Enantioselective Organocatalytic Synthesis of γ-Valerolactone by Hydrosilylation of Methyl Levulinate

Thesis for MSc Degree

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Abstract

Enantiopure γ-valerolactone (GVL) has many applications and can be produced by stereoselectively reducing the inexpensive biomass compound levulinic acid (LA) or derivative alkyl levulinates (ALs). A green and highly selective method of performing this synthesis is by asymmetric organocatalyzed hydrosilylation. Coupling a bulky chiral cation and a fluoride anion catalyst both activates the hydride-donating silane and induces stereoselectivity in the reaction. In this thesis the principle above has been applied in the N-benzylquininium fluoride (BQF) catalyzed hydrosilylation of methyl levulinate (ML) to GVL by tris(trimethylsiloxy)silane (TTSH), leading to an ee of roughly 25%. Likewise the catalyst N-benzylquinidinium fluoride (BQDF), which is the pseudo-enantiomer of BQF, has been utilized resulting in the same selectivity, but of the opposite chirality. To explore the effect of the chiral cation and fluoride catalyst separately, N-benzylquininium chloride (BQC) (or pseudo-enantiomer N-benzylquinidinium chloride (BQDC)) combined with tetra-*n*-butyl- ammonium fluoride (TBAF) have been used to catalyze the hydrosilylation reaction. Small amounts of BQC or BQDC lead to a stable ee of around 12%, but a diminished yield.

Abbreviations

et al. *et alii*

i.e. *id est*

***i*BL** isobutyl levulinate

µl microliter

µm micrometer

µmol micromole

^{1}H-NMR proton nuclear magnetic resonance spectroscopy

AAL α-angelica lactone

AL alkyl levulinate

BL *n*-butyl levulinate

BnL benzyl levulinate

BorL borneol levulinate

BQC N-benzylquininium chloride

BQDC N-benzylquinidinium chloride

BQDF N-benzylquinidinium fluoride

BQDH N-benzylquinidinium hydroxide

BQF N-benzylquininium fluoride

BQH N-benzylquininium hydroxide

BuOH *n*-butanol

$CDCl_3$ deuterated chloroform

ee enantiomeric excess

$Eu(hfc)_3$ europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate]

FA formic acid

FID flame ionization detector

GVL γ-valerolactone

H_2 molecular hydrogen

HF hydrogen fluoride

HPA 4-hydroxypentanoic acid

KF potassium fluoride

LA levulinic acid

MenL menthol levulinate

ML methyl levulinate

mmol millimole

$NaClO_4$ sodium perchlorate

PMHS polymethylhydrosiloxane

PSYCHE Pure Shift Yielded by Chirp Excitation

TBAF tetra-*n*-butylammonium fluoride

TBN tri-*n*-butylamine

TMOSH trimethoxysilane

TTSH tris(trimethylsiloxy)silane

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1 Introduction

1.1 Biomass

The unsustainable consumption of fossil carbon reserves is a big challenge currently facing humanity. Alternative and efficient routes for the production of energy and chemicals from sustainable resources are therefore needed. Biomass can serve as a source of renewable energy as well as of key reagents for the chemical industry. In this respect, lignocellulosic biomass has received much attention. Lignocellulose consists mainly of cellulose, hemicellulose and lignin. Lignin is a natural, polyaromatic polymer which is a source of aromatic molecules. Cellulose and hemicellulose are carbohydrate polymers and can be obtained from a wide range of plant resources. Depolymerization of (hemi)cellulose by hydrolysis can produce several C5-C6 sugars, such as glucose, mannose and xylose.

Further processing of these sugars can provide a large variety of platform molecules. Of these, levulinic acid (LA)[1] and γ-valerolactone (GVL) are of special interest for this thesis.

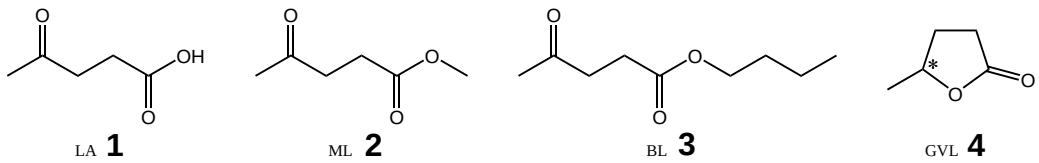
1.2 Levulinic acid and γ-Valerolactone

1.2.1 Levulinic acid

Levulinic acid (LA) is the trivial name of 4-oxopentanoic acid. It is a promising chemical building block as LA can be the source of numerous value added products, such as valeric acid, 2-methyltetrahydrofuran and γ-valerolactone. These chemicals have multiple applications as pharmaceuticals, resin, additives and biofuels, among others.

The synthesis of LA was first documented by the Dutch scientist G.J. Mulder in 1840. It was acquired by heating fructose in the presence of a mineral acid, yielding LA and formic acid (FA).[2] An intensive effort has been made to produce LA on a large scale since then. Currently, the Biofine process is the most developed for industrial LA production.[1] The utilization of diverse inexpensive and renuewable lignocellulosic wastes, such as

paper mill sludge, urban waste paper and residues from the agricultural sector, allows LA to be produced in a large scale for a competitive price. For example, the Italian company GFBiochemicals is projected to produce 10,000 megatons of LA for the year 2017.[3]



Scheme 1.1: Levulinic acid (LA) **1**, alkyl levulinate (AL) substrates methyl levulinate (ML) **2** and *n*-butyl levulinate (BL) **3** and product γ-valerolactone (GVL) **4**.

Given the aim of this thesis, alkyl levulinates (ALs) are of particular interest as they can also be used as a substrate for GVL synthesis.[4] An alkyl levulinate can be obtained by esterification of levulinic acid with an alcohol as was first described by Conrad in 1877.[5] ALs can also be produced from cellulose directly in a one-pot process.[6,7] Tominaga *et al.* reported that a yield of 75% methyl levulinate (ML) can be obtained by having cellulose react with methanol at 180 °C in the presence of acid.[8]

1.2.2 γ-Valerolactone

γ-Valerolactone (GVL), also known as γ-methyl-γ-butyrolactone or 4- hydroxypentanoic acid lactone, is a very stable, colorless liquid with a boiling point of 207 °C. GVL occurs naturally in fruit and has low toxicity. The safe nature of GVL is illustrated by its use as a food additive.[9] Currently the main focus is on the prospect of utility as a fossil fuel substitute or additive.[10,11]

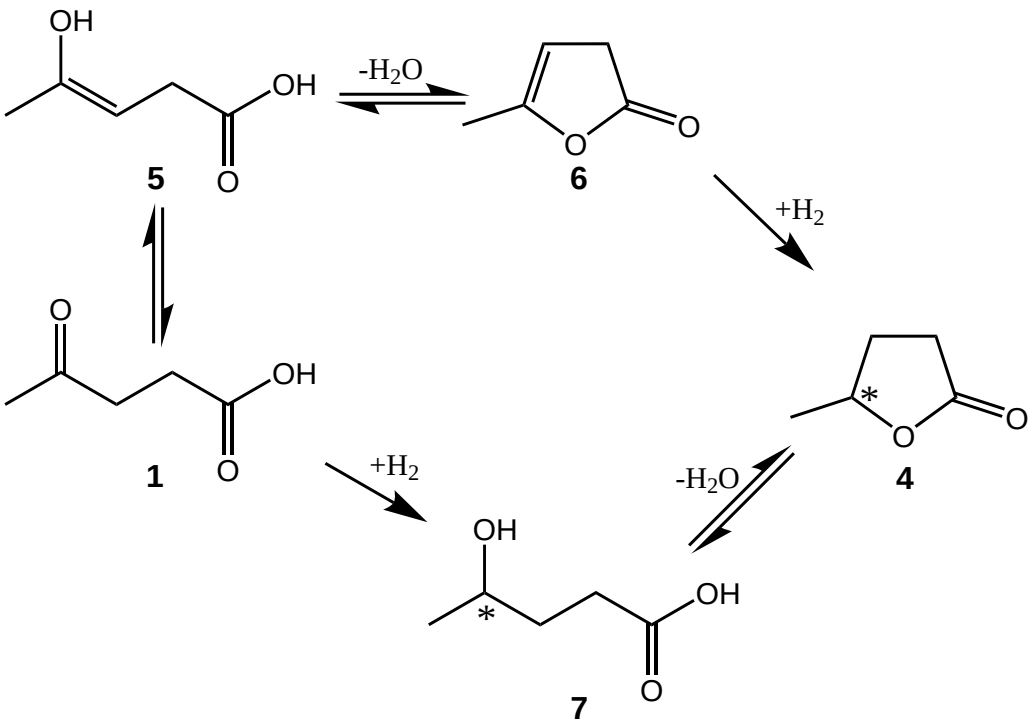
The compound is moderately polar and mixes well with many diverse fluids, including gasoline but also water.[12] Inversely, GVL itself is a practical organic solvent,[13] which can be modified for specific solvation.[14,15]

An especially interesting and underappreciated aspect of the GVL molecule is the presence of a chiral center. Enantiopure GVL is a chiral solvent, which has potential for aiding in recognition[16] and separation of other chiral compounds.[17,18] It can be converted to a chiral ionic liquid, gaining

possible use in asymmetric synthesis or stereoselective polymerization.[19]

In organic synthesis GVL is a platform compound[20] with many applications,[21–23] whose value is further increased by optical purity. Optically pure GVL is needed in the synthesis of certain beetle pheromones[24] and pesticides,[25] but can also be utilized for synthesizing psychotropic[26] and antiparasitic drugs[27] and it works as an inhibitor of enzymes which promote heart disease and other afflictions.[28] This plethora of applications forms the drive to develop a practical and cost-effective way of producing GVL enantioselectively from LA, which is renewable and environmentally friendly.

1.2.3 The hydrogenation of LA to GVL



Scheme 1.2: GVL formation from LA. Top pathway: keto-LA **1** *via* enol-LA **5** condenses to AAL **6**, which hydrogenates to GVL **4**. Bottom pathway: LA **1** hydrogenates to HPA **7**, which condenses to GVL **4**.

The synthesis of GVL from LA can occur *via* two general pathways. LA

1 can be dehydrated to α-angelica lactone (AAL) **6**[29] followed by hydrogenation to GVL **4**.[30,31] Langlois *et al.* have proposed the initial dehydration step in this route starts with the enol form **5** of keto acid LA **1** which undergoes intramolecular esterification.[32]

The other route follows a reverse order of steps: First, LA **1** (or AL) is hydrogenated to 4-hydroxypentanoic acid (HPA) **7** (or the AL equivalent), followed by intramolecular esterification to GVL **4** and water (or the relevant alcohol). Due to the stability of the lactone ring, the ring closure step in this route is energetically favored and can occur automatically in moderately acidic or alkaline environment.

1.2.3.1 Heterogeneous catalysis

Since 1881[33] many processes have been developed to produce GVL from LA or AL using heterogeneous metal catalysts. The reactions typically run at a relatively low temperature ranged from room temperature to 265 °C with molecular hydrogen (1-150 bar) as reducing reactant. For instance, Sabatier *et al.* reported a GVL production passing a 250 °C gas mixture of LA and H_2 over a nickel catalyst[34] and Schuette *et al.* converted LA to GVL in ether (among other solvents) with hydrogen (2.3-3 bar) and a PtO_2 catalyst at room temperature.[35]

Many variations have been researched using a multitude of combinations of reaction conditions and precious metal catalysts. Especially ruthenium on a carbon support is of note for providing high conversion and selectivity in all kinds of reaction conditions.[36–38] This is illustrated by Manzer *et al.*, who compared Ru, Rh, Pd, Re, Ir, Pt and Ni (5 *wt%* on carbon) for hydrogenation of LA to GVL in 1,4-dioxane at 150 °C and under 55 bar of H_2. With high selectivity the Ru catalyst gave the highest conversion of 79% after 2 h reaction time, whereas the reaction with the second best result reached only 38% conversion, using the Ir catalyst.[22]

More economical options are found in the use of base metals, like the mentioned Ni,[22,34] but also CuO/Cr_2O_3.[39] Hengne *et al.* reported 100% LA conversion and >99.9% selectivity to GVL with both Cu on ZrO_2 and Cu on Al_2O_3 support at 200 °C and 35 bar H_2 for 5 h in water. By obtaining these excellent results using relatively moderate reaction conditions, Hengne *et al.* showed the use of base metals can be a serious alternative to precious metals for LA to GVL hydrogenation.[40]

Due to the costs, environmental impact and safety concerns associated with (the production of) H_2, alternative hydrogen sources have been explored. For instance, in the work of Yang *et al.*, EL was converted to GVL by isopropyl alcohol with a Raney Ni catalyst in 9 h at room temperature with a yield of 99%.[41] Of special interest is the use of formic acid (FA) as a source of hydrogen, since FA is a by-product in the production of LA from biomass.[42] Du *et al.* had success utilizing FA for transfer hydrogenation of LA to GVL by catalysis with 0.8 *wt%* Au nanoparticles supported on ZrO_2, performed in water at 150 °C and under 5 bar N_2 for 6 h.[43] Deng *et al.* have demonstrated the possible use of (in first instance homogeneous) ruthenium catalysts for hydrogenation utilizing FA instead of H_2. However, they concluded the actual hydrogen source for the hydrogenation was most likely still H_2 gas, albeit generated *in situ*.[44] This is illustrated by the fact the best results are obtained when the catalysis of the reaction is split into two phases in a dual bed reactor, each using an optimized heterogeneous catalyst for the intended purpose, being FA decomposition to H_2 on the one hand and LA hydrogenation to GVL on the other.[45] A mechanism for FA sourced hydrogenation without intermittent H_2 formation was posited in 1993 by Leitner *et al.*, utilizing homogeneous rhodium: oxidative addition of FA to the Rh catalyst, followed by decarboxylation results in a reductive rhodium dihydride complex.[46]

1.2.3.2 Homogeneous catalysis

For LA or AL hydrogenation, the body of work on homogeneous catalysis is not as large as for heterogeneous catalysis. However, there have been several chemically interesting developments, usually under less severe reaction conditions than heterogeneous catalysis, which is of benefit for a greener process.

Since 1977 ruthenium phosphine complexes have been employed for catalysis of homogeneous LA hydrogenation[47] with great success, like Delhomme *et al.* who reported a conversion of 99%.[48]
Fagan applied a ruthenium Cp* (*i.e.* pentamethylcyclopentadienyl) bridge ligand complex catalyst to transfer hydrogen from H_2 to ML and reached >90% yield.[49] In another variation, Fabos *et al.* used ruthenium-based Shvo catalysts and FA as the hydrogen source to synthesize GVL homogeneously with great success.[50] The Shvo ligand abstracts H_2 from FA and donates the hydrogen to the polar carbonyl group of LA. They obtained a

yield of 99% GVL.

Clearly, homogeneous catalysis also has the ability to provide good results when hydrogenating LA or AL to GVL. Moreover, there is an added benefit of broad possibilities of asymmetric influences.

1.2.3.3 Asymmetric synthesis

In the quest for creating enantiopure GVL several noteworthy procedures have been reported. In 1975 Kenji Mori published the total synthesis of beetle pheromone sulcatol. This non-biomass related synthesis contains the chirality-retaining formation of (*S*)- and (*R*)-GVL from (*R*)- and (*S*)-glutamic acid, respectively, with an undetermined yield.[24] Soai *et al.* methylated the aldehyde functional group of ethyl 4-oxobutyrate asymmetrically with Me_2Zn and a chiral norephedrine catalyst to form (*S*)-ethyl-4-hydroxypentanoate, the ester formed by ethanol and chiral (*S*)-HPA. After intramolecular transesterification, (*S*)-GVL was obtained with a yield of 95% and an enantiomeric excess (ee) of 90%.[51] Tai and co-workers produced chiral GVL with a decent result by performing asymmetric hydrogenation of ML by H_2 over a heterogeneous catalyst. They report achieving 78% yield of (*R*)-GVL with an ee of 38% by using a Raney Ni catalyst which is modified by chiral tartaric acid.[52]

Similar to the work of Tai *et al.*, GVL is most prevalently synthesized enantioselectively by applying asymmetric catalysis to the hydrogenation of an LA or AL substrate. A process based on an inexpensive biomass-derived resource is a major advantage. However, in general a homogeneous catalyst is used due to the higher selective potential of tested chiral ligands.

The results of several homogeneous methods of synthesizing chiral GVL from LA or AL are shown in table 1.1. Results 1 and 2 were obtained by Karnik *et al.* by performing hydrogenation with $NaBH_4$ without a catalyst. For enantioselectivity they modified the substrate by synthesizing esters of levulinic acid with the chiral alcohols menthol and borneol (respectively menthol levulinate (MenL) and borneol levulinate (BorL). The asymmetric influence of the more bulky borneol is considerably larger.[53] For formation of the hydrogenation agent SnH_2used for result 3, $SnCl_2$ and diisobutylaluminium hydride (DIBAH) were combined. The chiral influence for this reaction was an (*S*)-proline derived chiral diamine present in the reaction mixture.[54]

Table 1.1: GVL yield and ee results of LA and/or AL hydrogenation reactions utilizing several homogeneous methods of chiral influence, mostly being catalysis. Ru and Rh signify homogeneous ruthenium- and rhodium-complexes. α-N_p signifies an alpha-naphthyl substituent.

	Substr.	**Catalyst**	**Hydrogen Source**	**Chiral Influence**	**GVL (%)**	**ee (%)**	**Ref.**
1	MenL	-	$NaBH_4$	MenL	45	*S*,27	[53]
2	BorL	-	$NaBH_4$	BorL	50	*S*,61	[53]
3	EL	-	SnH_2	diamine	77	*R*,60	[54]
4	EL	Ru	H_2	BINAP	95	*R*/*S*,99	[55]
5	LA	Ru	H_2	BINAP	66	*R*/*S*,99	[55]
6	LA	Ru	H_2	SEGPHOS	100	*S*,82	[56]
7	AL	Rh	Ph_2SiH_2	DIOP	98	*S*,39	[57]
8	AL	Rh	α-N_pPhSiH_2	DIOP	99	*S*,79	[57]
9	EL	Rh	Ph_2SiH_2	pyBOX	91	*S*,95	[58]
10	EL	Yeast	Sucrose	Yeast	60	*S*,98	[59]
11	BL	Yeast	Sucrose	Yeast	46	*S*,98	[59]
12	EL	Enzyme	iPrOH	Enzyme	95	*S*,99	[60]

The experiments for results 4,5 and 6 are similar. LA or EL are hydrogenated on H_2 pressure, catalyzed by ruthenium with a chiral phosphine ligand, either 2,2′-bis(diphenylphosphino)-1,1′binaphthyl (BINAP) or 5,5′-bis(diphenylphosphino-4,4′-bi-1,3-benzodioxole (SEGPHOS). SEGPHOS is a very similar ligand to BINAP, creating a different steric situation due to a smaller angle between bulky aromatic rings. For their article containing results 4 and 5, Starodubtseva and co-workers researched several Ru/BINAP complexes and AL substrates, acquiring impressive >90% ee values for almost all combinations.[55] Result 6 of Tukacs *et al.* is relevant, because Starodubtseva performed her LA hydrogenation likely via *in situ* generated EL, where Tukacs synthesized GVL directly from LA, showing an esterification step before hydrogenation can be avoided.[56]

Results 7 through 9 are especially relevant for this thesis as hydrogenation of AL was conducted by hydrosilylation. However, these reactions were catalyzed by a homogeneous rhodium-complex, making them expensive, hardly renewable and possibly toxic.
The enantioselectivity is affected by 2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane (DIOP),[57] a chiral phosphine like BI-

NAP though much smaller, and pyBOX,[58] which is a pyridine linked bis (oxazoline)-ligand that gave impressive asymmetric influence. It is interesting to note that Ojima *et al.* (results 7 and 8) used two silanes on multiple LA-substrates, like ML, EL, isobutyl levulinate (*i*BL) and benzyl levulinate (BnL). The silanes showed different enantioselectivity, but the substrates per silane all gave the same result, signifying the size of the alcohol used for esterification with LA is not of influence in this reaction.

Enantiopure GVL can also be produced with biochemical means, as results 10, 11 and 12 show. As expected, enzymatic synthesis gave very high stereoselectivity, either by applying bakers' yeast, as is,[59] or pure enzyme (*S*)-specific carbonyl reductase CPCR2, isolated from *Candida Parapsilosis*.[60] Enzymes are complex catalysts which can be demanding when reaction conditions, purification and price is concerned. Therefore, there is a demand for stable, unexpensive and easily separated alternatives to biocatalysis, especially if provided by what otherwise would be waste products.

1.3 Hydrosilylation

Silane (SiH_4) is the silicon analogue of methane. According to the Pauling scale[61] silicon has an electronegativity of 1.90, hydrogen 2.20 and carbon 2.55.[62] Therefore, the polarity of the Si-H bond is opposite to the C-H bond. As a consequence, silane is an unstable compound which can spontaneously combust in a mixture with oxygen.[63]

Silanes are silicon containing compounds which are based on silane, where one or more hydrogens are substituted with other elements. When the silicon has a bond with a carbon, the compound is defined as an organosilane. The reactivity of organosilanes decreases as the number of carbon substituents rises and many of these compounds are stable under mild conditions when not activated by a catalyst.

Due to the different polarity of the bond between silicon and hydrogen, the hydrogen atom has a partial negative charge. This can be exploited by introducing an electron-donor to the silicon, thereby activating the Si-H bond and creating a hydride-donating reagent. In the typical hydrosilylation, a silicon-hydrogen bond is added across a double bond of an organic molecule. For instance, the reduction of olefins by hydrosilane has often

been reported.[64–66] For this thesis the focus is on hydrosilylation of a ketone (more specifically a keto-acid or keto-ester, namely LA or AL).

For green chemistry purposes, hydrosilylation is a reaction of special interest because of the potential of the silane polymer polymethylhydrosiloxane (PMHS).[67] The siloxane PMHS is a non-toxic,[68] stable liquid which can be utilized when activated as a reactive hydrosilylation agent at room temperature. It is obtained from waste of the silicon industry. PMHS is inexpensive, easy to use and a perfect reactant for synthesis within the concept of the circular economy. The principle of reduction by PMHS is the same as for hydrosilylation with other silanes. Therefore, published ketone hydrosilylations with any silane are regarded as potential models for LA or AL reduction by PMHS.

1.3.1 Ketone reduction by (chiral) hydrosilylation

In hydrosilylation of a ketone (or aldehyde), the hydride reduces the carbonyl carbon while the silicon and carbonyl oxygen form a silyl ether. As was noted in section 1.2.3.3 of this chapter when referring to an AL keto-ester substrate, this process can be activated by rhodium.[57,58,69] Many other transition metals have been used for catalyzing hydrosilylation of the carbonyl group, like Re,[70,71] Ir,[72] Ru,[73] Mo,[74,75] Zr,[76] Au and Ag,[77] but also first row metals like Cu,[78–80] Ni,[81,82] Co,[83] Fe[84–86] and Ti.[87] Non-transition metals Sn[88] and Zn[89,90] have likewise shown catalytic activity for this reaction. In general, metal-catalyzed hydrosilylation of ketones is believed to follow a mechanism posited by Ojima *et al.* in 1976 in which the silane and the metal form a metal-hydride complex which reduces the substrate.[91]

Incorporating chiral ligands in the catalytic metal complexes has shown effectiveness in inducing stereoselectivity in the hydrosilylation of ketones.[89,92,93] For instance, Yun *et al.* reported a carbonyl reduction with PMHS and a chiral Ti complex with a yield of 95% and an ee of 99%.[94] However, when using metal catalysts there are disadvantages, like toxicity, long term environmental impact, difficulty of catalyst recovery for possible reuse and the cost of the material. With the aim of a cleaner GVL synthesis, the focus of this thesis is directed away from metals and toward alternative catalysts.

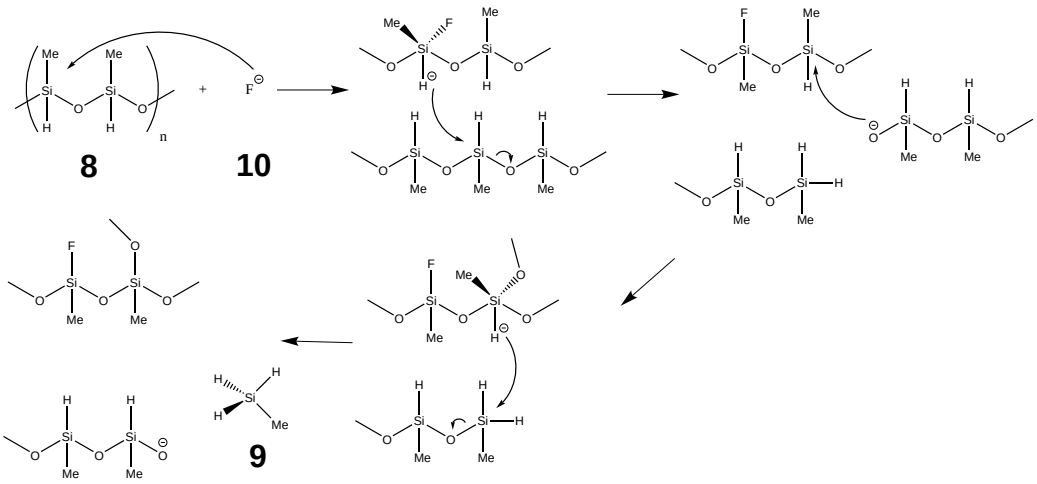
The relative electropositivity of silicon makes silanes susceptible to nucleophilic attack, leading to the possibility of nucleophile catalyzed hydrosilylation. Silicon has the greatest affinity for oxygen and fluorine, as these

are the most electronegative elements.[62] Taking advantage of these affinities and the difference between them is standard practice in the production of fine chemicals. An important part of multi-step organic synthesis is protection of reactive groups from undesired reactions. For instance, after deprotonation with base, alkoxide groups can easily be protected with (non-hydro)silanes by forming silyl ethers and making use of the stability of the silicon-oxygen bond. For deprotection, fluoride anions are introduced. The even greater preference for silicon-fluorine bond formation releases the alcohol group from the silane.[95]

Hydrosilylation of ketones has been succesfully catalyzed by alkoxy anions in high yield (80-100%).[96–98] This is an especially interesting method, since catalysis with alkoxy bases containing a chiral centre has shown stereoselective induction. Kohra *et al.* have reported a 78% yield and an ee of 44% for a chiral aromatic dilithium diolate-catalyzed hydrosilylation of (model substrate) acetophenone with trimethoxysilane (TMOSH) in THF at 0 °C for 15-20 h.[99] Schiffers *et al.* utilized lithium (*R*)-binol to catalyze the reaction of acetophenone with TMOSH in a 30/1 ether/TMEDA mixture at 0 °C for 24 h, with a yield of 92% and 70% ee.[100] Where Corriu *et al.* for achiral alkoxy catalysis showed the use of a potassium salt, the chiral reactions are (so far) catalyzed by specialized lithium compounds. Lithium is in high demand due to application in batteries for portable electronics and electric cars. Although lithium-ions are naturally present in water and soil and have in low concentrations no significant impact on the environment by itself, the psychoactive effects and toxicity for humans make disposing of lithium compounds an issue. The stereoselectivities in the work of Schiffers *et al.* are considerable. However, the presence of the tetramethylethylenediamine (TMEDA) is essential for optimal results.[100] TMEDA is a toxic and hazardous compound and therefore not an obvious choice for use in green chemistry.

Lastly, hydrosilylation can be activated by fluoride. Corriu *et al.* catalyzed hydrosilylation of ketones heterogeneously with stoichiometric amounts of KF and CsF, yielding about 80% at moderate temperatures, with several silanes.[101] This is an uneconomic use of catalyst and it is an unpractical method for introducing a quantifiable stereoselective influence. tetra-*n*-butylammonium fluoride (TBAF) is a fluoride salt which is highly soluble in organic solvents and the ideal compound for introducing fully dissolved F^- in less polar reaction mixtures. Kobayashi *et al.* have utilized a catalytic amount of tetra-*n*-butylammonium fluoride (TBAF) to activate chemoselective hydrosilylation of ketones with PMHS in THF at -70 °C in

15 min., obtaining 80+% yields.[102] These reaction conditions show fluoride catalyzed PMHS is very reactive. In general monohydrosilanes, *i.e.* silanes with one hydrogen atom directly connected to a silicon atom, are less reactive. Therefore, the likely explanation lies in the fact PMHS is a polymer. Revunova *et al.* have performed a study on the fluoride-catalyzed hydrosilylation reaction using PMHS and have proposed the mechanism displayed in scheme 1.3.[103] The PMHS polymer **8** breaks down in trihydrosilane $MeSiH_3$ **9**, which explains the high reactivity of PMHS.

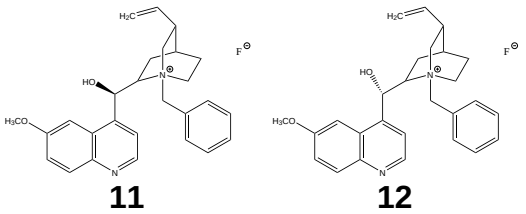


Scheme 1.3: Fluoride **10**-catalyzed PMHS **8** rearrangement to $MeSiH_3$ **9**.

After hydrosilylation of a ketone as performed by Kobayashi *et al.*, the produced silylether is cleaved to obtain the alcohol product. They report a work up method with excess TBAF and a method with multiple equivalents of KF. The TBAF work up has the advantage of instant total quenching of the reaction. However, there will be a large amount of TBAF present in the reaction mixture, creating possible difficulties in analysis and purification of the product. Quenching with KF takes more time and has no clear end point for the reaction time.

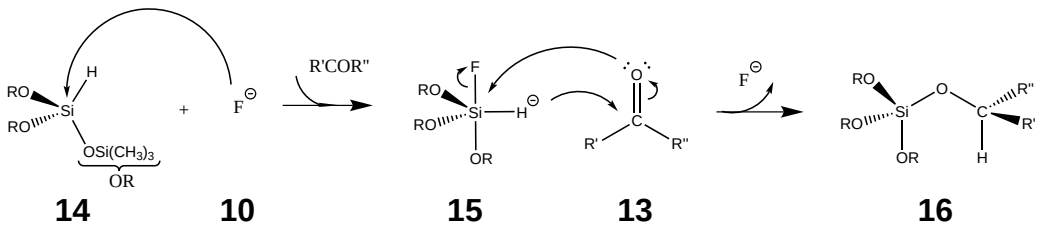
Drew *et al.* have introduced a stereoselective influence to fluoride-catalyzed hydrosilylation by substituting TBAF for N-benzylquinidinium fluoride (BQF).[104] BQF is a derivative of quinine, historically an anti-malaria drug extracted from the *Cinchona* which also provides the bitter taste of tonic water.[105] The quinine molecule has two chiral centers and several rings which give it a curved shape. With presence of a quinine derivative in a

reaction mixture, there is potential of the curvature obstructing one prochiral face of the reaction center more than the other, thereby creating stereoselectivity. The steric hindrance resulting in an asymmetrical effect can be described as a chiral fence.[58] Drew *et al.* have also researched the pseudo-enantiomer of BQF **11**, N-benzylquinidinium fluoride (BQDF) **12**. This is a diastereomer of BQF with semi-mirrored curvature, resulting in BQDF catalyzing with a propensity to produce the opposite stereoselectivity compared to BQF.



Scheme 1.4: BQF **11** and pseudo-enantiomer BQDF **12**.

The stereoselectivity of a reaction is improved with prolonged contact between reactants and the chiral influence. To optimize enantioselectivity, Drew *et al.* have performed hydrosilylations with silanes which are considerably less reactive than PMHS. In hydrosilanes the access to the reactive silicon is decreased following the bulk of the substituents. Therefore, Drew *et al.* have chosen to research tris(trimethylsiloxy)silane (TTSH). The mechanism of fluoride(**10**)-catalyzed TTSH hydrosilylation of a ketone **13** using TTSH **14** is the pentasilicate **15** mechanism resulting in a silyl ether **16**, as based on the mechanism described by Corriu *et al.* and displayed in scheme 1.5.[96]



Scheme 1.5: Fluoride **10**-catalyzed TTSH **14** hydrosilylation of ketone **13** mechanism.

1.4 The aim of this thesis

The aim of this thesis is to study the fluoride-catalyzed hydrosilylation of LA or AL to produce GVL in general and to perform this reaction enantioselectively in particular, using chiral auxiliaries.

To this end, LA or esters thereof (*i.e.* alkyl levulinates) will be brought into solution, THF, with a silane, with a fluoride source and a chiral influence. Experimentation will be done on the ratios of the compound and concerning the specific identity of the compounds themselves, meaning the types of silanes, the specific source of fluoride and the method of quenching.

2 Experimental Section

2.1 General

All chemicals were used as received unless stated otherwise. All air and/or moisture sensitive compounds were stored under argon atmosphere. Additionally, all possibly unstable compounds were stored at 4 °C. The solvent THF was supplied anhydrous, containing 250 ppm butylated hydroxytoluene (BHT) as oxidation-inhibitor and under inert gas atmosphere, which was maintained during use with argon.

Quantitative GC measurements were performed utilizing a Shimadzu GC-2010 gas chromatograph with a flame ionization detector (FID) and helium as carrier gas. 1 µl of samples, including anisole as internal standard, were injected on an Agilent CP-Wax 57 CB polar column of 25 m length, with a 0.25 mm inner diameter and 0.20 µm film. Qualitative GC measurements were performed utilizing a Shimadzu GC-MS set-up containing a GC-2010 gas chromatograph with helium as carrier gas and an Agilent VF-5ms column of 30 m length, with a 0.25 mm inner diameter and 0.25 µm film and a GCMS-QP 2010 mass spectrometer. 0.1 µl of (diluted) samples were injected unto the column. To obtain accurate response factors for quantitative meausurement, roughly 1.4 eq TBAF was added to calibration samples to mimic the reaction mixture matrix, when relevant.

Determinations of ee by GC were performed utilizing a Perkin Elmer Instruments AutoSystem XL gas chromatograph with an FID and helium as carrier gas. The installed column was an Agilent Cyclodex B chiral column of 60 m length, with a 0.25 mm inner diameter and 0.25 µm film. 1 µl of samples, which for optimal chiral resolution were diluted to a GVL concentration of 0.055 M, were injected unto the column manually. Peak areas were determined by fitting with Originlabs Origin 9.1 software.

All samples for all GC measurements were THF-based reaction mixtures (pure or diluted with THF) or solutions in THF.

For ^{1}H-NMR and Pure Shift Yielded by Chirp Excitation (PSYCHE) NMR measurements a 400 MHz Agilent MRF400 spectrometer was used at room

temperature. All samples were dissolved in deuterated chloroform ($CDCl_3$). For ee measurements 0.1 mmol pure GVL and 0.2 mmol europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate] ($Eu(hfc)_3$) were dissolved in 0.65 ml $CDCl_3$ by shaking vigorously.

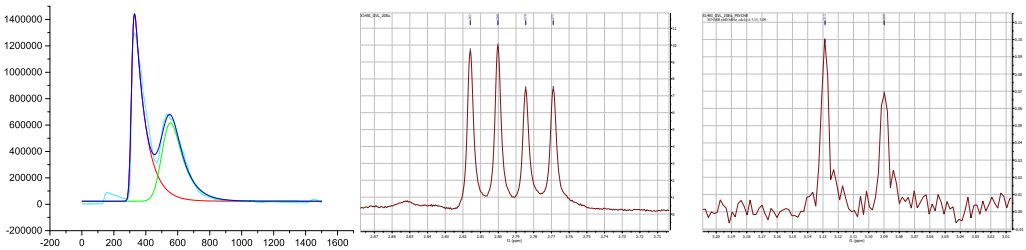


Figure 2.1: Chiral GC and chirally shifted NMR peaks of the same GVL product for corroboration of determined ee values. The peaks in the left picture signify GVL enantiomers measured by GC with a chiral column. The middle and right picture show NMR peaks signifying protons of the methyl group of both enantiomers of the same synthesized GVL, split by chiral shift reagent $Eu(hfc)_3$. The middle picture is a segment of a ^{1}H-NMR spectrum, the right picture is a segment of a PSYCHE decoupled NMR spectrum.

Chiral GC column ee determination was compared to ee measurement using NMR and a chiral shift reagent. Figure 2.1 shows for GC, ^{1}H-NMR and PSYCHE NMR measurements of the same GVL sample enantiomer peak area differences which translate to ee values of respectively 15%, 10% and 16%. The similarity of the values suggests the chiral GC method of determining ee gives a fair indication of enantioselectivity of the reactions. Alternatively, the widely different methods of determining optical purity have a similar error.

2.2 BQF and BQDF synthesis using HF

BQF and BQDF were synthesized following the method described by Drew *et al.*[104] A solution of BQC (or BQDC) in water was loaded onto an Amberlyst A-26 (hydroxide form) column, which was washed with water. After evaporation of the eluent N-benzylquininium hydroxide (BQH) (or N-benzylquinidinium hydroxide (BQDH)) was obtained. BQH (or BQDH) was treated with a 1 M solution of hydrogen fluoride (HF), which after freeze-drying yielded BQF (or BQDF). Due to the inherent danger of working with HF, this synthesis was performed by Fang Liu with the help of

Ana Hernández Giménez.

2.3 Experimental Methods

The performed GVL syntheses are done according to a combination of the methods described by Kobayashi *et al.*[102] and Drew *et al.*[104] The typical non-enantioselective reaction was performed as follows: In a 25 ml round bottom flask 2.0 mmol ML and 2.5 mmol silane (1.25 eq) were dissolved in 4 ml THF and stirred at 900 rpm. To start the reaction 12 µl of 1 M TBAF in THF solution (*i.e.* 12 µmol TBAF (0.006 eq)) was added to the reaction mixture instantly. The reaction was quenched by adding an excess of roughly 3 ml of 1 M TBAF in THF solution (*i.e.* 3 mmol TBAF (1.4 eq)). Conversion and yield were determined by GC analysis performed on the reaction mixture. For enantioselective reactions using BQC or BQDC as chiral influence, 0.06 µmol BQC (or BQDC; 0.03 eq) is added to the ML/silane mixture before activation, all else remaining the same as for non-enantioselective reactions. For enanioselective reactions using BQF or BQDF as catalyst and chiral influence, 2.0 mmol ML and 0.06 µmol BQF (or BQDF; 0.03 eq) is dissolved in 4 ml THF and stirred at 900 rpm. For activation 2.5 mmol silane (1.25 eq) was added dropwise, all else remaining the same as for non-enantioselective reactions.

For NMR measurements, the GVL product was purified over a silica column using an eluent of 2:1 hexanes:ethylacetate. The R_f of GVL was 0.30.

2.4 Analysis

2.4.1 Calculating conversion and yield and normalization

Amounts of ML, BL and GVL were calculated based on calibration series containing various amounts of the relevant compound and a constant amount of internal standard anisole in THF. Separate calibration series were made containing additional TBAF, to simulate TBAF quenched reaction mixtures. TBAF is a major influence on the response factors of other compounds. The results of samples of reaction mixtures which for large scale sampling already contained the anisole standard during reaction were multiplied by an extra factor 1.19. This factor was by experi-

mentation consistently found to reflect the discrepancy between measured quantities in reaction mixtures and actual amounts of added reagents.

2.4.2 Quenching with KF

To determine the ee of produced GVL, reactions were quenched with KF, following a procedure based on the description by Kobayashi *et al.*[102] After GVL synthesis as described in section 2.3, instead of quenching with TBAF, the solvent was evaporated. The concentrate was dissolved in a mixture of 1.5 ml acetone and 1.5 ml diethyl ether and roughly 10 mmol KF (5 eq) was added. The suspension was stirred vigorously for 2 h at room temperature and filtrated through a folding filter. The residue was washed with diethyl ether. The solvent was removed from the filtrate and washings by evaporation and the concentrate dissolved in THF for chiral GC analysis.

2.4.3 TBAF removal using $NaClO_4$

To determine ee development during reaction, samples of reaction mixtures were instantly quenched with excess TBAF (as decribed in section 2.3 after which the TBAF was (partially) removed using a method based on the work of Craig *et al.*[106] The reaction mixture was evaporated and the concentrate was dissolved in 30 ml phosphate buffer (pH 7.5) containing an excess of roughly 3 mmol sodium perchlorate ($NaClO_4$) (1.5 eq) and a white, voluminous, flaky precipitate of tetrabutylammonium perchlorate was formed. The suspension was vacuum-filtrated and the residue was washed by 20 ml phosphate buffer (pH 7.5). Filtrate and washings were saturated with NaCl and extracted with 3x100 ml ethyl acetate. The organic phase was dried with Na_2SO_4. After filtration with folding filter and evaporation *via* rotary evaporator, the residue was dissolved in THF, ready for analysis with GC.

3 Results and Discussion

3.1 Hydrosilylation of LA and AL

Levulinic acid (LA) is not a suitable substrate for fluoride catalyzed hydrosilylation to γ-valerolactone (GVL), whereas the alkyl levulinate (AL) methyl levulinate (ML) is. Table 3.1 shows reactions with LA consistently result in full esterification for all used silanes and ML consistently converts fully to GVL. Yield deviations from 100% are the result of matrix effects on measurement accuracy. This is supported by analysis with GC-MS (figure 3.1), which confirms the complete lack of substrate in all cases and the discrepancy between esterification and yield between LA and ML reactions, without showing any (other) by-products.

The organosilanes polymethylhydrosiloxane (PMHS), trimethoxysilane (TMOSH) and tris(trimethylsiloxy)silane (TTSH) are all suitable for full hydrosilylation of ML to GVL, as shown in table 3.1. The choice for experimentation with these silanes and the differences in temperature and reaction times are based on the work of Drew *et al.*.[104] They demonstrated that TTSH is most promising where enantioselective hydrosilylation is concerned. Therefore, TTSH is the silane that was used for the experimental determination of the possibility of a succesful enantioselective GVL synthesis.

Table 3.1: Conversion and GVL yield of hydrosilylation reactions of LA or ML with various silanes. [a] 30 min reaction at -70 °C. [b] 1 d reaction at RT. [c] 5 d reaction at RT.

Substrate	Silane	Conversion (%)	Yield (%)	By-products (%)
LA	PMHS[a]	100	0	BL 100
ML	PMHS[a]	100	101	-
LA	TMOSH[b]	100	0	ML 46, BL 54
ML	TMOSH[b]	99	94	-
LA	TTSH[c]	100	0	BL 100
ML	TTSH[c]	100	108	-

Reactions with substrate LA did not yield GVL. Instead, for the reaction

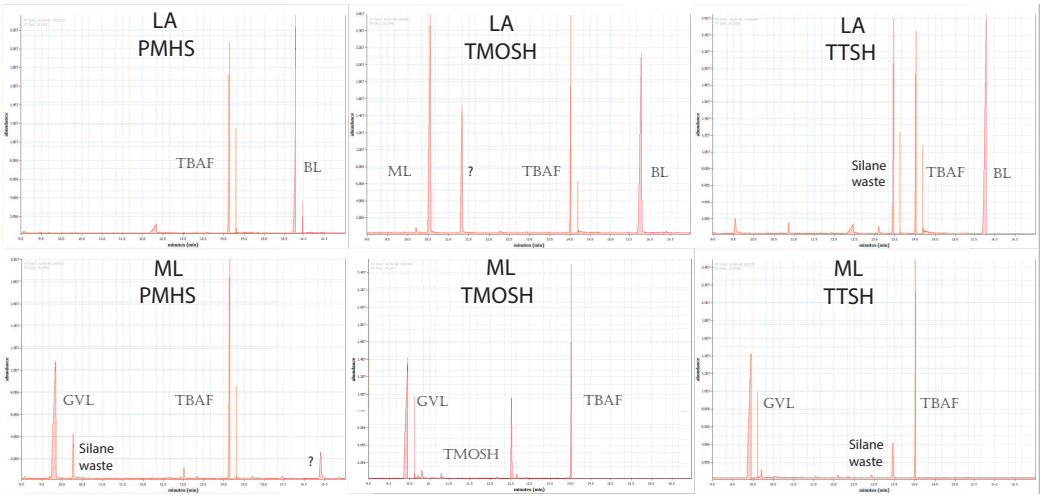
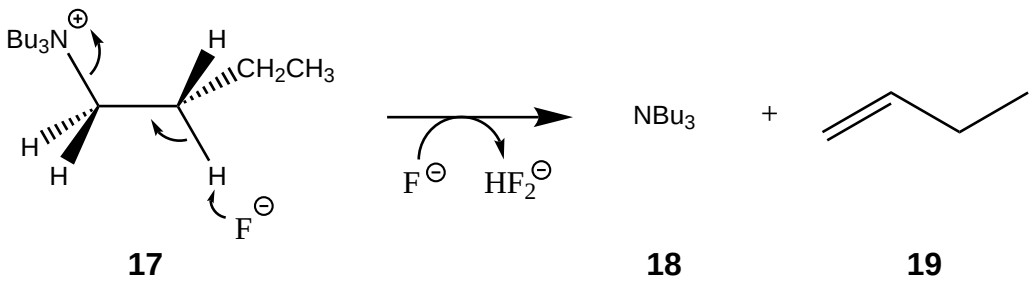


Figure 3.1: GC-MS results, comparing substrates LA and ML and comparing silanes PMHS, TMOSH and TTSH.

mixtures which contained PMHS and TTSH, full esterification to *n*-butyl levulinate (BL) occurred following quenching with TBAF. For the TMOSH reaction mixture, roughly half of the LA was made into ML by reaction with a methoxy substituent of the silane and the other half was turned to BL by TBAF.

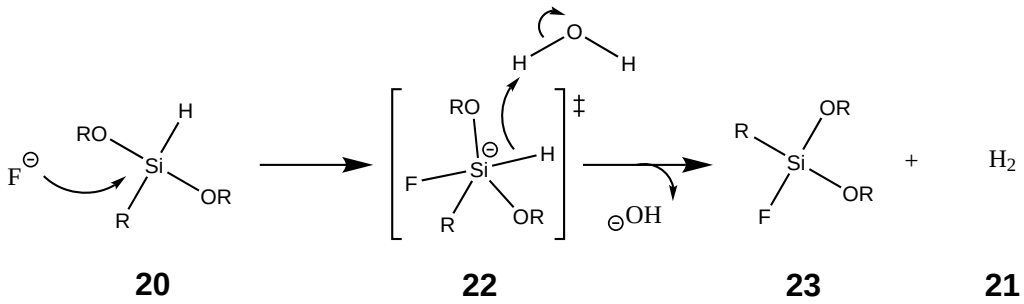
The produced BL was confirmed to be *n*-butyl levulinate by comparison with off-the-shelf *n*-butyl levulinate. It was formed from LA and TBAF, however there was no *n*-butanol present in the TBAF solution. Sharma *et al.* have reported TBAF decomposition by bimolecular elimination (E2) according to scheme 3.1.[107] A β-hydrogen of one of the butyl groups of TBAF **17** is attacked by fluoride, while from the neighboring carbon tri-*n*-butylamine (TBN) **18** in the anti position is eliminated. This way 1-butene **19** is formed. 1-Butene was not found in our reaction mixtures. It has a boiling point of -6.3 °C, which suggests evaporation before detection was a possibility. Proton NMR of the TBAF solution has shown moderate peaks deviating from the TBAF spectrum, which demonstrated the presence of TBN. Butanol could be formed by a reaction of 1-butene and water. However, acidic instead of basic conditions are desired and, according to Markovnikov's rule, 2-butanol instead of n-butanol will be produced.



Scheme 3.1: TBAF decomposition into TBN and 1-butene.

Further experimentation is needed to determine the reason why LA was less reactive than ML for GVL synthesis, for instance with an LA salt substrate and with varying LA/silane ratios. The obvious difference between LA and ML was the acidic carboxyl group of LA. Yap *et al.* showed that H_2 was produced in the presence of water and OH^- by hydrolytic oxidation of organosilanes in THF.[108] In our reaction, fluoride was an analog of their hydroxide. Upon addition of TBAF to start the hydrosilylation, silane **20** was activated and hydrogen gas **21** was formed due to a reaction between the pentacoordinate silane **22** and the 5 *wt%* water added with the TBAF solution, as shown in scheme 3.2 (the resulting fluorosilane **23** could break down to silanol in reaction with OH^- and further to siloxane waste). The acid group of LA could increase hydrogen gas production, leaving a levulinate anion and depleting the reactive silane. LA salt and extra silane could test this hypothesis. The performed LA reactions contained a 1.5 eq silane excess and the added water accounted for 0.125 eq hydride use. All silane was spent, since none was encountered following reaction and no formed LA ester further converted to GVL. This leaves 0.375 eq silane is to be explained.

Starodubtseva *et al.* have shown ML was more reactive that LA in a ruthenium catalyzed system with molecular hydrogen as reducing agent.[109] However, there was still 69% LA conversion with 95% selectivity to GVL in their report, whereas no GVL was produced when LA was utilized as substrate in any of our hydrosilylations.



Scheme 3.2: Hydrogen gas formation by fluoride-activated silane with water acid/base-reaction.

3.2 Establishing an Optimal TTSH Amount for Enantioselective Hydrosilylation

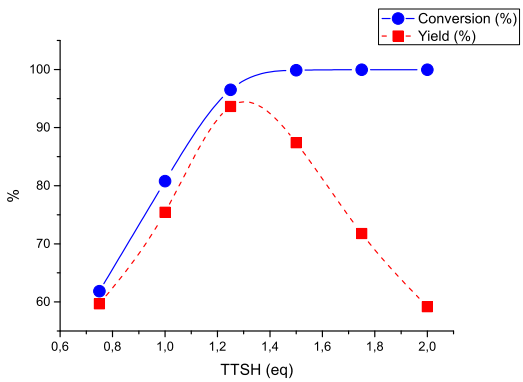


Figure 3.2: Conversion and yield of hydrosilylation of ML as a function of TTSH.

The optimal amount of TTSH for hydrosilylation of ML is 1.25 eq. This is shown in 3.2 and illustrated in figure 3.2, which shows the yield for GVL synthesis with this amount of silane is 94%.

Higher TTSH amounts possibly resulted in significant measuring error and underreporting of full GVL yield. Reaction mixtures containing 1.25 eq TTSH or more led to full conversion of the substrate. However, TTSH amounts above 1.25 eq resulted in lower yields and a corresponding gap in the mass balance. This could be an effect of the large volume of the silane. Upwards to 25% of the reaction mixture consisted of TTSH, a vastly different molecule than the solvent THF with likely different interaction properties with the GC column and relevant compounds. No by-products or breakdown products resulting from possible further hydrosilylation of GVL (like 1,4-pentadiol) have been found.

Table 3.2: Conversion and GVL yield of hydrosilylation reactions using a variable amount of TTSH.

TTSH (eq)	Conversion (%)	GVL yield (%)	Mass gap (%)
0.76	62	60	2
0.98	81	75	5
1.23	96	94	3
1.47	100	87	12
1.72	100	72	28
1.99	100	59	41

BL was regarded as unconverted substrate, because remaining ML of not fully converted reactions turned partially to BL as a result of quenching with TBAF (similar to LA esterification as described in section 3.1). This transesterification was very slow and did not noticably compete with GVL synthesis, while BL itself could also function as a substrate for the hydrosilylation reaction, as shown in section 3.3.2. Therefore, the sum of ML and BL corresponded to the amount of unconverted substrate before quenching and was used for calculating the conversion of the hydrosilylation.

3.3 Enantioselective GVL Synthesis by Catalysis with BQF/BQDF

To study the influence of catalysis by N-benzylquininium fluoride (BQF) or N-benzylquinidinium fluoride (BQDF) on the hydrosilylation of ML, various amounts were added.

3.3.1 Enantioselective Catalysis by BQF

Catalyzing hydrosilylation of ML with BQF has consistently resulted in an increased presence of the *R*-enantiomer of GVL over the *S*-enantiomer. The chirality of the major enantiomer has been established by comparison with enantiopure, off-the-shelf GVL. The enantioselectivity of the reactions was higher when higher amounts of BQF where added. This effect showed diminishing returns with reaction mixtures which contained more than about 1 mol% of BQF and it seems to plateau. However, the maximum enantioselectivity might not have been reached and further experimentation would help to establish certainty. GVL yield was consis-

tently higher with higher BQF amounts and the expectation is more catalyst above 3.17 mol% will lead to a higher yield, yet the limited solubility of BQF in THF could go against this.

Table 3.3: Conversion, yield and GVL ee of BQF-catalyzed hydrosilylation.

BQF (mol%)	Conversion (%)	Yield (%)	Mass gap (%)	ee (%), *R*
0.00	21	16	5	0
0.62	17	25	-8	17
0.78	20	29	-9	24
1.05	31	35	-4	26
1.41	28	30	-2	24
1.95	39	41	-2	28
3.17	52	48	4	30

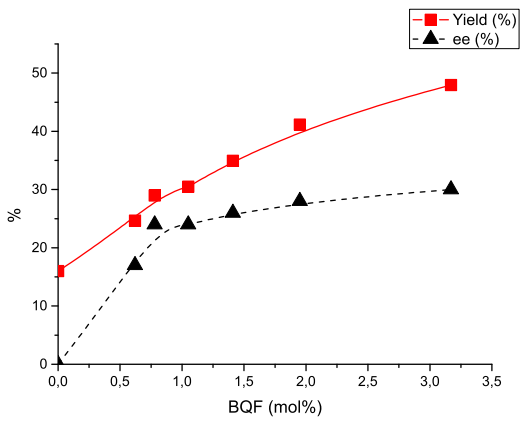


Figure 3.3: Yield and GVL ee of BQF-catalyzed hydrosilylation as a function of BQF.

The reaction performed without BQF was not enantioselective, as determined with chiral GC and confirmed with NMR with $Eu(hfc)_3$. This reaction only received fluoride in the form of TBAF as part of the quenching procedure and the yield of 16% was fully the result of quenching.

The amount of dissolved BQF in the reaction mixtures was unclear at the start of the reactions, due to limited BQF solubility in THF. During the reaction the compound did dissolve. This might have been a result of increased solubility of BQF in methanol, which was produced during closing of the GVL ring. Hydrosilylation reactions performed in THF/methanol mixtures were not preferred to reactions in THF due to the resulting lower enantioselectivity.

3.3.2 Enantioselective Catalysis by BQDF

Table 3.4: Conversion, yield and GVL ee of BQDF-catalyzed hydrosilylation.

BQDF (mol%)	Conversion (%)	Yield (%)	Mass gap (%)	ee (%), *S*
0.00	21	16	5	0
0.11	25	26	-2	3
0.18	22	29	-6	9
0.30	21	27	-6	13
0.67	30	30	0	23
0.94	32	32	0	24
1.44	37	36	1	25
2.10	40	39	2	26
3.00	42	39	2	26
3.00	42	41	1	28
5.13	51	46	5	23

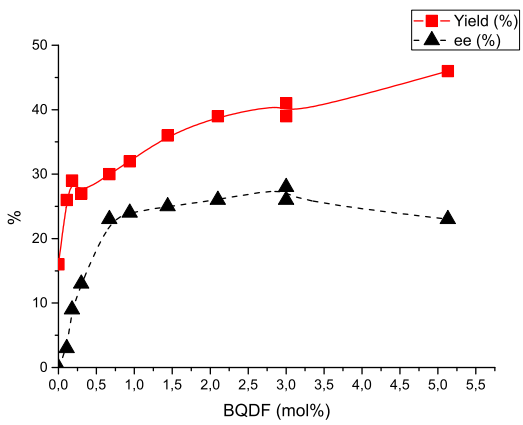


Figure 3.4: Yield and GVL ee of BQDF-catalyzed hydrosilylation reactions, as a function of BQDF.

Catalysis of hydrosilylation by BQDF consistently resulted in an excess of the *S*-isomer of GVL, as was confirmed by comparison with a solution of pure, off-the-shelf *S*-GVL. This is the opposite chirality of the ee resulting from catalysis with BQF, the pseudo-enantiomer of BQDF.

The measure of enantioselectivity was dependent on the amount of BQDF in solution, as shown in table 3.4 and figure 3.4. The trend in ee shows a steep rise following the increasing amount of catalyst, up to about 1 mol% of BQDF. Larger BQDF amounts resulted in diminishing ee returns and the enantioselectivity seems to plateau at around an ee of 26%.

The measure of GVL synthesis was dependent on the amount of BQDF in solution. Figure 3.4 shows a rise in the trend of the yield following the in-

creasing amount of catalyst. Further experimentation is needed to confirm higher yields are possible with larger amounts of BQDF, as suggested by the trend displayed in this figure.

These results are very similar to those of BQF catalyzed reactions, albeit in opposite chirality.

Larger amounts of BQDF could result in higher reaction rates, leading to a higher GVL yield. Figure 3.5 shows higher catalyst concentrations led to higher yields. Lack of major convergence or overlap suggests the maximum yield has possibly not yet been reached.

Exchanging the substrate ML for BL or benzyl levulinate (BnL) had no significant effect on the enantioselectivity of GVL synthesis. This is explained by the distance between the ester-group and the point of reduction on the levulinate substituent, which is the carbonyl group. The bulky butyl or aromatic ring were simply to far away to hinder the hydrosilylation. However, there is a strong indication of a significant influence of larger AL substituents on the yield, making the ML substrate superior.

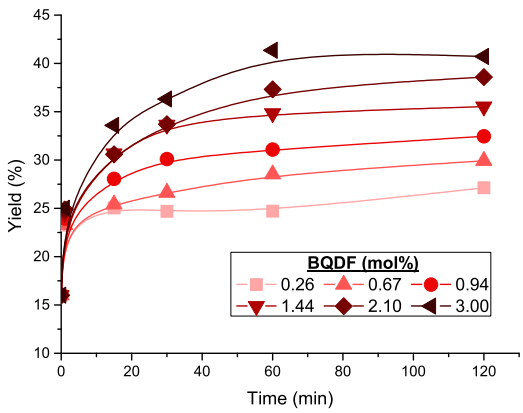


Figure 3.5: Yield of BQDF-catalyzed hydrosilylation as a function of time.

PMHS is not suitable for significantly enantioselective hydrosilylation of ML. In section 3.1 was mentioned that full non-enantioselective hydrosilylation was possible with the silane PMHS, though the potential for enantioselective reactions was so far deemed to be limited. Exchanging TTSH for PMHS in the BQDF catalyzed hydrosilylation of ML has resulted in an ee of 5% of the *S*-isomer compared to about 25% of *S*-GVL excess for reactions with TTSH. This is explained by the reactivity of PMHS compared to TTSH. PMHS performs full hydrosilylation in 10 min at -70°C, while TTSH needs at least 2 h at RT. In reaction mixtures with PMHS there simple is no time for contact with the chiral influence.

3.4 Enantioselective GVL Synthesis by Catalysis with TBAF and BQC/BQDC

The catalytic salts BQF and BQDF performed two functions at once: The fluoride anion catalyzed the hydrosilylation, while the benzylquininium or benzylquinidinium cation provided a chiral environment to induce enantioselectivity. These functions were studied independently from each other by using TBAF as a source of fluoride and N-benzylquininium chloride (BQC) or N-benzylquinidinium chloride (BQDC) as the chiral influence.

3.4.1 Establishing an Optimal TBAF Amount for Initiation of Enantioselective Hydrosilylation

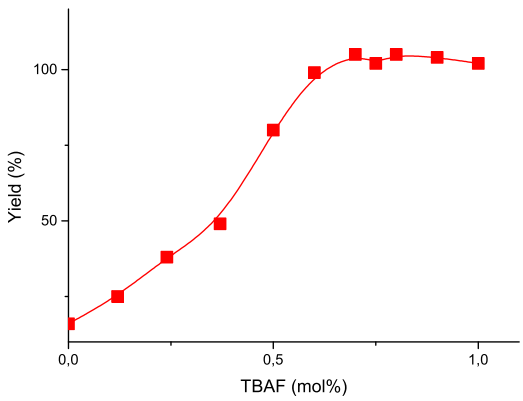


Figure 3.6: Yield of hydrosilylation with TTSH, as a function of time.

The optimal amount of TBAF for catalysis of enantioselective hydrosilylation of ML is about 0.6 mol%. This was the smallest amount that could catalyze for full conversion to GVL, as is shown in table 3.5 and figure 3.6. Lower amounts of TBAF resulted in lower maximum yields. A high yield is advantageous, because the enantioselective influence of the chiral environment is based on partial obstruction of the reaction. A high yield could compensate for this influence. However, high amounts of TBAF could be detrimental to the result, because the amphiphilic character of phase-transfer agent TBAF could interfere with the reaction and could make accurate quantitative measurement more difficult.

Table 3.5: Conversion and GVL yield of reactions using a variable amount of initiatory TBAF.

TBAF (mol%)	Conversion (%)	GVL yield (%)	Mass gap (%)
0.00	21	16	5
0.12	26	24	2
0.24	37	38	-1
0.37	45	49	-4
0.49	77	80	-3
0.59	93	99	-6
0.70	99	105	-6
0.78	99	105	-6
0.88	99	104	-5
0.99	100	105	-5

3.4.2 Enantioselective Catalysis by TBAF and BQC

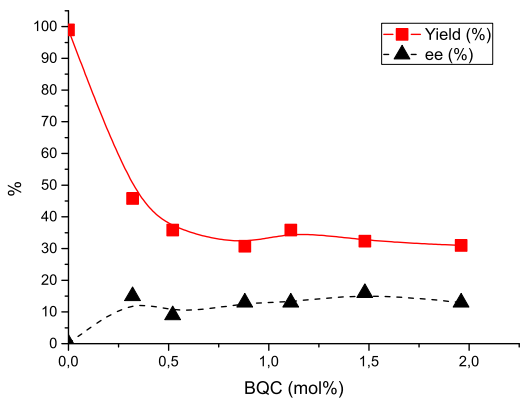


Figure 3.7: Yield and GVL ee of BQC and TBAF catalyzed hydrosilylation reactions, as a function of BQC.

Hydrosilylations in presence of BQC consistently led to an excess of the *R*-isomer of GVL.

At each amount of BQC, the ee is roughly around 13%, as shown in figure 3.7 and table 3.6. This suggests that the maximum threshold for measurable enantiomeric influence of BQC is met for all these reactions and that it lies between 0 and 0.32 mol%. This could be a reflection of the low solubility of BQC in THF.

Compared with non-enantioselective hydrosilylations, the introduction of BQC severely diminished the yield. Without BQC there was full conversion to GVL and with roughly 1 mol% the yield is only 30%. This value was the same for reactions with higher amounts of BQC, signifying maximum obstruction possibly as a result of maximum solvation of BQC.

These results show the addition of BQC to the reaction mixture obstructs

hydrosilylation in mostly a non-enantioselective fashion. Possibly coordination of the tetrabutylammonium cation plays a role, as this ion is not present during comparatively smooth reactions which are catalyzed by BQF or BQDF. However, this would have to be in combination with the chloride anion or benzylquininium cation, because TBAF by itself is a very productive catalyst.

Table 3.6: Conversion, yield and GVL ee of hydrosilylation in presence of BQC.

BQC (mol%)	Conversion (%)	Yield (%)	Mass gap (%)	ee (%), *R*
0.00	93	99	-6	0
0.32	36	46	-10	15
0.52	31	35	-5	9
0.88	27	31	-3	13
1.11	31	36	-5	13
1.48	29	32	-3	16
1.96	27	31	-4	13

3.4.3 Enantioselective Catalysis by TBAF and BQDC

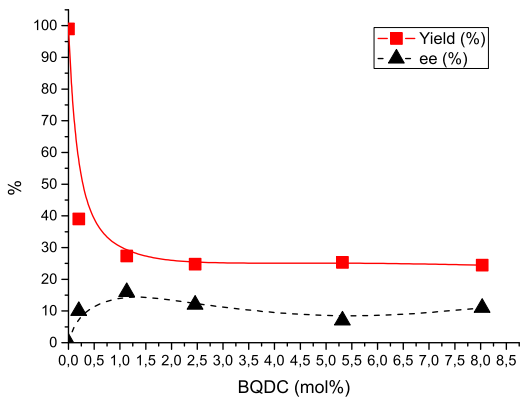


Figure 3.8: yield and GVL ee of BQDC and TBAF catalyzed hydrosilylation reactions, as a function of BQDC.

Hydrosilylation of ML in presence of N-benzylquinidinium chloride (BQDC) has consistently led to an excess of the *S*-isomer of GVL. This is the opposite chirality as the excess of reactions in presence of BQC, the pseudo-enantiomer of BQDC.

Table 3.7 and figure 3.8 show that for divergent amounts of added BQDC the ee values were roughly around 11% without showing an upwards or downwards trend. At the same time the trend in the yield went down for higher BQDC amounts, to plateau from 1 mol% BQDC upwards at about 26% GVL.

These results are very similar to the results of the hydrosilylations in presence of BQC, and the same explanations apply.

Table 3.7: Conversion, yield and GVL ee of hydrosilylation in presence of BQDC.

BQDC (mol%)	**Conversion (%)**	**Yield (%)**	**Mass gap (%)**	**ee (%), *S***
0.00	93	99	-6	0
0.19	38	39	-1	10
1.10	22	27	-6	16
2.35	22	25	-3	12
5.09	20	25	-6	7
7.72	17	24	-8	11

4 Conclusions

With the aim of synthesizing GVL enantioselectively by hydrosilylation, a number of LA derived substrates have been used. It has not been possible to produce GVL from LA itself, but the use of ML as a resource has been very productive, leading to full and selective conversion in non-chiral reactions and performing best in enantioselective reactions. BL and BnL have also been tried and are useable for stereoselective GVL synthesis at about the same level of enantioselectivity as ML, albeit with likely severely diminished yields compared to ML reactions.

Silanes PMHS, TMOSH and TTSH are all applicable for producing GVL from ML. TTSH has been proven to respond well to enantioselective influences leading to moderate ees, where PMHS only reaches 5% due to it's strong reactivity.

Catalyzing the hydrosilylation of ML with BQF has shown to result in, optimally, ees of 25 to 30% of *R*-GVL, with at least 50% yields, the reach of which is not yet known. When applying pseudo-enantiomer BQDF, the results are the same. However the enantioselectivity leads to an excess of the *S*-isomer.

Combining TBAF and BQC or BQDC has not provided the desired results. While there is a significant enantioselective effect of about 12% in both cases, BQC and BQDC (again fortunately in opposite directions), this effect does not seem to scale at all. Also, the yield is depressed to a maximum of 30% starting already at small amounts of added chiral agent. These limits might be connected to the low solubility of BQC and BQDC in combination with TTSH in THF. It thereby seems the tetrabutylammonium cation and the chloride anion are not the best of partners for this in principle sound idea of separation of benzylquininium chiral influence and fluoride catalyst to reach for the optimum concentration of both elements.

Enantiopure γ-valerolactone (GVL) has many applications and can be produced by stereoselectively reducing the inexpensive biomass compound levulinic acid (LA) or derivative alkyl levulinates (ALs). A green and highly selective method of performing this synthesis is by asymmetric

organocatalyzed hydrosilylation. Coupling a bulky chiral cation and a fluoride anion catalyst both activates the hydride-donating silane and induces stereoselectivity in the reaction. In this thesis the principle above has been applied in the N-benzylquininium fluoride (BQF) catalyzed hydrosilylation of methyl levulinate (ML) to GVL by tris(trimethylsiloxy)silane (TTSH), leading to an ee of roughly 25%. Likewise the catalyst N-benzylquinidinium fluoride (BQDF), which is the pseudo-enantiomer of BQF, has been utilized resulting in the same selectivity, but of the opposite chirality. To explore the effect of the chiral cation and fluoride catalyst separately, N-benzylquininium chloride (BQC) (or pseudo-enantiomer N-benzyl- quinidinium chloride (BQDC)) combined with tetra-*n*-butylammonium fluoride (TBAF) have been used to catalyze the hydrosilylation reaction. Small amounts of BQC or BQDC lead to a stable ee of around 12%, but a diminished yield.

5 Outlook

The main aim is synthesizing GVL most enantioselectively, directly or indirectly from LA, in a clean and cheap manner. I'll describe a few possible additions to the work in this thesis and starting points for relevant further scientific exploration.

5.1 Substrate

A few substrates have already been tried (LA, ML, BL, BnL) and it seems larger alcohol groups on the ester don't increase enantioselectivity of the reaction, but do make it more difficult for the GVL ring to close or otherwise decrease the maximum obtainable yield compared to ML. However it can't be said for certain that, for instance, ethyl levulinate somehow would perform better.

Another option is exotic combinations to attempt to replace the free floating chiral agent. The BQF molecule contains an alcohol group which could be esterified to LA and there are numerous other chiral alcohols that could take it's place. However, the distance to the carbonyl group where the actual reduction takes place is still quite far.

5.2 Silane

TTSH shows some selectivity, but 27% still leaves much to be desired. Possibly this could be improved by cooling the reaction (currently running at RT and mostly done in 2 h) and slowing everthing down, leaving more time for contact between the reaction and the chiral influence.

Perhaps a silane which is even bulkier than TTSH would be less reactive and more sterically obstructive to be perfectly suitable for slow, highly stereoselective hydride donation. It will be difficult to find one. Moreover, the original plan was to prove the prinicple of hydrosilylation with a

model silane and next switch to the very cheap PMHS.

When considering PMHS it becomes clear this compound has few redeeming qualities for stereoselective synthesis. It breaks down in dihydridesilanes, making it highly reactive with minimal steric characteristics. When the goal is spatial obstruction, it would be more convenient if the molecule had faces or substituents.

Again the practical suggestion would be to cool the reaction down. However, when PMHS was used, it was already cooled to -70°C with a reaction time of probably within 10 minutes. Maybe liquid nitrogen would help making PMHS more useful for enantioselective reactions. With measures like this PMHS probably becomes less desirable.

5.3 Catalyst

Drew *et al.* noted the fluoride anion catalyst could be substituted for the somewhat less efficient hydroxide anion to similar effect.[104] Mere base is cheaper and more desirable in use than fluoride. Catalyst substitution becomes extra interesting when considering chiral alkoxy bases. Kohra *et al.* demonstrated asymmetric hydrosilylation of a ketone using a lithium chiral alkoxy salt as catalyst, obtaining in the best cases an ee of 69%.[99]

Separating the benzylquininium cation and fluoride anion is still an interesting idea. For this to succeed solubility is likely a main issue. Some combinations have already been tried with no success. The most practical solutions for solvation problems of salts in organic solvents like THF utilize large steric structures, like crownethers or aromatic rings, which could interfere with the enantioselective effect of the benzylquininium cation with the substrate. However, this could possibly also have an agregative positive effect. Another option would be changing the solvent.

Strangely, the expected negative effect of TBAF quenching on the ee has not been encountered when removing TBAF before measuring as opposed to quenching with KF. If this can be confirmed, that would mean semi-instant yield production through quenching is also quite stereoselective. In this case a way of high yield quenching might increase selectivity while saving reaction time.

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