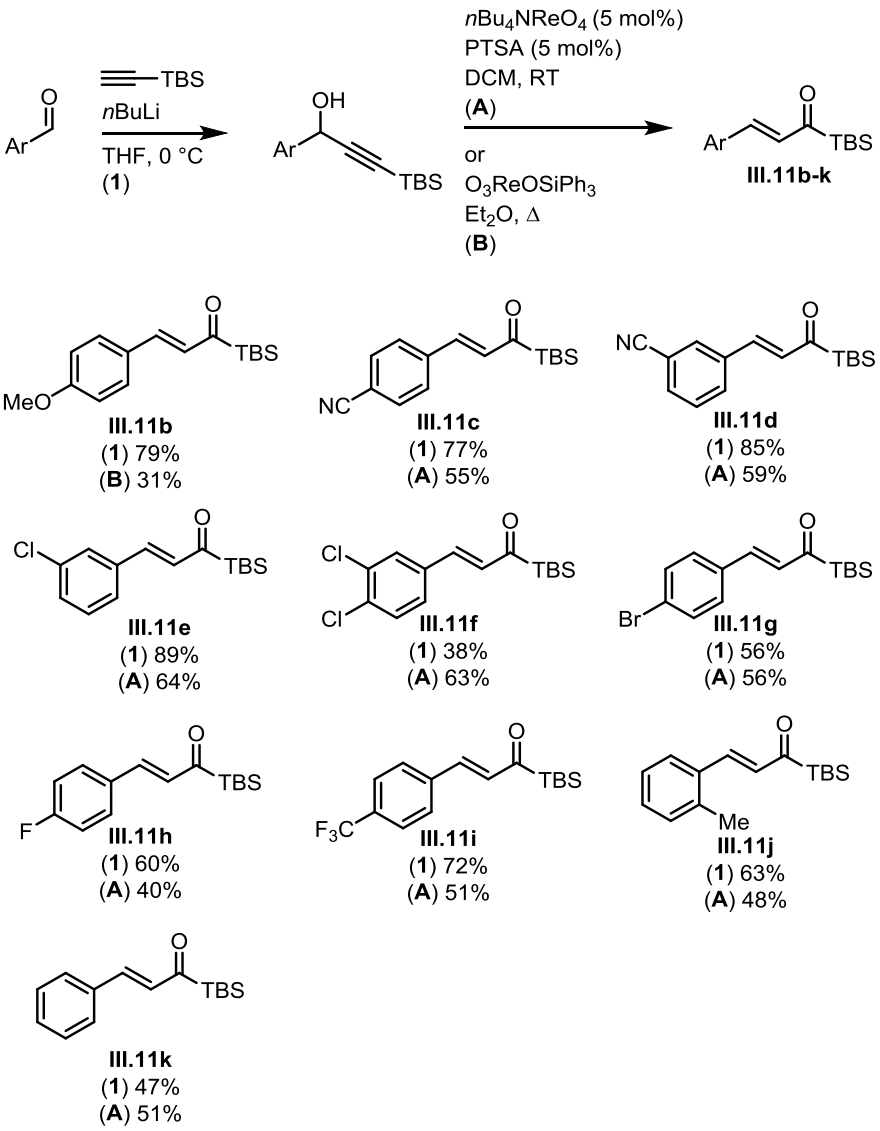
Most of the α,β-unsaturated acylsilanes were synthesised according to the procedure reported by Nikolaev and Orellana.[51] Their method mainly gives access to β-aryl α,β-unsaturated acylsilanes. Substituents on the aromatic ring greatly impact the feasibility of the Meyer-Schuster rearrangement. While electron withdrawing groups and inductive electron donating groups are well tolerated under normal conditions (**A**), mesomeric electron donating groups inhibit the

reaction. Therefore they used an alternative rhenium catalyst, i.e. Osbourne's reagent, to trigger the rearrangement (**B**). This alternative catalyst was obtained by reacting rhenium(VII) oxide with triphenylsilanol in toluene under strictly inert conditions. After removal of the solvent, the product was recrystallized in dry diethyl ether at -20 °C. The catalyst was obtained as off-white crystals which became greenish upon decomposition at room temperature (Scheme III-44).



Scheme III-44 Synthesis of Osbourne's reagent.

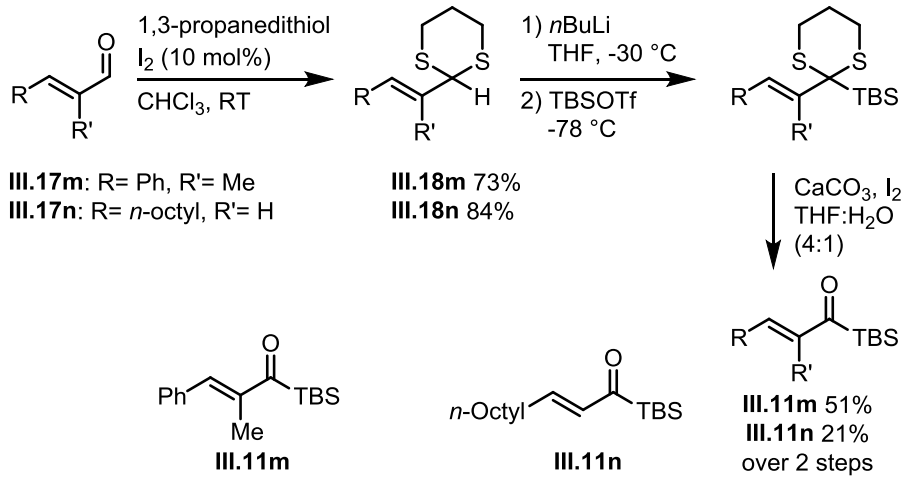
Most of the acylsilanes were obtained following procedure (**A**) affording alkyl-, halogen-, nitrile- and trifluoromethyl- substituted β-aryl acysilanes with moderate to good yields. The synthesis of the *p*-methoxy substituted β-aryl acylsilane however required the use of the homemade rhenium catalyst (**B**) giving the rearranged product in low yield (Scheme III-45).



Scheme III-45 Synthesis of α,β-unsaturated acylsilanes via the Meyer-Schuster rearrangement.

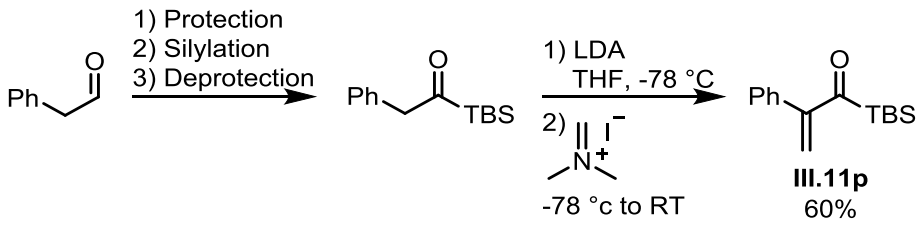
The preparation of the α-methyl-β-phenyl-α,β-unsaturated acylsilane **III.11m** was achieved using an umpolung strategy reported in the literature.[55] The enal **III.17m** was first converted to the corresponding 1,3-dithiane **III.18m** with 73% yield. Subsequent deprotonation with *n*BuLi and addition of *tert*-butyldimethylsilyl

triflate yielded the crude silylated dithiane which upon hydrolysis in the presence of calcium carbonate and iodine afforded the desired acylsilane **III.11m** in 51% over two steps. The same methodology was used for the synthesis of the β-alkyl-α,β-unsaturated acylsilane **III.11n** which was obtained with 18% overall yield (Scheme III-46).



Scheme III-46 Umpolung method for the synthesis of α,β-unsaturated acylsilanes.

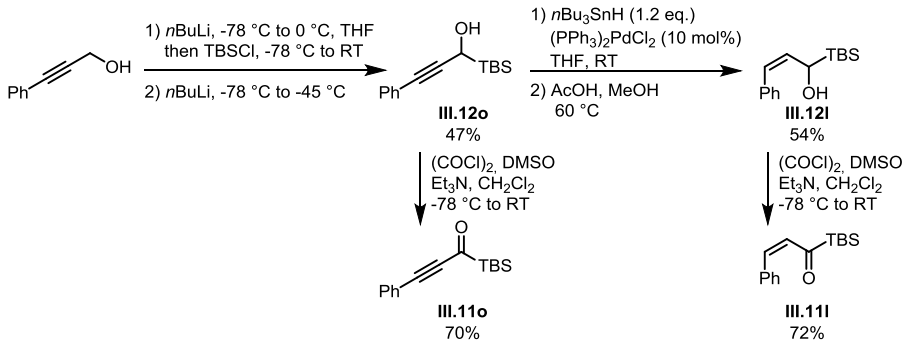
A similar strategy was used for the synthesis of the benzylic acylsilane which was in turn converted to the β-unsubstituted enoylsilane **III.11p** by reaction with Eschenmoser's salt in 60% yield over one step (Scheme III-47).[56]



Scheme III-47 synthesis of a β-unsubstituted enoylsilane with Eschenmoser's salt.

Finally the two last α,β-unsaturated acylsilanes **III.11l** and **III.11o** were synthesised starting from a propargylic alcohol as described in

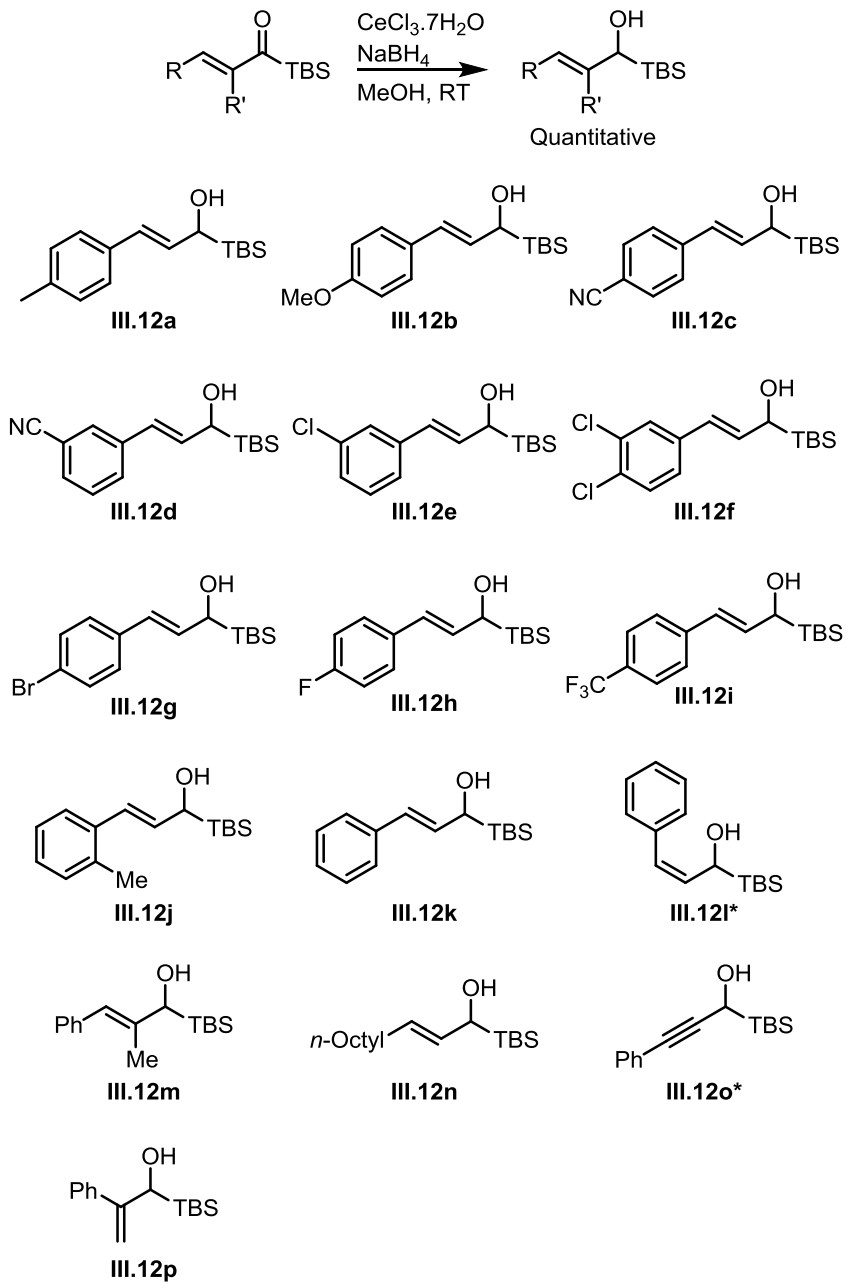
the literature.[2c, 57] The first step is common to both acylsilanes and consists in the silylation of the alcohol followed by a retro-Brook rearrangement affording the propargylic α-hydroxysilane **III.12o** in a racemic form. On one hand, the Swern oxidation of **III.12o** afforded the propargylic acylsilane **III.11o** in 70% yield. On the other hand, a palladium-catalysed hydrostannylation of the racemic α-hydroxypropargylsilane **III.12o** followed by protodestannylation in acidic medium yielded the (*Z*)-α-hydroxyallylsilane **III.12l** which upon oxidation under Swern's conditions led to the desired (*Z*)-α,β-unsaturated acylsilane **III.11l** (Scheme III-48).



Scheme III-48 Synthesis of α,β-unsaturated acylsilane from racemic α-hydroxysilanes.

3.2.3.1.2 Racemic reductions

All the racemic references for the chiral HPLC analyses were obtained by reduction of the α,β-unsaturated acylsilanes **III.11a-p** under Luche's conditions.[58] Every substrates underwent instantaneous and quantitative reduction to the corresponding α-hydroxyallylsilanes **III.12a-p** (Scheme III-49).



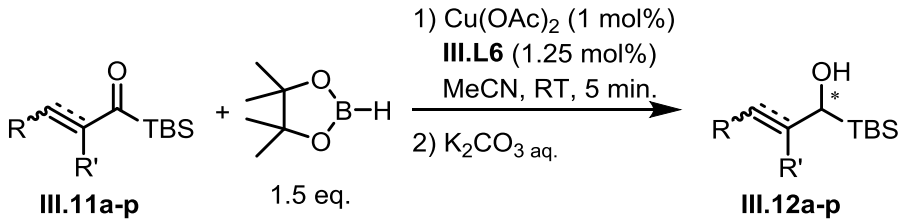
* Racemic references were obtained during the synthesis of the acylsilanes before Swern oxidation.

Scheme III-49 Reduction of α,β-unsaturated acylsilanes with sodium borohydride under Luche's conditions.

3.2.3.1.3 Enantioselective hydroborylation

The α,β-unsaturated acylsilanes were submitted to the enantioselective hydroborylation conditions (Table III-9).

Table III-9 Scope of the enantioselective hydroborylation of α,β-unsaturated acylsilanes.



III.11a-p 1.5 eq. **III.12a-p**

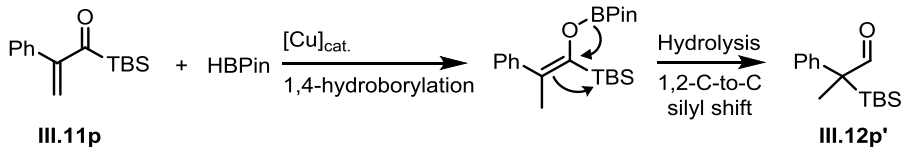
Entry	R[a]	R'	Product	Yield (%)[c]	*ee*[d] (%)
1	4-MeC_6H_4	H	(*S*)-III.12a[e]	92	92
2	4-(MeO)C_6H_4	H	III.12b	76	94
3	4-CNC_6H_4	H	III.12c	91	78
4	3-CNC_6H_4	H	III.12d	98	84
5	3-ClC_6H_4	H	III.12e	95	87
6	3,4-$Cl_2C_6H_3$	H	III.12f	85	84
7	4-BrC_6H_4	H	III.12g	91	86
8	4-FC_6H_4	H	III.12h	95	85
9	4-$CF_3C_6H_4$	H	III.12i	87	87
10	2-MeC_6H_4	H	III.12j	96	81
11	(*E*)-C_6H_5	H	III.12k	78	89
12	(*Z*)-C_6H_5	H	III.12l	90	32
13[b]	C_6H_5	Me	III.12m	52	90
14[b]	*n*-Octyl	H	III.12n	26	94
15	C_6H_5	/	III.12o	90	50
16	H	C_6H_5	III.12p	n.d.	/

[a] If not stated otherwise, the double bonds display an (*E*) geometry. [b] Modified reaction conditions: 5 mol% $Cu(OAc)_2$, 6.25 mol% **III.L6**, 40 °C, 16h. [c] Isolated yields after flash column chromatography over silica gel. [d] Determined by chiral HPLC analysis. [e] The absolute configuration was determined by XRD analysis.

All β-aryl-α,β-unsaturated substrates **III.11a-k** obtained with the method of Nikolaev and Orellana reacted well under the

enantioselective conditions affording very high yields regardless the substitution pattern of their aromatic ring (entry 1-11). The electronic properties of the substituents however seem to affect the enantioselectivity. Electron rich acylsilanes **III.11a** and **III.11b** gave the corresponding α-hydroxyallylsilanes **III.12a** and **III.12b** with high enantiomeric excesses (entry 1 and 2), while a slight drop in enantioselectivity was observed for electron poor acylsilanes **III.11c** and **III.11d** (entry 3 and 4). Various halogenated acylsilanes **III.11e-1h** (entry 5-8) as well as trifluoromethylated **III.11i** (entry 9) were well tolerated under the developed conditions yielding the corresponding α-hydroxysilanes **III.12e-i** with very good *ee*. *Ortho*-substituted acylsilane **III.11j** (entry 10) suffered from slightly lower enantioselectivity compared to its *para*-substituted analogue **III.11a** (entry 1). Then the substitution pattern of the double bond was studied. While the (*E*) isomer **III.11k** gave **III.12k** with good *ee* (entry 11), the corresponding (*Z*) isomer **III.11l** underwent a dramatic drop in *ee* during the reduction (entry 12). Oppositely to the previous examples, the α-methylated acylsilane **III.11m** did not react under the optimal conditions (entry 13). This is likely due to the steric strain of its α-substituent.The β-octyl substituted **III.11n** did not react either (entry 14). The problem was solved by raising the catalytic loading to 5 mol% and the temperature to 40 °C. Under these adapted conditions **III.12m** and **III.12n** were obtained with moderate to low yields after overnight stirring, i.e. 52% and 26% respectively. However, despite diminished yields, **III.12m** and **III.12n** were both obtained with very high *ee*'s (entry 13 and 14). Interestingly despite moderate enantiomeric excess alkynyl acylsilane **III.11o** was transformed to the

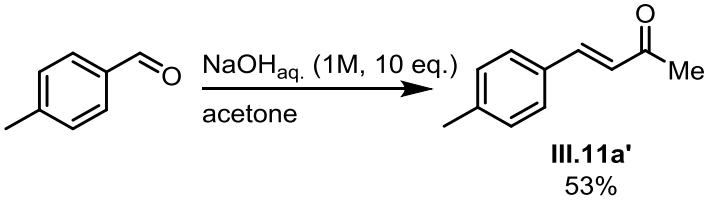
corresponding propargylic α-hydroxysilane **III.12o** in 90% yield without any competing β-addition to the triple bond (entry 15). Finally, the β-unsubstituted enoylsilane **III.11p** was completely converted to a single product under the optimal conditions. However, upon hydrolysis, the expected α-hydroxysilane **III.12p** was not obtained (entry 16). Instead, an α,α-disubstituted propionaldehyde **III.12p'** derivative was isolated. This product probably resulted from the 1,4-hydroborylation of **III.11p**. Subsequent reaction of the boryl enol ether function triggered a 1,2-C-to-C silyl shift leading the final product (Scheme III-50).



Scheme III-50 Unexpected 1,4-hydroborylation of β-unsubstituted enoylsilane and subsequent formation of an α,α-disubstituted propionaldehyde derivative.

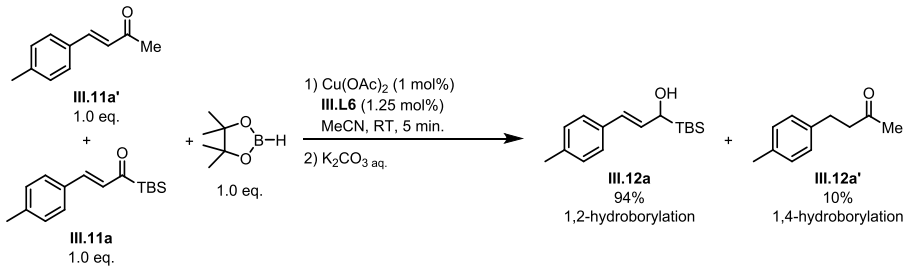
3.2.3.1.4 Chemoselectivity of the reaction

In order to evaluate the chemoselectivity of the developed copper-catalysed hydroborylation reaction, a competition experiment was designed. It was decided to submit an equimolar mixture of **III.11a** and its analogous ketone **III.11a'** to the optimal hydroborylation conditions. Consequently, **III.11a'** was synthesised in one step from *p*-tolualdehyde and acetone in the presence of sodium hydroxide in 53% yield (Scheme III-51).



Scheme III-51 Synthesis of III.11a', the ketone equivalent of III.11a.

Next, **III.11a** and **III.11a'** were added to a solution of copper hydride under the developed conditions. After five minutes, the reaction was quenched and hydrolysed according to the optimal conditions. The crude mixture was then submitted to ^{1}H NMR analysis in the presence of terephthalaldehyde as an internal standard. The spectrum revealed a satisfyingly high selectivity of the catalyst for the hydroborylation of the acylsilane function over the corresponding ketone. The α-hydroxyallylsilane **III.12a** was the main product with 94% yield. The enone **III.11a'** remained mainly unconverted and was recovered with 90% yield. However, 10% of the enone was hydroborylated in 1,4 position affording **III.12a'**. The other reduction products of **III.11a'**, i.e. the 1,2-reduction product and the total reduction product, were not detected on the NMR spectrum. It should be mentioned that the combined yield of 104% is due to the precision of the syringe resulting in a slight excess of pinacoleborane in the reaction medium (Scheme III-52).



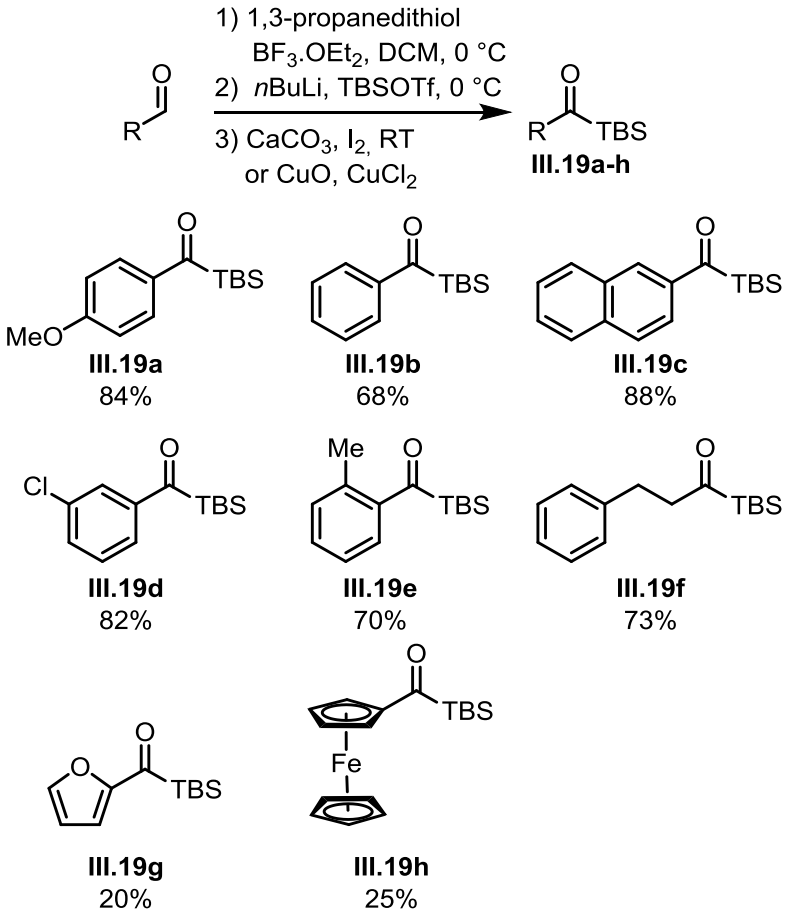
Scheme III-52 Competition experiment between an α,β-unsaturated acylsilane and an enone.

3.2.3.2 Aromatic and aliphatic acylsilanes

After having confirmed that an array of α,β-unsaturated acylsilanes react well under the developed 1,2-selective hydroborylation conditions, aromatic and aliphatic acylsilanes were evaluated in the copper-catalysed hydroborylation reaction.

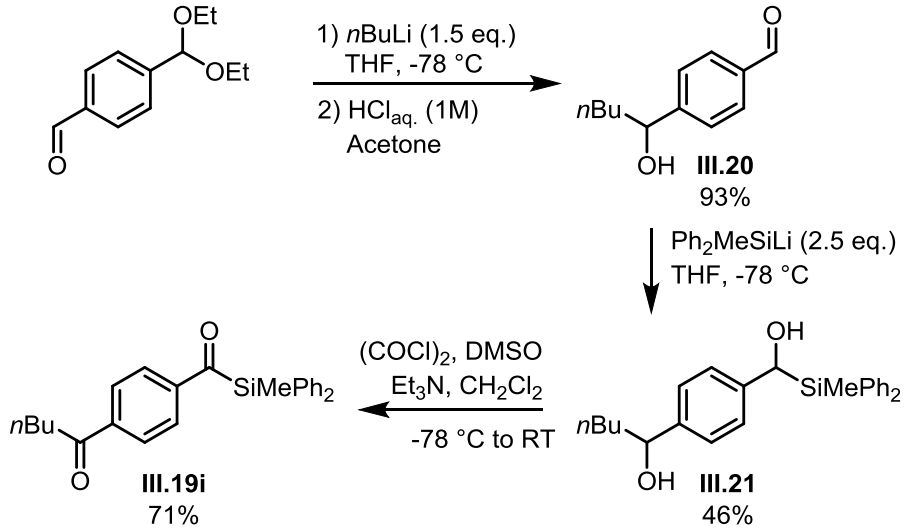
3.2.3.2.1 Synthesis of the substrates

The Corey-Brook strategy was used for the synthesis of most of the acylsilanes of this section.[59] Aromatic aldehydes substituted with various phenyl ring tolerated well the reaction conditions and afforded the desired products with very high yields over three steps. 2-naphtaldehyde and dihydro-cinnamaldehyde reacted smoothly as well. Alternatively, special care must be taken to achieve the synthesis of furyl- and the ferrocenylacylsilanes. While the deprotection step of the first required a mixture of copper(II) oxide and copper(II) chloride in acetone,[60] the latter needed lower temperatures, i.e. -25 °C, during the deprotonation step (Scheme III-53).



Scheme III-53 Synthesis of the aromatic and aliphatic acylsilanes.

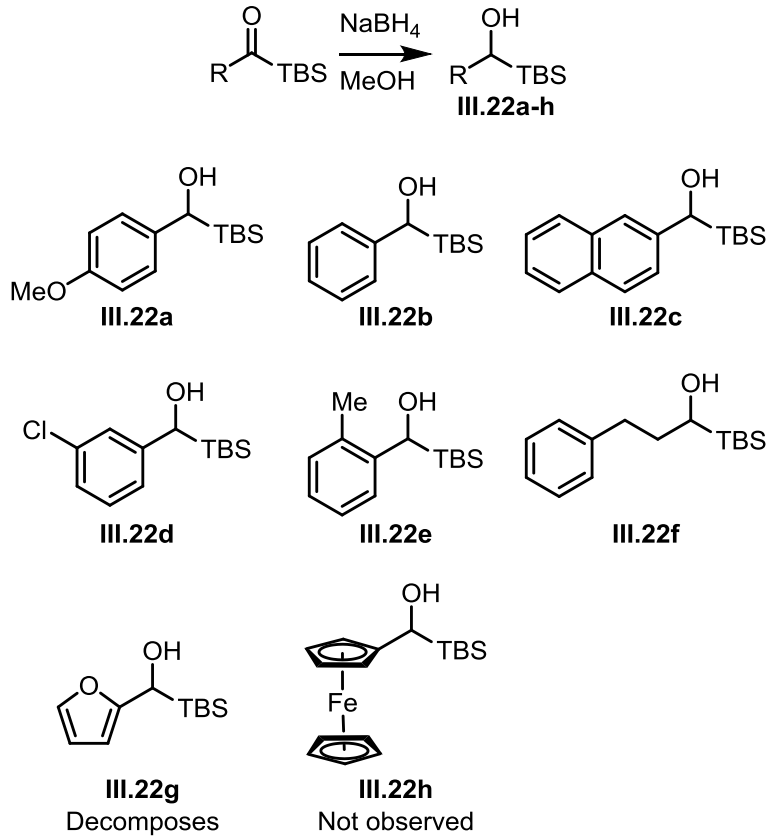
In order to study the chemoselectivity of the copper-catalysed hydroborylation reaction, an acylsilane bearing two electrophilic carbonyl groups was elaborated. First, *n*BuLi was added to terephthalaldehyde diethyl acetal. Subsequent hydrolysis of the acetal under acidic conditions led to the aldehyde **III.20**. Addition of dimethylphenylsilyl lithium to **III.20**, afforded diol **III.21** with a moderate yield of 46%. Finally, a double Swern oxidation was performed on the diol leading to the desired acylsilane **III.19i** as a bright yellow gum with good yield (Scheme III-54).



Scheme III-54 Three step synthesis of the 4-pentanoyl substituted acylsilanes III.19i.

3.2.3.2.2 Racemic reductions

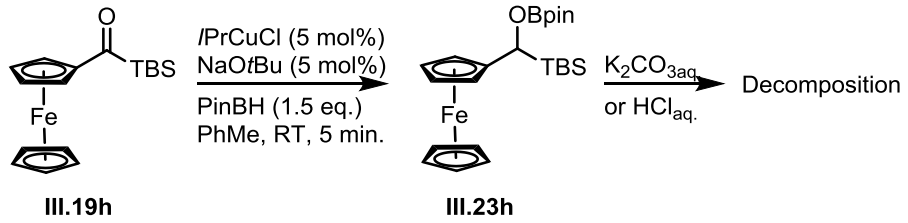
Again, most of the acylsilanes were efficiently reduced by sodium borohydride in quantitative yields (Scheme III-55).



Scheme III-55 Racemic reduction of acylsilanes with sodium borohydride.

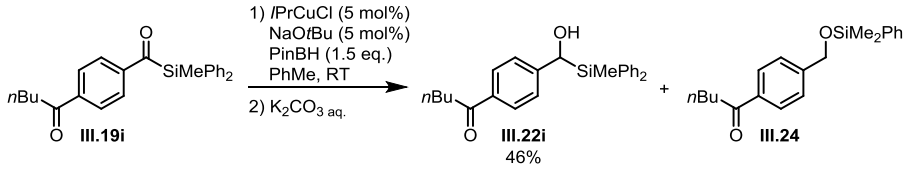
Even though the furylacylsilane was efficiently reduced to the corresponding racemic α-hydroxysilane **III.22g**, the product proved to be unstable and HPLC conditions could not be found to separate the enantiomers. The ferrocenylacylsilane was completely unstable under the reduction conditions and the desired product **III.22h** could not even be observed (Scheme III-55). However, it was possible to run the racemic copper-catalysed hydroborylation reaction on this acylsilane. The crude α-boryloxyferrocenylsilane **III.23h** was observed to be relatively clean by ^{1}H NMR. Unfortunately, hydrolysis under the classical condition, i.e. with an aqueous potassium carbonate solution, led cleanly to the conversion of the **III.23h** to

ferrocenecarboxaldehyde. Alternatively, hydrolysis under acidic conditions led to the decomposition of the product (Scheme III-56).



Scheme III-56 Copper-catalysed hydroborylation of III.19h and hydrolysis of the resulting α-boryloxysilane.

To overcome the regioselectivity issues that might arise from reduction with sodium borohydride, the biscarbonylated acylsilane **III.19i** was reduced using the racemic copper-catalysed pathway. Satisfyingly, the copper-catalysed hydroborylation revealed chemoselective to the acylsilane function. Yet, the racemic product was only isolated with moderate yield. This was attributed to high electron withdrawing ability of the electron poor aromatic substituent. Indeed, appreciable amounts of the corresponding silyl ether **III.24** were observed as a result of the spontaneous Brook rearrangement of the target α-hydroxysilane **III.22i** (Scheme III-57).

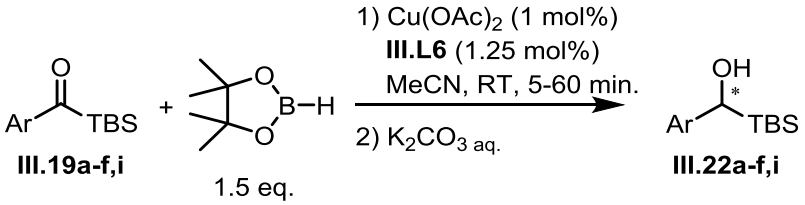


Scheme III-57 Copper-catalysed racemic hydroborylation of 4-pentanoyl substituted acylsilane III.19i.

3.2.3.2.3 Enantioselective hydroborylation

With most of the racemic references in hand, the scope of the enantioselective copper-catalysed hydroborylation was next studied with acylsilanes **III.19a-f,i** (Table III-10).

Table III-10 Scope of the enantioselective hydroborylation of aromatic and aliphatic acylsilanes.



Entry	R	Product	Yield[b] (%)	*ee*[c] (%)
1	4-(MeO)C_6H_4	III.22a	91	96
2	C_6H_5	(*S*)-III.22b[d]	83	94
3	2-Naphtyl	III.22c	87	92
4	3-ClC_6H_4	III.22d	92	89
5	4-PentoylC_6H_4	III.22i	44	70
6[a]	2-MeC_6H_4	III.22e	17	81
7[a]	$C_6H_5CH_2CH_2$	III.22f	79	81

[a] Modified reaction conditions: 5 mol% $Cu(OAc)_2$, 6.25 mol% **III.L6**, 40 °C, 16h. [b] Isolated yields after flash column chromatography over silica gel. [c] Determined by chiral HPLC analysis. [d] The absolute configuration was determined by optical rotation analysis and comparison with the literature.

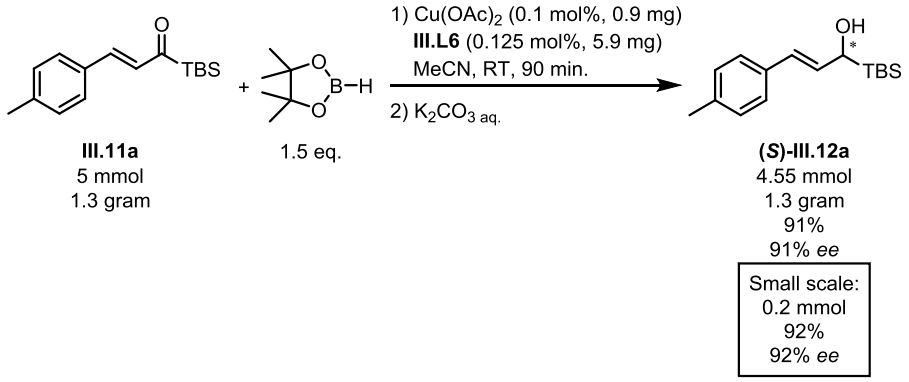
The asymmetric reaction conditions were successfully applied to aromatic acylsilanes **III.19a-d,i**. The same reactivity pattern as for α,β-unsaturated acylsilanes was observed. Acylsilanes **III.19a-d** reacted well independently on the electronic properties of their substituents (entry 1-4). A trend in terms of enantioselectivity could again be observed as electron rich acylsilane **III.19a** gave higher *ee* upon reduction (entry 1) than the electron poor **III.19d** and **III.19i** (entry 4 and 5). The simple α-hydroxyphenylsilane **III.22b** was obtained with 94% enantiomeric excess (entry 2). Comparison of the optical rotation of **III.22b** with a reference of the literature[17] allowed

the determination of its absolute configuration to be (*S*), similarly to the model α-hydroxyallylsilane **(*S*)-III.12a**. Selective hydroborylation of the challenging ketone-bearing **III.19i** highlighted the extremely desirable chemoselectivity of the catalytic system for acylsilanes as no ketone reduction was observed (entry 5). Moderate yield was however obtained due to spontaneous Brook rearrangement of the electron poor **III.22i** under the reaction conditions as already observed in the racemic hydroborylation reaction (see: 3.2.3.2.2). In opposition to α,β-unsaturated substrates, *ortho* substitution of arylacylsilanes resulted in a complete loss of reactivity. As previously, raising the catalyst loading and the temperature of the reaction solved the problem. Still, **III.22e** was only obtained in 17% yield along with most of **III.19e** recovered (entry 6). The aliphatic acylsilane was not converted either under the optimal conditions. Satisfyingly, applying the modified reaction conditions to aliphatic acylsilane **III.19f** gave very good yield and *ee* after hydroborylation (entry 7).

3.2.4 Larger scale experiments

The scope of the reaction being studied, it was questioned whether the conditions could be applied to acylsilanes on a synthetically useful scale. Therefore, 5 mmol of the model α,β-unsaturated acylsilane **III.11a** was submitted to the optimal conditions developed earlier. On this scale, there is no more accuracy issue for the weighing of the chiral ligand. Hence, the reaction could be carried out with 0.1 mol% of catalyst. The reaction was successful and reached full conversion within 90 minutes affording 1.2 grams of **(*S*)-III.12a** in 91% enantiomeric excess (Scheme III-58). This result is impressive since

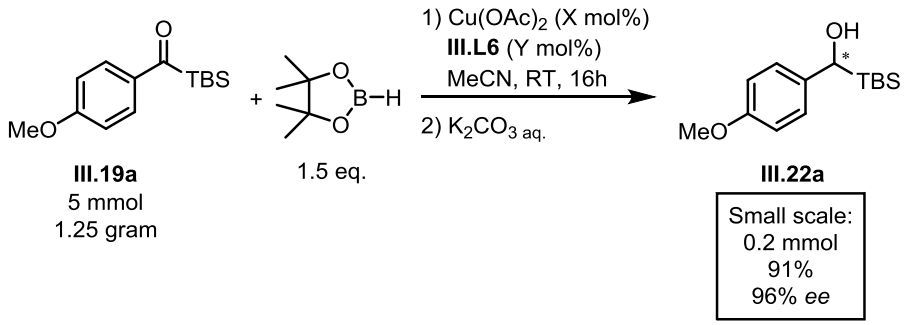
no significant variation from the small scale experiment was detected in terms of results.



Scheme III-58 Application of the asymmetric copper-catalysed hydroborylation reaction of α,β-unsaturated acylsilanes on a 5 mmol scale.

Next, attention was turned to the hydroborylation of the aromatic acylsilane **III.19a** on a 5 mmol scale (Table III-11). Unfortunately, with a catalytic loading of 0.1 mol% the conversion was only partial after four days. However, the hydroborylated adduct was the sole product of the reaction. After hydrolysis, the α-hydroxysilane **III.22a** was isolated with 44% yield and a diminished enantiomeric excess of 88% compared to the small scale experiment. Gratifyingly, raising the catalyst loading to 1 mol% efficiently transformed the substrate on a 5 mmol scale with excellent 97% isolated yield and 95% enantiomeric excess. Again, no significant difference compared to the small scale experiment is observed.

Table III-11 Application of the asymmetric copper-catalysed hydroborylation reaction of aromatic acylsilanes on a 5 mmol scale.

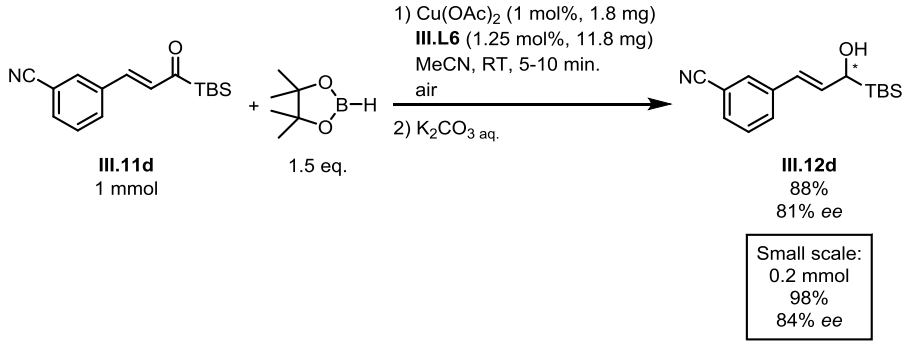


Entry	X	Y	Yield[a]	*ee*[c]
1	0.1 (0.9 mg)	0.125 (5.9 mg)	44%[b]	88%
2	1 (9 mg)	1.25 (59 mg)	97%	95%

[a] Isolated yields after flash column chromatography over silica gel. [b] Despite uncomplete conversion of the acylsilane, the reaction was quenched after 4 days. [c] Determined by chiral HPLC analysis

Finally, a copper-catalysed hydroborylation reaction was set up under ambient atmosphere on a 1 mmol scale in order to confirm the robustness of the developed methodology. The electron poor acylsilane **III.11d** was chosen as substrate and the reaction was conducted with 1 mol% catalyst loading. Very simply, the copper source and the ligand were loaded in an oven-dried test tube under air. The solvent and the hydride source were successively added, followed by a solution of **III.11d**. After stirring five to ten minutes without precautions, no more conversion was observed. The crude mixture was hydrolysed and after purification the product **III.12d** was obtained in 88% yield and 81% *ee* along with some unreacted **III.11d**. Under these conditions, a little drop in yield is observed compared to the regular reaction under inert atmosphere. This result is attributed to the partial quenching of the copper-hydride species by moisture. This

small difference in yield is however acceptable since the unreacted **III.11d** was easily recovered. Additionally, the enantiomeric excess is essentially the same as on small scale under inert conditions (Scheme III-59).

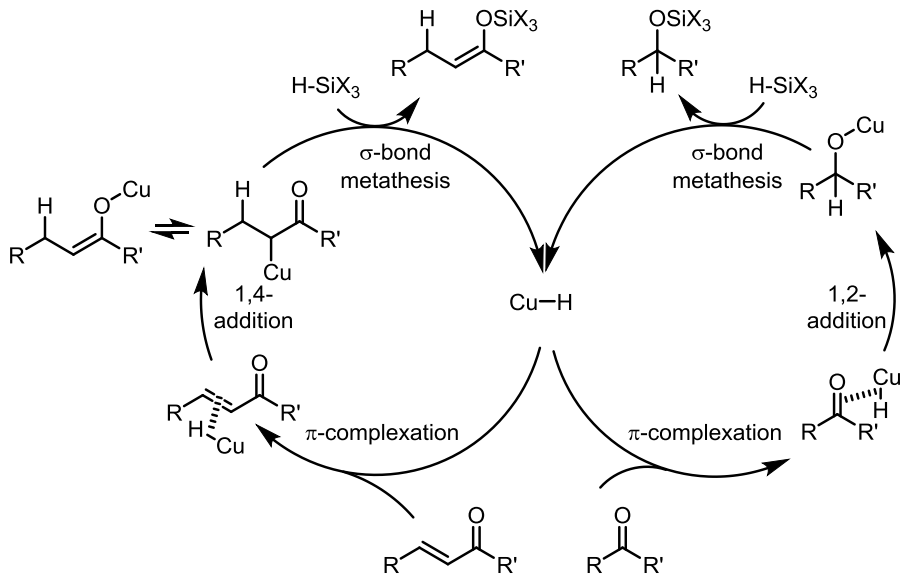


Scheme III-59 Asymmetric copper-catalysed hydroborylation of III.11d under air.

3.3 Hypothesis for the reaction's regioselectivity

Selective 1,2-hydride additions to α,β-unsaturated carbonyl compounds are unusual in copper catalysis. Indeed, copper hydrides were historically used to avoid such 1,2-additions associated with harder hydrides.[61] In the present study however, several diphosphine-copper hydride complexes and (NHC)copper hydride complexes afforded selectively the 1,2-addition products upon reaction with α,β-unsaturated acylsilanes.

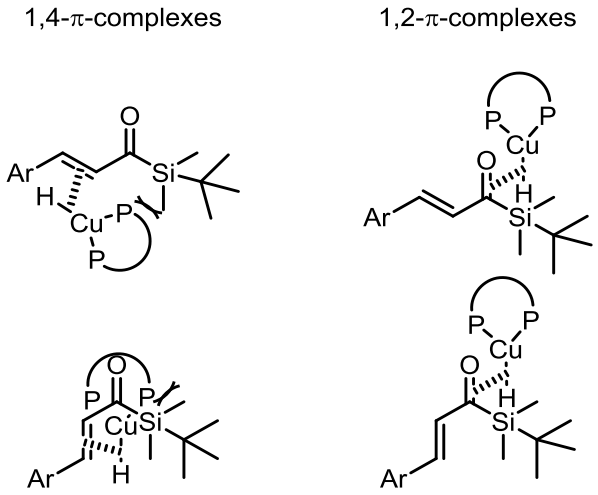
The mechanisms of the copper-catalysed 1,2- and 1,4-hydride addition are assumed to initially involve the formation of a π-complex[61b, 62] between the copper hydride and the reactive unsaturation, i.e. a C-C double bond for 1,4-additions or a C-O double bond for 1,2-additions. The hydride is subsequently added to the unsaturation affording a copper enolate and a copper alkoxide respectively. The copper-hydride is then regenerated by σ-bond metathesis with the stoichiometric hydride source simultaneously affording the reduction product (Scheme III-60).



Scheme III-60 Mechanisms for the copper-catalysed 1,2- and 1,4-hydride addition.

Based on a discussion with Professor Raphaël Robiette from the Université catholique de Louvain, a hypothesis was made to explain the 1,2-selectivity of the developed copper-catalysed hydroborylation of α,β-unsaturated acylsilanes. Steric effects of the silyl group of the acylsilanes during the formation of the π-complex were invoked to rationalise the regioselectivity of the addition. Indeed, the bulky silyl group could play a role in the regioselective π-complexation of the copper-hydride with the carbonyl function rather than with the α,β-unsaturation. Efficient complexation with the unsaturation being pivotal for the hydride addition, 1,4-addition might be prevented by the strong steric clash between the bulky ligands on the copper, i.e. diphosphines or NHC's, and the silyl group during the approach of the copper-hydride towards the C-C double bond. Indeed, such a complex would bring these bulky species close to each other. Alternatively, based on the same logic, a π-complex with the carbonyl function is

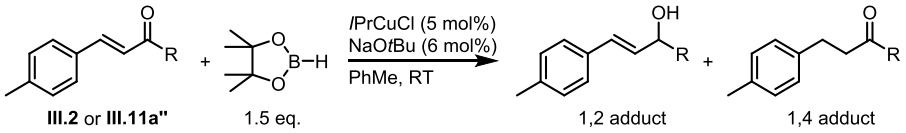
sterically favoured since the ligands are oriented away from the silane, towards the less hindered carbonyl oxygen. Additionally, the carbonyl double bond being more polarised than C-C double bond, the copper atom would be complexed closer to the oxygen atom, hence the ligands would be even further away from the bulky silyl group (Scheme III-61).



Scheme III-61 Proposed structures of the π-complexes involved in the copper-diphosphine-catalysed hydroborylation of acylsilanes.

To support, this hypothesis and to discard potential effects specific to the silicon atom, copper-catalysed hydroborylations were carried out on the acylsilane **III.2** and on the analogous enone **III.11a''** that was prepared by the aldolisation of *p*-tolualdehyde with *tert*-butyl methyl ketone (Table III-12). As presented earlier, **III.2** was catalytically hydroborylated 1,2-selectively in the presence of *I*PrCu-H. When **III.11a''** was subjected to the same hydroborylation conditions, the 1,2-reduction product was obtained as the major product with 79% isolated yield and the 1,4-reduction product was isolated with 10% yield.

Table III-12 Copper-catalysed hydroborylation of bulky α,β-unsaturated substrates.



III.2 or **III.11a"** 1.5 eq. 1,2 adduct 1,4 adduct

Entry[a]	R	1,2 adduct	1,4 adduct
1	$SiMe_3$	quantitative	Not observed
2	*t*Bu	79%	10%

[a] Yields were determined after flash column chromatography over silica gel.

Based on these results, the effect of steric parameters on the regioselectivity of the copper-hydride addition may be assumed but further experiments are needed to get more insight into the reaction's mechanism.

3.4 Valorisation of the chiral α-hydroxysilanes in synthesis

The conditions for the asymmetric copper-catalysed hydroborylation of acylsilanes being developed, it was decided to undertake research on the derivatisation of the resulting α-hydroxysilanes.

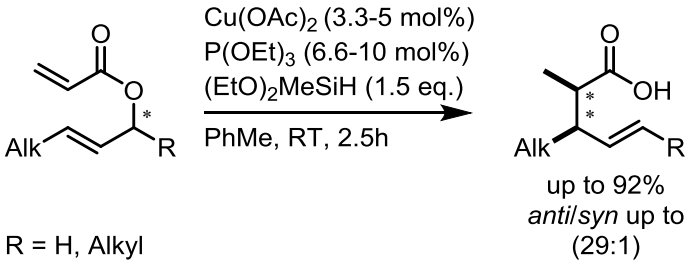
3.4.1 Copper-catalysed reductive Claisen rearrangement

This work was carried out with the help of Mr. Alexander Timm.

3.4.1.1 Strategy

As pointed out in the introduction of this chapter, allylic α-hydroxysilanes are particularly useful in Claisen rearrangements. The strength of these reagents is that they can behave as temporary chiral primary allylic alcohols. Hence, the chirality of the α-hydroxysilane can be transferred through the Claisen rearrangement to the product, and the silyl group can easily be removed if desired. The other advantage of α-hydroxyallylsilane derivatives is the steric bulk of the silyl group. Indeed, the size of the silane usually induces high levels of diastereoselectivity.

Recently, Pauline Chiu and co-workers reported a copper-catalysed reductive Claisen rearrangement of primary and secondary allylic alcohol derivatives.[63] After acryloylation, the allylic alcohols undergo a Claisen rearrangement triggered by copper hydride in the presence of a silane as a hydride source. It was found that the copper complex catalyses the 1,4-hydrosilylation of the acryloyl moiety. The resulting enolate then engages in the Claisen rearrangement with the neighbouring allylic function affording pentenoic acids with very good yields and appreciable diastereoselectivity (Scheme III-62).

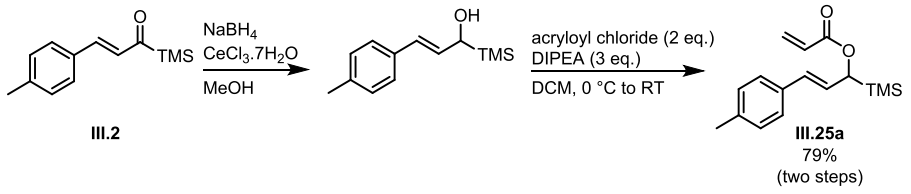


Scheme III-62 Chiu's copper-catalysed reductive Claisen rearrangement of allylic alcohol derivatives.

In this section, the chiral α-hydroxyallylsilanes obtained by the copper-catalysed hydroborylation of α,β-unsaturated acylsilanes will be evaluated as substrates in the copper-catalysed reductive Claisen rearrangement.

3.4.1.2 Proof of concept

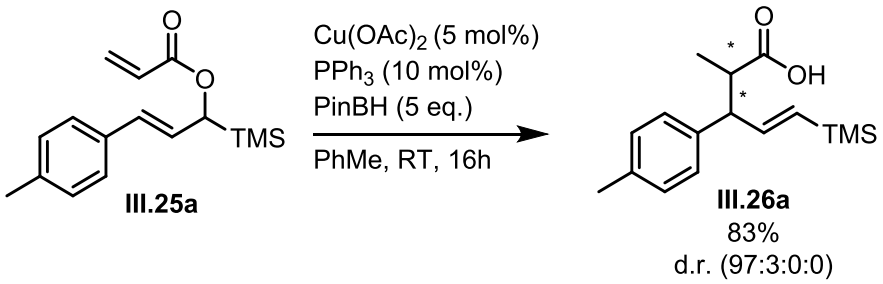
Before working with chiral substrates, the feasibility of the reaction was evaluated with a racemic starting material. The investigation started with the racemic allylic α-hydroxytrimethylsilane **III.9** obtained after reduction of the corresponding acylsilane **III.2** by sodium borohydride under Luche's conditions. The hydroxyl function was then protected by acryloyl chloride in the presence of diisopropylethylamine (DIPEA) affording the desired Claisen candidate **III.25a** with 79% yield over two steps (Scheme III-63).



Scheme III-63 Synthesis of the α-acryloyloxysilane III.25a.

The α-acryloyloxyallylsilane **III.25a** was subsequently submitted to the reductive conditions. However, modifications were brought to

Chiu's procedure. Indeed, it was decided to work with a slightly higher catalyst loading, i.e. 5 mol% instead of 3.3 mol%. Additionally, trimethylphosphite was replaced by the more convenient triphenylphosphine and pinacolborane was used as the hydride donor replacing diethoxymethylsilane. Under these conditions, the expected Claisen rearrangement took place and afforded the corresponding silylpentenoic acid **III.26a** with 83% yield and a great diastereomeric ratio of 97:3:0:0 (Scheme III-64).



Scheme III-64 Copper-catalysed reductive Claisen rearrangement of an α-acryloyloxyallylsilane.

The previous results being very satisfactory, the reductive conditions were next applied to the bulkier *tert*-butyldimethylsilyl bearing α-hydroxysilane **III.12a**. The synthesis of the racemic acryloyl derivative was conducted following the same pathway as earlier affording the rearrangement candidate **III.25b** with 58% overall yield from **III.11a**.

Subsequently, the Claisen rearrangement was carried out on **III.25b** without complications leading the desired product **III.26b** with 79% yield and 95:5:0:0 diastereomeric ratio (Scheme III-65).

Scheme III-65 Copper-catalysed reductive Claisen rearrangement of III.25b.

3.4.1.3 Chirality transfer

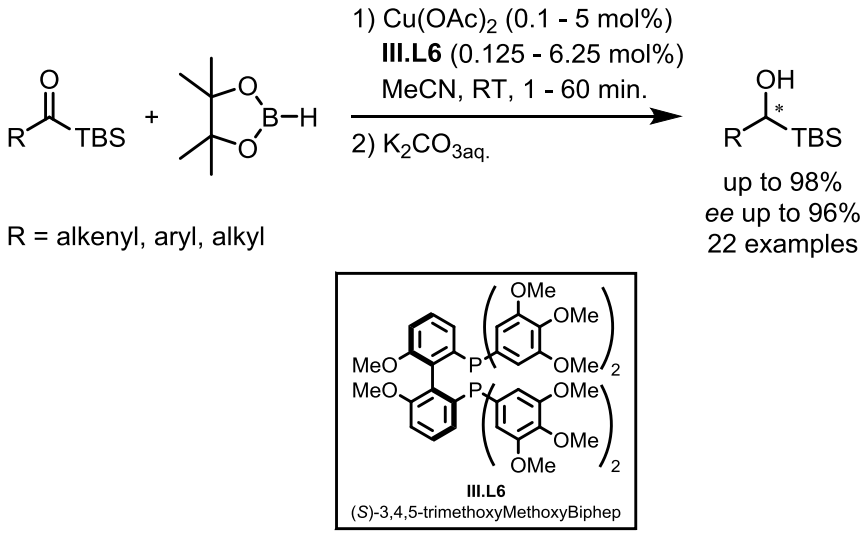
As the use of bulky silyl groups did not seem to affect the Claisen rearrangement, it was decided to run the reaction with enantioenriched derivatives issued from the copper-catalysed asymmetric reaction developed earlier. First, the chiral (*S*)-α-hydroxyallylsilane **(*S*)-III.12a** obtained in 91% enantiomeric excess from an earlier large scale experiment was acryloylated affording **(*S*)-III.25b**. Similarly to the racemic substrate, the chiral derivative underwent the copper-catalysed reductive Claisen rearrangement with great success and **(*S*)-III26b** was isolated with 91% yield and 95:5:0:0 diastereomeric ratio. After benzylation of the carboxylic acid function, the resulting ester was submitted to chiral HPLC analysis and revealed that the chirality had been completely transferred during the Claisen rearrangement process (Scheme III-66).

* Determined by chiral HPLC analysis of the benzyl ester derivative.

Scheme III-66 Chirality transfer in the copper-catalysed reductive Claisen rearrangement of α-hydroxyallylsilane derivatives.

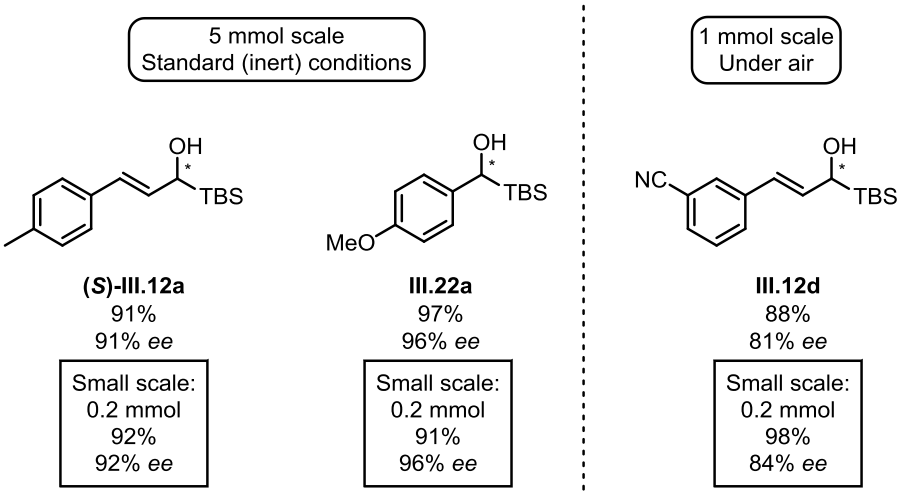
4 Conclusion and perspectives

In this chapter, an interesting copper-catalysed 1,2-hydroborylation reaction of α,β-unsaturated acylsilanes was discovered. After an optimisation process, the asymmetric version of the reaction was developed using a chiral diphosphine ligand belonging to the methoxybiphep family. A key parameter of the reaction is the use of pinacoleborane as hydride source since the resulting α-boryloxysilane undergoes smooth hydrolysis affording the desired α-hydroxyallylsilanes. Subsequently, the system was successfully adapted to the hydroborylation of aromatic and aliphatic acylsilanes. The limits of the methodology were reached with β-alkyl-enoylsilanes, α-alkyl-β-aryl-enoylsilane and *o*-tolylacylsilanes. These limitations were solved to some extent by raising the catalytic loading, the reaction temperature and the reaction time. In total, 22 different acylsilanes were transformed to the corresponding α-hydroxysilanes in an asymmetric fashion following the developed copper-catalysed hydroborylation reaction (Scheme III-67).



Scheme III-67 Copper-catalysed asymmetric hydroborylation of acylsilanes.

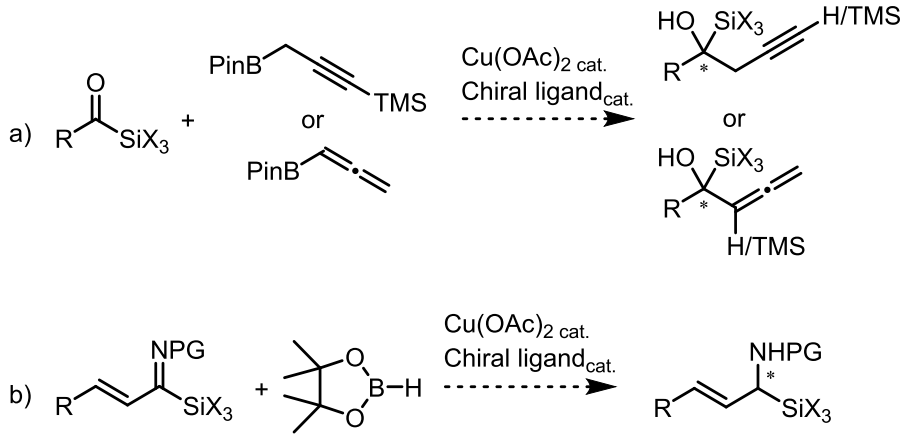
In addition to the broad scope of valid substrates, the reaction proved to be chemoselective. Indeed, a competition experiment was designed and it turned out that, despite the steric bulk of the silyl group, the acylsilane function is preferably hydroborylated over the ketone function. To further establish the robustness of the methodology, an α,β-unsaturated acylsilane and an aromatic acylsilane were successfully hydroborylated on a 5 mmol scale affording the product without significant difference from the small scale experiments. Similarly, another α,β-unsaturated acylsilane underwent the hydroborylation on a 1 mmol scale under air with a little loss in yield but essentially the same enantiomeric excess as the corresponding small scale experiment (Scheme III-68).



Scheme III-68 Robustness of the developed system illustrated by large scale and under-air experiments.

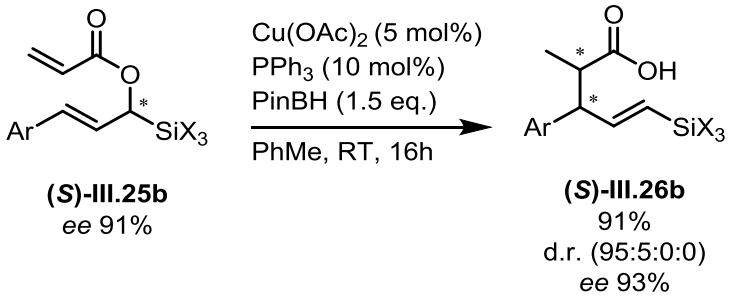
The present catalytic system is highly valuable since it operates at room temperature with low catalytic loadings affording optically active α-hydroxysilanes in very good yields and enantiomeric excesses within a few minutes only. Additionally, the copper source, the chiral ligand and the hydride source are commercially available.

Since copper-catalysed additions to acylsilanes are scarce, this copper-catalysed reaction could be used as a model for the development of similar methodologies. For example, copper-catalysed propargylations and allenylations of aldehydes, ketones and aldimines were recently described[64] and could be easily adapted to the copper-catalysed asymmetric propargylation of acylsilanes leading to tertiary α-hydroxysilane from bench-stable pronucleophiles (Scheme III-69a). Alternatively, instead of the nucleophilic partner, the electrophile could be modified as well. Indeed, the enantioselective copper-catalysed hydroborylation could be applied to silyl ketimines affording useful α-chiral amines (Scheme III-69b).[65]



Scheme III-69 Potential copper-catalysed propargylation and allenylation of acylsilanes (a) and copper-catalysed hydroborylation of silyl ketimines (b).

Next, the products of the 1,2-hydroborylation reaction were evaluated as substrates in further organic transformations. Allylic α-hydroxysilanes were especially appealing and their acryloyl derivatives were found to be substrates of choice in the copper-catalysed reductive Claisen rearrangement. After reaction, the corresponding silylpentenoic acids were isolated in great yield with excellent diastereoselectivity and excellent transfer of chirality (Scheme III-70). In the future, the scope of this reaction should be extended to different acryloyl groups and to diverse α-hydroxyallylsilane derivatives.

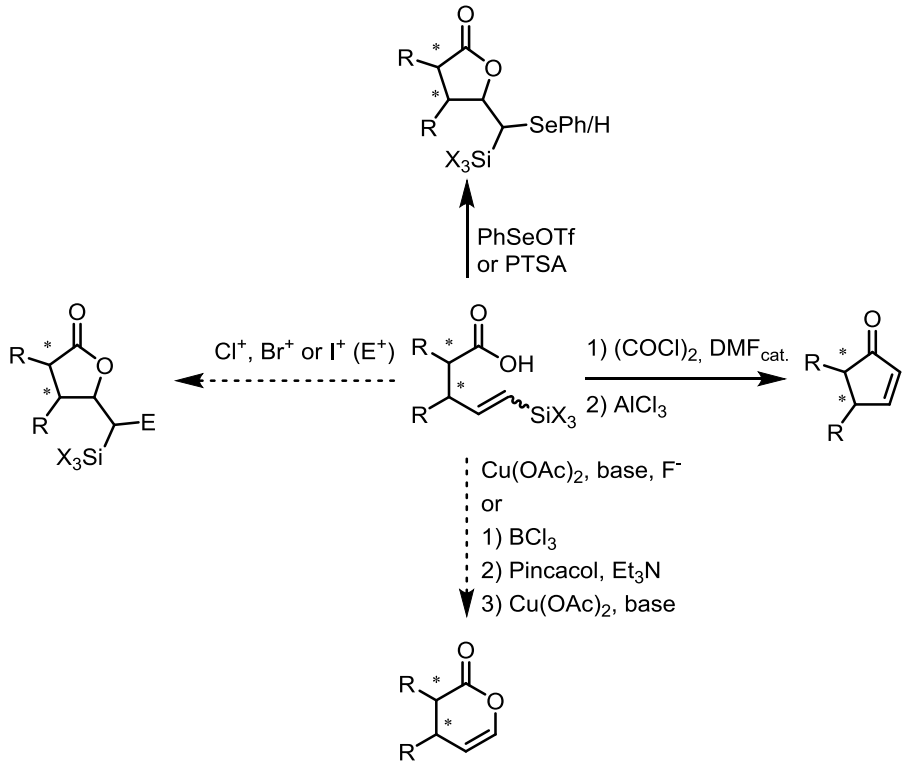


(*S*)-III.25b
ee 91%

(*S*)-III.26b
91%
d.r. (95:5:0:0)
ee 93%

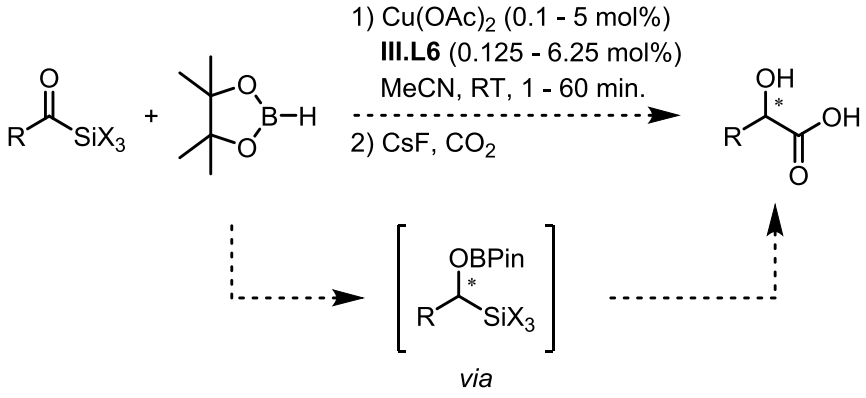
Scheme III-70 Copper-catalysed reductive Claisen rearrangement of optically active α-hydroxyallylsilane derivatives.

The resulting products already found applications in the synthesis of biologically relevant molecules, as pointed out in the introduction of this chapter, (see: 1.3.2) and are useful substrate in cyclisation reaction, e.g. lactonisations[66] or intramolecular Friedel-Kraft acylations[17, 67] leading to lactones and cyclopentenones respectively. Furthermore, a similar compound has been used in a diastereoselective lactonisation/electrophilic capture sequence[68] and analogous halolactonisation reactions[69] can be imagined. Moreover, an intramolecular Chan-Lam-Evans-type coupling[70] could be developed from these compounds upon fluoride-mediated activation of the vinylsilane function or upon transformation to the corresponding vinylboron species (Scheme III-71).



Scheme III-71 Uses of silylpentenoic acids in the synthesis of optically active building blocks.

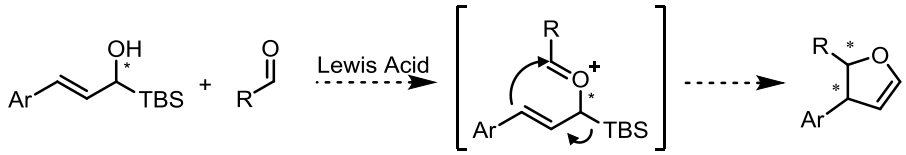
The α-hydroxysilane derivatives are also known to react in the Brook rearrangement leading to α-siloxyanion equivalents which are used to capture various electrophiles. Notably, α-silyoxysilanes were reported to furnish α-siloxyanions upon reaction with a fluoride source. These nucleophilic species were used for the capture of carbon dioxide and allyl or alkyl halides.[34] The capture of carbon dioxide by this method is very attractive since it affords α-hydroxy acids which are precursors to various drugs in the pharma industry.[71] In this chapter, we developed the asymmetric hydroborylation and hydrosilylation of acylsilanes. Before hydrolysis, the crude mixture contains optically active α-boryloxysilanes and α-siloxysilanes respectively. An interesting research project would be to short-cut the reaction and to transfer the crude mixture on a fluoride source under a carbon dioxide atmosphere. This two-step/one-pot method would be an elegant way to access optically active pharmacologically relevant molecule from acylsilanes (Scheme III-72).



Scheme III-72 One pot-two step synthesis of α-hydroxyacids from acylsilanes by the fluoride-mediated Brook-rearrangement of α-boryloxysilanes.

An even more appealing, and way more challenging, project would be the asymmetric addition of Suginome's reagent to aldehydes[27-28]

followed by the Brook rearrangement and capture of carbon dioxide. This method would afford the same α-hydroxy acids from commercially available aldehydes, hence avoiding the synthesis of acylsilanes. Indeed, Ohmiya and co-workers recently reported a similar copper-catalysed addition of Suginome's reagent to aldehydes followed by a copper-Brook rearrangement and coupling of the resulting benzylic copper species with an arylpalladium(II) species.[72] Alternatively, the allylic α-hydroxysilanes obtained from the copper-catalysed hydroborylation reaction could be used in an intramolecular Sakurai-type allylation reaction upon condensation with aldehydes affording dihydrofuran derivatives (Scheme III-73).



Scheme III-73 Optically active α-hydroxyallylsilanes in the intramolecular Sakurai allylation reaction.

In conclusion, the chemistry developed in this chapter opened the door for exciting projects. On one hand, acylsilanes proved to be suitable substrates in asymmetric copper-catalysis. This good reactivity makes place for the development and the discovery of other copper-catalysed reactions of acylsilanes and their derivatives. On the other hand, the products obtained from the copper-catalysed hydroborylation of acylsilanes show interesting properties and open the way for the innovative synthesis of diverse optically active organic building blocks.

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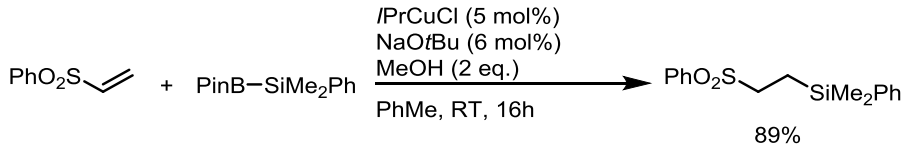
Chapter IV General conclusions

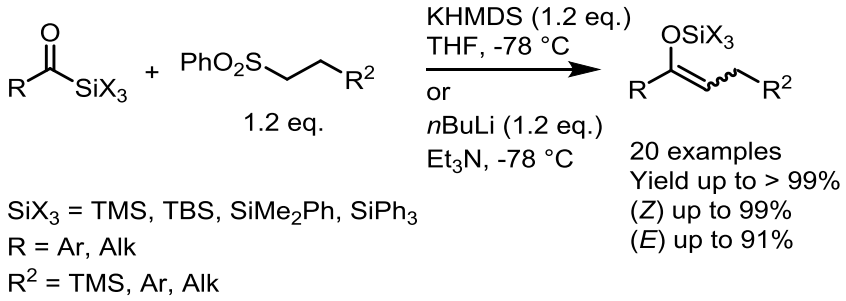
This Ph.D. work, was based on the observation that copper-catalysed transformations of acylsilanes are scarce in the literature. Hence, the reactivity of acylsilanes in the presence of copper-based catalysts was studied.

The starting point of this project was the development of a copper-catalysed domino β-silylative/acylsilane-capture/Brook rearrangement/sulfone-elimination reaction of vinylsulfones. This challenging goal could not be reached because of the low reactivity of the α-cupro-sulfone intermediate that inhibited the reaction. However, the efforts made to develop the original objective led us to a journey through related fields of chemistry and interesting results were obtained. An unprecedented copper-catalysed β-silylation reaction of vinylsulfones was first developed (Scheme IV-1).



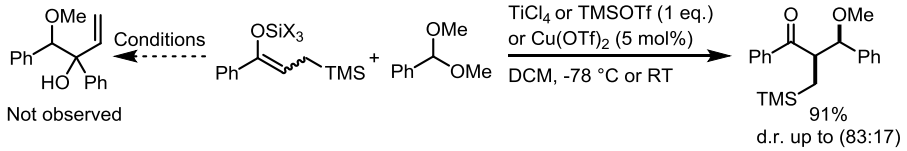
Scheme IV-1 Copper-catalysed β-silylation of vinylsulfones.

Next, Reich's silyl enol ether synthesis was improved by the discovery of substrate-independent stereoselective reaction conditions that were successfully applied to the synthesis of 20 stereo-defined silyl enol ethers (Scheme IV-2).



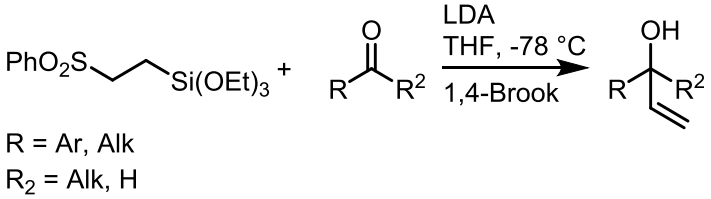
Scheme IV-2 Stereoselective conditions for Reich's silyl enol ether synthesis.

During the course of this exemplification, several ambivalent silyl enol ether/allylsilane species were obtained. Consequently, those reagents were selectively engaged in Mukaiyama-aldol reactions. Alternatively, conditions for the Hosomi-Sakurai-allylation remained elusive (Scheme IV-3).



Scheme IV-3 Selective conditions for the Mukaiyama aldol reaction of β-silylated silyl enol ethers.

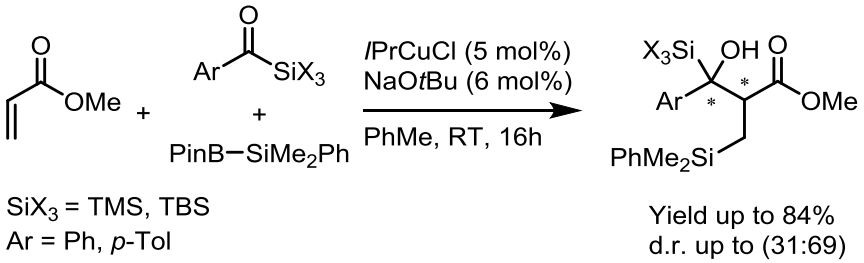
Subsequently, a new sulfone, i.e. β-(triethoxysilyl)sulfone, was synthesised and proved to be an interesting vinyl anion equivalent upon deprotonation and addition to carbonylated electrophiles (Scheme IV-4).



Scheme IV-4 β-(triethoxysilyl)sulfone as a vinyl anion equivalent.

Finally, the initial goal of the thesis was reconsidered and the replacement of vinyl sulfone by methyl acrylate as Michael acceptor

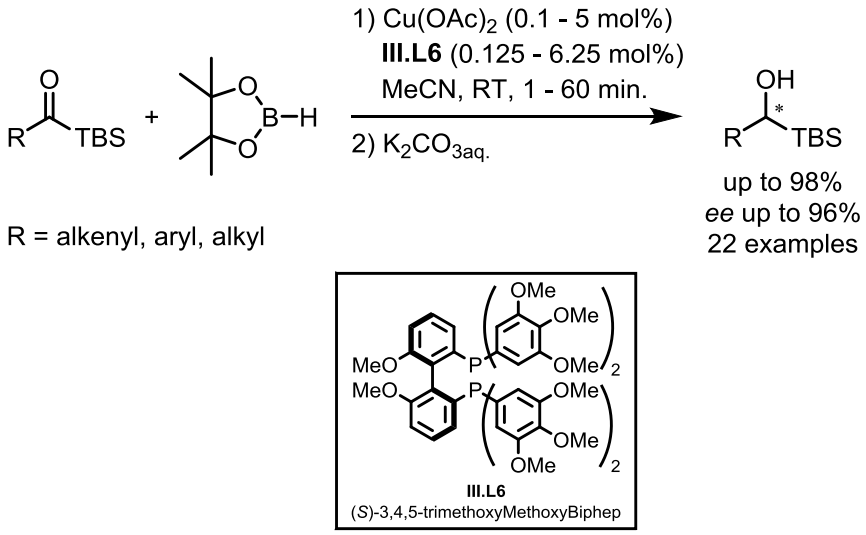
led to the discovery of a copper-catalysed β-silylative/aldolisation reaction of methyl acrylate with the capture of acylsilanes. This very promising reaction affords highly substituted tertiary α-hydroxysilanes in a single step. Furthermore, this reaction is one of the few copper-catalysed transformations of acylsilanes to date (Scheme IV-5).



Scheme IV-5 Copper-catalysed β-silylative/aldol reaction of methyl acrylate with acylsilanes.

Next, the general goal of the thesis was pursued and the discovery of copper-catalysed transformations of acylsilane was further investigated. In this context, a new approach was designed. The copper-catalysed β-addition of pronucleophiles to α,β-unsaturated acylsilanes was studied with the expectation of triggering a Cu-Brook rearrangement of the resulting copper-O-enolate.

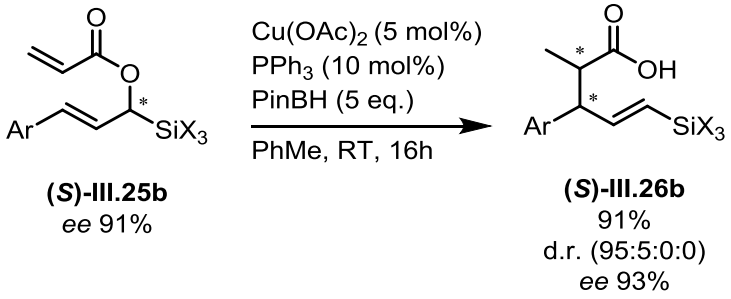
During the initial experiments, an intriguing 1,2-hydride addition to α,β-unsaturated acylsilanes was observed. This unexpected reaction affording secondary α-hydroxyallylsilanes was consequently examined and optimised. Enantioselective conditions for this transformation were discovered and the method was efficiently applied to α,β-unsaturated acylsilanes but also to aromatic and aliphatic acylsilanes (Scheme IV-6).



Scheme IV-6 Copper-catalysed 1,2-hydroborylation of acylsilanes.

The developed method proved to be robust. Indeed, it was easily scalable without significant variation of the results and was tolerant to ambient atmosphere. Notably, the catalytic loading is low, the reaction operates at room temperature and the reagents are commercially available. A hypothesis based on steric parameters was made to explain the intriguing 1,2-selectivity of this catalytic hydride addition. Initial experiments support this hypothesis.

Finally, the allylic α-hydroxysilanes obtained above were efficiently used in a copper-catalysed reductive Claisen-rearrangement with excellent diastereoselectivity and chirality transfer (Scheme IV-7).



Scheme IV-7 Copper-catalysed reductive Claisen-rearrangement of allylic α-acryloyloxysilanes.

The results exposed in both chapters afford satisfying results but more importantly, they pave the way for new related research topics that would broaden the scope of the developed reactions and enlighten the applications and opportunities of this work. These perspectives are detailed in the conclusion and perspectives sections of each chapter.

In conclusion, in the context of this thesis as often in science, significant results did not appear were or when they were expected. However, it was shown that designing research projects based on the theory, the literature and on the background of the experimental chemist can lead to unexpected yet stimulating results. It can be assumed that the general goal of this work has been reached since two copper-catalysed transformations of acylsilanes were discovered and one of those extensively studied. However, the actual research projects that were imagined were unsuccessful and the expected products were not even observed. Nevertheless, those projects opened doors to breakthroughs in related topics and led to the discovery of targeted copper-catalysed transformations of acylsilanes.

Experimental part

1 Instrumentation and chemicals

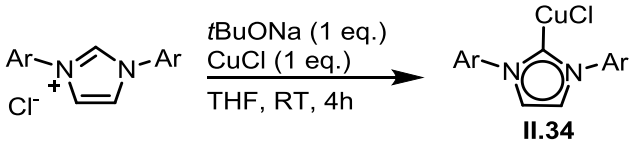
Unless otherwise noted, all manipulations were performed under an argon atmosphere using flame dried flasks. Diethyl ether and THF were distilled on sodium/benzophenone under an argon atmosphere. Toluene was distilled on sodium under an argon atmosphere. Dichloromethane and acetonitrile were distilled on CaH_2 under an argon atmosphere. Solvents used for work-up were of technical grade. Commercial reagents were purchased from Acros, Sigma-Aldrich, ABCR or TCI and used as received unless stated otherwise. Aldehydes were distilled before used. Unless stated otherwise, ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded in deuteriochloroform ($CDCl_3$) at ambient temperature on a Bruker DPX 300 MHz Fourier Transform Spectrometer. All the spectra were calibrated relative to chloroform at δ 7.26 ppm for ^{1}H and δ 77.16 ppm for ^{13}C, relative to benzene at δ 7.16 ppm for ^{1}H and δ 128.06 ppm for ^{13}C or relative to dichloromethane at δ 5.32 ppm for ^{1}H and δ 53.84 ppm for ^{13}C. Spectral features were assigned as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and brs = broad singlet. High resolution Mass Spectra were obtained from a Thermo Scientific QExactive, with accurate mass reported for the molecular ion or suitable fragment ions. Column chromatography was carried out on silica gel (ROCC 60, 40-63 μm). HPLC analyses were recorded on a Waters 600 apparatus with PDA 996 detector and 717 autosampler injector. Products were diluted in ethanol or in the specified eluent. Specific rotations were measured with an Anton Paar MCP 100 polarimeter. TLC analyses were performed on commercial aluminium plates bearing a 0.25 mm layer of Merck Silica gel $60F_{254}$.

2 Synthesis of the main substrates

2.1 Sythesis of the copper complexes

- Chloro[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]copper(I), **II.34**

The *I*Pr.HCl ligand was synthesised according to a reported procedure that is not described here.[1] The *I*PrCuCl complex was synthesised by complexation of *I*Pr.HCl to CuCl according to a procedure from the literature.[2]

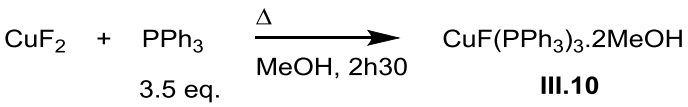


II.34

An oven-dried Schlenk flask was charged with 1,3-bis(2,6-di-*i*-propylphenyl) imidazolium chloride (1.70 g, 4.0 mmol). Fresh CuCl (0.40 g, 4.0 mmol), NaO*t*-Bu (0.39 g, 4.0 mmol), and THF (20 mL) were added to this Schlenk flask. The resulting suspension was stirred at room temperature for 4 h, then filtered over celite and concentrated *in vacuo*. The complex **II.34** was obtained as a pure grey powder without further purification (1.84 g, 95%). The spectral data are consistent with the literature.

^{1}H NMR (δ, ppm) (300 MHz, CD_2Cl_2)	7.52 (dd, *J* = 8.2, 7.3 Hz, 2H), 7.33 (d, *J* = 7.8 Hz, 4H), 7.17 (s, 2H), 2.54 (hept, *J* = 6.9 Hz, 4H), 1.26 (d, *J* = 6.9 Hz, 12H), 1.21 (d, *J* = 6.9 Hz, 12H).
^{13}C NMR (δ, ppm) (75 MHz, CD_2Cl_2)	146.3, 135.0, 130.9, 124.7, 123.8, 29.2, 25.1, 24.1.

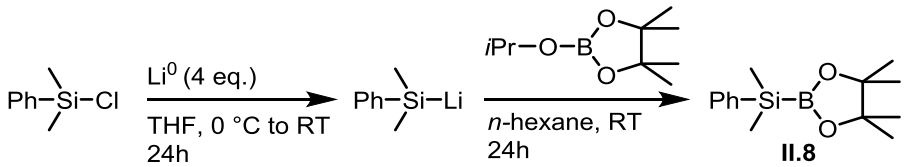
- [$CuF(PPh_3)_3$],2MeOH, **III.10**



A modified procedure from the literature was used.[3] A 200 mL round-bottom flask was loaded with triphenylphosphine (11.20 g, 42.7 mmol, 3.5 eq.), copper(II) fluoride (1.24 g, 12.2 mmol, 1 eq.) and wet methanol (100 mL). The mixture was heated to reflux during 2h30. The solution was filtered and half of the solvent was removed under reduced pressure and then stored at 4 °C overnight. The white crystals formed were then filtered and a second harvest of complex was obtained after concentration of the filtrate to obtain 20 mL. The final complex was obtained as a white solid with 70% yield (6.53 g). The spectral data are consistent with the literature.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.40 – 7.15 (m, 45H), 3.47 (s, 6H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	136.2 (d, *J* = 5.8 Hz), 134.1 (d, *J* = 18.7 Hz), 129.5, 128.6 (d, *J* = 10.5 Hz), 50.8
^{19}F NMR (δ, ppm) (282MHz, $CDCl_3$)	-208.6
^{31}P NMR (δ, ppm) (202 MHz, $CDCl_3$)	-4.17

2.2 Synthesis of Suginome's reagent



A modified procedure from the literature was used.[4] Metallic lithium in mineral oil (1.65 g, 240 mmol, 4 equiv.) was washed with *n*-hexane

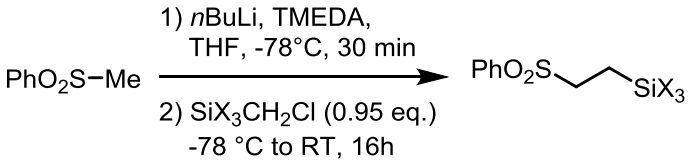
and added in small portion to THF (60 mL) under an argon flow. The flask was placed in an ice bath and dimethylphenylchlorosilane (10 mL, 60 mmol, 1 equiv.) was added dropwise. The red mixture was vigorously stirred overnight at room temperature and added dropwise *via* syringe to a solution of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (24.4 mL, 120 mmol, 2 equiv.) in *n*-hexane (30 mL). The mixture was stirred overnight at room temperature, and the volatile materials were removed *in vacuo*. The residue was taken in *n*-hexane (60 mL) and filtered through celite under argon (celite was dried *in vacuo* before use). The solvent was removed under reduced pressure and the product was purified by fractioned distillation (bp = 120 °C at 0.1 mbar) to give **II.8** as a colourless oil (12.58 g, 80%).The spectral data are consistent with the literature.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.71 – 7.57 (m, 2H), 7.45 – 7.31 (m, 3H), 1.30 (s, 12H), 0.40 (s, 6H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	139.2, 134.3, 128.7, 127.8, 83.5, 25.1, -3.0.

2.3 Synthesis of the sulfones

2.3.1 From methyl phenyl sulfone

The sulfones were synthesised according to a procedure inspired by the literature.[5]



X = Me or EtO

*n*BuLi (1.05 eq.) was added dropwise to a stirred solution of methylphenylsulfone (1.05 eq.) and TMEDA (1.05 eq.) in dry THF (3 $mL.mmol^{-1}$ of the electrophile) under an argon atmosphere at -78 °C. After stirring for 30 min, the desired (silyl)methyl chloride (1 eq.) was added dropwise at -78 °C. The reaction mixture was stirred from -78 °C to room temperature overnight. The reaction mixture was quenched with saturated NH_4Cl solution. The layers were separated and the aqueous was extracted three times with diethylether. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated. Purification by column chromatography afforded the sulfones as a white solids.

- Trimethyl(2-(phenylsulfonyl)ethyl)silane, **II.38a**

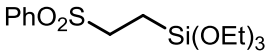
$C_{11}H_{18}O_2SSi$
Molecular Weight: 242,4080

Following the procedure starting from (trimethylsilyl)methyl chloride (12.2 mmol).

Flash chromatography PE/EtOAc 93:7. Yield 2.44g (82%) as a white solid (2.44 g, 82%). Spectral data are consistent with the literature.[6]

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.97 – 7.83 (m, 2H), 7.72 – 7.53 (m, 3H), 3.08 – 2.92 (m, 2H), 0.98 – 0.87 (m, 2H), -0.00 (s, 9H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	138.8, 133.7, 129.33, 128.3, 52.8, 9.2, -1.9.

- triethoxy(2-(phenylsulfonyl)ethyl)silane, **II.38i**



$C_{14}H_{24}O_5SSi$
Molecular Weight: 332,4860

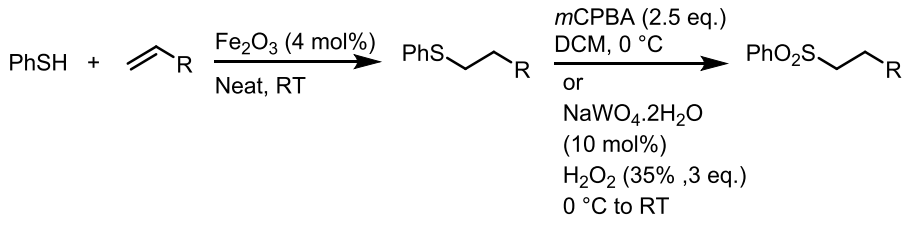
Following the procedure from (triethoxysilyl)methyl chloride (4.75 mmol).

Flash chromatography PE/EtOAc 85:15. Yield 0.68 g (44%) as a white gummy solid.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.93 – 7.82 (m, 2H), 7.67 – 7.59 (m, 1H), 7.58 – 7.48 (m, 2H), 3.74 (q, *J* = 6.9 Hz, 6H), 3.16 – 3.02 (m, 2H), 1.14 (t, *J* = 7.2 Hz, 9H), 1.06 – 0.90 (m, 2H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	138.54, 133.67, 129.27, 128.28, 58.78, 51.52, 18.23, 4.01.
MS (HRMS ESI)	Calcd for $[M+Na]^+$ Found: 355.10055 $C_{14}H_{24}O_5SSiNa$ 355.10059

2.3.2 From thiophenol

The sulfones were synthesised in two steps from alkenes and thiophenol according to the literature.[7]



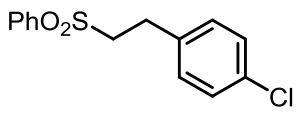
Step 1:[7a] Iron(III) oxide (4 mol%) was charged in an open vial. The alkene (1 eq.) and thiophenol (1 eq.) were subsequently added. The neat reaction mixture was stirred at room temperature until complete conversion of the starting material as monitored by TLC. The reaction were usually completed within 10 minutes. The catalyst was removed by filtration through a pad of silica gel eluting with Et_2O. The

volatiles were removed *in vacuo* affording the sulfides which were used in the next step without further purification.

Step 2:[7b] The crude sulfides (1 eq.) were dissolved in DCM (3 $mL.mmol^{-1}$) and cooled to 0 °C. To the stirring mixture, *m*CPBA (2.5 eq.) was added and the evolution of the reaction was monitored by TLC. After complete conversion of the substrate, the mixture was filtered through a pad of celite. The filtrate was washed with Na_2SO_3, $NaHCO_3$, and brine. The sulfones were purified by recrystallization with the given solvents and obtained as colourless solids.

Step 2':[7c] The crude sulfides (1 eq.) were dissolved in a (10:1) EtOAc/H_2O mixture (2 $mL.mmol^{-1}$). To the stirring mixture, sodium tungstate dihydrate (10 mol%) was added and the temperature was reduced to 0 °C. Hydrogen peroxide (35% solution, 3 eq.) was added. The reaction was further stirred at 0 °C for 30 minutes followed by 1 hour at room temperature. The evolution of the reaction was monitored by TLC. After complete conversion of the substrate, the crude mixture was washed with a saturated aqueous Na_2SO_3 solution and extracted twice with EtOAc. The organic phases were gathered, dried over Na_2SO_4 and the solvents were removed *in vacuo* .The sulfones were purified by flash column chromatography with the indicated eluent and obtained as colourless solids.

- 1-chloro-4-(2-(phenylsulfonyl)ethyl)benzene, **II.38b**



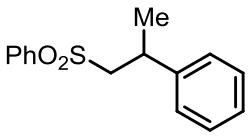
$C_{14}H_{13}ClO_2S$
Molecular Weight: 280,7660

Following **step 1** and **2** from 4-chlorostyrene (5 mmol).

Recrystallization from refluxing PE/DCM. Overall yield 1.02g (73%) as colourless crystals (1.02 g, 73%).

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.98 – 7.87 (m, 2H), 7.73 – 7.64 (m, 1H), 7.58 (ddt, *J* = 8.3, 6.6, 1.3 Hz, 2H), 7.31 – 7.18 (m, 2H), 7.09 – 7.01 (m, 2H), 3.44 – 3.24 (m, 2H), 3.13 – 2.94 (m, 2H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	142.2, 139.1, 136.0, 134.0, 129.8, 129.6, 129.1, 128.2, 57.5, 28.3.
MS (HRMS ESI)	Calcd for $[M+H]^+$ Found: 281.03973 $C_{14}H_{14}O_2ClS$ 281.03975

- ((2-phenylpropyl)sulfonyl)benzene, **II.38c**

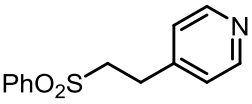


$C_{15}H_{16}O_2S$
Molecular Weight: 260,3510

Following **step 1** and **2** starting from α-methylstyrene (5 mmol). Recrystallization from refluxing PE/DCM. Overall yield 0.85 g (65%) as colourless crystals. The spectral data are consistent with the literature.[8]

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.86 – 7.74 (m, 2H), 7.65 – 7.54 (m, 1H), 7.52 – 7.43 (m, 2H), 7.25 – 7.12 (m, 3H), 7.11 – 7.04 (m, 2H), 3.49 – 3.29 (m, 3H), 1.45 (d, *J* = 6.7 Hz, 2H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	144.1, 140.0, 133.6, 129.3, 128.9, 128.0, 127.0, 126.9, 63.5, 35.2, 22.3.

- 4-(2-(phenylsulfonyl)ethyl)pyridine, **II.38d**



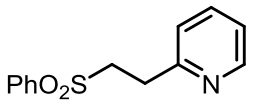
$C_{13}H_{13}NO_2S$
Molecular Weight: 247,3120

Following **step 1** and **2'** from 4-vinylpyridine (5 mmol).

Flash chromatography EtOAc. Yield 1.13 g (90%) as a colourless solid. The spectral data are consistent with the literature.[9]

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	8.59 – 8.39 (m, 2H), 8.00 – 7.87 (m, 2H), 7.76 – 7.64 (m, 1H), 7.65 – 7.52 (m, 2H), 7.14 – 6.99 (m, 2H), 3.44 – 3.31 (m, 2H), 3.15 – 3.00 (m, 2H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	150.2, 146.7, 138.8, 134.2, 129.6, 128.2, 123.7, 56.3, 28.2.

- 2-(2-(phenylsulfonyl)ethyl)pyridine, **II.38e**



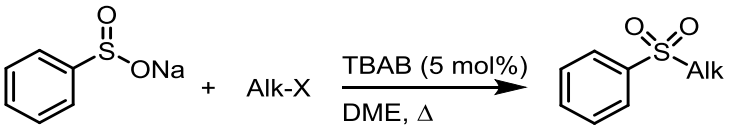
$C_{13}H_{13}NO_2S$
Molecular Weight: 247,3120

Following **step 1** and **2'** from 2-vinylpyridine (5 mmol).

Flash chromatography EtOAc. Yield 0.72 g (58%) as a colourless solid. The spectral data are consistent with the literature.[9]

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	8.44 (d, *J* = 4.6 Hz, 1H), 7.96 – 7.88 (m, 2H), 7.70 – 7.47 (m, 4H), 7.21 – 7.06 (m, 2H), 3.69 – 3.51 (m, 2H), 3.28 – 3.17 (m, 2H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	157.2, 149.4, 139.2, 137.0, 133.8, 129.4, 128.3, 123.5, 122.1, 55.3, 30.8.

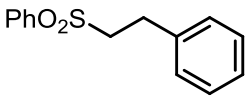
2.3.3 From sodium benzenesulfinate[10]



According to the literature, TBAB (0.05 eq.) and the desired alkyl halide (1 eq.) were added to a suspension of sodium benzenesulfinate (1.05 eq.) in DME (1.25 mL.mmol^{-1} of alkyl halide). The mixture was refluxed until complete conversion of the starting material. The

reaction was diluted with water and extracted three times with Et_2O. The organic phases were gathered, dried over $MgSO_4$ and the solvents were removed *in vacuo*. The crude product was purified by column chromatography on silica gel with the given eluents affording the pure sulfone as white solids or colourless oils.

- (phenethylsulfonyl)benzene, **II.38f**



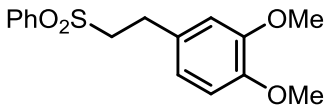
$C_{14}H_{14}O_2S$
Molecular Weight: 246,3240

Following the procedure starting from (2-bromoethyl)benzene (10 mmol).

Flash chromatography PE/EtOAc 85:15. Yield 0.49 g (20%) as a white solid. The spectral data are consistent with the literature.[11]

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	8.00 – 7.89 (m, 2H), 7.72 – 7.63 (m, 1H), 7.62 – 7.53 (m, 2H), 7.34 – 7.17 (m, 3H), 7.15 – 7.07 (m, 2H), 3.54 – 3.24 (m, 2H), 3.22 – 2.91 (m, 2H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	139.1, 137.6, 133.9, 129.5, 129.0, 128.4, 128.2, 127.1, 57.7, 28.9.

- 1,2-dimethoxy-4-(2-(phenylsulfonyl)ethyl)benzene, **II.38g**



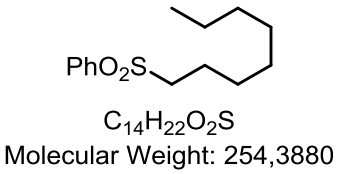
$C_{16}H_{18}O_4S$
Molecular Weight: 306,3760

Following the procedure starting from 4-(2-bromoethyl)-1,2-dimethoxybenzene (5 mmol).

Flash chromatography PE/EtOAc 50:50. Yield 0.91 g (59%) as a white solid.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.97 – 7.90 (m, 2H), 7.72 – 7.63 (m, 1H), 7.58 (ddt, *J* = 8.3, 6.6, 1.4 Hz, 2H), 6.75 (d, *J* = 8.1 Hz, 1H), 6.69 – 6.60 (m, 2H), 3.83 (s, 3H), 3.83 (s, 3H), 3.41 – 3.28 (m, 2H), 3.07 – 2.94 (m, 2H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	149.2, 148.1, 139.2, 133.9, 130.0, 129.5, 128.2, 120.4, 111.6, 111.5, 57.9, 56.1, 56.0, 28.5.
MS (HRMS ESI)	Calcd for $[M+H]^+$ $C_{16}H_{19}O_4S$ Found: 307.09979 307.09986

- (octylsulfonyl)benzene, **II.38h**



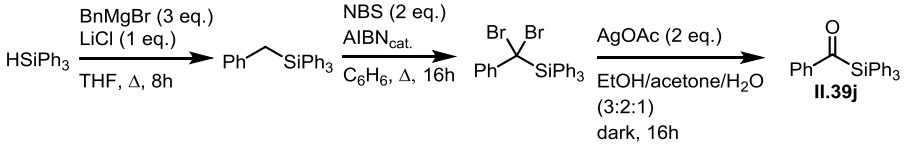
Following the procedure starting from octyl bromide (5 mmol). Flash chromatography PE/Et_2O 90:10. Yield 1.29 g (quantitative) as a colourless oil. The spectral data are consistent with the literature.[12]

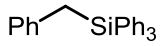
^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.95 – 7.86 (m, 2H), 7.71 – 7.50 (m, 3H), 3.13 – 3.00 (m, 2H), 1.82 – 1.63 (m, 2H), 1.48 – 1.08 (m, 10H), 0.93 – 0.79 (m, 3H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	139.3, 133.7, 129.4, 128.2, 56.4, 31.8, 29.1, 29.0, 28.4, 22.8, 22.7, 14.2.

2.4 Synthesis of the acylsilanes

2.4.1 Following Brook's original strategy

II.39j was synthesised according to the literature in three steps.[13]

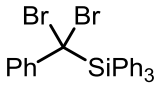




Chemical Formula: $C_{25}H_{22}Si$
Molecular Weight: 350,5360

Step 1:[13a] To a suspension of LiCl (0.39 g, 9.2 mmol) in 22 mL of THF was added benzylmagnesium bromide (1.2 M in THF, 27.6 mmol), followed by triphenylsilane (2.40 g, 9.2 mmol) in 68 mL of THF, at room temperature under argon. After the reaction mixture was stirred at reflux for 8 h, the reaction was terminated by the addition of an aqueous solution of NH_4Cl at room temperature. The resulting heterogeneous mixture was filtered through Celite with the aid of ether. The organic phase was dried over Na_2SO_4 and concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (PE) before recrystallization from boiling EtOAc/MeOH (5:1) to afford benzyltriphenylsilane (2.61 g, 80%) as a white solid. The spectral data are consistent with the literature.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.47 – 7.36 (m, 9H), 7.36 – 7.29 (m, 6H), 7.15 – 6.98 (m, 3H), 6.91 – 6.75 (m, 2H), 2.93 (s, 2H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	138.4, 136.1, 134.4, 129.7, 129.3, 128.1, 127.9, 124.6, 23.6.



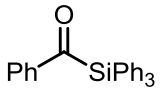
Chemical Formula: $C_{25}H_{20}Br_2Si$
Molecular Weight: 508,3280

Step 2:[13b] A round-bottom flask was charged with benzyltriphenylsilane (0.5 g, 1.43 mmol) and benzene (7 mL), followed by N-bromosuccinimide (0.53 g, 2.99 mmol) and AIBN (12 mg, 0.07 mmol). The mixture was refluxed overnight and filtered through a plug of cotton. The solvent were removed *in vacuo*. The crude product was dissolved in DCM and washed once with a saturated aqueous solution of $Na_2S_2O_3$ and twice with brine. The organic phase was dried over $MgSO_4$ and evaporated to afford the crude product.

Purification was carried out by column chromatography on silica gel (PE/DCM 90:10) affording (dibromo(phenyl)methyl)triphenylsilane as a white solid (0.48 g, 66%). The spectral data are consistent with the literature.

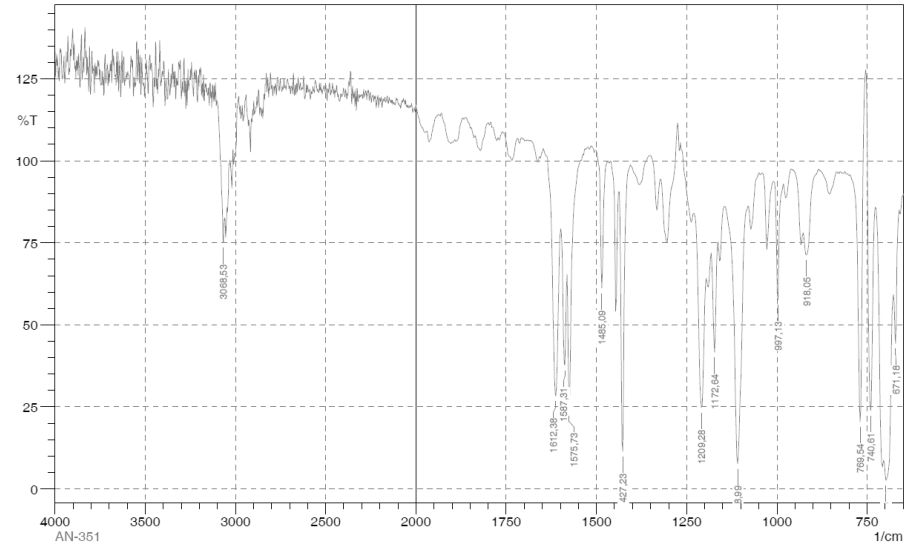
^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.73 – 7.62 (m, 6H), 7.54 – 7.41 (m, 5H), 7.34 (t, *J* = 7.4 Hz, 6H), 7.24 – 7.08 (m, 3H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	141.6, 137.5, 132.0, 130.3, 130.1, 128.4, 127.7, 127.5, 61.0.

Step 3:[13b] (dibromo(phenyl)methyl)triphenylsilane (0.39 g, 0.76 mmol) was dissolved with EtOH (1 mL), acetone (0.6 mL) and water (0.3 mL). Silver acetate (0.25 g, 1.52 mmol) was added and the mixture was stirred at room temperature in the dark overnight. The mixture was filtered through a pad of silica gel eluting with diethylether. The filtrate was evaporated, dissolved with DCM and washed with brine. The crude product was chromatographed on silica gel (PE/Et_2O 90:10) affording phenyl(triphenylsilyl)methanone **II.39j** as a pale yellow solid (0.22 g, 80%). The spectral data are consistent with the literature.



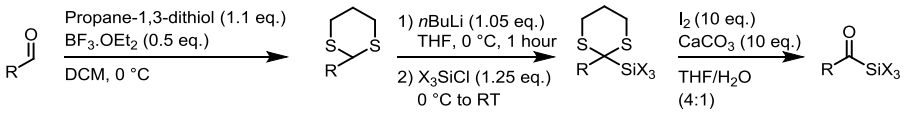
Chemical Formula: $C_{25}H_{20}OSi$
Molecular Weight: 364,5190

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.82 – 7.74 (m, 2H), 7.66 – 7.57 (m, 6H), 7.51 – 7.42 (m, 4H), 7.42 – 7.37 (m, 5H), 7.37 – 7.28 (m, 3H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	230.8, 142.3, 136.5, 133.1, 132.4, 130.3, 128.7, 128.6, 128.3.
IR (cm^{-1}, thin film)	1612 (C=O), 1587 (Ph-CO), 1575 (Ph-CO).



2.4.2 Corey-Brook strategy for aliphatic and aromatic acylsilanes

Several aromatic and aliphatic acylsilanes were synthesised according to a three-step procedure inspired by the literature.[14]



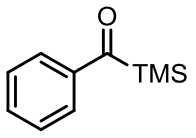
Step 1:[14a] To a solution of the respective aldehyde in dry DCM was added propane-1,3-dithiol (1.1 equiv.). The reaction mixture was cooled down to 0°C and $BF_3 \cdot Et_2O$ (0.5 equiv.) was added dropwise. It was stirred at 0°C for about 1h before it was allowed to warm to room temperature. The mixture was quenched with saturated $NaHCO_3$ solution and extracted three times with CH_2Cl_2. The combined organic layers were washed brine, dried over $MgSO_4$ and evaporated. The crude 1,3-dithianes were obtained as white solids or colourless oils and used without further purification.

Step 2:[14b] *n*BuLi (1.05 eq.) was added to a stirred solution of 1,3-dithiane (1 eq.) in dry THF (2.2 $mL.mmol^{-1}$) at 0 °C under an argon

atmosphere. After 1h, TMSCl, $PhMe_2SiCl$ or TBSOTf(1.25 eq.) was added. The reaction mixture was stirred at 0°C until complete conversion of the 1,3-dithianes as monitored by TLC. Water was then added and the mixture was extracted with DCM. The organic layer was dried and the solvent was evaporated under reduced pressure. The crude silylated 1,3-dithianes were used without further purification.

Step 3:[14b] To a solution of the silylated 1,3-dithiane (1 eq.) in THF/H_2O (4:1, 5 $mL.mmol^{-1}$) at 0°C were added calcium carbonate (10 eq.) and iodine (10 eq.). The mixture was stirred at room temperature for 16h and Et_2O and a saturated solution of $Na_2S_2O_3$ were then added successively. After stirring for 10 min, the crude mixture was filtered through Celite and extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude compound was purified by column chromatography over silica gel with the indicated eluent affording the pure aromatic acylsilanes as bright yellow oils or solids and the aliphatic acylsilanes as colourless oils or solids.

- Phenyl(trimethylsilyl)methanone, **II.39a**



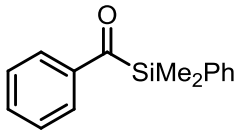
$C_{10}H_{14}OSi$
Molecular Weight: 178,3060

Following **step 1, 2 and 3** starting from benzaldehyde (5 mmol).

Flash chromatography PE/Et_2O 96:4. Overall yield 0.77g (86%) as a bright yellow oil. The spectral data are consistent with the literature.[15]

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.89 – 7.76 (m, 2H), 7.62 – 7.39 (m, 3H), 0.38 (s, 9H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	235.8, 141.3, 132.7, 128.6, 127.5, -1.4.

- (dimethyl(phenyl)silyl)(phenyl)methanone, **II.39b**

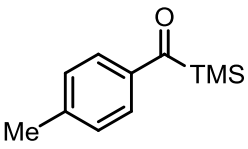


$C_{15}H_{16}OSi$
Molecular Weight: 240,3770

Following **step 1, 2 and 3** starting from benzaldhyde (5 mmol). Flash chromatography PE/Et_2O 95:5. Overall yield 0.89 g (74%) as a bright yellow oil. The spectral data are consistent with the literature.[16]

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.78 – 7.71 (m, 2H), 7.62 – 7.56 (m, 2H), 7.52 – 7.43 (m, 1H), 7.42 – 7.31 (m, 5H), 0.62 (s, 6H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	232.0, 141.7, 135.1, 133.7, 132.9, 130.0, 128.5, 128.2, 128.2, 3.3.

- *p*-tolyl(trimethylsilyl)methanone, **II.39c**

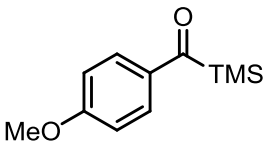


$C_{11}H_{16}OSi$
Molecular Weight: 192,3330

Following **step 1, 2 and 3** starting from *para*-tolualdehyde (5 mmol). Flash chromatography PE/Et_2O 96:4. Overall yield 0.82 g (85%) as a bright yellow oil. The spectral data are consistent with the literature.[17]

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.80 – 7.70 (m, 2H), 7.37 – 7.22 (m, 2H), 2.41 (s, 3H), 0.38 (s, 9H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	235.0, 143.6, 139.3, 129.4, 127.8, 21.8, -1.2.

- (4-methoxyphenyl)(trimethylsilyl)methanone, **II.39d**

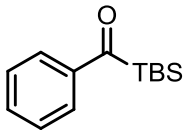


$C_{11}H_{16}O_2Si$
Molecular Weight: 208,3320

Following **step 1, 2 and 3** starting from *p*-anisaldehyde (5 mmol). Flash chromatography PE/Et_2O 90:10. Overall yield 0.82 g (79%) as a bright yellow oil. The spectral data are consistent with the literature.[18]

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.91 – 7.78 (m, 2H), 7.03 – 6.89 (m, 2H), 3.86 (s, 3H), 0.36 (s, 9H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	233.0, 163.3, 135.3, 130.0, 113.9, 55.6, -1.1.

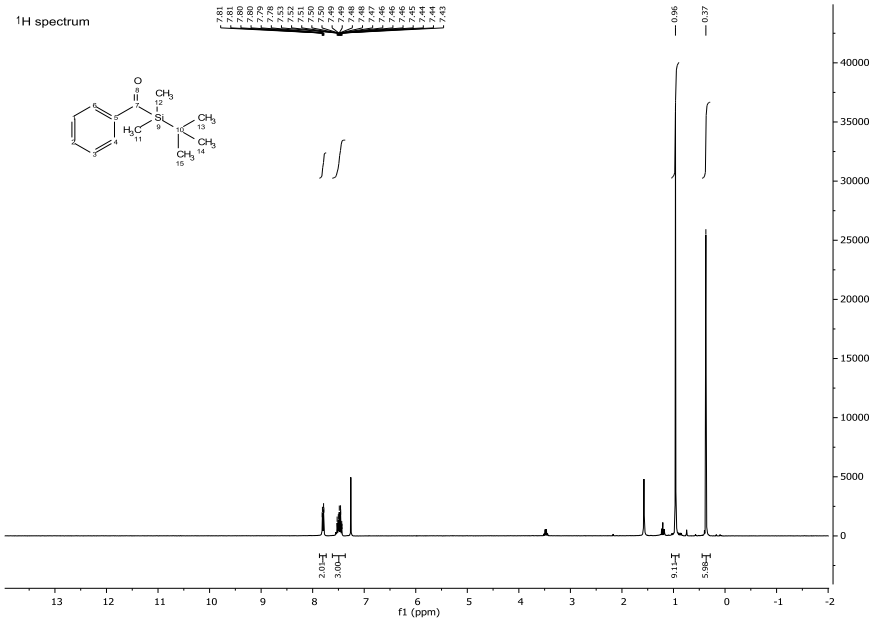
- (*tert*-butyldimethylsilyl)(phenyl)methanone, **II.39e/III.19b**

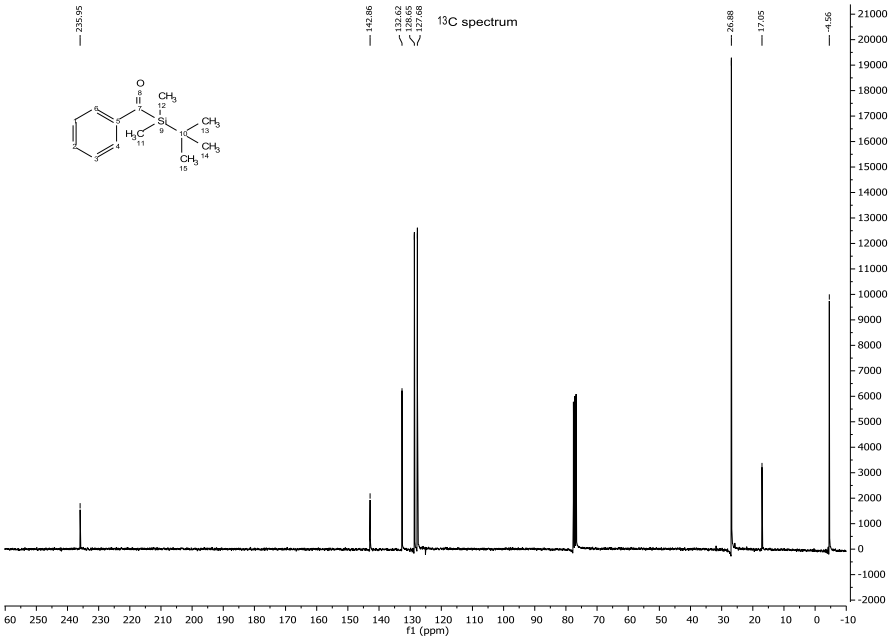


$C_{13}H_{20}OSi$
Molecular Weight: 220,3870

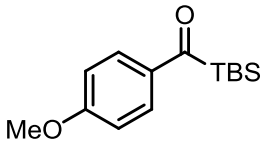
Following **step 2 and 3** starting with commercial 2-phenyl-1,3-dithiane (5 mmol). Flash chromatography: PE/Et_2O 95:5. Yield: 0.75g (68 % over two steps) as a yellow oil. The spectral data are consistent with the literature.[15]

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.85 – 7.74 (m, 2H), 7.62 – 7.38 (m, 3H), 0.96 (s, 9H), 0.37 (s, 6H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	235.9, 142.9, 132.6, 128.6, 127.7, 26.9, 17.0, -4.6.





- (*tert*-butyldimethylsilyl)(4-methoxyphenyl)methanone, **II.39f/III.19a**

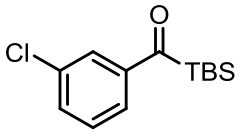


$C_{14}H_{22}O_2Si$
Molecular Weight: 250,4130

Following **step 1, 2 and 3** starting with 4-methoxybenzaldehyde (10 mmol).
Flash chromatography: PE/Et_2O 94:6.
Yield: 1.61g (67 %) as a yellow solid.
The spectral data are consistent with the literature.[19]

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.82 (d, J = 9.0 Hz, 2H), 6.94 (d, J = 8.9 Hz, 2H), 3.86 (s, 3H), 0.95 (s, 9H), 0.36 (s, 6H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	232.8, 163.2, 136.7, 130.2, 113.8, 55.6, 26.9, 17.0, -4.4.

- (*tert*-butyldimethylsilyl)(3-chlorophenyl)methanone, **II.39g/III.19d**

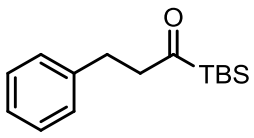


$C_{13}H_{19}ClOSi$
Molecular Weight: 254,8290

Following **step 1, 2 and 3** starting with 3-chlorobenzaldehyde (5 mmol).
Flash chromatography: EP/Et_2O 95:5
Yield: 1.05g (82 %) as a yellow solid.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.73 (td, J = 1.5, 0.7 Hz, 1H), 7.68 (dt, J = 7.5, 1.4 Hz, 1H), 7.48 (ddd, J = 7.9, 2.1, 1.3 Hz, 1H), 7.40 (t, J = 7.7 Hz, 1H), 0.95 (s, 9H), 0.37 (s, 6H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	234.7, 144.1, 135.1, 132.5, 130.0, 127.2, 126.2, 26.8, 17.1, -4.6.
MS (HRMS ESI)	Calcd for $[M+H]^+$ Found: 255.09648 $C_{13}H_{20}OClSi$ 255.09665

- 1-(*tert*-butyldimethylsilyl)-3-phenylpropan-1-one, **II.39h** and **III.19f**



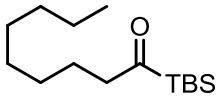
$C_{15}H_{24}OSi$
Molecular Weight: 248,4410

Following step **1, 2 and 3** starting with 3-phenylpropanal (3 mmol).

Flash chromatography: EP/Et2O 97:3. Yield: 0.54g (73 % over three steps) as a colorless solid. The spectral data are consistent with the literature.[20]

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.41 – 7.30 (m, 2H), 7.26 (t, J = 6.6 Hz, 3H), 3.09 – 2.96 (m, 2H), 2.92 (m, 2H), 0.99 (s, 9H), 0.25 (s, 6H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	246.6, 141.9, 128.6, 128.5, 126.0, 52.2, 28.7, 26.6, 16.7, -6.9.

- 1-(*tert*-butyldimethylsilyl)nonan-1-one, **II.39i**

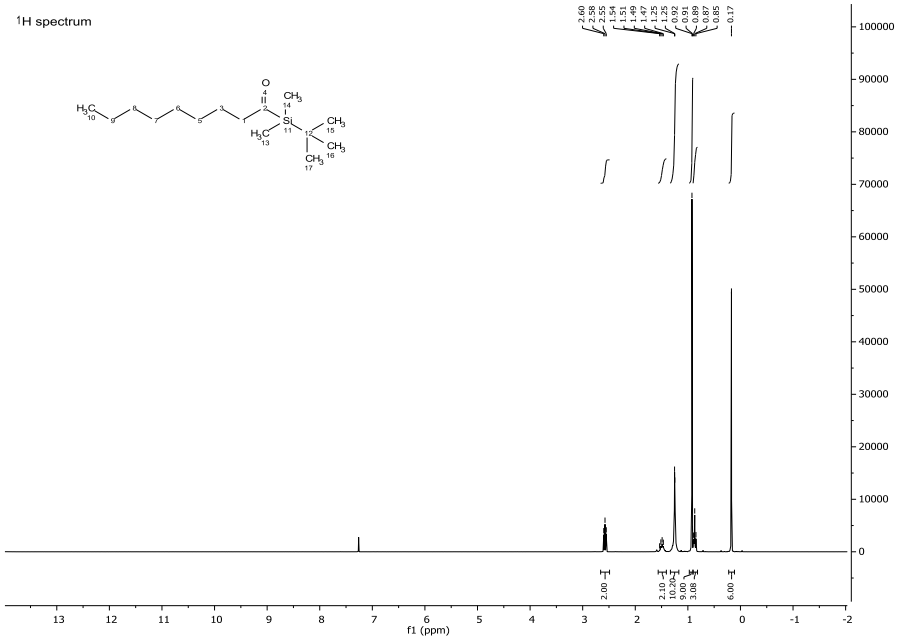


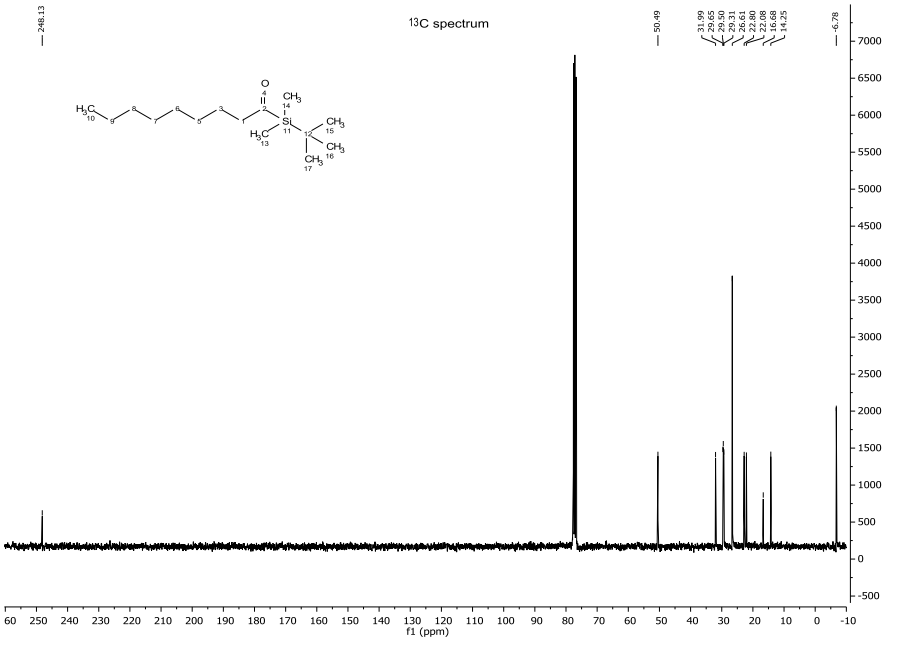
$C_{15}H_{32}OSi$
Molecular Weight: 256,5050

Following **step 1, 2 and 3** starting with 3-nonanal (3 mmol).

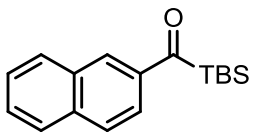
Flash chromatography: EP/Et2O 98:2. Yield: 0.42g (55 % over three steps) as a colourless oil. The spectral data are consistent with the literature.[21]

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	2.58 (t, *J* = 7.2 Hz, 2H), 1.57 – 1.39 (m, 2H), 1.36 – 1.15 (m, 10H), 0.92 (s, 9H), 0.90 – 0.83 (m, 3H), 0.17 (s, 6H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	248.1, 50.5, 32.0, 29.7, 29.5, 29.3, 26.6, 22.8, 22.1, 16.7, 14.3, -6.8.


1H spectrum
2.60
2.58
2.55
1.54
1.51
1.49
1.47
1.25
0.92
0.91
0.89
0.87
0.85
0.17
2.00
2.10
10.24
9.00
3.08
6.00
f1 (ppm)


13C spectrum
248.13
50.49
31.99
29.65
29.50
29.31
25.61
22.80
22.08
16.68
14.25
-6.78
f1 (ppm)

- (*tert*-butyldimethylsilyl)(naphthalen-2-yl)methanone, **III.19c**

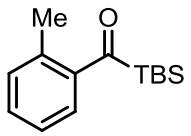


$C_{17}H_{22}OSi$
Molecular Weight: 270,4470

Following **step 1, 2 and step 3** starting with 2-naphthaldehyde (3 mmol). Flash chromatography: EP/Et_2O 98:2. Yield: 0.71g (84 %) as a yellow oil.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	8.35 (d, J = 1.1 Hz, 1H), 8.01 – 7.95 (m, 1H), 7.91 – 7.84 (m, 3H), 7.63 – 7.51 (m, 2H), 1.01 (s, 9H), 0.46 (s, 6H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	235.4, 140.3, 135.5, 132.7, 131.1, 129.8, 128.6, 128.4, 128.0, 126.8, 122.6, 26.9, 17.1, -4.3.
MS (HRMS ESI)	Calcd for $[M+H]^+$ Found: 271.15116 $C_{17}H_{23}OSi$: 271.15127

- (*tert*-butyldimethylsilyl)(o-tolyl)methanone, **III.19e**

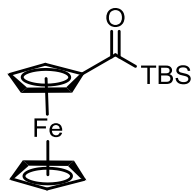


$C_{14}H_{22}OSi$
Molecular Weight: 234,4140

Following **step 1, 2 and 3** starting with 2-methylbenzaldehyde (5 mmol). Flash chromatography: PE/EtOAc 98:2. Yield: 0.82g (70 %) as a yellow oil.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.48 (dd, J = 7.3, 1.8 Hz, 1H), 7.36 – 7.13 (m, 3H), 2.38 (s, 3H), 0.96 (s, 9H), 0.29 (s, 6H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	243.1, 143.8, 135.1, 132.0, 130.4, 129.0, 125.3, 26.9, 20.4, 17.3, -5.0.
MS (HRMS APCI)	Calcd for $[M+H]^+$ Found: 235.15129 $C_{14}H_{23}OSi$: 235.15127

- (*tert*-butyldimethylsilyl)(ferrocenyl)methanone, **III.19h**



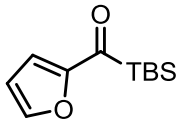
$C_{17}H_{24}FeOSi$
Molecular Weight: 328,3080

Following **step 1, 2** (step 2 was carried out at -20 °C) **and 3** starting with ferrocenecarboxaldehyde (3 mmol).

Flash chromatography: PE/EtOAc 95:5. Yield: 0.25g (51 %) as a red solid.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	4.81 (brs, 2H), 4.56 (brs, 2H), 4.21 (brs, 5H), 0.97 (brs, 9H), 0.40 (brs, 6H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	No ^{13}C NMR spectrum of quality could be obtained.
MS (HRMS ESI)	Calcd for $[M+H]^+$ Found: 327.10697 $C_{17}H_{25}OFeSi$ 327.10653

(*tert*-butyldimethylsilyl)(furan-2-yl)methanone, **III.19g**



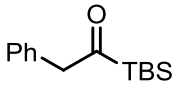
$C_{11}H_{18}O_2Si$
Molecular Weight: 210,3480

Following **step 1, 2** (step 2 was carried out at -78 °C) and **an alternative deprotection methodology**[18] (using CuO and $CuCl_2$ in acetone) starting with 2-furaldehyde (5 mmol).

Flash chromatography: PE/EtOAc 97:3. Yield: 0.42g (40 %) as an orange solid.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.57 (d, *J* = 1.0 Hz, 1H), 7.05 (d, *J* = 3.5 Hz, 1H), 6.52 (dd, *J* = 3.6, 1.6 Hz, 1H), 0.95 (s, 9H), 0.34 (s, 6H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	221.2, 159.1, 146.0, 115.2, 112.1, 26.7, 17.1, -5.9.
MS (HRMS ESI)	Calcd for $[M+H]^+$ Found: 211.11491 $C_{11}H_{19}O_2Si$ 211.11488

- 1-(*tert*-butyldimethylsilyl)-2-phenylethan-1-one



$C_{14}H_{22}OSi$
Molecular Weight: 234,4140

Following **step 1, 2 and 3** starting with phenylacetaldehyde (10 mmol).

Flash chromatography: PE/Et_2O 98:2.

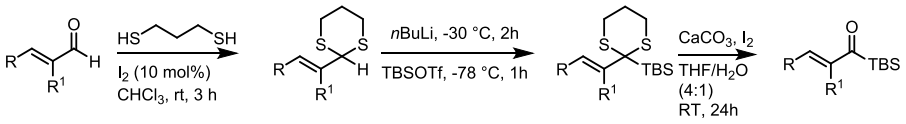
Yield: 1.41 g (60 %) as a colourless oil.

The spectral data are consistent with the literature.[22]

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.37 – 7.17 (m, 3H), 7.15 – 7.05 (m, 2H), 3.87 (s, 2H), 0.91 (s, 9H), 0.15 (s, 6H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	243.3, 133.1, 130.0, 128.6, 126.8, 56.7, 26.5, 16.8, -6.5.

2.4.3 Corey-Brook strategy for α,β-unsaturated acylsilanes

The acylsilanes were synthesised in three steps starting from enals according to the literature.[23]



R = Alk, Ph
R^1 = H, Alk

<u>Step 1</u>: The dithiol protection of the aldehydes was carried out according to the literature.

To a stirred solution of aldehyde (1.0 eq.) and 1,3-propanedithiol (1.1 eq.) in $CHCl_3$ (5 mL/mmol) at room temperature was added I_2 (0.1 eq.) in one portion. The reaction was stirred for 3 h, and then it was quenched with a saturated aqueous $Na_2S_2O_3$ solution. The organic phase was separated, and the aqueous layer was extracted with $CHCl_3$ (3x15 mL). The combined organic phases were washed with brine and

dried over $MgSO_4$. Then the solution was concentrated, and the crude dithianes were used in the next step without further purification.

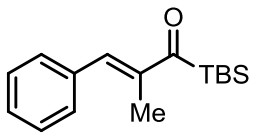
Step 2: The silylation of dithianes was carried out according to the literature.

To a stirred solution of dithiane (1.0 eq.) in THF (2.5 mL/mmol) at –30 °C was added *n*BuLi (1.2 eq., 1.6 M in hexanes) dropwise. The resulting mixture was kept for 2 h at the same temperature, then it was cooled to –78 °C, *tert*-butyldimethylsilyl triflate (TBSOTf, 1.2 eq.) was added into the reaction mixture, and it was kept for another hour at -78 °C. Then the mixture was quenched with saturated NH_4Cl and extracted with diethyl ether (3x15 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated to afford the crude silyldithianes.

Step 3: The deprotection of dithianes was carried out according to the literature.

To a stirred solution of the above crude silyldithianes (1.0 eq.) in the combined solvent (THF/H_2O = 4/1, 7.0 mL/mmol) was added $CaCO_3$ (8.0 eq.) and I_2 (6.0 eq.). The mixture was kept for 24 h at room temperature, then quenched with saturated $Na_2S_2O_3$. The mixture filtered through a pad of silica gel, washed with diethylether. Then the solution was washed with water and brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography to afford the pure acylsilanes.

- (*E*)-1-(*tert*-butyldimethylsilyl)-2-methyl-3-phenylprop-2-en-1-one, **III.11m**



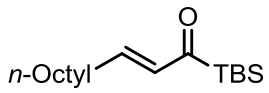
$C_{16}H_{24}OSi$
$M = 260.45\ g.mol^{-1}$

Following **step 1, 2 and 3** starting with commercial (*E*)-2-methyl-3-phenylacrylaldehyde (10.0 mmol).

Flash chromatography: PE. Overall Yield: 0.39 mg (37 %) as a yellow oil.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.49 – 7.33 (m, 6H), 1.98 (s, 3H), 0.98 (s, 9H), 0.35 (s, 6H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	235.9, 145.2, 144.6, 136.1, 129.8, 128.9, 128.7, 27.0, 17.1, 11.5, -3.8.
MS (HRMS APCI)	Calcd for $[M+H]^+$ Found: 261.1668 $C_{16}H_{25}OSi$: 261.1669

- (*E*)-1-(*tert*-butyldimethylsilyl)undec-2-en-1-one, **III.11n**



$C_{17}H_{34}OSi$
$M = 282.54\ g.mol^{-1}$

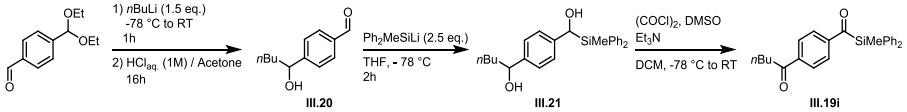
Following **step 1, 2 and 3** starting with (*E*)-undec-2-enal (10.0 mmol).

Flash chromatography: PE. Overall Yield: 0.24 mg (18 %) as a yellow oil.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	6.73 – 6.63 (m, 1H), 6.35 (dt, J = 15.0, 3.0 Hz, 1H), 2.25 – 2.17 (m, 2H), 1.49 – 1.42 (m, 2H), 1.30 – 1.25 (m, 10H), 0.93 (s, 9H), 0.87 (t, J = 3.0 Hz, 3H), 0.23 (s, 6H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	235.8, 147.1, 136.6, 32.8, 32.0, 29.5, 29.3, 28.3, 26.7, 25.8, 22.8, 16.8, 14.2, -5.8.
MS (HRMS APCI)	Calcd for $[M+H]^+$ Found: 283.2451 $C_{17}H_{35}OSi$: 283.2452

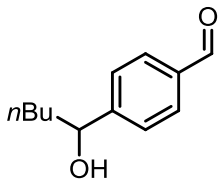
2.4.4 Synthesis of the ketone bearing aromatic acylsilane, **III.19i**

The synthesis of the acylsilane was carried out in three steps starting from the commercially available terephthalaldehyde diethyl acetal.



Step 1: 4-(1-hydroxypentyl)benzaldehyde **III.20** was prepared by addition of *n*BuLi to terephthalaldehyde diethyl acetal followed by deprotection in acidic media.

A Schlenk tube was charged with terephthalaldehyde diethyl acetal (2 mmol, 1 eq.) and THF (2.5 mL/mmol). *n*BuLi (1.5 eq., 1.6M in hexanes) was added dropwise at -78 °C. The temperature was raised to room temperature and the mixture was stirred for an additional hour. The reaction was quenched with water, the organic phase was separated and the aqueous phase was washed with Et_2O (3 X 15 mL).The organic phases were gathered, dried on $MgSO_4$ and the solvents were removed *in vacuo.* The residue was dissolved in acetone (2mL/mmol) and aqueous HCl (1M, 2mL/mmol) was added. The mixture was stirred overnight at room temperature. The mixture was diluted with a saturated solution of aqueous $NaHCO_3$ and was extracted with Et_2O (3 X 15mL). The organic phases were collected, dried on $MgSO_4$ and the volatiles were removed *in vacuo.* Purification by flash column chromatography on silica gel afforded the desired 4-(1-hydroxypentyl)benzaldehyde.



$C_{12}H_{16}O_2$
Molecular Weight: 192,2580

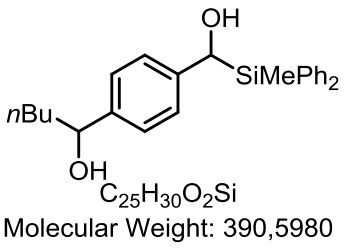
Following the procedure starting from terephthalaldehyde diethyl acetal (2 mmol).

Flash chromatography: PE/EtOAc 70:30. Yield: 0.36 g (93%) as a colourless oil.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	10.00 (s, 1H), 7.97 – 7.77 (m, 2H), 7.52 (d, J = 8.2 Hz, 2H), 4.78 (dd, J = 7.4, 5.6 Hz, 1H), 2.10 (s, 1H), 1.85 – 1.70 (m, 2H), 1.40 – 1.29 (m, 4H), 0.90 (t, J = 7.0 Hz, 3H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	192.2, 152.0, 135.7, 130.1, 126.5, 74.2, 39.1, 27.9, 22.7, 14.1.
MS (HRMS APCI)	Calcd for $[M+H]^+$ $C_{12}H_7O_2$ Found: 193.12232 193.12231

Step 2: 1-(4-(hydroxy(methyldiphenylsilyl)methyl)phenyl)pentan-1-ol **III.21** was prepared by addition of (methyldiphenylsilyl)lithium to 4-(1-hydroxypentyl)benzaldehyde **III.20**.

A solution of (methyldiphenylsilyl)lithium[24] in THF (2.5 eq) was added dropwise at -78 °C to a Schlenk tube containing 4-(1-hydroxypentyl)benzaldehyde (1.86 mmol, 1 eq.) in THF (2 mL/mmol). The reaction mixture was stirred at -78 °C for two hours. The reaction was quenched at -78 °C by addition of Et_2O and water under vigorous stirring. The organic phase was separated and the aqueous phase was washed with Et_2O. The combined organic phases were dried over $MgSO_4$, the solvents were evaporated and the resulting residue was submitted to flash column chromatography (PE/EtOAc 70:30) yielding the title compound.

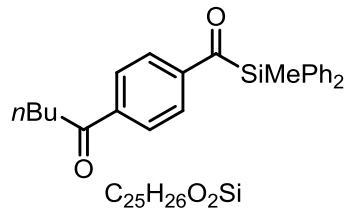


Yield: 0.39 g (46%) as a colourless oil.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.61 – 7.55 (m, 2H), 7.50 (dq, J = 6.5, 1.4 Hz, 2H), 7.45 – 7.32 (m, 6H), 7.18 (d, J = 8.2 Hz, 2H), 7.01 (d, J = 8.0 Hz, 2H), 5.08 (s, 1H), 4.61 (t, J = 6.7 Hz, 1H), 1.83 (brs, 2H), 1.79 – 1.57 (m, 2H), 1.40 – 1.29 (m, 3H), 1.22 (t, J = 7.0 Hz, 1H), 0.89 (t, J = 7.0 Hz, 3H), 0.50 (s, 3H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	142.8, 142.3, 135.5, 135.3, 134.5, 133.8, 129.9, 129.7, 128.0, 127.9, 125.9, 125.7, 74.6, 74.6, 69.1, 69.1, 38.9, 28.1, 22.7, 14.2, -6.7.
MS (HRMS APCI)	Calcd for $[M+H]^+$ Found: 387.21381 $C_{25}H_{31}O_2Si$ 387.21387

Step 3: 1-(4-((methyldiphenylsilyl)carbonyl)phenyl)pentan-1-one **III.19i** was prepared by subjecting 1-(4-(hydroxy(methyldiphenylsilyl)methyl)phenyl)pentan-1-ol **III.21** to a Swern oxidation.

A solution of oxalyl chloride (1.1 equiv.) in freshly distilled CH_2Cl_2 (2.0 mL/mmol) was cooled to −78 °C, and DMSO (2.2 equiv.) was carefully added under argon atmosphere. After stirring for 15 min, a solution of alcohol (1.0 equiv.) in CH_2Cl_2 (1.0 mL/mmol) and Et_3N (5.0 equiv.) were added successively. The cooling bath was removed, and the reaction mixture was allowed to warm to room temperature and stirred for 2 h. The solvent was removed under reduced pressure, and the residue was extracted with ethyl acetate. The extract was washed with a saturated aqueous Na_2CO_3 solution, brine, and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the crude product was purified by flash column chromatography to yield 1-(4-((methyldiphenylsilyl)carbonyl)phenyl)pentan-1-one.



$C_{25}H_{26}O_2Si$
Molecular Weight: 386,5660

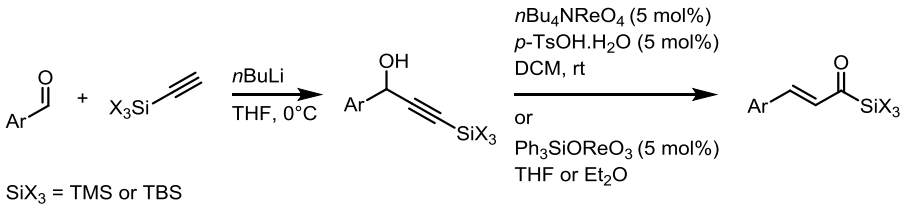
Following step 3 starting with 1-(4-(hydroxy(methyldiphenylsilyl)methyl)phenyl)pentan-1-ol (0.86 mmol).

Flash chromatography: PE/Et_2O 97:3. Yield: 0.24g (71 %) as a bright yellow oil.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.94 – 7.88 (m, 2H), 7.84 – 7.76 (m, 2H), 7.63 – 7.54 (m, 4H), 7.50 – 7.34 (m, 6H), 2.99 – 2.88 (m, 2H), 1.78 – 1.61 (m, 2H), 1.47 – 1.30 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H), 0.87 (s, 3H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	232.5, 200.2, 144.1, 139.9, 135.2, 133.3, 130.4, 128.5, 128.4, 128.3, 38.8, 26.3, 22.5, 14.0, -3.4.
MS (HRMS APCI)	Calcd for $[M+Na]^+$ Found: 409.15951 $C_{25}H_{26}O_2NaSi$ 409.15943

2.4.5 Perrhenate-catalysed synthesis of α,β-unsaturated acylsilanes

The acylsilanes were prepared according to a two-step procedure.[25]



SiX_3 = TMS or TBS

<u>Step 1</u>: A flame-dried round-bottomed flask equipped with a stir bar was charged with the appropriate silyl acetylene (1.0 eq.) and placed under an argon atmosphere. Freshly distilled THF was introduced into the flask *via* syringe to prepare a 0.2 M solution of the acetylene and the resulting solution was cooled to 0 ºC. While stirring at 0 ºC, a 1.6 M solution of *n*-butyllithium in hexanes (1.0 eq.) was added. After 30

minutes of stirring at 0 ºC the reaction was charged with the appropriate aldehyde (1.0 eq.). The progress of the reaction was monitored by TLC analysis. Upon completion, the reaction was quenched with a saturated aqueous solution of ammonium chloride and diluted with EtOAc. The layers were separated and the organic layer was washed with brine, dried using Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash column chromatography, eluting with the indicated solvent mixture to afford the desired alcohol.

Step 2: Two reaction protocols were used for the Meyer-Schuster rearrangement of propargylic alcohols to acylsilanes. Conditions A involved the use of *p*-TSA•H_2O and *n*Bu_4N•ReO_4 in DCM at RT. When this method failed or the substrates were deemed to be sensitive to acid-catalysed ionization Conditions B, which involved the use of $Ph_3SiOReO_3$ in anhydrous solvents (Et_2O or THF), were used.

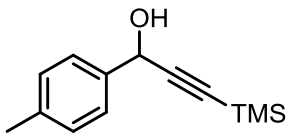
Conditions A

To a round-bottomed flask equipped with a stir bar and charged with *n*Bu_4N•ReO_4 (0.05 eq.), *p*-TsOH•H_2O (0.05 eq.) was added a 0.2 M solution of propargylic alcohol (1.00 eq.) in DCM. After overnight stirring at ambient temperature the reaction was diluted with water and the aqueous phase separated. The organic phase was washed with brine, dried with $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash column chromatography, eluting with the indicated solvent mixture to afford the desired product.

Conditions B

A flame-dried round-bottomed flask equipped with a stir bar was charged with $Ph_3SiOReO_3$[26] (0.05 eq.) followed by 0.2 M solution of propargylic alcohol (1.00 eq.) in freshly distilled Et_2O or THF. After overnight stirring at RT, the reaction was diluted with water and the aqueous phase separated. The organic phase was washed with brine, dried using sodium sulphate and concentrated *in vacuo*. The crude product was purified by flash column chromatography, eluting with the indicated solvent mixture to afford the desired product.

- 1-(p-tolyl)-3-(trimethylsilyl)prop-2-yn-1-ol

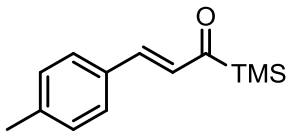


$C_{13}H_{18}OSi$
Molecular Weight: 218,3710

Following **step 1** starting with 4-methylbenzaldehyde (8 mmol) and ethynyltrimethylsilane (8 mmol). Flash chromatography: PE/EtOAc 95:5 Yield: 1.44g (82 %) as a colorless oil. The spectral data are consistent with the literature.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.43 (d, J = 8.1 Hz, 2H), 7.20 (d, J = 7.8 Hz, 2H), 5.42 (s, 1H), 2.37 (s, 3H), 2.17 (s, 1H), 0.21 (s, 9H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	138.4, 137.6, 129.4, 126.8, 105.2, 91.4, 65.0, 21.3, 0.0.

- (*E*)-3-(p-tolyl)-1-(trimethylsilyl)prop-2-en-1-one, **III.2**



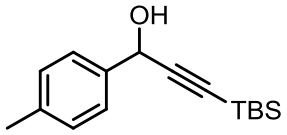
$C_{13}H_{18}OSi$
Molecular Weight: 218,3710

Following **step 2** (condition A) starting with 1-(p-tolyl)-3-(trimethylsilyl)prop-2-yn-1-ol (2.8 mmol).

Flash chromatography: PE/EtOAc 95:5. Yield: 0.48g (78 %) as an orange solid. The spectral data are consistent with the literature.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.55 – 7.38 (m, 3H), 7.21 (d, J = 8.0 Hz, 2H), 6.86 (d, J = 16.4 Hz, 1H), 2.38 (s, 3H), 0.32 (s, 9H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	236.4, 143.3, 141.1, 132.2, 130.7, 129.8, 128.4, 21.7, -1.8.

- 3-(*tert*-butyldimethylsilyl)-1-(p-tolyl)prop-2-yn-1-ol



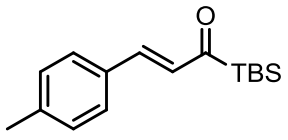
$C_{16}H_{24}OSi$
Molecular Weight: 260,4520

Following **step 1** starting with 4-methylbenzaldehyde (8 mmol) and *tert*-butyl(ethynyl)dimethylsilane (8 mmol).

Flash chromatography: EP/EtOAc 90:10. Yield: 2.06g (98 %) as a colorless oil. The spectral data are consistent with the literature.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.45 (d, J = 7.8 Hz, 2H), 7.19 (d, J = 7.8 Hz, 2H), 5.43 (s, 1H), 2.37 (s, 3H), 2.24 (s, 1H), 0.97 (s, 9H), 0.32 – -0.06 (s, 6H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	138.3, 137.7, 129.4, 126.9, 105.9, 89.8, 65.0, 26.2, 21.3, 16.7, -4.5.

- (*E*)-1-(*tert*-butyldimethylsilyl)-3-(p-tolyl)prop-2-en-1-one,



$C_{16}H_{24}OSi$
Molecular Weight: 260,4520

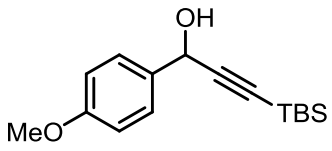
III.11a

Following **step 2** (condition A) starting with 3-(*tert*-butyldimethylsilyl)-1-(p-tolyl)prop-2-yn-1-ol (4.41 mmol).

Flash chromatography: PE/Et_2O 95:5 Yield: 0.61g (53 %) as an orange solid. The spectral data are consistent with the literature.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.46 (d, J = 8.1 Hz, 2H), 7.36 (d, J = 16.2 Hz, 1H), 7.20 (d, J = 7.9 Hz, 2H), 6.99 (d, J = 16.1 Hz, 1H), 2.38 (s, 3H), 0.97 (s, 9H), 0.30 (s, 6H).
^{13}C NMR (δ, ppm) (75 MHz, C_6D_6)	232.9, 140.6, 140.4, 132.8, 130.5, 129.9, 128.6, 26.8, 21.3, 17.0, -6.0.

- 3-(*tert*-butyldimethylsilyl)-1-(4-methoxyphenyl)prop-2-yn-1-ol

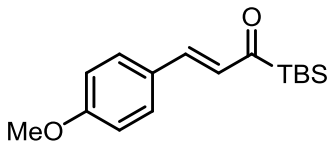


$C_{16}H_{24}O_2Si$
Molecular Weight: 276,4510

Following **step 1** starting with 4-methoxybenzaldehyde (2 mmol) and *tert*-butyl(ethynyl)dimethylsilane (2 mmol). Flash chromatography: PE/Et_2O 75:25. Yield: 0.43g (79 %) as a colorless oil.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.48 (d, J = 8.3 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 5.41 (s, 1H), 3.81 (s, 3H), 2.17 (s, 1H), 0.96 (s, 9H), 0.14 (d, J = 1.4 Hz, 6H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	159.8, 132.9, 128.3, 114.0, 106.0, 89.8, 64.8, 55.4, 26.2, 16.7, -4.5.
MS (HRMS APCI)	Calcd for $[M+H-H_2O]^+$ Found: 259.15117 $C_{16}H_{23}OSi$ 259.15127

- (*E*)-1-(*tert*-butyldimethylsilyl)-3-(4-methoxyphenyl)prop-2-en-1-one, **III.11b**

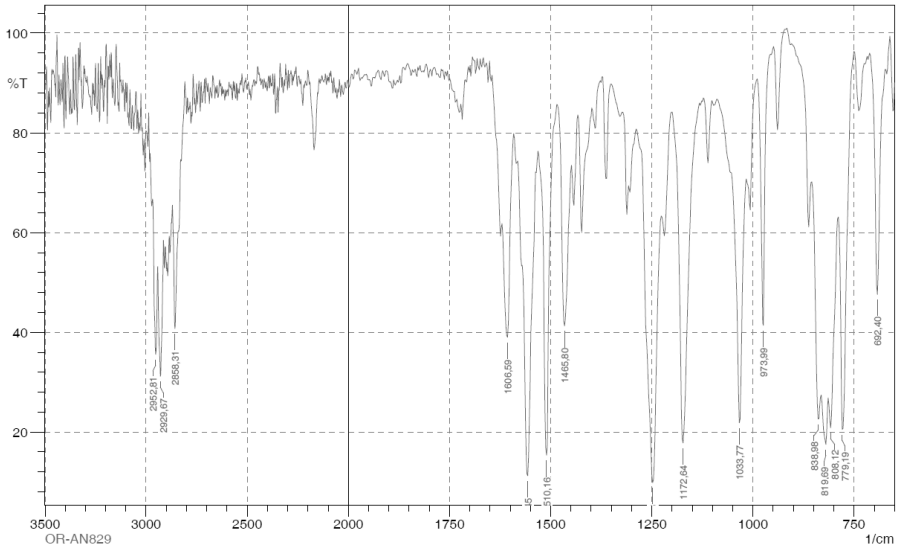


$C_{16}H_{24}O_2Si$
Molecular Weight: 276,4510

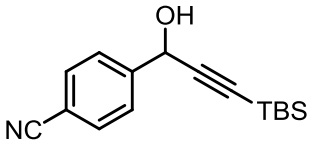
Following **step 2** (condition B) starting with 3-(*tert*-butyldimethylsilyl)-1-(4-methoxyphenyl)prop-2-yn-1-ol (1.0 mmol).

Flash chromatography: PE/Et_2O 95:5. Yield: 0.08g (27 %) as a yellow solid.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.52 (d, J = 8.7 Hz, 2H), 7.35 (d, J = 16.2 Hz, 1H), 6.98 – 6.87 (m, 3H), 3.85 (s, 3H), 0.97 (s, 9H), 0.29 (s, 6H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	234.9, 161.7, 140.7, 130.2, 129.4, 127.7, 114.5, 55.6, 26.8, 16.9, -5.9.
MS (HRMS APCI)	Calcd for $[M+H]^+$ Found: 277.16182 $C_{16}H_{25}O_2Si$ 277.16183
IR (cm^{-1}, thin film)	1607 (C=C), 1556 (C=O), 1248 (Me-OAr), 1034 (Si-Me ; Si-*t*Bu), 974 (C=C).



- 4-(3-(*tert*-butyldimethylsilyl)-1-hydroxyprop-2-yn-1-yl)benzonitrile



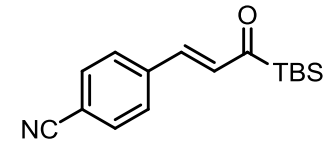
$C_{16}H_{21}NOSi$
Molecular Weight: 271,4350

Following **step 1** starting with 4-formylbenzonitrile (2 mmol) and *tert*-butyl(ethynyl)dimethylsilane (2 mmol).

Flash chromatography: EP/Et_2O 80:20. Yield: 0.42g (77 %) as a white off solid.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.67 (s, 4H), 5.51 (s, 1H), 2.37 (s, 1H), 0.94 (s, 9H), 0.14 (s, 6H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	145.5, 132.5, 127.4, 118.8, 112.2, 104.4, 91.4, 64.3, 26.2, 16.7, -4.6.
MS (HRMS ESI)	Calcd for $[M+H]^+$ Found: 272.14647 $C_{16}H_{22}ONSi$ 272.14652

- (*E*)-4-(3-(*tert*-butyldimethylsilyl)-3-oxoprop-1-en-1-yl)benzonitrile, **III.11c**

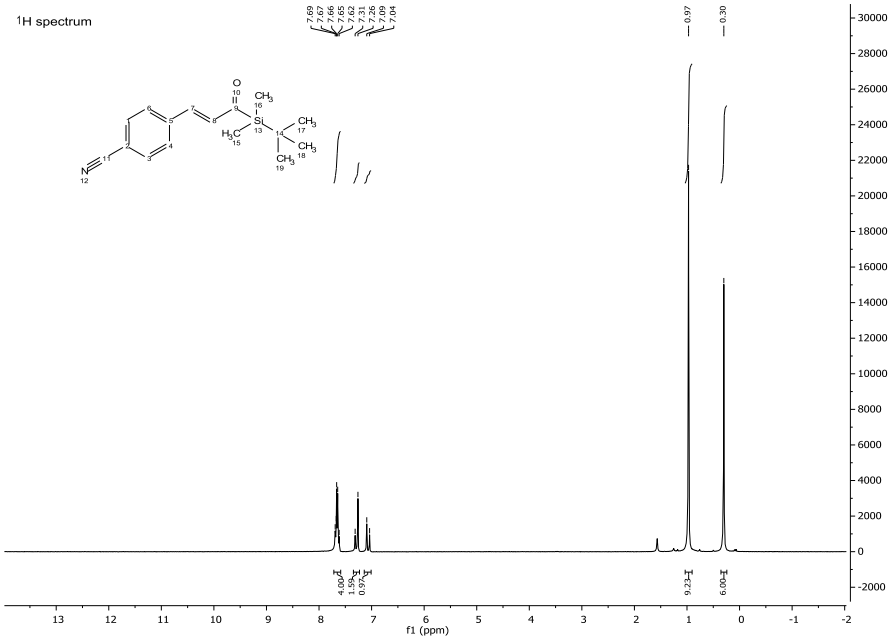


$C_{16}H_{21}NOSi$
Molecular Weight: 271,4350

Following **step 2** (condition A) starting with 4-(3-(*tert*-butyldimethylsilyl)-1-hydroxyprop-2-yn-1-yl)benzonitrile (1.43 mmol).

Flash chromatography: PE/Et_2O 90:10. Yield: 0.12g (31 %) as a red solid.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.74 – 7.57 (m, 4H), 7.29 (d, J = 16.0 Hz, 1H), 7.07 (d, J = 16.1 Hz, 1H), 0.97 (s, 9H), 0.30 (s, 6H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	235.6, 139.6, 137.2, 132.8, 132.7, 128.8, 118.5, 113.5, 26.7, 17.0, -6.2.
MS (HRMS ESI)	Calcd for $[M+H]^+$ Found: 272.14632 $C_{16}H_{22}ONSi$ 272.14652
IR (cm^{-1}, thin film)	2226 (C≡N), 1637 (C=C), 1568 (C=O), 1037 (Si-Me; Si-*t*Bu).


1H spectrum
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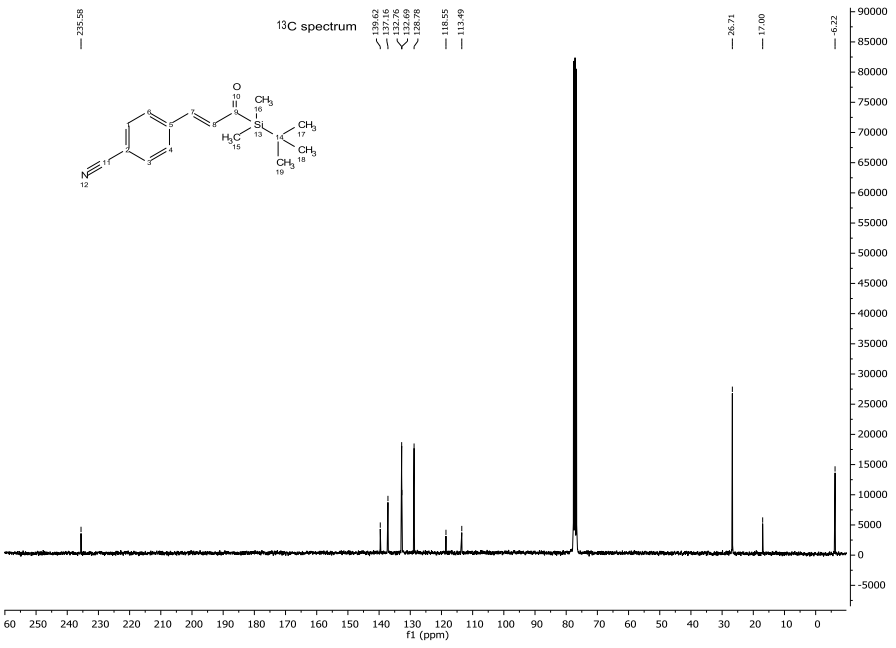
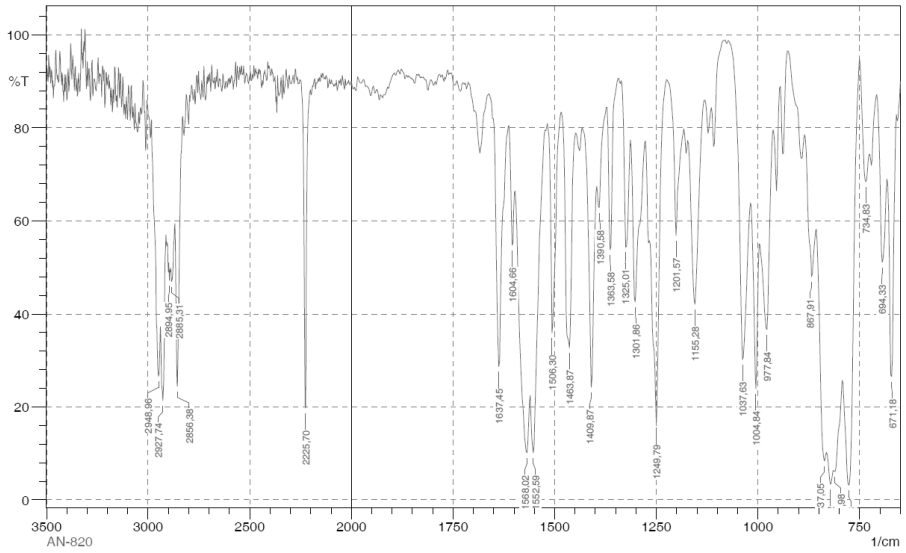
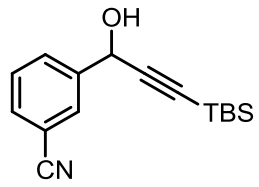
7.67
7.66
7.65
7.62
7.31
7.26
7.09
7.04
0.97
0.30
4.00
1.95
1.00
9.23
6.00
f1 (ppm)


13C spectrum
235.58
139.62
137.16
132.76
132.60
128.78
118.55
113.49
26.71
17.00
-6.22
f1 (ppm)



- 3-(3-(*tert*-butyldimethylsilyl)-1-hydroxyprop-2-yn-1-yl)benzonitrile

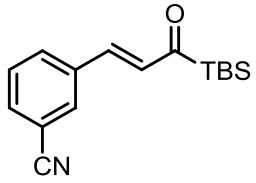


$C_{16}H_{21}NOSi$
Molecular Weight: 271,4350

Following **step 1** starting with 3-formylbenzonitrile (2 mmol) and *tert*-butyl(ethynyl)dimethylsilane (2 mmol). Flash chromatography: PE/Et_2O 80:20. Yield: 0.47g (85 %) as a colourless oil.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.89 – 7.83 (m, 1H), 7.83 – 7.75 (m, 1H), 7.62 (dt, J = 7.9, 1.3 Hz, 1H), 7.49 (t, J = 7.8 Hz, 1H), 5.50 (s, 1H), 2.39 (s, 1H), 0.95 (s, 9H), 0.15 (s, 6H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	142.0, 132.0, 131.2, 130.4, 129.5, 118.7, 112.7, 104.4, 91.5, 64.0, 26.2, 16.6, -4.6.
MS (HRMS ESI)	Calcd for $[M+Na]^+$ Found: 294.12840 $C_{16}H_{21}ONNaSi$ 294.12846

- (*E*)-3-(3-(*tert*-butyldimethylsilyl)-3-oxoprop-1-en-1-yl)benzonitrile, **III.11d**



$C_{16}H_{21}NOSi$
Molecular Weight: 271,4350

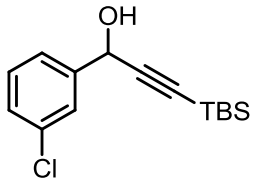
Following **step 2** (condition A) starting with 3-(3-(*tert*-butyldimethylsilyl)-1-hydroxyprop-2-yn-1-yl)benzonitrile (1.7 mmol).

Flash chromatography: PE/EtOAc 90:10

Yield: 0.27g (59 %) as an orange oil.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.82 (t, J = 1.7 Hz, 1H), 7.76 (dt, J = 7.9, 1.5 Hz, 1H), 7.65 (dt, J = 7.8, 1.4 Hz, 1H), 7.51 (t, J = 7.8 Hz, 1H), 7.26 (d, J = 16.1 Hz, 1H), 7.05 (d, J = 16.1 Hz, 1H), 0.97 (s, 9H), 0.30 (s, 6H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	235.4, 136.8, 136.4, 133.3, 132.4, 132.0, 131.6, 129.9, 118.3, 113.5, 26.7, 17.0, -6.2.
MS (HRMS APCI)	Calcd for $[M+H]^+$ Found: 272.14632 $C_{16}H_{22}ONSi$ 272.14652

- 3-(*tert*-butyldimethylsilyl)-1-(3-chlorophenyl)prop-2-yn-1-ol



$C_{15}H_{21}ClOSi$
Molecular Weight: 280,8670

Following **step 1** starting with 3-chlorobenzaldehyde (2 mmol) and *tert*-butyl(ethynyl)dimethylsilane (2 mmol).

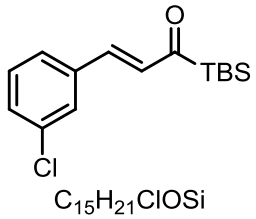
Flash chromatography: PE/EtOAc 95:5.

Yield: 0.50g (89 %) as a colorless oil.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.60 – 7.52 (m, 1H), 7.48 – 7.38 (m, 1H), 7.36 – 7.27 (m, 2H), 5.44 (s, 1H), 2.12 (s, 1H), 0.96 (s, 9H), 0.15 (s, 6H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	142.4, 134.5, 130.0, 128.6, 127.1, 125.0, 105.0, 90.8, 64.5, 26.2, 16.7, -4.6.

MS (HRMS APCI)	Calcd for $[M+H-H_2O]^+$ Found: 263.10179 $C_{15}H_{20}ClSi$ 263.10173

- (*E*)-1-(*tert*-butyldimethylsilyl)-3-(3-chlorophenyl)prop-2-en-1-one, **III.11e**



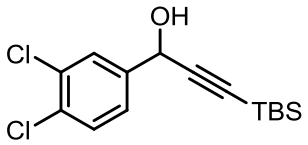
$C_{15}H_{21}ClOSi$
Molecular Weight: 280,8670

Following **step 2** (condition A) starting with 3-(*tert*-butyldimethylsilyl)-1-(3-chlorophenyl)prop-2-yn-1-ol (1.79 mmol).

Flash chromatography: PE/EtOAc 97:3. Yield: 0.32g (64 %) as an orange oil.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.52 (t, J = 1.8 Hz, 1H), 7.45 – 7.39 (m, 1H), 7.37 – 7.30 (m, 2H), 7.26 (d, J = 16.1 Hz, 1H), 7.00 (d, J = 16.1 Hz, 1H), 0.96 (s, 9H), 0.29 (s, 6H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	235.5, 138.6, 137.0, 135.0, 131.7, 130.3, 130.3, 128.1, 126.7, 26.7, 16.9, -6.1.
MS (HRMS APCI)	Calcd for $[M+H]^+$ Found: 281.11255 $C_{15}H_{22}OClSi$ 281.11230

- 3-(*tert*-butyldimethylsilyl)-1-(3,4-dichlorophenyl)prop-2-yn-1-ol



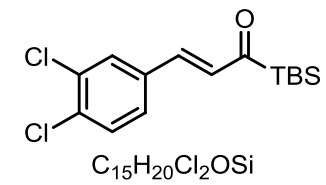
$C_{15}H_{20}Cl_2OSi$
Molecular Weight: 315,3090

Following **step 1** starting with 3,4-dichlorobenzaldehyde (3 mmol) and *tert*-butyl(ethynyl)dimethylsilane (3 mmol).

Flash chromatography: PE/Et_2O 97:3. Yield: 0.38g (38 %) as a colorless oil.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.66 (d, J = 2.0 Hz, 1H), 7.45 (d, J = 8.3 Hz, 1H), 7.38 (dd, J = 8.3, 2.1 Hz, 1H), 5.42 (s, 1H), 2.25 (bs, 1H), 0.95 (s, 9H), 0.14 (s, 6H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	140.6, 132.7, 132.5, 130.6, 128.9, 126.1, 104.6, 91.2, 63.9, 26.9, 16.7, -4.6.
MS (HRMS APCI)	Calcd for $[M+H]^+$ Found: 315.07314 $C_{15}H_{21}Cl_2OSi$ 315.07332

- (*E*)-1-(*tert*-butyldimethylsilyl)-3-(3,4-dichlorophenyl)prop-2-en-1-one, **III.11f**



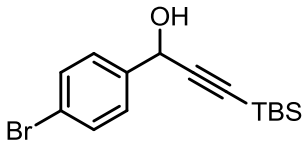
$C_{15}H_{20}Cl_2OSi$
Molecular Weight: 315,3090

Following step 2 (condition A) starting with 3-(*tert*-butyldimethylsilyl)-1-(3,4-dichlorophenyl)prop-2-yn-1-ol (1.13 mmol).

Flash chromatography: PE/Et_2O 95:5. Yield: 0.22g (63 %) as an orange oil.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.62 (d, J = 2.0 Hz, 1H), 7.46 (d, J = 8.3 Hz, 1H), 7.37 (dd, J = 8.3, 2.0 Hz, 1H), 7.21 (d, J = 16.1 Hz, 1H), 6.98 (d, J = 16.2 Hz, 1H), 0.96 (s, 9H), 0.29 (s, 6H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	235.4, 137.2, 135.2, 134.3, 133.4, 131.7, 131.0, 129.9, 127.5, 26.7, 17.0, -6.2.
MS (HRMS APCI)	Calcd for $[M+H]^+$ Found: 315.07327 $C_{15}H_{21}OCl_2Si$ 315.07332

- 1-(4-bromophenyl)-3-(*tert*-butyldimethylsilyl)prop-2-yn-1-ol



$C_{15}H_{21}BrOSi$
Molecular Weight: 325,3210

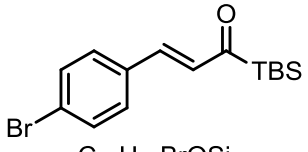
Following **step 1** starting with 4-bromobenzaldehyde (3 mmol) and *tert*-butyl(ethynyl)dimethylsilane (3 mmol).

Flash chromatography: PE/EtOAc 95:5.

Yield: 0.55g (56 %) as a colorless oil.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.54 – 7.48 (m, 2H), 7.46 – 7.38 (m, 2H), 5.42 (s, 1H), 2.22 (brs, 1H), 0.95 (s, 9H), 0.14 (s, 6H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	139.5, 131.8, 128.6, 122.5, 105.2, 90.6, 64.5, 26.2, 16.7, -4.6.
MS (HRMS APCI)	Calcd for $[M+H]^+$ Found: 325.06110 $C_{15}H_{22}BrOSi$ 325.06178

- (*E*)-3-(4-bromophenyl)-1-(*tert*-butyldimethylsilyl)prop-2-en-1-one, **III.11g**



$C_{15}H_{21}BrOSi$
Molecular Weight: 325,3210

Following **step 2** (condition A) starting with 1-(4-bromophenyl)-3-(*tert*-butyldimethylsilyl)prop-2-yn-1-ol (1.68 mmol).

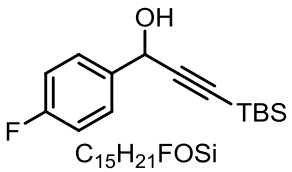
Flash chromatography: PE/Et_2O 97:3

Yield: 0.31g (56 %) as an orange solid.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.56 – 7.48 (m, 2H), 7.45 – 7.38 (m, 2H), 7.27 (d, J = 16.2 Hz, 1H), 7.00 (d, J = 16.1 Hz, 1H), 0.96 (s, 9H), 0.29 (s, 6H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	235.4, 138.9, 134.0, 132.3, 131.1, 129.8, 124.7, 26.7, 16.9, -6.1.

MS (HRMS ESI)	Calcd for $[M+H]^+$ Found: 325.06203 $C_{15}H_{22}OBrSi$ 325.06178

- 3-(*tert*-butyldimethylsilyl)-1-(4-fluorophenyl)prop-2-yn-1-ol

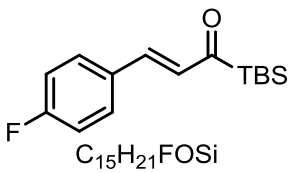


$C_{15}H_{21}FOSi$
Molecular Weight: 264,4154

Following **step 1** starting with 4-fluorobenzaldehyde (3 mmol) and *tert*-butyl(ethynyl)dimethylsilane (3 mmol). Flash chromatography: PE/Et_2O 93:7. Yield: 0.48g (60 %) as a colorless oil.

^1H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.65 – 7.46 (m, 2H), 7.13 – 6.99 (m, 2H), 5.44 (s, 1H), 2.20 (brs, 1H), 0.95 (s, 9H), 0.14 (s, 6H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	162.8 (d, J = 246.8 Hz), 136.4 (d, J = 3.3 Hz), 128.7 (d, J = 8.3 Hz), 115.6 (d, J = 21.7 Hz), 105.5, 90.4, 64.5, 26.2, 16.7, -4.6.
^{19}F NMR (δ, ppm) (282MHz, $CDCl_3$)	-113.84.
MS (HRMS ESI)	Calcd for $[M+H-H_2O]^+$ Found: 247.13127 $C_{15}H_{20}FSi$: 247.13128

- (*E*)-1-(*tert*-butyldimethylsilyl)-3-(4-fluorophenyl)prop-2-en-1-one, **III.11h**

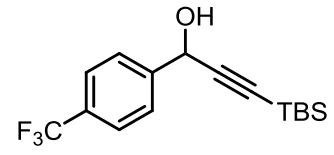


$C_{15}H_{21}FOSi$
Molecular Weight: 264,4154

Following **step 2** (condition A) starting with 3-(*tert*-butyldimethylsilyl)-1-(4-fluorophenyl)prop-2-yn-1-ol (1.81 mmol). Flash chromatography: PE/EtOAc 95:5. Yield: 0.19g (40 %) as an orange solid.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.61 – 7.48 (m, 2H), 7.32 (d, J = 16.1 Hz, 1H), 7.14 – 7.03 (m, 2H), 6.95 (dd, J = 16.1, 0.6 Hz, 1H), 0.97 (s, 9H), 0.29 (s, 6H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	235.2, 164.1 (d, J = 251.6 Hz), 139.2, 131.3 (d, J = 3.4 Hz), 130.7 (d, J = 2.4 Hz), 130.3 (d, J = 8.5 Hz), 116.2 (d, J = 22.0 Hz), 26.8, 16.9, -6.0.
^{19}F NMR (δ, ppm) (282MHz, $CDCl_3$)	-109.34.
MS (HRMS APCI)	Calcd for $[M+H]^+$ Found: 265.14175 $C_{15}H_{22}OFSi$ 265.14185

- 3-(*tert*-butyldimethylsilyl)-1-(4-(trifluoromethyl)phenyl)prop-2-yn-1-ol



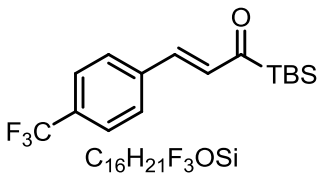
$C_{16}H_{21}F_3OSi$
Molecular Weight: 314,4232

Following **step 1** starting with 4-(trifluoromethyl)benzaldehyde (3 mmol) and *tert*-butyl(ethynyl)dimethylsilane (3 mmol).

Flash chromatography: PE/EtOAc 95:5. Yield: 0.69g (72 %) as a pale greenish oil.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.74 – 7.56 (m, 4H), 5.51 (s, 1H), 2.40 (bs, 1H), 0.95 (s, 9H), 0.15 (s, 6H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	144.3, 130.6 (q, J = 32.5 Hz), 127.1, 125.6 (q, J = 3.8 Hz), 124.2 (q, J = 272.1 Hz), 104.9, 91.0, 64.4, 26.2, 16.7, -4.6.
^{19}F NMR (δ, ppm) (282MHz, $CDCl_3$)	-62.56.
MS (HRMS APCI)	Calcd for $[M+H]^+$ Found: 315.13833 $C_{16}H_{22}OF_3Si$ 315.13865

- (*E*)-1-(*tert*-butyldimethylsilyl)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one, **III.11i**



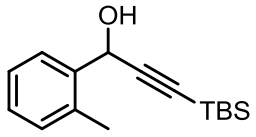
$C_{16}H_{21}F_3OSi$
Molecular Weight: 314,4232

Following **step 2** (condition A) starting with 3-(*tert*-butyldimethylsilyl)-1-(4-(trifluoromethyl)phenyl)prop-2-yn-1-ol (2.18 mmol).

Flash chromatography: PE/Et_2O 95:5. Yield: 0.35g (51 %) as an orange solid.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.65 (s, 4H), 7.34 (d, J = 16.2 Hz, 1H), 7.07 (d, J = 16.2 Hz, 1H), 0.97 (s, 9H), 0.30 (s, 6H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	235.6, 138.6, 138.1, 132.4, 131.9 (q, J = 32.6 Hz), 128.6, 126.0 (q, J = 3.3 Hz), 124.0 (q, J = 272.3 Hz), 26.7, 17.0, -6.1.
^{19}F NMR (δ, ppm) (282MHz, $CDCl_3$)	-62.85.
MS (HRMS ESI)	Calcd for $[M+H]^+$ Found: 315.13873 $C_{16}H_{22}F_3OSi$: 315.13865

- 3-(*tert*-butyldimethylsilyl)-1-(o-tolyl)prop-2-yn-1-ol



$C_{16}H_{24}OSi$
Molecular Weight: 260,4520

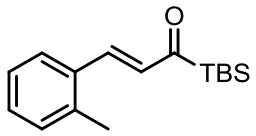
Following **step 1** starting with 2-methylbenzaldehyde (3 mmol) and *tert*-butyl(ethynyl)dimethylsilane (3 mmol).

Flash chromatography: PE/Et_2O 95:5. Yield: 0.49g (63 %) as a colorless oil.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.71 – 7.63 (m, 1H), 7.28 – 7.21 (m, 2H), 7.21 – 7.16 (m, 1H), 5.61 (s, 1H), 2.45 (s, 3H), 2.06 (bs, 1H), 0.95 (s, 9H), 0.14 (s, 3H), 0.14 (s, 3H).

^{13}C NMR (δ, ppm)	138.2, 136.3, 130.9, 128.5, 126.7, 126.3, 105.6, 90.0, 63.1,
(75 MHz, $CDCl_3$)	26.2, 19.1, 16.7, -4.5.
MS	Calcd for $[M+Na]^+$ Found: 283.14885
(HRMS ESI)	$C_{16}H_{24}ONaSi$: 283.14886

- (*E*)-1-(*tert*-butyldimethylsilyl)-3-(o-tolyl)prop-2-en-1-one, **III.11j**

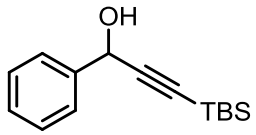


$C_{16}H_{24}OSi$
Molecular Weight: 260,4520

Following **step 2** (condition A) starting with 3-(*tert*-butyldimethylsilyl)-1-(o-tolyl)prop-2-yn-1-ol (1.88 mmol).
Flash chromatography: PE/Et_2O 97:3.
Yield: 0.24g (48 %) as an orange oil.

^{1}H NMR (δ, ppm)	7.70 (d, J = 16.1 Hz, 1H), 7.59 (dd, J = 7.9, 1.6 Hz, 1H),
(300 MHz, $CDCl_3$)	7.32 – 7.26 (m, 1H), 7.25 – 7.18 (m, 2H), 6.91 (d, J = 16.1 Hz, 1H), 2.45 (s, 3H), 0.98 (s, 9H), 0.32 (s, 6H).
^{13}C NMR (δ, ppm)	235.7, 139.4, 138.3, 133.9, 132.9, 131.0, 130.3, 126.5,
(75 MHz, $CDCl_3$)	126.2, 26.8, 20.0, 16.9, -5.8.
MS	Calcd for $[M+H]^+$ Found: 261.16696
(HRMS APCI)	$C_{16}H_{25}OSi$: 261.16692

- 3-(*tert*-butyldimethylsilyl)-1-phenylprop-2-yn-1-ol



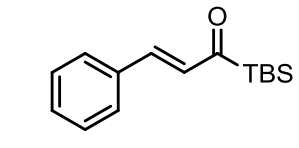
$C_{15}H_{22}OSi$
Molecular Weight: 246,4250

Following **step 1** starting with benzaldehyde (2 mmol) and *tert*-butyl(ethynyl)dimethylsilane (2 mmol).
Flash chromatography: PE/Et_2O 95:5.
Yield: 0.23g (47 %) as a colorless oil.
The spectral data are consistent with the literature.[27]

^{1}H NMR (δ, ppm)	7.60 – 7.51 (m, 2H), 7.44 – 7.29 (m, 3H), 5.47 (s, 1H),
(300 MHz, $CDCl_3$)	2.10 (brs, 1H), 0.95 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H).

^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	140.6, 128.7, 128.5, 126.9, 105.7, 90.2, 65.2, 26.2, 16.7, -4.5.

- (*E*)-1-(*tert*-butyldimethylsilyl)-3-phenylprop-2-en-1-one, **III.11k**



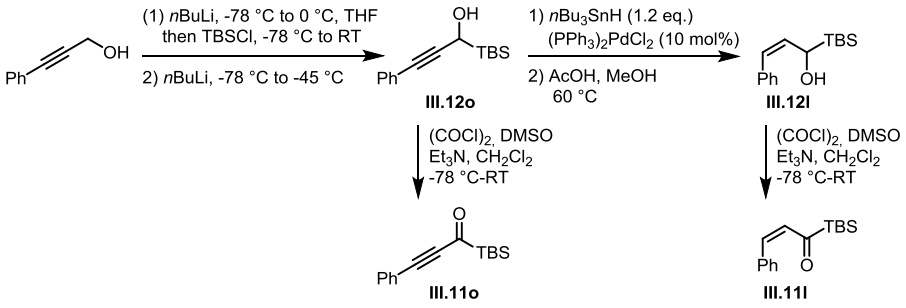
$C_{15}H_{22}OSi$
Molecular Weight: 246,4250

Following **step 2** (condition A) starting with 3-(*tert*-butyldimethylsilyl)-1-phenylprop-2-yn-1-ol (0.93 mmol). Flash chromatography: PE/Et_2O 95:5. Yield: 0.12g (51 %) as an orange solid. The spectral data are consistent with the literature.[28]

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.63 – 7.50 (m, 2H), 7.49 – 7.29 (m, 4H), 7.03 (d, J = 16.2 Hz, 1H), 0.97 (s, 9H), 0.30 (s, 6H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	235.7, 140.8, 135.1, 131.3, 130.5, 129.1, 128.5, 26.8, 17.0, -5.9.

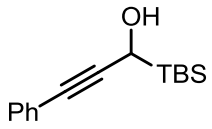
2.4.6 Synthesis of α,β-unsaturated acylsilane by a Retro-Brook rearrangement-based strategy

The acylsilanes **III.11l** and **III.11o** were synthesised from 3-phenyl-2-propyn-1-ol in several steps according to the literature.[29]



Step 1 : Racemic 1-(*tert*-butyldimethylsilyl)-3-phenylprop-2-yn-1-ol **III.12o** was synthesized from the corresponding propargylic alcohol, according to the literature.[29a]

To a solution of 3-phenylprop-2-yn-1-ol (1 eq.) in THF (1.0 mL/mmol) was added *n*BuLi in hexanes (1.2 eq., 1.6 M solution) at -78 °C, and the mixture was stirred at 0 °C for 30 minutes. To the solution was added a solution of TBSCl (1.1 eq.) in THF (1.0 mL/mmol) at -78 °C. After stirring at RT for 4 h, *n*BuLi in hexanes (1.3 eq., 1.6 M solution) was added dropwise to the solution at -78 °C, and the mixture stirred at -45 °C for 2 h. The reaction was quenched by 10% AcOH in THF at -78 °C. The mixture was extracted with Et_2O, and the organic layer was washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$. The solvent was evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel to give racemic title compound.



$C_{15}H_{22}OSi$

Molecular Weight: 246,4250

Following **step 1** starting with 3-phenylprop-2-yn-1-ol (21.4 mmol).

Flash chromatography: PE/EtOAc 95:5.

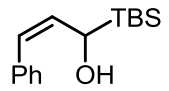
Yield: 2.48g (47%) as a colorless oil.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.43 – 7.32 (m, 2H), 7.32 – 7.28 (m, 3H), 4.46 (s, 1H), 1.70 (brs, 1H), 1.04 (s, 9H), 0.19 (s, 3H), 0.17 (s, 3H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	131.5, 128.4, 128.1, 123.6, 90.7, 88.2, 55.2, 27.0, 17.2, -7.6, -8.3.
MS (HRMS APCI)	Calcd for $[M+H]^+$ Found: 247.1512 $C_{15}H_{23}OSi$: 247.1513

Step 2: Racemic (*Z*)-1-(*tert*-butyldimethylsilyl)-3-phenylprop-2-en-1-ol **III.12l** was synthetized from the racemic 1-(*tert*-

butyldimethylsilyl)-3-phenylprop-2-yn-1-ol **III.12o** by a palladium-catalysed hydrostannylation, followed by a protodestannylation in acidic media, according to the literature.[29b]

A Schlenk tube was charged under an argon atmosphere with dichlorobis(triphenylphosphine)palladium(II) (0.1 eq.), freshly distilled THF (3.0 mL/mmol) and 1-(*tert*-butyldimethylsilyl)-3-phenylprop-2-yn-1-ol (1 eq.). Tributyltin hydride (1.2 equiv.) was added and the reaction mixture was stirred overnight at room temperature. The solvent was evaporated *in vacuo* giving a crude residue, which was purified by flash column chromatography on silica gel. The resulting (*E*)-1-(*tert*-butyldimethylsilyl)-3-phenyl-3-(tributylstannyl)prop-2-en-1-ol (1 eq.) was dissolved in methanol (5 mL/mmol). Acetic acid (2.5 mL/mmol) was added and the mixture was stirred overnight at 60 °C. The reaction mixture was concentrated *in vacuo*. The residue was exposed to aqueous $NaHCO_3$ and was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated *in vacuo* to give a crude residue, which was purified by flash column chromatography on silica gel yielding the corresponding racemic (*Z*)-1-(*tert*-butyldimethylsilyl)-3-phenylprop-2-en-1-ol.



$C_{15}H_{24}OSi$
Molecular Weight: 248,4410

Following **step 2** starting with 1-(*tert*-butyldimethylsilyl)-3-phenylprop-2-yn-1-ol (3 mmol).

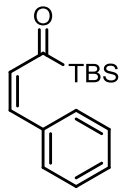
Flash chromatography: PE/EtOAc 97:3. Yield: 0.29 g (39%) as a colorless oil.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.38 – 7.29 (m, 2H), 7.29 – 7.19 (m, 3H), 6.44 (d, J = 11.7 Hz, 1H), 5.84 (dd, J = 11.7, 11.0 Hz, 1H), 4.81 (dd, J = 11.1, 1.3 Hz, 1H), 1.37 (s, 1H), 0.97 (s, 9H), 0.10 (s, 3H), -0.00 (s, 3H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	137.2, 133.8, 128.8, 128.3, 128.3, 127.0, 62.3, 27.1, 17.3, -6.9, -8.5.
MS (HRMS ESI)	Calcd for $[M+H-H_2O]^+$ Found: 231.15645. $C_{15}H_{23}OSi$: 231.15635

Step 3: The oxidation of the racemic alcohols was carried out according to the Swern reaction conditions.[29a]

A solution of oxalyl chloride (1.1 eq.) in freshly distilled CH_2Cl_2 (2.0 mL/mmol) was cooled to −78 °C, and DMSO (2.2 eq.) was carefully added under nitrogen atmosphere. After stirring for 15 min, a solution of alcohol (1.0 eq.) in CH_2Cl_2 (1.0 mL/mmol) and Et_3N (5.0 eq.) were added successively. The cooling bath was removed, and the reaction mixture was allowed to warm to room temperature and stirred for 2 h. The solvent was removed under reduced pressure, and the residue was extracted with ethyl acetate. The extract was washed with a saturated aqueous Na_2CO_3 solution, brine, and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the crude products were purified by flash column chromatography with the indicated eluents to yield the acylsilanes.

- (*Z*)-1-(*tert*-butyldimethylsilyl)-3-phenylprop-2-en-1-one, **III.11l**

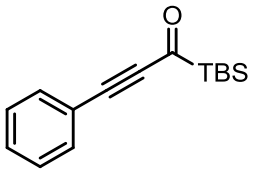


$C_{15}H_{22}OSi$
Molecular Weight: 246,4250

Following **step 3** starting with (*Z*)-1-(*tert*-butyldimethylsilyl)-3-phenylprop-2-en-1-ol (1.2 mmol).
Flash chromatography: PE/EtOAc 97:3. Yield: 0.22g (75%) as an orange oil.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.59 – 7.53 (m, 2H), 7.42 – 7.33 (m, 4H), 7.02 (d, J = 16.2 Hz, 1H), 0.97 (s, 9H), 0.30 (s, 6H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	235.5, 140.8, 135.0, 131.1, 130.5, 129.0, 128.4, 26.7, 16.9, -6.0.
MS (HRMS APCI)	Calcd for $[M+H]^+$ Found: 247.15123 $C_{15}H_{23}OSi$: 247.15127

- 1-(*tert*-butyldimethylsilyl)-3-phenylprop-2-yn-1-one, **III.11o**



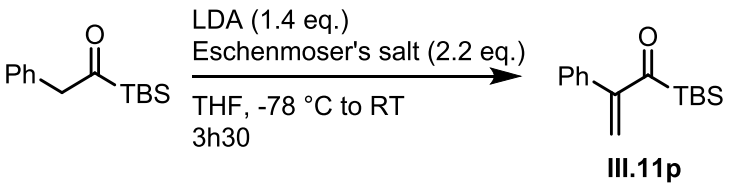
$C_{15}H_{20}OSi$
Molecular Weight: 244,4090

Following **step 3** starting with 1-(*tert*-butyldimethylsilyl)-3-phenylprop-2-yn-1-ol (2.0 mmol).
Flash chromatography: PE. Yield: 340 mg (70%) of yellow solid.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.58 – 7.55 (m, 2H), 7.48 – 7.36 (m, 3H), 1.02 (s, 9H), 0.31 (s, 6H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	225.6, 132.9, 130.8, 128.8, 120.7, 99.9, 92.0, 26.6, 17.2, -7.20.
MS (HRMS APCI)	Calcd for $[M+H]^+$ Found: 245.1355 $C_{15}H_{21}OSi$: 245.1356

2.4.7 Synthesis of β-unsubstituted enoylacylsilane **III.11p** with Eschenmoser's salt

The acylsilane was synthesised in one step from the previously prepared 1-(*tert*-butyldimethylsilyl)-2-phenylethan-1-one according to the literature.[30]



III.11p

To a solution of diisopropylamine (1.4 eq.) in THF (3 mL.mmol^{-1} of amine) was added *n*BuLi (1.4 eq., 1.6M in hexanes). After stirring for 5 minutes, the solution was cooled to -78 °C. A solution of 1-(*tert*-butyldimethylsilyl)-2-phenylethan-1-one (1 eq.) in THF (3 mL.mmol^{-1}) was added. After 1h30 at -78 °C, the solution was added to a saturated solution of N,N-dimethylmethyleneammonium iodide (Eschenmoser's salt, 2.2 eq.) in THF at -78 °C *via* cannula. The solution was warmed to room temperature over 2h after which saturated aqueous NH_4Cl was added. The organic phase was discarded and the aqueous phase was washed twice with Et_2O. The organic phases were gathered, dried over Na_2SO_4, concentrated *in vacu*o and purified by flash column chromatography over silica gel to afford the pure product.

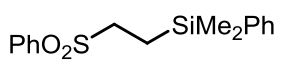
Following the procedure starting with 1-(*tert*-butyldimethylsilyl)-2-phenylethan-1-one (2 mmol).

Flash chromatography: PE/Et_2O 97:3. Yield: 0.29g (60%) as a colourless oil.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.41 – 7.30 (m, 3H), 7.26 (m, 2H), 6.09 (d, *J* = 0.6 Hz, 1H), 5.89 (d, *J* = 0.6 Hz, 1H), 0.96 (s, 9H), 0.24 (s, 6H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	238.1, 155.3, 136.4, 130.0, 128.3, 128.3, 125.3, 26.8, 17.2, -4.7.
MS (HRMS APCI)	Calcd for $[M+H]^+$ $C_{15}H_{23}OSi$ Found: 247.15123 247.15127

3 Synthesis and characterisation of the compounds obtained in Chapter II

3.1 Copper-catalysed β-silylation of vinylsulfone



$C_{16}H_{20}O_2SSi$
Molecular Weight: 304,4790

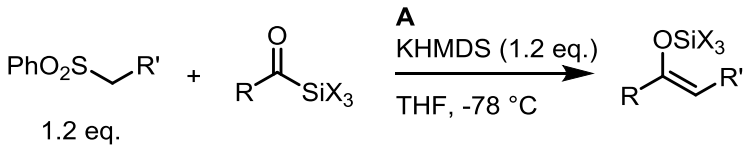
A Schlenk tube was charged with *I*PrCuCl (5 mol%), sodium *tert*-butoxide (6 mol%) and the phenyl vinyl sulfone (0.38 mmol, 1 eq.). The solids were dissolved with freshly distilled toluene (10 $mL.mmol^{-1}$) and the mixture was stirred for 5 minutes at room temperature before addition of Suginome's reagent (1 eq.). Anhydrous methanol (2 eq.) was finally added to the mixture which was further stirred at room temperature overnight. The mixture was filtered through a pad of silica gel eluting with Et_2O, the solvents were evaporated and the crude product was purified by flash chromatography affording the pure dimethyl(phenyl)(2-(phenylsulfonyl)ethyl)silane 0.10g (89%) as a colourless oil. The spectral data are consistent with the literature.[6]

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.94 – 7.81 (m, 2H), 7.72 – 7.50 (m, 3H), 7.46 – 7.29 (m, 5H), 3.05 – 2.88 (m, 2H), 1.21 – 1.08 (m, 2H), 0.29 (s, 6H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	138.7, 136.6, 133.6, 133.5, 129.6, 129.3, 128.3, 128.2, 52.5, 8.5, -3.3.

3.2 Regio- and stereoselective silyl enol ether formation

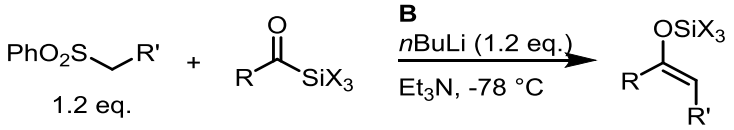
3.2.1 General conditions

- (*Z*)-Selective conditions (Conditions **A**)



A Schlenk tube was charged with a sulfone (1.2 eq.) and freshly distilled THF. After addition of KHMDS (0.5 M, 1.2 eq.) at room temperature, the mixture was cooled down to -78 °C. A saturated solution of acylsilane (0.2 mmol, 1 eq.) in THF was added dropwise and the reaction mixture was stirred overnight at -78 °C. The reaction was quenched by the addition of wet Et_3N (5 $mL.mmol^{-1}$), diluted with Et_2O and filtered through a pad of silica gel eluting with Et_2O. The volatiles were removed *in vacuo* and the crude mixture was purified by flash column chromatography eluting with the indicated solvent affording the silyl enol ethers with (*Z*) selectivity.

- (*E*)-selective conditions (Conditions **B**)

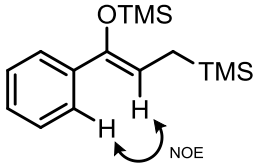


A Schlenk tube was charged with a sulfone (1.2 eq.) and commercial anhydrous Et_3N. After addition of *n*BuLi (0.5 M, 1.2 eq.) at room temperature, the mixture was cooled down to -78 °C. A saturated solution of acylsilane (0.2 mmol, 1 eq.) in Et_3N was added dropwise

and the reaction mixture was stirred overnight at -78 °C. The reaction was quenched by dilution with wet Et_2O and filtration through a pad of silica gel eluting with Et_2O. The volatiles were removed *in vacuo* and the crude mixture was purified by flash column chromatography eluting with the indicated solvent affording the silyl enol ethers (*E*)-selectively.

3.2.2 Scope of the reaction: cross experiments

- (*Z*)-trimethyl(3-phenyl-3-((trimethylsilyl)oxy)allyl)silane, **(*Z*)-II.40aa**

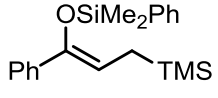


$C_{15}H_{26}OSi_2$
Molecular Weight: 278,5420

Following **conditions A** with trimethyl(2-(phenylsulfonyl)ethyl)silane **II.38a** and phenyl(trimethylsilyl)methanone **II.39a**. Flash chromatography: *n*-hexane. Yield: 41.8 mg (75%) as a colourless oil. > 99% (*Z*). The spectral data are consistent with the literature.[31]

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.47 – 7.40 (m, 2H), 7.36 – 7.14 (m, 3H), 5.27 (t, *J* = 8.4 Hz, 1H), 1.57 (d, *J* = 8.4 Hz, 2H), 0.14 (s, 9H), 0.05 (s, 9H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	147.9, 139.7, 128.0, 126.8, 125.1, 107.3, 16.9, 0.8, -1.5

- (*Z*)-(3-((dimethyl(phenyl)silyl)oxy)-3-phenylallyl)trimethylsilane **(*Z*)-II.40ab**



$C_{20}H_{28}OSi_2$
Molecular Weight: 340,6130

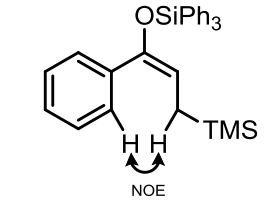
Following **conditions A** with trimethyl(2-(phenylsulfonyl)ethyl)silane **II.38a** and

(dimethyl(phenyl)silyl)(phenyl)methanone **II.39b**.

Flash chromatography: *n*hexane. Yield: 48.4 mg (71 %) as a colourless oil. 97% (*Z*).

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.62 – 7.57 (m, 2H), 7.44 – 7.32 (m, 5H), 7.25 – 7.12 (m, 3H), 5.25 (t, *J* = 8.5 Hz, 1H), 1.48 (d, *J* = 8.5 Hz, 2H), 0.35 (s, 6H), -0.03 (s, 9H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	147.6, 137.9, 137.9, 133.6, 129.7, 128.6, 127.9, 127.9, 127.4, 107.6, 16.9, -0.9, -1.6.

- (*E*)-trimethyl(3-phenyl-3-((triphenylsilyl)oxy)allyl)silane, **(*E*)-II.40aj**



$C_{30}H_{32}OSi_2$

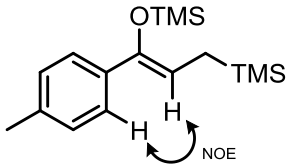
Molecular Weight: 464,7550

Following **conditions B** with trimethyl(2-(phenylsulfonyl)ethyl)silane, phenyl(triphenylsilyl)methanone.

Flash chromatography: PE/EtOAc 95:5. Yield: 79.2 mg (85%) as a colourless oil. 89% (*E*).

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	((*E*) isomer) 7.68 – 7.61 (m, 6H), 7.44 – 7.27 (m, 12H), 7.26 – 7.01 (m, 2H), 5.05 (t, *J* = 8.7 Hz, 1H), 1.36 (d, *J* = 8.7 Hz, 2H), -0.23 (s, 9H). ((*Z*) isomer) 7.68 – 7.61 (m, 6H), 7.44 – 7.27 (m, 12H), 7.26 – 7.01 (m, 2H), 5.14 (t, *J* = 8.6 Hz, 1H), 1.45 (d, *J* = 8.7 Hz, 2H), -0.05 (s, 9H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	((*E*) isomer) 147.8, 137.8, 135.7, 134.4, 130.2, 128.7, 128.0, 128.0, 127.5, 107.8, 17.1, -1.7. Signals for the (*Z*)-isomer were not detected.

- (*Z*)-trimethyl(3-(p-tolyl)-3-((trimethylsilyl)oxy)allyl)silane, **(*Z*)-II.40ac**

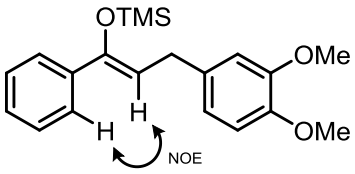


$C_{16}H_{28}OSi_2$
Molecular Weight: 292,5690

Following **conditions A** with trimethyl(2-(phenylsulfonyl)ethyl)silane **II.38a** and p-tolyl(trimethylsilyl)methanone **II.39c**. Flash chromatography: *n*hexane. Yield: 43.5 mg (75%) as a colourless oil. > 99% (*Z*).

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.34 (m, 2H), 7.15 – 6.93 (m, 2H), 5.22 (t, *J* = 8.4 Hz, 1H), 2.34 (s, 3H), 1.56 (d, *J* = 8.3 Hz, 2H), 0.14 (s, 9H), 0.05 (s, 9H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	148.1, 137.0, 136.7, 128.8, 125.2, 106.5, 21.3, 16.6, 0.9, -1.3.
MS (HRMS ESI)	Calcd for $[M+H]^+$ Found: 293.17510 $C_{16}H_{29}OSi_2$ 293.17514

- (*Z*)-((3-(3,4-dimethoxyphenyl)-1-phenylprop-1-en-1-yl)oxy)trimethylsilane, **(*Z*)-II.40ga**

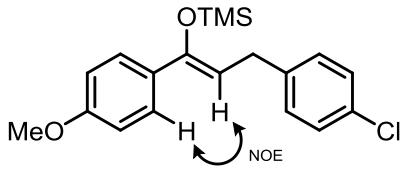


$C_{20}H_{26}O_3Si$
Molecular Weight: 342,5100

Following **conditions A** with 1,2-dimethoxy-4-(2-(phenylsulfonyl)ethyl)benzene **II.38g** and phenyl(trimethylsilyl)methanone **II.39a**. Flash chromatography: PE/EtOAc 80:20. Yield: 22.6 mg (33%) as a colourless oil. 85% (*Z*).

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	((*Z*) isomer) 7.54 – 7.47 (m, 2H), 7.35 – 7.24 (m, 3H), 6.80 (m, 3H), 5.42 (t, *J* = 7.2 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.52 (d, *J* = 7.1 Hz, 2H), 0.17 (s, 9H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	((*Z*) isomer) 149.7, 149.0, 147.4, 139.1, 134.2, 128.2, 127.8, 125.6, 120.2, 111.9, 111.4, 110.2, 56.1, 56.0, 32.1, 0.8.

- (Z)-((3-(4-chlorophenyl)-1-(4-methoxyphenyl)prop-1-en-1-yl)oxy)trimethylsilane, **(*Z*)-II.40bd**



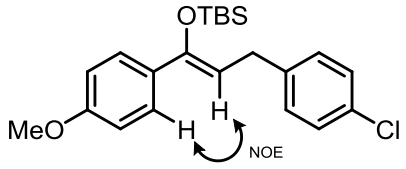
$C_{19}H_{23}ClO_2Si$
Molecular Weight: 346,9260

Following **conditions A** with 1-chloro-4-(2-(phenylsulfonyl)ethyl)benzene **II.38b** and (4-methoxyphenyl)(trimethylsilyl)methanone **II.39d**.

Flash chromatography: PE/EtOAc 93:7. Yield: 65.5 mg (94%) as a colourless oil. 86% (*Z*).

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	((*Z*) isomer) 7.48 – 7.41 (m, 2H), 7.32 – 7.25 (m, 2H), 7.21 (m, 2H), 6.90 – 6.83 (m, 2H), 5.27 (t, *J* = 7.2 Hz, 1H), 3.83 (s, 3H), 3.53 (d, *J* = 7.2 Hz, 2H), 0.17 (s, 9H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	((*Z*) isomer) 159.5, 150.1, 140.3, 131.6, 129.8, 128.6, 128.5, 127.0, 113.6, 107.6, 55.4, 31.8, 0.8.
MS (HRMS APCI)	Calcd for $[M+H]^+$ Found: 347.12274 $C_{19}H_{24}O_2ClSi$ 347.12286

- (*Z*)-*tert*-butyl((3-(4-chlorophenyl)-1-(4-methoxyphenyl)prop-1-en-1-yl)oxy)dimethylsilane **(*Z*)-II.40bf**



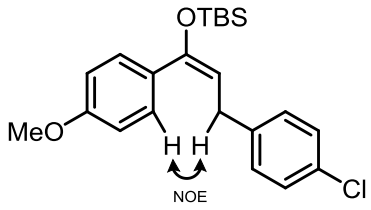
$C_{22}H_{29}ClO_2Si$
Molecular Weight: 389,0070

Following **conditions A** with 1-chloro-4-(2-(phenylsulfonyl)ethyl)benzene **II.38b** and (*tert*-butyldimethylsilyl)(4-methoxyphenyl)methanone **II.39f**.

Flash chromatography: PE/EtOAc 95:5. Yield: 67.7 mg (87%) as a colourless oil. 97% (*Z*).

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.43 – 7.36 (m, 2H), 7.26 – 7.16 (m, 4H), 6.89 – 6.80 (m, 2H), 5.13 (t, *J* = 7.2 Hz, 1H), 3.81 (s, 3H), 3.51 (d, *J* = 7.2 Hz, 2H), 1.00 (s, 9H), -0.03 (s, 6H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	159.4, 150.3, 140.4, 132.1, 131.6, 129.9, 128.5, 127.5, 113.4, 108.2, 55.4, 31.7, 26.0, 18.5, -3.7.
MS (HRMS ESI)	Calcd for $[M+H]^+$ Found: 389.156977 $C_{22}H_{30}O_2ClSi$ 389.16981

- (*E*)-*tert*-butyl((3-(4-chlorophenyl)-1-(4-methoxyphenyl)prop-1-en-1-yl)oxy)dimethylsilane



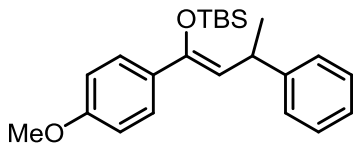
$C_{22}H_{29}ClO_2Si$
Molecular Weight: 389,0070

Following **conditions B** with 1-chloro-4-(2-(phenylsulfonyl)ethyl)benzene **II.38b** and (*tert*-butyldimethylsilyl)(4-methoxyphenyl)methanone **II.39f**.

Flash chromatography: PE/EtOAc 92:8. Yield: 65.1 mg (84%) as a colourless oil. 75% (*E*).

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.45 – 7.05 (m, 6H), 6.91 – 6.79 (m, 2H), 5.11 (t, *J* = 7.9 Hz, 1H), 3.80 (s, 3H), 3.40 (d, *J* = 7.9 Hz, 2H), 0.92 (s, 9H), 0.05 (s, 6H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	159.4, 151.2, 140.6, 131.6, 129.6, 129.6, 128.6, 127.5, 113.4, 107.5, 55.3, 33.3, 25.9, 18.3, -4.3.

- *tert*-butyl((1-(4-methoxyphenyl)-3-phenylbut-1-en-1-yl)oxy)dimethylsilane, **II.40cf**



$C_{23}H_{32}O_2Si$
Molecular Weight: 368,5920

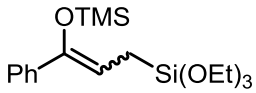
Following **conditions A** with ((2-phenylpropyl)sulfonyl)benzene **II.38c** and (*tert*-butyldimethylsilyl)(4-methoxyphenyl)methanone **II.39f**.

Flash chromatography: PE/EtOAc 97:3. Yield: 27.6 mg (37%) as a colourless oil. ~50% (*Z*).

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	(Major isomer) 7.43 – 7.27 (m, 5H), 7.26 – 7.12 (m, 2H), 6.89 – 6.77 (m, 2H), 5.15 (d, *J* = 8.5 Hz, 1H), 4.02 (dq, *J* = 9.7, 7.0 Hz, 1H), 3.80 (s, 3H), 1.38 (d, *J* = 7.0 Hz, 3H), 1.00 (s, 9H), -0.03 (s, 3H), -0.10 (s, 3H). (Minor isomer) 7.43 – 7.27 (m, 5H), 7.26 – 7.12 (m, 2H), 6.89 – 6.77 (m, 2H), 5.18 (d, *J* = 9.3 Hz, 1H), 3.80 (s, 3H), 3.60 (dq, *J* = 10.5, 6.9 Hz, 1H), 1.33 (d, *J* = 6.9 Hz, 2H), 0.91 (s, 9H), 0.06 (s, 3H), 0.00 (s, 3H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	(Major isomer) 159.3, 148.3, 147.7, 132.5, 128.4, 127.7, 127.1, 125.8, 115.5, 113.3, 55.4, 35.8, 26.1, 22.7, 18.5, -3.8, -3.8. (Minor isomer) 159.3, 149.0, 147.3, 130.5, 129.7, 128.6, 126.9, 125.9, 115.1, 113.3, 55.3, 38.0, 25.9, 24.3, 18.3, -4.2, -4.3.

MS (HRMS APCI)	Calcd	for	$[M+H]^+$	Found: 369.22426
	$C_{23}H_{33}O_2Si$ 369.22443			

- 7,7-diethoxy-2,2-dimethyl-4-phenyl-3,8-dioxa-2,7-disiladec-4-ene, **II.40ia**



$C_{18}H_{32}O_4Si_2$
Molecular Weight: 368,6200

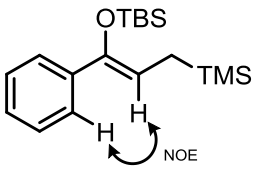
By modification of the procedure with triethoxy(2-(phenylsulfonyl)ethyl)silane (1 mmol, 1 eq.), phenyl(trimethylsilyl)methanone (1 mmol, 1 eq.) and LDA (1.1 eq.) as a base.

Flash chromatography: PE/EtOAc 85:15. Yield: 211.7 mg (57%) as a colourless oil. Isomeric ratio: (80:20), the geometry of the double bonds was not attributed.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	(Major isomer) 7.58 – 7.40 (m, 3H), 7.37 – 7.27 (m, 2H), 5.09 (t, *J* = 8.7 Hz, 1H), 3.81 (q, *J* = 7.0 Hz, 6H), 1.63 (d, *J* = 8.6 Hz, 2H), 1.21 (t, *J* = 7.0 Hz, 9H), 0.12 (s, 9H). (Minor isomer) 7.58 – 7.40 (m, 3H), 7.37 – 7.27 (m, 2H), 5.27 (t, *J* = 8.1 Hz, 1H), 3.85 (q, *J* = 7.0 Hz, 6H), 1.74 (d, *J* = 8.1 Hz, 2H), 1.23 (t, *J* = 6.9 Hz, 9H), 0.13 (s, 9H).

3.2.3 Scope of the reaction: acylsilanes

- (*Z*)-*tert*-butyldimethyl((1-phenyl-3-(trimethylsilyl)prop-1-en-1-yl)oxy)silane, **(*Z*)-II.40ae**



$C_{18}H_{32}OSi_2$
Molecular Weight: 320,6230

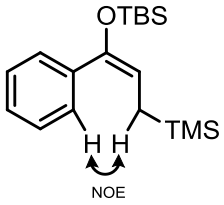
Following **conditions A** with trimethyl(2-(phenylsulfonyl)ethyl)silane **II.38a** and (*tert*-butyldimethylsilyl)(phenyl)methanone

II.39e.

Flash chromatography: PE/Et_2O 95:5. Yield: 55.7 mg (87%) as a colourless oil. > 99% (*Z*).

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.50 – 7.32 (m, 2H), 7.32 – 7.09 (m, 3H), 5.09 (t, *J* = 8.5 Hz, 1H), 1.55 (d, *J* = 8.5 Hz, 2H), 0.96 (s, 9H), 0.00 (s, 9H), -0.08 (s, 6H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	148.2, 140.4, 128.0, 127.0, 125.9, 108.0, 26.1, 18.5, 16.7, -1.4, -3.7.
MS (HRMS ESI)	Calcd for $[M+H]^+$ Found: 321.20672 $C_{18}H_{33}OSi_2$ 321.20645

- (*E*)-*tert*-butyldimethyl((1-phenyl-3-(trimethylsilyl)prop-1-en-1-yl)oxy)silane, **(*E*)-II.40ae**



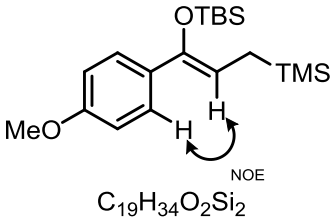
$C_{18}H_{32}OSi_2$
Molecular Weight: 320,6230

Following **conditions B** with trimethyl(2-(phenylsulfonyl)ethyl)silane **II.38a** and (*tert*-butyldimethylsilyl)(phenyl)methanone **II.39e**.

Flash chromatography: PE/Et_2O 95:5. Yield: 56.4 mg (88%) as a colourless oil. 86% (*E*).

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.44 – 7.34 (m, 2H), 7.34 – 7.26 (m, 2H), 7.27 – 7.20 (m, 1H), 5.05 (t, *J* = 8.8 Hz, 1H), 1.48 (d, *J* = 8.8 Hz, 2H), 0.89 (s, 9H), 0.01 (s, 6H), 0.00 (s, 9H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	148.1, 138.3, 128.6, 127.9, 127.3, 107.1, 25.9, 18.3, 16.8, -1.5, -4.3.
MS (HRMS ESI)	Calcd for $[M+H]^+$ Found: 321.20675 $C_{18}H_{33}OSi_2$ 321.20645

- (*Z*)-*tert*-butyl((1-(4-methoxyphenyl)-3-(trimethylsilyl)prop-1-en-1-yl)oxy)dimethylsilane, **(*Z*)-II.40af**

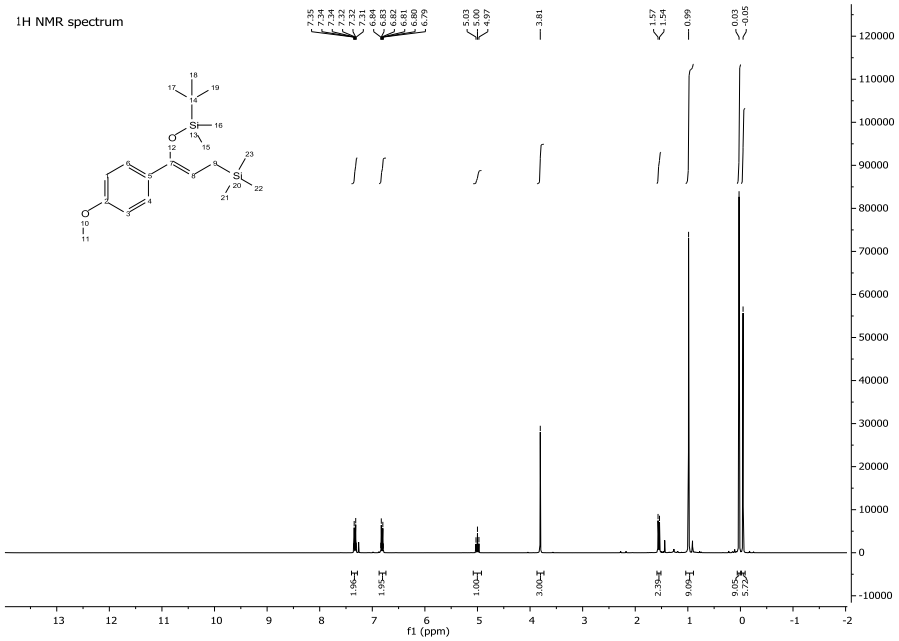


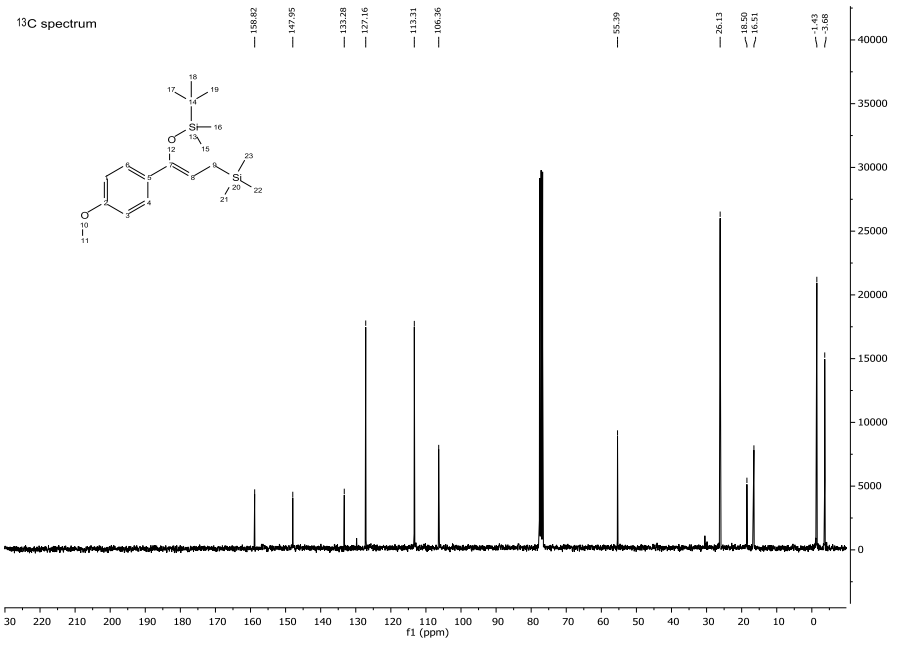
$C_{19}H_{34}O_2Si_2$
Molecular Weight: 350,6490

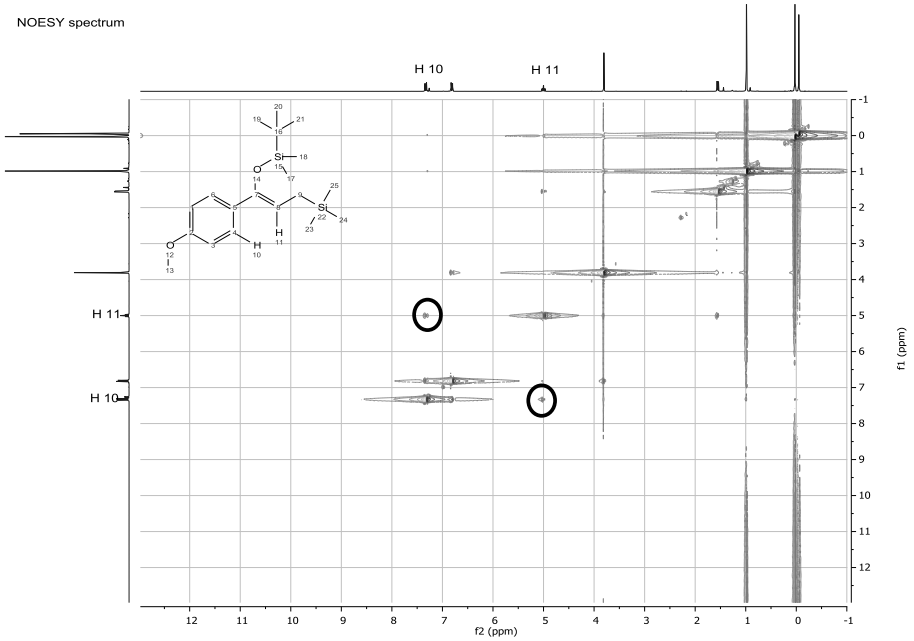
Following **conditions A** with trimethyl(2-(phenylsulfonyl)ethyl)silane **II.38a** (0.15 mmol) and (*tert*-butyldimethylsilyl)(4-methoxyphenyl)methanone **II.39f** (0.13 mmol).

Flash chromatography: PE/Et_2O 90:10. Yield: 38.7 mg (85%) as a colourless oil. 96% (*Z*).

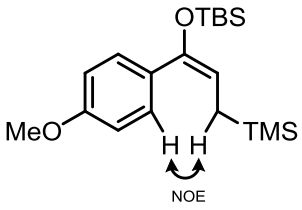
^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.33 (d, *J* = 8.8 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 5.00 (t, *J* = 8.4 Hz, 1H), 3.81 (s, 3H), 1.55 (d, *J* = 8.4 Hz, 2H), 0.99 (s, 9H), 0.03 (s, 9H), -0.05 (s, 6H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	158.8, 148.0, 133.3, 127.2, 113.3, 106.4, 55.4, 26.1, 18.5, 16.5, -1.4, -3.7.
MS (HRMS APCI)	Calcd for $[M+H]^+$ Found: 351.21692 $C_{19}H_{35}O_2Si$ 351.21701


1H NMR spectrum
7.35
7.34
7.34
7.32
7.32
7.31
6.84
6.83
6.82
6.81
6.80
6.79
5.03
5.00
4.97
3.81
1.57
1.54
0.99
0.03
-0.05
1.96
1.95
1.00
3.00
2.39
9.09
9.05
5.72
f1 (ppm)


13C spectrum
158.82
147.95
133.28
127.16
113.31
106.36
55.39
26.13
18.50
16.91
-1.43
-3.68
f1 (ppm)



- (*E*)-*tert*-butyl((1-(4-methoxyphenyl)-3-(trimethylsilyl)prop-1-en-1-yl)oxy)dimethylsilane, **(*E*)-II.40af**



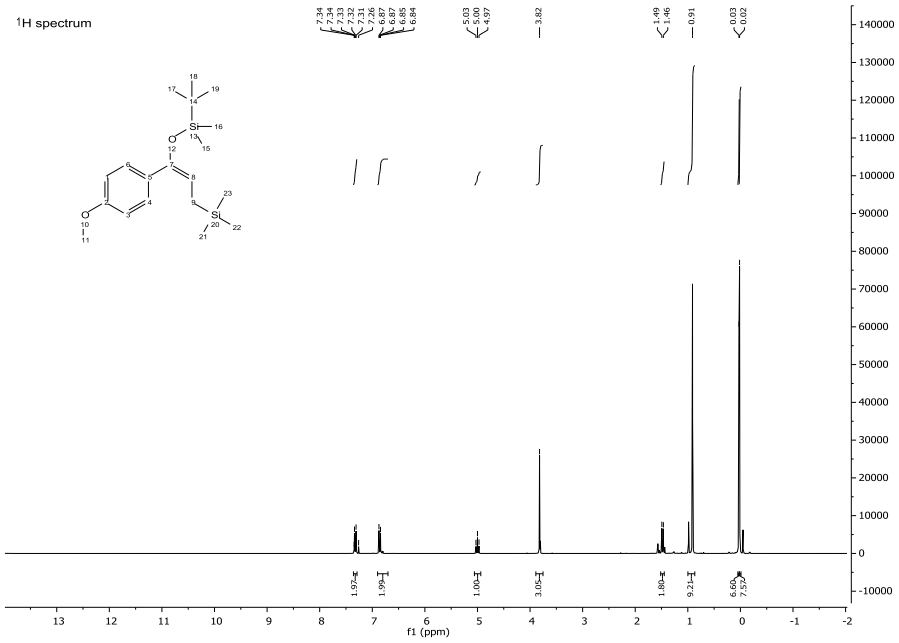
$C_{19}H_{34}O_2Si_2$
Molecular Weight: 350,6490

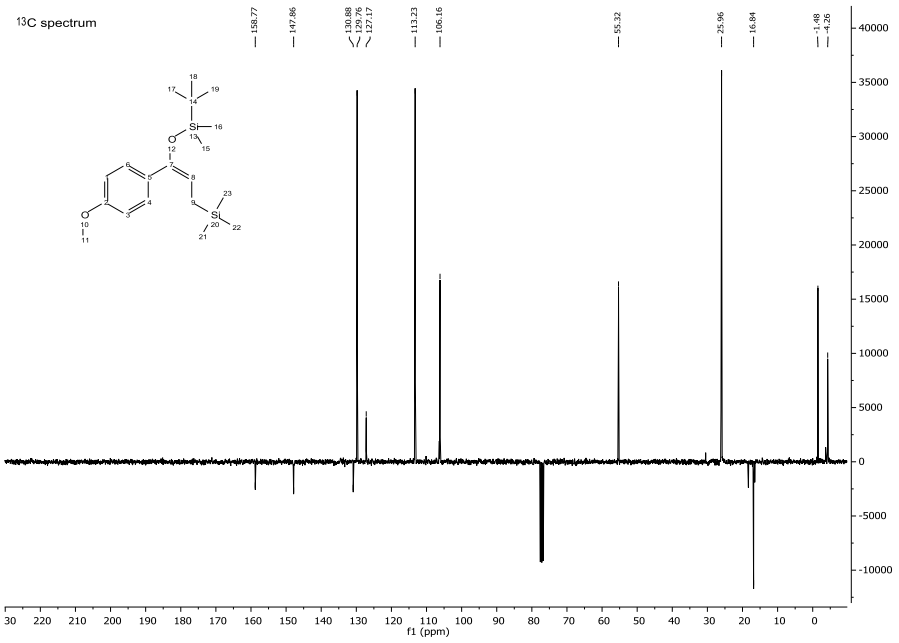
Following **conditions B** with trimethyl(2-(phenylsulfonyl)ethyl)silane **II.38a** (0.24 mmol) and (*tert*-butyldimethylsilyl)(4-methoxyphenyl)methanone **II.39f** (0.2 mmol).

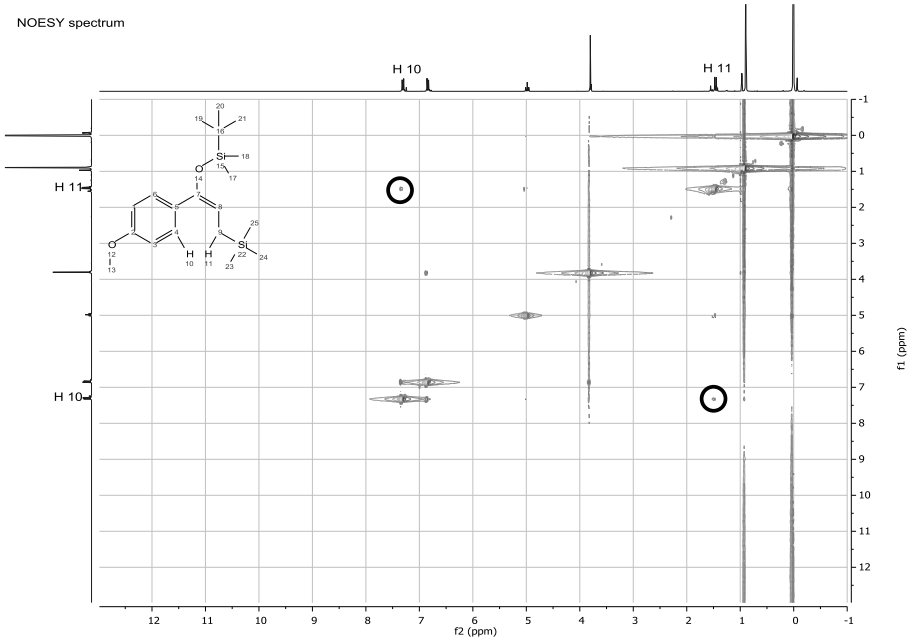
Flash chromatography: PE/Et_2O 90:10. Yield: 56.4 mg (80%) as a colourless oil. 89% (*E*).

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.37 – 7.30 (m, 2H), 6.91 – 6.79 (m, 2H), 5.00 (t, *J* = 8.7 Hz, 1H), 3.82 (s, 3H), 1.48 (d, *J* = 8.8 Hz, 2H), 0.91 (s, 9H), 0.03 (s, 6H), 0.02 (s, 9H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	158.8, 147.9, 130.9, 129.8, 113.2, 106.2, 77.2, 55.3, 26.0, 18.3, 16.8, -1.5, -4.3.

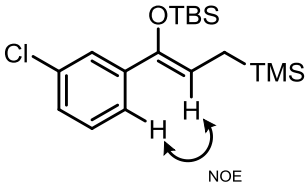
MS	Calcd for $[M+H]^+$	Found: 351.21684
(HRMS APCI)	$C_{19}H_{35}O_2Si$ 351.21701	







- (*Z*)-*tert*-butyl((1-(3-chlorophenyl)-3-(trimethylsilyl)prop-1-en-1-yl)oxy)dimethylsilane, **(*Z*)-II.40ag**



$C_{18}H_{31}ClOSi_2$
Molecular Weight: 355,0650

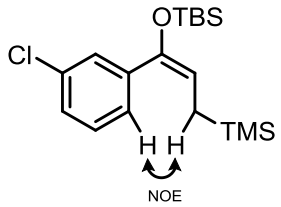
Following **conditions A** with trimethyl(2-(phenylsulfonyl)ethyl)silane **II.38a** and (*tert*-butyldimethylsilyl)(3-chlorophenyl)methanone **II.39g**.

Flash chromatography: PE/Et_2O 95:5. Yield: 33.1 mg (47%) as a colourless oil. 94% (*Z*).

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.40 – 7.32 (m, 1H), 7.28 – 7.22 (m, 1H), 7.20 – 7.11 (m, 2H), 5.14 (t, *J* = 8.5 Hz, 1H), 1.55 (d, *J* = 8.5 Hz, 2H), 0.96 (s, 9H), -0.00 (s, 9H), -0.06 (s, 6H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	146.9, 142.2, 134.0, 129.3, 126.9, 125.9, 123.8, 109.4, 26.1, 18.5, 17.0, -1.4, -3.7.

MS	Calcd	for	$[M+H]^+$	Found: 355.16729
(HRMS APCI)	$C_{18}H_{32}ClOSi_2$ 355.16747			

- (*E*)-*tert*-butyl((1-(3-chlorophenyl)-3-(trimethylsilyl)prop-1-en-1-yl)oxy)dimethylsilane, **(*E*)-II.40ag**



$C_{18}H_{31}ClOSi_2$
Molecular Weight: 355,0650

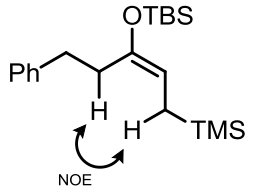
Following **conditions B** with trimethyl(2-(phenylsulfonyl)ethyl)silane **II.38a** and (*tert*-butyldimethylsilyl)(3-chlorophenyl)methanone **II.39g**.

Flash chromatography: PE/Et_2O 95:5. Yield: 65.8 mg (97%) as a colourless oil. 83% (*E*).

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.41 – 7.32 (m, 1H), 7.26 – 7.18 (m, 3H), 5.06 (t, *J* = 8.9 Hz, 1H), 1.46 (d, *J* = 8.9 Hz, 2H), 0.89 (s, 9H), 0.02 (s, 6H), 0.00 (s, 9H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	146.7, 140.1, 133.8, 129.2, 128.6, 127.4, 126.6, 108.2, 25.9, 18.3, 17.0, -1.5, -4.3.

MS	Calcd	for	$[M+H]^+$	Found: 355.16744
(HRMS APCI)	$C_{18}H_{32}ClOSi_2$ 355.16747			

- (*E*)-*tert*-butyldimethyl((5-phenyl-1-(trimethylsilyl)pent-2-en-3-yl)oxy)silane, **(*E*)-II.40ah**



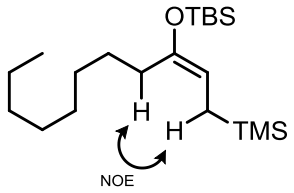
$C_{20}H_{36}OSi_2$
Molecular Weight: 348,6770

Following **conditions B** with trimethyl(2-(phenylsulfonyl)ethyl)silane **II.38a** and 1-(*tert*-butyldimethylsilyl)-3-phenylpropan-1-one **II.39h**.

Flash chromatography: PE/Et_2O 95:5. Yield: 20.0 mg (29%) as a colourless oil. 83% (*E*).

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.35 – 7.14 (m, 5H), 4.63 (t, *J* = 8.6 Hz, 1H), 2.85 – 2.70 (m, 2H), 2.39 – 2.27 (m, 2H), 1.23 (d, *J* = 8.6 Hz, 2H), 0.96 (s, 9H), 0.15 (s, 6H), -0.01 (s, 9H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	149.0, 142.6, 128.5, 128.4, 125.9, 103.4, 33.6, 33.5, 26.0, 18.3, 16.4, -1.6, -4.2.
MS (HRMS APCI)	Calcd for $[M+H]^+$ Found: 349.23768 $C_{20}H_{37}OSi_2$ 349.23775

- (*E*)-*tert*-butyldimethyl((1-(trimethylsilyl)undec-2-en-3-yl)oxy)silane, **(*E*)-II.40ai**



$C_{20}H_{44}OSi_2$
Molecular Weight: 356,7410

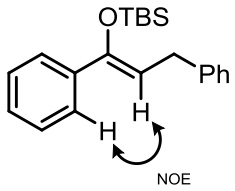
Following **conditions B** with trimethyl(2-(phenylsulfonyl)ethyl)silane **II.38a** and 1-(*tert*-butyldimethylsilyl)nonan-1-one **II.39i**.

Flash chromatography: PE/Et_2O 95:5. Yield: 17.6 mg (25%) as a colourless oil. 91% (*E*).

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	4.58 (t, *J* = 8.5 Hz, 1H), 2.06 – 1.96 (m, 2H), 1.49 – 1.36 (m, 2H), 1.33 – 1.16 (m, 12H), 1.00 – 0.83 (m, 12H), 0.11 (s, 6H), -0.01 (s, 9H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	150.2, 102.8, 32.1, 31.1, 29.7, 29.6, 29.4, 27.1, 26.0, 22.8, 18.2, 16.3, 14.3, -1.6, -4.2.
MS (HRMS APCI)	Calcd for $[M+H]^+$ Found: 357.29982 $C_{20}H_{45}OSi_2$ 357.30035

3.2.4 Scope of the reaction: sulfones

- (*Z*)-*tert*-butyl((1,3-diphenylprop-1-en-1-yl)oxy)dimethylsilane, **(*Z*)-II.40fe**



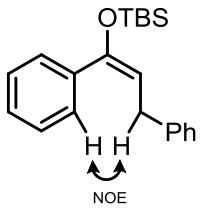
$C_{21}H_{28}OSi$
Molecular Weight: 324,5390

Following **conditions A** with (phenethylsulfonyl)benzene **II.38f** and (*tert*-butyldimethylsilyl)(phenyl)methanone **II.39e**.

Flash chromatography: PE/Et_2O 95:5. Yield: 61.7 mg (95%) as a colourless oil. 93% (*Z*).

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.53 – 7.46 (m, 2H), 7.37 – 7.13 (m, 8H), 5.31 (t, *J* = 7.2 Hz, 1H), 3.59 (d, *J* = 7.2 Hz, 2H), 1.02 (s, 9H), -0.00 (s, 6H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	150.2, 141.7, 139.7, 128.6, 128.5, 128.1, 127.7, 126.2, 125.9, 110.4, 32.5, 26.1, 18.5, -3.8.
MS (HRMS APCI)	Calcd for $[M+H]^+$ $C_{21}H_{29}OSi$ Found: 325.19765 325.19822

- (*E*)-*tert*-butyl((1,3-diphenylprop-1-en-1-yl)oxy)dimethylsilane, **(*E*)-II.40fe**



$C_{21}H_{28}OSi$
Molecular Weight: 324,5390

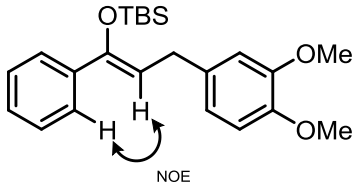
Following **conditions B** with (phenethylsulfonyl)benzene **II.38f** and (*tert*-butyldimethylsilyl)(phenyl)methanone **II.39e**.

Flash chromatography: PE/Et_2O 95:5.

Yield: 30.8 mg (47%) as a colourless oil. 86% (*E*).

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.46 – 7.31 (m, 2H), 7.32 – 7.09 (m, 8H), 5.17 (t, *J* = 8.0 Hz, 1H), 3.40 (d, *J* = 8.0 Hz, 2H), 0.86 (s, 9H), 0.00 (s, 6H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	151.1, 142.0, 137.7, 128.5, 128.5, 128.5, 128.3, 128.0, 126.0, 109.0, 33.9, 25.9, 18.3, -4.3.
MS (HRMS APCI)	Calcd for $[M+H]^+$ $C_{21}H_{29}OSi$ Found: 325.19829 325.19822

- (*Z*)-*tert*-butyl((3-(3,4-dimethoxyphenyl)-1-phenylprop-1-en-1-yl)oxy)dimethylsilane, **(*Z*)-II.40ge**



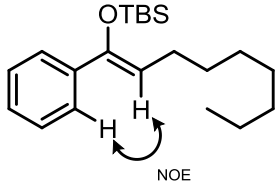
$C_{23}H_{32}O_3Si$
Molecular Weight: 384,5910

Following **conditions A** with 1,2-dimethoxy-4-(2-(phenylsulfonyl)ethyl)benzene **II.38g** and (*tert*-butyldimethylsilyl)(phenyl)methanone **II.39e**.

Flash chromatography: PE/Et_2O 60:40. Yield: 70.7 mg (92%) as a colourless oil. 92% (*Z*).

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.54 – 7.44 (m, 2H), 7.36 – 7.22 (m, 3H), 6.81 (s, 3H), 5.29 (t, *J* = 7.2 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.53 (d, *J* = 7.1 Hz, 2H), 1.02 (s, 9H), 0.00 (s, 6H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	150.0, 149.0, 147.3, 139.6, 134.4, 128.1, 127.7, 126.2, 120.3, 112.0, 111.4, 110.7, 56.1, 55.9, 32.0, 26.0, 18.5, -3.8.
MS (HRMS APCI)	Calcd for $[M+H]^+$ Found: 385.21930 $C_{23}H_{33}O_3Si$ 385.21935

- (*Z*)-*tert*-butyldimethyl((1-phenylnon-1-en-1-yl)oxy)silane, **(*Z*)-II.40he**



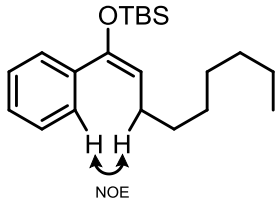
$C_{21}H_{36}OSi$
Molecular Weight: 332,6030

Following **conditions A** with 1,2-(octylsulfonyl)benzene **II.38h** and (*tert*-butyldimethylsilyl)(phenyl)methanone **II.39e**.

Flash chromatography: PE/Et_2O 95:5. Yield: 69.7 mg (Quantitative) as a colourless oil. 71% (*Z*).

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.49 – 7.19 (m, 5H), 5.12 (t, *J* = 7.1 Hz, 1H), 2.21 (q, *J* = 7.2 Hz, 2H), 1.49 – 1.21 (m, 10H), 1.00 (s, 9H), 0.94 – 0.87 (m, 3H), -0.03 (s, 6H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	149.3, 140.1, 128.0, 127.4, 126.0, 112.3, 32.0, 31.0, 29.4, 29.3, 27.8, 26.0, 22.8, 18.5, 14.3, -3.9.
MS (HRMS APCI)	Calcd for $[M+H]^+$ $C_{21}H_{37}OSi$ Found: 333.26082 333.26082

- (*E*)-*tert*-butyldimethyl((1-phenylnon-1-en-1-yl)oxy)silane, **(*E*)-II.40he**



$C_{21}H_{36}OSi$
Molecular Weight: 332,6030

Following **conditions B** with 1,2-(octylsulfonyl)benzene **II.38h** and (*tert*-butyldimethylsilyl)(phenyl)methanone **II.39e**.

Flash chromatography: PE/Et_2O 95:5. Yield: 38.5 mg (58%) as a colourless oil. 86% (*E*).

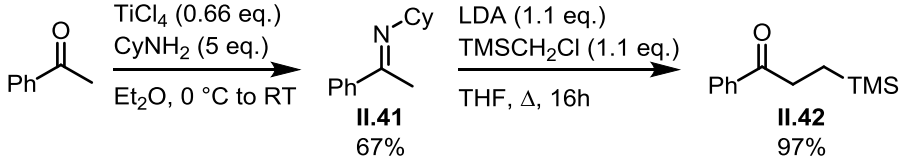
^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.46 – 7.27 (m, 5H), 5.02 (t, *J* = 7.7 Hz, 1H), 2.09 (q, *J* = 7.5 Hz, 2H), 1.42 – 1.20 (m, 10H), 0.91 (s, 9H), 0.87 (t, *J* = 6.5 Hz, 3H), 0.03 (s, 6H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	149.4, 138.1, 128.5, 127.8, 127.6, 111.6, 32.0, 31.0, 29.4, 29.3, 27.8, 25.9, 22.8, 18.3, 14.2, -4.4.
MS (HRMS APCI)	Calcd for $[M+H]^+$ $C_{21}H_{37}OSi$ Found: 333.26079 333.26082

3.3 Applications of β-silylated silyl enol ethers

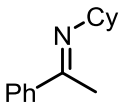
3.3.1 Synthesis of the substrates

For practical reasons, the β-silylated silyl enol ethers were not synthesised by the Brook rearrangement of acylsilanes but rather by enolisation/silylation of the corresponding ketone **II.42**.

The model ketone was synthesised in two steps from acetophenone following procedures inspired from the literature.[32]



Step 1: the imine **II.41** was synthesised according to the literature.[32a]



$C_{14}H_{19}N$

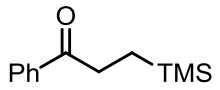
Molecular Weight: 201,3130

Under an argon atmosphere, a round-bottom flask was charged with acetophenone (30 mmol, 1 eq.), Et_2O (1 $mL.mmol^{-1}$) and cyclohexylamine (5 eq.). The mixture was cooled to 0 °C and TiCl4 (1M in DCM, 0.66 eq.) was added dropwise over 30 minutes before removal of the ice-bath. The reaction was monitored by TLC. After total conversion of the ketone, the reaction was quenched by addition of an aqueous solution of NaOH (0.5 M, 100 mL) and extracted with Et_2O (3 X 15 mL). The

organic phases were dried over Na_2SO_4, the volatiles were removed *in vacuo* and the product was purified by kugelrohr distillation (120 °C, 0.5 mmHg) affording N-cyclohexyl-1-phenylethan-1-imine as a colourless oil 3.97 g (67%). The spectral data are consistent with the literature.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.87 – 7.67 (m, 2H), 7.53 – 7.32 (m, 3H), 3.48 (tt, *J* = 10.2, 4.1 Hz, 1H), 2.25 (s, 3H), 1.91 – 1.24 (m, 10H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	162.6, 142.1, 129.2, 128.3, 126.8, 60.1, 33.7, 25.9, 25.1, 15.5.

Step 2: the addition of the imine to the silane was inspired from the literature.[32b]

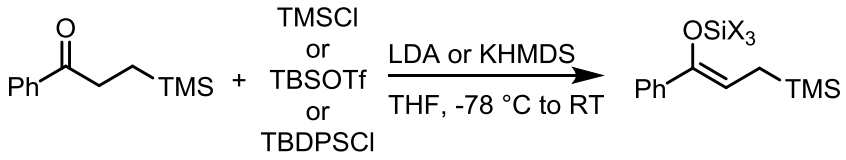


$C_{12}H_{18}OSi$
Molecular Weight: 206,3600

A Schlenk-tube was charged with diisopropylamine (1.2 eq.) and THF (3mL) before addition of nBuLi (1.6 M in hexanes, 1.1 eq.). The mixture was cooled to 0 °C before the addition of a solution of N-cyclohexyl-1-phenylethan-1-imine (5 mmol, 1 eq.) in THF (1mL). The reaction mixture was stirred at 0 °C for 45 minutes before addition of (chloromethyl)trimethylsilane (1.1 eq.) and stirring was continued at the same temperature for one hour. The mixture was then refluxed overnight. The reaction was quenched by addition of a buffer solution (2.5 mL AcOH, 1.2 g AcONa, 25 mL H_2O), extracted with Et2O (3 X 10 mL). The organic phases were washed with saturated $Na_2CO_{3aq.}$ and dried over MgSO4. The product was purified by flash column chromatography affording 1-phenyl-3-(trimethylsilyl)propan-1-one 1.00 g (97%) as a colourless oil. The spectral data are consistent with the literature.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	8.00 – 7.92 (m, 2H), 7.60 – 7.51 (m, 1H), 7.53 – 7.40 (m, 2H), 3.02 – 2.87 (m, 2H), 0.99 – 0.86 (m, 2H), 0.05 (s, 9H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	201.4, 137.0, 132.9, 128.7, 128.2, 33.3, 11.1, -1.6.

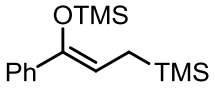
The enolisation/silylation of the ketone **II.42** was inspired from the literature.[33]



1.0 - 1.2 eq.

A round-bottom flask was charged with diisopropylamine (1.1 eq.) and THF (10 mL.mmol-1) before addition of *n*BuLi (1.6 M in hexanes, 1.1 eq.) at the indicated temperature or with KHMDS (0.5 M in toluene, 1.6 eq.). 1-phenyl-3-(trimethylsilyl)propan-1-one (1 mmol, 1 eq.) was added dropwise and the mixture was stirred at the same temperature for 30 minutes before dropwise addition of TMSCl (1.0 eq.) or TBSOTf (1.0 eq.) or TBDPSCl (1.2 eq.) and the reaction was allowed to reach room temperature overnight. Saturated aqueous NH_4Cl (5 mL.mmol^{-1}) and H_2O (25 mL.mmol^{-1}) were added before extraction with PE (3 X 20 mL). The organic phases were washed with brine and dried over $MgSO_4$. The product was purified by Kugelrohr distillation or flash column chromatography to afford the desired silyl enol ethers.

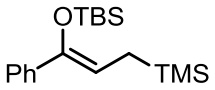
- (*Z*)-trimethyl(3-phenyl-3-((trimethylsilyl)oxy)allyl)silane, **(*Z*)-II.40aa**



$C_{15}H_{26}OSi_2$
Molecular Weight: 278,5420

Following the procedure at 0 °C with LDA and TMSCl. Purification was carried out by kugelrohr distillation (125 °C, 1 mbar) affording the title compound as a colourless oil quantitatively (100% (*Z*)). The spectral data are the same as those described earlier.

- (*Z*)-*tert*-butyldimethyl((1-phenyl-3-(trimethylsilyl)prop-1-en-1-yl)oxy)silane, **II.43a**

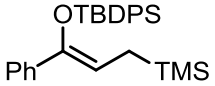


$C_{18}H_{32}OSi_2$
Molecular Weight: 320,6230

Following the procedure at -78 °C with LDA and TBSOTf. Purification was carried out by flash chromatography (PE) affording the title compound 0.29 g (89%) as a colourless oil (> 95% (*Z*)). The spectral data are consistent with the literature.[34]

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.44 – 7.37 (m, 2H), 7.31 – 7.17 (m, 3H), 5.12 (t, *J* = 8.5 Hz, 1H), 1.57 (d, *J* = 8.5 Hz, 3H), 0.98 (s, 9H), 0.02 (s, 9H), -0.06 (s, 6H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	148.2, 140.4, 128.0, 127.0, 125.9, 108.0, 26.1, 18.5, 16.7, -1.4, -3.7.

- (*Z*)-*tert*-butyldiphenyl((1-phenyl-3-(trimethylsilyl)prop-1-en-1-yl)oxy)silane, **II.43b**



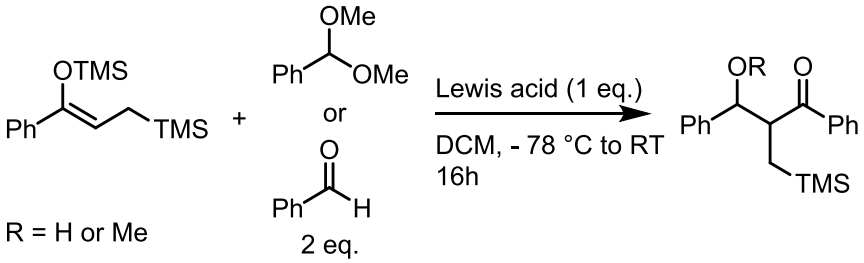
$C_{28}H_{36}OSi_2$
Molecular Weight: 444,7650

Following the procedure at -78 °C with KHMDS and TBDPSCl. Purification was carried out removing the solvents *in vacuo*, dissolving the crude product in *n*-pentane and filtration over a pad of celite eluting with *n*-pentane affording the title compound 0.38 g (86%) as a colourless oil (> 99% (*Z*)). The spectral data are consistent with the literature.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.73 – 7.58 (m, 4H), 7.43 – 7.22 (m, 9H), 7.14 – 7.02 (m, 2H), 4.94 (t, *J* = 8.6 Hz, 1H), 1.35 (d, *J* = 8.6 Hz, 2H), 1.04 (s, 9H), -0.07 (s, 9H).

3.3.2 Mukaiyama aldol reactions

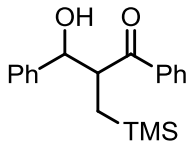
3.3.2.1 With strong Lewis acids



Under an argon atmosphere, a Schlenk-tube was charged with benzaldehyde or benzaldehyde dimethyl acetal (2 eq.), DCM (10 mL.mmol^{-1}) and was cooled to -78 °C. $TiCl_4$ (1 M in DCM, 1.1 eq.) or TMSOTf (1.1 eq.) was added and the mixture was stirred at the same temperature for 10 minutes. A saturated solution of the β-silyl silyl enol ether (1 eq.) in DCM was added dropwise and the reaction

mixture was allowed to slowly reach room temperature overnight. The reaction was quenched by addition of saturated aqueous NH_4Cl, extracted with DCM and the organic phases were dried over $MgSO_4$ before removal of the volatiles *in vacuo*. The products were analysed as crude mixtures or purified by flash column chromatography with the indicated eluent affording the pure aldol adducts. The diastereomeric ratios were determined by ^1H NMR analysis.

- 3-hydroxy-1,3-diphenyl-2-((trimethylsilyl)methyl)propan-1-one, **II.44a**



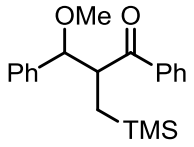
$C_{19}H_{24}O_2Si$
Molecular Weight: 312,4840

Following the procedure with benzaldehyde (0.5 mmol) and TMSOTf. The product was analysed as a crude mixture.

Conversion: 80% and d.r. (63:37) based on the crude ^1H NMR.

^1H NMR (δ, ppm) (300 MHz, $CDCl_3$)	(Major dia) 7.97 – 7.82 (m, 2H), 7.63 – 7.15 (m, 8H), 4.95 (d, *J* = 4.4 Hz, 1H), 3.95 – 3.88 (m, 1H), 2.96 (brs, 1H), 1.22 (dd, *J* = 14.5, 11.1 Hz, 1H), 0.83 (dd, *J* = 14.5, 3.0 Hz, 1H), -0.20 (s, 9H). (Minor dia) 7.97 – 7.82 (m, 2H), 7.63 – 7.15 (m, 8H), 4.85 (d, *J* = 6.6 Hz, 1H), 3.92 – 3.81 (m, 1H), 3.29 (brs, 1H), 1.06 (dd, *J* = 14.6, 9.6 Hz, 1H), 0.73 (dd, *J* = 14.6, 5.0 Hz, 1H), -0.14 (s, 9H).
MS (HRMS ESI)	Calcd for $[M+Na]^+$ Found: 335.14375 $C_{19}H_{24}O_2SiNa$ 335.14378

- 3-methoxy-1,3-diphenyl-2-((trimethylsilyl)methyl)propan-1-one, **II.44b**



$C_{20}H_{26}O_2Si$
Molecular Weight: 326,5110

Following the procedure with benzaldehyde dimethyl acetal (0.5 mmol) and TMSOTf.

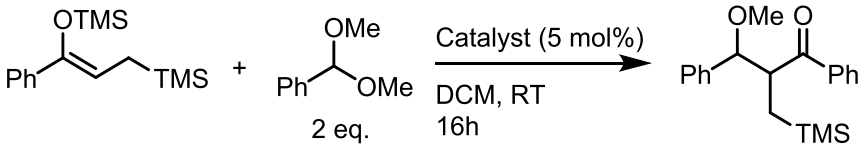
Flash chromatography: PE/EtOAc 95:5.

Yield: 74.5 mg (91%) as a colourless oil.

d.r. (83:17) based on the ^{1}H NMR.

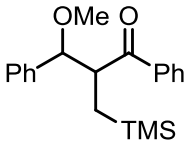
^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	(Major dia) 8.14 – 7.59 (m, 2H), 7.58 – 7.02 (m, 8H), 4.30 (d, *J* = 8.1 Hz, 1H), 3.91 – 3.74 (m, 1H), 3.18 (s, 3H), 1.28 – 1.13 (m, 2H), -0.12 (s, 9H). (Minor dia) 8.14 – 7.59 (m, 2H), 7.58 – 7.02 (m, 8H), 4.26 (d, *J* = 9.7 Hz, 1H), 3.91 – 3.74 (m, 1H), 2.97 (s, 3H), 1.28 – 1.13 (m, 2H), -0.31 (s, 9H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	(Major dia) 202.8, 140.1, 137.5, 132.7, 128.9 - 127.5 (signals of five carbon could not be assigned), 86.6, 57.0, 50.1, 17.2, -0.6. (Minor dia) 204.8, 140.0, 139.1, 132.8, 128.9 - 127.5 (signals of five carbon could not be assigned), 89.6, 57.0, 48.4, 17.1, -1.0.
MS (HRMS ESI)	Calcd for $[M+Na]^+$ Found: 349.15941 $C_{20}H_{26}O_2SiNa$ 349.15943

3.3.2.2 With soft Lewis acids



Under an argon atmosphere, a Schlenk-tube was charged with a Lewis acid (5 mol%), DCM (1 mL.mmol^{-1}) and benzaldehyde dimethyl acetal (2 eq.). A saturated solution of the β-silyl silyl enol ether (0.25 mmol, 1 eq.) in DCM was added dropwise and the reaction was stirred overnight at room temperature. The reaction mixture was filtered through a pad of silica gel eluting with Et_2O, the solvents were removed *in vacuo* and the aldol adducts were analysed as crude mixtures.

- 3-methoxy-1,3-diphenyl-2-((trimethylsilyl)methyl)propan-1-one, **II.44b**

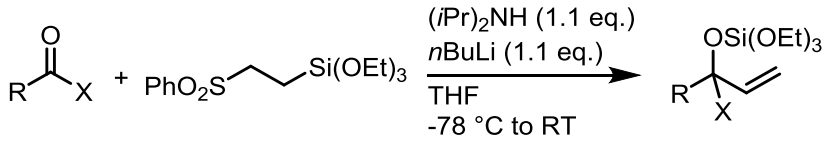


$C_{20}H_{26}O_2Si$
Molecular Weight: 326,5110

Following the procedure with $Cu(OTf)_2$ as the catalyst.

Complete conversion and d.r. (73:27) based on the crude ^1H NMR. The major diastereoisomer is the same as for the strong Lewis acid promoted reaction. The spectral data are the same as those described previously.

3.4 β-(triethoxysilyl)sulfone as vinyl anion equivalent

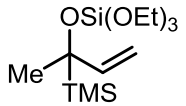


X = H, Alk, TMS

Under an argon atmosphere, a Schlenk tube was charged with diisopropylamine (1.1 eq.) and *n*BuLi (1.1 eq.) was added dropwise

followed by THF (5 mL.mmol^{-1}). The reaction mixture was cooled down to -78 °C before dropwise addition of triethoxy(2-(phenylsulfonyl)ethyl)silane (0.2 mmol, 1 eq.). After 30 minutes of stirring at -78 °C, the desired electrophile (1 eq.) was added dropwise to the reaction mixture and the temperature was raised to room temperature overnight. The reaction was quenched by addition of wet Et_3N and filtrated through a pad of silica gel eluting with Et_2O. The volatiles were evaporated *in vacuo* and the crude mixture was analysed qualitatively or purified by flash column chromatography with the indicated eluent affording the pure allylated products.

- triethoxy(2-(trimethylsilyl)but-3-en-2-yl)silane, **II.47a**

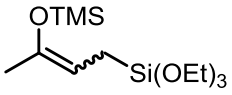


$C_{13}H_{30}O_4Si_2$
Molecular Weight: 306,5490

Following the procedure with 1-(trimethylsilyl)ethan-1-one (0.2 mmol). Flash chromatography: PE/EtOAc 85:15. Yield: not determined as the compound was isolated as a mixture with two other products described hereafter. Composes 54% of the mixture.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	5.99 (dd, *J* = 17.2, 10.9 Hz, 1H), 5.00 – 4.94 (m, 1H), 4.94 – 4.88 (m, 1H), 3.82 (q, *J* = 7.0 Hz, 6H), 1.43 (s, 3H), 1.21 (t, *J* = 7.0 Hz, 9H), 0.01 (s, 9H).

7,7-diethoxy-2,2,4-trimethyl-3,8-dioxa-2,7-disiladec-4-ene, **II.40ik**

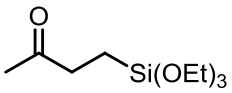


$C_{13}H_{30}O_4Si_2$
Molecular Weight: 306,5490

Observed as a mixture after the flash chromatography of the latter product. The double bond geometry was not attributed. Composes 24% of the mixture.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$): 4.80 – 4.56 (m, 1H), 4.00 – 3.56 (q, *J* = 7.0 Hz, 6H), 2.15 (s, 3H), 1.33 – 1.11 (m, 11H), 0.17 (s, 9H).

4-(triethoxysilyl)butan-2-one

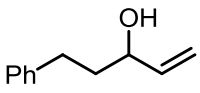


$C_{10}H_{22}O_4Si$
Molecular Weight: 234,3670

Observed as a mixture after the flash chromatography of the latter products. Composes 22% of the mixture.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$): 3.81 (q, *J* = 7.0 Hz, 6H), 2.59 – 2.46 (m, 2H), 1.56 (s, 3H), 1.22 (t, *J* = 7.0 Hz, 9H), 0.92 – 0.83 (m, 2H).

- 5-phenylpent-1-en-3-ol, **II.47b**



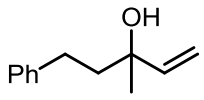
$C_{11}H_{14}O$
Molecular Weight: 162,2320

Following the procedure with 3-phenylpropanal (0.2 mmol).

Flash chromatography: PE/EtOAc 95:5. Yield: not determined. (83% conversion of the substrate to the product based on the crude ^{1}H NMR spectrum). The spectral data are consistent with the literature.[35]

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.34 – 7.24 (m, 2H), 7.24 – 7.18 (m, 3H), 5.91 (ddd, *J* = 17.2, 10.4, 6.2 Hz, 1H), 5.25 (dt, *J* = 17.2, 1.4 Hz, 1H), 5.14 (dt, *J* = 10.4, 1.3 Hz, 1H), 4.14 (m, 1H), 2.82 – 2.63 (m, 2H), 1.93 – 1.81 (m, 2H).

- 3-methyl-5-phenylpent-1-en-3-ol, **II.47c**

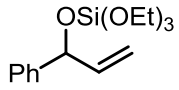


$C_{12}H_{16}O$
Molecular Weight: 176,2590

Following the procedure with 4-phenylbutan-2-one (0.2 mmol).
No flash chromatography was carried out. (56% conversion of the substrate to the product based on the crude ^{1}H NMR spectrum). The spectral data are consistent with the literature.[36]

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.33 – 7.14 (m, 5H), 5.98 (dd, *J* = 17.3, 10.8 Hz, 1H), 5.27 (dd, *J* = 17.3, 1.2 Hz, 1H), 5.12 (dd, *J* = 10.7, 1.2 Hz, 1H), 2.66 (m, 2H), 1.91 – 1.80 (m, 2H), 1.35 (s, 3H).

- triethyl (1-phenylallyl) silicate, **II.47d**

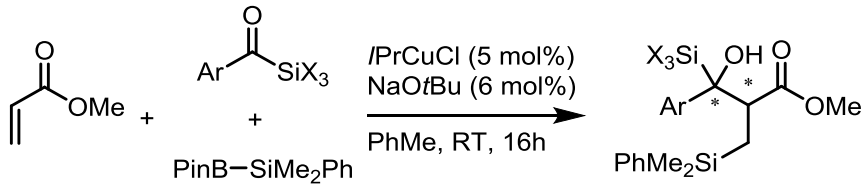


$C_{15}H_{24}O_4Si$
Molecular Weight: 296,4380

Following the procedure with benzaldehyde (0.2 mmol).
No flash chromatography was carried out. (19% conversion of the substrate to the product based on the crude ^{1}H NMR spectrum).

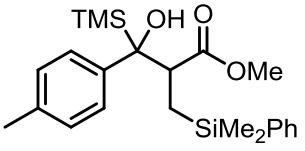
^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	With the exception of the allylic region, the crude spectrum was too messy to attribute the signals.

3.5 Domino β-silylation/aldolisation of acrylates



Under an argon atmosphere, a Schlenk-tube was charged with *I*PrCuCl (5 mol%) and NaO*t*Bu (6 mol%). Freshly distilled toluene (5 mL.mmol^{-1}) was added and the mixture was stirred at room temperature for 5 minutes. A toluene solution of the acylsilane (0.2 mmol, 1 eq.) and the acrylate (0.2 mmol, 1 eq.) was added followed by Suginome's reagent (0.24 mmol, 1.2 eq.). The mixture was stirred overnight at room temperature. The crude reaction mixture was washed with a diluted aqueous solution of K_2CO_3 and extracted twice with Et_2O. The organic phases were gathered, dried over Na_2SO_4 and the solvents were removed *in vacuo*. The crude product was purified by flash column chromatography with the indicated eluent affording the pure domino adducts.

- methyl 2-((dimethyl(phenyl)silyl)methyl)-3-hydroxy-3-(p-tolyl)-3-(trimethylsilyl)propanoate, **II.51c**

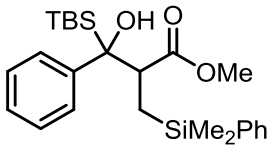


$C_{23}H_{34}O_3Si_2$
Molecular Weight: 414,6920

Following the procedure with p-tolyl(trimethylsilyl)methanone **II.39c**.
Flash chromatography: PE/Et_2O 90:10.
Yield: 69.8 mg (84%) as a colourless oil.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	(major dia) 7.55 – 7.46 (m, 1H), 7.42 – 7.28 (m, 4H), 7.15 – 6.95 (m, 4H), 3.40 (s, 3H), 3.28 (brs, 1H), 3.05 (dd, *J* = 12.7, 1.9 Hz, 1H), 2.33 (s, 3H), 1.25 (dd, *J* = 14.9, 12.7 Hz, 1H), 0.57 (dd, *J* = 14.9, 1.9 Hz, 1H), 0.20 (s, 3H), 0.15 (s, 3H), -0.16 (s, 9H). (minor dia) 7.55 – 7.46 (m, 1H), 7.42 – 7.28 (m, 5H), 7.15 – 6.95 (m, 5H), 3.47 (brs, 1H), 3.22 (dd, *J* = 13.1, 2.8 Hz, 1H), 2.96 (s, 3H), 2.27 (s, 3H), 1.64 (dd, *J* = 14.9, 13.1 Hz, 1H), 1.19 (dd, *J* = 14.9, 2.8 Hz, 1H), 0.34 (s, 3H), 0.30 (s, 3H), -0.07 (s, 9H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	(major dia) 177.2, 140.5, 138.2, 134.8, 133.8, 129.1, 128.9, 127.8, 124.7, 73.6, 51.7, 46.0, 21.1, 12.4, -2.7, -3.0, -3.2. (minor dia) 176.4, 143.3, 138.3, 134.9, 133.7, 129.2, 128.6, 127.9, 124.4, 74.9, 50.8, 47.4, 21.0, 16.1, -2.0, -2.4, -3.2.
MS (HRMS ESI)	Calcd for $[M+Na]^+$ Found: 437.19398 $C_{23}H_{34}O_3Si_2Na$ 437.19387

- methyl 3-(*tert*-butyldimethylsilyl)-2-((dimethyl(phenyl)silyl)methyl)-3-hydroxy-3-phenylpropanoate, **II.51e**



$C_{25}H_{38}O_3Si_2$
Molecular Weight: 442,7460

Following the procedure with (*tert*-butyldimethylsilyl)(phenyl)methanone **II.39e**.

Flash chromatography: PE/Et_2O 95:5. Yield: 59.0 mg (67%) as a colourless oil. d.r. (37:63) determined by ^{1}H NMR experiment.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	(major dia) 7.55 – 7.03 (m, 10H), 3.42 (s, 3H), 3.39 – 3.29 (brs, 1H), 3.01 (dd, *J* = 12.7, 1.8 Hz, 1H), 1.13 (dd, *J* = 14.9, 12.7 Hz, 1H), 0.48 (s, 9H), 0.52 – 0.40 (m, 1H), 0.16 (s, 3H), 0.14 (s, 3H), 0.11 (s, 3H), -0.08 (s, 3H). (minor dia) 7.55 – 7.03 (m, 10H), 3.58 (brs, 1H), 3.22 (dd, *J* = 13.2, 2.9 Hz, 1H), 2.87 (s, 3H), 1.61 (dd, *J* = 14.8, 13.2 Hz, 1H), 1.34 – 1.21 (m, 1H), 0.57 (s, 9H), 0.33 (s, 3H), 0.29 (s, 3H), 0.23 (s, 3H), 0.01 (s, 3H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	(major dia) 177.1, 144.2, 138.1, 133.8, 129.1, 128.2, 127.8, 125.7, 125.4, 74.2, 51.7, 47.6, 27.1, 18.6, 12.1, -2.8, -3.3, -6.2, -6.6. (minor dia) 176.1, 146.6, 138.2, 133.7, 129.2, 127.9, 127.8, 125.8, 125.2, 75.7, 50.6, 49.2, 27.3, 18.8, 16.3, -2.4, -3.3, -4.2, -5.8.
MS (HRMS ESI)	Calcd for $[M+Na]^+$ Found: 465.22537 $C_{25}H_{38}O_3Si_2Na$ 465.22517

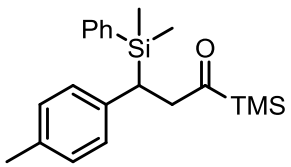
4 Synthesis and characterisation of the compounds obtained in Chapter III

4.1 Initial strategy experiments

4.1.1 Addition of Suginome's reagent

A Schlenk tube was charged with *I*PrCuCl (5 mol%), NaO*t*Bu (6 mol%) and the α,β-unsaturated acylsilane **III.2** (1 eq.). The solids were dissolved in toluene (5 mL.mmol^{-1}), Suginome's reagent **II.8** (1 eq.) was added dropwise followed by the indicated electrophile (1 or 2 eq.). The reaction mixture was stirred overnight at the indicated temperature. The mixture was filtered through a pad of silica gel eluting with Et_2O, the solvents were removed *in vacuo* and the crude mixture was purified by flash chromatography over silica gel with the indicated eluent.

- 3-(dimethyl(phenyl)silyl)-3-(p-tolyl)-1-(trimethylsilyl)propan-1-one, **III.4**

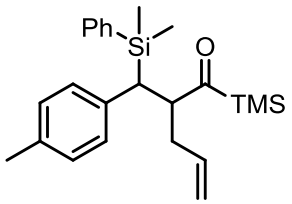


$C_{21}H_{30}OSi_2$
Molecular Weight: 354,6400

Following the procedure with MeOH (2 eq.) as the electrophile and (*E*)-3-(p-tolyl)-1-(trimethylsilyl)prop-2-en-1-one **III.2** (0.2 mmol) at room temperature. Flash chromatography: PE/EtOAc 95:5. Yield: 24.6 mg (35%) as a colourless oil.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.53 – 7.29 (m, 5H), 7.04 – 6.93 (m, 2H), 6.86 – 6.74 (m, 2H), 3.12 (dd, *J* = 16.8, 9.4 Hz, 1H), 3.00 (dd, *J* = 9.4, 4.2 Hz, 1H), 2.77 (dd, *J* = 16.8, 4.3 Hz, 1H), 2.26 (s, 3H), 0.21 (s, 3H), 0.18 (s, 3H), 0.05 (s, 9H).

- 2-((dimethyl(phenyl)silyl)(p-tolyl)methyl)-1-(trimethylsilyl)pent-4-en-1-one, **III.5** (major isomer)



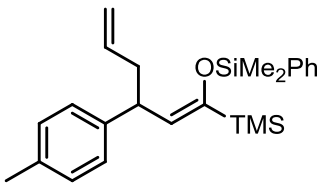
$C_{24}H_{34}OSi_2$
Molecular Weight: 394,7050

Following the procedure with a mixture of $Pd(OAc)_2$ (1 mol%), PPh_3 (3.5 mol%) and allyl methyl carbonate (2 eq.) as electrophile, and (*E*)-3-(p-tolyl)-1-(trimethylsilyl)prop-2-en-1-one **III.2** (0.2 mmol) at 40 °C.

Flash chromatography: PE:EtOAc 97:3. Yield: 62.2 mg (79%) of a mixture of two isomers (4:1 ratio) as a colourless oil.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.57 – 7.28 (m, 5H), 6.98 (d, *J* = 7.8 Hz, 2H), 6.75 (d, *J* = 8.0 Hz, 2H), 5.34 (ddt, *J* = 17.2, 10.2, 7.1 Hz, 1H), 4.93 – 4.79 (m, 1H), 4.65 (dq, *J* = 16.9, 1.4 Hz, 1H), 3.54 (ddd, *J* = 10.2, 7.0, 3.6 Hz, 1H), 2.74 (d, *J* = 9.8 Hz, 1H), 2.28 (s, 3H), 0.22 (s, 3H), 0.11 (s, 9H), 0.06 (s, 3H).
MS (HRMS ESI)	Calcd for $[M+Na]^+$ Found: 417.20399 $C_{24}H_{34}OSi_2Na$ 417.20404

- (*E*)-(1-((dimethyl(phenyl)silyl)oxy)-3-(p-tolyl)hexa-1,5-dien-1-yl)trimethylsilane, **III.6**

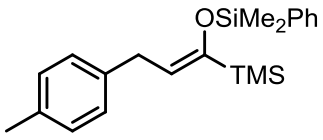


$C_{24}H_{34}OSi_2$
Molecular Weight: 394,7050

was assumed to be the minor isomer of the mixture and could not be obtained as a pure compound. Most of the characteristic peaks were however identified from the ^{1}H NMR spectrum of the isomeric mixture.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.39 – 7.34 (m, 5H), 6.99 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 8.1 Hz, 2H), 5.89 (ddt, *J* = 17.2, 10.3, 5.1 Hz, 1H), 5.28 (dq, *J* = 17.3, 1.8 Hz, 1H), 5.14 (dq, *J* = 10.5, 1.6 Hz, 1H), 4.12 (ddt, *J* = 12.8, 5.1, 1.6 Hz, 1H), 4.03 (ddt, *J* = 12.9, 5.1, 1.6 Hz, 1H), 3.88 (d, *J* = 11.1 Hz, 1H), 2.28 (s, 3H), 0.26 (s, 3H), 0.22 (s, 3H), 0.15 (s, 9H). A one-proton peak is missing and is believed to be overlapping with the signal of the major isomer between 5.40 and 5.32 ppm.

- (*E*)-(1-((dimethyl(phenyl)silyl)oxy)-3-(p-tolyl)prop-1-en-1-yl)trimethylsilane, **III.7**



$C_{21}H_{30}OSi_2$
Molecular Weight: 354,6400

Following the procedure with *I*PrCuCl (100 mol%) and NaO*t*Bu (100 mol%), without electrophile in the reaction medium, and (*E*)-3-(p-tolyl)-1-(trimethylsilyl)prop-2-en-1-one **III.2** (0.2 mmol) at 40 °C. Quenching the reaction was carried out by addition of wet triethylamine (1 mL).

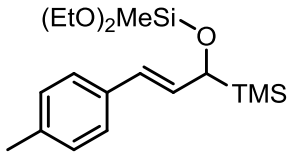
Flash chromatography: PE:EtOAc 95:5. Yield: 21.8 mg (30%) of the pure title compound and 35.9 mg (50%) of a mixture containing the title compound and the β-silylated acylsilane (3-(dimethyl(phenyl)silyl)-3-(p-tolyl)-1-(trimethylsilyl)propan-1-one) **III.4** (1:2 global ratio) as colourless oils.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.68 – 7.62 (m, 2H), 7.42 – 7.35 (m, 3H), 7.14 – 7.00 (m, 4H), 5.21 (t, *J* = 6.8 Hz, 1H), 3.36 (d, *J* = 6.8 Hz, 2H), 2.33 (s, 3H), 0.48 (s, 6H), 0.05 (s, 9H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	157.3, 138.6, 138.3, 135.3, 133.5, 129.7, 129.1, 128.4, 127.9, 124.3, 31.7, 21.2, -0.2, -1.5.

MS	Calcd	for	$[M+Na]^+$	Found: 377.17258
(HRMS ESI)	$C_{21}H_{30}OSi_2Na$ 377.17274			

4.1.2 Addition of hydrides

- (-5-ethoxy-2,2,5-trimethyl-3-(4-methylstyryl)-4,6-dioxa-2,5-disilaoctane, **III.8**



$C_{18}H_{32}O_3Si_2$
Molecular Weight: 352,6210

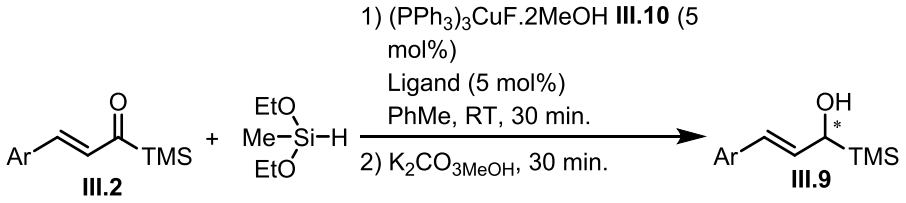
A Schlenk tube was charged with *I*PrCuCl (5 mol%), NaO*t*Bu (6 mol%), benzyl bromide (1.5 eq.) and (*E*)-3-(p-tolyl)-1-(trimethylsilyl)prop-2-en-1-one **III.2** (0.2 mmol, 1 eq.).The solids were dissolved in toluene (5 $mL.mmol^{-1}$), diethoxymethylsilane (1.5 eq.) was added dropwise. The reaction mixture was stirred overnight at 40 °C. The mixture was filtered through a pad of silica gel eluting with Et_2O, the solvents were removed *in vacuo* and the crude mixture was purified by flash chromatography over silica gel eluting with PE/Et_2O (97:3) affording the title compound as a colourless oil. Yield: 25.6 mg (32%).

^{1}H NMR (δ, ppm)	7.24 (d, *J* = 8.2 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 6.41			
(300 MHz, $CDCl_3$)	(dd, *J* = 15.8, 1.5 Hz, 1H), 6.27 (dd, *J* = 15.8, 6.1 Hz, 1H), 4.35 (dd, *J* = 6.1, 1.6 Hz, 1H), 3.81 (qd, *J* = 7.0, 4.0 Hz, 4H), 2.33 (s, 3H), 1.21 (t, *J* = 7.0 Hz, 6H), 0.12 (s, 3H), 0.06 (s, 9H).			
MS	Calcd	for	$[M+Na]^+$	Found: 375.17828
(HRMS ESI)	$C_{18}H_{32}O_3Si_2Na$ 375.17822			

4.2 Copper-catalysed hydroborylation of acylsilanes

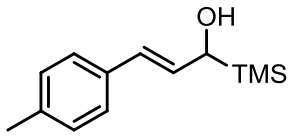
4.2.1 Chiral phosphine ligand screening

The conditions for the chiral HPLC analyses were developed by Ir. Laurent Collard.



This screening was carried out on a scale of 0.1 mmol substrate.

Standard procedure: An oven-dried test tube was charged under air with a chiral ligand (5 mol%) and copper(I) fluoride tristriphenylphosphine complex **III.10** (5 mol%). Distilled toluene (5 $mL.mmol^{-1}$) was added and the mixture was stirred at room temperature for 5 minutes. The acylsilane was added as a solid followed by methyldiethoxysilane (5 eq.). The mixture was stirred at room temperature for 30 minutes and quenched by the addition of a saturated aqueous solution of potassium carbonate (5 $ml.mmol^{-1}$). After 30 additional minutes, the mixture was transferred to a separation funnel, diluted with Et_2O and washed with water. The aqueous phase was extracted a second time with Et_2O, the organic phase were dried over Na_2SO_4 and the solvents were removed *in vacuo*. The crude samples of (*E*)-3-(p-tolyl)-1-(trimethylsilyl)prop-2-en-1-ol **III.9** were analysed without further purification.



$C_{13}H_{20}OSi$
Molecular Weight: 220,3870

The enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel OJ-H column, *i*-hexane/EtOH 98:2, 20 °C, 1 mL/min, detection at 263 nm. Retention times 11.35 min and 12.47 min.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$): 7.26 (d, *J* = 8.1 Hz, 2H), 7.12 (d, *J* = 7.9 Hz, 2H), 6.43 (d, *J* = 16.2 Hz, 1H), 6.35 (dd, *J* = 15.9, 5.3 Hz, 1H), 4.17 (d, *J* = 5.2 Hz, 1H), 2.33 (s, 3H), 1.42 (brs, 1H), 0.09 (s, 9H).

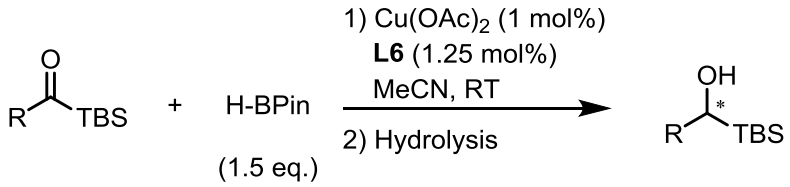
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$): 136.8, 134.9, 131.0, 129.4, 126.1, 125.7, 69.1, 21.3, -3.9.

Entry[a]	Ligand	*ee* (%)
1	(*R*)-Segphos (**III.L2**)	65
2	(*R*)-DTBM-Segphos (**III.L3**)	39
3	(*R*)-DTBM-Segphos[b]	3
4	(*R*)-DM-Segphos	57
5	(*R*)-Binap	40
6	(*S*)-*p*Tolyl-Binap (**III.L1**)	-46
7	(*R*)-3,5-Xylyl-Binap	6
8	SL-J002-1[c] (**III.L4**)	<10
9	SL-J003-1[c]	<10
10	SL-J004-1[c]	<10
11	SL-J007-1[c]	<10
12	SL-J009-1[c]	<10
13	SL-J013-1[c]	<10
14	SL-J216-1[c]	<10
15	(*R*)-MeOBiphep	59
16	(*R*)-3,5-Xylyl-MeOBiphep	55
17	(*R*)-3,5-*i*Pr-4-NMe_2-MeOBIPHEP	<30
18	(*R*)-*i*Pr-MeOBIPHEP	<30

19	(*R*)-3,5-*t*-Bu-MeOBIPHEP	33
20	(*R*)-DTBM-MeOBIPHEP	33
21	(*S*)-3,4,5-MeO-MeOBIPHEP[d] (**III.L6**)	-65
22	(*R*)-2-Furyl-MeOBIPHEP	<30
23	SL-T001-1[c] (**III.L5**)	44
24	SL-T002-1[c]	36
25	SL-J688-2[c]	20
26	SL-J681-2[c]	0
27	(1*R*,1′*R*,2*S*,2′*S*)-DuanPhos	0
28	(*R*,*R*)-Me-DUPHOS	0
29	(*S*,*S*′,*R*,*R*′)-TangPhos	0

[a] The reactions were carried out according to the procedure. [b] A preformed diphosphine copper(I) bifluoride complex gently provided by Corentin Rasson was used instead of **III.10**. [c] Josiphos's, TaniaPhos's and JosPoPhos's are named after their Solvias catalogue numbers. The catalogue can be downloaded from https://www.solvias.com/docs/download/en/000_Brochures_amp_Flyers/Ligands_and_Catalysts_Catalogue.pdf. [d] The conversion of the copper-catalysed hydrosilylation reaction was complete within a minute.

4.2.2 Scope of the reaction



The synthesis of α-hydroxysilanes was carried out on a 0.2 mmol scale with 1 mol% catalyst loading. The racemic references for chiral HPLC analysis were obtained by reduction of the acylsilanes by

sodium borohydride in methanol, cerium(III) chloride was added to the reaction mixture for α,β-unsaturated acylsilanes.[37]

Standard Hydroborylation: A flame-dried Schlenk tube was charged with (*S*)-(-)-2,2'-Bis[di(3,4,5-trimethoxyphenyl)phosphino]-6,6'-dimethoxy-1,1'-biphenyl **L6** (2.4 mg, 1.25 mol%) under argon. A solution of copper(II) acetate in freshly distilled acetonitrile (0.5mL, 4 mM, 1 mol%) was added followed by pinacolborane (44 µL, 1.5 eq.). When the reaction mixture had turned pale yellow a saturated solution of acylsilane in freshly distilled acetonitrile was added. The reaction mixture was stirred at room temperature until complete conversion of the acylsilane monitored by TLC.

Modified Hydroborylation: A flame-dried Schlenk tube was charged with (*S*)-(-)-2,2'-Bis[di(3,4,5-trimethoxyphenyl)phosphino]-6,6'-dimethoxy-1,1'-biphenyl **L6** (11.8 mg, 6.25 mol%) and copper(II) acetate (1.8 mg, 5 mol%) under argon. Freshly distilled acetonitrile (0.5 mL) was added followed by pinacolborane (44 µL, 1.5 eq.). When the reaction mixture had turned pale yellow a saturated solution of acylsilane (1 eq.) in freshly distilled acetonitrile was added. The reaction mixture was stirred at 40 °C overnight.

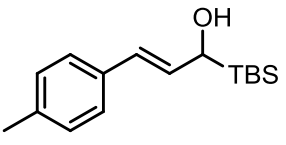
Two hydrolysis conditions were used depending on the substrates.

Hydrolysis 1: The reaction mixture was diluted with Et_2O (10 mL) and transferred to a separation funnel containing water (14 mL) and a saturated aqueous K_2CO_3 solution (1 mL). The funnel was shaken vigorously and the organic phase was separated. The aqueous phase was washed with Et_2O (10 mL). The organic phases were dried over Na_2SO_4 and the solvents were removed under vacuum. The crude

product was purified by flash column chromatography eluting with the specified solvent to yield the desired α-hydroxysilanes.

Hydrolysis 2: A saturated aqueous K_2CO_3 solution (1 mL) was added to the reaction mixture and was stirred vigorously at room temperature for 5 minutes. The reaction mixture was transferred to a separating funnel containing water (14 mL) and washed with Et_2O (2 X 10 mL). The organic phases were dried over Na_2SO_4 and the solvents were removed under vacuum. The crude product was purified by flash column chromatography eluting with the specified solvent to yield the desired α-hydroxysilanes.

- (*S*)-(*E*)-1-(*tert*-butyldimethylsilyl)-3-(p-tolyl)prop-2-en-1-ol, **III.12a**



$C_{16}H_{26}OSi$
Molecular Weight: 262,4680

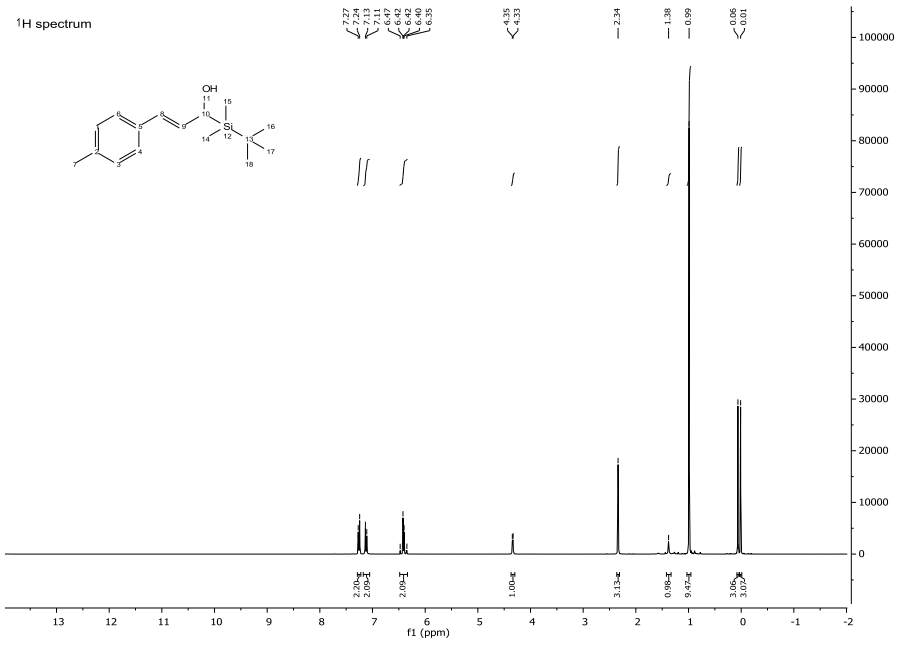
Following the Standard Hydroborylation and Hydrolysis 1 starting with (*E*)-1-(*tert*-butyldimethylsilyl)-3-(p-tolyl)prop-2-en-1-one **III.11a** (0.20 mmol).

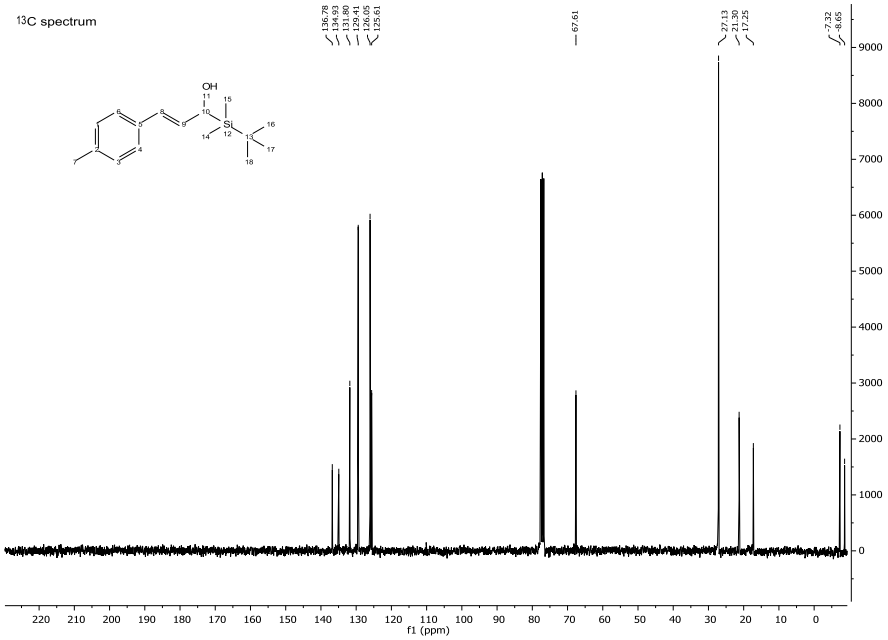
Flash chromatography: PE/EtOAc 90:10. Yield: 47.2 mg (92 %) as a white solid. *ee* = 91%. The enantiomeric ratio was determined by chiral HPLC analysis, Chiralpack IA column, *i*-hexane/EtOH 95:5, 20 °C, 1 mL/min, detection at 267 nm. Retention times 5.47 min (minor) and 6.21 min (major). $[\alpha]_D^{20}$ = -106 (*c* 7.5 g/L, DCM).

The absolute configuration was determined by XRD analysis.

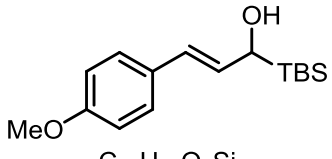
^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.26 (d, J = 8.1 Hz, 2H), 7.12 (d, J = 7.7 Hz, 2H), 6.56 – 6.26 (m, 2H), 4.34 (d, J = 4.5 Hz, 1H), 2.34 (s, 3H), 1.38 (s, 1H), 0.99 (s, 9H), 0.06 (s, 3H), 0.01 (s, 3H).

^{13}C NMR (δ, ppm)	136.8, 134.9, 131.8, 129.4, 126.0, 125.6, 67.6, 27.1, 21.3,
(75 MHz, $CDCl_3$)	17.2, -7.3, -8.6.
MS	Calcd for $[M+H-H_2O]^+$ Found: 245.17189
(HRMS APCI)	$C_{16}H_{25}Si$ 245.17200





- (*E*)-1-(*tert*-butyldimethylsilyl)-3-(4-methoxyphenyl)prop-2-en-1-ol, **III.12b**



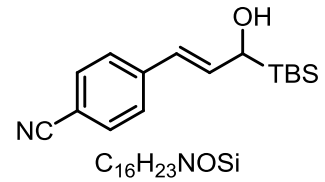
$C_{16}H_{26}O_2Si$
Molecular Weight: 278,4670

Following the Standard Hydroborylation with Hydrolysis 1 starting with (*E*)-1-(*tert*-butyldimethylsilyl)-3-(4-methoxyphenyl)prop-2-en-1-one **III.11b** (0.18 mmol).

Flash chromatography: EP/EtOAc 96:4. Yield: 38.3 mg (76 %) as a white solid. *ee*: 94 %. The enantiomeric ratio was determined by chiral HPLC analysis, Chiralpack IA column, *i*-hexane/EtOH 90:10, 20 °C, 1 mL/min, detection at 268 nm. Retention times 5.42 min (minor) and 6.30 min (major). $[\alpha]_D^{20}$ = -66 (*c* 5.95 g/L, DCM).

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.34 – 7.27 (m, 2H), 6.90 – 6.80 (m, 2H), 6.40 (dd, 1H), 6.29 (dd, J = 15.9, 6.1 Hz, 1H), 4.32 (d, J = 6.0 Hz, 1H), 3.81 (s, 3H), 1.33 (s, 1H), 0.98 (s, 9H), 0.06 (s, 3H) , 0.00 (s, 3H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	158.9, 130.6, 130.6, 127.3, 125.4, 114.2, 67.6, 55.5, 27.1, 17.2, -7.3, -8.6.
MS (HRMS APCI)	Calcd for $[M+H-H_2O]^+$ Found: 261.16682 $C_{16}H_{25}OSi$

- (*E*)-4-(3-(*tert*-butyldimethylsilyl)-3-hydroxyprop-1-en-1-yl)benzonitrile, **III.12c**

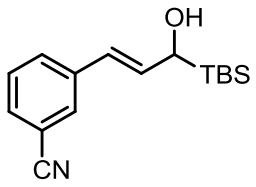


$C_{16}H_{23}NOSi$
Molecular Weight: 273,4510

Following the Standard Hydroborylation with Hydrolysis 1 starting with (*E*)-4-(3-(*tert*-butyldimethylsilyl)-3-oxoprop-1-en-1-yl)benzonitrile **III.11c** (0.18 mmol). Flash chromatography: PE/EtOAc 85:15 Yield: 44.8 mg (91 %) as white solid. *ee* = 79 %. The enantiomeric ratio was determined by chiral HPLC analysis, Chiralpack IA column, *i*-hexane/EtOH 90:10, 20 °C, 1 mL/min, detection at 288 nm. Retention times 6.85 min (minor) and 7.96 min (major). $[\alpha]_D^{20}$ = -140 (*c* 8.55 g/L, DCM).

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.58 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 6.61 (dd, J = 15.9, 5.0 Hz, 1H), 6.48 (dd, J = 15.9, 1.8 Hz, 1H), 4.42 (dd, J = 5.0, 1.8 Hz, 1H), 1.25 (s, 1H), 0.99 (s, 9H), 0.06 (s, 3H) , 0.02 (s, 3H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	142.3, 137.4, 132.6, 126.5, 123.4, 119.3, 109.9, 67.6, 27.1, 17.3, -7.2, -8.7.
MS (HRMS APCI)	Calcd for $[M+H]^+$ Found: 274.16198 $C_{16}H_{24}NOSi$ 274.16217

- (*E*)-3-(3-(*tert*-butyldimethylsilyl)-3-hydroxyprop-1-en-1-yl)benzonitrile, **III.12d**

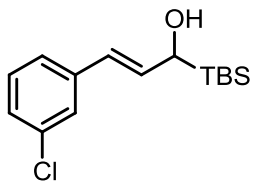


$C_{16}H_{23}NOSi$
Molecular Weight: 273,4510

Following the Standard Hydroborylation with Hydrolysis 1 starting with (*E*)-3-(3-(*tert*-butyldimethylsilyl)-3-oxoprop-1-en-1-yl)benzonitrile **III.11d** (0.20 mmol). Flash chromatography: PE/EtOAc 85:15 Yield: 53.8 mg (98 %) as a colorless oil. *ee*: 84%. The enantiomeric ratio was determined by chiral HPLC analysis, Chiralpack IA column, *i*-hexane/EtOH 90:10, 20 °C, 1 mL/min, detection at 269 nm. Retention times 7.08 min (minor) and 7.96 min (major). $[\alpha]_D^{20}$ = -116 (*c* 7.2 g/L, DCM).

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.60 (t, J = 1.7 Hz, 1H), 7.54 (dt, J = 7.6, 1.6 Hz, 1H), 7.47 (dt, J = 7.7, 1.5 Hz, 1H), 7.39 (t, J = 7.6 Hz, 1H), 6.54 (dd, J = 15.9, 4.7 Hz, 1H), 6.45 (dd, J = 15.9, 1.2 Hz, 1H), 4.40 (dd, J = 4.7, 1.3 Hz, 1H), 1.26 (s, 1H), 0.99 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	139.0, 136.1, 130.3, 130.1, 129.5, 129.4, 123.0, 119.1, 112.9, 67.5, 27.1, 17.3, -7.2, -8.7.
MS (HRMS ESI)	Calcd for $[M+Na]^+$ Found: 296.14410 $C_{16}H_{23}ONNaSi$ 296.14411

- (*E*)-1-(*tert*-butyldimethylsilyl)-3-(3-chlorophenyl)prop-2-en-1-ol, **III.12e**



$C_{15}H_{23}ClOSi$
Molecular Weight: 282,8830

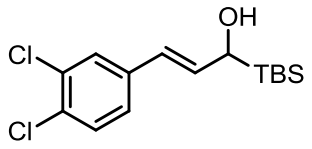
Following the Standard Hydroborylation with Hydrolysis 1 starting with (*E*)-1-(*tert*-butyldimethylsilyl)-3-(3-

chlorophenyl)prop-2-en-1-one **III.11e** (0.19 mmol).

Flash chromatography: PE/EtOAc 95:5. Yield: 52.6 mg (95 %) as a white gum. *ee*: 84 %. The enantiomeric ratio was determined by chiral HPLC analysis, Chiralpack IA column**,** *i*-hexane/EtOH 98:2, 20 °C, 1 mL/min, detection at 264 nm. Retention times 15.64 min (minor) and 17.50 min (major). $[\alpha]_D^{20}$ = -95 (*c* 10.6 g/L, DCM).

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.32 (q, J = 1.4 Hz, 1H), 7.25 – 7.08 (m, 3H), 6.47 (dd, J = 15.9, 4.7 Hz, 1H), 6.40 (d, J = 16.5 Hz, 1H), 4.37 (dd, J = 4.7, 0.9 Hz, 1H), 1.46 (s, 1H), 0.99 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H).
^{13}C NMR (δ, ppm) (75 MHz, CD_2Cl_2)	140.2, 135.3, 134.8, 130.2, 126.9, 126.1, 124.7, 124.0, 67.7, 27.1, 17.4, -7.2, -8.7.
MS (HRMS APCI)	Calcd for $[M+H-H_2O]^+$ Found: 265.11733 $C_{15}H_{22}ClSi$ 265.11738

- (*E*)-1-(*tert*-butyldimethylsilyl)-3-(3,4-dichlorophenyl)prop-2-en-1-ol, **III.12f**



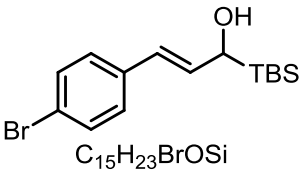
$C_{15}H_{22}Cl_2OSi$
Molecular Weight: 317,3250

Following the Standard Hydroborylation with Hydrolysis 1 starting with (*E*)-1-(*tert*-butyldimethylsilyl)-3-(3,4-dichlorophenyl)prop-2-en-1-one **III.11f** (0.19 mmol).

Flash chromatography: PE/Et_2O 80:20. Yield: 52.1 mg (85 %) as a colorless oil. *ee* = 84 %. The enantiomeric ratio was determined by chiral HPLC analysis, Chiralpack IA column, *i*-hexane/EtOH 95:5, 20 °C, 1 mL/min, detection at 269 nm. Retention times 5.89 min (minor) and 6.43 min (major). $[\alpha]_D^{20}$ = -106 (*c* 15.2 g/L, DCM).

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.40 (d, J = 2.1 Hz, 1H), 7.35 (d, J = 8.3 Hz, 1H), 7.15 (dd, J = 8.4, 2.1 Hz, 1H), 6.46 (dd, J = 15.9, 5.0 Hz, 1H), 6.36 (dd, J = 15.9, 1.4 Hz, 1H), 4.36 (dd, J = 5.0, 1.4 Hz, 1H), 1.42 (bs, 1H), 0.98 (s, 9H), 0.05 (s, 3H), 0.01 (s, 3H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	137.9, 135.2, 132.7, 130.6, 130.4, 127.7, 125.3, 122.9, 67.5, 27.1, 17.3, -7.2, -8.7.
MS (HRMS APCI)	Calcd for $[M-H]^-$ Found: 315.07287 $C_{15}H_{21}Cl_2OSi$ 315.07332

- (*E*)-3-(4-bromophenyl)-1-(*tert*-butyldimethylsilyl)prop-2-en-1-ol, **III.12g**



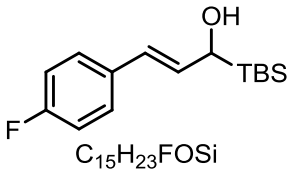
$C_{15}H_{23}BrOSi$
Molecular Weight: 327,3370

Following the Standard Hydroborylation with Hydrolysis 1 starting with (E)-3-(4-bromophenyl)-1-(*tert*-butyldimethylsilyl)prop-2-en-1-one **III.11g** (0.20 mmol).

Flash chromatography: PE/Et_2O 90:10. Yield: 58.7 mg (91 %) as a white solid. *ee* = 86 %. The enantiomeric ratio was determined by chiral HPLC analysis, Chiralpack IA column, *i*-hexane/EtOH 95:5, 20 °C, 1 mL/min, detection at 269 nm. Retention times 6.11 min (minor) and 6.71 min (major). $[\alpha]_D^{20}$ = -100 (*c* 16.5 g/L, DCM).

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.45 – 7.38 (m, 2H), 7.25 – 7.16 (m, 2H), 6.52 – 6.42 (dd, J = 15.9, 4.2 Hz, 1H), 6.42 (d, J = 16.1 Hz, 1H), 4.35 (d, J = 4.2 Hz, 1H), 1.41 (brs, 1H), 0.98 (s, 9H), 0.06 (s, 3H), 0.01 (s, 3H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	136.7, 133.8, 131.8, 127.6, 124.2, 120.5, 67.5, 27.1, 17.3, -7.3, -8.7.
MS (HRMS APCI)	Calcd for $[M+H-H_2]$ Found: 325.06175 $C_{15}H_{22}BrOSi$ 325.06178

- (*E*)-1-(*tert*-butyldimethylsilyl)-3-(4-fluorophenyl)prop-2-en-1-ol, **III.12h**



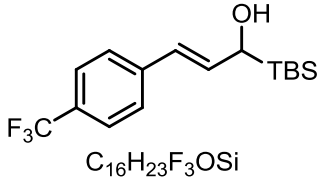
$C_{15}H_{23}FOSi$
Molecular Weight: 266,4314

Following the Standard Hydroborylation with Hydrolysis 1 starting with (*E*)-1-(*tert*-butyldimethylsilyl)-3-(4-fluorophenyl)prop-2-en-1-one **III.11h** (0.20 mmol).

Flash chromatography: PE/Et_2O 85:15. Yield: 49.5 mg (95 %) as a colorless gum. *ee* = 85 %. The enantiomeric ratio was determined by chiral HPLC analysis, Chiralpack IA column, *i*-hexane/EtOH 95:5, 20 °C, 1 mL/min, detection at 258 nm. Retention times 5.58 min (minor) and 6.17 min (major). $[\alpha]_D^{20}$ = -92 (*c* 22.3 g/L, DCM).

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.38 – 7.26 (m, 2H), 7.06 – 6.91 (m, 2H), 6.44 (d, J = 16.6 Hz, 1H), 6.34 (dd, J = 15.9, 5.3 Hz, 1H), 4.34 (d, J = 5.2 Hz, 1H), 1.39 (bs, 1H), 0.99 (s, 9H), 0.06 (s, 3H), 0.01 (s, 3H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	162.0 (d, J = 245.8 Hz), 133.9 (d, J = 3.4 Hz), 132.6 (d, J = 2.4 Hz), 127.5 (d, J = 7.8 Hz), 124.5, 115.6 (d, J = 21.5 Hz), 67.5, 27.1, 17.2, -7.3, -8.7.
^{19}F NMR (δ, ppm) (282MHz, $CDCl_3$)	-115.66.
MS (HRMS ESI)	Calcd for $[M-H]^-$ $C_{15}H_{22}FOSi$ Found: 265.14180 265.14185

- (*E*)-1-(*tert*-butyldimethylsilyl)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-ol, **III.12i**



$C_{16}H_{23}F_3OSi$
Molecular Weight: 316,4392

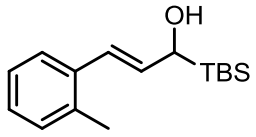
Following the Standard Hydroborylation with Hydrolysis 1 starting with (*E*)-1-

(*tert*-butyldimethylsilyl)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one **III.11i** (0.20 mmol).

Flash chromatography: PE/Et_2O 80:20. Yield: 57.3 mg (87 %) as a white solid. *ee* = 81 %. The enantiomeric ratio was determined by chiral HPLC analysis, Chiralpack IA column, *i*-hexane/EtOH 95:5, 20 °C, 1 mL/min, detection at 269 nm. Retention times 5.22 min (minor) and 5.63 min (major). $[\alpha]_D^{20}$ = -91 (*c* 17.6 g/L, DCM).

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.55 (d, J = 8.2 Hz, 2H), 7.43 (d, J = 8.1 Hz, 2H), 6.58 (dd, J = 15.9, 4.7 Hz, 1H), 6.50 (d, J = 16.3 Hz, 1H), 4.40 (d, J = 4.6 Hz, 1H), 1.48 (brs, 1H), 0.99 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	141.2, 135.9, 128.7 (q, J = 32.5 Hz), 126.2, 125.7 (q, J = 3.9 Hz), 124.4 (q, J = 271.2 Hz), 123.9, 67.6, 27.1, 17.3, -7.2, -8.7.
^{19}F NMR (δ, ppm) (282MHz, $CDCl_3$)	-62.38.
MS (HRMS ESI)	Calcd for $[M+H-H_2]^+$ Found: 315.13895 $C_{16}H_{22}OF_3Si$ 315.13865

- (*E*)-1-(*tert*-butyldimethylsilyl)-3-(o-tolyl)prop-2-en-1-ol, **III.12j**



$C_{16}H_{26}OSi$
Molecular Weight: 262,4680

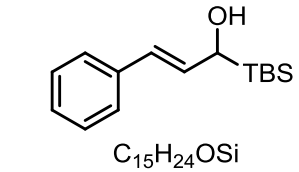
Following the Standard Hydroborylation with Hydrolysis 1 starting with (*E*)-1-(*tert*-butyldimethylsilyl)-3-(o-tolyl)prop-2-en-1-one **III.11j** (0.20 mmol).

Flash chromatography: PE/Et_2O 90:10. Yield: 51.4 mg (96 %) as a white solid. *ee* = 81 %. The enantiomeric ratio was determined by chiral HPLC analysis, Chiralpack IA column, *i*-hexane/EtOH 95:5, 20 °C, 1 mL/min, detection at 258 nm. Retention

times 4.98 min (minor) and 5.51 min (major). $[\alpha]_D^{20}$ = -62 (*c* 13.4 g/L, DCM).

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.43 – 7.35 (m, 1H), 7.22 – 7.07 (m, 3H), 6.66 (dd, J = 15.8, 1.9 Hz, 1H), 6.32 (dd, J = 15.7, 6.0 Hz, 1H), 4.38 (dd, J = 6.0, 2.0 Hz, 1H), 2.35 (s, 3H), 1.42 (bs, 1H), 1.00 (s, 9H), 0.07 (s, 3H), 0.02 (s, 3H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	137.0, 135.2, 134.3, 130.3, 127.0, 126.2, 125.5, 123.6, 67.9, 27.1, 20.1, 17.3, -7.2, -8.7.
MS (HRMS ESI)	Calcd for $[M+H-H_2O]^+$ Found: 245.17207 $C_{16}H_{25}Si$ 245.17200

- (*E*)-1-(*tert*-butyldimethylsilyl)-3-phenylprop-2-en-1-ol, **III.12k**

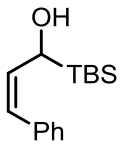


$C_{15}H_{24}OSi$
Molecular Weight: 248,4410

Following the Standard Hydroborylation with Hydrolysis 1 starting with (*E*)-1-(*tert*-butyldimethylsilyl)-3-phenylprop-2-en-1-one **III.11k** (0.20 mmol). Flash chromatography: PE/EtOAc 95:5. Yield: 38.7 mg (78 %) as a white solid. *ee* = 89 %. The enantiomeric ratio was determined by chiral HPLC analysis, Chiralpack IA column, *i*-hexane/EtOH 95:5, 20 °C, 1 mL/min, detection at 260 nm. Retention times 5.12 min (minor) and 5.73 min (major). $[\alpha]_D^{20}$ = -105 (*c* 8.7 g/L, DCM). The spectral data are consistent with the literature.[38]

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.38 – 7.27 (m, 4H), 7.24 – 7.17 (m, 1H), 6.56 – 6.35 (m, 2H), 4.36 (d, J = 3.1 Hz, 1H), 1.38 (s, 1H), 0.99 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	137.7, 132.9, 128.7, 127.0, 126.1, 125.6, 67.6, 27.1, 17.3, -7.3, -8.7.

- (*Z*)-1-(*tert*-butyldimethylsilyl)-3-phenylprop-2-en-1-ol, **III.12l**



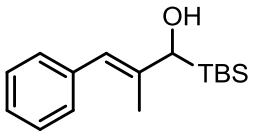
$C_{15}H_{24}OSi$
Molecular Weight: 248,4410

Following the Standard Hydroborylation with Hydrolysis 1 starting with (*Z*)-1-(*tert*-butyldimethylsilyl)-3-phenylprop-2-en-1-one **III.11l** (0.20 mmol).

Flash chromatography: EP/EtOAc 96:4. Yield: 44.9 mg (90 %) as a colorless oil. *ee* = 32 %. The enantiomeric ratio was determined by chiral HPLC analysis, Chiralpack IB column, *i*-hexane/*i*-propanol 97:3, 20 °C, 1 mL/min, detection at 252 nm. Retention times 4.86 min (major) and 5.65 min (minor). $[\alpha]_D^{20}$ = -68 (*c* 13.7 g/L, DCM).

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.38 – 7.29 (m, 2H), 7.29 – 7.19 (m, 3H), 6.44 (d, J = 11.7 Hz, 1H), 5.84 (dd, J = 11.7, 11.0 Hz, 1H), 4.81 (dd, J = 11.1, 1.3 Hz, 1H), 1.37 (s, 1H), 0.97 (s, 9H), 0.10 (s, 3H), -0.00 (s, 3H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	137.2, 133.8, 128.8, 128.3, 128.3, 127.0, 62.3, 27.1, 17.3, -6.9, -8.5.
MS (HRMS ESI)	Calcd for $[M+H-H_2O]^+$ Found: 231.15645 $C_{15}H_{23}OSi$: 231.15635

- (*E*)-1-(*tert*-butyldimethylsilyl)-2-methyl-3-phenylprop-2-en-1ol, **III.12m**



$C_{16}H_{26}OSi$
Molecular Weight: 262,4680

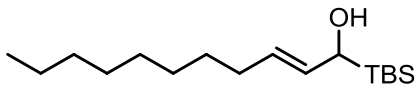
Following the Modified Hydroborylation with Hydrolysis 1 starting with (*E*)-1-(*tert*-butyldimethylsilyl)-3-(o-tolyl)prop-2-en-1-one **III.11m** (0.20 mmol).

Flash chromatography: PE/Et_2O 95:5.

Yield: 26.7 mg (52 %) as a colorless oil. *ee* = 90 %. The enantiomeric ratio was determined by chiral HPLC analysis, Chiralpack IA column, *i*-hexane/*i*-PrOH 99:1, 20 °C, 1 mL/min, detection at 255 nm. Retention times 5.804 min (minor) and 6.077 min (major). $[\alpha]_D^{20}$ = -6 (*c* 11.0 g/L, DCM).

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.34 – 7.22 (m, 4H), 7.23 – 7.10 (m, 1H), 6.39 (s, 1H), 4.16 (d, J = 1.3 Hz, 1H), 1.86 (d, J = 1.3 Hz, 3H), 1.41 (brs, 1H), 0.97 (s, 9H), 0.08 (s, 3H), -0.01 (s, 3H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	142.1, 138.3, 129.0, 128.7, 126.1, 122.7, 72.0, 27.0, 17.4, 16.9, -6.2, -8.2.
MS (HRMS ESI)	Calcd for $[M+H]^+$ $C_{16}H_{27}OSi$ Found: 263.18257

- (*E*)-1-(*tert*-butyldimethylsilyl)undec-2-en-1-ol, **III.12n**



$C_{17}H_{36}OSi$
Molecular Weight: 284,5590

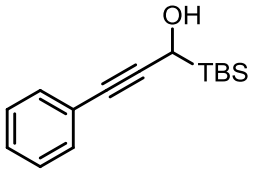
Following the Modified Hydroborylation with Hydrolysis 1 starting with (*E*)-1-(*tert*-butyldimethylsilyl)undec-2-en-1-one **III.11n** (0.20 mmol).

Flash chromatography: PE/EtOAc 95:5. Yield: 14.9 mg (26 %) as a colorless oil. *ee* = 94 %. The enantiomeric ratio was determined by chiral HPLC analysis, Chiralpack IA column, *i*-hexane/EtOH 99.5:0.5, 20 °C, 1 mL/min, detection at 210 nm. Retention times 4.994 min (minor) and 5.389 min (major). $[\alpha]_D^{20}$ = -22 (*c* 7.4 g/L, DCM).

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	5.63 (ddt, J = 15.3, 6.5, 1.2 Hz, 1H), 5.48 (dtd, J = 15.2, 6.6, 1.4 Hz, 1H), 4.07 (dd, J = 6.6, 1.3 Hz, 1H), 2.11 – 1.95 (m, 2H), 1.35 – 1.20 (m, 13H), 0.95 (s, 9H), 0.92 – 0.83 (m, 3H), 0.00 (s, 3H), -0.06 (s, 3H).

^{13}C NMR (δ, ppm)	132.2, 128.0, 67.1, 32.6, 32.0, 29.8, 29.6, 29.5, 29.3, 27.1,
(75 MHz, $CDCl_3$)	22.8, 17.1, 14.3, -7.5, -8.8.
MS	Calcd for $[M+H-H_2O]^+$ Found: 267.25010
(HRMS APCI)	$C_{17}H_{35}Si$ 267.25025

- 1-(*tert*-butyldimethylsilyl)-3-phenylprop-2-yn-1-ol, **III.12o**



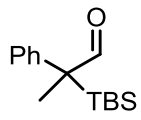
$C_{15}H_{22}OSi$
Molecular Weight: 246,4250

Following the General Procedure with Hydrolysis 1 starting with 1-(*tert*-butyldimethylsilyl)-3-phenylprop-2-yn-1-one **III.11o** (0.20 mmol).

Flash chromatography: PE/EtOAc 95:5. Yield: 44.4 mg (90 %) as a colorless oil. *ee*: 50 %. The enantiomeric ratio was determined by chiral HPLC analysis, Chiralpack IB column, i-hexane/i-propanol 95:5, 20 °C, 1 mL/min, detection at 251 nm. Retention times 4.95 min (minor) and 5.52 min (major). $[\alpha]_D^{20}$ = -55 (*c* 9.95 g/L, DCM).

^{1}H NMR (δ, ppm)	7.43 – 7.32 (m, 2H), 7.32 – 7.28 (m, 3H), 4.46 (s, 1H),
(300 MHz, $CDCl_3$)	1.70 (brs, 1H), 1.04 (s, 9H), 0.19 (s, 3H), 0.17 (s, 3H).
^{13}C NMR (δ, ppm)	131.5, 128.4, 128.1, 123.6, 90.7, 88.2, 55.2, 27.0, 17.2, -7.6, -8.3.
(75 MHz, $CDCl_3$)	
MS	Calcd for $[M+H]^+$ $C_{15}H_{23}OSi$: Found: 247.1512
(HRMS APCI)	247.1513

- 2-(*tert*-butyldimethylsilyl)-2-phenylpropanal, **III.12p'**



$C_{15}H_{24}OSi$
Molecular Weight: 248,4410

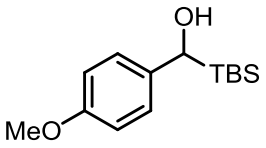
This unexpected compound was obtained following the General Procedure with Hydrolysis 1 starting with 1-(*tert*-

butyldimethylsilyl)-2-phenylprop-2-en-1-one **III.11p** (0.20 mmol).

Flash chromatography: PE/Et_2O 95:5. The title compound was isolated as a colorless oil.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	10.10 (s, 1H), 7.52 – 7.32 (m, 4H), 7.29 – 7.16 (m, 1H), 1.69 (s, 3H), 0.70 (s, 9H), 0.13 (s, 3H), 0.13 (s, 3H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	204.6, 140.5, 128.6, 126.6, 125.9, 52.9, 27.7, 19.9, 16.8, -5.8, -6.2.
MS (HRMS APCI)	Calcd for $[M+Na]^+$ Found: 271.14882 $C_{15}H_{24}OSiNa$ 271.14886

- (*tert*-butyldimethylsilyl)(4-methoxyphenyl)methanol, **III.22a**

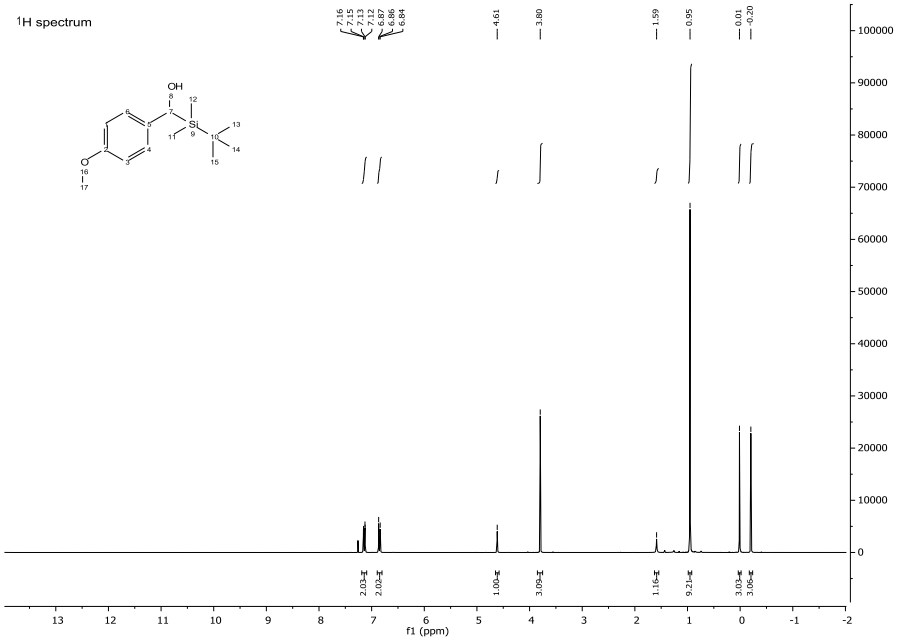


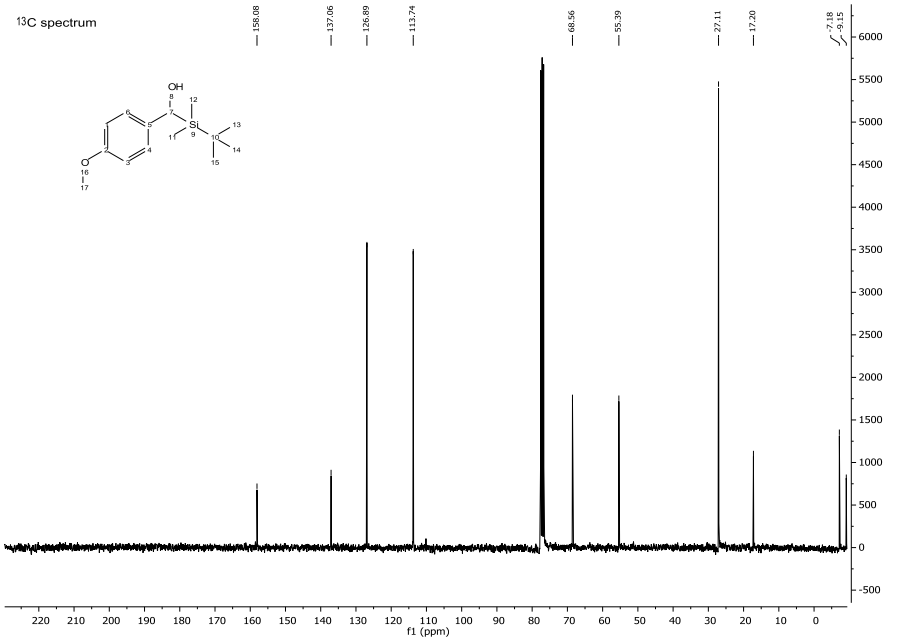
$C_{14}H_{24}O_2Si$
Molecular Weight: 252,4290

Following the General Procedure with Hydrolysis 2 starting with (*tert*-butyldimethylsilyl)(4-methoxyphenyl)methanone **III.19a** (0.21 mmol).

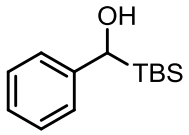
Flash chromatography: PE/EtOAc 95:5. Yield: 47.7 mg (91 %) as a colorless solid. *ee* = 96 %. The enantiomeric ratio was determined by chiral HPLC analysis, Chiralpack IA column, *i*-hexane/EtOH 99.5:0.5, 20 °C, 1 mL/min, detection at 233 nm. Retention times 14.14 min (minor) and 15.29 min (major). $[\alpha]_D^{20}$ = -100 (*c* 11.4 g/L, DCM).

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.17 – 7.10 (m, 2H), 6.92 – 6.79 (m, 2H), 4.61 (s, 1H), 3.80 (s, 3H), 1.59 (brs, 1H), 0.95 (s, 9H), 0.01 (s, 3H), -0.20 (s, 3H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	158.1, 137.1, 126.9, 113.7, 68.6, 55.4, 27.1, 17.2, -7.2, -9.1.
MS (HRMS APCI)	Calcd for $[M+H]^+$ Found: 253.16167 $C_{14}H_{25}O_2Si$ 253.1618


1H spectrum
7.16
7.15
7.13
7.12
6.87
6.86
6.84
4.61
3.80
1.59
0.95
0.01
-0.20
2.03
2.00
1.00
3.09
1.16
9.21
3.03
3.06
f1 (ppm)


13C spectrum
158.08
137.06
126.89
113.74
68.56
55.39
27.11
17.20
7.18
-4.15
f1 (ppm)

- (*S*)-(*tert*-butyldimethylsilyl)(phenyl)methanol, **III.22b**



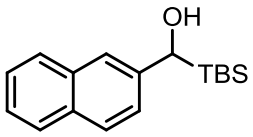
$C_{13}H_{22}OSi$
Molecular Weight: 222,4030

Following the General Procedure with Hydrolysis 2 starting with (*tert*-butyldimethylsilyl)(phenyl)methanone **III.19b** (0.20 mmol).

Flash chromatography: PE/EtOAc 95:5. Yield: 36.6 mg (83 %) as a colorless oil. *ee* = 94 %. The enantiomeric ratio was determined by chiral HPLC analysis, Chiralpack OD-H column, *i*-hexane/EtOH 90:10, 20 °C, 1 mL/min, detection at 225 nm. Retention times 5.53 min (minor) and 7.83 min (major). $[\alpha]_D^{20}$ = -93 (*c* 9.35 g/L, DCM). (lit.[39], $[\alpha]_D^{24}$ = -81.6 (*c* 10.2 g/L, DCM) *ee*=82% (*S*)). The spectral data are consistent with the literature.[39]

^{1}H NMR (δ, ppm)	7.35 – 7.27 (m, 2H), 7.24 – 7.13 (m, 3H), 4.69 (s, 1H),
(300 MHz, $CDCl_3$)	1.65 (brs, 1H), 0.97 (s, 9H), 0.01 (s, 3H), -0.19 (s, 3H).
^{13}C NMR (δ, ppm)	145.0, 128.3, 126.0, 125.6, 69.2, 27.1, 17.3, -7.1, -9.3.
(75 MHz, $CDCl_3$)	

- (*tert*-butyldimethylsilyl)(naphthalen-2-yl)methanol, **III.22c**



$C_{17}H_{24}OSi$
Molecular Weight: 272,4630

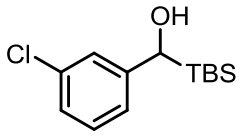
Following the General Procedure with Hydrolysis 2 starting with (*tert*-butyldimethylsilyl)(naphthalen-2-yl)methanone **III.19c** (0.19 mmol).

Flash chromatography: PE/Et_2O 90:10. Yield: 45.3 mg (87 %) as a colorless solid. *ee* = 92 %. The enantiomeric ratio was determined by chiral HPLC analysis, Chiralpack IB column, *i*-hexane/EtOH 95:5, 20 °C, 1 mL/min,

detection at 231 nm. Retention times 7.56 min (major) and 8.98 min (minor). $[\alpha_D^{20}$ = -85.466 (*c* 16.1 g/L, DCM).

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.86 – 7.73 (m, 3H), 7.68 (dd, J = 1.9, 0.9 Hz, 1H), 7.53 – 7.37 (m, 2H), 7.34 (dd, J = 8.5, 1.8 Hz, 1H), 4.86 (d, J = 0.8 Hz, 1H), 1.77 (s, 1H), 1.01 (s, 9H), 0.05 (s, 3H), -0.17 (s, 3H).
^{13}C NMR (δ, ppm) (75 MHz, CD_2Cl_2)	143.3, 133.9, 132.6, 128.0, 127.9, 127.8, 126.4, 125.5, 125.2, 123.5, 69.4, 27.2, 17.5, -6.9, -9.2.
MS (HRMS ESI)	Calcd for $[M+H]^+$ $C_{17}H_{25}OSi$ Found: 273.16691 273.16692

- (*tert*-butyldimethylsilyl)(3-chlorophenyl)methanol, **III.22d**



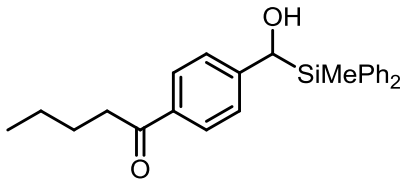
$C_{13}H_{21}ClOSi$
Molecular Weight: 256,8450

Following the General Procedure with Hydrolysis 2 starting with (*tert*-butyldimethylsilyl)(3-chlorophenyl)methanone **III.19d** (0.19 mmol).

Flash chromatography: PE/EtOAc 95:5. Yield: 44.5 mg (92 %) as a colorless oil. *ee* = 89%. The enantiomeric ratio was determined by chiral HPLC analysis, Chiralpack IB column, *i*-hexane/EtOH 95:5, 20 °C, 1 mL/min, detection at 208 nm. Retention times 5.75 min (major) and 8.20 min (minor). $[\alpha]_D^{20}$ = -75 (*c* 10.8 g/L, DCM).

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.25 – 7.19 (m, 2H), 7.17 – 7.11 (m, 1H), 7.12 – 7.02 (m, 1H), 4.66 (s, 1H), 1.71 (bs, 1H), 0.97 (s, 9H), -0.00 (s, 3H), -0.19 (s, 3H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	147.3, 134.3, 129.5, 126.1, 125.5, 123.6, 68.7, 27.1, 17.3, -7.0, -9.4.
MS (HRMS ESI)	Calcd for $[M+H]^+$ $C_{13}H_{22}OClSi$ Found: 257.11225

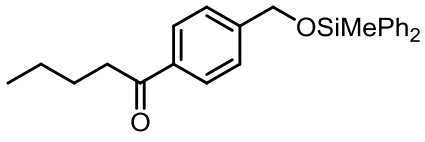
- 1-(4-(hydroxy(methyldiphenylsilyl)methyl)phenyl)pentan-1-one, **III.22i**



$C_{25}H_{28}O_2Si$
Molecular Weight: 388,5820

Following the General Procedure with Hydrolysis 1 starting with (*tert*-butyldimethylsilyl)(naphthalen-2-yl)methanone **III.19i** (0.20 mmol). Flash chromatography: PE/Et_2O 85:15. Yield: 45.3 mg (87 %) as a colorless solid. *ee* = 70 %. The enantiomeric ratio was determined by chiral HPLC analysis, Chiralpack IB column, *i*-hexane/*i*-PrOH 90:10, 20 °C, 1 mL/min, detection at 265 nm. Retention times 9.44 min (major) and 12.01 min (minor). $[\alpha]_D^{20}$ = -25 (*c* 10.3 g/L, DCM).

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.82 – 7.76 (m, 2H), 7.60 – 7.55 (m, 2H), 7.52 – 7.48 (m, 2H), 7.46 – 7.39 (m, 2H), 7.36 (dddd, J = 16.3, 8.1, 6.4, 1.2 Hz, 4H), 7.11 – 7.04 (m, 2H), 5.15 (s, 1H), 2.98 – 2.86 (m, 2H), 1.91 (brs, 1H), 1.77 – 1.65 (m, 2H), 1.48 – 1.34 (m, 2H), 0.95 (t, J = 7.4 Hz, 3H), 0.49 (s, 3H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	148.6, 135.5, 135.2, 135.1, 133.8, 133.2, 130.1, 130.0, 128.1, 128.1, 128.0, 125.5, 69.3, 38.4, 26.7, 22.7, 14.1, -6.9.
MS (HRMS APCI)	Calcd for $[M+H]^+$ Found: 389.19304 $C_{25}H_{29}O_2Si$ 389.19313

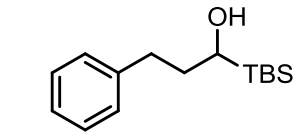


$C_{25}H_{28}O_2Si$
Molecular Weight: 388,5820

Upon spontaneous Brook rearrangement under the hydrolysis conditions, the corresponding silyl ether 1-(4-(((methyldiphenylsilyl)oxy)methyl) phenyl)pentan-1-one **III.24** was isolated.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.98 – 7.87 (m, 2H), 7.67 – 7.57 (m, 4H), 7.48 – 7.32 (m, 8H), 4.84 (s, 2H), 2.99 – 2.91 (m, 2H), 1.78 – 1.66 (m, 2H), 1.59 (brs, 1H), 1.49 – 1.34 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H), 0.68 (s, 3H).
MS (HRMS ESI)	Calcd for $[M+H]^+$ Found: 389.19304 $C_{25}H_{29}O_2Si$ 389.19313

- 1-(*tert*-butyldimethylsilyl)-3-phenylpropan-1-ol, **III.22f**

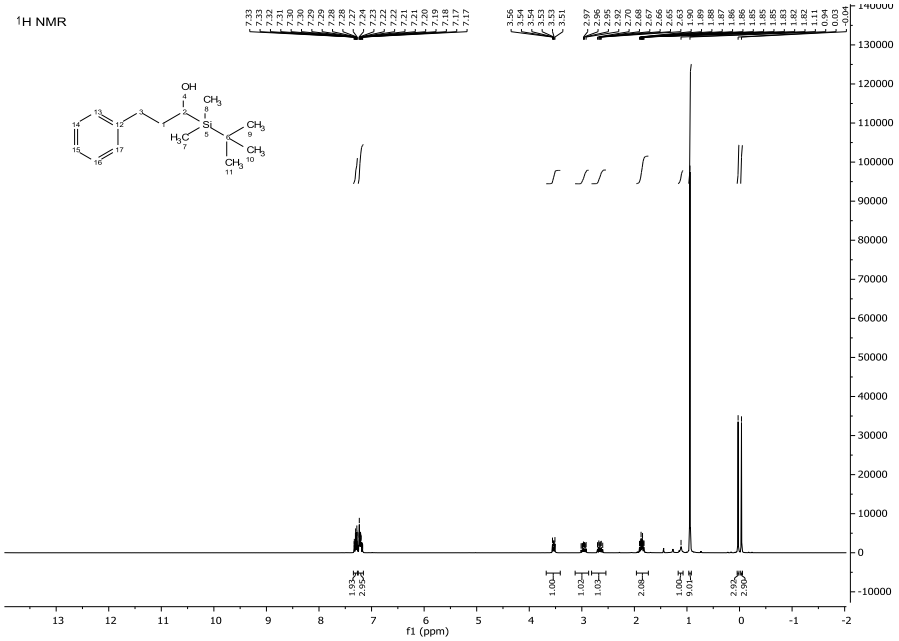


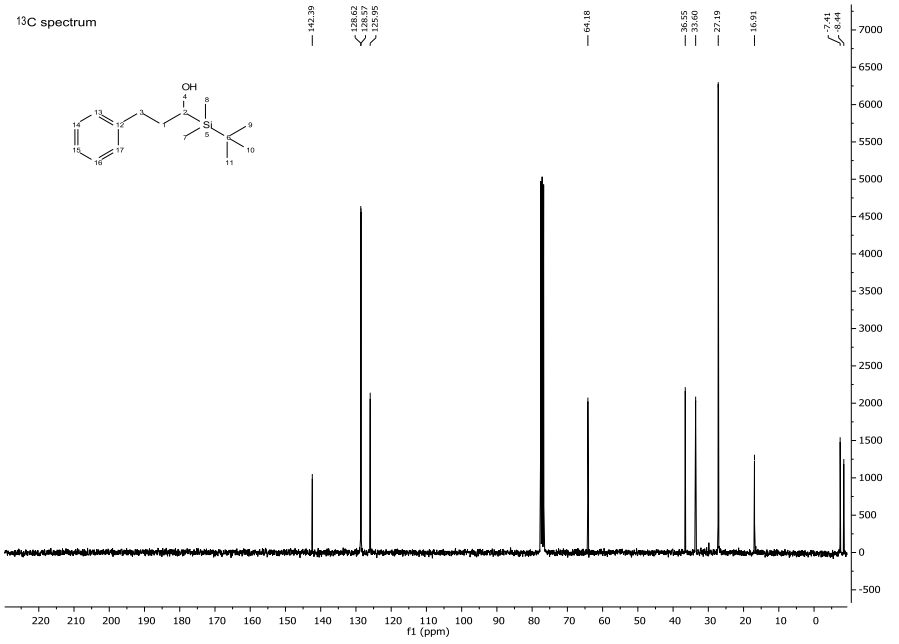
$C_{15}H_{26}OSi$
Molecular Weight: 250,4570

Following the Modified Hydroborylation with Hydrolysis 2 starting with 1-(*tert*-butyldimethylsilyl)-3-phenylpropan-1-one **III.19f** (0.20 mmol).

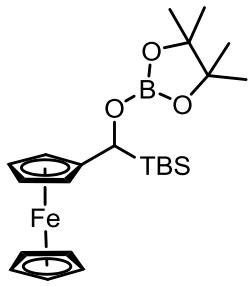
Flash chromatography: PE/Et_2O 90:10. Yield: 39.5 mg (79 %) as a colorless oil. *ee* = 81 %. The enantiomeric ratio was determined by chiral HPLC analysis, Chiralpack IA column, *i*-hexane/*i*-PrOH 97:3, 20 °C, 1 mL/min, detection at 210 nm. Retention times 5.84 min (minor) and 6.88 min (major). $[\alpha]_D^{20}$ = 17 (*c* 12.0 g/L, DCM).

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.35 – 7.27 (m, 2H), 7.22 (dt, J = 8.0, 2.0 Hz, 3H), 3.62 – 3.43 (m, 1H), 2.97 (ddd, J = 13.5, 9.2, 6.7 Hz, 1H), 2.75 – 2.56 (m, 1H), 1.97 – 1.75 (m, 2H), 1.11 (s, 1H), 0.94 (s, 9H), 0.03 (s, 3H), -0.04 (s, 3H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	142.4, 128.6, 128.6, 125.9, 64.2, 36.5, 33.6, 27.2, 16.9, -7.4, -8.4.
MS (HRMS ESI)	Calcd for $[M+Na]^+$ Found: 273.16440 $C_{15}H_{26}ONaSi$ 273.16451


1H NMR
f1 (ppm)


13C spectrum
142.39
128.62
128.57
125.95
64.18
36.55
33.60
27.19
16.91
-7.41
-8.44
f1 (ppm)

- *tert*-butyldimethyl(ferrocenyl((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxy)methyl)silane, **III.23h**



$C_{23}H_{37}BFeO_3Si$
Molecular Weight: 456,2860

Following the racemic copper-catalysed hydroborylation with *I*PrCuCl (5 mol%), NaO*t*Bu (6 mol%), toluene (5 mL.mmol^{-1}) and pinacoleborane (1.5 eq.). Starting with (*tert*-butyldimethylsilyl)(ferrocenyl)methanone **III.19h** (0.2 mmol).

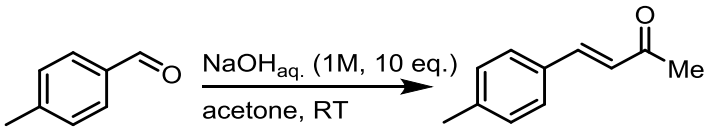
The product could not be isolated, but was observed as the major product of the reaction.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$) 4.75 (s, 1H), 4.20 (s, 5H), 4.15 – 3.98 (m, 4H), 1.33 (s, 12H), 0.86 (s, 9H), -0.09 (s, 3H), -0.17 (s, 3H).

4.2.3 Chemoselective hydroborylations

4.2.3.1 Synthesis of the enone

(*E*)-4-(p-tolyl)but-3-en-2-one **III.11a'** was prepared according to a procedure from the literature.[40]

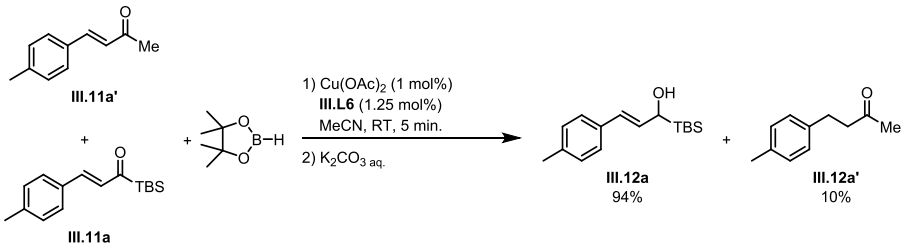


III.11a'

A round-bottom flask was charged with *p*-tolualdehyde (2 mmol, 1 eq.) and acetone (20 mL). The mixture was cooled to 0 °C and aqueous NaOH (20 mL, 1 M) was added dropwise. The mixture was stirred at room temperature until complete conversion of the aldehyde. The acetone was removed *in vacuo* and the crude product was twice extracted with Et_2O. The organic phase were dried over Na2SO4 and the volatiles were removed *in vacuo*. The crude mixture was submitted to flash column chromatography (PE/Et_2O 90:10) and isolated with 53% yield (0.17 g) as a yellow solid. The spectral data are consistent with the literature.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.49 (d, *J* = 17.0 Hz, 2H), 7.44 (d, *J* = 8.5 Hz, 3H), 7.20 (d, *J* = 7.9 Hz, 2H), 6.68 (d, *J* = 16.3 Hz, 1H), 2.38 (s, 4H), 2.37 (s, 4H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	198.6, 143.6, 141.2, 131.8, 129.9, 128.4, 126.4, 27.6, 21.6.

4.2.3.2 Competition experiment

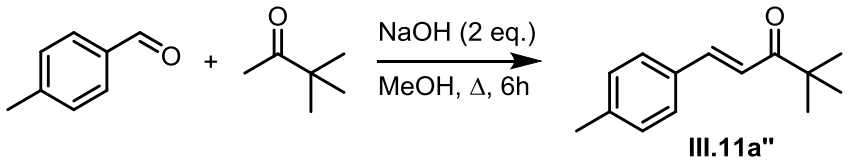


A flame-dried Schlenk tube was charged with (*S*)-(-)-2,2'-Bis[di(3,4,5-trimethoxyphenyl)phosphino]-6,6'-dimethoxy-1,1'-biphenyl **L6** (2.4 mg, 1.25 mol%) under argon. A solution of copper(II) acetate in freshly distilled acetonitrile (0.5mL, 4 mM, 1 mol%) was added followed by pinacolborane (29 µL, 1.0 eq.). When the reaction mixture had turned pale yellow a saturated solution of the acylsilane **III.11a** (0.2 mmol, 1 eq.) and the enone **III.11a'** (0.2 mmol, 1 eq.) in freshly distilled acetonitrile was added. The reaction mixture was stirred at room temperature for 5 minutes. The reaction mixture was diluted with Et_2O (10 mL) and transferred to a separation funnel containing water (14 mL) and a saturated aqueous K_2CO_3 solution (1 mL). The funnel was shacked vigorously and the organic phase was separated. The aqueous phase was washed with Et_2O (10 mL). The organic phases were dried over Na_2SO_4 and the solvents were removed under vacuum. The crude reduction mixture was analysed by ^1H NMR with terephthalaldehyde as internal standard. The α-hydroxysilane **III.12a** (94% NMR yield) and the ketone **III.12a'**[41] (10% NMR yield) were observed to be the reduction products by comparison with reported ^1H NMR spectra from the literature. No other reduction products were detected.

4.2.4 Hypothesis for the reaction's regioselectivity

4.2.4.1 Synthesis of the enone

(*E*)-4,4-dimethyl-1-(p-tolyl)pent-1-en-3-one **III.11a''** was prepared according to a procedure from the literature.[42]



III.11a"

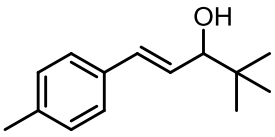
A round bottom flask was charged with *p*-tolualdehyde (2.00 mmol, 1eq.) and MeOH (20 mL). Solid sodium hydroxide (4.00 mmol, 2 eq.) was added at room temperature followed by t-butyl methyl ketone (2.05 mmol, 1.025 eq.). The reaction mixture was refluxed for 6 hours. Methanol was removed *in vacuo*, the crude was dissolved in EtOAc (10 mL), washed with brine (10 mL) and the organic phase was extracted. The aqueous phase was extracted twice with EtOAc. The organic phases were dried over Na_2SO_4, the volatiles were removed *in vacuo* and the crude mixture was submitted to flash column chromatography affording the title compound as a colourless solid (0.16g, 41%).

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.67 (d, *J* = 15.6 Hz, 1H), 7.47 (d, *J* = 8.1 Hz, 2H), 7.19 (d, *J* = 7.9 Hz, 2H), 7.09 (d, *J* = 15.6 Hz, 1H), 2.37 (s, 3H), 1.23 (s, 9H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	204.4, 143.0, 140.7, 132.3, 129.7, 128.4, 119.8, 43.3, 26.5, 21.6.
MS (HRMS ESI)	Calcd for $[M+H]^+$ $C_{14}H_{19}O$ Found: 203.14326 203.14304

4.2.4.2 Copper-catalysed hydroborylation of the **III.11a''**

In a flame-dried Schlenk tube, *I*PrCuCl (5 mol%) and NaO*t*Bu (6 mol%) were dissolved in toluene (5 mL.mmol^{-1}) under argon and the mixture was stirred at room temperature for 5 minutes. Pinacolborane (1.5 eq.) was added followed by a saturated solution of the enone **III.11a''** (0.2 mmol, 1 eq.) in freshly distilled toluene. The reaction mixture was stirred at room temperature until complete conversion. The reaction mixture was diluted with Et_2O (10 mL) and transferred to a separation funnel containing water (14 mL) and a saturated aqueous K_2CO_3 solution (1 mL). The funnel was shacked vigorously and the organic phase was separated. The aqueous phase was washed with Et_2O (10 mL). The organic phases were dried over Na_2SO_4 and the solvents were removed under vacuum. The crude mixture was submitted to flash column chromatography (PE/Et_2O 98:2) affording the reduction products as colourless oils.

- (*E*)-4,4-dimethyl-1-(p-tolyl)pent-1-en-3-ol

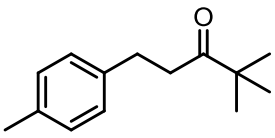


$C_{14}H_{20}O$
Molecular Weight: 204,3130

Isolated as the major product following the procedure. Yield: 32.2 mg (79%) as a colourless oil.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.29 (d, *J* = 8.1 Hz, 2H), 7.13 (d, *J* = 7.9 Hz, 2H), 6.54 (d, *J* = 16.0 Hz, 1H), 6.24 (dd, *J* = 15.9, 7.3 Hz, 1H), 3.91 (d, *J* = 7.3 Hz, 1H), 2.34 (s, 3H), 1.55 (brs, 1H), 0.97 (s, 9H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	137.6, 134.2, 131.9, 129.4, 128.6, 126.5, 81.3, 35.4, 25.9, 21.3.
MS (HRMS ESI)	Calcd for $[M+H-H_2O]^+$ Found: 187.14830 $C_{14}H_{19}$ 187.14813

- 4,4-dimethyl-1-(p-tolyl)pentan-3-one



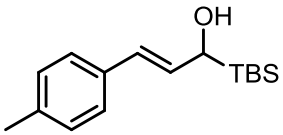
$C_{14}H_{20}O$
Molecular Weight: 204,3130

Isolated as the minor product following the procedure. Yield: 4.4 mg (10%) as a colourless oil.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.08 (s, 4H), 2.88 – 2.73 (m, 4H), 2.31 (s, 3H), 1.11 (s, 9H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	207.6, 138.6, 135.6, 129.3, 128.4, 38.8, 29.9, 26.5, 21.1, 1.2.
MS (HRMS ESI)	Calcd for $[M+H-H_2O]^+$ Found: 187.14827 $C_{14}H_{19}$ 187.14813

4.2.5 Large scale experiments

4.2.5.1 α,β-unsaturated acylsilane

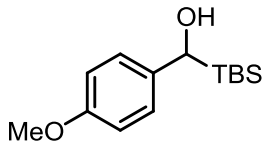


5 mmol scale
Yield: 91%
ee: 91%

A flame-dried Schlenk tube was charged with (S)-(-)-2,2'-Bis[di(3,4,5-trimethoxyphenyl)phosphino]-6,6'-dimethoxy-1,1'-biphenyl **L6** (5.9 mg, 0.125 mol%) under argon. A solution of copper(II) acetate in freshly distilled acetonitrile (1.25mL, 4 mM, 0.1 mol%) was added. The mixture was diluted with acetonitrile (3 mL) followed by the addition of pinacolborane (1 mL, 1.5 eq.). When the reaction mixture had turned pale yellow a saturated solution of (**E**)-1-(*tert*-butyldimethylsilyl)-3-(p-tolyl)prop-2-en-1-one **III.11a** (1.30 g, 5 mmol) in freshly distilled acetonitrile was added. The reaction mixture was stirred at room temperature for 90 minutes until complete conversion of the acylsilane monitored by TLC. The reaction mixture

was diluted with Et_2O (60 mL) and transferred to a separation funnel containing water (80 mL) and a saturated aqueous K_2CO_3 solution (6 mL). The funnel was shaken vigorously and the organic phase was separated. The aqueous phase was washed with Et_2O (60 mL). The organic phases were dried over Na_2SO_4 and the solvents were removed under vacuum. The crude product was purified by flash column chromatography eluting with PE/Et_2O (95:5) affording (E)-1-(*tert*-butyldimethylsilyl)-3-(p-tolyl)prop-2-en-1-ol **(*S*)-III.12a** as a white solid. Yield: 1.19 g (91%). *ee*: 91%. The analytical data are the same as those described for the small scale experiment.

4.2.5.2 Aromatic acylsilane

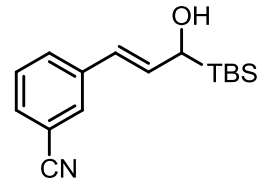


5 mmol scale
Yield: 97%
ee: 95%

A flame-dried Schlenk tube was charged with (S)-(-)-2,2'-Bis[di(3,4,5-trimethoxyphenyl)phosphino]-6,6'-dimethoxy-1,1'-biphenyl **L6** (59 mg, 1.25 mol%) and copper(II) acetate (9 mg, 1 mol%). The solids were dissolved in freshly distilled acetonitrile (5 mL) followed by the addition of pinacolborane (1 mL, 1.5 eq.). When the reaction mixture had turned pale yellow a solution of (*tert*-butyldimethylsilyl)(4-methoxyphenyl)methanone **III.19a** (1.25 g, 5 mmol) in freshly distilled acetonitrile (5 mL) was added. The reaction mixture was stirred overnight at room temperature. A saturated aqueous K_2CO_3 solution (5 mL) was added and the reaction mixture was stirred vigorously for 5 minutes. The reaction mixture was diluted with Et_2O (60 mL) and transferred to a separation funnel containing water (80 mL). The organic phase was separated. The aqueous phase was

extracted with Et_2O (60 mL). The organic phases were dried over Na_2SO_4 and the solvents were removed under vacuum. The crude product was purified by flash column chromatography eluting with PE/Et_2O (90:10) affording (*tert*-butyldimethylsilyl)(4-methoxyphenyl)methanol **III.22a** as a white solid. Yield: 1.21 g (97%). *ee*: 95%. The analytical data are the same as those described for the small scale experiment.

4.2.5.3 Copper-catalysed hydroborylation under air



1 mmol scale under air
Yield: 88%
ee: 81%

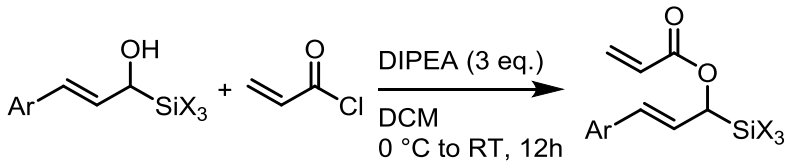
An oven-dried test-tube was charged under air with copper(II) acetate (1.8 mg, 1 mol%) and (S)-(-)-2,2'-Bis[di(3,4,5-trimethoxyphenyl)phosphino]-6,6'-dimethoxy-1,1'-biphenyl **L6** (11.8 mg, 1.25 mol%). The solids were dissolved in commercial anhydrous acetonitrile (2.5 mL) before the addition of pinacoleborane (0.22 mL, 1.5 eq.). A solution of (E)-3-(3-(*tert*-butyldimethylsilyl)-3-oxoprop-1-en-1-yl)benzonitrile **III.11d** (0.28 g, 1.02 mmol) in commercial anhydrous acetonitrile (2.5 mL) was added and the mixture was stirred for 15 minutes at room temperature until no more conversion of the substrate was detected. The reaction mixture was diluted with Et_2O (20 mL) and transferred to a separation funnel containing water (40 mL). The organic phase was separated. The aqueous phase was extracted with Et_2O (20 mL). The organic phases were dried over Na_2SO_4 and the solvents were removed under vacuum. The crude product was purified by flash column chromatography eluting with PE/Et_2O (85:15) affording (E)-3-(3-(*tert*-

butyldimethylsilyl)-3-hydroxyprop-1-en-1-yl)benzonitrile **III.12d** as a colourless oil. Yield: 0.25 g (88%). *ee*: 81%. The analytical data are the same as those described for the small scale experiment.

4.2.6 Copper-catalysed reductive Claisen rearrangement

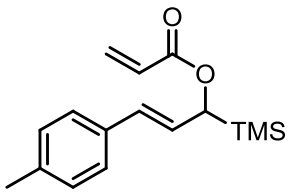
4.2.6.1 Acryloylation of the α-hydroxyallylsilanes

A procedure inspired from the literature was used for the synthesis of the racemic and enantioenriched α-acryloyloxyacylsilanes.[43]



To a mixture of the α-hydroxyallylsilanes (1 eq.) and iPr_2NEt (DIPEA, 3 eq.) in DCM (2 $mL.mmol^{-1}$) at 0 ºC was added acryloyl chloride (2 eq.) slowly. The reaction mixture was allowed to warm to room temperature and stirred for 12 h. Water was then added and the organic layer was separated. The aqueous layer was extracted with Et_2O three times. The combined organic layers were dried over anhydrous MgSO4, concentrated, and subjected to flash column chromatography to afford the desired enoates.

- (*E*)-3-(p-tolyl)-1-(trimethylsilyl)allyl acrylate, **III.25a**



$C_{16}H_{22}O_2Si$
Molecular Weight: 274,4350

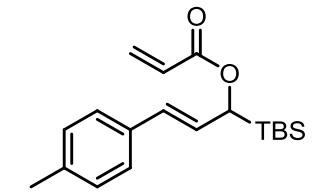
Following the procedure starting with (*E*)-3-(p-tolyl)-1-(trimethylsilyl)prop-2-en-1-ol **III.9** (2.86 mmol).

Flash chromatography: PE/Et_2O 98:2. Yield: 0.57 g (73%) as a white solid.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.24 (d, *J* = 8.2 Hz, 2H), 7.10 (d, *J* = 7.9 Hz, 2H), 6.50 – 6.32 (m, 2H), 6.27 – 6.14 (m, 2H), 5.84 (dd, *J* = 10.3, 1.6 Hz, 1H), 5.44 (dd, *J* = 6.8, 1.5 Hz, 1H), 2.32 (s, 3H), 0.10 (s, 9H).

^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	166.1, 137.1, 134.5, 130.5, 129.3, 128.8, 127.7, 126.2, 125.8, 70.8, 21.3, -3.6.
MS (HRMS ESI)	Calcd for $[M+Na]^+$ Found: 297.12815 $C_{16}H_{22}O_2SiNa$ 297.12813

- (*E*)-1-(*tert*-butyldimethylsilyl)-3-(p-tolyl)allyl acrylate, **III.25b**



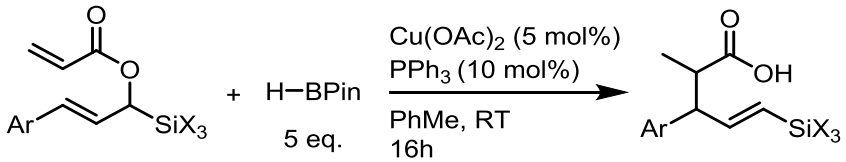
$C_{19}H_{28}O_2Si$
Molecular Weight: 316,5160

Following the procedure starting with (*E*)-1-(*tert*-butyldimethylsilyl)-3-(p-tolyl)prop-2-en-1-ol **III.12a** (1.00 mmol). Flash chromatography: PE/Et_2O 98:2. Yield: 302.4 mg (95%) as a colorless oil.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.23 (d, *J* = 8.1 Hz, 2H), 7.10 (d, *J* = 7.9 Hz, 2H), 6.51 – 6.32 (m, 2H), 6.28 – 6.11 (m, 2H), 5.85 (dd, *J* = 10.3, 1.6 Hz, 1H), 5.59 (dd, *J* = 6.7, 1.4 Hz, 1H), 2.32 (s, 3H), 0.95 (s, 9H), 0.09 (s, 3H), 0.05 (s, 3H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	165.9, 137.0, 134.5, 130.6, 129.3, 128.9, 127.8, 126.5, 126.2, 69.0, 27.0, 21.3, 17.2, -7.2, -8.0.
MS (HRMS ESI)	Calcd for $[M+Na]^+$ Found: 339.17531 $C_{19}H_{28}O_2SiNa$ 339.17508

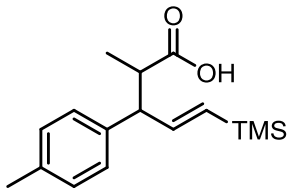
4.2.6.2 Procedure for the copper-catalysed Claisen rearrangement of the α-acryloyloxyallylsilanes

Conditions inspired from the literature were used without optimisation.[43]



A Schlenk tube was charged with $Cu(OAc)_2$ (5 mol%) and triphenylphosphine (10 mol%). Toluene (1 $mL.mmol^{-1}$) was added and the mixture was stirred at room temperature for 15 minutes before the addition of pinacoleborane (5 eq.). The mixture was further stirred at room temperature until the appearance of a red/orange colour (approximatively 30 minutes). A saturated solution of the α-acryloyloxyallylsilanes in toluene was added and the mixture was stirred overnight. The reaction solution was filtered through a pad of silica gel eluting with Et_2O and the solvents were removed *in vacuo*. The crude product was purified by flash column chromatography with the indicated eluent to afford the desired product as an inseparable diastereomeric mixture. The diastereomeric ratio (d.r.) was determined by ^1H NMR spectroscopy.

- (*E*)-2-methyl-3-(p-tolyl)-5-(trimethylsilyl)pent-4-enoic acid, **III.26a**



$C_{16}H_{24}O_2Si$
Molecular Weight: 276,4510

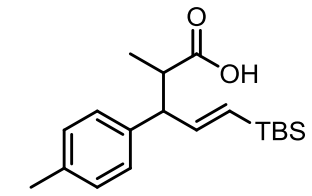
Following the procedure starting with racemic (*E*)-3-(p-tolyl)-1-(trimethylsilyl)allyl acrylate **III.25a** (0.2 mmol).

Flash chromatography: PE/Et_2O 40:60. Yield: 45.6 mg (82%) as a colorless oil. d.r. (97:3:0:0).

^1H NMR (δ, ppm) (300 MHz, $CDCl_3$)	(Major isomer) 7.08 (s, 4H), 6.01 (dd, *J* = 18.4, 8.5 Hz, 1H), 5.74 (dd, *J* = 18.4, 0.8 Hz, 1H), 3.46 (t, *J* = 9.0 Hz, 1H), 2.88 – 2.72 (m, 1H), 2.31 (s, 3H), 1.19 (d, *J* = 6.9 Hz, 3H), 0.03 (s, 9H).

^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	(Major isomer) 182.6, 145.7, 139.1, 136.2, 133.0, 129.3, 127.7, 55.6, 44.7, 21.2, 15.8, -1.1.
MS (HRMS APCI)	Calcd for $[M+H]^+$ Found: 277.16166 $C_{16}H_{25}O_2Si$ 277.16183

- (*E*)-5-(*tert*-butyldimethylsilyl)-2-methyl-3-(p-tolyl)pent-4-enoic acid, **III.26b** and **(*S*)-III.26b**



$C_{19}H_{30}O_2Si$
Molecular Weight: 318,5320

Following the procedure starting with racemic (*E*)-1-(*tert*-butyldimethylsilyl)-3-(p-tolyl)allyl acrylate **III.25b** (0.2 mmol). Flash chromatography: PE/Et_2O 40:60. Yield: 50.1 mg (79%) as a colourless oil. d.r. (95:5:0:0).

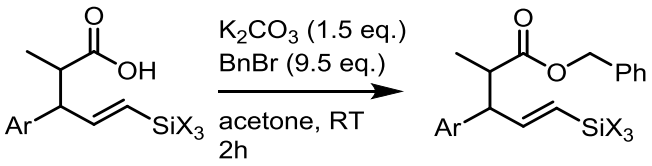
Following the procedure starting with enantioenriched (*E*)-1-(*tert*-butyldimethylsilyl)-3-(p-tolyl)allyl acrylate **III.25b** (*ee* = 91%, 0.2 mmol).

Flash chromatography: PE/Et_2O 40:60. Yield: 58.2 mg (91%) as a colourless oil. d.r. (95:5:0:0).

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	(Major isomer) 7.12 (s, 4H), 6.06 (dd, *J* = 18.4, 8.6 Hz, 1H), 5.78 (dd, *J* = 18.4, 0.9 Hz, 1H), 3.53 (t, *J* = 9.1 Hz, 1H), 2.99 – 2.79 (m, 1H), 2.33 (s, 3H), 1.25 (d, *J* = 7.0 Hz, 3H), 0.87 (s, 9H), 0.02 (s, 3H), -0.00 (s, 3H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	(major isomer) 180.5, 147.0, 139.1, 136.2, 130.1, 129.3, 127.7, 55.7, 44.6, 26.6, 21.2, 16.7, 15.6, -5.9, -6.2.
MS (HRMS APCI)	Calcd for $[M+H]^+$ 319.20878 Found: 319.20869 $C_{19}H_{31}O_2Si$

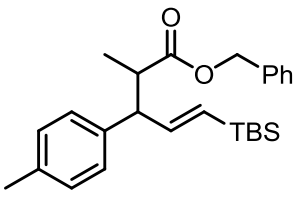
4.2.6.3 Procedure for the esterification of the silylpentenoic acids

The chiral HPLC analysis were conducted on the ester derivatives of the obtained silylpentenoic acid. The esterification was carried out according to the literature.[43]



To the silylpentenoic acid (1 eq.) in acetone (7 $mL.mmol^{-1}$) was added K_2CO_3 (1.5 eq.) followed by benzylbromide (9.5 eq.). The reaction mixture was stirred at room temperature for 2 h, then filtered through a loose plug of cotton wool. The filtrate was concentrated *in vacuo*, and subjected to flash column chromatography with the indicated eluent to afford the benzyl ester.

- benzyl (*E*)-5-(*tert*-butyldimethylsilyl)-2-methyl-3-(p-tolyl)pent-4-enoate



$C_{26}H_{36}O_2Si$
Molecular Weight: 408,6570

Following the procedure starting with racemic (*E*)-5-(*tert*-butyldimethylsilyl)-2-methyl-3-(p-tolyl)pent-4-enoic acid **III.26b** (0.16 mmol).

Flash chromatography: PE/Et_2O 98:2. Yield: 54.4 mg (83%) as a colourless oil.

Following the procedure starting with enantioenriched (*E*)-5-(*tert*-butyldimethylsilyl)-2-methyl-3-(p-tolyl)pent-4-enoic acid **(*S*)-III.26b** (*ee* = 91%, 0.08 mmol).

Flash chromatography: PE/Et_2O 98:2. Yield: 29.4 mg (84%) as a colourless oil. *ee*: 93%. The enantiomeric ratio was determined by

chiral HPLC analysis, Chiralpack IA column, *i*-hexane/*i*-PrOH 99.5:0.5, 20 °C, 1 mL/min, detection at 210 nm. Retention times 4.66 min (major) and 5.08 min (minor).

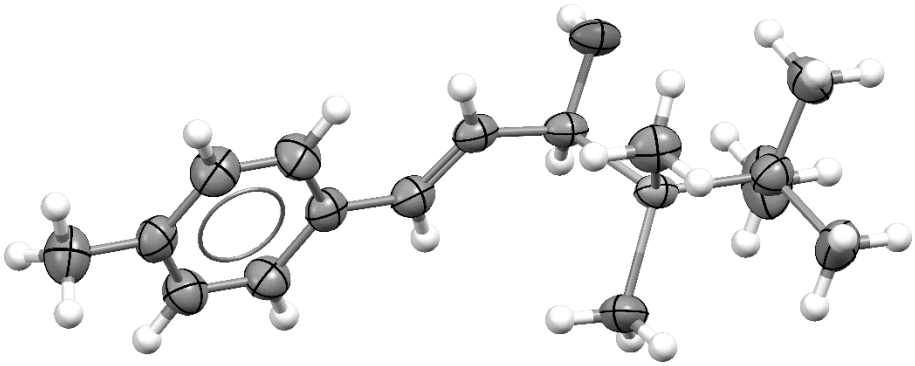
^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.30 – 7.26 (m, 4H), 7.06 (m, 5H), 6.05 (dd, *J* = 18.4, 8.5 Hz, 1H), 5.74 (d, *J* = 18.4 Hz, 1H), 5.02 – 4.62 (m, 2H), 3.49 (dd, *J* = 10.0, 8.6 Hz, 1H), 2.87 (dq, *J* = 10.1, 6.9 Hz, 1H), 2.31 (s, 3H), 1.23 (d, *J* = 6.9 Hz, 3H), 0.84 (s, 9H), -0.00 (s, 3H), -0.03 (s, 3H).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	175.5, 147.6, 139.3, 136.1, 136.0, 129.7, 129.3, 128.5, 128.2, 128.1, 127.8, 66.1, 56.5, 45.1, 26.6, 21.2, 16.7, 16.1, -5.9, -6.1.
MS (HRMS ESI)	Calcd for $[M+H]^+$ Found: 409.25562 $C_{26}H_{37}O_2Si$ 409.25573

5 Crystallographic data

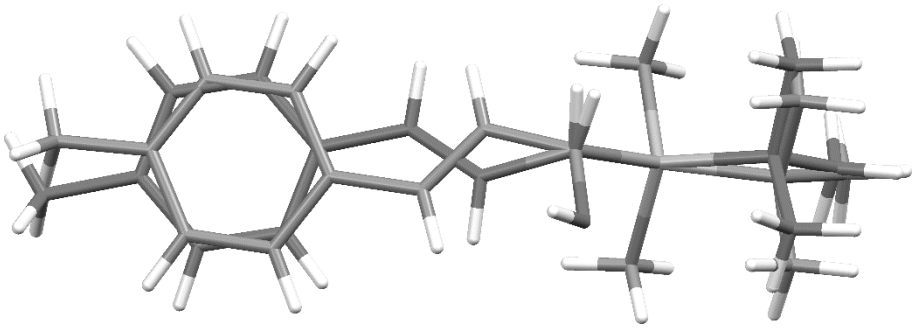
This measurement was carried out by Dr. Koen Robeyns.

Single crystals suitable for X-ray diffraction experiments were obtained by slow evaporation of an ethereal solution of **III.12a**.

Diffraction data were recorded on a Mar345 image plate, using Mo Kα radiation (Rigaku Rotating anode Ultra X18, Fox 3D mirrors). The crystal was mounted on a nylon loop and flash cooled to 150K in a N_2 gas-flow prior to the X-ray experiment. All data were integrated using CrysAlis^{PRO} and the implemented absorption correction was applied. Structures were solved by SHELXT and refined by full-matrix least-squares on $|F^2|$ by SHELXL-2014. Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were placed on calculated positions in riding mode with temperature factors fixed at 1.2 times Ueq of the parent atoms and 1.5 times Ueq for methyl groups. The compound crystallizes in the orthorhombic chiral space group $P2_12_12_1$ with 4 molecules in the asymmetric unit (Z'=4) and a total of 16 moieties in the unit cell. An ORTEP representation of one such molecules is shown. Two molecules show disorder. The crystal data and refinement parameters of the resolved structure are presented. Molecular figures were created by Mercury.



Scheme 0-1 Ortep representation of a single moiety as found in the crystal structure, the H-atom on the chiral carbon is pointing down, giving an S-configuration.



Scheme 0-2 The observed disorder can be seen as a mirror plane running through the main axis of the molecule.

*Table 0-1 Crystal data and structure refinement for **III.12a**.*

Identification code	an001
Empirical formula	C_{16} H_{26} O Si
Formula weight	262.46
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 15.4243(4) Å
	b = 15.4601(4) Å
	c = 28.3644(8) Å
Volume	6763.8(3) $Å^3$

Z	16
Density (calculated)	1.031 Mg/m^3
Absorption coefficient	0.128 mm^{-1}
F(000)	2304
Crystal size	0.50 x 0.35 x 0.10 mm^3
θ range for data collection	2.850 to 25.682°.
Reflections collected	25324
Independent reflections	12456 [$R_{(int)}$ = 0.0457]
Completeness to θ = 25.242°	97.3 %
Absorption correction	multi-scan
Max. and min. transmission	1.00000 and 0.88133
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	12456 / 290 / 883
Goodness-of-fit on F^2	1.037
Final R indices [I>2sigma(I)]	R_1 = 0.0462, wR_2 = 0.1097
R indices (all data)	R_1 = 0.0584, wR_2 = 0.1161
Absolute structure parameter	-0.01(6)
Largest diff. peak and hole	0.356 and -0.271 $e.Å^{-3}$

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