Investigations into the Frustrated Lewis Pair-Catalyzed Hydrogenation of Epoxides

MASTERTHESIS

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Abstract

Traditionally hydrogenation of unsaturated substrates is a transition metal (TM)-catalyzed or stoichiometric transformation. The report about heterolytic H_2-activation via Frustrated Lewis Pairs (FLP) allows the performance of classic TM-catalyzed reactions in an organocatalytic fashion. In the last decade the substrate scope for FLP-catalyzed hydrogenation has grown steadily. However, to the best of our knowledge epoxides have not yet been successfully reduced. The epoxide motive is an important building block in organic synthesis or product in natural product synthesis. Currently, hydrogenation of epoxides to alcohols is a stoichiometric or a TM-complex catalyzed transformation.

Here, attempts to FLP-catalyzed hydrogenations of epoxides to alcohols are described. The known FLPs $B(C_6F_5)_3$/1,4-dioxane and $B(C_6F_5)_3$/diethyl ether, which are used for the FLP-catalyzed hydrogenation of carbonyl moieties, were tested for possible hydrogenation of epoxides. Meinwald rearrangement of the epoxide to an aldehyde is observed. With this result a tandem isomerization-hydrogenation reaction was envisioned. Here an epoxide rearranges to an aldehyde, upon which it should be reduced to an alcohol. Unfortunately, this reaction was not successful.

The reactivity of less electron-poor Lewis acids in FLP-catalyzed hydrogenation of epoxides was investigated. Upon investigations of adduct formation between the Lewis acids with *trans*-phenylpropane oxide, a Lewis acid dependent reactivity of the epoxide was found. *trans*-phenylpropane oxide dimerizes upon stoichiometric exposure to $B(C_6F_5)_3$, but isomerizes to an aldehyde when exposed to $B(C_7H_8)_3$. *trans*-phenylpropane oxide does not form a Lewis adduct with $B(C_6F_5)_2Mes$. Therefore, it is proposed that a new FLP was found.

Transfer hydrogenation (TH) of epoxides was attempted by $B(C_6F_5)_3$-catalyzed hydride abstraction from a diene. However, hydride transfer was prevented most likely by the interaction of $B(C_6F_5)_3$ with epoxides. The finding that $B(C_6F_5)_2Mes$ and *trans*-phenylpropane oxide form a FLP opens possibilities for future research, especially in combination with $B(C_6F_5)_2Mes$ -catalyzed TH.

List of Abbreviations

H_2	Dihydrogen
TM	transition metal
FLP	Frustrated Lewis Pair
LA	Lewis acid
LB	Lewis base
HOMO	highest occupied molecular orbital
LUMO	lowest unoccupied molecular orbital
1a	Tris(pentafluorophenyl)borane
TH	transfer hydrogenation
GB	glove box
ee	enantiomeric excess
EWG	electron withdrawing group
NMR	nuclear magnetic resonance
δ	chemical shift
ppm	parts per million
J	coupling constant
Hz	Hertz
s	singlet
d	doublet
qd	quartet of doublets
t	triplet
m	multiplet
ESI-MS	Electron spray Ionization Mass spectroscopy
GC-MS	Gas chromatography-mass spectroscopy
g	gram
mL	milliliter
rt	room temperature
h	hour
bp	boiling point
Å	Ångström
THF	Tetrahydrofuran
Et_2O	Diethyl ether
CH_2Cl_2	Dichloromethane
C_6D_6	deuterated Benzene
m.s.	molecular sieves

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1. Introduction

1.1. Reduction and Hydrogenation

In organic chemistry the term reduction, though technically referring to the overall gain of electrons, is often associated to the net-uptake of hydrogen by a substrate. These reactions for the reduction of unsaturated bonds with hydrogen sources as reducing agent are called hydrogenation reactions.

Molecular hydrogen, H_2, is considered the most clean and atom economically hydrogenation agent. Breaking the marriage of H_2, as G.J. Kubas called it in 2006, is one of the main challenges in hydrogenation chemistry.[1] The H-H bond strength is about 104 kcal/mol (bond enthalpy) and therefore the bond is difficult to break.[2] Being able to reversibly cleave and recombine the H-H bond is important for catalysis as well as H_2 storage and H_2 production.[1] Different strategies as how to break this bond have been found and are introduced here after.

1.1.1. Homolytic Cleavage of H_2 by Transition Metal Complexes

The traditional approach to split H_2 is by homolytic cleavage with transition metal (TM) complexes. The overall transformation can be summarized in the interaction of a metal complex with H_2 in order to separate the electrons of the H-H bond and form a metal-dihydride complex.[1] Figure 1 shows in more detail the anticipated steps of a homolytic cleavage.

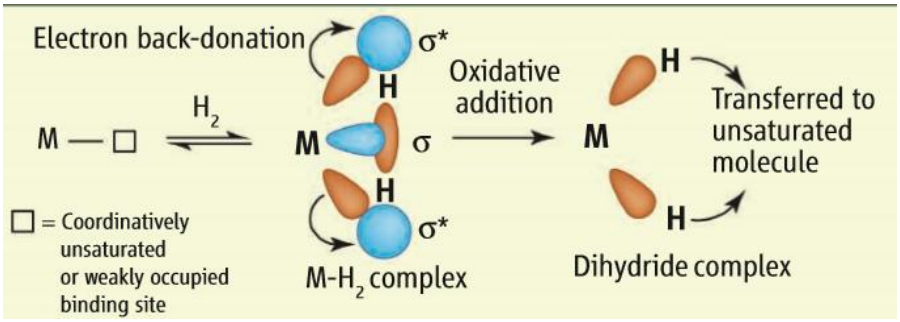


Figure 1: Homolytic H_2 activation by a metal; figure taken from Kubas.[1]

A coordinatively unsaturated metal complex will interact with the H_2 molecule in a side-on fashion. An initial sigma complex is formed by frontier orbital interaction. Thereby the σ-bonding electrons of the highest occupied molecular orbital (HOMO) of the H_2 molecule donate electron density into an empty d-orbital of the metal complex. This interaction is stabilized by the HOMO of the metal complex, which back-donates electron density into the σ*-orbital of the H_2 molecule. Strong back donation fills the H-H antibonding σ*-orbital to such an extent that the H-H bond will break. The overall oxidative addition of H_2 to the metal leads to the formation of a metal-dihydride complex.

1.1.2. Catalytic hydrogenation based upon homolytic H_2 cleavage

Based on homolytic H_2 activation, different homogeneous catalytic systems have been introduced, which proofed to be highly valuable for organic synthesis. Noble metals complexes with eg. Rhodium (Rh), Ruthenium (Ru), Iridium (Ir), Palladium (Pd) and Platinum (Pt) are able to homolytically split H_2 and transfer the resulting hydrides to unsaturated substrates in a catalytic manner. Some noble metal

complexes have found broad application in industry. One example is the Rh-based Wilkinson catalyst used for olefin hydrogenation (Figure 2).[3]

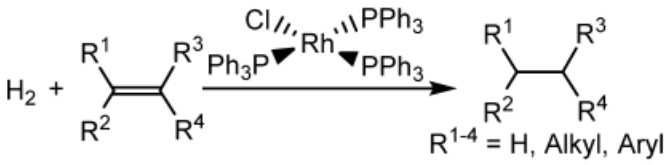


Figure 2: Olefin reduction catalyzed by Wilkinson catalyst; figure taken from Stephan et al.[3]

1.1.3. Heterolytic Cleavage of H_2 by Cooperative Interaction of Metal Centre and its Ligand

H_2 can also be activated heterolytically by cooperative interaction of a metal center and its ligand. The overall transformation is based on the polarization of H_2 and splitting it into a hydride and a proton. A (metal)hydride complex is formed and the proton is transferred eg. to the substrate or to the ligand. Cooperation with a base, in form of the complex ligand, a second metal atom or a second molecule, is important. Figure 3 shows heterolytic H_2 activation by cooperative interaction of an Ir-complex and its ligand.[4]

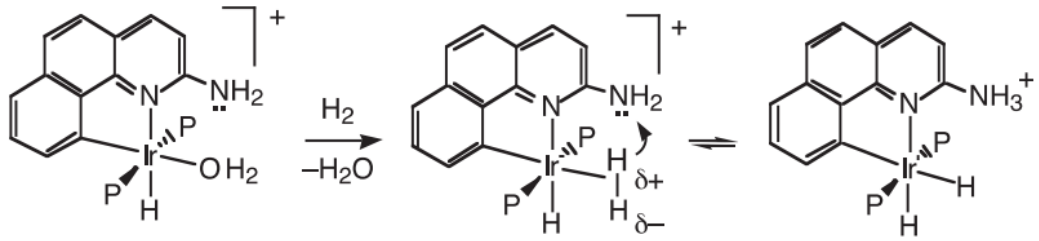
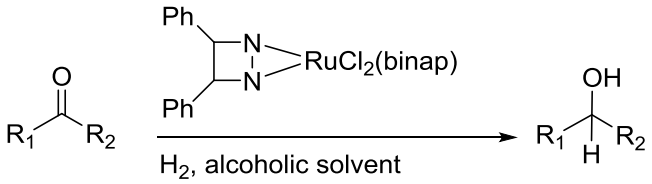


Figure 3: Heterolytic H_2 activation by cooperative interaction of metal center and its ligand; figure taken from Kubas.[5]

An electron poor metal centre interacts with H_2 in a side on fashion and receives electron density from the $\sigma_{H\text{-}H}$ – bond. The H-H bond gets polarized due to a second interaction of H_2 with a base (here the NH_2-ligand). The base deprotonates H_2 by donating electron density into the σ*- orbital of the H-H bond. Thereby it takes over the task of back donation, which was required for homolytic cleavage. Overall a metal hydride with a protonated ligand is formed. Both, oxidation state and coordination do not change.

1.1.4. Catalytic hydrogenation based upon heterolytic H_2 cleavage

Electron poor TM complexes, which heterolytically cleave H_2, are used for homogeneous hydrogenation catalysis in organic synthesis. An example is Noyoris' Ru-based system, which can be used for ketone hydrogenation (Scheme 1). The ethylenediamine ligand assists in the cleavage of H_2 by inducing a direct proton transfer from the η^2-coordinated H_2 on the Ru-metal to the basic amine.[5]

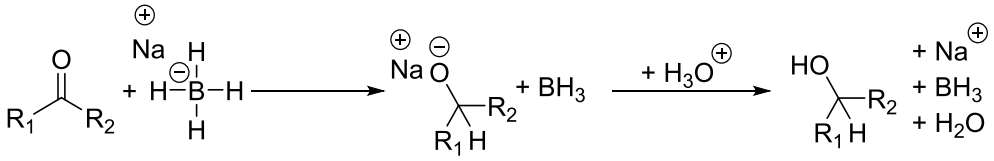


Scheme 1: Ketone hydrogenation catalyzed by Ru-system of Noyori; adapted from Kubas.[5]

1.1.5. Stoichiometric Hydrogenation based on Transfer Hydrogenation

Metalhydrides can also be formed from combining a metal with a hydrogen source other than H_2. Protonation of the metal complex, addition of a hydride donor to a metal salt or β-elimination in an alkylmetal-complex are common ways to synthesize a metal hydride. The hydrides can be transferred to a substrate and thereby reduce it in a stoichiometric manner.

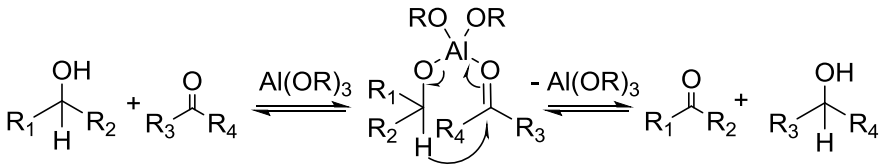
Using TM as hydride donors for stoichiometric reduction is very expensive. Main group hydride donors like $NaBH_4$ and $LiAlH_4$ are commercially available and widely used in organic synthesis to reduce substrates with chemo - and regioselectivity.[6] Scheme 2 shows the stoichiometric reduction of a carbonyl group to an alcohol with $NaBH_4$.



Scheme 2: Reduction of a carbonyl compound by $NaBH_4$.

This reduction goes via a nucelophilic attack of the hydride on the electrophilic carbonyl moiety to yield an alkoxide ion. The intermediate ion is then further protonated to an alcohol by addition of an aqueous acid. $NaBH_4$ can be used in aqueous or alcohol solutions and is therefore an easy to handle and safe reducing agent. $LiAlH_4$ requires Schlenk conditions due to its violent reaction with water.

The Meerwein – Ponndorf – Verley reduction is a transfer hydrogenation (TH) in which a hydride is transferred from one unsaturated system to another. Scheme 3 shows the mechanism of an aluminium facilitated TH in which a carbonyl group is reduced by an alcohol as reducing agent.[3]



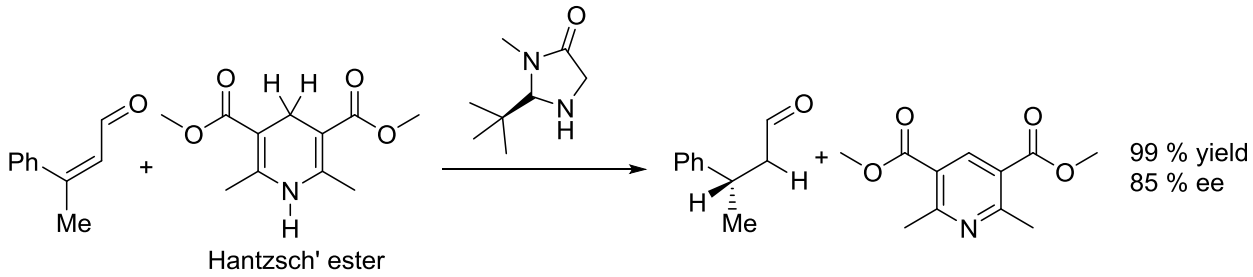
Scheme 3: Reduction of a carbonyl compound by TH.[7]

The reaction proceeds via a six-membered transition state which is established when the aluminium alkoxide coordinates to both the alcohol oxygen and the carbonyl oxygen. From the α-carbon of the

alcohol a hydride shift to the carbonyl-carbon occurs. Protonation of the oxygen on the activated carbonyl moiety finalizes the formal hydrogenation.

Purely organic hydride donors are also used for TH and give the benefit of working completely metal free. Hantzsch' ester is such a purely organic hydride donor. It is a synthetic analogue of the biological reductant NADH and commercially available. Instead of having to split the H-H bond of H_2 a C-H bond needs to be activated and broken. The heterolytic bond dissociation energy of the C_4-H bond is 74 kcal/mol [8] and therefore significantly smaller than the 104 kcal/mol bond dissociation energy for the H-H bond of H_2 gas. The driving force for TH here is the energy loss of the system by establishing an aromatic system.

Scheme 4 shows the enantioselective organocatalytic hydride reduction[9] of an α,β-unsaturated aldehyde by TH from Hantzsch' ester to the substrate.



Scheme 4: Enantioselective reduction of an alkene by TH from Hantzsch' ester; adapted from MacMillan et al.[9]

An iminium ion is formed by imine condensation of the purely organic amine catalyst with the unsaturated aldehyde. This introduces chiral information into system as well as that it activates the substrate by lowering its LUMO.[9] Proton- and hydride-transfer from the Hantzsch' ester reduce the double bond.

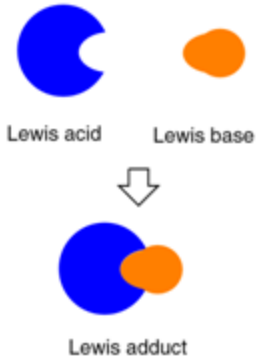
The most obvious advantage of using hydrogen sources other than H_2 itself is their being fluids and solids instead of gases which makes them easier to handle. This comes with the disadvantage of having to isolate and dispose one equivalent of waste after the reduction. Both advantage and disadvantage make these hydrogen sources suitable for academia, but not for large-scale industry applications.

1.2. Frustrated Lewis Pair Chemistry

Homolytic splitting of H_2 in homogeneous catalysis often requires noble metals. Those metals are precious and expensive. In addition their metal complexes can be very toxic. First row TM or main group compounds as catalysts for heterolytic H_2 splitting are expected to be future good alternatives to noble TM catalysts.

In the following a conceptually new approach for the heterolytic H_2 splitting by cooperative interaction of main group compounds is introduced, which leads to the subsequent organocatalytic hydrogenation of unsaturated substrates.

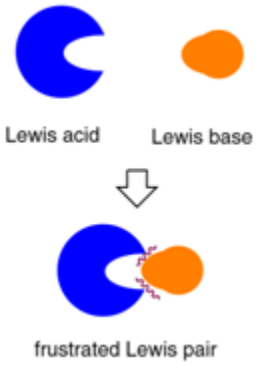
1.2.1 The Principle of Frustrated Lewis Pairs



In 1923 Gilbert N. Lewis defined an (Lewis) acid as a molecule that behaves as electron pair acceptor due to a low-lying LUMO and a (Lewis) base as a molecule that behaves as electron pair donor due to a high-lying HOMO.[10] Combining Lewis acid (LA) and Lewis base (LB) was traditionally thought to result in the formation of a dative donor-acceptor adduct or Lewis adduct (Figure 4).[11]

Figure 4: Schematic illustration of the formation of a Lewis adduct by the combination of LA and LB; figure taken from Alcarazo.

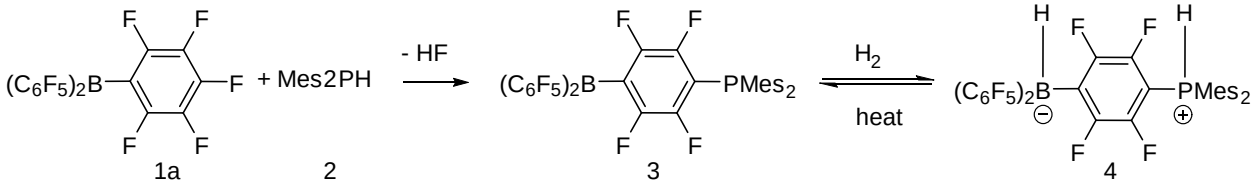
This adduct formation neutralizes the reactivity of both molecules in a similar way as Brønsted acid and base neutralize each other. The chemistry of LA and LB forms the basis to many organic and organometallic reactions and our understanding of them.[12]



In 2006 Stephan and coworkers described a Frustrated Lewis Pair (FLP) as an unquenched mixture of LA and LB.[13] The observation that steric bulk prevents adduct formation between LA and LB was reported before by Brown.[14] The molecules cannot form a dative bond and thereby the reactivity of both molecules is preserved (Figure 5).[11]

Figure 5: Schematic illustration of the formation of a FLP by combination of LA and LB; figure taken from Alcarazo.

Stephan and coworkers discovered that LA (**1a**) and LB (**2**) did not form a Lewis adduct, but instead formed compound **3** via nucleophilic attack of **2** on a substituent of the **1a** (Scheme 5).[13]



Scheme 5: Synthesis of FLP 3 and subsequent H_2 activation by 3 to yield 4; reproduced from Stephan et al.[13]

Compound **3** is a bifunctional molecule due to its Lewis acidic and Lewis basic character. Steric hindrance and ring strain prevent dative bond formation and self-quenching. Upon testing this new bifunctional molecule and its assumed preserved reactivity[11], it was observed that H_2 – gas was heterolytically split in a reversible manner to form a phosphonium borohydride salt (**4**).

The Stephan group claims to be the first to report about a metal free system, which can facilitate both the liberation and addition of H_2. This finding opened the way to fundamentally new strategies for the development of catalysts for small molecule activation based on main group elements.[15] Rational design of these systems was now possible and led to a constantly growing scope of substrates.

Over the past decade substrates such as imines[16], enamines[17], arenes[18], allenes[19], olefins[20], protected nitriles[6], aziridines[6], silylenols ethers[21], N-heterocycles[22], oxime ethers[23], aldehydes[24] and ketones[24-25] were shown to be hydrogenated by FLP hydrogenation catalysis in high yields.

Apart from H_2 other small molecules like ethers[26], silanes[27], alkynes[28], CO_2[29], N_2O[30], NO[31] were successfully activated by FLP. However, in this introduction the focus will lie on FLP mediated H_2 activation and catalytic hydrogenation.

1.2.2. FLPs of $B(C_6F_5)_3$ in Combination with Different Lewis Bases

Hydrogenation catalysis mediated by many different combinations of LA and LB has been reported about after the initial publication of FLP mediated H_2 activation.

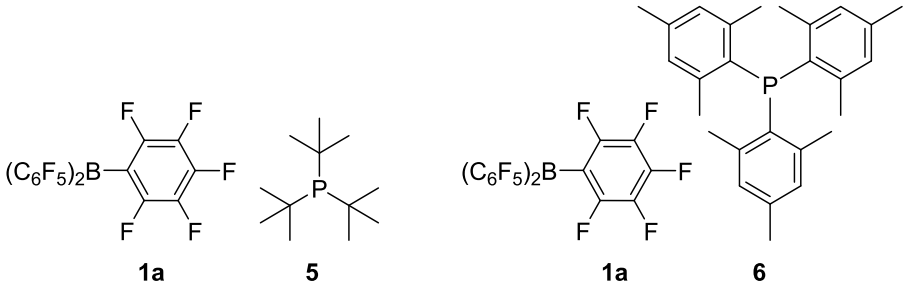
The boron based LA tris-pentafluorophenyl-borane (**1a**) is the most commonly used LA so far. It is a commercially available, highly electrophilic LA[24b] which is used in industry as polymerization co-catalyst in the Ziegler-Natta process.[32] It was shown that **1a** does not activate H_2 by itself.[33]

Many different LBs have been reported to be able to heterolytically split H_2 with **1a** in a cooperative manner. In the following an attempt is made to show the development of FLP hydrogenation catalysis over time going from very basic phosphine LBs via nitrogen based LBs to weakly basic oxygen containing LBs. Also a carbon based LB will be discussed briefly. Along the way the importance of finding a suitable steric and electronic match between LA and LB will become clear.

1.2.2.1. Phosphorus – based Lewis Bases

After the initial report about H_2 activation by an intramolecular phosphorus-boron FLP many other intermolecular phosphorus-boron combinations have been tested.

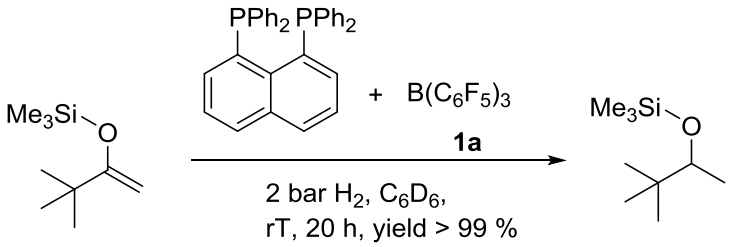
In 2007 Stephan and coworkers reported about two PR_3 type phosphorus-based LBs (R = *t*Bu (**5**), Mes (**6**)) which could both form an intermolecular FLP with **1a** (Scheme 6).[34]



Scheme 6: two different FLPs; adapted from Stephan et al.[34]

The steric bulk around the phosphorus atom was suggested to prevent an adduct formation as well as a nucleophilic attack on the *para*-carbon of the aromatic rings in the LA. Applying 1 bar of H_2 at 25 °C to the mixture of **1a** / **5** or **1a** / **6** was sufficient to form a phosphonium hydridoborate salt and D_2 experiments confirmed that indeed the gas had been heterolytically split. No comment on the reversibility of this process was made.

Later the Erker group reported about the successful activation and transfer of H_2 to silyl enol ethers in a catalytic manner (Scheme 7). 1,8-bis(diphosphino)naphthalene was used as LB in cooperation with **1a** to activate H_2 in a reversible manner.[21]



Scheme 7: Catalytic reduction of silyl enol ether to silyl ether by FLP hydrogenation catalysis; reproduced from Erker et al.[21]

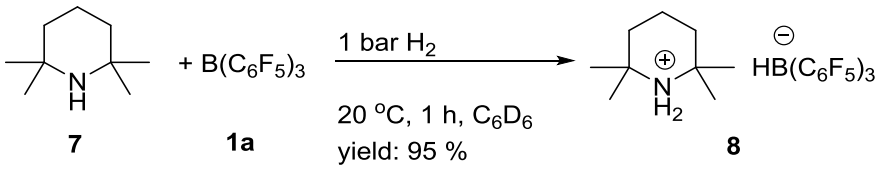
Many other bulky phosphorus – based LB have been analyzed for their ability to split H_2 with **1a** in a cooperative manner.

1.2.2.2. Nitrogen – based Lewis Bases

The basicity of nitrogen-containing molecules is usually lower than of phosphorus-containing molecules. In addition, nitrogen-containing molecules, such as imines, are unsaturated and therefore possible

substrates to FLP hydrogenation. It was soon suggested to use inexpensive, stable amines in combination with **1a** to form an FLP and activate H_2 in a cooperative manner.

Repo, Rieger and coworkers tested 2,2,6,6-tetramethylpiperidine (**7**) as LB. Under very mild conditions this sterically demanding amine **7** in combination with **1a** was able to heterolytically split H_2 and form an amino-borane salt (**8**) in high yields (Scheme 8).[35] No comment on the reversibility of this process was made.

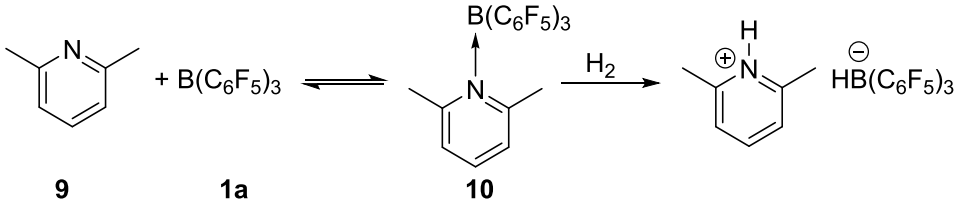


Scheme 8: Heterolytic H_2 activation by FLP of 7/1a; adapted from Repo, Rieger et al.[35]

The limits of steric hindrance in terms of their benefit to H_2 activation and consecutive hydride transfer were then shown in a report about sterically demanding aldimines and ketimines as possible LBs. Several aldimines and ketimines were reported to be able to split H_2 with **1a**. Subsequently they were reduced in a catalytic manner.

Increasing the bulkiness of the substituents on the carbon of the ketimine from -Ph to -*t*Bu showed the limits of steric hindrance since the phenyl- substituted ketimine was reduced with 94 % yield[6] whereas the *t*Bu- substituted ketimine showed no conversion to its amine after 48 h. The rate-limiting factor turned out to be product dissociation of the amine product from **1a.** A direct competition between steric congestion favored for product dissociation and inherent Lewis basicity needed for H_2 activation.

In 2010 the Stephan group changed the way of thinking about FLPs by stating that LA and LB can be in equilibrium state between forming a classical Lewis adduct and showing FLP behavior.[36] They showed that 2,6-lutidine (**9**) forms a reversible dative bond with **1a**. Upon addition of 1 bar H_2 an ammonium hydroborate salt (**10**) was formed which proves the FLP reactivity of this system (Scheme 9).

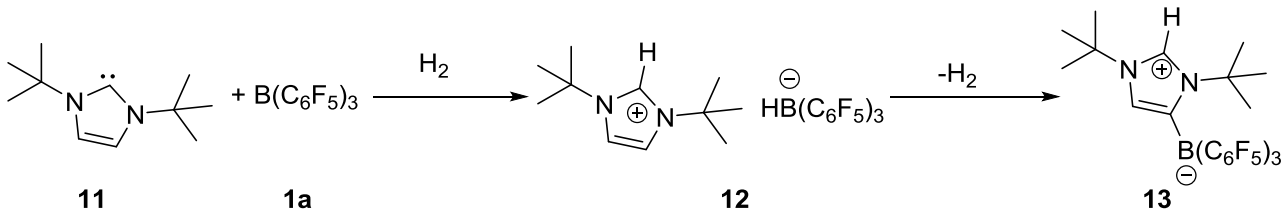


Scheme 9: Reversible Lewis adduct formation between 1a and 9 enables H_2 by FLP chemistry; reproduced from Stephan et al.[36]

Overall, this first work with N-B FLPs shows that nitrogen-boron FLPs can activate and transfer H_2 in a manner similar to P-B FLPs. The substrate can actively participate in the heterolytic splitting of H_2 without decrease in yield.

1.2.2.3. Carbon - based Lewis Bases

The group of Tamm designed a FLP with an imidazolin-2-ylidene type carbene base and **1a** based on the knowledge that these type of carbenes are similar to electron rich organophosphines.[37] The imidazoliumborate salt (**12**) of 1,3-di-*tert*-butyl-imidazolin-2-ylidene (**11**) and **1a** was formed upon addition of H_2 at 20 °C within 10 min. Unfortunately, the salt degraded over time to form **13** by H-atom migration over the carbene ring (Scheme 10).

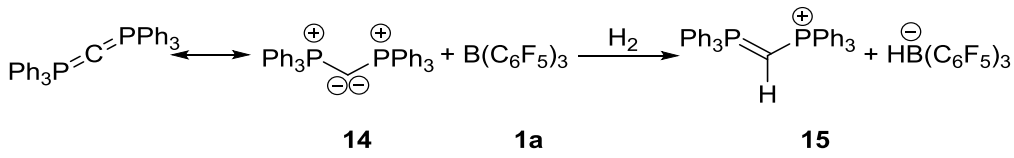


Scheme 10: FLP facilitated H_2 activation by a FLP of 1a and 11. Subsequent H-migration and loss of H_2 leads to 13; adapted from Tamm et al.[37]

The authors concluded to use extra substituents in 4- and 5- position of the carbene in future work to prevent the H-shift. No catalysis attempts were reported in this publication.

Another approach for carbon/boron based FLP was proposed by Goddard and coworkers. Carbodiphosphines have a zero valent carbon with four valence electrons. This C^0 is assumed to be very nucleophilic and was calculated to have a very high proton affinity.[38] Therefore the addition of steric bulk on the phosphorus atoms should make these molecules good LBs for FLP chemistry.

Hexaphenylcarbodiphosphorane (**14**) in combination with **1a** was exposed to H_2 at -78 °C to form a salt (**15**) in 91 % yield (Scheme 11).[38] No catalysis attempts were reported in this publication.

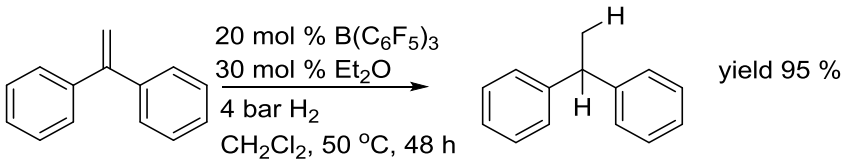


Scheme 11: FLP facilitated H_2 activation by a FLP of 1a and 14; adapted from Goddard et al.[38]

1.2.2.4. Ethers as Oxygen – based Lewis Bases

Oxygen – containing molecules are very weak LBs compared to P-, N- or C- based LBs. They tend to form adducts with boron based LAs due to the oxophilicity of boron.[39]

However, the use of ethers as LBs for FLP-catalyzed hydrogenation was reported.[40] H/D scrambling in CD_2Cl_2 is detected upon stoichiometric investigation of the reactivity of diethyl ether and **1a** at 4 bar H_2 and room temperature within 15 minutes. Subsequently, this FLP was reported to be able to reduce 1,1-diphenylethylene under mild conditions (Scheme 12).[40]



Scheme 12: Olefin reduction by solvent mediated FLP hydrogenation catalysis with a FLP of 1a and diethyl ether; adapted from Stephan et al.[40]

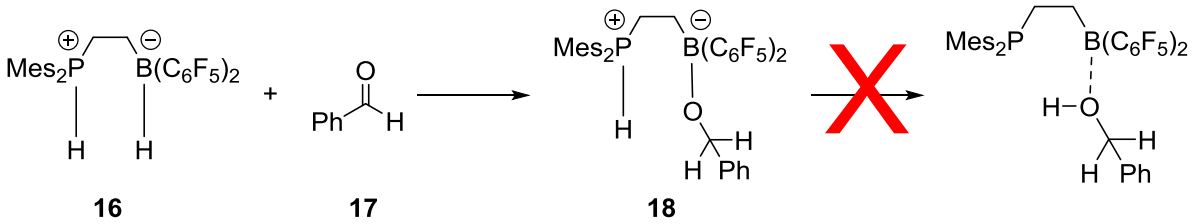
Increase of the ether catalyst loading to 160 mol % resulted in faster and higher conversion. Based on this, Ashley and coworkers reported about the use of ethers as both LB and solvent in FLP-catalyzed hydrogenation. The FLP of $B(C_6Cl_5)(C_6F_5)_2$ and THF is able to heterolytically split H_2.[41] The system successfully reduces bulky electron-deficient imines at lower temperatures compared to the reaction conditions of the FLP **1a**/imine.[6] 1,4-dioxane is also used for this imine reduction as LB and solvent. However, due to the lower basicity of the donor solvent a longer reaction time is required.[42]

1.2.3. Metal – free Reduction of Carbonyl Moieties

Traditionally ketones (and aldehydes) were catalytically reduced (by H_2) with Ru- and Rh-complexes or stoichiometric amounts of Al- or B-based hydrides. Only KO*t*Bu as non-TM compound is known to catalytic reduced ketones and aldehydes under very harsh conditions.[3]

After the introduction of FLP catalyzed reductions, it has been a struggle to find a combination of LA / LB capable of reducing carbonyl moieties. This is mainly due to the high oxophilicity of boron. In the process a B-O bond is formed. A reoccurring problem was the failed protonation of this bond by the conjugated Brønsted acid of the LB. If this protonation were successful, the desired alcohol product would have been obtained. In a few examples this will be illustrated.

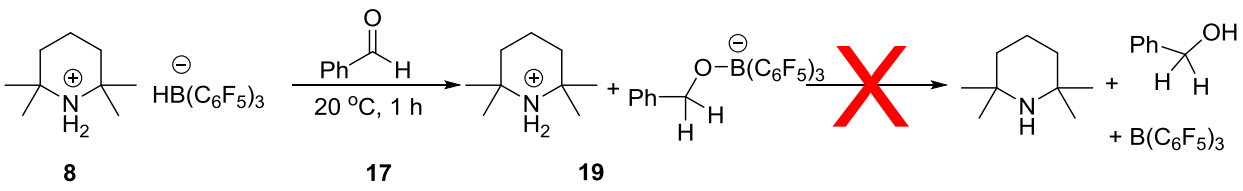
The Erker group reports a stoichiometric reaction of a pre-hydrogenated FLP-H_2 **16** with benzaldehyde (**17**) to compound **18** (Scheme 13).[43]



Scheme 13: Attempt to reduce 17 in a stoichiometric manner by the pre-hydrogenated FLP 16; adapted from Erker et al.[43]

Hydride transfer from boron to carbon reduces the carbonyl moiety of **17**. The proton transfer from phosphorus to oxygen to obtain the desired alcohol product did not occur. A phosphonium boronic ester (**18**) is formed. This can be explained by the higher Lewis basicity of the phosphorus-based LB functionality compared to the carbonyl oxygen.

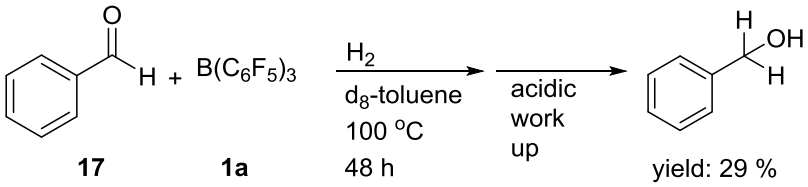
Another attempt to reduce **17** was done with the pre-hydrogenated FLP-H_2 **8** (Scheme 14).[35]



Scheme 14: Attempt to reduce 17 in a stoichiometric manner by the pre-hydrogenated FLP 8; adapted from Repo, Rieger et al.[35]

Again only the hydride transfer product was obtained instead of the alcohol product. Similar to Scheme 13 the protonation of the oxygen-boron bond is prevented. The lower basicity of oxygen compared to nitrogen is considered the reason for the failed hydrogenation. Both N- and P-based LB are such strong LBs that their protonated species are fairly weak acids. These acids are not sufficiently strong enough to protonate the B-O bond of compound **19**.

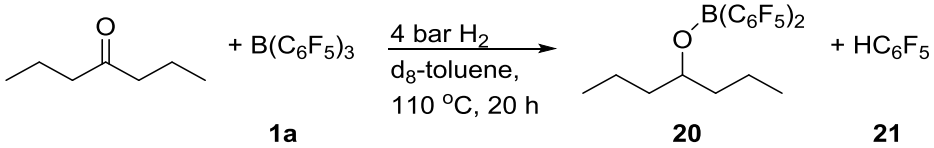
After identifying protonation as the key problem to successful hydrogenation of carbonyl moieties, carbonyl moieties like aromatic aldehydes and aliphatic ketones were envisioned as LBs in an intermolecular FLP with **1a**. In 2012 the Repo group reported about a stoichiometric two step hydrogenation of **17** facilitated by **1a** and the substrate itself (Scheme 15).[44]



Scheme 15: Reduction of 17 by FLP activated hydride transfer and subsequent Brønsted acidic protonation; adapted from Repo et al.[44]

H_2 was heterolytically split by the benzaldehyde-**1a** FLP and a hydride was transferred from the borohydride to the carbon of the carbonyl functionality. A second aqueous work up step was required to obtain the benzyl-alcohol by hydrolysis of the B-O bond. This proves the ability of carbonyl moieties to function as LB in an FLP with **1a** for H_2 splitting in a cooperative manner. It also shows that a boron-based LA can activate H_2 in the presence of carbonyl moieties.

Later, the Stephan group reported about the heterolytic splitting of H_2 by the cooperative interaction of an aliphatic ketone and **1a**. Scheme 16 shows the hydroboration of heptanone to the neutral borinic ester (**20**) and pentafluoro-benzene (**21**).[45]



Scheme 16: Heterolytic H_2 activation results in borinic ester formation; adapted from Stephan et al.[45]

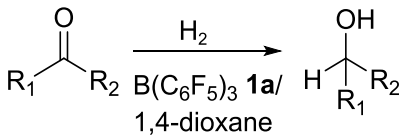
H_2 was heterolytically split by the ketone-**1a** FLP. The carbon of the carbonyl functionality received a hydride from the borohydride species. Subsequently, the B-C bond was protonated instead of the desired B-O bond. This results in the formation of **20** and **21**.

The hydrogenation of the aliphatic ketone in Scheme 16 failed due to the fact that the conjugated Brønsted acid of its carbonyl moieties is unable to protonate the B-O bond. Therefore the FLP-catalyzed hydrogenation of carbonyl moieties needs to involve the formation of a stronger conjugated Brønsted acid. Donor solvents like Et_2O, 1,4-dioxane and THF are considered very weak oxygen-based LBs. However, their conjugated Brønsted acids are exceptionally strong. For example, oxygen-protonated 1,4-dioxane is reported to have a pKa = -2.9 (in aqueous H_2SO_4).[42] As mentioned earlier, etheral solvents were shown to activate H_2 with boron-based LAs. Therefore, this group of LBs was examined for the FLP-catalyzed hydrogenation of carbonyl moieties.

1.2.3.1. Aldehyde and Ketone Reduction and Hydrogenation

In 2014 the Ashley group as well as the Stephan group separately reported about the first metal-free hydrogenation of various aldehydes and ketones.[24]

The Ashley group specifically combined 1,4-dioxane with **1a** in order to form a FLP which can reduce carbonyl functionalities at 5-12 bar H_2 pressure (Scheme 17).[24b]



Scheme 17: Reduction of carbonyl moieties by solvent mediated FLP hydrogenation catalysis; adapted from Ashley et al.[24b]

It is proposed that **1a** and 1,4-dioxane are forming an equilibrium between classical Lewis adduct and FLP, of which the later is able to heterolyticaly split H_2 to form an oxygen-protonated 1,4-dioxane molecule as well as a borohydride. The order in which protonation of the carbonyl oxygen and hydride transfer to the carbon carbonyl moiety occur, has not been properly investigated yet.

The scope was extended to aliphatic ketones and electron-poor aromatic ketones and aldehydes, which were hydrogenated with good to excellent yields. Steric hindrance and electron donating substituents prevented the successful hydrogenation or led to dehydration (of e.g. acetophenone).

The low Lewis basicity of 1,4-dioxane is thought to be the reason for long reaction times. Increasing the H_2-pressure is suggested to shorten the reaction time.

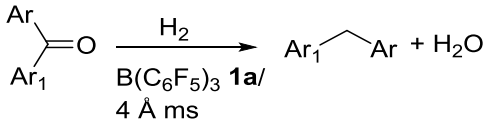
Solvent forms hydrogen bonds with protonated substrate thereby preventing the protonation of B-C bond of **1a**. Due to the excess of solvent the product dissociation is more favorable. The product-**1a** adduct is replaced by the solvent-**1a** adduct.

The Stephan group used Et_2O and other etheral solvents in combination with **1a** at 60 bar H_2 pressure (70 °C, 12 h) to hydrogenate alkyl-, aryl- and cyclohexyl- ketones in good to excellent yields.[24a] H_2

activation, protonation of the carbonyl oxygen and hydride transfer to the carbon carbonyl moiety are proposed to occur in a similar way as for the 1,4-dioxane FLP system.

More recently, the Stephan group described the reduction of ketones and electron rich aldehydes in the non-polar solvent toluene at 60 bar H_2 pressure was reported.[25] α- cyclodextrin or 4 Å molecular sieves (ms) contain Lewis basic oxygen atoms, which served as LB in the heterogeneous FLP with **1a.**

The yields for diaryl ketones were quite low due to a deoxygenation side reaction, which was then optimized to result in a reductive deoxygenation tandem reaction (Scheme 18).[25]



Scheme 18: Deoxygenation of diaryl ketones by FLP chemistry; adapted from Stephan et al.[25]

The hydrogenation and consecutive deoxygenation were both reported to be catalytic. One equivalent of water, which is considered a catalyst poison, is produced as side product. It is removed by the 4 Å ms.

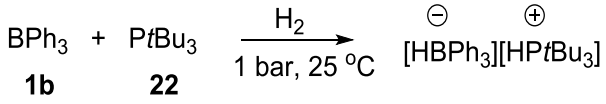
1.2.4. Lewis Acids for Frustrated Lewis Pair Catalysis

As mentioned earlier **1a** is the most common LA used in FLP-catalyzed hydrogenation. It is a hard LA.[15] Due to the high oxophilicity of **1a** use of this LA is limiting in substrate scope, solvent choice and functional group. In addition the moisture and air sensitivity[46] of **1a** require reactions to be done at Schlenk-conditions.

LAs based on other main-group elements like Al, Si, P as well as carbon-centered LAs are described in literature.[46] Our focus lies on the boron based LAs. Therefore these other LAs will not be further discussed.

Completely new LAs and variation of **1a** have been designed and synthesized seeking to solve problems associated with **1a**. They have been tested for H_2 activation, hydrogenation and catalytic activity. Some examples and their principle, according to which they have been synthesized, are discussed hereafter.

Stephan and coworkers tested the ability of less Lewis acidic LAs to split H_2 with P-based LBs. They found that triphenyl-borane (**1b**) could activate H_2 with tri-*tert*-butylphosphine (**22**) in a cooperative manner (Scheme 19).[34] No catalytic attempts using this FLP have been reported.



Scheme 19: Heterolytic H_2 activation by a FLP of 1b and 22; reproduced from Stephan et al.[34]

The Soos group introduced the size-exclusion principle, which uses steric constrain as main design element.[15] Figure 6 illustrates the idea of size-exclusion.

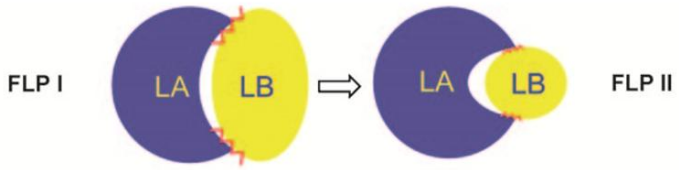
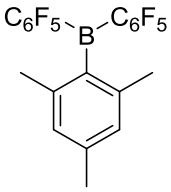


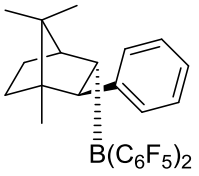
Figure 6: The size exclusion principle refers to the possibility of increasing the steric bulk around the LA and thereby preventing Lewis adduct formation with a larger group of LBs; figure taken from Soos et al.[15]

Soos and coworkers reported that Lewis adduct formation with a certain LB can be prevented by introducing more steric bulk around the LA center. Their aim was to design LAs like in FLP II (Figure 6) for smaller or more Lewis basic LBs to sterically prevent complexation.[15]

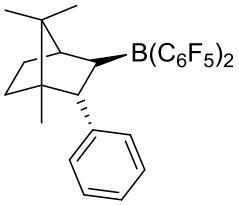


1c

According to the mentioned principle mesityl-di-pentafluorophenyl-borane (**1c**) has been designed and synthesized. The mesitylene substituent makes the LA more bulky and therefore less accessible. In addition the intrinsic Lewis acidity of the boron center is expected to be lower compared to **1a. 1c** can activate H_2 cooperatively with quinuclidine or DABCO and is successfully tested in imine reduction.[15]

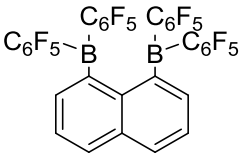


1d-A



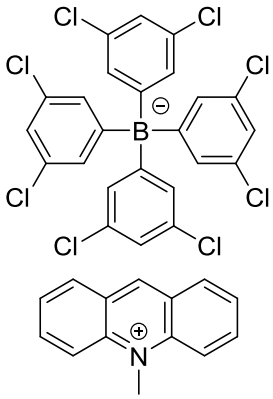
1d-B

The Klankermeyer group was the first to report about enantioselective hydrogenation facilitated by a FLP. A camphor derived chiral borane (**1d**) is synthesized as two diastereomers which can heterolytically split H_2 with tBu$_3$P as cooperative LB.[47] Without the P-based LB imine reduction is tested with both diastereomers of **1d. 1d-A** splits H_2 fastest and reduces one imine in quantitative yield and with 48 % ee towards the S-amine. **1d-B** reduces the same imine with high yields and up to 83 % ee towards the R-amine. The group of Klankermeyer hereby developed a FLP version of enantioselective catalysis using the traditional idea from asymmetric TM-catalysis to introduce chiral information into a system by using an enantiomeric enriched ligand.



1e

The Berke group reports about a bis-borane LA (**1e**), which can activate H_2 with 2,2,6,6,-tetramethylpiperidine as LB.[48] Due to the two LA centers in close proximity to each other, this bidentate LA is expected to show increased reactivity. Also the extraordinary[48] low-lying LUMO makes this molecule a superelectophile[48] with super Lewis acid[48] character. Imine reduction using this FLP was successful. The H_2 splitting is still expected to be facilitated by only one of the LAs and its LB counterpart similar to the **1a**/imine reduction.[6]

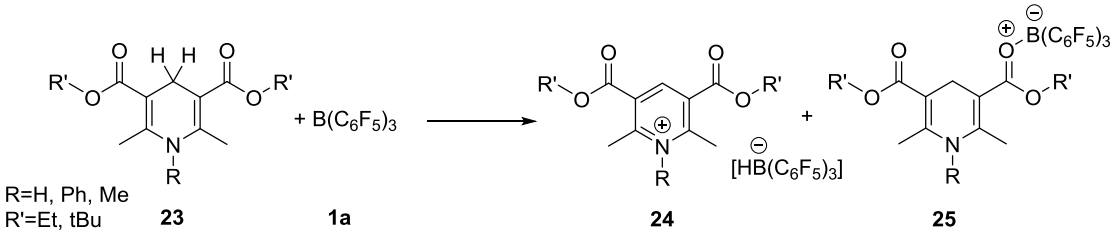


1f

The Ingleson group recently reported about a carbon based LA in form of an N-methylacridinium cation with *tetra*(3,5-dichlorophenyl)-borate as its anion (**1f**).[46] These cations have a high hydride ion affinity, but a low oxophilicity, which makes their salts potential new LAs for FLP catalysis in aqueous solutions.[46] The total LA salt is a significantly weaker LA than **1a**. It has been shown that **1f** forms a FLP with the N-LB 2,6-lutidine, which can heterolytically activate H_2 even in the presence of H_2O. Therefore this FLP is expected to be neither moisture nor air sensitive. Preliminary results about the catalytic hydrogenation of N-benzylidene-*tert*-butylamine show the potential of this new carbon based LA.

1.2.5. Transfer Hydrogenation with FLPs

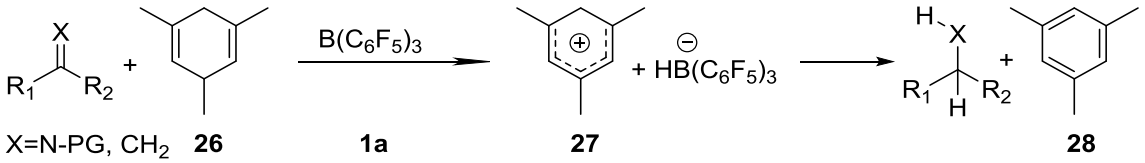
As mentioned earlier the Hantzsch' ester is considered a commercially available hydrogen donor. Stephan, Crudden and coworkers tested the hydride abstraction from Hantzsch' ester and its analogues by **1a** (Scheme 20).[8]



Scheme 20: C-H bond activation by 1a at Hantzsch' ester derivatives results in salt (24) and adduct (25) formation, 24 is the desired product; adapted from Stephan, Crudden at al.[8]

For the original Hantzsch' ester (R = H, R' = Et) they obtained the desired pyridium borohydrate salt (**24**) in 60 % yield. An adduct (**25**) between the ester moieties of the Hantzsch' ester and **1a** forms as a side product. Upon adding substituents onto nitrogen (R = Me or Ph, R' = Et) no adduct with **1a** is formed, but instead **24** is obtained in 90-98 % yield. By increasing the steric bulk at the ester moieties of the original Hantzsch's ester (R = H, R' = *t*Bu) adduct formation was prevented and **24** was formed in 90 % yield. Using a hydride donor with multiple coordination sites for **1a** is the disadvantage of this approach.

Oestreich and coworkers recently introduced the unsaturated hydrogen donor 1,3,5-trimethyl-2,4-cyclohexadiene (**26**) which in combination with **1a** was able to hydrogenate imines[49] and 1,1-disubstituted alkenes[50] via TH (Scheme 21).



Scheme 21: Reduction by 1a facilitated TH from 26 to unsaturated substrates (PG = protection group); adapted from Oestreich et al.[49-50]

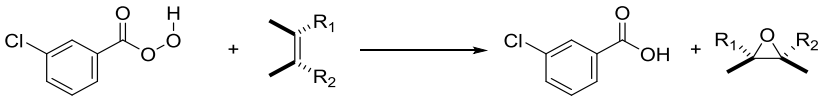
Upon hydride abstraction by **1a** a Wheland complex (**27**) is formed, which is suspected to first protonate the substrate in order to activate it, before the borohydrate can reduce the activated compound. The three methyl groups of **26** were introduced to stabilize **27** by hyperconjugation. The formation of aromatic mesitylene (**28**) is assumed to be the driving force of this TH process. H_2 gas production was considered a serious competing reaction. Reduction with an imine/**1a** FLP by in situ formed H_2 gas was not excluded. Cationic hetero- and homodimerization are side reactions, which are considered for the alkene reduction.

1.3. Epoxides

The epoxide motive is an important building block in organic synthesis or product in natural product synthesis. The ring strain of the triangle in an epoxide functional group leads to high reactivity.[51] In the following an approach for synthesis and transformations of epoxides are discussed.

1.3.1. Synthesis of Epoxides

One way to synthesize epoxides is via oxidation of an alkene. *meta*-Chloroperoxybenzoic acid (*m*CPBA) is a peroxyacid which is commonly used as oxygen-donor for this process. Scheme 22 shows the mechanism of the *m*CPBA-facilitated oxidation of alkenes to epoxides.



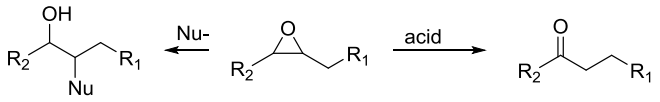
Scheme 22: General synthesis of an epoxide from an alkene by *m*CPBA.

π-electrons of the alkene double bond attack the electrophilic oxygen atom in the peroxide functional group. The O-O bond of *m*CPBA is broken and the carbonyl-oxygen is protonated by the hydrogen of the *m*CPBA hydroxyl-group. In this process *m*CPBA is converted to 3-chlorobenzoic acid. On the former alkene the epoxide ring is closed by the formation of a second O-C bond. The reaction goes through a concerted transition state.[52] The stereochemistry of the substrate is retained.

There are many other protocols according to which epoxides may be synthesized. One example is the Sharpless epoxidation. For 'his work on chirally catalyzed oxidation reactions' K. Barry Sharpless received half of the Chemistry Nobel Prize in 2001 (he shared it with William S. Knowles and Ryoji Noyori).[53]

1.3.2. Transformation of Epoxides

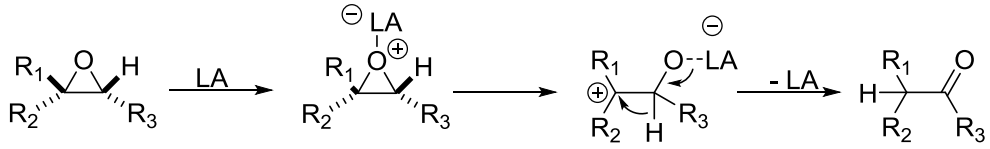
High reactivity of epoxides enables lots of different transformations. In this introduction reductive ring opening by nucleophiles and acid catalyzed isomerization to carbonyl compounds are discussed in detail (Scheme 23).



Scheme 23: Reductive ring opening and acid catalyzed isomerization of an epoxide

1.3.2.1. Isomerization to Carbonyl Compounds

Acidic conditions lead to the isomerization of epoxides into carbonyl compounds. This rearrangement is called Meinwald rearrangement.[51] Brønsted acids as well as LAs are reported to facilitate this isomerization in a stoichiometric or catalytic manner.[54] Scheme 24 shows the estimated mechanism of a LA mediated Meinwald rearrangement.

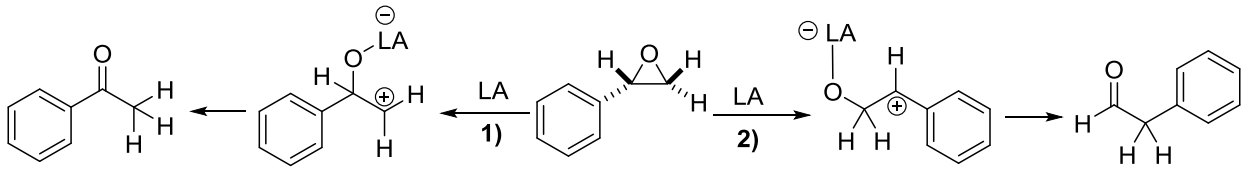


Scheme 24: Meinwald rearrangement of an epoxide to a carbonyl compound via a 1,2-hydride shift; reproduced from Kim.[55]

The isomerization protocol with LAs is praised for its simplicity and high efficiency.[51] BF_3OEt_2, lithium salts, $MgBr_2$ or methylaluminium bis(4-bromo-2,6-di-tert-butylphenoxide) (MABR) are reagents which are traditionally used for the isomerization of epoxides.[51] They are toxic or required to be used in stoichiometric amounts.[51] Therefore new reagents are required which can be used in catalytic amounts.

Yamamoto and coworkers report about the Lewis acid $B(C_6F_5)_3$ (**1a**) which is able to isomerize aliphatic epoxides and styrene oxide to carbonyl compounds in toluene at very low catalyst loadings.[54] Styrene oxides were reported to be isomerized with e.g. $Bi(OTf)_3\ xH_2O$ by Mohan and coworkers at similar low catalyst loadings.[56]

Two carbonyl compounds are the possible products from an epoxide isomerization. Scheme 25 shows the different cationic intermediates through which aromatic epoxides go during isomerization.

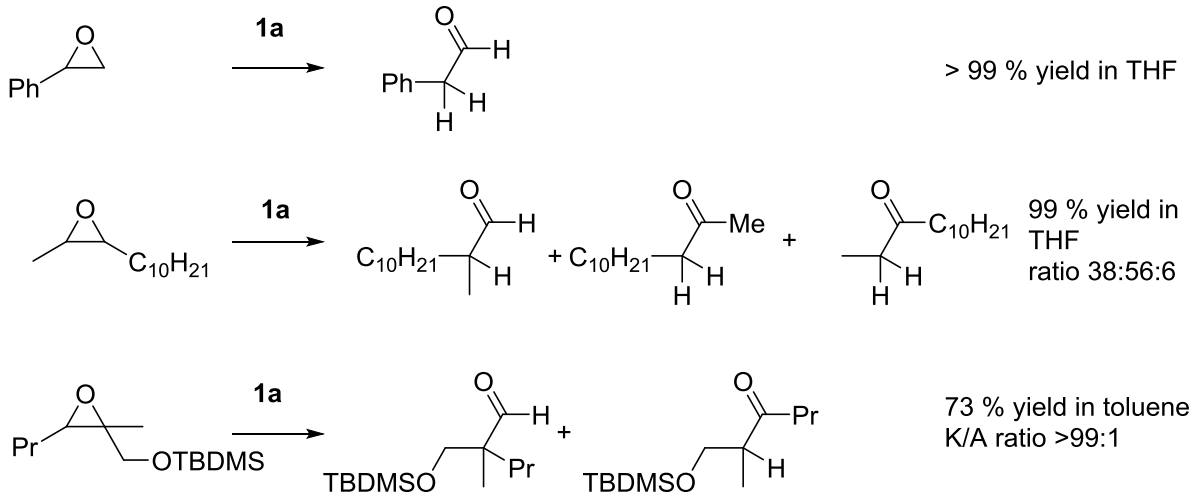


Scheme 25: 1,2-hydrogen shift in the Meinwald isomerization of aromatic epoxide results in a ketone (path 1) or aldehyde (path 2)

The ketone is formed via pathway 1, which is the thermodynamic product. In pathway 2 a benzylic carbocation is formed by C-O bond cleavage. This intermediate is the more stable one and results in the

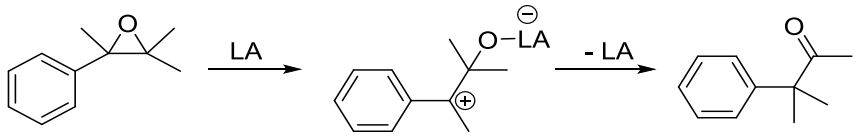
aldehyde product. The product of pathway 2 represents the kinetic product. Regioselectivity towards the aldehyde over the ketone or vise versa is in general assumed to be dependent on the nature of the LA as well as the solvent and the migratory aptitude of the epoxide substituents.[56]

The migratory aptitude[57] of the epoxide substituents in β-position to the aryl substituent depends on the nature of the substituent. Phenyl-, acyl- and benzoyl- substituents migrate preferably over hydrogen substituents. Alkyl- substituents have a very low migratory aptitude.[57] The system goes via the most stable carbocation. Cyano- or nitro- substituents are reported by Mohan and coworkers to prevent isomerization totally.[56] Also the number of substituents has an effect on the regioselectivity.[54] Yamamoto and coworkers report about the regioselective isomerization of epoxides by **1a.** Depending on the amount of substituents the epoxide preferably isomerizes into its corresponding aldehyde or ketone (Scheme 26).



Scheme 26: Regioselectivity of the Meinwald rearrangement depends on steric bulk around the epoxide functionality; adapted from Yamamoto et al.[54]

Different LAs are sought to gain regioselectivity in the isomerization process. $Bi(OTf)_3$ xH_2O is used to isomerize aryl-substituted epoxides selectively to aldehydes.[56] Stilbene oxide derivates are selectively isomerized to their aldehydes by $Cu(BF_4)_2$ xH_2O.[51] Jana and coworkers describe a methyl-group migration facilitated by the LA $InCl_3$ (Scheme 27) in order to form the aldehydes over the ketone.[58]



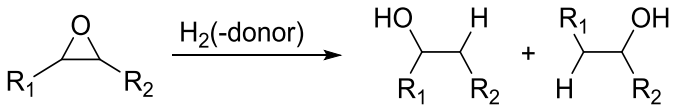
Scheme 27: methyl-shift during isomerization of a tetra-substituted epoxide leads to ketone formation; adapted from Jana.[58]

The benzylic C-O bond of 1,1,2-trimethyl-phenyl epoxide is broken and a 1,2-methyl shift takes place to obtain 2,2-dimethyl-2-phenyl-acetone. Balamurugan and coworkers report similar results about the $AuCl_3/AgSbF_6$ mediated isomerization of 1,1,2-trimethyl-phenyl epoxide.[57]

The solvent has effect on the isomerization. Balamurugan and coworkers report about rearrangement of phenyl-substituted epoxides with $AuCl_3/AgSbF_6$ in dioxane. Other solvents did not give the same results. *Tris*-substituted epoxides were only isomerized by **1a** in toluene.[54] Mohan and coworkers reported CH_2Cl_2 to be the best solvent for the isomerization with $Bi(OTf)_3$.[56] Isomerization in THF leads to byproducts and using Et_2O increases the reaction time. Jana and coworkers do all their reactions in THF, which means hydride-shift as well as methyl-shift can happen in THF with the right LA. One might suggest that depending on the solvent the mechanism of isomerization changes from concerted (apolar solvent) to stepwise (polar solvents).[57]

1.3.2.2. Reductive Ring Opening by Nucleophilic Attack

Due to ring strain usually milder conditions are required for the cleavage of the C-O bond in an epoxide. Even though epoxide rings can be opened by many different nucleophiles, the focus of this thesis will lie on the hydrogenation of epoxides with hydrogen donors. Scheme 28 shows the general reaction equation of a hydrogenation of an epoxide with any hydrogen donor.



Scheme 28: General products of the reductive ring opening of an epoxide by a hydrogen donor.

Aluminium – and boron – hydrides like $LiAlH_4$ and $NaBH_4$ are the most common used stoichiometric hydride donors. Upon acidic work up the desired alcohols are obtained. Figure 7 shows an example of a stoichiometric epoxide ring opening by $LiAlH_4$. The hydrogenation is one step in the natural product synthesis protocol of (+)-Cyperolone.[59]

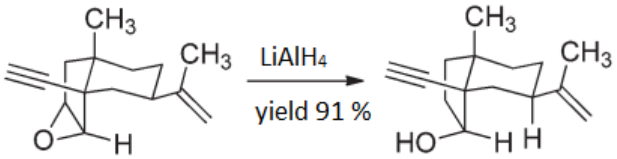
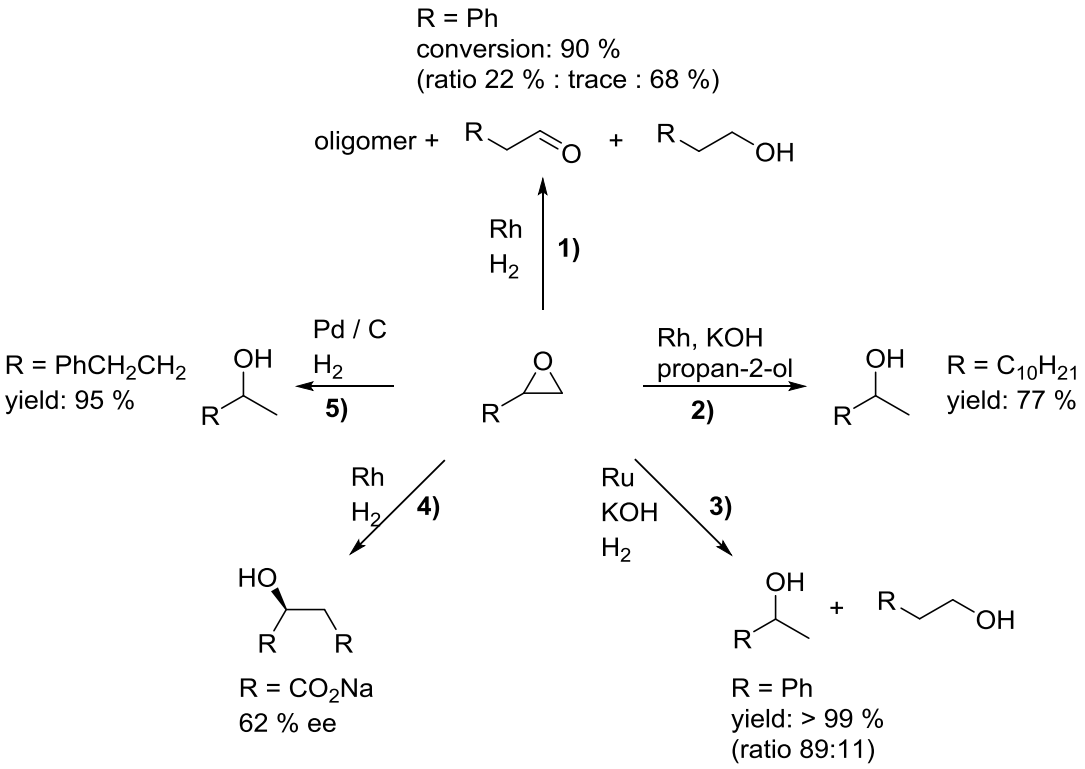


Figure 7: Regioselective hydrogenation of an internal epoxide by $LiAlH_4$; adapted from Kirsch et al.[59]

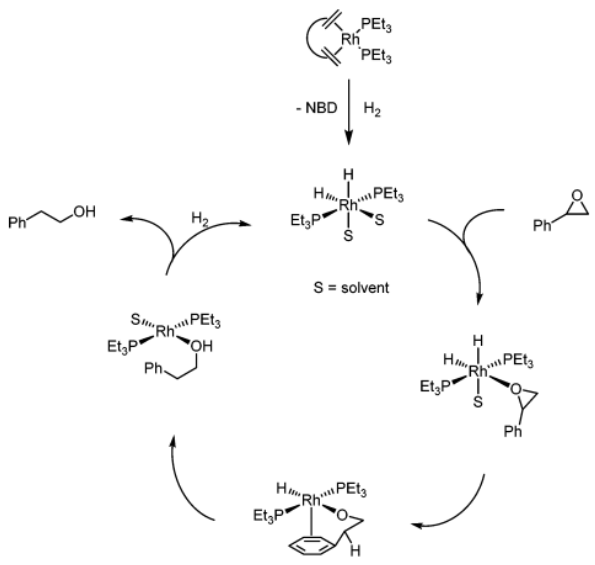
The sterically less hindered side of the epoxide ring is attacked by the nucleophilic aluminium anion. The selectivity is a result of the large size of the anion.

Catalytic reductive ring opening of epoxides is mainly based on Rh-complexes.[60] However, Wilkinsons' catalyst is shown to be inert to epoxide functionalities due to its neutral charge.[60] Paquette and coworkers describe the hydrogenation of a double bond in the presence of an epoxide functional group.[61] Cationic Rh-complexes are reported to hydrogenate terminal epoxides. Scheme 29 gives an overview of different approaches to hydrogenate terminal epoxides.



Scheme 29: Overview of hydrogenation of epoxides by catalytic reductive ring opening protocols 1) Rh-catalyzed hydrogenation of styrene oxide to 2-phenylethanol under mild conditions; adapted from Mochida et al.[62] 2) Transfer hydrogenation of 1,2-epoxydodecane to 2-dodecanol; adapted from Slama et al.[63] 3) Ru-catalyzed hydrogenation of styrene oxide to 1-phenylethanol under mild conditions; adapted from Ikariya et al.[64] 4) Asymmetric reduction of sodium epoxysuccinate to L – (-) – Malic acid disodium salt under mild conditions; adapted from Coleman et al.[65] 5) Heterogeneous hydrogenation of a terminal epoxide to a secondary alcohol under mild conditions; adapted from Hirota et al.[66]

In 1981 Mochida and coworkers reported about the cationic rhodium complex $[Rh(nbd)(PEt_3)_2]^+$ which catalyzes the hydrogenation of styrene oxide selectively to the primary alcohol 2-phenylethanol with 90 % conversion (Scheme 29 path 1).[62] Figure 8 shows the proposed mechanism.



Oxidative addition of H_2 is followed by epoxide coordination to the metal complex. A hydride insertion selectively into the benzylic C-O bond might determine the regioselectivity of the reaction. The reduction might also proceed via the formation of an aldehyde intermediate of styrene oxide prior to hydride insertion. The alcohol product is obtained by reductive elimination. Oligomers are the major by-products. However, secondary alcohol products or ketones are not formed.

Figure 8: Mechanism of the hydrogenation of styrene oxide by catalytic reductive ring opening; figure taken from Doyle et al.

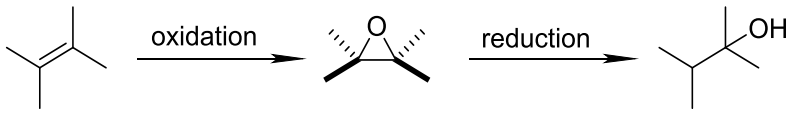
Another Rh-complex with a 1,10-phenanthroline ligand catalyzed the transfer hydrogenation of aliphatic epoxides with propan-2-ol as hydrogen donor (Scheme 29, path 2).[63] KOH is required as additional base. 77 % regioselectivity towards the secondary alcohol was obtained. The lack of an aromatic system or inhibited isomerization might be the reason for this.

The use of metal/NH bifunctionality to hydrogenate epoxides was reported by Ikariya and coworkers.[64] They describe a Cp*RuCl(cod)($P(Ph)_2$-CH_2-CH_2-NH_2) complex which is able to reduce terminal epoxides in propan-2-ol at mild conditions (Scheme 29, path 3).[64] Quantitative conversion with a regioselectivity of 89 % towards the secondary alcohol was obtained.[64] It is proposed that propan-2-ol assists in the H_2 activation and additionally serves as hydrogen source to a limited extent.[64]

The first asymmetric reductive ring opening was reported by Coleman and coworkers (Scheme 29, path 4).[65] The chiral, cationic Rh-complex [Rh(nbd)(*N',N'*-bis((S)-α-(1-naphthyl)ethyl-*N',N'*-bis(diphenylphosphino)ethylenediamine)]$^+$ was used to hydrogenate sodium epoxysuccinate to L–(-) – Malic acid disodium salt with 62 % ee under mild conditions.[65] The carboxyl functionalities at the substrate are required. This might be related to the boron-based counter anion BF_4^- of the Rh-complex. The use of different counter anions is not reported. D_2 experiments indicate direct hydrogenation via C-O bond cleavage instead of initial isomerization before hydrogenation.

Very high yields in combination with high selectivity towards the secondary alcohol is obtained in the heterogeneous hydrogenation of terminal epoxides over Pd / C.[66] Hirota and coworkers report about the hydrogenation of 1,2-epoxy-4-phenyl-butane to 1-phenyl-3-butanol at 5 bar H_2 with more than 95 % selectivity (Scheme 29, path 5).[66]

The combination of epoxide formation and reductive ring opening leads to an envisioned pathway for the simple functionalization of a double bond with an alcohol functional group by consecutive oxidation and hydrogenation of an alkene double bond (Scheme 30).



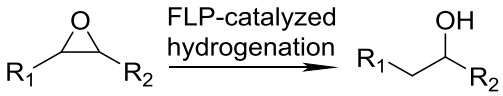
Scheme 30: Functionalization of an olefin double bond by oxidation and reduction via an epoxide intermediate product.

2. Project Aim

Since the introduction of FLP chemistry, the substrate scope for hydrogenation catalysis by FLP activated H_2 has grown vastly. Oxygen-containing substrates were the exception until recently. The solvent mediated FLP catalyzed hydrogenation of carbonyl moieties stands out in its simplicity due to the use of commercially available chemicals.

Epoxides are important oxygen-containing functional groups in organic synthesis. Currently, hydrogenation of epoxides to alcohols by reductive ring opening is a stoichiometric or a TM-complex catalyzed transformation.

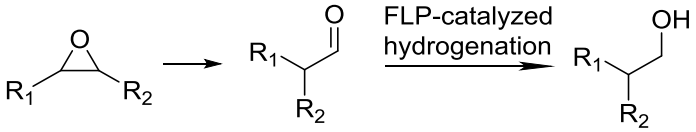
The overall aim of the project is to investigate the possibility of epoxide hydrogenation by FLP-catalysis to obtain alcohol functionalities (Scheme 31).



Scheme 31: Project aim – FLP-catalyzed hydrogenation of an epoxide.

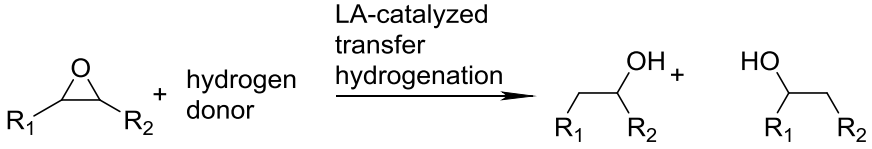
Various epoxides will be exposed to reported FLP systems based on **1a** as LA as well as other non-commercially available boron-based LAs. In addition, a new LA will be synthesized and tested for FLP hydrogenation chemistry. Furthermore, the ability of epoxides to form a FLP with those LAs is evaluated. These investigations are envisioned to give information about the general reactivity of epoxides towards boron based LAs.

In addition, a tandem reaction is envisioned by combining the Meinwald rearrangement of epoxides with the reduction of aldehydes (Scheme 32).



Scheme 32: Tandem isomerization-hydrogenation reaction of epoxides to primary alcohols.

Finally, the concept of boron-based LA catalyzed transfer hydrogenation is tested for epoxide hydrogenation (Scheme 33).



Scheme 33: LA-catalyzed TH of epoxides to secondary alcohols.

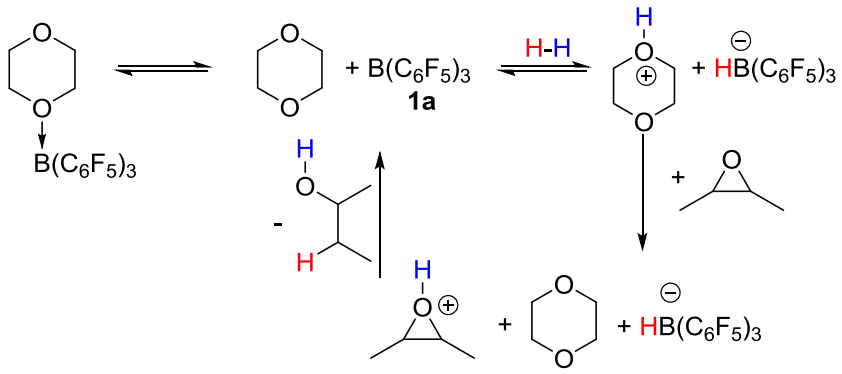
3. Results and Discussion

3.1. Attempted FLP-catalyzed Hydrogenation of Epoxides

Ashley and Stephan separately reported about the reduction of carbonyls to alcohols by FLP-catalyzed hydrogenation using ethereal solvents as LB.[24] Epoxide hydrogenation to alcohols was approached using these reported protocols.

3.1.1. Attempts to Hydrogenate Epoxides Catalyzed by a FLP of 1a/1,4-dioxane

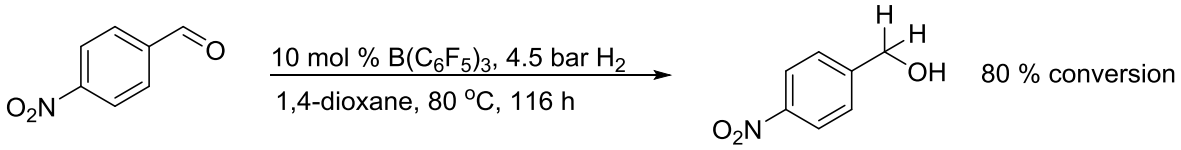
Hydrogenation of epoxides based on the carbonyl hydrogenation protocol from Ashley was proposed.[24b] The referred to protocol is based on the observation that 1,4-dioxane and **1a** can activate H_2 under mild conditions in the presence of oxygen containing carbonyl moieties. Based on the reduction of carbonyl moieties a similar mechanism for the reduction of epoxides was envisioned. Scheme 34 shows the proposed mechanism for the hydrogenation of epoxides by FLP-catalyzed hydrogenation.



Scheme 34: Suggested mechanism for the FLP-catalyzed epoxide hydrogenation.

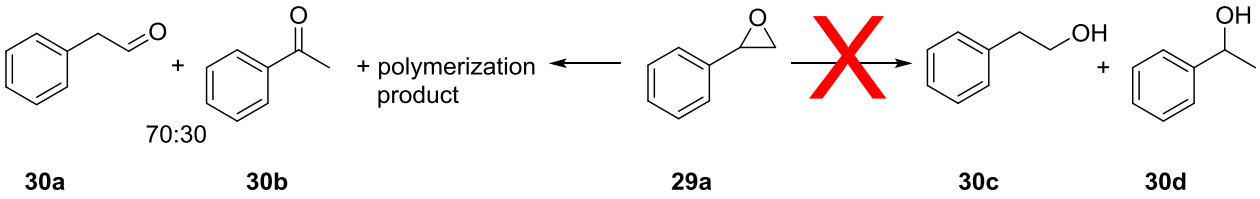
A reversible Lewis adduct between 1,4-dioxane / **1a** is formed. Upon thermal treatment this adduct dissociates and becomes a FLP capable of splitting H_2. Thereby they form a borohydride and a 1-oxygen-protonated-4-dioxane of low pKa (pKa = -2.9 in aqueous H_2SO_4).[42] The oxygen atom of the epoxide moiety is protonated by the highly Brønsted acidic conjugated acid of 1,4-dioxane to form a cationic species. This species is then further reduced to the corresponding alcohol by nucleophilic attack of the borohydride on the carbon of the epoxide moiety.

In order to test the reproducibility of the reported hydrogenation in our laboratory, 4-nitro-benzaldehyde was reduced to 4-nitro-benzalcohol using the hydrogenation protocol according to Ashley. The hydrogenation is reported to be successful with a conversion of 82 %[24b] (based on NMR integration with a capillary of 1,3,5-trimethoxybenzene in C_6D_6 as internal standard). We were able to reproduce the reported results at similar conditions (Scheme 35) with 80 % conversion.



Scheme 35: FLP-catalyzed hydrogenation of 4-nitro-benzaldehyde to 4-nitro-benzalcohol.

The hydrogenation protocol of Scheme 35 was then tested on various epoxides. First, the attempt to hydrogenate styrene oxide (**29a**) is described (Table 1, entry 1). The reaction was done on a larger scale than the literature reaction (1 mmol instead of 0.1 mmol). This way it is envisioned that minor product formation is easier to detect. Upon solvent removal the ^{1}H NMR of the attempted hydrogenation of **29a** showed signals of phenylacetaldehyde (**30a**, bp 195 °C) and acetophenone (**30b**, bp 202 °C) in a ratio of 70:30. The expected signals for 2-phenylethanol (**30c**) or 1-phenylethanol (**30d**) were not observed in ^{1}H NMR. Equally, **29a** signals were not found. This indicates full conversion of **29a** into a non-hydrogenated product. Signals of unknown compounds in the aliphatic region of the spectrum point to oligomer- or polymerization products formed in addition to the identified isomerization products. Scheme 36 summarizes the result of the first hydrogenation attempt of **29a.**



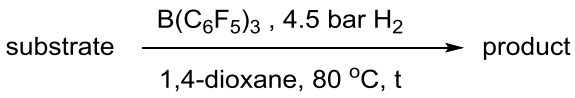
Scheme 36: Product of the attempted hydrogenation of 29a by solvent mediated FLP-catalysis.

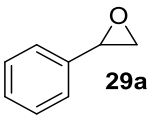
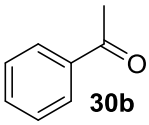
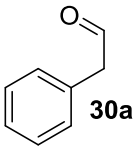
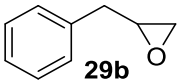
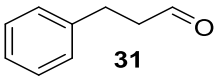
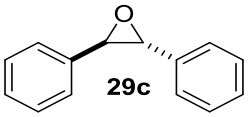
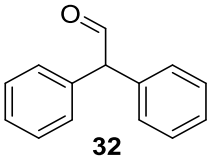
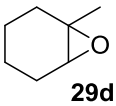
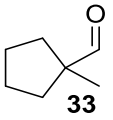
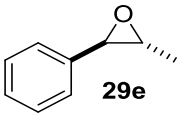
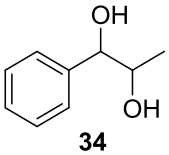
LA catalyzed isomerization of **29a** to **30a** is known in literature.[56-58] This Meinwald rearrangement of **29a** by **1a** specifically yields 99 % **30a** in THF.[54] The mechanism of this isomerization is explained in the introduction (1.3.2.1). In another report **29a** isomerizes in similar yield to **30a** in 1,4-dioxane catalyzed by $AuCl_3/AgSbF_6$.[57] Therefore the ketone/aldehyde ratio of 30:70 as obtained for the attempted hydrogenation of **29a** indicates that the reversible adduct formation between **1a** and 1,4-dioxane disturbs the regioselectivity of the Meinwald rearrangement.

To exclude the role of H_2 in this isomerization process, a blank reaction was run for which the same ^{1}H NMR and ketone-aldehyde ratio was obtained (Table 1, entry 2).

The original hydrogenation protocol by Ashley was further tested on several epoxides, which are not reported to be isomerized by **1a** specifically. The results are shown in Table 1.

Table 1: Attempts for the FLP-catalyzed hydrogenation of epoxides using the protocol of Ashley et al.[24b]



	$B(C_6F_5)_3$ / mol%	Substrate	*t* / h	Product(s)	Conv. / % [c]
1 [a]	4.5	 **29a**	20	 **30b**  **30a** 30:70	>99
2 [a]	6.1 No H_2		20		>99
3 [a]	3.5	 **29b**	19	 **31**	>99 (27)
4 [a]	13.5		20		>99
5 [b]	10.0	 **29c**	17	 **32**	82
6 [b]	10.5	 **29d**	86	 **33**	>99
7 [d]	10.5	 **29e**	68	 **34**	22

[a] reactions were done on 1 mmol scale

[b] reactions were done on 0.1 mmol scale in a J-Young tube.

[c] conversions determined based on NMR (capillary with 1,3,5-trimethoxybenzene in C_6D_6 as internal standard), isolated yield in parentheses

[d] reaction was done on 0.1 mmol scale in a Y-Joung tube at 100 °C, 4.8 bar H_2

1a catalyzes the isomerization of various epoxides in very high to quantitative conversion. This happened, although **29a-29d** were exposed to reducing conditions.

Aldehydes are readily identified in ^{1}H NMR and ^{13}C NMR spectroscopy due to their characteristic signal in the low field area of the spectrum. Signals in ^{1}H NMR around 9 ppm and ^{13}C NMR around 200 ppm are observed for the aldehyde-hydrogen and carbonyl-carbon, respectively. This fact turned out to be useful since little literature data is reported of aldehydes in 1,4-dioxane as NMR solvent.

Exposing **29b** to the hydrogenation protocol of Ashley resulted in the isomerization to 3-phenylpropanal (**31**, entry 3). The signals of phenylacetone were not obtained in ^{1}H NMR. The crude ^{1}H NMR spectrum did not show signals of the starting material **29b**. Therefore the isolated yield is not representative for the overall conversion of **29b**. Increasing the catalyst loading from 5 mol % to 10 mol % did not change the result (entry 4).

From the unsuccessful reduction of terminal epoxides **29a** and **29b** it is concluded that more substituents and more steric bulk on the epoxide functional group might be necessary to prevent the LA facilitated isomerization.

The disubstituted epoxide *trans*-stilbene oxide (**29c**) is supposed to give more steric hindrance around the epoxide moiety. However, no hydrogenation product was obtained. Rather, **29c** seems to be very prone to **1a** induced 1,2-phenyl shift. 2,2-diphenylacetaldehyde (**32**) was obtained in 82 % conversion (entry 5).

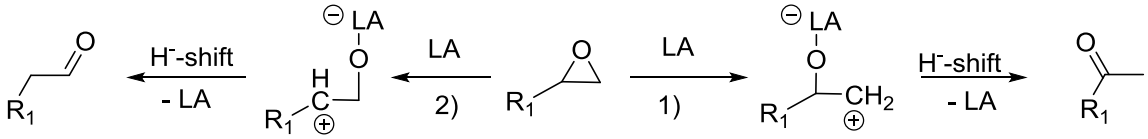
In literature the isomerization of **29c** is catalyzed by various metal-based LA.[56-58] The migratory aptitude of phenyl groups is the highest known in literature.[57] Therefore, in pursuit of finding an epoxide, which does not isomerize to an aldehyde, purely phenyl substituted epoxides like **29c** and its derivatives are excluded from further investigations.

The entirely aliphatic cyclic epoxide 1-methyl-cyclohexane oxide (**29d**) was synthesized. Compound **29d** isomerized within 5 minutes to 1-methyl-1-cyclopentanecarboxaldehyde (**33**, entry 6). Mohan reports about the $Bi(OTf)_3$ facilitated isomerization of **29d** to ketone and **33** in a 98:11 ketone/aldehyde ratio.[56]

The isomerization mechanisms for **29a**, **29b, 29c** and **29d** are shown in appendix A.

All isomerizations seemed to be completed before H_2 gas was added to the reaction mixture. This refers to the high reactivity of epoxides. Due to their three-membered ring a high ring strain is present and this explains the high reactivity. Coordination of the LA to the etheral-oxygen of an epoxide is favored by the high oxophilicity of the boron centre of **1a.** Due to the absence of a nucleophile the activation of an epoxide by a LA leads to isomerization instead. The fast isomerization explains why direct hydrogenation is not possible under these reaction conditions.

29b, 29c and **29d** preferable isomerize to their corresponding aldehyde. A higher tendency for the aldehyde can be explained by looking at the isomerization mechanism (Scheme 37).



Scheme 37: Isomerization of an epoxide in a regioselective manner to a ketone (pathway 1) or an aldehyde (pathway 2).

The epoxide either opens towards a primary carbocation (pathway 1) or towards a secondary carbocation (pathway 2), which is the more stable ion. The aldehyde is formed via the more stable secondary carbocation. It is the kinetic product of this isomerization. Especially for phenyl-substituted

epoxides the ketone is the more stable product due to its possibility to delocalize electrons over the ring. It is therefore the thermodynamic product of isomerization. However, it is formed via a less stable primary carbocation. Therefore the kinetic product formation is favored over the formation of the thermodynamic compound.

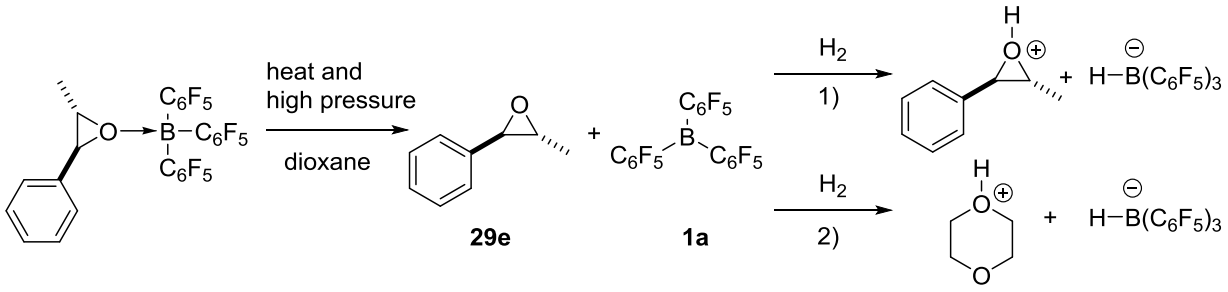
As mentioned previously, Ashley and coworkers report about the successful hydrogenation of carbonyl moieties catalyzed by the 1,4-dioxane/**1a** FLP.[24b] In our experiments, isomerization of several epoxides towards aldehydes is observed instead of hydrogenation to the alcohol products. The substrate scope of Ashley and coworkers also includes aldehydes. Therefore an isomerization – hydrogenation sequence might be envisioned.

Two explanations can be offered for the failed one pot isomerization – hydrogenation sequence. First, the turn over number (TON) of **1a** in the catalytic isomerization cycle might be very low. The isomerization might degrade **1a** during the reaction. H_2 splitting by the cooperative interaction of the 1,4-dioxane/**1a FLP** then becomes impossible and hydrogenation of an aldehyde functionality cannot take place. Second, the substrate scope of Ashley et al. is limited to aldehydes with electron withdrawing groups (EWG) e.g. the nitro-functional group on the aldehyde substrate in Scheme 35. **29a, 29b, 29c** and **29d** all isomerize to more electron rich aldehydes. Their carbonyl group is not as polarized as the carbonyl group of aldehydes with EWG. This influences the reactivity of the carbonyl group towards protonation and hydride attack.

The substrate scope for ketones is reported to be much larger.[24] Even aliphatic ketones are included. Therefore the search for epoxides, which do not isomerize, is enlarged to epoxides, which isomerize to ketones. Balamurugan and coworkers show that the addition of an alkyl-substituent to the epoxide can lead to ketone formation instead of aldehyde formation.[57] This is due to the low migratory aptitude of a methyl group to shift form one carbon to the other.

trans-Phenylpropylene oxide (**29e**) was synthesized and exposed to the hydrogenation protocol according to Ashley and coworkers. However, none of the possible hydrogenation products were obtained. Instead phenyl-1,2-propandiol (**34**) was formed in low yield (entry 7). It is assumed that **34** was formed by LA catalyzed hydrolysis with water impurity. Nevertheless, **29e** is the first epoxide in our series, which does not isomerize under these reaction conditions. **1a** might be too sterically hindered to be able to isomerize **29e** to one of its corresponding ketones.

Epoxides are stronger LBs than 1,4-dioxane. Therefore, dative bond formation between the oxygen atom of **29e** and the boron atom of **1a** is assumed to be the reason for failed reduction. This bond could prevent effective protonation of the epoxide-oxygen by the proton of the activated H_2. However, it is more likely that strong coordination of **1a** to oxygen prevents H_2 activation completely. More forcing conditions than applied to so far might be required for the cleavage of the suggested dative bond between **1a** and **29e**. In case, a reversible Lewis adduct is established, heterolytic H_2 splitting by the cooperative interaction of either the **29e**/**1a** FLP (Scheme 38, pathway 1) or the 1,4-dioxane**/1a** FLP (Scheme 38, pathway 2) can be imagined**.** In order to investigate the reversibility of the suggested dative bond between **29e** and **1a**, high-pressure experiments were proposed.

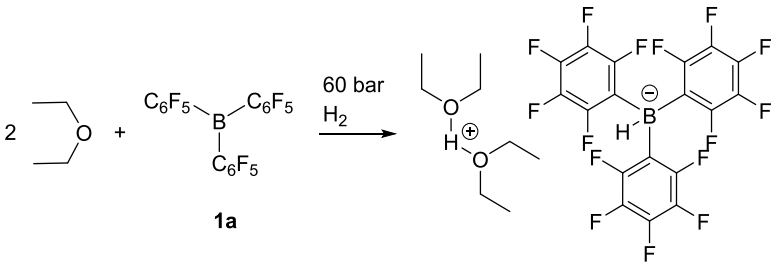


Scheme 38: Envisioned H_2 activation by a FLP of 29e/1a (pathway 1) or 1,4-dioane/1a (pathway 2).

In conclusion, **29a**, **29b**, **29c** and **29d** regioselectively isomerize into electron rich aldehydes. Those are not further reduced by the hydrogenation protocol of Ashley and coworkers. **29e** is the first epoxide in our series, which does not isomerize in 1,4-dioxane. Therefore, an epoxide, which does not isomerize upon addition to **1a**, has been found. Dative bond formation between epoxide and **1a** is proposed to be the reason for the failed hydrogenation. Therefore high-pressure experiments were suggested.

3.1.2. High-pressure Experiments Aiming for Hydrogenation of *trans*-Phenylpropane Oxide

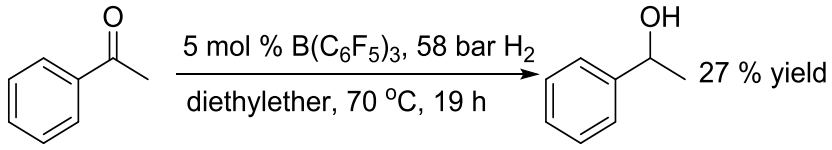
The high-pressure hydrogenation protocol for epoxides based on the heterolytic splitting of H_2 by the FLP diethylether (Et_2O) / **1a** was applied, since this method was used for the hydrogenation of carbonyl moieties, explored by Stephan and coworkers.[24a] They use a FLP (Scheme 39) which upon H_2 splitting forms a borohydride and a solvent stabilized proton.[24a]



Scheme 39: Heterolytic H_2 activation by a FLP of 1a/diethylether; adapted from Stephan et al.[24a]

The mechanism for the reduction of carbonyl moieties is assumed to be similar to the mechanism proposed by Ashley and coworkers. The conjugated acid of Et_2O has a pKa of -3.6, which means it is a stronger Brønsted acid than protonated 1,4-dioxane (pKa= -2.9 in aqueous H_2SO_4).[42] The higher Lewis basicity of Et_2O results in a faster reduction of ketones with the ether-**1a** FLP compared to the 1,4-dioxane-**1a** FLP.

In order to test the reproducibility of the reported hydrogenation in the autoclave set up of our lab, the high-pressure hydrogenation protocol according to Stephan was applied to reduce acetophenone to 1-phenylethanol. It is reported to be successful with a conversion of 90 %.[24a] We were able to perform the reported reaction at similar conditions (Scheme 40) with 27 % yield (based on NMR integration).

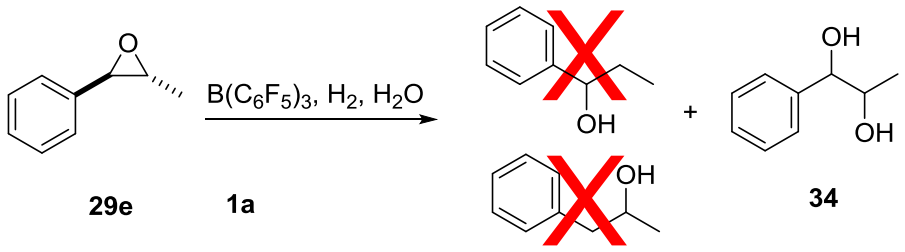


Scheme 40: FLP-catalyzed hydrogenation of acetophenone to 1-phenylethanol.

Technical problems like non-sufficient stirring in autoclave and less control over temperature due to a too short thermometer devise, might have led to a lower yield than reported. Also a blank experiment without **1a** was performed to test the quality of the autoclave set up. Based on these two reactions and their outcome, it was decided that the reduction according to Stephan is possible in our set up.

The high-pressure protocol was tested on **29e** in various donor and non-donor solvents. The later was done to investigate the possibility of hydrogenation catalysis by a FLP of **29e / 1a** similar as it is described in literature for imine reduction.[6] The results of all experiments are shown in Table 2.

Table 2: Attempts for the FLP-catalyzed hydrogenation of 29e under high pressure.

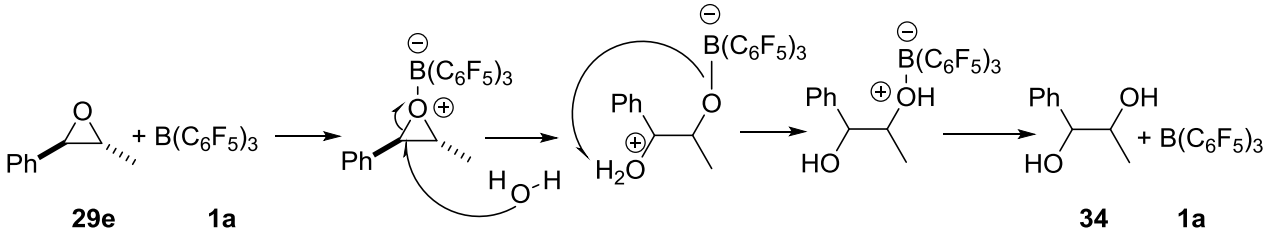


Entry	$B(C_6F_5)_3$ / mol%	Solvent	p / bar	T / °C	t / h	Yield [d] alcohol / %	Yield [d] diol / %	Yield ketone [e] / %
1[a]	5	1,4-dioxane	55	70	19	0	14	0
2[a]	10	Diethylether	62	70	21	0	23	7
3[a]	10	Toluene	60	70	19	0	24[c]	0
4[a]	10	CH_2Cl_2	62	70	22	0	30	0
5[b]	10	d_8-toluene	4.8	100	44	0	0	0

[a] reactions were done on 1 mmol scale
[b] reaction was done on 0.1 mmol scale in a J-Young tube
[c] isolated yield
[d] yields based on NMR integration
[e] phenylacetone

LA-catalyzed hydrolysis of **29e** to phenyl-1,2-propanediol (**34**) in low yields was obtained for the reaction in donor solvents like 1,4-dioxane and Et_2O (entry 1 and 2), the non-donor solvent toluene (entry 3) and the halogenated solvent CH_2Cl_2 (entry 4) although the epoxide was exposed to reducing conditions. **34** was isolated and characterized by ^1H NMR and ^{13}C NMR spectroscopy.

Water is considered to be a weak nucleophile. Therefore an acid – Brønsted or Lewis – is required for the hydrolysis reaction. The mechanism of the **1a**-catalyzed hydrolysis of an epoxide is shown in Scheme 41.



Scheme 41: Mechanism for the 1a mediated hydrolysis of 29e to 34.

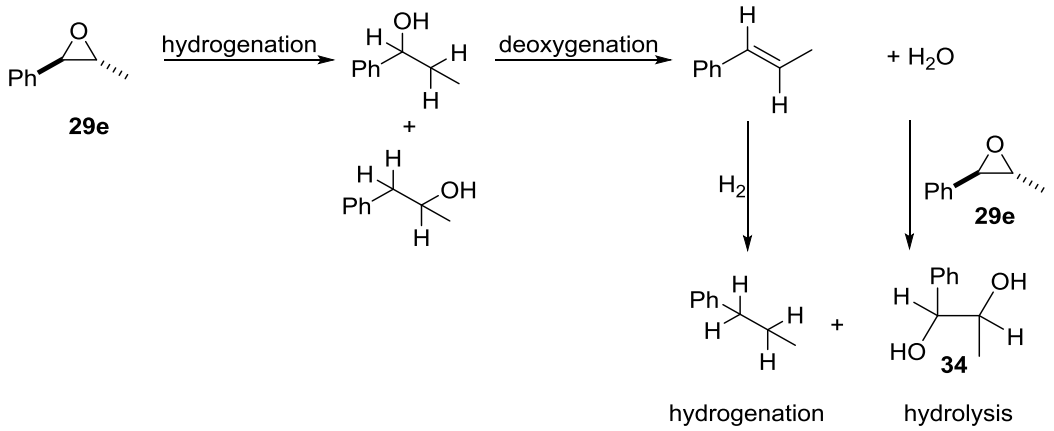
First, **29e** is activated by the coordination of **1a** to the oxygen of the epoxide ring. Subsequently, a nucelophilic attack of water on either of the epoxide carbons occurs. Then a proton shift leads to the formal protonation of the LA-oxygen bond, which breaks to release **34**.

The source of water needs to be identified. Technical matters are first taken into consideration. Hydrolysis could have happened during work up. Deuterated solvents are stored over 4 Å molecular sieves, but solvent evaporation was not done under Schlenk-conditions. The epoxide, if it has not reacted during its time in autoclave, is still very reactive due to ring strain and has most likely **1a** quite strongly coordinated to it.

Another source for water could be the chemicals or the glassware. However, efforts have been made to dry (and degas) all solvents, chemicals and glassware prior to bringing them into the GB. Nevertheless, in Table 1 diol formation was obtained for the reduction attempt of **29e** in 1,4-dioxane as well. Though very unlikely, 1,4-dioxane or **29e** might have been wet after all.

The autoclave itself might be considered the most likely source for water. Due to its size it was filled outside the GB. It was also not preheated or flushed prior to being filled and pressurized.

There is also the possibility of water being formed in a step during the overall reaction. The hydrogenation – deoxygenation – hydrolysis pathway is proposed (Scheme 42).



Scheme 42: Alternative pathway to diol 34 via a hydrogenation-deoxygenation-hydrolysis pathway.

After initial hydrogenation of **29e**, the alcohol product is further reduced to its corresponding olefin. This deoxygenation reaction yields one equivalent of water, which can be used for the hydrolysis of unreacted epoxide. The olefin can be reduced further to its corresponding alkane. The maximal yield for **34** according to Scheme 42 is 50 %. The deoxygenation of diarly ketones facilitated by **1a**/4 Å molecular sieves is known in literature.[25]

NMR signals for the olefin or alkane product were not obtained in any of the high-pressure experiments of Table 2. Boiling points of both olefin (bp 175 °C) and alkane (bp 159 °C) are likely to be high enough to ensure that they did not evaporate during the removal of solvent such as 1,4-dioxane (bp 101 °C) or toluene (bp 111 °C).

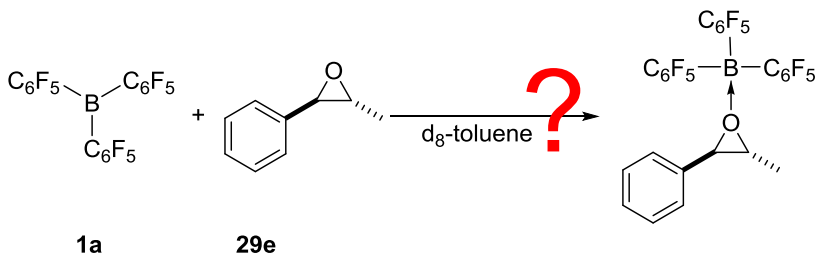
In conclusion, the hydrogenation protocol of Stephan and coworkers failed to reduce **29e.** Equally, attempts to reduce **29e** by H_2 activation in non-donor solvents by the interaction of **1a/29e** failed. Instead of reduction, hydrolysis of **29e** to **34** was observed. **1a** seems a strong enough LA to catalyze this hydrolysis. For future high-pressure experiments the autoclave needs to be prepared differently to ensure a water-free reduction environment.

3.2. Investigation into the Reactivity between 1a and *trans*-Phenylpropane Oxide

Strong dative bond formation between epoxides and **1a** was suggested to be the reason for the failed reduction attempts so far (Chapter 3.1.1.). In literature NMR spectroscopic data is frequently referred to when a distinction needs to be made on whether LA and LB form a classical Lewis pair or a FLP. If the signals in NMR of the single LA and LB components did not change upon adding them together, the pair was considered to be a FLP.

The definition of a FLP has changed over time. Adduct formation does not need to be prevented totally; it just needs to be reversible. In order to investigate the possible adduct formation of **1a** with **29e** and its

reversibility, stoichiometric experiments were performed in d_8-toluene and analyzed by ^{19}F, ^{11}B and ^{1}H NMR spectroscopy (Scheme 43).



Scheme 43: Stoichiometric amounts of 29e and 1a were analyzed in d_8-toluene.

^{19}F and ^{11}B NMR spectra of the experiment in Scheme 43 were examined and compared to NMR spectra of known adducts. Figure 9 shows the ^{19}F spectrum of **1a** (**a**), **1a**/1,4-dioxane (**b**)**, 1a**/pyridine (**c**) and **1a/29e** (**d**). By describing an epoxide as cyclic ether, one might predict that **29e** forms an adduct with **1a** similar to the reversible adduct of 1,4-dioxane and **1a**. However, this is not the case.

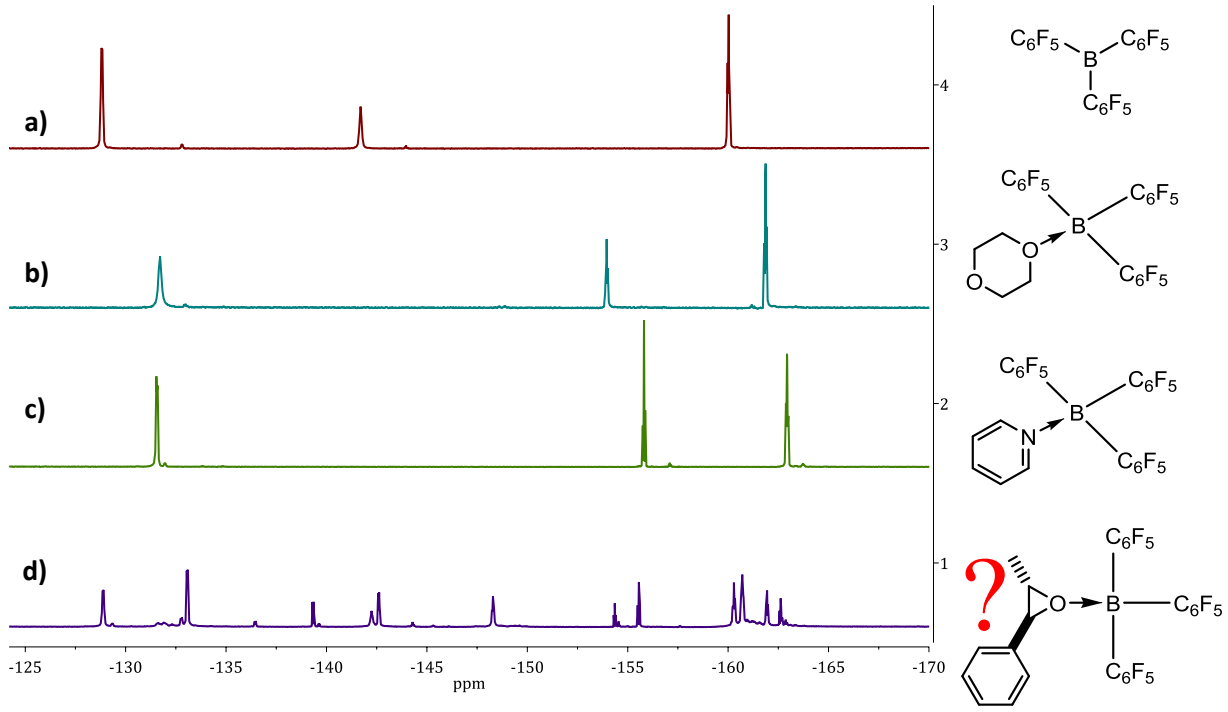


Figure 9: ^{19}F NMR spectra of stoichiometric mixtures of 1a (a), 1a/dioxane (b), 1a/pyridine (c) and 1a/29e (d) as well as their envisioned structures; NMR spectra are taken at room temperature in C_6D_6 (a-c) and d_8-toluene (d).

The ^{19}F NMR measurements were done without making use of an internal standard. Therefore, relative shift differences are compared to gain information about the configuration of **1a**.

1a alone shows three signals for all fluorine atoms in the molecule with a chemical shift difference between the *ortho*- and *para*- fluorine atom of $\Delta_{o,p}$ = 13 ppm and between the *para*- and *meta*- fluorine atom of $\Delta_{p,m}$ = 18 ppm (Figure 9, a). The reversible Lewis adduct of **1a**/1,4-dioxane also shows three ^{19}F

signals (Figure 9, b). The chemical shift difference have altered significantly ($\Delta_{o,p}$ = 22 ppm, $\Delta_{p,m}$ = 8 ppm). The NMR spectrum of **1a**/pyridine (Figure 9, c) shows similar chemical shift differences compared to **1a**/1,4-dioxane ($\Delta_{o,p}$ = 24 ppm, $\Delta_{p,m}$ = 7 ppm). According to Piers and coworkers a *para,meta*- chemical shift difference larger than 15 ppm is associated with 3-coordinted pentafluorophenyl borane, whereas 4-coordinated species exhibit a upfield shift of the *para*-signal in combination with a smaller *para,meta*-chemical shift difference.[67] Therefore, according to ^{19}F NMR 1,4-dioxane as well as pyridine form a Lewis adduct with **1a**. In the ^{19}F NMR spectrum of the mixture **29e**/**1a** (Figure 9, d) about 12 different signals are obtained, of which the ones at -139 ppm, -154 ppm and -162 ppm belong to C_6F_5H (**21**). The formation of **21** and the amount of ^{19}F signals suggest the presence of various fluorine-containing compounds. This disagrees with the initial assumption that **29e** and **1a** form an adduct.

In literature the ^{11}B chemical shifts of different pentafluorophenyl-borane species are reported. A selection is shown in Figure 10.

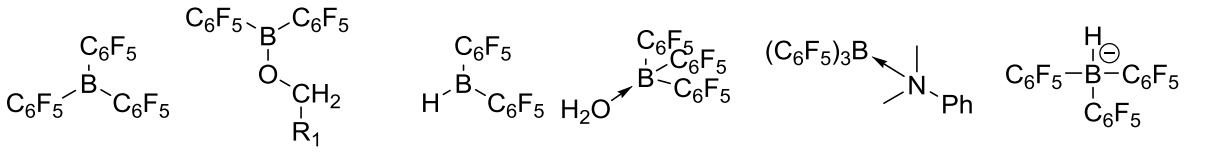


Figure 10: Different boron compounds and their reported chemical shift in ^{11}B NMR spectroscopy; A) in 1,2-difluorobenzene [68], B) in CD_2Cl_2 [45], C) in C_6D_6 [69], D) in 1,2-difluorobenzene [68], E) in C_6D_6 [70], F) in d_8-toluene [34].

A trend can be identified, since the signals of 3-coordinated boranes are observed in the low field area whereas the signals of 4-coordinated species shift to the high field. Anionic borane species have the lowest chemical shift.

Figure 11 shows the ^{11}B NMR spectrum of **1a** (**a**)**, 1a/**1,4-dioxane (**b**)**, 1a**/pyridine (**c**) and **1a**/**29e** (**d**).

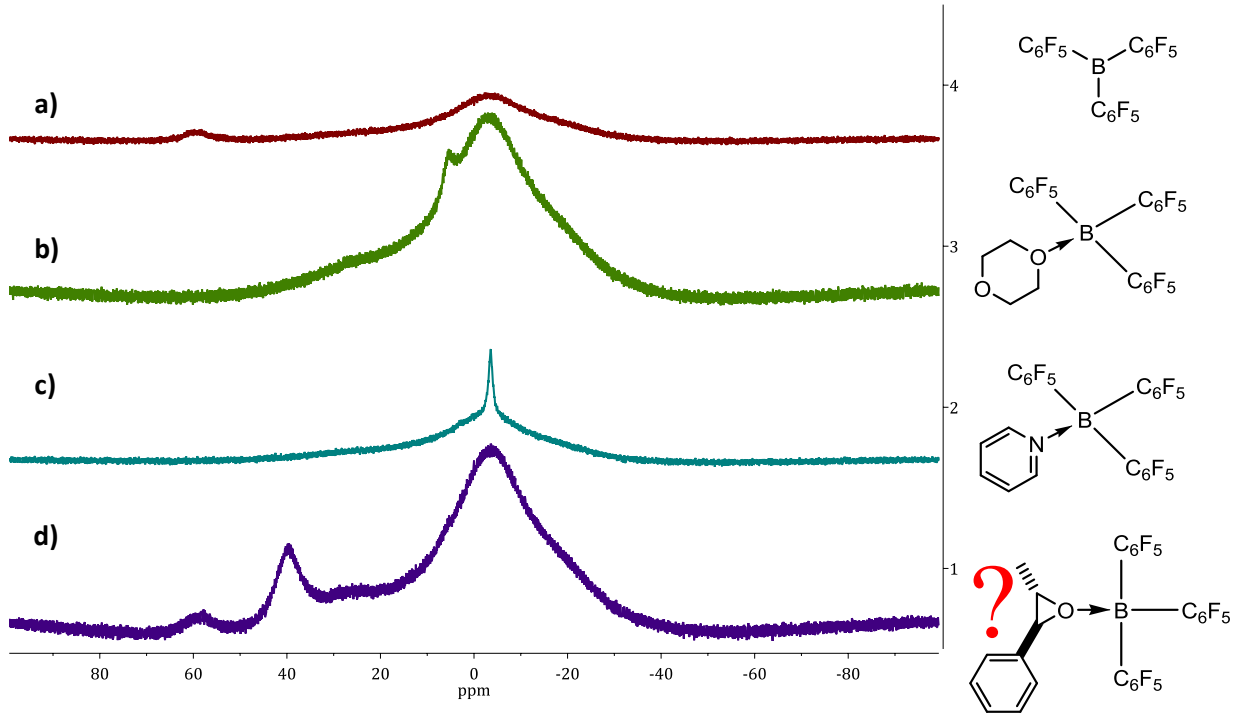


Figure 11: ^{11}B NMR spectra of stoichiometric mixtures of 1a (a), 1a/dioxane (b), 1a/pyridine (c) and 1a/29e (d) as well as their envisioned structures; NMR spectra are taken at room temperature in C_6D_6 (a-c) and d_8-toluene (d).

The most apparent signal in ^{11}B NMR is found at δ 0 ppm and belongs to the boron containing glassware in the probe of the NMR machine as well as the NMR tube itself.

The ^{11}B NMR signal of the 3-coordinated **1a** (Figure 11, a, δ 59.9 ppm) shifts to the high field upon 1,4-dioxane addition (Figure 11, b, δ 5.4 ppm) as well as upon pyridine addition (Figure 11, c, δ - 3.5 ppm). This indicates the formation 4-coordinated Lewis adduct. The ^{11}B NMR spectrum of the **29e**/**1a** mixture shows a high-field shift of the boron signal (Figure 11, d, δ 38 ppm). This indicates the formation of a 3-coordinated species as well as B-O bond formation.[45]

In order to investigate which compound was formed instead of the adduct between **29e** and **1a**, the ^{1}H NMR was examined. Figure 12 shows the ^{1}H NMR spectra of **29e** (a) and of the stoichiometric mixture of **29e**/**1a** (b).

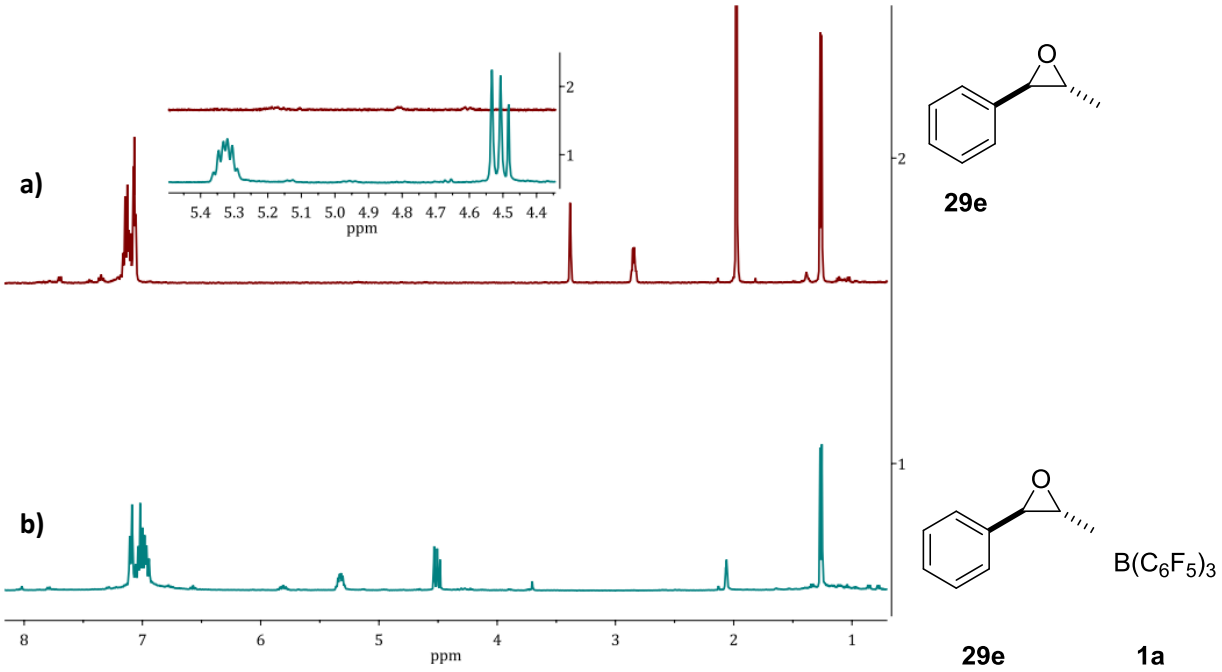
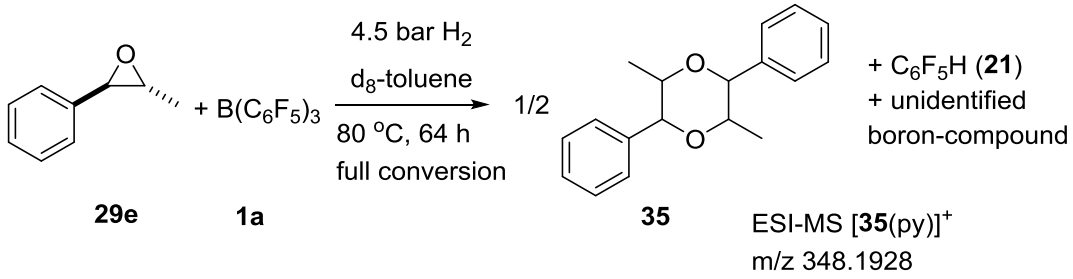


Figure 12: ^{1}H NMR of 29e in C_6D_6 (a) and of a stoichiometric mixture of 29e and 1a in d_8-toluene (b); the area around 5 ppm is zoomed in.

29e was fully consumed and signals of a new compound were observed around 0.8 ppm, 4.5 ppm and 5.34 ppm. Unfortunately, attempts to isolate this compound by column chromatography were unsuccessful. However, based on NMR analysis by COSY, HMQC, APT, ^{13}C and ^{1}H NMR as well as mass spectroscopy 2,5-dimethyl-3,6-diphenyl-1,4-dioxane (**35**) is considered the most likely product. Scheme 44 shows the full conversion of **29e** to a four-substituted, symmetric 1,4-dioxane molecule.



Scheme 44: Synthesis of 35 dimerization of 29e.

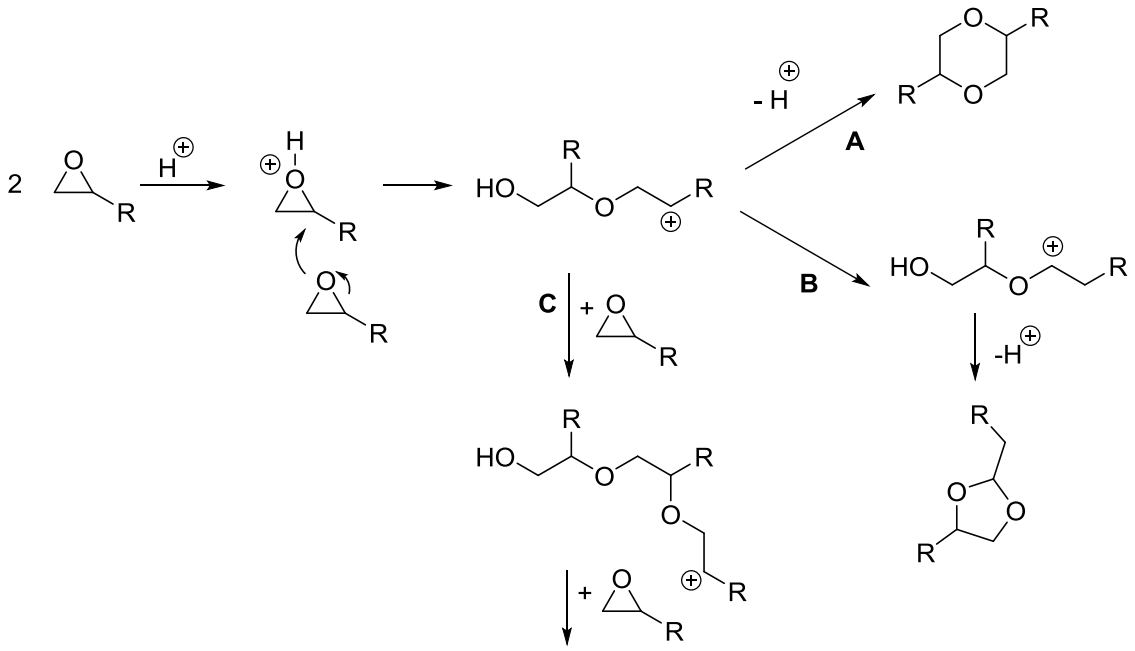
Long-term exposure to H_2 as well as heat did not change the signal pattern in the ^{1}H NMR spectrum. **21** is formed over time by B-C bond protonolysis of **1a**. The FLP **1a**/1,4-dioxane is reported to cleave H_2[24b]. If **35** and **1a** form a FLP capable of H_2 activation, a possible proton source for the protonolysis of **1a** might

be **35**-H^+. Brønsted acid-mediated degradation of **1a** is discussed by Stephan and coworkers as well as Repo and coworkers.[44-45] Water impurity is another proton sources for the protonolysis.

In a similar reaction to Scheme 44 8 % conversion of **29e** to **35** is observed (Table 2, entry 5 – 10 mol % **1a**, d_8-toluene, 100 °C, 44 h, 4.8 bar H_2). This suggested that **1a** is required in high to stoichiometric amounts.

In literature substrate dimerization as well as Brønsted dimerization of the protonated substrate with an aromatic LB are reported to be side reactions of FLP- catalyzed olefin hydrogenation.[40, 71]

The acid mediated synthesis of substituted 1,4-dioxane molecules is known in literature.[72] Phenyldioxanes are reported to be synthesized from styrene oxide by acid catalysts like clay[72a], BF_3 ether[72b], toluene sulfonic acid[72b] and $NbCl_5$.[72c] LAs as well as Brønsted acids seem to be capable of mediating this dimerization. Scheme 45 shows the mechanism of Brønsted acid mediated styrene oxide dimerization according to Sudalai et al.[73]



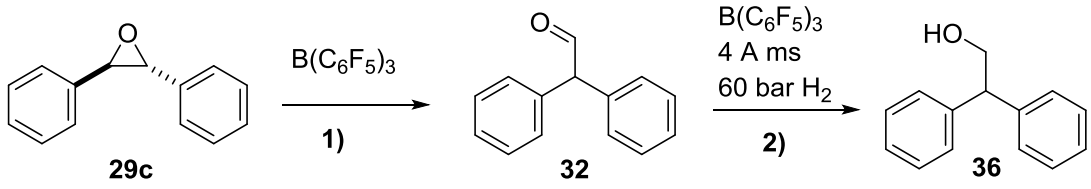
Scheme 45: Brønsted mediated dimerization and oligomerization of styrene oxide to 6-membered (A) and 5-membered rings (B) as well as oligomer structures (C); figure taken from Sudalai et al.[73]

Protonation of the etheral oxygen in the epoxide moiety activates the carbon for nucleophilic attack of a second etheral oxygen. The intermediate cationic dimer can then ring-close to 1,4-dioxane (**A**). Equally, a hydrogen shift can occur in the linear molecule. This results in the formation of a 1,3-dioxolane (**B**). The intermediate cationic dimer can also react with another epoxide to start oligomerization (**C**). Ring closure then results in the formation of crown ethers. EWGs seem to favor a 1,2-hydride shift during the cyclization, which lead to the selective formation of 1,3-dioxolanes.[74] This theory seems to be confirmed by the synthesis of methoxy-substituted phenyldioxanes with *p*-toluene sulphonic acid as catalyst.[75]

In conclusion, stoichiometric amounts of **29e** and **1a** do not form an adduct, but rather dimer **35** in a cationic dimerization reaction. **1a** is degraded by B-C bond protonolysis.

3.3. Investigation into the Tandem Isomerization – Hydrogenation Reaction of Stilbene Oxide

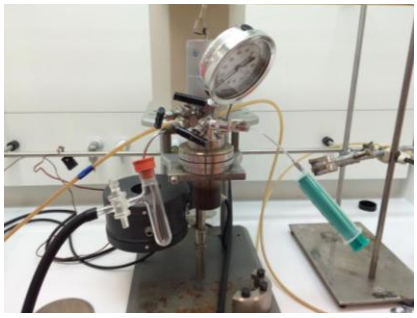
A tandem isomerization-hydrogenation reaction catalyzed by the FLP **1a**-4 Å molecular sieves was proposed based on the report of Stephan and coworkers and earlier results of this project. In literature the reduction of carbonyl moieties with H_2 catalyzed by **1a** and 4 Å molecular sieves (ms) was described.[25] It is the first report about the reduction of electron-rich aldehydes like cyclohexanecarbaldehyde and 2,2-diphenylacetaldehyde (**32**). The later is a product of the **1a**-catalyzed Meinwald rearrangement of **29c** (Chapter 3.1.1.)**.** Inspired by the Stephan communication and our earlier observation a tandem reaction was envisioned. Scheme 46 shows the isomerization of **29c** (step 1) and the consecutive hydrogenation by H_2 (step 2).



Scheme 46: Envisioned tandem-reaction consisting of the isomerization of 29c to 32 and the subsequent reduction of 32 to 36 via FLP-catalyzed hydrogenation.

As reported earlier, **29c** is isomerized (step 1) to its corresponding aldehyde **32** through a phenyl shift of one of the phenyl-substituents to C2. The further reduction (step 2) can be facilitated by a FLP of the same LA and 4 Å ms as LB to obtain the alcohol product **36**.

The reduction of **32** is reported to be performed at high pressures and in the non-donor solvent toluene. The autoclave was prepared differently from earlier experiments (Figure 13).



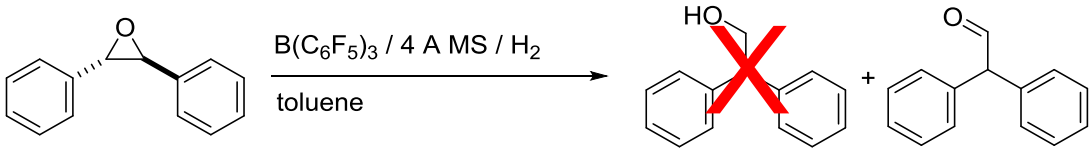
Activated molecular sieves were loaded into the autoclave. The set up was closed and preheated to approximately 40 °C. At elevated temperature the autoclave was flushed several times with H_2 gas. The mixture was injected via a N_2/H_2-counter flow system. The green syringe was used to draw the mixture into the autoclave. This way we expected to be able to work under Schlenk-type conditions.

Figure 13: Mixture injection into the autoclave set up by N_2/H_2 counter flow. A Schlenk flask under N_2 atmosphere contains the mixture. Inside the autoclave a H_2 atmosphere is present which is released while connecting the Schlenk flask to the autoclave (tube through septum). By suction with a syringe the mixture is transferred into the autoclave.

An additional advantage of working with 4 Å molecular sieves is their ability to capture water molecules. This way water was assumed to be less a problem in the autoclave set up.

First investigations into this envisioned tandem reaction have been made. The results are presented in Table 3.

Table 3: Attempts towards a tandem isomerization-reduction of 29c to 36 in under high pressure.



29c **1a** **36** **32**

Entry	$B(C_6F_5)_3$ mol %	4 Å m.s. [a]/ mg	T / °C	p / bar H_2	t / h	Yield. alcohol / % [e]	Yield. aldehyde / % [e]
1	5	300	70	42	18.5	0	>99
2	5	-	-	-	- [b]	-	38
3	15	-	-	-	- [b]	-	>99
4	15	400	60	58	19.5 [b]	0	95
5 [c]	15+15	200	70	59	23	0	>99
6 [d]	15	100	70	57	21.5 [b]	0	-

[a] molecular sieves
[b] reaction mixture was stirred in GB for 15 minutes
[c] 15 mol % additional Lewis acid was added after stirring the reaction mixture for 15 minutes in GB
[d] aldehyde used as starting material, reaction reported in literature.[25]
[e] based on NMR integration

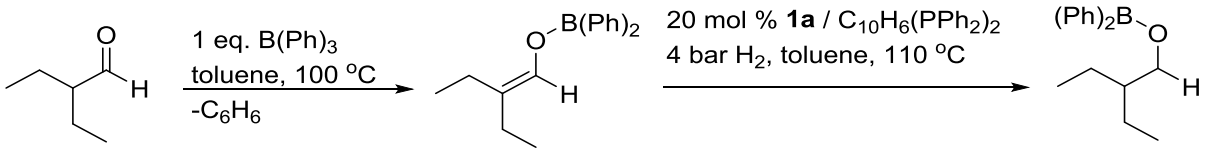
A first attempt was made with a catalyst loading of 5 mol% **1a** (entry 1)**.** The mixture was prepared and injected into the autoclave immediately since *in situ* isomerization of **29c** was presumed. However, 0 % yield of the desired alcohol product 2,2-diphenyl ethanol (**36**) was determined by NMR analysis. Instead, **29c** was isomerized in quantitative yield to **32**.

The earlier in this thesis reported isomerization of **29c** was performed in the donor solvent 1,4-dioxane. In 1,4-dioxane **29c** isomerizes to **32** in 43 % yield within 5 minutes. Over time this yield increased to 82 % after 17 h. As mentioned in the introduction, solvents have an effect on the isomerization of epoxides. Therefore the presumed *in situ* isomerization of **29c** in toluene within a short amount of time was questioned.

The required catalyst loading for a fast and complete isomerization of **29c** to **32** was investigated (entry 2 and 3). In the GB a solution of **29c** and 5 mol% or 15 mol% catalyst loading was stirred for 15 minutes in toluene to obtain 38 % conversion and quantitative conversion to **32**, respectively. Based on this result a catalyst loading of 15 mol% was decided to continue working with even though the reported catalyst loading for the reduction of **32** (step 2) is 5 mol% (and 100 mg 4 Å MS).

A next attempt towards the envisioned tandem reaction was performed (entry 4) by using 15 mol% **1a** catalyst loading and stirring the reaction mixture for 15 minutes prior to loading it into the autoclave. This way interaction of the molecular sieves with **1a,** which could slow down or interfere with isomerization, is prevented. However, the use of higher catalyst loading and the allowed isomerization time did not result in the formation of **36**. Instead, **29c** was converted to **32** in 95 % yield.

At this point the quality of **1a** after the catalytic isomerization process was questioned. Therefore an attempt towards a two-pot tandem reaction was made by first isomerizing **29c** with **1a** and then prior to loading the autoclave adding 15 mol% additional LA **1a** to the reaction mixture (entry 5). Unfortunately, this only resulted in the quantitative isomerization of **29c** to **32**. ^{19}F NMR of this mixture (entry 5) showed full decomposition of **1a** to C_6F_5H (**21**) and an unidentified boron compound in the ^{11}B NMR spectrum. Interference of two boron compounds could be assumed to prevent the H_2 activation and reduction of **32** to **36**, though in literature the coexistence of two boron compounds is not reported to be a problem for reductive ring opening of epoxides.[76] Hutchins and coworkers report about the BF_3*OEt_2 facilitated hydrogenation of styrene oxide with BH_3CN^-. Equally, Stephan and coworkers report about the protection of an aldehyde moiety by one boron containing molecule and reduction of an unsaturated bond by another boron containing molecule.[45] Scheme 47 shows the conversion of an aldehyde into an enol by LA interaction and the subsequent reduction mediated by a FLP of **1a** and a P-based LB. A neutral borinic ester is formed.



Scheme 47: Boron enolate formation and its subsequent reduction to a borinic ester; adapted from Stephan et al.[45]

One could argue on whether the total amount of 30 mol% catalyst loading does not form an enol with **32,** but the enol hydrogen signal in NMR for benzyl-substituted enols is expected around 6 ppm.[77] Those signals were not obtained in either of the experiments from Table 3.

At this point the reproducibility of step 2 (in Scheme 46) in our autoclave set up was questioned. In literature this hydrogenation step is reported to be successful with a yield of 86 % isolated yield.[25] Upon testing this hydrogenation in our set up with 15 mol% **1a** instead of 5 mol% no conversion to **36** was obtained (entry 6). It turned out that the literature reaction could not be reproduced due to unknown reasons.

One reason for the prevented reduction might be the handling of the autoclave set up. The mixture is injected under N_2-counterflow. Too much N_2 might have still been in the system and prevent H_2 gas from dissolving into the mixture. Another reason might be the molecular sieves – LA ratio. Since a higher catalyst loading is used compared to the reported one, insufficient interaction of **1a** with the molecular sieves can inhibit H_2 activation. Finally, one might argue that deoxygenation has occurred, which is reported for diaryl ketones under these conditions.[25] For this **29c** has to isomerize to its ketone

deoxybenzoin first, which was not observed in earlier experiments (Table 1, entry 5 or Table 3 entry 2 and 3) and is therefore very unlikely to have occurred now.

Due to restricted time the tandem isomerization-hydrogenation reaction was not further investigated.

In summary, a catalyst loading of 15 mol% **1a** is required for a fast and full conversion of **29c** to **32.** Subsequent reduction of **32** to **36** facilitated by a FLP of **1a** and 4 Å molecular sieves has not been obtained. This might be due to the inability to reproduce the literature procedure in our autoclave set up. Therefore, little can be said about the general possibility to hydrogenate substrates in a tandem isomerization-hydrogenation reaction with FLP. Further investigations into these reactions are needed to make a general statement about the possibility of FLP – catalyzed tandem isomerization – reduction reaction.

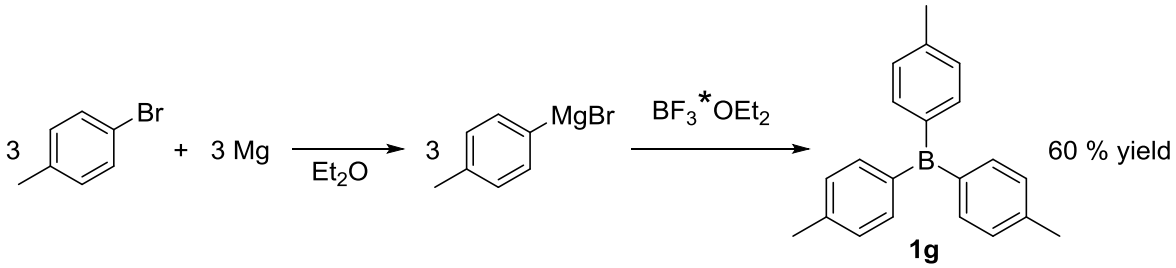
3.4. Investigation into the Use of Different Lewis Acids for the FLP-catalyzed Hydrogenation of *trans*-Phenylpropane Oxide

As described in the earlier chapters of this thesis, **1a** is a very electrophilic and very strong LA, which rather seems to coordinate to epoxide moieties than form a FLP, which can activate H_2 in the presence of an epoxide. Replacing **1a** with another boron-based LA is one approach, which can be envisioned in the attempt to hydrogenate epoxides with FLP catalysis. Several boron based LAs were introduced, which form FLPs and heterolytically cleave H_2 in a similar manner as the **1a**/LB FLP systems (see introduction 1.2.4.). In the following, two other boron based LAs are used in attempts to hydrogenate **29e.**

3.4.1. $B(tol)_3$

Less electron withdrawing substituents make a boron-based LA less electrophilic. It was suggested that those LAs would also coordinate less strong to epoxides and therefore be able to cleave H_2 in the presence of epoxide moieties. Stephan and coworkers reported about the successful H_2 activation by a FLP of $B(Ph)_3$ and P-*t*Bu.[34] This indicates the ability of less electron-poor LAs to activates H_2 in a cooperative manner with a LB.

$B(tol)_3$ (**1g**) as analogue to the reported $B(Ph)_3$ was synthesized in a two step Grignard reaction from *para*-bromotoluene and $BF_3.OEt_2$ in 60 % yield (Scheme 48).

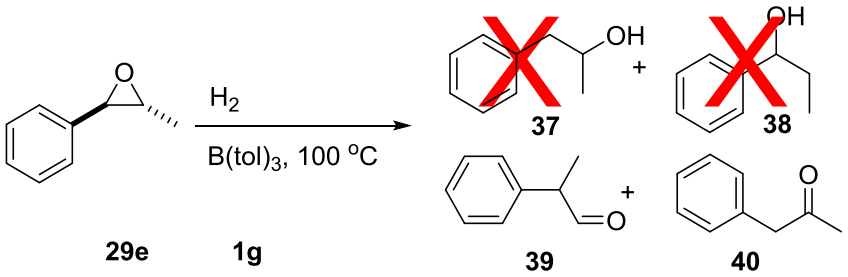


Scheme 48: Synthesis of 1g.

In the first step *para*-bromotoluene is reduced to a Grignard reagent by magnesium-insertion. In the second step three carbon-boron-bonds are formed by nucleophilic substitution reactions between the C-nucleophilic organomagnesiumhalides and the electrophilic LA boron-trifluoride.

With this new LA in hand, the **1g**/**29e** FLP-catalyzed hydrogenation of **29e** was studied. The experiments were done on NMR scale in a J-Young tube. The results are summarized in Table 4.

Table 4: Attempts for the FLP-catalyzed hydrogenation of 29e in a J-Young tube.



Entry	$B(tol)_3$ / mol %	p /bar H_2	Solvent	t /h	Yield alcohol / %[a]	Conv. 29e / %[a]	Yield. aldehyde / %[a]	Yield. ketone / %[a]
1	100	4.8	d_8-toluene	18.5	0	93	59	34
2	10	4.8	d_8-toluene	90	0	44	33	10
3[b]	20	4.5	d_8-toluene	22.5	0	53	38	16
4	10	4.8	1,4-dioxane	63	0	0	0	0

[a] based on NMR integration
[b] 70 °C

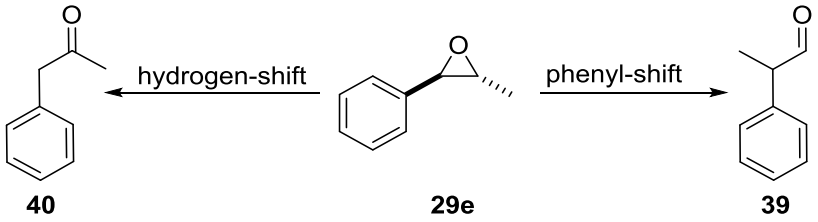
According to NMR analysis the desired alcohol products 1-phenyl-2-propanol (**37**) or 1-phenyl-1-propanol (**38**) were not obtained. **1g** mediated isomerization to 2-phenylpropionaldehyde (**39**) and phenylacetone (**40**) was obtained in low yields (entry 1-3) even though **29e** is exposed to reducing conditions. H_2 activation and transfer to **29e** or its isomerization products is therefore considered not to be successful.

Coordination of **1g** to an oxygen containing molecules is confirmed by ^{11}B NMR (signal at 40 ppm). Therefore, adduct formation of **1g and 29e** seems not to be prevented. However, the adduct is likely to be less strong and can be considered reversible.

1,4-dioxane seems to prevent isomerization (entry 4). Based on the concept of weak LB coordinate to weak LA, 1,4-dioxane is assumed to coordinate strongly to **1g**. This results in lesser accessibility of the boron centre for epoxide coordination and therefore prevented isomerization. Therefore, a solvent dependent reactivity of **29e** is determined.

As mentioned earlier in this thesis, substrate coordination hinders H_2 activation and decomposes the LA over time. Based on ^{1}H NMR and ^{11}B NMR analysis **1g** is decomposed over time. Again, the stability of **1g** at the given reaction conditions was not tested. Therefore heat could also be a factor in the decomposition of **1g.** Different pathways and proton sources for this decomposition are discussed in chapter 3.6.

The aldehyde **39** and ketone **40** products are LA catalyzed isomerization products. They are formed by either a hydrogen shift (Scheme 49, left path) or a phenyl shift (Scheme 49, right path).



Scheme 49: Isomerization of 29e to 39 or 40.

The phenyl-group has a higher migratory aptitude than hydrogen. This might explain the preferred isomerization to **39**. In addition the isomerization to **39** creates a new chiral centre at C2.

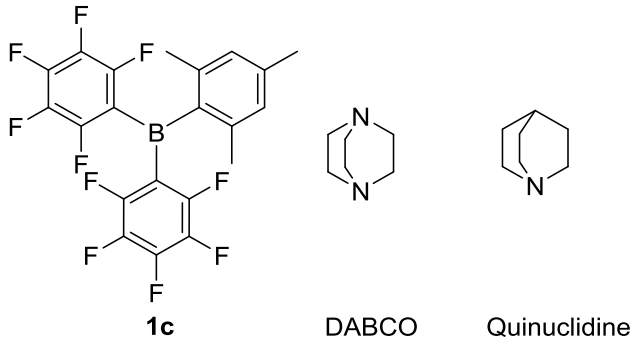
The highly electrophilic **1a** barely isomerizes **29e** to **40** in diethylether (Table 2, entry 2, 7 % yield). Isomerization products were not observed in 1,4-dioxane or d_8-toluene (Table 1, entry 7 and Table 2, entry 5). **1g** does isomerize **29e** in toluene, but not in 1,4-dioxane. Therefore, a LA dependent reactivity of **29e** is determined in addition to the solvent dependent reactivity of **29e**. This LA dependent reactivity can be explained by the higher accessibility of **1g** for **29e** due to reduced steric bulk around the boron center of **1g**. The additional lower electrophilicity of the boron center atom seem to decrease the coordination affinity of a LA to an epoxide. In the case of **1g** this leads to slow isomerization of **29e** in low yields.

In conclusion, H_2 is not cleaved and transferred to an unsaturated substrate by the cooperative interaction of **1g/29e**. Rather, **1g** forms a reversible adduct with **29e**, which leads to the isomerization of **29e** to **39** and **40** in low yields. **39** bears a new chiral carbon center. Reduction of the isomerization products was not obtained. A LA and a solvent dependent reactivity of **29e** was found.

In the future, lower Lewis acidity of the LA needs to be combined with less accessibility of the LA for epoxides in order to achieve H_2 activation. In retrospect further investigations into the epoxide hydrogenation mediated by a FLP of **1g** and a stronger LB, like P-based, LBs should have been done.

3.4.2. $B(C_6F_5)_2Mes$

It was chosen to describe the problem of FLP – catalyzed epoxide hydrogenation as an (ir)reversible adduct formation problem. In that case the choice for a LA according to the size-exclusion principle from the Soos group seemed a promising approach (see introduction 1.2.4.).[15] The FLP of **1c** in combination with either of the nitrogen based LBs quinuclidine or DABCO was chosen to test on FLP – catalyzed epoxide hydrogenation (Scheme 50). An additional benefit of this FLP is the fact that the intrinsic Lewis acidity of the boron center in **1c** is expected to be lower compared to the Lewis acidity of **1a.**

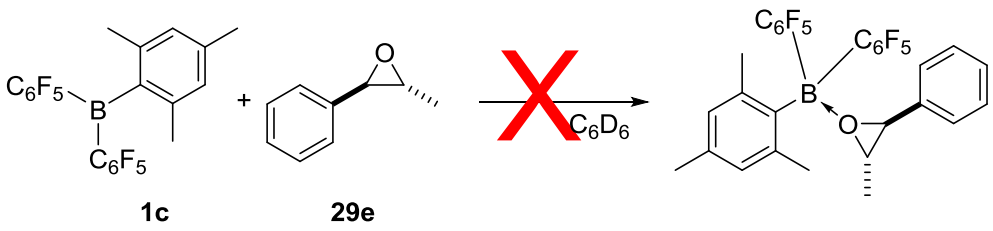


Scheme 50: A FLP can be formed of either 1c and DABCO or 1c and Quinulcidine.

M. Otte synthesized **1c**.

The FLP system **1c**/DABCO was analyzed by NMR. All proton signals were identified as the signals of DABCO and the mesitylene-substituent hydrogen atoms of **1c**. In the ^{19}F NMR spectrum three signals are obtained with large *para,meta* – chemical shift differences pointing to the presence of free **1c** in solution. In combination with the ^{11}B NMR spectrum prevented Lewis adduct formation between DABCO and **1c** can be confirmed (for NMR spectra see reference 15). The mesitylene signals of **1c** in proton NMR are expected to represent additional indicators for LA decomposition in future experiments.

Efforts were made to determine whether **29e** and **1c** form a classical Lewis adduct or a FLP (Scheme 51).

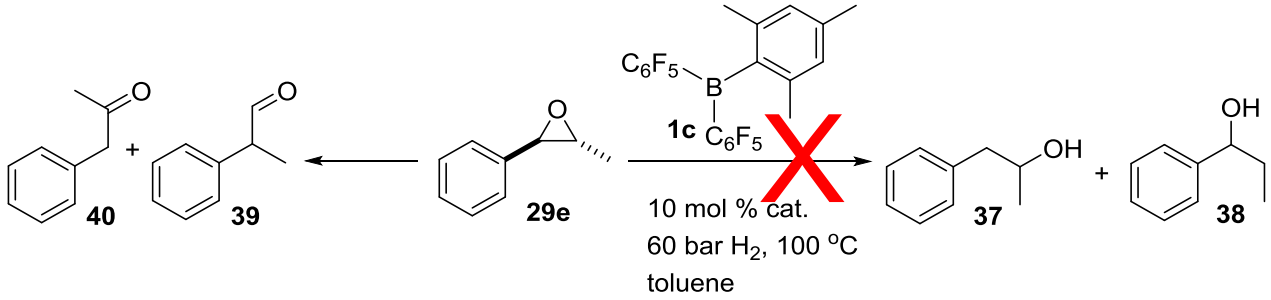


Scheme 51: Lewis adduct formation of 29e and 1c is prevent by the steric bulk around 1c.

In proton NMR the signals of **29e** and **1c** are identified without major changes in chemical shift. ^{19}F NMR shows three major signals belonging to free **1c** and in a ration of 10:1 to three minor signals of an unidentified fluorine compound. This led to the conclusion that **1c** is sterically demanding enough to prevent adduct formation with **29e** and **29e/1c** can be introduced as a new FLP (for NMR spectra see Appendix J).

Soos and coworkers perform their imine hydrogenation reactions at 4 bar H_2 pressure (C_6D_6, 20 °C).[15] Nevertheless, in order to reduce the reaction time and generally to apply more forcing conditions, it was decided to do the hydrogenation reaction in the autoclave. The set up was prepared in a similar way as described in Chapter 3.3.

First, the newly identified FLP **1c/29e** was exposed to H_2 in order to investigate their ability to activate H_2 (Scheme 52).

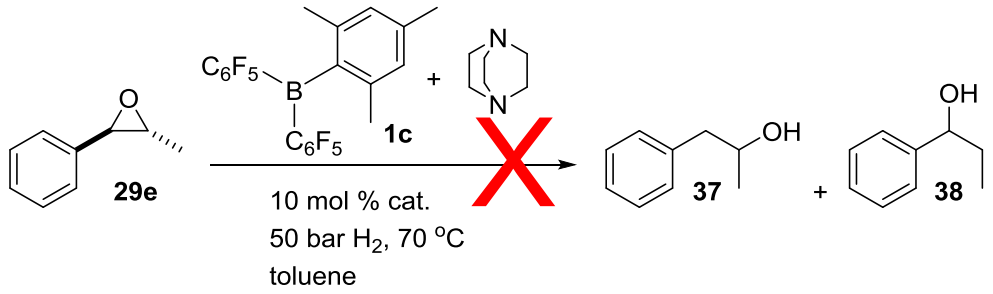


Scheme 52: Attempt for the FLP-catalyzed hydrogenation of 29e to 37 and 38 using 1c.

In NMR analysis 0 % conversion of **29e** to the desired products **37** or **38** was determined. Instead, signals for **39** (29 % yield) and **40** (14 % yield) were identified. The total conversion of **29e** is 43 %. Based upon ^{19}F and ^{11}B NMR spectroscopy H_2 activation could not be proven. Diol signals of **34** could not be identified. This indicates the water-free status of the autoclave reached by the improved loading method.

As mentioned before the aldehyde- and ketone-product are LA catalyzed isomerization products. As it is the case for **1g**, **1c** also isomerizes **29e** in low yields in toluene. The common lower electrophilicity of both LAs is assumed to be the reason for isomerization.

In a consecutive experiment **29e** was exposed to **1c/**DABCO at 50 bar H_2 (Scheme 53).



Scheme 53: Attempt to reduce 29e to 37 and 38 by 1c/DABCO FLP-catalyzed hydrogenation.

Overall 0 % conversion of **29e** to **37** or **38** was determined by NMR analysis. The reason for this might be found in the failed H_2 activation itself or in the failed transfer of hydrogen from the **1c**-H^-/DABCO-H^+ salt to **29e**. The activation of H_2 by DABCO and **1c** is reported in literature.[15] If hydrogen transfer to an unsaturated substrate is prevented, activated H_2 will most likely be used to form mesitylene by B-C bond protonation within **1c**. Mesitylene formation was not observed. This might be an indication for failed H_2 activation by **1c**/DABCO in the presence of **29e**. However, it does not prove it.

Isomerization of **29e** to **39** or **40** was not observed in the reaction of Scheme 53. This might be due to the presence of DABCO. As mentioned before, DABCO does not form an adduct with **1c**, but it might coordinate weakly to **1c** and thereby occupy **1c** enough to not engage in isomerization of **29e**. However, a significant difference in reaction temperature (Δ_T = 30 °C) might also be the reason for prevented isomerization.

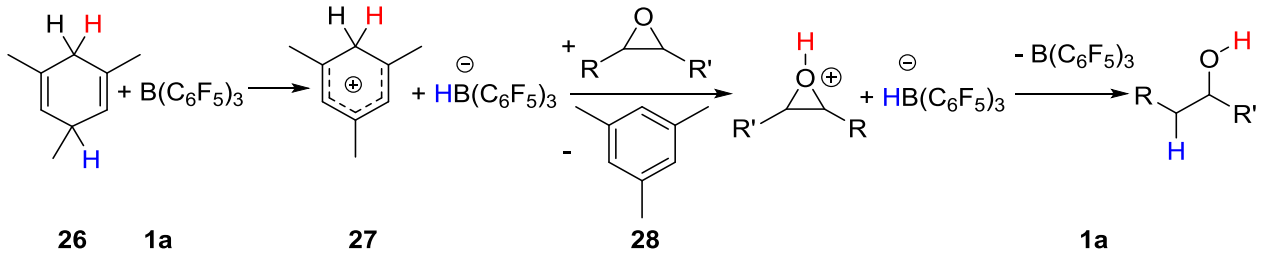
In conclusion, the epoxide **29e** does not form an adduct with **1c**. Reduction of **29e** by H_2 activated with this FLP failed. Reduction of **29e** with the reported FLP **1c**/DABCO failed as well. H_2 activation by these FLPs was suggested to be the reason for prohibited hydrogenation. Therefore, another LB needs to be found which can activate H_2 with **1c** in the presence of **29e**.

In addition, isomerization of **29e** to **39** and **40** was observed in low yields over time. This again shows the LA dependent reactivity of **29e.** The preferred isomerization of **29e** over **1c**/**29e** mediated H_2 activation suggests that epoxides cannot be used as LBs in the H_2 activation with **1c**.

3.5. Attempted Transfer Hydrogenation of Epoxides

Hydrogenation of epoxides by TH with the use of an alternative reducing reagent than H_2 was proposed, based on the report of Oestreich and coworkers.[49-50] This method was proposed due to persistent epoxide coordination to **1a**, which is assumed to prevent H_2 activation and/or reduction. The all time presence of **1a** in its anionic borohydride form was aimed for to prevent substrate-LA interaction. If successful this method is not as elegant as reducing epoxides with H_2, but it still proves that hydrogenation of epoxides with boron based FLP chemistry is possible.

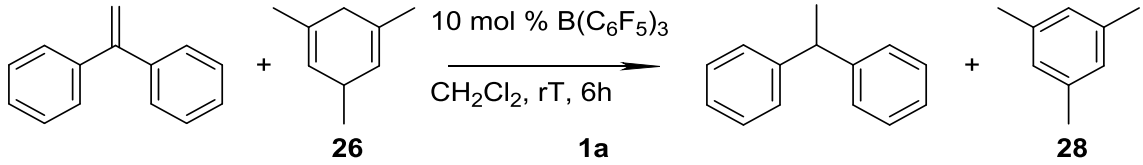
Oestreich and coworkers introduced 1,3,5-trimethyl-2,4-cyclohexadiene (**26**) of which **1a** can abstract a hydride in order to form a borohydride and a high energy Wheland complex (**27**). In the envisioned epoxide hydrogenation process this cationic **27** protonates the etheral oxygen of the epoxide moiety. A nucleophilic attack of the borohydride on the established carbocation then leads to the fully hydrogenated alcohol product. The TH process is catalytic in **1a,** but stoichiometric amounts of **26** are required. Scheme 54 shows the envisioned TH from **26** to an epoxide facilitated by **1a**.



Scheme 54: Proposed synthesis of an alcohol by TH from 26 to an epoxide.

Oestreich and coworkers applied their TH protocol to reduce 1,1-diphenylethylene to 1,1-diphenylethane. The reported isolated yield is 97 %.[50] We handled certain alterations to the reported Oestreich procedure. A higher catalyst loading (10 mol %) was used as well as CH_2Cl_2 as solvent instead of 1,2-difluorobenzene. Also the substrate was added last to the reaction mixture instead of adding **1a** last as Oestreich does it. This was done in an attempt to have all of **1a** present in the anionic form of a borohydride to prevent side reactions like coordination of epoxide. In addition a higher amount of **26** (5.5 eq. instead of 1.3 eq.) was used.

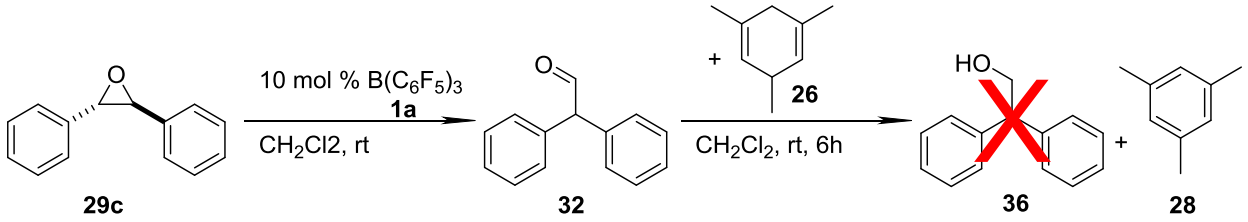
In order to test the altered conditions they were applied to reduce 1,1-diphenylethylene to 1,1-diphenylethane (Scheme 55). Full conversion based on GC-MS was determined.



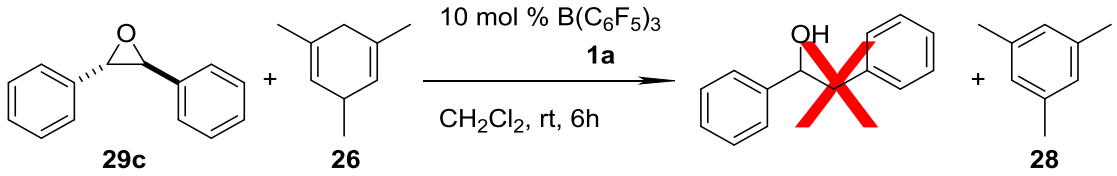
Scheme 55: 1a-catalyzed TH of 1,1-diphenylethylene to 1,1-diphenylethane.

Oestreich and coworkers report 97 % isolated yield for this reaction using their conditions.[50] Therefore it was concluded that the conditions applied could be tested in epoxide TH.

The altered procedure was first tested on **29c**, which has a better-understood reaction with **1a**. As was reported earlier (Chapter 3.1 and 3.3.) **29c** isomerizes to **32** if exposed to **1a**. Due to our aim for constant borohydride supply there is also a possibility to obtain the alcohol of **29c** prior to isomerization. The possible pathways and products of the envisioned TH process of **29c** are shown in Scheme 56 and 57.



Scheme 56: Attempted reduction of 29c via an isomerization-TH sequence.



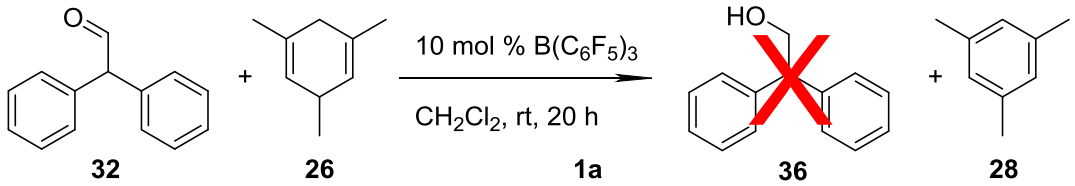
Scheme 57: Attempted direct reduction of 29c via TH from 26 to 29c.

Scheme 56 shows the envisioned isomerization – TH reaction. Scheme 57 shows the alternative direct TH pathway.

GC-MS analysis as well as NMR spectroscopy was applied to analyze the reaction mixture. The masses 120 g/mol, 122 g/mol and 196 g/mol, which correspond to **26**, **28** and **32,** have been obtained. NMR analysis confirmed full conversion of **29c** to **32**. Upon GC- integration 91 % conversion of **26** to **28** was determined. It seems as if **1a** is free to isomerize **29c** and form a borohydride in the presence of the newly established aldehyde. The transfer of the hydride and proton to **32** has failed.

This illustrates the possibility of borohydride existence in the presence of an electron rich aldehyde as described in literature.[25] The aim to have **1a** in its anionic species in the presence of **29c** was reached. However, the envisioned easier TH to the epoxide substrate failed. The order, in which mesitylene formation and **29c** isomerization was achieved, might be the reason for the failure.

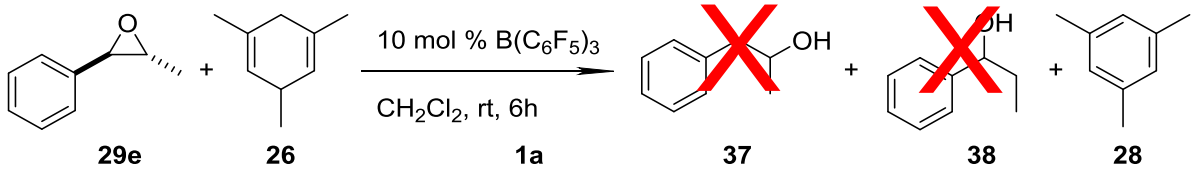
To further investigate the problem, **32** was exposed to the same conditions as the epoxides. If mesitylene was obtained prior to **29c** isomerization, then reduction of **32** cannot have taken place due to the absence of hydrogen donor. Scheme 58 shows the envisioned reaction.



Scheme 58: Attempted reduction of 30 via TH.

No conversion of **32** to **36** was obtained by GC-MS or NMR. In ^{11}B NMR a signal at 40 ppm indicates the formation of B-O interaction.[45] This points to the adduct formation of **32** and **1a**.

Further investigation into the TH of epoxides according to an altered procedure of Oestreich and coworkers were done with **29e** (Scheme 59).



29e **26** **1a** **37** **38** **28**

Scheme 59: Attempted reduction of 29e to 37 and 38 by TH from 26, mediated by 1a C-H bond activation

The reaction was done in a J-Young tube bearing the advantage of being able to monitor the reaction over time. In NMR analysis signals around 4 ppm, which would be characteristic for alcohol products, were not obtained. Overall, 0 % conversion of **29e** was determined. **26** has reacted to mesitylene in 40 % conversion. Insufficient stirring of the reaction mixture might be the reason for the low mesitylene yield.

Upon addition of the epoxide mixture to the solution of **26** and **1a** gas formation was visible in form of bubbles. This indicates the preferred reaction of the Wheland complex with the borohydride to get H_2 gas instead of protonating the etheral oxygen of **29e**. Oestreich and coworkers discus the eventuality of seeing this side reaction occur in their communication about imine TH.[49] Cationic oligomerization is reported to be a side reaction during olefin TH[50]. No oligomerization product of **29e** was identified in proton NMR.

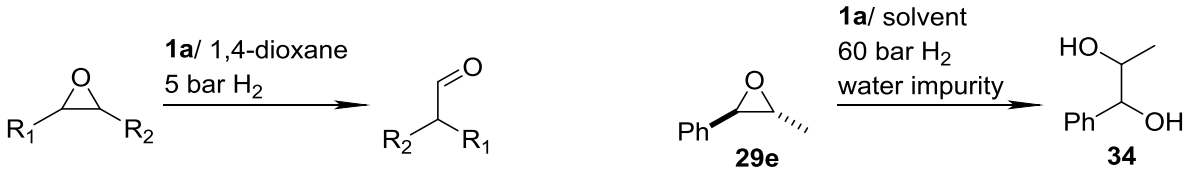
At reaction begin the ^{11}B NMR spectrum showed a signal at 40 ppm, indicating B-O interaction, most likely in the form of an adduct of **29e** to **1a**. The original **1a** LA was not observed in NMR anymore. Over time the ^{11}B signal shifted to the higher field (- 20ppm). The aimed for borohydride is supposed to give a signal around this chemical shift value. Therefore, the first indication for C-H bond activation by **1a** in the presence of an epoxide is found.

In order to investigate the reactivity of the hydrogen donor towards **1a** a mixture of **26** and a catalytic amount of **1a** was stirred for 15 minutes and analyzed by NMR and GC-MS. Quantitative conversion to **28** was obtained. This result indicates the high reactivity of the system and the ease at which the C-H bond of **26** is activated by **1a**. The addition of **1a** to the reaction mixture after substrate addition is therefore required in future reaction.

In summary, an adapted procedure for **1a** catalyzed TH of an olefin yielded similar yields as reported by Oestreich and coworkers. **29c** is isomerized to **32** by **1a** if exposed to these adapted TH conditions. No TH products of **29e** were obtained. Full conversion of **26** to **28** suggests the formation of the **1a**-H^- intermediate in the presence of **29c** or **32**. Finally, the TH system **26**/**1a** seems to be very reactive. Therefore, for the future it is advised to add the LA last to the reaction mixture.

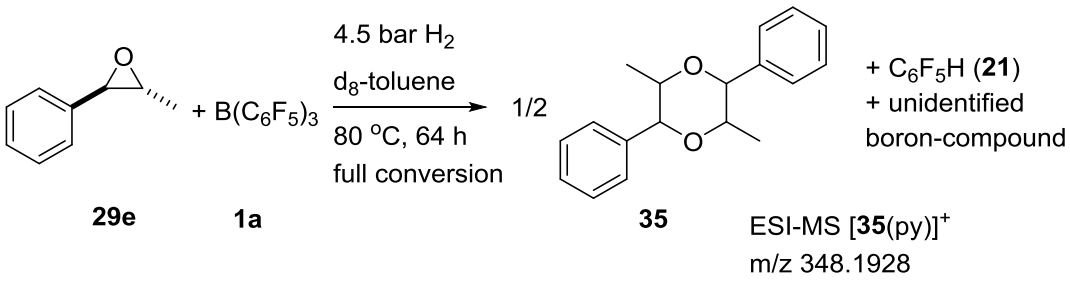
4. Conclusion

The exposure to a FLP of **1a**/1,4-dioxane capable of heterolytic H_2 cleavage resulted in the regioselective isomerization of **29a**, **29b**, **29c** and **29d** into electron rich aldehydes (Scheme 60, left). **29e** was the first epoxide, which did not isomerize in 1,4-dioxane. Hydrogenation attempts with higher H_2 pressures and is donor- as well as non-donor solvents resulted in the hydrolysis of **29e** to **34**, due to water impurities in the autoclave (Scheme 60, right).



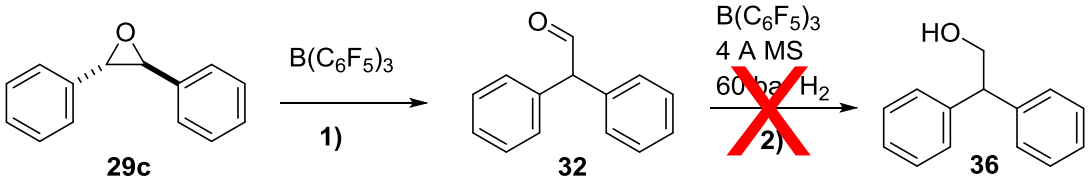
Scheme 60: Exposure of various epoxides to the FLP 1a/1,4-dioxane resulted in 1a mediated isomerization to aldehydes (left). 1a catalyzed the hydrolysis of 29e in different solvents (right).

Investigations into the Lewis adduct formation of **29e** and **1a** resulted in the identification of the cationic dimerization product **35** (Scheme 61). **1a** is degraded to **21** by B-C bond protonolysis.



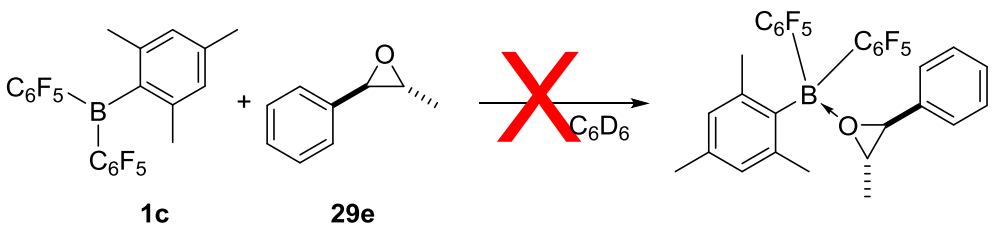
Scheme 61: Dimerization of 29e to 35.

Furthermore, the tandem isomerization-reduction sequence was investigated. The Meinwald rearrangement of **29c** was catalyst by 15 mol % **1a** to full conversion of **30** within 15 minutes**.** Subsequent reduction of **32** to **36** facilitated by a FLP of **1a** and 4 Å molecular sieves has not been observed (Scheme 62).



Scheme 62: Attempted tandem isomerization-hydrogenation reaction of 29c catalyzed by 1a/4 Å MS resulted in formation of 32.

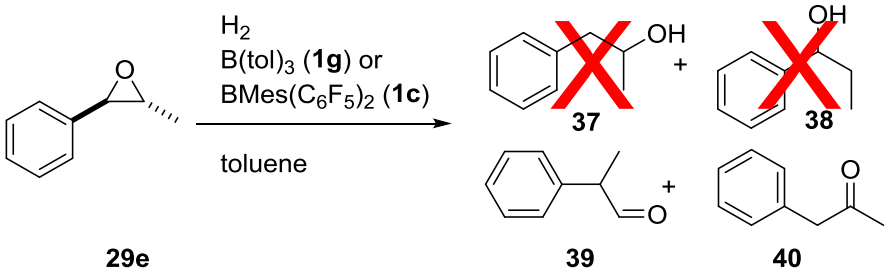
The more electron rich LAs **1g** and **1c** were synthesized. **29e** does not form a Lewis adduct with **1c**. Therefore, a new FLP was found (Scheme 63).



1c **29e**

Scheme 63: 1c and 29e form a FLP.

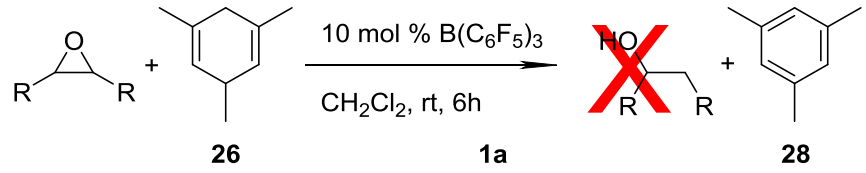
1g and **1c** were tested for the reduction of **29e** to **37** and **38** (Scheme 64). However, isomerization to **39** and **40** in low yields was observed instead. Therefore LA dependent reactivity of **29e** was found. **39** bears a new chiral carbon center.



29e **37** **38** **39** **40**

Scheme 64: Attempted hydrogenation of 29e resulted in isomerization to 39 and 40.

Finally, the concept of TH was tested for epoxide reduction. Although the TH system **26**/**1a** seems to be very reactive, no TH products of **29c**, **29e** or **32** were obtained (Scheme 65). High to full conversion of **26** to **28** was observed. This indicated the formation of **1a**-H^- in the presence of **29c** and **29e.**



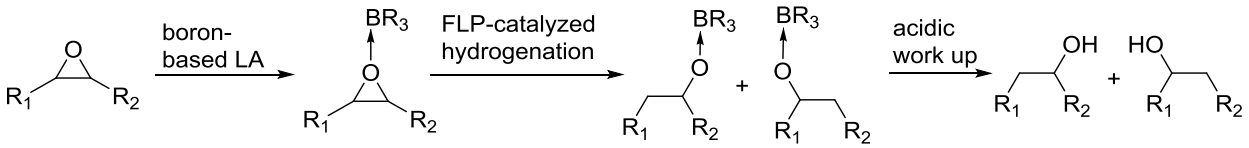
26 **1a** **28**

Scheme 65: Attempted TH of epoxides resulted in full conversion of 26 to 28.

5. Outlook

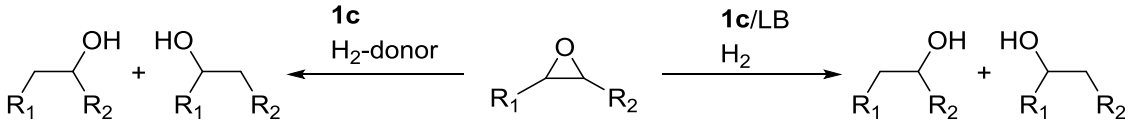
The tandem isomerization-reduction reaction as discussed in Chapter 3.3. consists of two steps envisioned to occur in a one pot procedure. Since the second step could not be reproduced in our set up, more effort can be made into the successful performance of this step. Upon the successful reduction of 32 in our set up, the overall reaction as depicted in Scheme 46 should be successful.

Furthermore, in this thesis LA dependent reactivity of **29e** was determined. The general affinity of boron to the etheral-oxygen of an epoxide might be made use of by introducing a (cheap) boron-based LA like $BF_3{}^*OEt_2$ as stoichiometric protection group for the etheral oxygen. H_2 activation by a FLP of a boron-based LA and a cooperative LB should not be interfered anymore by the epoxide moiety. After hydrogenation the B-O bond between the alcohol product and the stoichiometric LA will be cleaved by acidic work up. Scheme 66 shows the envisioned reaction.



Scheme 66: Envisioned hydrogenation of an epoxide by first introducing a protection group to the etheral-oxygen of the epoxide and subsequently using FLP-catalyzed hydrogenation to reduce the borinic ester. The protection group is removed by acidic work up.

Finally, the identification of the FLP **1c**/**29e** encourages the investigation into **1c**-catalyzed transformations of **29e** and other epoxides (Scheme 67, left). For example, **1c**-catalyzed TH of epoxides can be thought of. Therefore, investigations into **1c**-mediated hydride abstraction from **26** need to be performed. In addition, different LBs for **1c**/LB facilitated H_2-activation can be sought aiming for FLP-catalyzed hydrogenation of epoxides (Scheme 67, right). The steric bulk around **1c** is likely to prevent adduct formation with a large variety of LBs. Therefore, the focus lies on successful H_2-activation with these **1c**/LB combinations.



Scheme 67: Envisioned 1c-catalyzed TH of epoxides (left) and 1c/LB-catalyzed hydrogenation of epoxides (right).

6. Experimental section

6.1. General

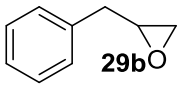
Synthesis:

Reagents were obtained commercially and used without further purification unless stated otherwise. Reactions were, if required, carried out in dry nitrogen atmosphere under standard Schlenk techniques or in MB200B MBRAUN glovebox system.
Dioxane was dried over sodium/benzophenone, distilled, degassed and stored over 4 Å molecular sieves in the GB. Et_2O and toluene were dried in a MBRAUN MB SPS-800 solvent purification system, degassed and stored over 4 Å molecular sieves in the GB. CH_2Cl_2 was dried over CaH_2, distilled, degassed and stored over 4 Å molecular sieves in the GB. Deuterated solvents were dried and degassed with three consecutive freeze-thaw-pump cycles and stored over 4 Å molecular sieves. Lower pressure experiments were performed in J-Young NMR tubes. High-pressure experiments were performed in a Parr 4843 autoclave. H_2 gas bottle (dry) was purchased from Linde Gas Benelux BV. and used without further purification.

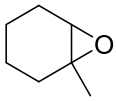
Instrumental:

^{1}H NMR (400 MHz) spectra and ^{13}C NMR (100 MHz) spectra were recorded on MRF400 or VNMRS400.
^{19}F NMR (376 MHz) spectra and ^{11}B NMR (128 MHz) spectra were recorded on MRF400. Chemical shifts are reported in ppm and referenced against residual solvent signal. GC-MS spectra were recorded on a Perkin Elmer Gas Chromatograph Clarus 680 with a mass spectrometer Clarus SQ8T (column PE Elite 5MS, 15mx0.25mmx0.25µm). ESI-MS data was obtained from a Micromass MS technologies LCT Premier XE.

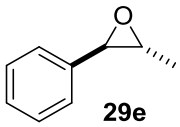
6.2. Epoxide Synthesis


29b

A solution of allylbenzene (1.0 g / 8.5 mmol) in dry CH_2Cl_2 (50 mL) was cooled to 0 °C prior to the addition of *m*CPBA (2.34 g / 1.2 eq / 10.2 mmol). The reaction mixture was allowed to warm up to room temperature and stirred vigorously overnight. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed twice with 25 % aq. K_2CO_3. After drying the organic phase over $MgSO_4$ the solvent was evaporated. The crude mixture was further purified over a silica column (PE/EtOAc 100:3) to yield 76 % of **29b** (862 mg / 6.43 mmol).
^{1}H NMR ($CDCl_3$, 400 MHz): 7.22-7.36 (m, 5H, Ph), 3.16 (m, 1H, CH), 2.93 (dd, *J* = 5.3 Hz, 14.4 Hz, 1H, CH-Ph), 2.84 (d, *J* = 5.3 Hz, 1H, Ch-Ph), 2.80 (t, *J* = 5.3 Hz, 1H, CH_2), 2.56 (dd, J = 2.8 Hz, 5.3 Hz, 1H, CH_2).
^{13}C NMR ($CDCl_3$, 100 MHz): 38.8 (CH_2), 46.9 (CH_2-Ph), 52.4 (CH), 126.7 (Ph), 128.5 (Ph), 129.0 (Ph), 137.2 (Ph).
NMR data was according to literature.[78]


29d

$NaHCO_3$ (1.78 g / 21.2 mmol) was dissolved in 70 mL H_2O. 1-Methyl-1-cyclohexene (1.2 mL / 10.4 mmol) was added via syringe. The reaction mixture was cooled to 0 °C. Over a time of 10 minutes *m*CPBA (2.95 g / 1.2 eq / 12.8 mmol) was added. The solution was left to stir vigorously overnight. The solution was extracted with diethylether (3 x 40 mL). The organic layer was then washed with cold NaOH (2 x 70 mL) and dried over $MgSO_4$. Solvent removal yielded 10 % of **29d** (115 mg / 1.0 mmol).
^{1}H NMR ($CDCl_3$, 400 MHz): 2.94 (d, *J* = 3.5 Hz, 1H, CH-O), 1.87 (m, 2H, 2xCH), 1.65 (m, 1H, CH), 1.55 (s, 1H, CH), 1.41 (m, 2H, 2xCH), 1.29 (s, 3H, CH_3), 1.2 (m, 2H, 2xCH).
^{13}C NMR ($CDCl_3$, 100 MHz): 19.6 (CH_3), 20.0 (CH_2), 23.9 (CH_2), 24.7 (CH_2), 29.9 (CH_2), 57.5 (CH-O), 59.6 (C-O).
NMR data was according to literature.[79]


29e

trans-phenylpropylene oxide (2.86 mg / 24.26 mmol) was dissolved in 175 mL CH_2Cl_2. A solution of $NaHCO_3$ (17.5 g / 0.21 mol) in 175 mL H_2O was added. The biphasic suspension was vigorously stirred. *m*CPBA (6.587 g / 1.1 eq / 26.80 mmol) was added at room temperature. The reaction mixture was vigorously stirred at room temperature for 4 h. Na_2SO_3 (22.75 g / 0.16 mol) was dissolved in 175 mL H_2O. This solution was added to the reaction mixture and stirred for 20 minutes. The reaction mixture was then extracted with CH_2Cl_2. The organic phase was washed with $NaHCO_3$ and H_2O. Later the organic phase was dried over $MgSO_4$ and the solvent was evaporated to yield 76 % of **29e** (2.47 g / 18.5 mmol).
^{1}H NMR (400 MHz, C_6D_6): 7.02-7-09 (m, 5H, Ph), 3.23 (d, *J* = 2 Hz, 1H, CH-Ph), 2.60 (qd, *J* = 5 Hz, 2 Hz, 1H, CH-CH_3), 1.00 (d, *J* = 5 Hz, 3H, CH_3).
^{13}C NMR (100 MHz, $CDCl_3$): 17 (CH_3), 58 (CH), 59 (CH), 126 (Ph), 127 (Ph), 128 (Ph), 138 (Ph).

6.3. General Procedures

General Procedure 1: (NMR tube)
Inside the GB $B(C_6F_5)_3$ and epoxide were dissolved in 0.4 mL 1,4-dioxane and transferred into a J-Young tube by syringe. An internal standard (sealed capillary filled with 1,3,5-methoxybenzene dissolved in C_6D_6, 0.26 M) was added. The mixture was analyzed by ^{1}H, ^{19}F, ^{11}B NMR upon which it was degassed by three freeze-pump-thaw cycles. H_2 gas was added at -196 ^{o}C and the mixture was afterwards allowed to warm up to room temperature before being heated up to the set temperature. After a given time the mixture was allowed to cool to room temperature and the H_2-pressure was released. The mixture was analyzed again by ^{1}H, ^{19}F and ^{11}B NMR.

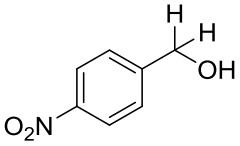
General Procedure 2: (autoclave)
Inside the GB $B(C_6F_5)_3$ and the substrate were dissolved in 5 mL solvent and transferred into a Schlenk-flask by syringe. The mixture was added into an autoclave outside the GB. 50 bar H_2 gas was added at room temperature. The mixture was heated up to 70 °C (heating mantle, no oil bath). After the given time the mixture was cooled to room temperature with the help of an ice-bath. H_2-pressure was released and the mixture was taken out of the autoclave by pipette. After evaporation of the solvent a sample was analyzed by ^{1}H NMR.

General Procedure 3: (NMR tube)
Inside the GB Lewis acid and the substrate were dissolved in 0.4 mL of solvent and transferred into a J-Young tube by syringe. The mixture was analyzed by ^{1}H, (^{19}F,) ^{11}B NMR upon which it was degassed by three freeze-pump-thaw cycles. H_2 gas was added at -196 ^{o}C and the mixture was afterwards allowed to warm up to room temperature before being heated up to the set temperature. After a given time the mixture was allowed to cool to room temperature and the H_2-pressure was released. The mixture was analyzed again by ^{1}H, (^{19}F) and ^{11}B NMR.

6.4. Attempted FLP-catalyzed Hydrogenation of Epoxides

Experimental section for FLP-catalysis experiments in 1,4-dioxane

Hydrogenation of 4-nitro-benzaldehyde to 4-nitro-benzalcohol:



According to general procedure 1 (no ^{19}F and ^{11}B NMR before reaction recorded) $B(C_6F_5)_3$ (5.2 mg / 0.01 mmol) and 4-nitrobenzaldehyde (16 mg / 0.1 mmol) were dissolved in 0.4 mL 1,4-dioxane and heated to 80 °C for 116 h at 4.5 bar H_2 to yield 80 % of 4-nitrobenzalcohol (based on NMR integration).

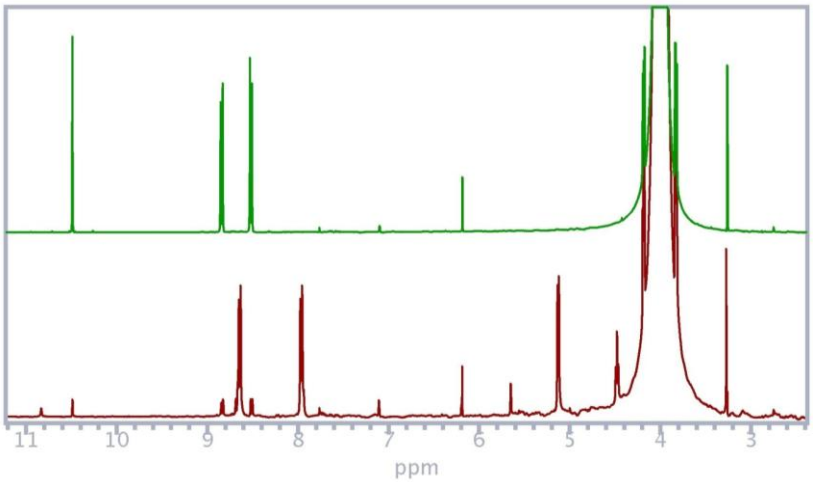
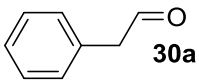


Figure 14: ^{1}H NMR of reaction before (upper) and after (lower) exposure to hydrogen gas.

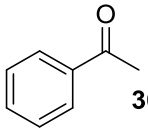
Identified compound in ^{1}H NMR before H_2 exposure (C_6D_6, 400 MHz):
nitrobenzylaldehyde[24b] δ 10.50 (s, 1H, CHO), 8.85 (d, *J* = 8.8 Hz, 2H, Ph), 8.53 (d, *J* = 8.8 Hz, 2H, Ph)
1,3,5-trimethoxybenzene δ 6.20 (s, 3H, Ph), 3.27 (s, 9H, O-CH_3)

Identified compound in ^{1}H NMR after H_2 exposure (C_6D_6, 400 MHz):
nitrobenzylalcohol[24b] δ 8.65 (d, *J* = 8.1 Hz, 2H, Ph), 7.97 (d, *J* = 8.2 Hz, 2H, Ph), 5.13 (d, *J* = 5.7 Hz, 2H, CH_2-OH)
nitrobenzylaldehyde[24b] δ 10.5 (s, 1H), 8.84 (d, *J* = 8.7 Hz, 2H), 8.51 (d, *J* = 8.7 Hz, 2H)
1,3,5-trimethoxybenzene δ 6.21 (s, 3H), 3.27 (s, 9H)

Attempt to reduce styrene oxide to 1-phenyl-ethanol or 2-phenyl ethanol:



30a

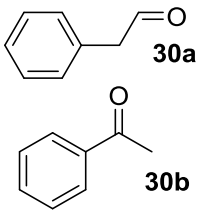


30b

Inside the glovebox $B(C_6F_5)_3$ (30 mg / 0.05 mmol) and **29a** (157 mg / 1.31 mmol) were dissolved in 4 mL 1,4-dioxane. The mixture was degassed by three freeze-pump-thaw cycles. H_2 gas was added at -196 °C and the mixture was heated to 80 °C for overnight reaction (H_2-pressure 4.5 bar). The mixture was allowed to cool to room temperature and the H_2-pressure was released. After evaporation of the solvent a sample was analyzed by ^{1}H NMR. Full conversion of **29a** to 70 % phenylacetaldehyde (**30a**) and 30 % acetophenone (**30b**) was determined by NMR integration.

Identified compound in crude ^{1}H NMR ($CDCl_3$, 400 MHz):
30a[80] δ 9.65 (s, 1H, CHO), 7.16 (m, 2H, Ph), 7.23 (m, 3H, Ph), 3.68 (CH_2, under the dioxane signal)
30b[24a] δ 7.96 (m, 2H, Ph), 7.42 (m, 3H, Ph), 2.61 (s, 3H, CH_3)

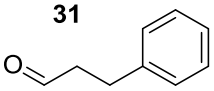
Blank experiment of attempt to reduce styrene oxide to 1-phenyl-ethanol or 2-phenyl ethanol:



Inside the glovebox $B(C_6F_5)_3$ (30 mg / 0.05 mmol) and **29a** (116mg / 0.97 mmol) were dissolved in 4 mL 1,4-dioxane. The mixture was degassed by three freeze-pump-thaw cycles. No H_2 gas was added and the mixture was heated to 80 °C in N_2-atmosphere for overnight reaction. The mixture was allowed to cool to room temperature. After evaporation of the solvent a sample was analyzed by ^{1}H NMR. Full conversion of **29a** to 70 % **30a** and 30 % **30b** was determined by NMR integration.

Identified compound in ^{1}H NMR ($CDCl_3$, 400 MHz):
30a[80] δ 9.65 (s, 1H), 7.16 (m, 2H), 7.23 (m, 3H), 3.68 (under dioxane signal)
30b[24a] δ 2.61 (s, 3H), 7.42 (m, 3H), 7.97 (m, 2H)

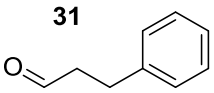
Attempt to reduce (2,3-epoxypropyl)benzene into 3-phenyl-1-propanol or 1-phenyl-2-propanol:



Inside the glovebox $B(C_6F_5)_3$ (25 mg / 0.05 mmol) and **29b** (189 mg / 1.41 mmol) were dissolved in 4 mL 1,4-dioxane. The mixture was degassed by three freeze-pump-thaw cycles. H_2 gas was added at -196 °C and the mixture was heated to 80 °C (H_2-pressure 4.5 bar). After 19 h the mixture was allowed to cool down to room temperature and the H_2-pressure was released. After evaporation of the solvent the mixture was purified by column chromatography (PE/EtOAc 10:1) to yield 27 % (50 mg / 0.37 mmol) of phenylpropanal (**31**).

^{1}H NMR of the isolated compound ($CDCl_3$, 400 MHz):
31[81] δ 9.83 (t, *J* = 1.4 Hz, 1H, CHO), 7.3 (m, 2H, Ph), 7.21 (m, 3H, Ph), 2.97 (t, *J* = 7.6 Hz, 2H, CH_2), 2.77 (t, *J* = 7.6 Hz, 2H, CH_2)

Second attempt to reduce (2,3-epoxypropyl)benzene into 3-phenyl-1-propanol or 1-phenyl-2-propanol:

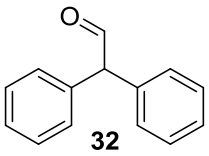


Inside the glovebox $B(C_6F_5)_3$ (25 mg / 0.05 mmol) and **29b** (100 mg / 0.75 mmol) were dissolved in 2 mL 1,4-dioxane. The mixture was degassed by three freeze-pump-thaw cycles. H_2 gas was added at -196 °C and the mixture was heated to 80 °C to react overnight (H_2-pressure 4.5 bar). Then the mixture was allowed to cool to room temperature and the H_2-pressure was released. After evaporation of the solvent a sample was analyzed by ^{1}H NMR and ^{13}C NMR in $CDCl_3$. Full conversion to **31** was observed based on NMR.

Identified compound in crude ^{1}H NMR ($CDCl_3$, 400 MHz):
31[81] δ 9.83 (t, *J* = 1.4 Hz, 1H), 7.28 (m, 2H), 7.21 (m, 3H), 2.97 (t, *J* = 7.5 Hz, 2H), 2.79 (t, *J* = 7.7 Hz, 2H)

Identified compound in crude ^{13}C NMR ($CDCl_3$, 100 MHz):
31[81]δ 201.6 (CHO), 140.3 (Ph), 128.6 (Ph), 128.3 (Ph), 126.3 (Ph), 45.3 (CH_2), 28.1 (CH_2)
^{1}H and ^{13}C NMR spectra can be found in Appendix B.

Attempt to reduce stilbene oxide to 1,2-diphenyl-ethanol:

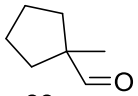


32

According to general procedure 1 $B(C_6F_5)_3$ (5.1 mg / 0.01 mmol) and **29c** (28.8 mg / 0.15 mmol) were dissolved in 0.4 mL 1,4-dioxane and heated to 80 °C for 17 h at 4.5 bar H_2 to yield 82 % of 2,2-diphenylacetaldehyde (**32**) based on NMR integration. A mixture of the commercially available **32** in 1,4-dioxane with internal standard was analyzed by ^{1}H NMR to identify the product.

Identified compound in ^{1}H NMR after H_2 exposure (C_6D_6, 400 MHz):
32 δ 10.3 (d, *J* = 2.3 Hz, 1H, CHO), 7.77 (m, 4H, Ph), 7.71 (m, 2H, Ph), 7.67 (m, 4H, Ph), 5.33 (d, *J* = 2.2 Hz, 1H, CH-Ph)
29c δ 4.30 (s, 2H), aromatic signals under signals of **32**
1,3,5-trimethoxybenzene δ 6.20 (s, 3H), 3.28 (s, 9H)
^{1}H NMR spectra before and after H_2 exposure can be found in Appendix C.

Attempt to reduce methyl-cyclohexane oxide to methyl-cyclohexanol:



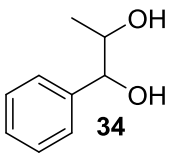
33

According to general procedure 1 $B(C_6F_5)_3$ (5.2 mg / 0.01 mmol) and **29d** (0.1 mmol / 11 mg) were dissolved in 0.4 mL 1,4-dioxane and heated to 80 °C for 86 h at 4.5 bar H_2 to full conversion (based on NMR integration) of **29d** to 1-methyl-1-cyclopentanecarboxaldehyde (**33**).

Identified compound in ^{1}H NMR after H_2 exposure (C_6D_6, 400 MHz):
33 δ 9.84 (s, 1H, CHO), 2.38 (m, 2H, CH_2), 2.15 (m, 2H, CH_2), 2.06 (m, 2H, CH_2), 1.78 (m, 2H, CH_2), 1.54 (s, 3H, CH_3)
1,3,5-trimethoxybenzene δ 6.20 (s, 3H), 3.27 (s, 9H)

Identified compound in ^{13}C NMR after H_2 exposure (C_6D_6, 400 MHz):
33 δ 204 (CHO), 54 (C-CH_3), 35 (2 x CH_2), 26 (2 x CH_2), 20 (CH_3)
1,3,5-trimethoxybenzene δ 162 (O-CH_3), 93 (Ph)
^{1}H NMR spectra before and after H_2 exposure as well as ^{13}C NMR after H_2 can be found in Appendix D.

Attempt to reduce *trans*-phenyl-propylene oxide to 1-pheny-ethanol or 3-phenyl-2-propanol:



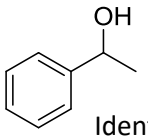
34

According to general procedure 1 $B(C_6F_5)_3$ (5.3 mg / 0.01 mmol) and **29e** (13.4 mg / 0.1 mmol) were dissolved in 0.6 mL 1,4-dioxane and heated to 100 °C for 68 h at 4.8 bar H_2 to yield 22 % of phenyl-1,2-propandiol (**34**) based on NMR integration.

Identified compound in ^{1}H NMR after H_2 exposure (C_6D_6, 400 MHz):
29e δ 7.72 (m, 5H, Ph), 3.4 (qd, *J* = 5 Hz, 2 Hz, 1H, CH), 2.6 (CH_2, under dioxane signal), 1.82 (d, *J* = 5 Hz, 3H, CH_3)
34 δ 7.72 (m, 5H, Ph), 4.61 (d, *J* = 10 Hz, 1H, CH-OH), 4.0 (CH-OH, signal under dioxane signal), 1.58 (d, *J* = 6 Hz, 3H, CH_3)
1,3,5-trimethoxybenzene δ 3.27 (s, 9H)
^{1}H NMR spectra before and after H_2 exposure can be found in Appendix E.

Experimental section for high-pressure experiments

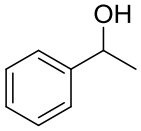
Blank experiment of hydrogenation of acetophenone to phenylethanol:



According to general procedure 2 acetophenone (2.5 mmol / 300 mg) was dissolved in 5 mL diethylether and heated to 70 °C for 18 h at 57 bar H_2 to yield 0 % of 1-phenylethanol.

Identified compound in crude ^{1}H NMR (C_6D_6, 400 MHz):
Acetophenone[24a] δ 7.96 (d, *J* = 7.7 Hz, 2H, Ph), 7.56 (t, *J* = 7 Hz, 1H, Ph), 7.47 (t, *J* = 7.2 Hz, 2H, Ph), 2.61 (s, 3H, CH_3)

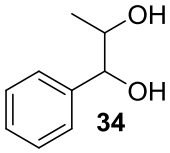
Hydrogenation of aceophenone to phenylethanol:



According to general procedure 2 $B(C_6F_5)_3$ (64 mg / 0.12 mmol) and acetophenone (2.5 mmol / 302 mg) were dissolved in 5 mL diethylether and heated to 70 °C for 19 h at 58 bar H_2 to yield 27 % of 1-phenylethanol based on NMR integration.

Identified compound in crude ^{1}H NMR (C_6D_6, 400 MHz):
Phenylethanol[24a] δ 7.36 (m, 4H, Ph), 7.29 (m, 1H, Ph), 4.91 (q, *J* = 6.4 Hz, 1H, CH-OH), 1.51 (d, *J* = 6.6 Hz, 3H, CH_3)

Attempt to reduce *trans*-phenyl-propylene oxide in 1,4-dioxane:

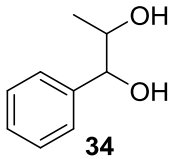


34

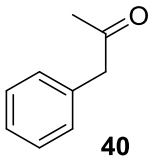
According to general procedure 2 $B(C_6F_5)_3$ (59 mg / 0.1 mmol) and **29e** (1.6 mmol / 210 mg) were dissolved in 5 mL 1,4-dioxane and heated to 70 °C for 19 h at 55 bar H_2 to yield 14 % of phenyl-1,2-propanediol (**34**) based on NMR integration.

Identified compounds in crude ^{1}H NMR (C_6D_6, 400 MHz):
29e δ 7.07 (m, 5H), 3.23 (d, *J* = 2 Hz, 1H), 2.61 (qd, *J* = 5 Hz, 2 Hz, 1H), 1.01 (d, *J* = 5 Hz, 3H)
34 δ 7.03 (m, 5H, Ph), 4.45 (br s, 1H, CH-OH), 4.00 (d, *J* = 10.35 Hz, 1H, CH-OH), 0.83 (d, *J* = 6 Hz, 3H, CH_3)

Attempt to reduce *trans*-phenyl-propylene oxide in diethylether:



34

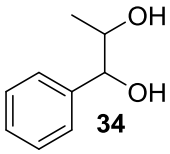


40

According to general procedure 2 $B(C_6F_5)_3$ (126 mg / 0.3 mmol) and **29e** (2.5 mmol / 333 mg) were dissolved in 5 mL diethylether and heated to 70 °C for 21 h at 62 bar H_2 to yield 23 % of phenyl-1,2-propanediol (**34**) and 7 % phenylacetone (**40**) based on NMR integration.

Identified compounds in crude ^{1}H NMR (C_6D_6, 400 MHz):
29e δ 7.04 (m, 5H), 3.23 (d, *J* =1.7 Hz, 1H), 2.61 (m, 1H), 1.01 (d, *J* = 5 Hz, 3H)
34 δ 6.93 (m, 5H), 4.45 (s, 1H), 4.00 (d, *J* = 10.4 Hz, 1H), 0.83 (d, *J* = 6.2 Hz, 3H)
40[82] δ 1.51 (s, 3H, CH_3), 3.14 (s, 2H, CH_2), aromatic signals under signals of **29e**

Attempt to reduce *trans*-phenyl-propylene oxide in toluene:



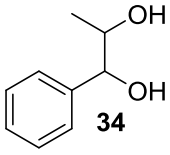
34

According to general procedure 2 $B(C_6F_5)_3$ (54 mg / 0.1 mmol) and **29e** (1 mmol / 134 mg) were dissolved in 5 mL toluene and heated to 70 °C for 19 h at 60 bar H_2. The crude mixture was further purified via column chromatography (hexane/EtOAc 10:1, r_f: 0.26) to obtain phenyl-1,2-propanediol (**34**) in 24 % (36 mg / 0.2 mmol) isolated yield.

^{1}H NMR of isolated compound (C_6D_6, 400 MHz):
34 δ 7.13 (m, 2H), 7.03 (t, *J* = 7.18 Hz, 2H), 6.96 (t, *J* = 7.18 Hz, 1H), 4.47 (br s, 1 H), 4.00 (dd, *J* = 11.2 Hz, 3.8 Hz, 1H), 0.85 (d, *J*= 6.2 Hz, 3H)

^{13}C NMR of isolated compound (C_6D_6, 100 MHz):
34 δ 139 (Ph), 128.8 (Ph), 128.2 (Ph), 127.3 (Ph), 67 (CHOH), 51 (CHOH), 22 (CH_3)
^{1}H NMR spectra before and after H_2 exposure can be found in Appendix F.

Attempt to reduce *trans*-phenyl-propylene oxide in dichloromethane:

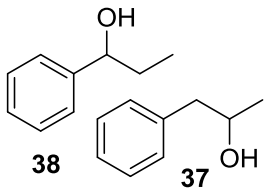


34

According to general procedure 2 $B(C_6F_5)_3$ (51.8 mg / 0.1 mmol) and **29e** (1.0 mmol / 136 mg) were dissolved in 5 mL CH_2Cl_2 and heated to 70 °C for 22 h at 62 bar H_2 to yield 30 % of phenyl-1,2-propanediol (**34**) based on NMR integration.

Identified compounds in crude ^{1}H NMR (C_6D_6, 400 MHz):
29e δ 7.1 (m, 5H), 3.23 (d, *J* = 2 Hz, 1H), 2.61 (qd, *J* = 2 Hz, 5 Hz, 1H), 1.01 (d, *J* = 5 Hz, 3H)
34 δ 6.94 (m, 5H), 4.45 (s, 1H), 4.00 (d, *J* = 10.6 Hz, 1H), 0.83 (d, *J* = 6 Hz, 3H)

Attempt to reduce *trans*-phenyl-propylene oxide in d_8-toluene:

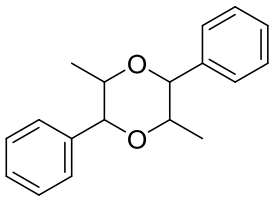


38 **37**

According to general procedure 3 $B(C_6F_5)_3$ (6 mg / 0.01 mmol) and 0.4 mL of a 0.25 M solution of **29e** (50 mg) in d_8-toluene (1.5 mL) were heated to 100 °C for 44 h at 4.8 bar H_2 to yield 0 % of 1-pheny-ethanol or 3-phenyl-2-propanol.

Identified compound in ^{1}H NMR after H_2 exposure (C_7D_8, 400 MHz):
29e δ 1.05 (d, *J* = 5.15 Hz, 3H), 2.58 (dq, *J* = 1.95 Hz, 5.1 Hz, 1H), 3.20 (d, *J* = 1.94 Hz, 1H), aromatic area under solvent peak
H_2 δ 4.49 (s)
35 δ 0.88 (d, *J* = 5.9 Hz, 3 H), 4.54 (d, *J* = 10.5 Hz, 1H), 5.34 (m, 1H), aromatic area under solvent peak
^{1}H NMR spectra before and after H_2 exposure can be found in Appendix H.

6.5.Dimerization of 29e to 2,5-dimethyl-3,6-diphenyl-1,4-dioxane



35

In a vial in the GB $B(C_6F_5)_3$ (78.5 mg / 0.15 mmol) and **29e** (18.2 mg / 0.13 mmol) were dissolved in d_8-toluene (0.8 mL). The homogeneous mixture was split and injected into 2 J-Young tubes by syringe. Mixture 1 was analyzed by ^1H, ^{19}F and ^{11}B NMR upon which it was degassed (three freeze-thaw-pump cycles), charged with H_2 gas (4.8 bar) and heated for 64 h at 80 °C. Mixture 2 was heated at 80 °C for 64 h and served as the blank experiment. Both mixtures were analyzed again by ^1H, ^{19}F and ^{11}B NMR. Also COSY, HMQC and APT spectra were obtained from mixture 1. Full conversion of **29e** to **35** was determined for both mixtures. A mass spectrum of the crude mixture was obtained.

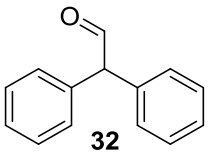
ESI-MS [**35** (pyridine)]$^+$ m/z 348.1928 g/mol (calc. 348.1964 g/mol)

Identified compound in ^1H NMR (C_7D_8, 400 MHz):
35 δ 1.26 (d, *J* = 6 Hz, 6H, CH_3), 4.52 (d, *J* = 10.4 Hz, 2H, OCH), 5.33(m, 2H, OCH), 7.0 (Ph, underneath toluene signals)
C_6F_5H[44] δ 5.81 (m, 1H)

Identified compound in ^{13}C NMR (C_7D_8, 100 MHz):
35 δ 21.39 (CH_3), 49.56 (OCH), 77.35 (OCH), 127.9 (Ph), 128.2 (Ph), 129 (Ph), 137.3 (Ph)
All NMR spectra after H_2 exposure can be found in Appendix G.

6.6. Attempted Tandem Isomerization – Hydrogenation of Stilbene Oxide

Attempted one-pot tandem isomerization/hydrogenation of stilbene oxide to 2,2-diphenyl ethanol

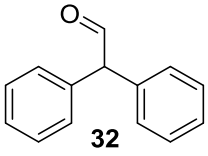


32

An additional stirring rod and 298 mg 4 Å molecular sieves were loaded into an autoclave. The autoclave was then preheated and flushed with H_2. According to general procedure 2 $B(C_6F_5)_3$ (12.6 mg / 0.025 mmol) and **29c** (0.5 mmol / 98.4 mg) were dissolved in 5 mL toluene and heated to 70 °C for 18.5 h at 42 bar H_2 to obtain 2,2-diphenylacetaldehyde (**32**) in quantitative yield.

Identified compound in crude ^1H NMR (C_6D_6, 400 MHz):
32 δ 4.46 (m, 1H), 7.01 (m, 10H) 9.57 (m, 1H)

Isomerization of stilbene oxide to 2,2-diphenylacetaldehyde

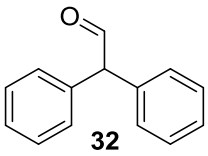


32

In a vial in the GB $B(C_6F_5)_3$ (25.8 mg / 0.05 mmol) and **29c** (195.5 mg / 1 mmol) were dissolved in 1 mL toluene and stirred for 15 minutes. The mixture (0.4 mL) was added into a J-Young NMR tube together with an internal standard to be analyzed by ^1H NMR. 2,2-diphenylacetaldehyde (**32**) was obtained in 38 % yield based on NMR integration.

Identified compound in crude ^1H NMR (C_6D_6, 400 MHz):
1,3,5-trimethoxybenzene δ 3.28 (s, 9H), 6.20 (s, 3H)
32 δ 4.39 (d, *J* = 2.56 Hz, 1H), 9.53 (d, *J* = 2.6 Hz, 1H), aromatic area underneath toluene

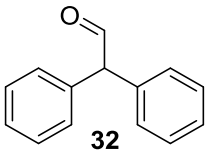
29c δ 3.53 (s, 2H) aromatic area underneath toluene



In a vial in the GB $B(C_6F_5)_3$ (76.1 mg / 0.15 mmol) and **29c** (195 mg / 1 mmol) were dissolved in 1 mL toluene and stirred for 15 minutes. The mixture (0.4 mL) was added into a J-Young NMR tube together with an internal standard to be analyzed by ^{1}H NMR. Full conversion to 2,2-diphenylacetaldehyde (**32**) was determined based on NMR integration.

Identified compound in crude ^{1}H NMR (C_6D_6, 400 MHz):
1,3,5-trimethoxybenzene δ 3.28 (s, 9H), 6.20 (s, 3H)
32 δ 4.42 (d, *J* = 2.6 Hz, 1H), 9.51 (d, *J* = 2.6 Hz, 1H), aromatic area underneath toluene

<u>Attempted one-pot tandem isomerization/hydrogenation of stilbene oxide to 2,2-diphenyl ethanol – 15 mol% LA</u>

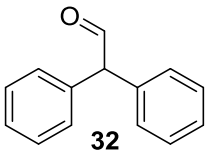


An additional stirring rod and 401 mg 4 Å molecular sieves were loaded into an autoclave. The autoclave was then preheated and flushed with H_2. According to general procedure 2 $B(C_6F_5)_3$ (77.2 mg / 0.15 mmol) and **29c** (1 mmol / 197.7 mg) were dissolved in 2 mL toluene and stirred for 15 minutes. The mixture was injected into the autoclave and heated to 60 °C for 19.5 h at 58 bar H_2 to yield 95 % of 2,2-phenylacetaldehyde (**32**) based on NMR integration.

Identified compound in crude ^{1}H NMR (C_6D_6, 400 MHz):
1,3,5-trimethoxybenzene δ 3.28 (s, 9H), 6.20 (s, 3H)
32 δ 4.42 (d, *J* = 2.6 Hz, 1H), 9.55 (d, *J* = 2.6 Hz, 1H), aromatic area underneath toluene
C_6F_5H[44] δ 5.57 (m, 1H)

Identified compound in crude ^{19}F NMR (C_6D_6, 376 MHz):
C_6F_5H[44] δ -139 (dt, *J* = 22.8 Hz, 8.7 Hz, 2F), -154.22 (t, *J* = 20.5 Hz, 1F), -162.44 (tt, *J* = 21 Hz, 7.8 Hz, 2F)

<u>Attempted two-pot tandem isomerization/hydrogenation of stilbene oxide to 2,2-diphenyl ethanol - extra LA</u>

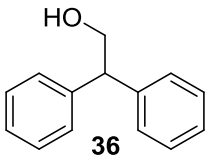


An additional stirring rod and 195 mg 4 Å molecular sieves were loaded into an autoclave. The autoclave was then preheated and flushed with H_2. According to general procedure 2 $B(C_6F_5)_3$ (77.5 mg / 0.15 mmol) and **29c** (1 mmol / 196 mg) were dissolved in 2 mL toluene and stirred for 15 minutes. Again $B(C_6F_5)_3$ (77.9 mg / 0.15 mmol) dissolved in 1 mL toluene was added. The mixture was injected into the autoclave and heated to 70 °C for 23.5 h at 59 bar H_2 to obtain 2,2-phenylacetaldehyde (**32**) in quantitative yield.

Identified compound in crude ^{1}H NMR (C_6D_6, 400 MHz):
1,3,5-trimethoxybenzene δ 3.28 (s, 9H), 6.20 (s, 3H)
32 δ 4.43 (d, *J* = 2.6 Hz, 1H), 9.57 (d, *J* = 2.6 Hz, 1H), aromatic area underneath toluene
C_6F_5H[44] δ 5.87 (m, 1H)

Identified compound in crude ^{19}F NMR (C_6D_6, 376 MHz):
C_6F_5H[44] δ -139 (dt, *J* = 23 Hz, 8.8 Hz, 2F), -154.2 (t, *J* = 20 Hz, 1F), -162.45 (tt, *J* = 21 Hz, 8 Hz, 2F)

Attempted reduction of 2,2-diphenyl acetaldehyde to 2,2-diphenyl ethanol



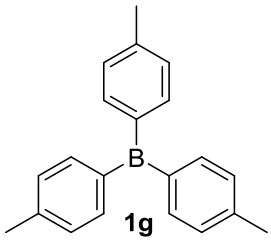
36

An additional stirring rod and 125 mg 4 Å molecular sieves were loaded into an autoclave. The autoclave was then preheated and flushed with H_2. According to general procedure 2 $B(C_6F_5)_3$ (79 mg / 0.15 mmol) and 2,2-diphenylacetaldehyde (1 mmol / 194 mg) were dissolved in 3 mL toluene and heated to 70 °C for 21.5 h at 57 bar H_2 to yield 0 % of 2,2-diphenyl ethanol (**36**).

Identified compound in crude ^{1}H NMR (C_6D_6, 400 MHz):
1,3,5-trimethoxybenzene δ 3.28 (s, 9H), 6.20 (s, 3H)
32 δ 4.42 (d, *J* = 2.6 Hz, 1H), 9.57 (d, *J* = 2.6 Hz, 1H), aromatic area underneath toluene
C_6F_5H[44] δ 5.86 (m, 1H)

Identified compound in crude ^{19}F NMR (C_6D_6, 376 MHz):
C_6F_5H[44] δ -139 (dt, *J* = 23 Hz, 8.8 Hz, 2F), -154 (t, *J* = 20 Hz, 1F), -162 (m, 2F)

6.7. Synthesis of tris-*para*-toluenebor ane: $B(tol)_3$



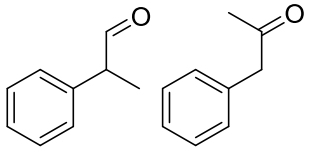
1g

To a suspension of magnesium (313.5 mg / 12.9 mmol) in 5 mL dry Et_2O in a reflux set up under nitrogen atmosphere a few droplets of an initiator solution, containing I_2 (one bead) and 1,2-dibromoethane (4 droplets) in dry Et_2O (2 mL), was added via a droplet funnel. Bromotoluene (2057 mg / 12 mmol) dissolved in 10 mL dry Et_2O was added drop wise to the suspension inducing a color change to dark green. The reaction mixture was refluxed for 1 h.
The mixture was transferred into a solution of 48 % $BF_3.OEt_2$ (0.74 mL / 3 mmol) in 15 mL dry EtO_2. The reaction mixture turned light yellow and was allowed to stir overnight at room temperature. The mixture became white over night and was filtered under N_2 atmosphere. Evaporation of the solvent of the filtrate resulted in a red-brown powder, which was dissolved in 13 mL dry toluene and stirred overnight. The mixture was filtered again under N_2 atmosphere. Toluene was removed by evaporation under vacuum to obtain $B(tol)_3$ in 60 % yield (510 mg / 1.8 mmol, based on BF_3). The resulting white-brown solid was analysis with ^{1}H, ^{13}C and ^{11}B NMR and stored in the GB. NMR data was according to literature.[83]

Identified compound in ^{1}H NMR (C_6D_6, 400 MHz):
δ 7.71 (d, *J* = 7.84 Hz, 6H, Ph), 7.11 (d, *J*= 7.84 Hz, 6H, Ph), 2.14 (s, 9H, CH_3)
Identified compound in ^{11}B NMR (C_6D_6, 128 MHz):
δ 65.4 (s)
Identified compound in ^{13}C NMR (C_6D_6, 100 MHz):
δ 141 (Ph), 140 (Ph), 138 (Ph), 128 (Ph), 21(CH_3)

6.8. Hydrogenation attempts with $B(tol)_3$

Stoichiometric reduction attempt of **29e** to 1-phenyl propanol or 3-phenyl-2-propanol:



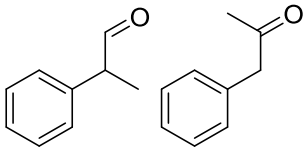
39 **40**

According to general procedure 3 $B(C_7H_7)_3$ (28.5 mg / 0.1 mmol) was dissolved in 0.4 mL of a 0.25 M solution of **29e** (50 mg) in d_8-toluene (1.5 mL) and heated to 100 °C for 18.5 h at 4.8 bar H_2 to yield 59 % 2-phenyl-propanal (**39**) and 34 % phenylacetone (**40**) based on NMR integration).

Identified compound in ^1H NMR after H_2 exposure (C_7D_8, 400 MHz):
29e δ 1.05 (d, *J* = 4.9 Hz, 3H), 2.58 (qd, *J* = 1.96 Hz, 5.1 Hz, 1H), 3.20 (d, *J* = 1.88 Hz, 1H), aromatic area under solvent peak
1g δ 2.18 (s, 9H), 7.09 (m, 6H), 7.65 (m, 6H)
39[84] δ 9.27 (d, 1H, CHO), 2.97 (q, *J* = 7.1 Hz, 1H, CH), 1.12 (m, 3H, CH_3), aromatic area under solvent peak
40[82] δ 3.15 (s, 2H), 1.61 (s, 3H), aromatic area under solvent peak
H_2 δ 4.48 (s)

Identified compound in ^{11}B NMR after H_2 exposure (C_7D_8, 128 MHz):
1g δ 65 (s)
^1H and ^{11}B NMR spectra can be found in Appendix I.

Reduction attempt of **29e** to 1-phenyl propanol or 3-phenyl-2-propanol with 10 mol% **1g**

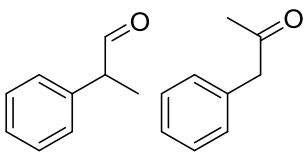


39 **40**

According to general procedure 3 $B(C_7H_7)_3$ (2.8 mg / 0.01 mmol) was dissolved in 0.4 mL of a 0.25 M solution of **29e** (50 mg) in d_8-toluene (1.5 mL) and heated to 100 °C for 90 h at 4.8 bar H_2 to yield 33 % 2-phenyl-propanal (**39**) and 10 % phenylacetone (**40**) based on NMR integration.

Identified compound in ^1H NMR after H_2 exposure (C_7D_8, 400 MHz):
29e δ 3.22 (d, *J* = 1.95 Hz, 1H), 2.60 (qd, *J* = 1.9 Hz, 5.2 Hz, 1H), 1.07 (d, *J* = 5.2 Hz, 3H) aromatic area under solvent peak
39[84] δ 9.29 (s, 1H), 2.98 (q, *J* = 7 Hz, 1H), 1.14 (d, *J* = 7.09 Hz, 3H), aromatic area under solvent peak
40[82] δ 3.17 (s, 2H), 1.63 (s, 3H), aromatic area under solvent peak

Reduction attempt of **29e** to 1-phenyl propanol or 3-phenyl-2-propanol with 20 mol% **1g**



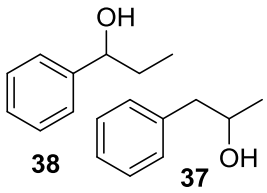
39 **40**

According to general procedure 3 $B(C_7H_7)_3$ (5.7 mg / 0.02 mmol) was dissolved in 0.4 mL of a 0.25 M solution of **29e** (50 mg) in d_8-toluene (1.5 mL) and heated to 100 °C for 22.5 h at 4.8 bar H_2 to yield 38 % 2-phenyl-propanal (**39**) and 16 % phenylacetone (**40**) based on NMR integration.

Identified compound in ^1H NMR after H_2 exposure (C_7D_8, 400 MHz):
H_2 δ 4.48
29e δ 3.18 (d, *J* = Hz, 1H), 2.58 (qd, *J* = Hz, 1H), 1.05 (d, *J* = Hz, 3H), aromatic area under solvent peak

39[84] δ 9.27 (s, 1H), 2.97 (d, *J*= 7.05 Hz, 1H), 1.12 (d, *J* = 6.96 Hz, 3H), aromatic area under solvent peak

Reduction attempt of **29e** to 1-phenyl propanol or 3-phenyl-2-propanol in 1,4-dioxane



According to general procedure 1 $B(C_7H_7)_3$ (2.7 mg / 0.01 mmol) was dissolved in 0.4 mL of a 0.25 M solution of **29e** (50 mg) in 1,4-dioxane (1.5 mL) and heated to 100 °C for 63 h at 4.8 bar H_2 to yield 0 % 1-phenyl propanol (**38**) or 3-phenyl-2-propanol (**37**) based on NMR integration.

Identified compound in ^{1}H NMR after H_2 exposure (C_6D_6, 400 MHz):
29e δ 7.73 (m, 2H), 7.67 (m, 2H), 3.40 (m, 1H), 1.82 (d, *J* = 5.23 Hz, 3H), 1H under dioxane signal
1,3,5-trimethoxybenzene δ 3.27 (m, 9H), 6.21 (m, 3H)

6.9. Hydrogenation attempts with $BMes(C_6F_5)_2$

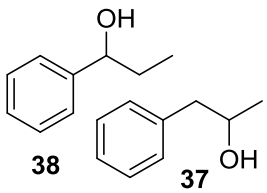
Investigation into the possible adduct formation of **29e** and **1c**:

In a vial in the GB **1c** (52 mg / 0.110 mmol) and **29e** (17 mg / 0.126 mmol) were dissolved in 0.6 mL C_6D_6 and injected into a J-Young tube by syringe. The mixture was analyzed by ^{1}H and ^{19}F NMR.

Identified compound in ^{1}H NMR (C_6D_6, 400 MHz):
29e δ 7.09 (m, 5H), 3.23 (d, *J* = 1.8 Hz, 1H), 2.61 (qd, *J* = 5.2 Hz, 1.9 Hz, 1H), 1.01 (d, *J* = 5.2 Hz, 3H)
1c[15] δ 1.96 (s, 6H, *ortho*-CH_3), 2.08 (s, 3H, *para*-CH_3), 6.65 (s, 2H, Ph)

Identified compound in ^{19}F NMR (C_6D_6, 376 MHz):
1c[15] δ -129.25 (m, 2F, *ortho*-Ph), -144.89 (tt, *J* = 20.7 Hz, 5.5 Hz, 1F, *para*-Ph), -160.80 (m, 2F, *meta*-Ph)
^{1}H and ^{19}F NMR spectra can be found in Appendix J.

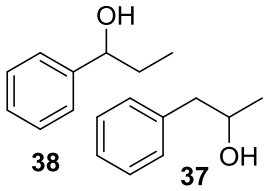
Hydrogenation attempt of **29e** catalyzed by FLP $B(C_6F_5)_2Mes$/**29e** (no extra LB):



According to general procedure 2 $B(C_6F_5)_2Mes$ (50 mg / 0.12 mmol) and **29e** (0.98 mmol / 132 mg) were dissolved in 6 mL toluene and pressurized with 60 bar H_2. The mixture was heated to 100 °C for 72 h to yield 0 % of 1-phenylpropanol (**38**) or 3-phenyl-2-propanol (**37**) based on NMR integration.

Identified compound in crude ^{1}H NMR (C_6D_6, 400 MHz):
29e δ 7.09 (m, 5H), 3.23 (m, 1H), 2.61 (qd, *J* = 5 Hz, 2 Hz, 1H), 1.01 (d, *J* = 5 Hz, 3H)
34 δ 0.83 (d, *J* = 6.2 Hz, 3H), 4.00 (d, *J* = 10.4 Hz, 1H), 4.5 (m, 1H), aromatic area under solvent peak
39[84] δ 9.29 (s, 1H), 2.96 (q, *J* = 7.2 Hz, 1H), 1.11 (d, *J* = 7 Hz, 3H), aromatic area under solvent peak
40[82] δ 3.14 (d, *J* = 1.7 Hz, 1H), 1.58 (s, 3H), aromatic area under solvent peak
Mesitylene δ 2.12 (s, 3H, Ph), 6.68 (s, 9H, CH_3)
^{1}H NMR spectrum can be found in Appendix K.

Hydrogenation attempt of **29e** catalyzed by FLP $B(C_6F_5)_2Mes$/DABCO:

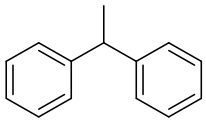


According to general procedure 2 $B(C_6F_5)_2Mes$ (23.6 mg / 0.05 mmol), DABCO (5.2 mg / 0.05 mmol) and **29e** (0.5 mmol / 69 mg) were dissolved in 5 mL toluene and heated to 70 °C for 18.5 h at 50 bar H_2 to yield 0 % of 1-phenylpropanol (**38**) or 3-phenyl-2-propanol (**37**).

Identified compound in crude ^1H NMR (C_6D_6, 400 MHz):
29e δ 1.01 (dd, *J*= 5.1 Hz, 3H), 2.61 (m, 1H), 3.23 (br s, 1H), 7.01 (m, 5H)
H_2 δ 4.65 (s)
^1H NMR spectrum can be found in Appendix L.

6.10. Attempted Transfer Hydrogenation of Epoxides

TH of 1,1-diphenylethylene to 1,1-diphenylethane:

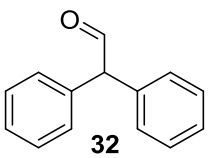


In a vial in the GB $B(C_6F_5)_3$ (7.9 mg, 0.015 mmol) and 1,3,5-trimethyl-2,4-cyclohexadiene (101 mg, 0.828 mmol, 5.5 eq.) were dissolved in 0.1 mL d-CD_2Cl_2 and stirred for 5 min. In a second vial in the GB 1,1-diphenylethylene (27.1 mg, 0.15 mmol) was dissolved in 0.4 mL d-CD_2Cl_2. This solution was added to the first solution, which upon addition turned yellow. The reaction mixture was left to stir for 6 h at room temperature in the GB. Over time the solution turned purple. The crude reaction mixture was analyzed by ^1H and ^{11}B NMR as well as GC-MS. Full conversion to 1,1-diphenylethane was detected based on NMR integration. Full conversion to mesitylene was detected based on GC-MS analysis.

GC-MS: m/z 120.0265 (Mesitylene), 182.1591 (1,1-diphenylethane)

Identified compound in ^1H NMR (CD_2Cl_2, 400 MHz):
1,1-diphenylethane[50] δ 1.78 (d, *J* = 7.30 Hz, 3H, CH_3), 4.28 (q, *J* = 7.30 Hz, 1H, CH), 7.31 (t, *J* = 7.06 Hz, 2H, Ph), 7.39 (m, 8H, Ph)
Mesitylene δ 2.42 (s, 9 H), 6.94 (s, 3H)

Attempted TH of **29c** to 1,2-diphenyl ethanol:

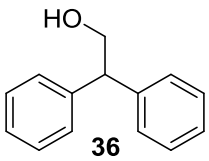


In a vial in the GB $B(C_6F_5)_3$ (8.1 mg, 0.015 mmol) and 1,3,5-trimethyl-2,4-cyclohexadiene (100 mg, 0.820 mmol, 5.5 eq.) were dissolved in 0.1 mL d-CD_2Cl_2 and stirred for 5 min. In a second vial in the GB **29c** (29.3 mg, 0.15 mmol) was dissolved in 0.4 mL d-CD_2Cl_2. This solution was added to the first solution. The reaction mixture was left to stir for 6 h at room temperature in the GB. The crude reaction mixture was analyzed by ^1H and ^{11}B NMR as well as GC-MS. Full conversion to 2,2-diphenylacetaldehyde (**32**) was detected based on NMR integration. 91 % conversion to mesitylene was detected based on GC-MS analysis.

GC-MS: m/z 120.1110 (Mesitylene), 122.0037 (diene), 196.1161 (**32**)

Identified compound in ^{1}H NMR (CD_2Cl_2, 400 MHz):
32 δ 4.99 (d, *J* = 2 Hz, 1H), 7.27 (m, 4H), 7.39 (m, 2H), 7.44 (m, 4H), 9.95 (d, *J* = 2 Hz, 1H)
Mesitylene δ 2.32 (s, 9H), 6.85 (s, 3H)

Attempted TH of 2,2-diphenylacetaldehyde to 1,2-diphenyl ethanol:



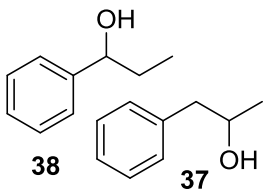
36

In a vial in the GB $B(C_6F_5)_3$ (4 mg, 0.007 mmol) and 1,3,5-trimethyl-2,4-cyclohexadiene (50 mg, 0.41 mmol, 2.75 eq.) were dissolved in 0.4 mL CD_2Cl_2 and stirred for 5 min. In a second vial in the GB 2,2-diphenylacetaldehyde (**32**, 12.6 mg, 0.065 mmol) was dissolved in 0.4 mL CD_2Cl_2. This solution was added to the first solution. The reaction mixture was left to stir for 6 h at room temperature in the GB. The crude reaction mixture was analyzed by ^{1}H and ^{11}B NMR as well as GC-MS. 0 % conversion to 1,2-diphenyl ethanol (**36**) was detected based on NMR integration. 99.1 % conversion to mesitylene was detected based on GC-MS analysis.

GC-MS: m/z 120.0265 (Mesitylene), 122.1782 (diene), 196.1161(**32**)

Identified compound in ^{1}H NMR (CD_2Cl_2, 400 MHz):
32 δ 4.97 (d, *J* = 1.9 Hz, 1H), 7.32 (m, 4H), 7.41 (m, 2H), 7.47 (m, 4H), 10.03 (d, *J* = 2.1 Hz, 1H)
Mesitylene δ 2.37 (s, 3H), 6.90 (s, 9H)

Attempted TH of **29e** to 1-phenyl propanol or 3-phenyl-2-propanol:



38 **37**

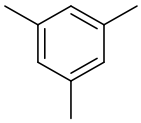
In a vial in the GB $B(C_6F_5)_3$ (7.7 mg, 0.015 mmol) and 1,3,5-trimethyl-2,4-cyclohexadiene (100 mg, 0.828 mmol, 5.5 eq.) were dissolved in 0.2 mL CH_2Cl_2. This mixture was transferred into a J-Young tube. In a second vial in the GB **29e** (20.1 mg, 0.15 mmol) was dissolved in 0.2 mL CH_2Cl_2. This solution was added to the first solution in the J-Young tube. Upon addition the solution turned yellow and gas bubbles evaporated. An internal standard (sealed capillary filled with 1,3,5-methoxybenzene dissolved in C_6D_6, 0.26 M) was added. The reaction mixture was analyzed by ^{1}H, ^{19}F and ^{11}B NMR. After that the reaction mixture was left overnight at room temperature without special preparations to mix the mixture. The crude reaction mixture was analyzed by ^{1}H, ^{13}C and ^{11}B NMR. 0 % conversion to 1-phenyl propanol (**37**) or 3-phenyl-2-propanol (**38**) was detected based on NMR integration. Mesitylene was obtained in 40 % yield based on NMR integration.

Identified compound in ^{1}H NMR (C_6D_6, 400 MHz):
1,3,5-trimethyl-2,4-cyclohexadiene[85] δ 1.04 (d, *J* = 7.4 Hz, 3H, CH_3), 1.72 (s, 6H, 2 x CH_3), 2.45 (d, *J* = 7.6 Hz, 2H, CH=C), 2.77 (br s, 1H, CH-CH_3), 5.36 (s, 2H, CH_2)
Mesitylene δ 2.29 (s, 9H), 6.81 (s, 3H)
29e δ 1.45 (d, *J* = 5.2 Hz, 3H), 3.01 (qd, *J* = 5.2 Hz, 1.9 Hz, 1H), 3.55 (d, *J* = 1.9 Hz, 1H), 7.32 (m, 5H)
1,3,5-trimethoxybenzene δ 6.20 (s, 9H), 3.28 (s, 3H)

Identified compound in ^{13}C NMR (C_6D_6, 100 MHz):
29e δ 17.6, 58.79, 59.20, 125, 127, 128, 138
1,3,5-trimethoxybenzene δ 93.11, 162
Mesitylene δ 20.87, 129, 137

1,3,5-trimethyl-2,4-cyclohexadiene[85] δ 22.7 (CH_3), 23.2 (2xCH_3), 32.3 (CH-CH_3), 35.7 (CH_2), 125 (CH), 129 (C-CH_3)

Analysis of a stoichiometric mixture of $B(C_6F_5)_3$ and 1,3,5-trimethyl-2,4-cyclohexadiene:



In a vial in the GB $B(C_6F_5)_3$ (4 mg / 0.007 mmol) and 1,3,5-trimethyl-2,4-cyclohexadiene (50 mg / 0.41 mmol) were dissolved in 0.4 mL d-CD_2Cl_2 and stirred for 15 min at room temperature in the GB. It was then analyzed by ^1H and ^{11}B NMR as well as GC-MS. Full conversion to mesitylene was detected based on NMR integration.

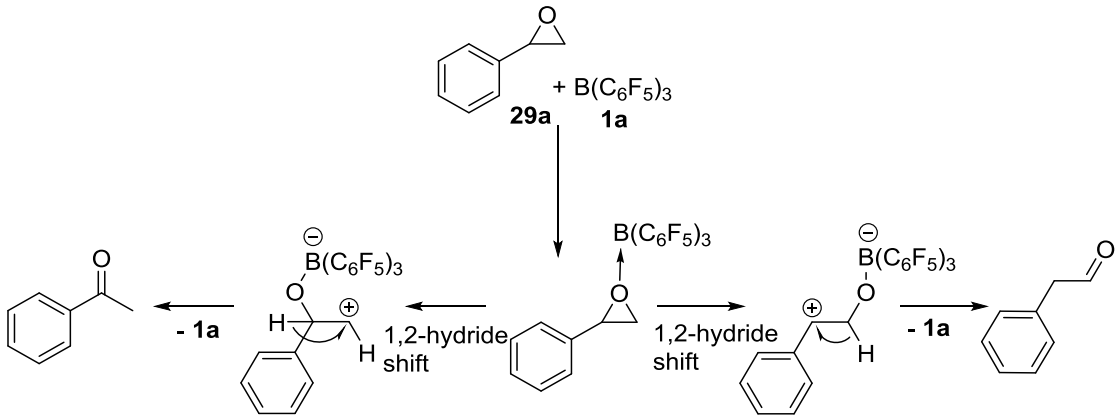
GC-MS: m/z 120.0937(Mesitylene)

Identified compound in ^1H NMR (C_6D_6, 400 MHz):
Mesitylene δ 2.34 (s, 9H), 6.87 (s, 3H)

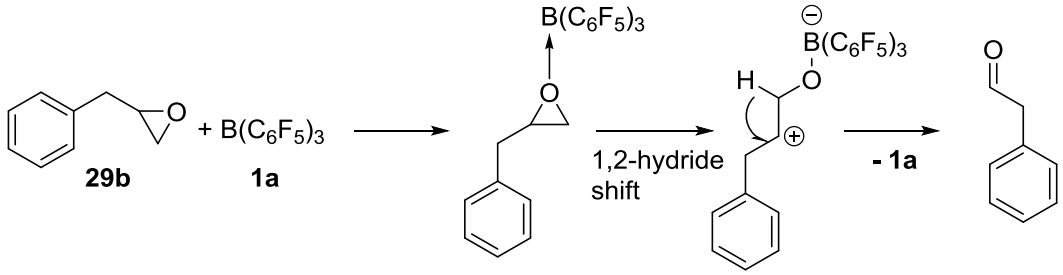
All ^{11}B NMR spectra of the attempted TH reactions can be found in Appendix M.

7. Appendix

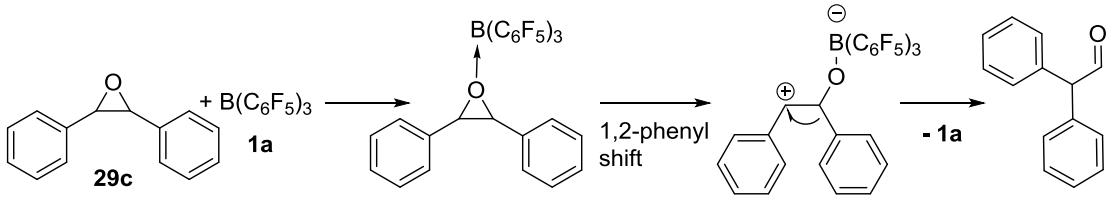
Appendix A



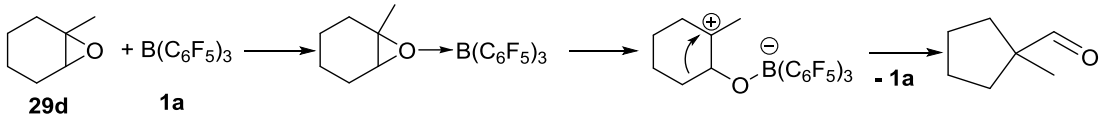
Scheme 68: Isomerization mechanism of styrene oxide (29a)



Scheme 69: Isomerization mechanism of (2,3-epoxypropyl)benzene (29b)



Scheme 70: Isomerization mechanism of Stilbene oxide (29c)



Scheme 71: Isomerization mechanism of 1-methyl-cyclohexane oxide (29d)

Appendix B

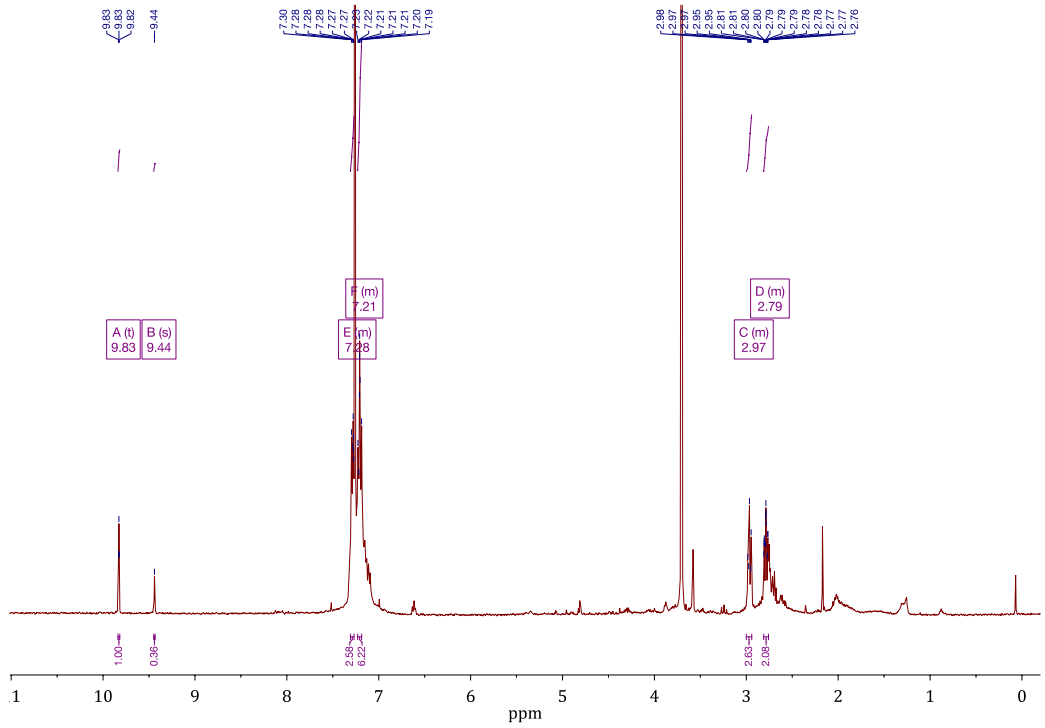


Figure 15: Crude ^{1}H NMR of 31.

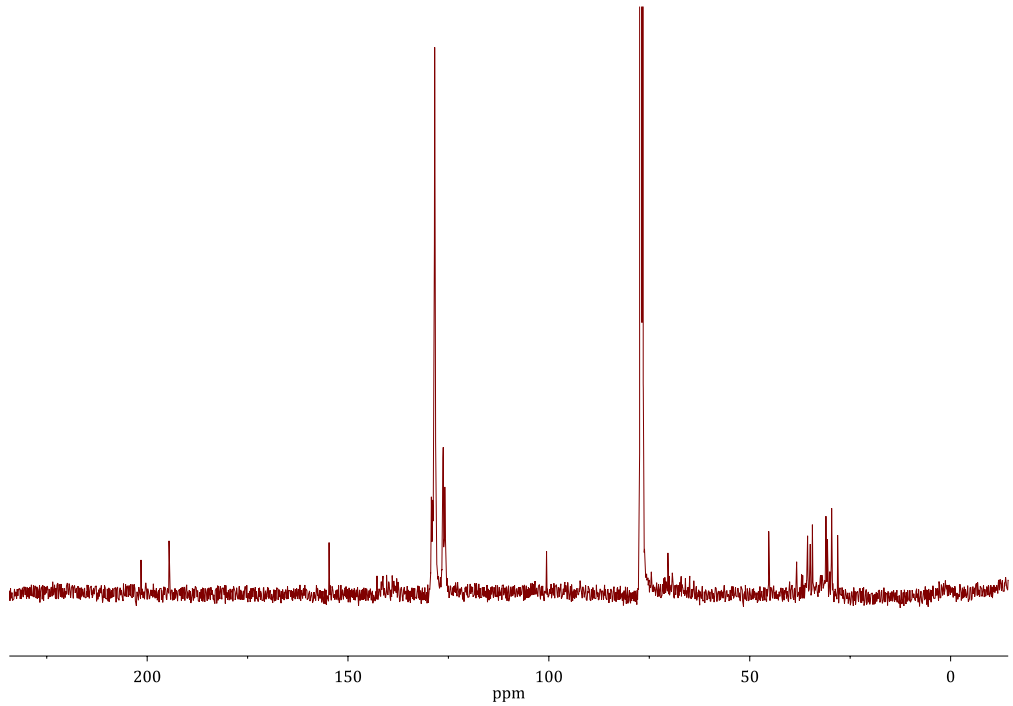


Figure 16: Crude ^{13}C NMR of 31.

Appendix C

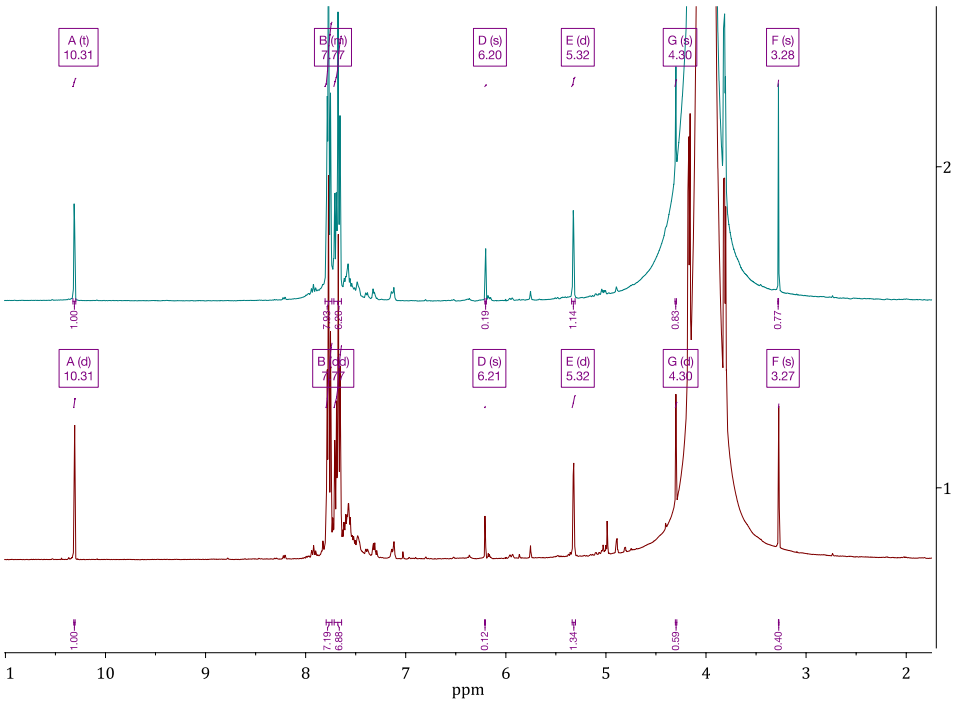


Figure 17: ^{1}H NMR of reaction 29c to 32 before (upper) and after (lower) exposure to H_2.

Appendix D

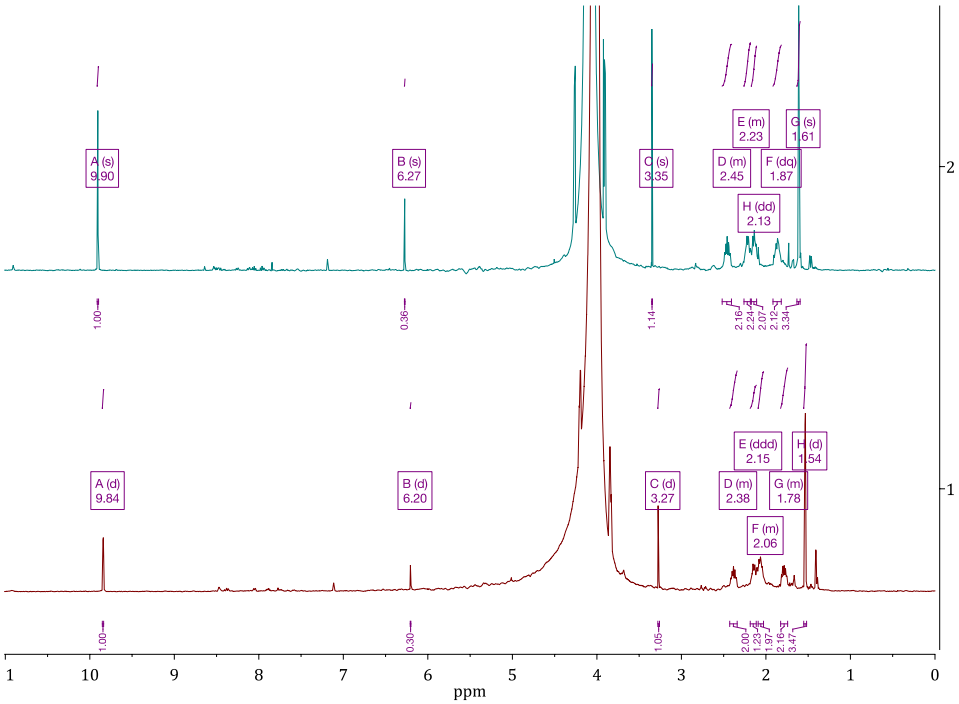


Figure 18: Crude ^{1}H NMR of reaction 29 d to 33 before (upper NMR) and after (lower NMR) exposure to H_2.

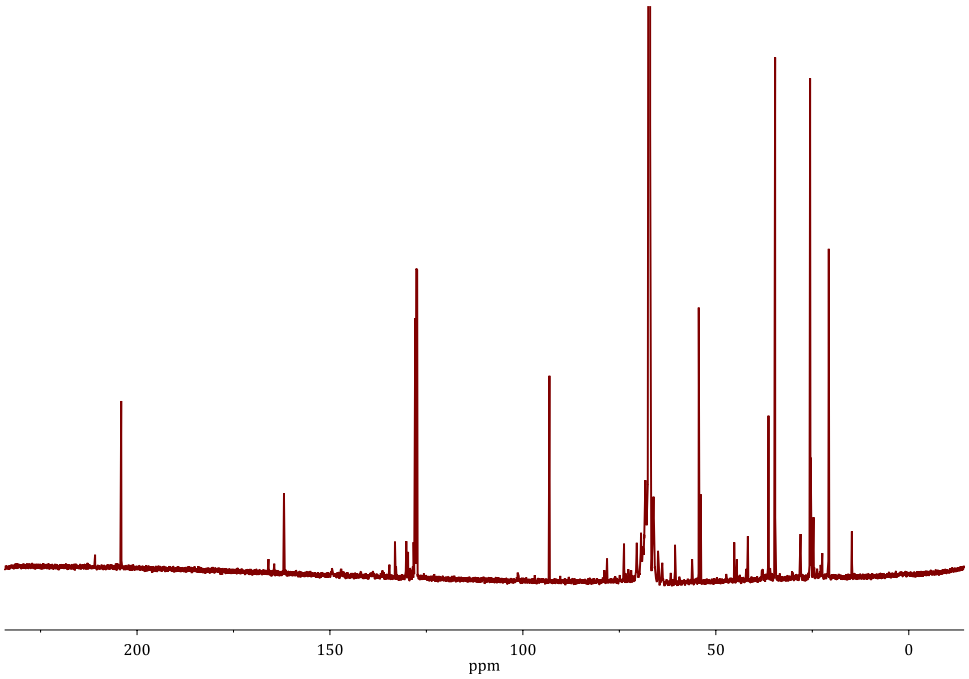


Figure 19: Crude ^{13}C NMR of 33.

Appendix E

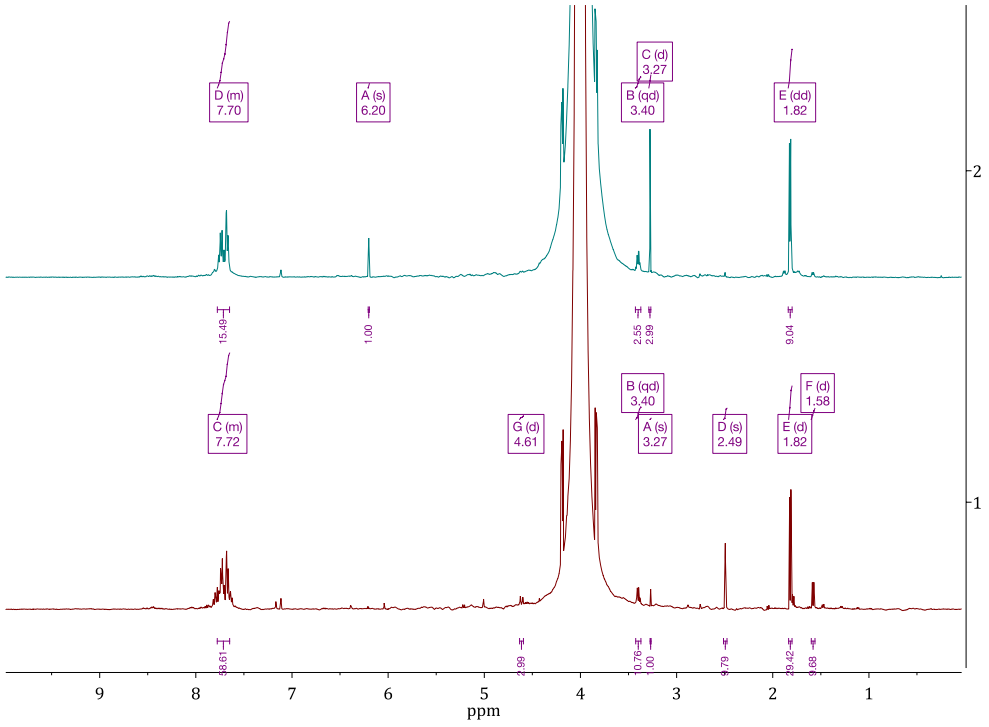


Figure 20: ^{1}H NMR of reaction 29e to 34 before (upper) and after (lower) exposure to H_2.

Appendix F

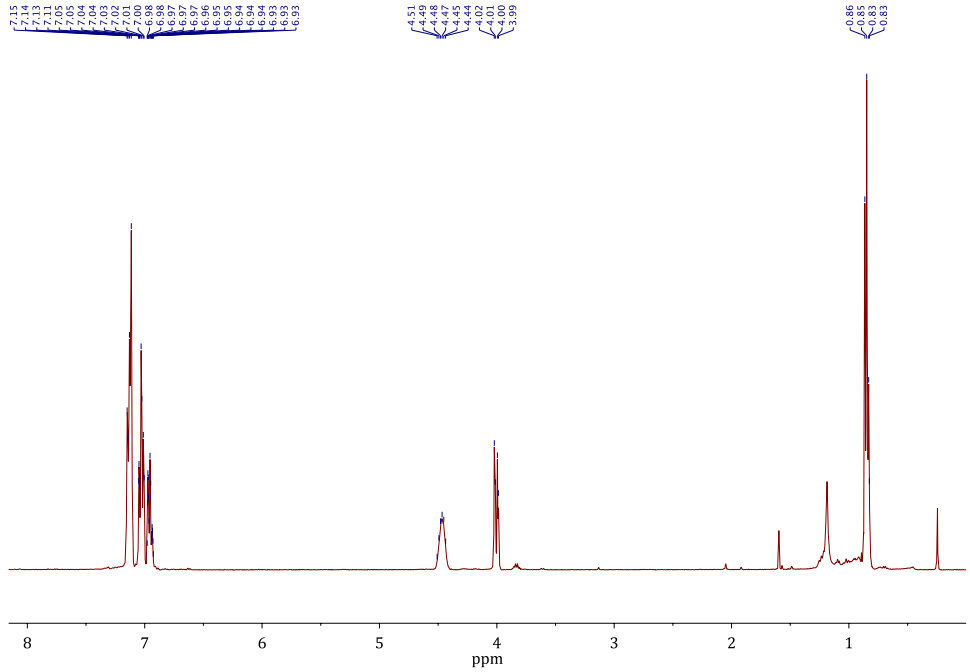


Figure 21: ^{1}H NMR of 34 after column chromatography.

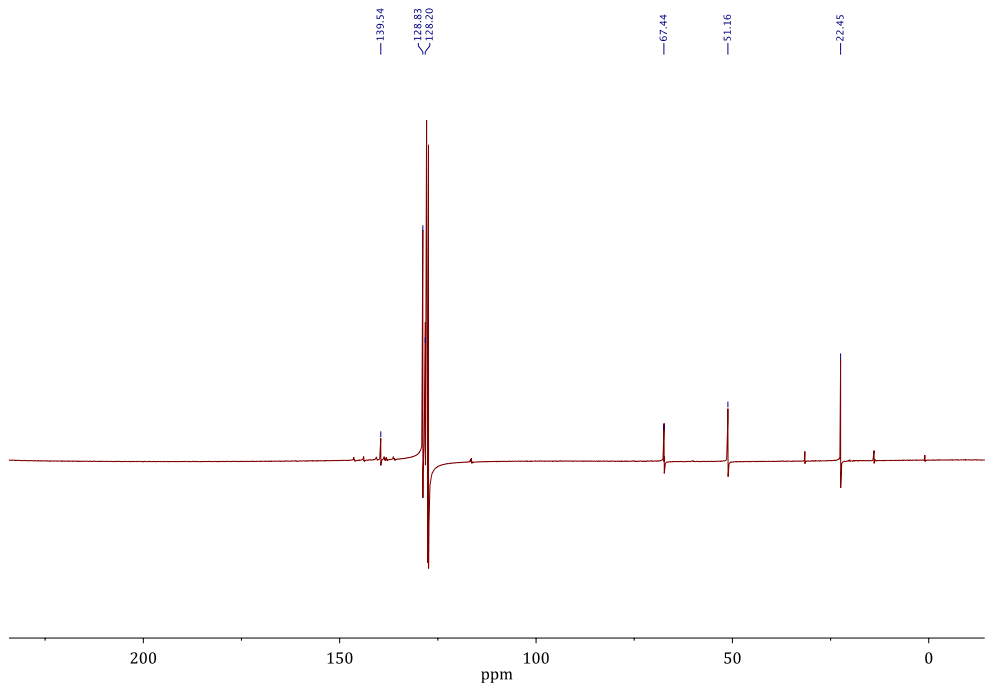


Figure 22: ^{13}C NMR of 34 after column chromatography.

Appendix G

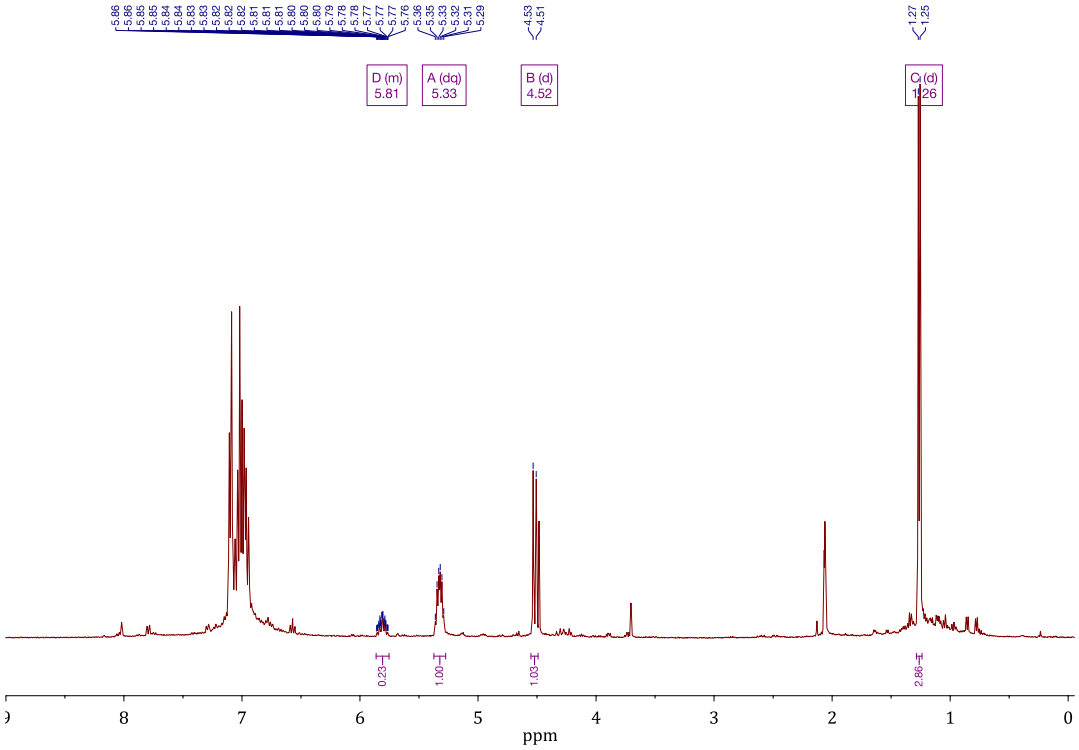


Figure 23: Crude ^{1}H NMR of 35.

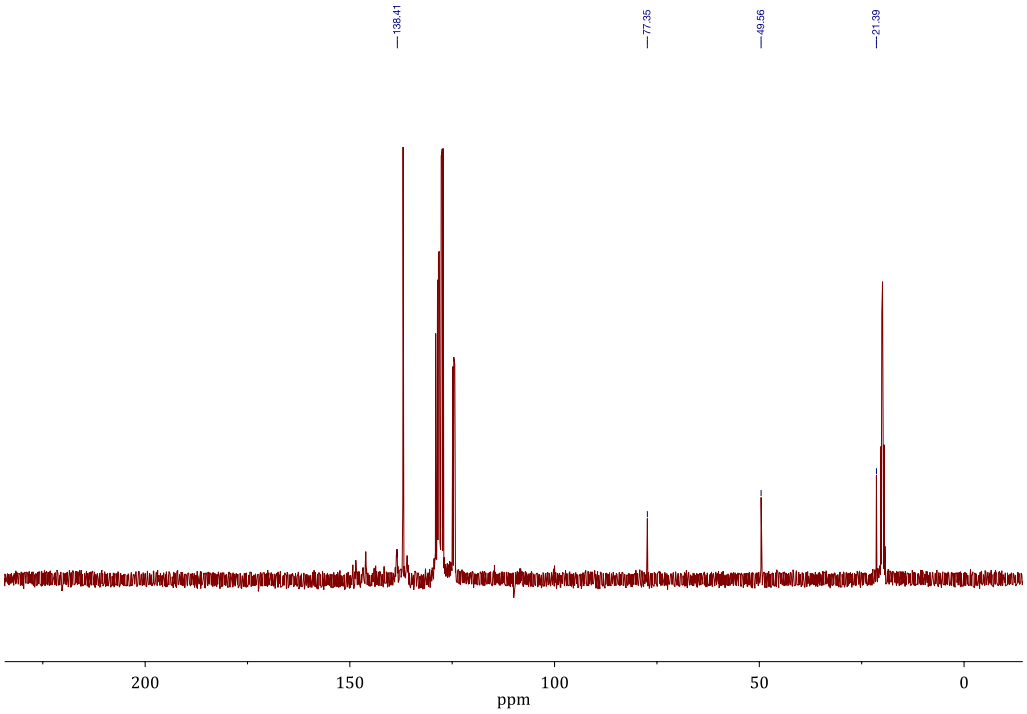


Figure 24: Crude ^{13}C NMR of 35.

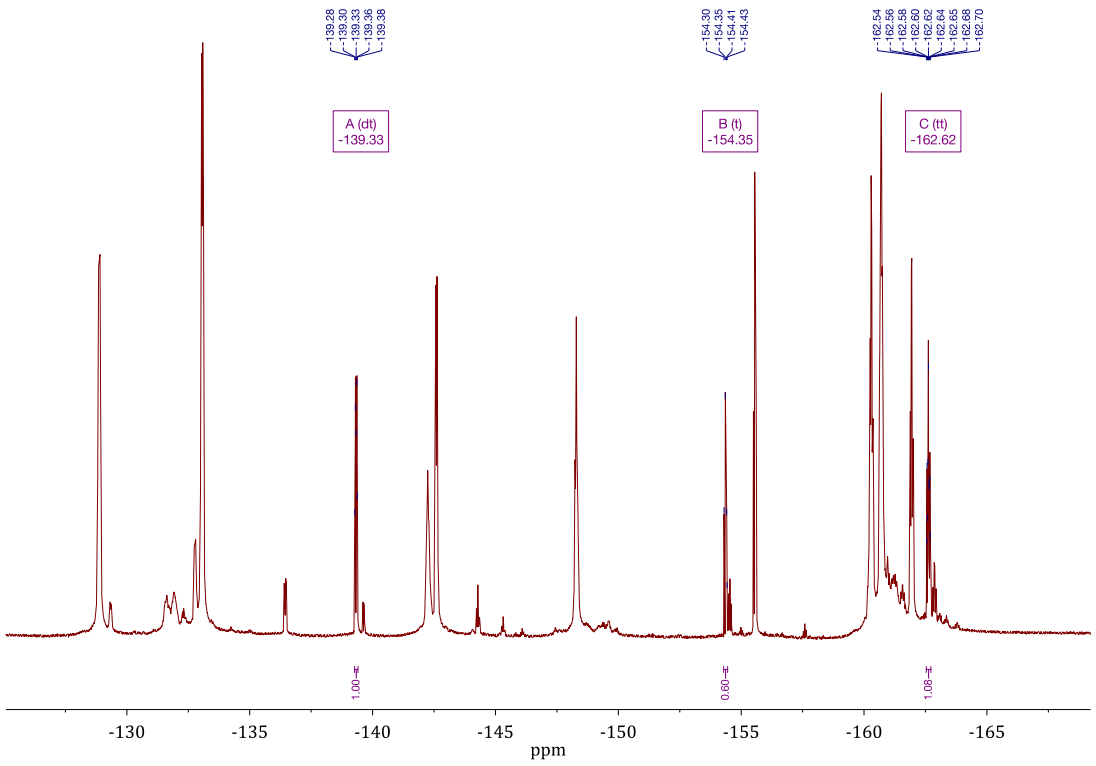


Figure 25: Crude ^{19}F NMR of the reaction mixture containing 35 and 1a.

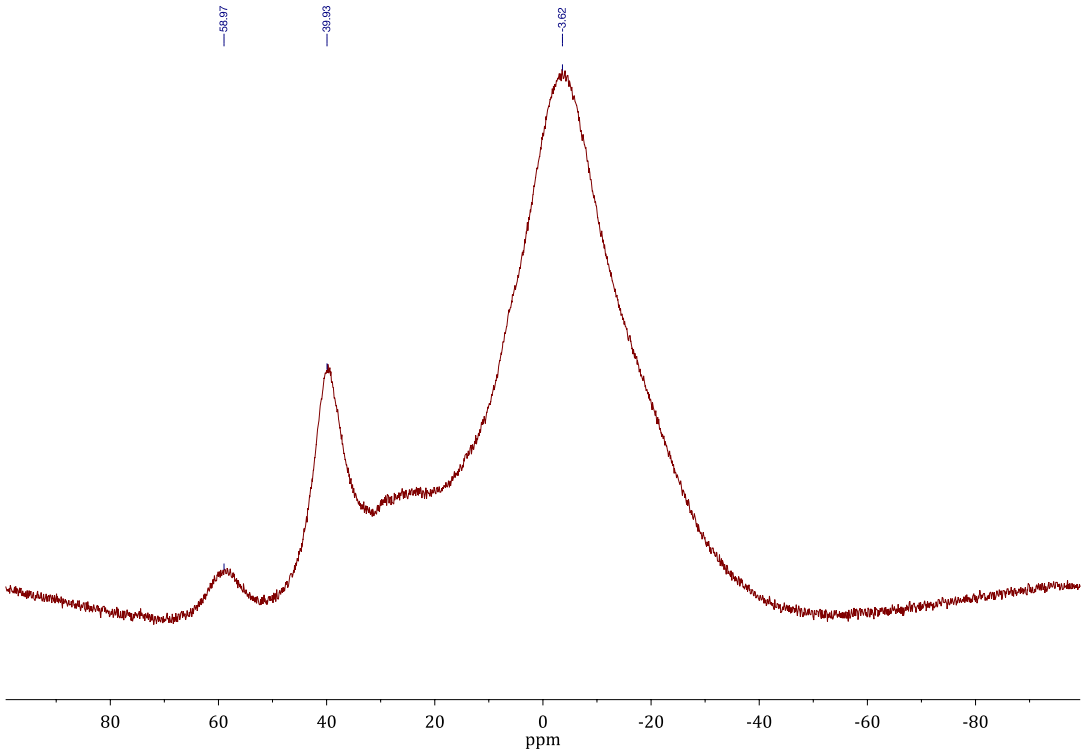


Figure 26: Crude ^{11}B NMR of the reaction mixture containing 35 and 1a.

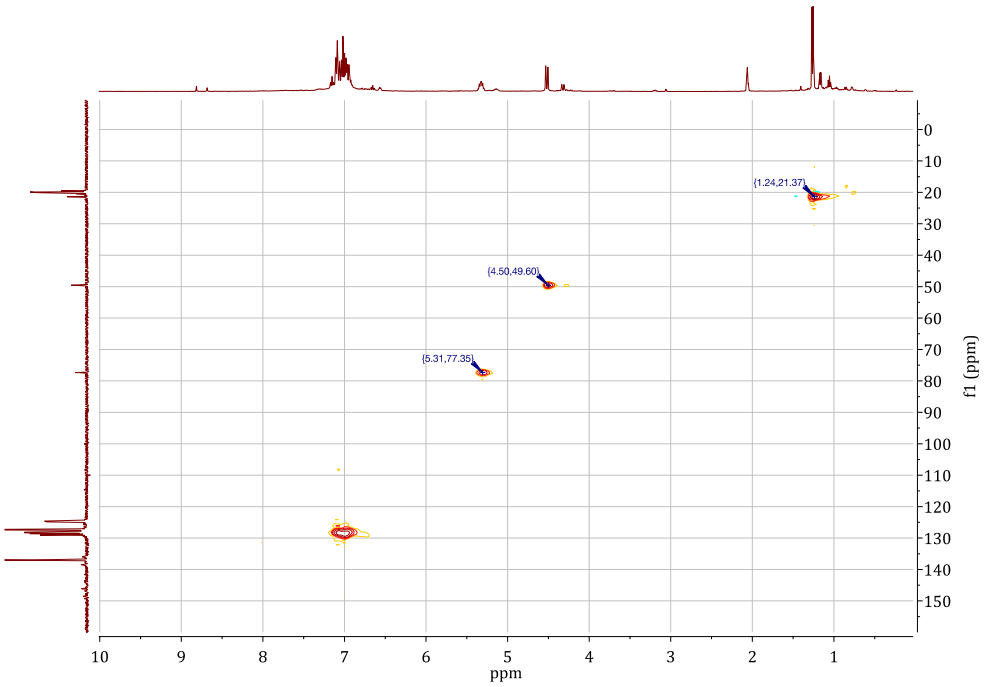


Figure 27: Crude HMQC of 35.

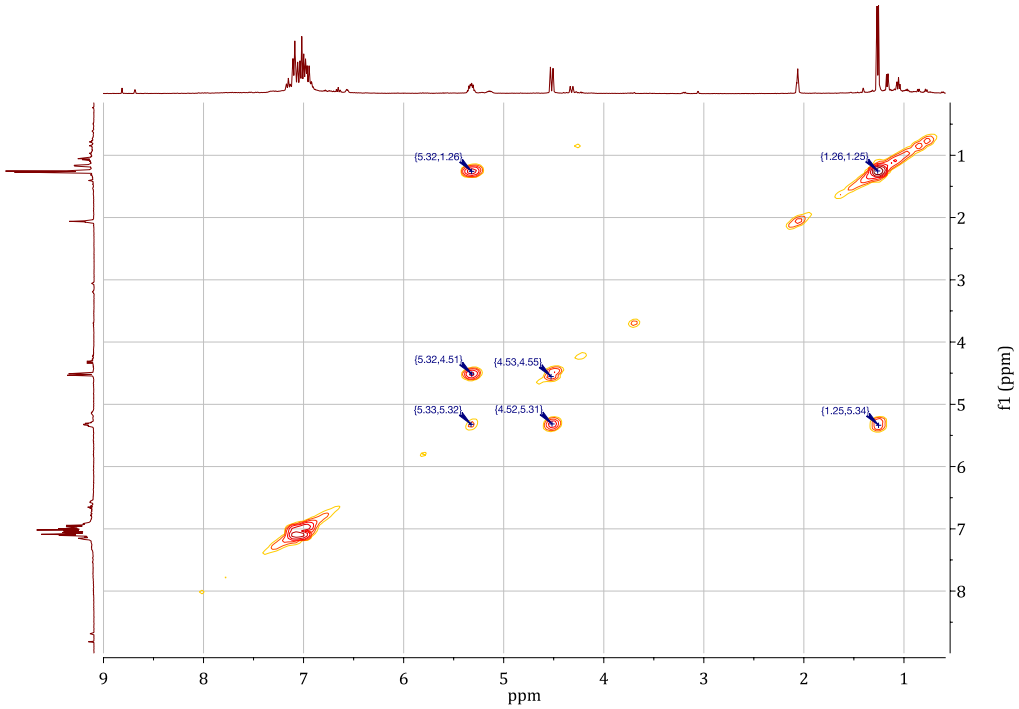


Figure 28: Crude COSY of 35.

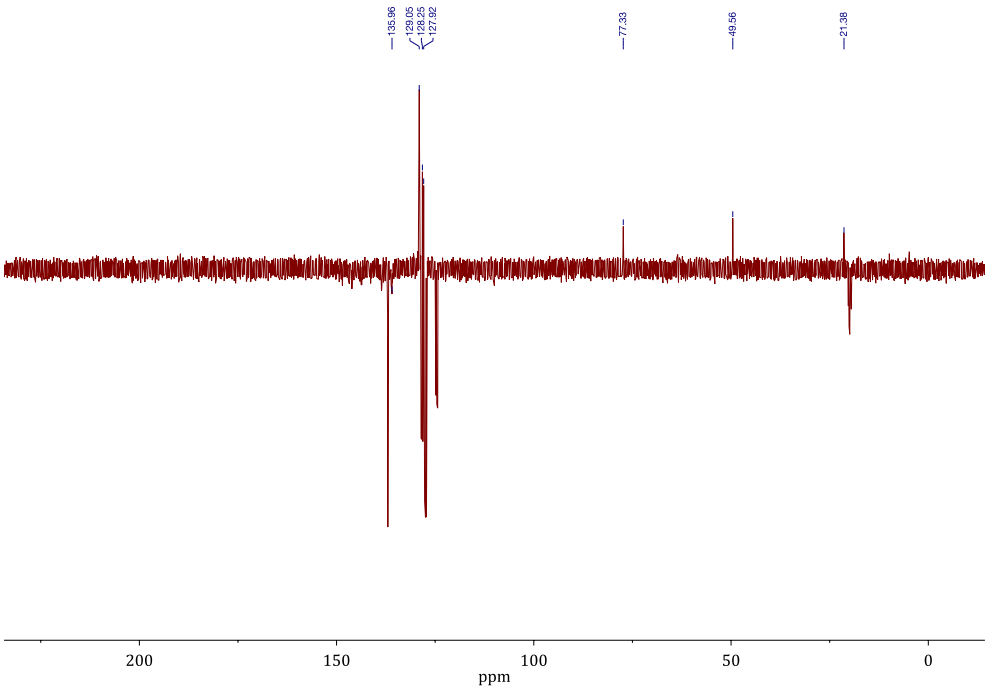


Figure 29: Crude APT of 35.

Appendix H

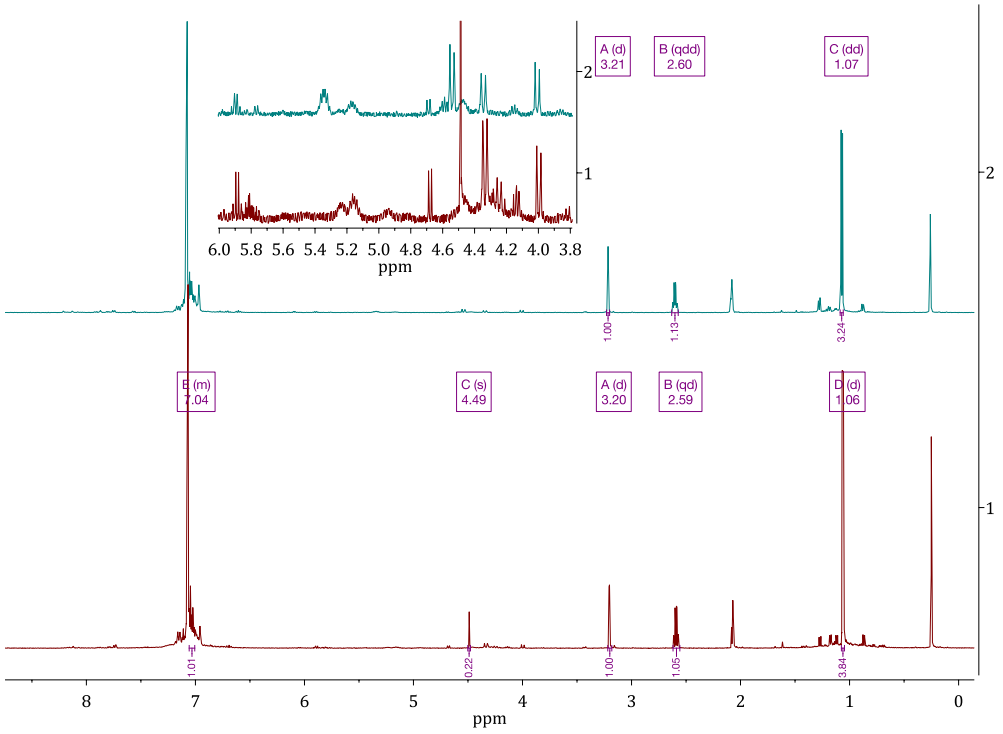


Figure 30: Crude ^{1}H NMR of the reaction 29e to 35 (10 mol % 1a).

Appendix I

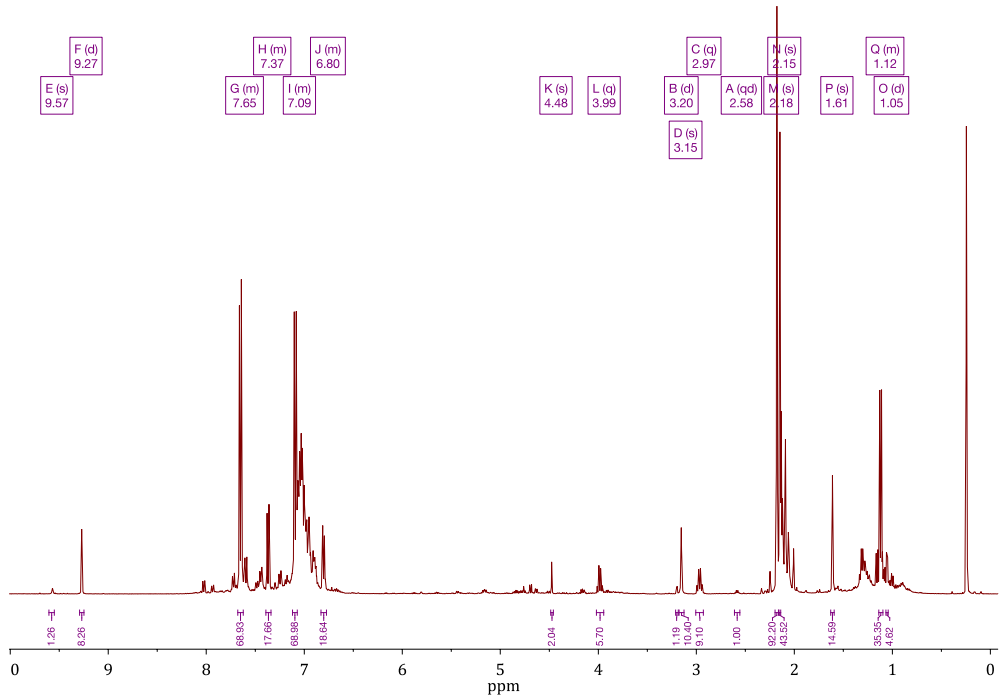


Figure 31: Crude ^{1}H NMR of stoichiometric reaction 29e with 1g.

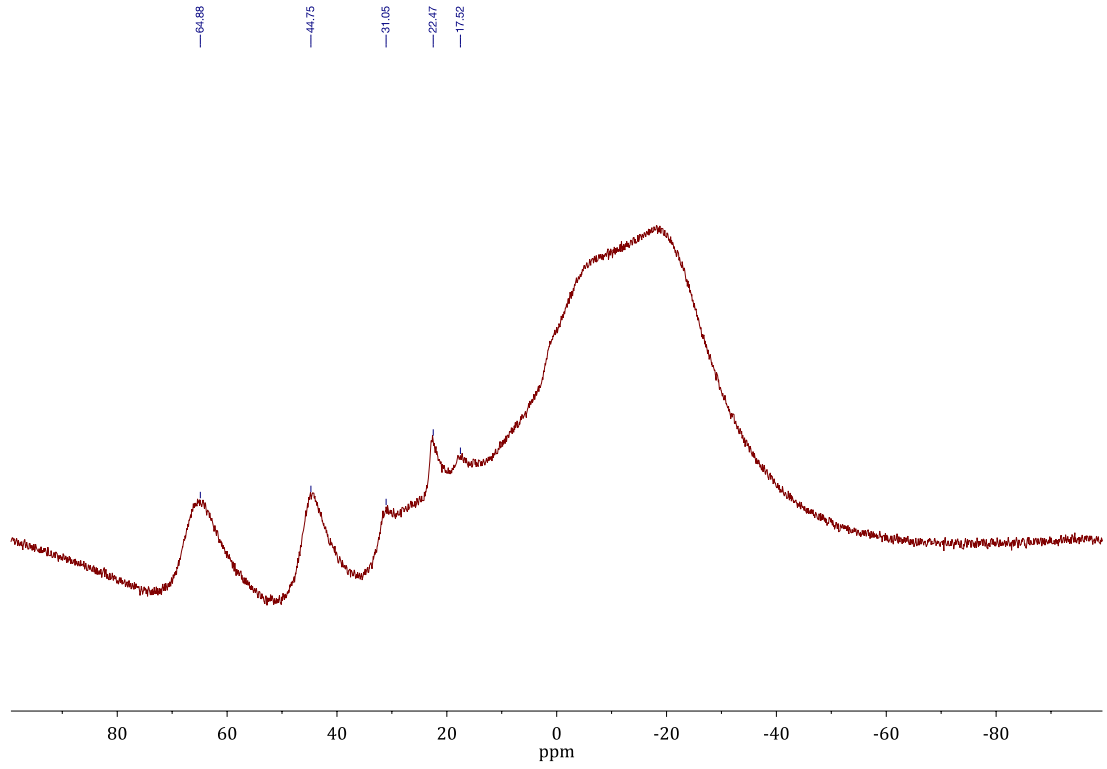


Figure 32: Crude ^{11}B NMR of stoichiometric reaction 29e with 1g.

Appendix J

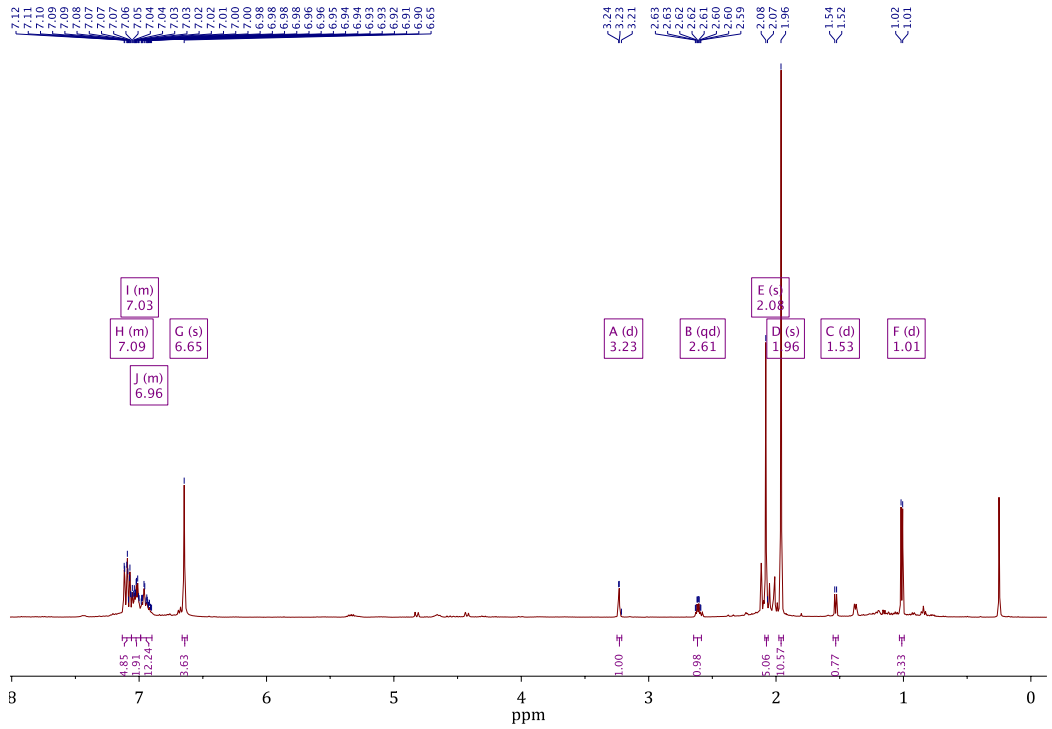


Figure 33: ^{1}H NMR of stoichiometric mixture 1c and 29e.

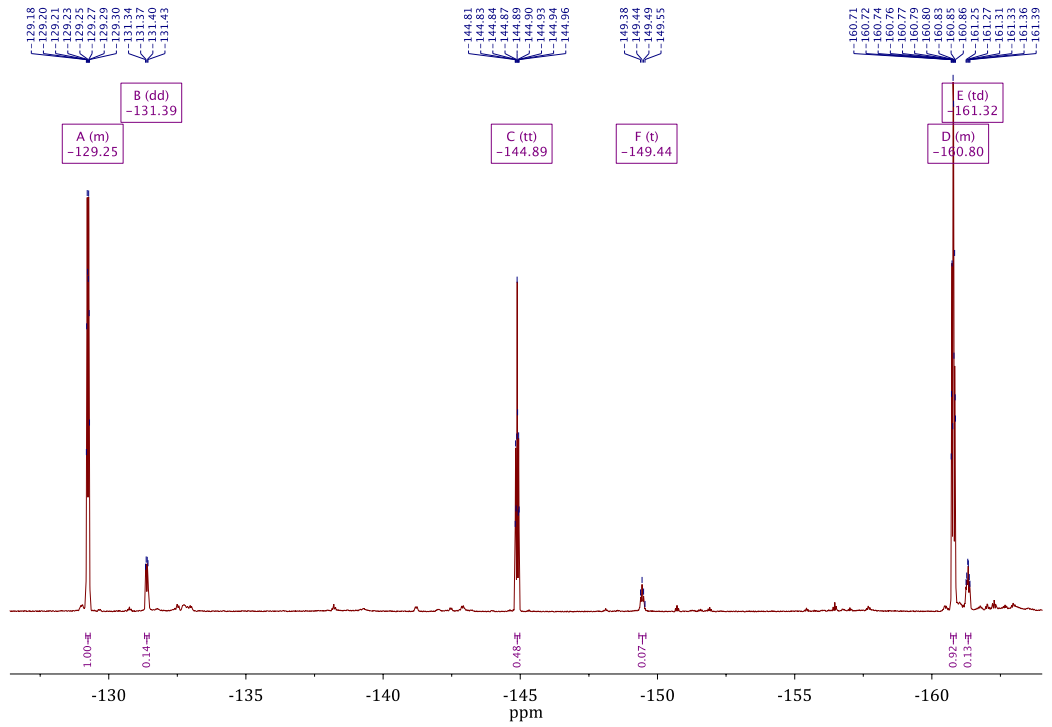


Figure 34: ^{19}F NMR of stoichiometric mixture 1c and 29e.

Appendix K

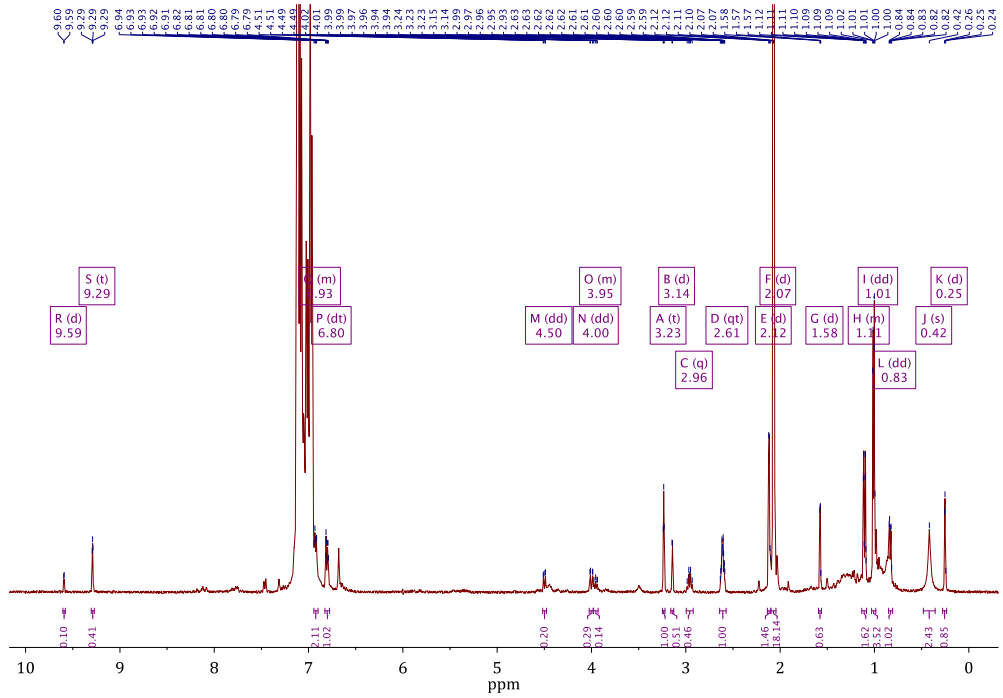


Figure 35: ^{1}H NMR of the attempted reduction of 29e with 1c.

Appendix L

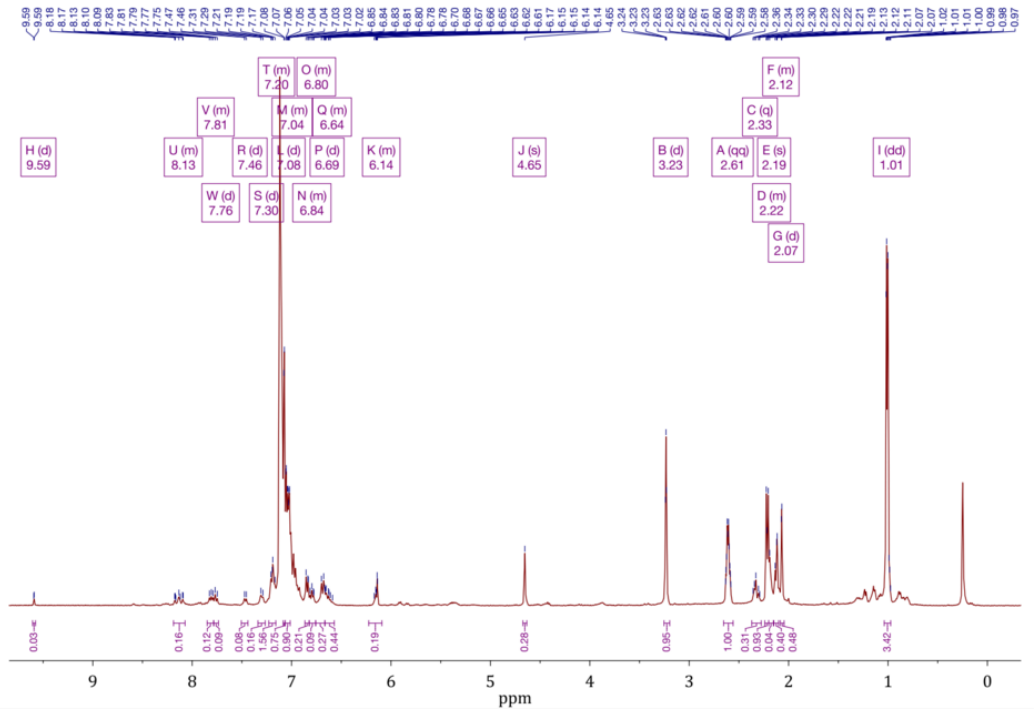


Figure 36: ^{1}H NMR of attempted reduction of 29e with 1c/DABCO.

Appendix M

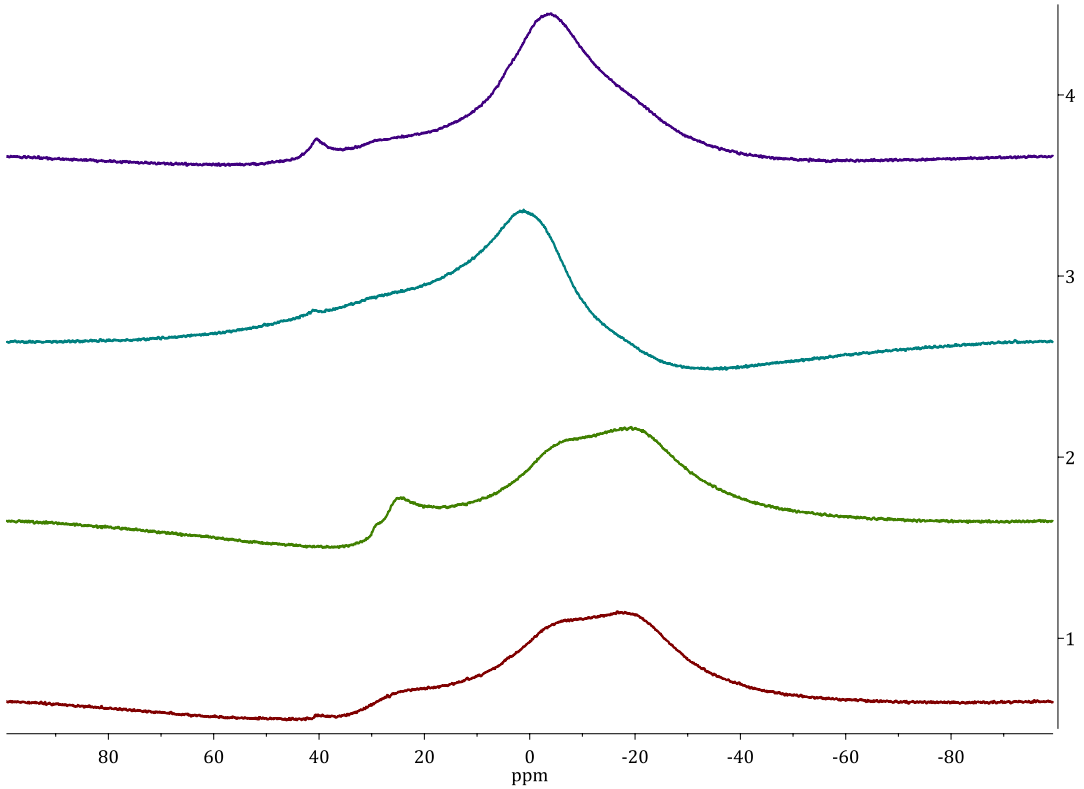


Figure 37: ^{11}B NMR of the attempted TH of 29c, 32, 29e and of the stoichiometric mixture 26/1a.

8. References

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