New C-C Bond Forming Reactions of Benzylic Alcohols and Thioesters

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„Wir müssen Ausdauer und vor allem Vertrauen in uns selbst haben. Wir müssen glauben, dass wir begabt sind und dass wir etwas erreichen können.“

Marie Curie

Contents

1. General Introduction

Chapter 1

The majority of chemical compounds found on earth are based on carbon-carbon bonds, making carbon one of the most abundant elements in our solar system. Hence, formations of carbon-carbon bonds are the most fundamental chemical reactions that occurred during the development of life on earth. Artificial formation of carbon-carbon bonds also has a long history and constitutes a major topic of organic chemistry. Nowadays an organic chemist has plenty of variations to form C-C bonds. However, since our world is threatened by climate change and depleting resources, also organic chemistry must find new solutions towards a more sustainable future.

1.1. C-C Bond Forming Acid Catalysis

1.1.1. Acids: History and Definition

The most influential field of catalysis employed in industries is by far acid catalysis.[1] This is not surprising, due to the immense amount of possible transformations. The reaction spectrum reaches from Friedel-Crafts alkylation, acylation and sulfonylation over oligomerization, isomerization, aromatic halogenation and nitration.

The acid base concept was first defined by Arrhenius, who won the Nobel Prize for chemistry in 1903. He described acid as any hydrogen containing compound, which is able to release a proton while a base is able to release a hydroxide ion.[2] Brønsted[3] and Lowry[4] changed the acid concept in 1923 by defining the acid base interaction as the exchange of a proton from an acid (HA) to the base (B, Scheme 1). In the same year Lewis proposed a definition of an acid (A) as electron pair acceptor with an empty orbital forming a dative or coordinative bond, whereas bases (B) are electron pair donors with a filled orbital.[5] Hence, Lewis acids are diverse and can be main group metal cations like Li/Na/K(I) or Mg/Ca/Zn(II), but also other metal ions, trigonal planar species, electron poor π-systems, but most commonly known Lewis acids are presumably B(III), Al(III) and Fe(III) compounds.

$$\mathrm{HA} + \mathrm{B} \rightleftharpoons \mathrm{A}^{-} + \mathrm{HB}^{+} \qquad \textit{Brønsted, Lowry}$$

$$\mathrm{B\!:} + \mathrm{A} \rightleftharpoons {}^{\delta+}\mathrm{B}\rightarrow\mathrm{A}^{\delta-} \qquad \textit{Lewis}$$

Scheme 1: Acid-base interaction based on Brønsted, Lowry and Lewis.[3–5]

Acids are quantitatively classified accordingly to the acid dissociation constant (K_a) in either strong or weak acids. The acid dissociation constant is the equilibrium constant of the dissociation of the acid in water. To describe the strength of an acid mostly the negative decadic logarithm (pK_a) is used (Scheme 2).

$$\mathrm{HA} + \mathrm{H_2O} \rightleftharpoons \mathrm{A^-} + \mathrm{H_3O^+}$$

$$K_a = \frac{\mathrm{c\,(H_3O^+)} \cdot \mathrm{c\,(A^-)}}{\mathrm{c\,(HA)}}\ ;\ \mathrm{p}K_a = -\log K_a$$

Scheme 2: Equilibrium of an acid in aqueous media and the derived acid dissociation constant K_a.

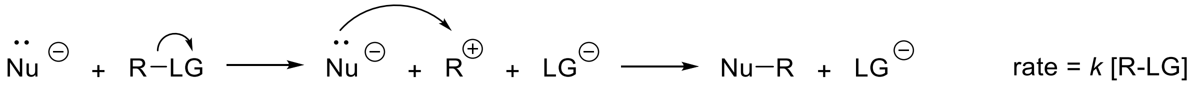
Lewis acids however, can be additionally classified by their hardness and softness which is described by Pearsons HSAB (hard/soft acid/base) concept.[6] Thereby, “hard” acids or bases exhibit small, non-polarizable atoms that with a large distance between the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO). Contrary, “soft” implies larger, polarizable atoms with a shorter distance between the HOMO and the LUMO. Coupling of two hard species leads to the formation of a strong ionic bond, whereas two soft species form strong covalent bonds. Organosulfur species for example interact in a soft-soft Lewis acid-base matter with transition-metals like Fe or Ni, generating covalent bonds.

Besides the stoichiometric use of acids, also acid catalysis is possible. It generally describes a partial proton transfer from an acid to the substrate, in which the free energy of the reaction transition state is decreased. In an acid catalyzed reaction, the protonated substrate reacts with a reactant. The release of the proton regenerates the acid catalyst and the desired product is obtained. Thereby, Lewis acids (LA), as well as Brønsted acids (BA) are immensely applied as catalysts in organic chemistry,[7] for example in C-C bond forming reactions. Acid catalyzed C-C formations are known for various reactions such as Diels-Alder reactions, cyclization reactions, allylic substitutions, conjugated additions, 1,2– and 1, 4-additions, rearrangements, esterification, Friedel crafts reactions and many more. This thesis, however, will only focus on C-C bond forming acid catalyzed unimolecular nucleophilic substitutions with a special focus on alcohols as reactants. Additionally, the Friedel Crafts alkylation with alcohols will be discussed as a subtype.

1.1.2. S_N 1-type Reactions

Nucleophilic substitutions are defined as replacement of one group by a nucleophile and they belong to the most fundamental reactions in organic chemistry. In S_N1-type reactions, a heterolytic cleavage between a carbon atom of the staring material and the leaving group (LG) generates a carbenium ion as intermediate in a first, rate-determining step (Scheme 3). In the second step, a nucleophile is attacking the intermediate, forming a new bond. This reaction is unimolecular, since the reaction rate is only dependent on the concentration of the starting material and not the nucleophile. The more stable the generated carbenium ion, the higher the rate constant. Therefore, especially tertiary, conjugated allylic, propargylic and benzylic substrates are likely to undergo S_N1 reactions.[8] Traditional S_N1-reactions are conducted with heteronucleophiles like indoles, whereas modern methods also allow the application of a broader scope of nucleophiles leading to new bond formations.

It is important to mention that nucleophilic reactions can not only occur on carbenium ions but also on carbonyl compounds. Ketones and aldehydes are generally weak electrophiles and therefore only used in combination with activating agents. More reactive organic acyl halides, however, generate toxic waste when the halide is released. Therefore, thioesters arise as interesting electrophiles, due to their low toxicity but similar electrophilicity as acyl chlorides. Further information on this topic will be outlined in chapter 4 and 5.



Scheme 3: General mechansim of an S_N1 reaction.

Since Olah published a pioneering work on the theoretical background of carbocations,[9] their controlled generation became an important process, particularly in industry. Today, many new reactions can be proposed based on the reactivity scale of Mayr.[10] Based on the reaction rate determined from experimental kinetic measurements, the electrophillicity of carbocations was determined. Electrophiles with a high electrophilicity parameter ($E > 0$) are extremely reactive and are often more difficult to generate, whereas carbocations with an $E < 0$, like carbocations bearing electron-donating substituents, are more stable (Figure 1).

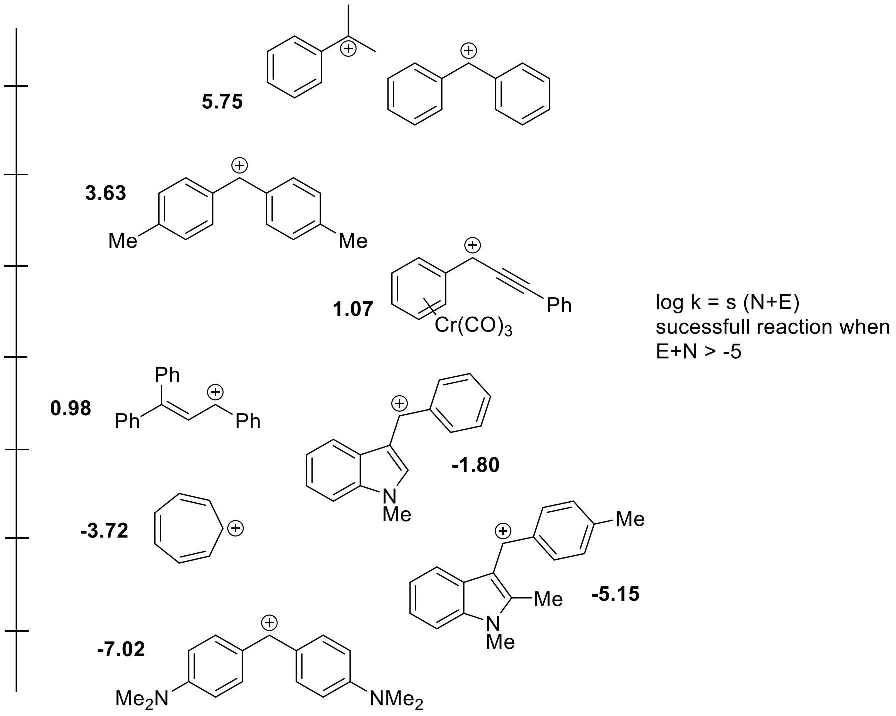


Figure 1: Some carbocations orders by the Mayr's scale; s = nucleophile-specific slope parameter , N = nucleophilic parameter, E = electrophilic parameter.

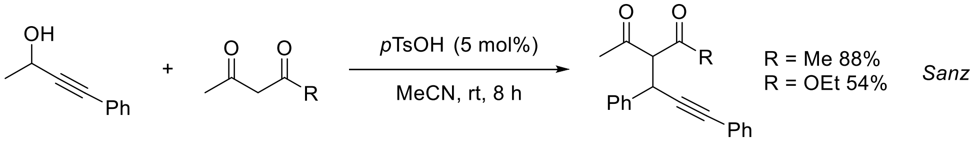
Mayer also found linear correlations with nucleophiles, which can also be quantitatively determined by a nucleophilic parameter *N*, which helps choosing suitable reaction partners to achieve successful and effective substitution reactions. As a rule of thumb, Mayr proposed a positive reaction outcome when choosing reaction partners with $E+N > -5$.[11]

Acids are able to convert neutral substrates into carbocationic substrates to enhance the leaving group ability. By this method, mainly alcohols have been activated, since they are intrinsically poor LG. The main advantage in S_N1 reactions of alcohols is the formation of water as side product, which is not harmful in comparison to products from halides or other LG and represents a reaction with a good atom economy. The substitution of activated alcohols is therefore frequently used in the synthesis of pharmaceutical products. Additionally, the direct catalytic nucleophilic substitution of alcohols could be a possible solution to many environmental issues.

Early approaches on activating alcohols in substitution reactions however, were based on stoichiometric amounts of acids.[12]

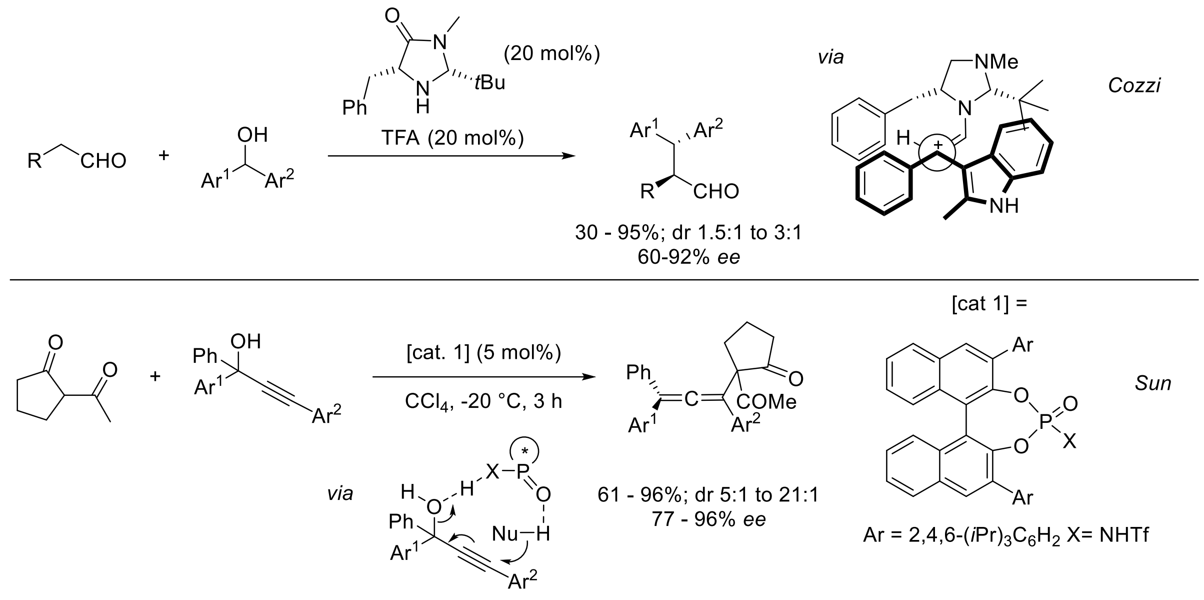
In the early 2000's LA catalyzed alcohol activation in S_N1 reaction gained much attention. Catalysts based on Bi,[13] B,[14] In,[15] Fe,[16] Ag,[17] or Sn[18] have been reported. But also metal complexes[19] and molecular iodine[20] were applied as suitable catalysts for the activation of alcohols. Early

Brønsted acid catalyzed S_N1 reactions of alcohols were shown by Sanz and co-workers. The group converted tertiary and secondary propargylic alcohols with dicarbonyl compounds in the presence of *para*-toluene sulfonic acid in 5 mol% (Scheme 4).[21] Also C3-propargylated indole derivatives have been synthesized by this method.[22] TsOH was additionally used in the synthesis of bicyclo[3.1.0]hexanes[23] and in a one-pot propargylation/cycloisomerization tandem reaction to substituted oxazole derivatives from amides.[24]



Scheme 4: Nucleophilic substitution of a propargylic alcohol with dicarbonyl compunds catalyzed by TsOH.[21]

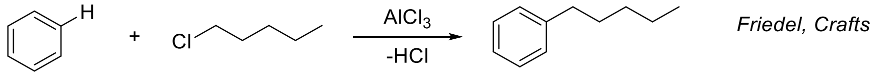
In recent years, enantioselective BA catalyzed nucleophilic substitutions of alcohols gained more and more attention.[25] Since enamines are suitable nucleophiles based on the rule of thumb by Mayr, Cozzi and coworkers developed an enantioselective, organocatalytic nucleophilic substitution by using a MacMillan catalyst (Scheme 5).[26] It generates a strongly nucleophilic enamine intermediate with a carbonyl compound, which is able to induce stereoinformation during the attack on a stable carbocation that is prior formed by trifluoroacetic acid (TFA) from a benzylic alcohol. But also chiral phosphoric acids have been proven to be effective catalysts in the nucleophilic conversion of alcohols. Sun and coworkers for example were able to synthesize chiral allenes from tertiary propargylic alcohols and cyclic diketones by using a highly acidic *N*-triflylphosphoramide (Scheme 5).[27]



Scheme 5: Enantioselective S_N1 reactions of alcohols reported by Cozzi and Sun.[26,27]

1.1.3. Friedel-Crafts Alkylation

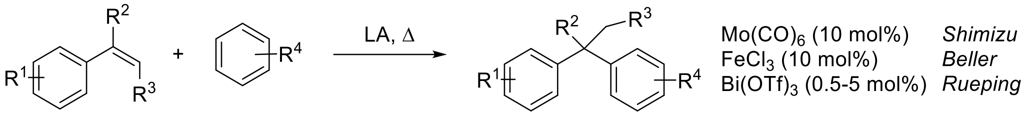
The first use of a LA in organic synthesis was reported by Charles Friedel and James Crafts in 1877. They applied aluminum trichloride to alkylate benzene with amylchloride (Scheme 6).[28] This reaction later became famous as Friedel-Crafts (FC) reaction, an electrophilic aromatic substitution, which can be conducted not only with alkyl, but also with acyl halides. Today, this reaction is the most applied method to substitute arenes, since it allows the formation of a wide range of aromatic products. Over the years, various Lewis acids based on B(III), Be(II), Ti(IV), Sb(V), Sb(IV) and other metals have been described to be activating agents in the Friedel-Crafts reaction.



Scheme 6: Initial Friedel-Crafts reaction of benzene and amylchloride with $AlCl_3$ described by Friedel and Crafts in 1877.[28]

Traditional approaches, however, have major drawbacks, like polyalkylation as main side reaction or the use of toxic halides. Hence, organic chemists were looking for selective, more environmentally and less toxic versions of the FC reaction by using metal or non-metal-based catalysts instead of stoichiometric additives and other electrophiles than alkyl halides. Especially the use of electrophiles that do not generate any waste like styrenes and other activated double bonds, and electrophiles as alcohols, which only generate water, is a major improvement. Interestingly, the first catalytic versions of the FC reaction with styrenes and water were investigated about 20 years ago, even though the traditional reaction is known for almost 150 years.

In 1977, Shimizu and co-workers discovered one of the first FC reaction of arenes with unsaturated double bonds by using Lewis acidic transition-metals like $Mo(CO)_6$ as catalysts.[29] Nine years later, the groups of Beller and Rueping followed up on this topic by employing less sensitive and less expensive Fe(III) and Bi(III) catalysts (Scheme 7).[30,31]

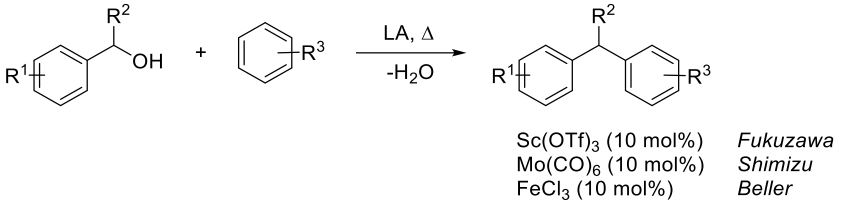


Scheme 7: Early LA-catalyzed FC alkylations with styrene derivatives.[29–31]

Since then, a lot of progress has been made in terms of applying other arenes and olefins. In 2018, an intramolecular LA catalyzed FC reaction was reported by Schindler and Watson forming 3,4-dihydro-2*H*-pyrans for the synthesis of tetrahydronaphthalenes by applying $FeCl_3$ as catalyst in 10 mol%.[32] Related intramolecular FC-type alkylations with styrene and activated double bonds have been described with various LA catalysts.[33] In recent years, especially organocatalytic BA of arenes and molecules containing unsaturated double bonds have been published. Organocatalysts like BINOL derived phosphoric acids are of special interests since they are able to induce enantioselectivity.[34] In 2019 for example, Kim and co-workers reported an asymmetric FC ring-opening reactions of 3-indolylsulfamidates with indole by using BINOL-derived phosphoric acids as catalysts.[35]

The first alkylations of arenes with benzyl alcohols were reported in the late 1990's. Uemura *et al.*[36] observed a cascade chlorination/FC reaction to 1,1-diarylalkanes, when applying 10 mol% $TeCl_4$ to a benzyl alcohol in benzene, whereas Fukuzawa[37,38] and Shimizu[29] performed systematic investigations with $Sc(OTf)_3$ and $Mo(CO)_6$ as catalysts in direct FC alkylations (Scheme 8). These findings were followed by reports based on rare-earth catalysts as $Yb(OTf)_3$, $La(OTf)_3$,[39] $NbCl_5$[40] and others,[41] but also molecular iodine[42] was able to act as catalyst in the FC reaction of alcohols. Beller and co-workers conducted a systematic screening of acids in FC benzylations, which resulted in late transition-metals (TM) being the most efficient catalysts.[43,44] Especially,

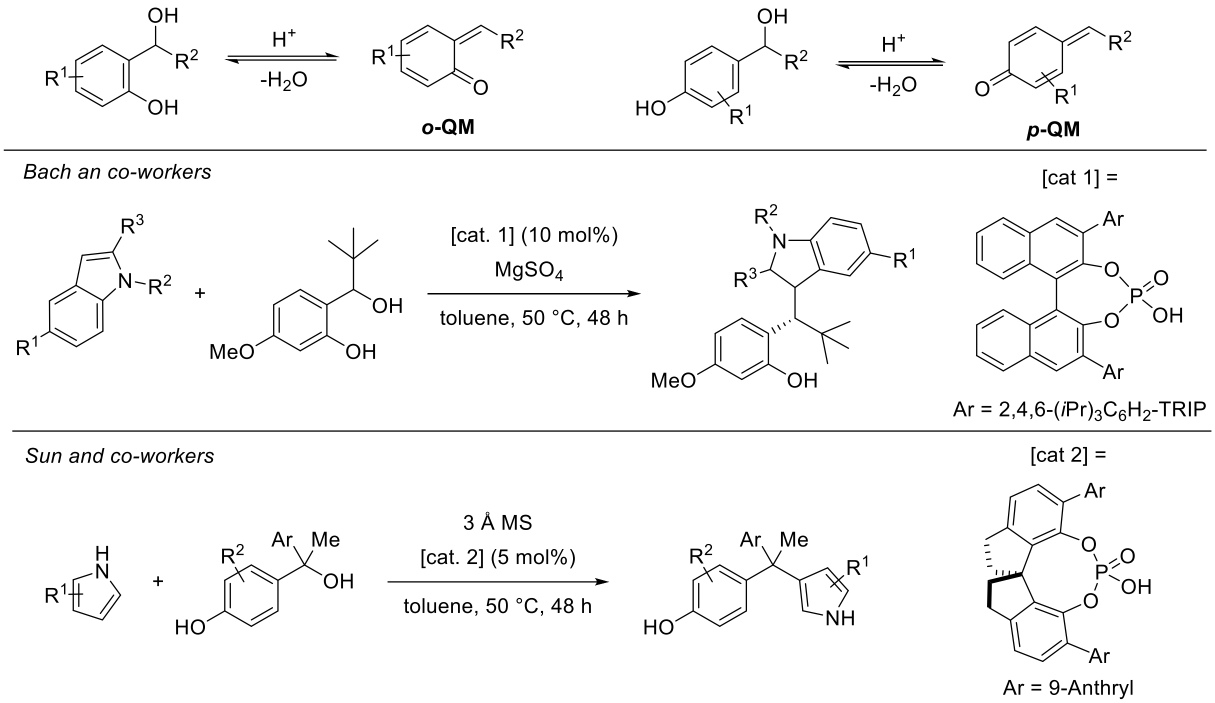
$FeCl_3$ appeared to be an attractive catalyst, due to its non-toxic and abundant properties. From there on, LA catalyzed FC alkylations with alcohols became a standard procedure. Not only benzylic alcohols were used as electrophiles but also allylic and propargylic alcohols and enantio- and diastereoselective LA catalyzed versions have been reported.[45]



Scheme 8: Early LA-catalyzed FC alkylations with benzylic alcohols.[29,37,38,43]

Beside metal-based LA reactions, also BA based organocatalytic FC reactions gained enormous attention due to positive features regarding the principles of green chemistry and sustainability.[46] *Para*-toluenesulfonic acid (TsOH) is one of the most applied metal-free BA employed as activating agent for alcohols and was primarily used by the group of Sanz.[22,47] Also some intramolecular reactions of alcohols were reported by Chan's and Sanz' group.[48]

An interesting field of BA catalyzed activation of alcohols is the formation of quinone-methides (QM) from benzylic alcohols. O*rtho*- and *para* QMs are intermediates, generated by dehydration of *o*- and *p*-hydroxy benzylic alcohols (Scheme 9). In recent years especially chiral phosphoric acids were used for these types of reaction. Pioneering work was performed by Bach and co-workers using indoles and electron-rich *o*-hydroxy benzylic alcohols (Scheme 9).[49] *Para*-QM generation is generally more challenging, due to increased distance between the formed carbonyl and the position of the water elimination. By applying bifunctional catalysts however, also a remote stereocontrol is possible. The group of Sun reported in 2015 an asymmetric addition of 2-methylpyrrole and various pyrroles as nucleophiles to *o*-QMs derived from racemic tertiary alcohols (Scheme 9).[50]

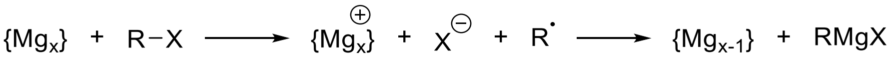


Scheme 9: Quinone-methide formation from benzylic alcohols catalyzed with BA.[49]

The activation of benzylic alcohols with BA will be further discussed in chapter 2 and 3.

1.2. C-C Bond Forming Grignard Reactions

Beside acid catalyzed C-C bond forming reactions, also the application of Grignard reagents can be widely used to generate new carbon-carbon bonds. Grignard reagents are highly reactive organometallic compounds based on magnesium and are a well-known class of C-nucleophiles. Victor Grignard was the first who discovered their existence in 1900 and was thereupon awarded with the Nobel Prize in 1912.[51] Since then Grignard reagents became integral parts of organic and inorganic chemistry and served as cornerstone for the development of other organometallic compounds. Despite the long history, the mechanism of forming Grignard compounds is still not completely clear. Most likely a single electron transfer (SET) from the magnesium to an organohalide (RX) is occurring, forming an intermediate radical $R^\bullet$ (for R = alkyl) that diffuses in solution close to the surface of the magnesium (Scheme 10).[52] Recombination of the radicals then furnishes RMgX, which is stabilized in etheric solvents. The insertion of Mg into the carbon halogen bond is thereby accompanied by the reversal of the polarity. These reagents can then be used as nucleophiles directly or to form magnesium carbenoids from other organohalides through a halogen-metal exchange. Knochel and coworkers developed the formation of the so-called turbo-Grignard reagent (*i*PrMgCl•LiCl), which accelerates the metal halogen exchange to give for example arylmagnesium reagents bearing a nitro group, which was not possible to be generated by conventional Grignard compounds.[53]

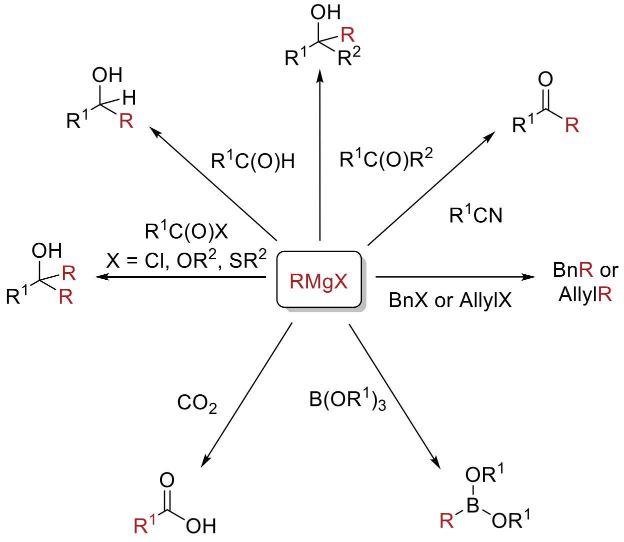


$$\{Mg_x\} + R{-}X \longrightarrow \overset{\oplus}{\{Mg_x\}} + X^{\ominus} + R^{\bullet} \longrightarrow \{Mg_{x-1}\} + RMgX$$

Scheme 10: Oversimplified mechanistic proposal of the Grignard reagent formation on a magnesium surface $\{Mg_x\}$.

In the typical "Grignard reaction" a Grignard reagent reacts in a nucleophilic substitution or addition with a carbonyl compound forming new C-C bonds. Hence a variety of ketones, aldehydes, carbonic acids, secondary or tertiary alcohols can be generated by this procedure (Scheme 11). An interesting example of a substitution reaction with Grignard reagents on thioesters will be shown in chapter 5. Additionally, Grignard reagents can be used in the conversion of other electrophiles like halides, borates, carbondioxide or cyanides. However, Grignard reagents generally exhibit a bad functional group tolerance, which led to the development of modified Grignard reactions by the addition of TM compounds. Nowadays most

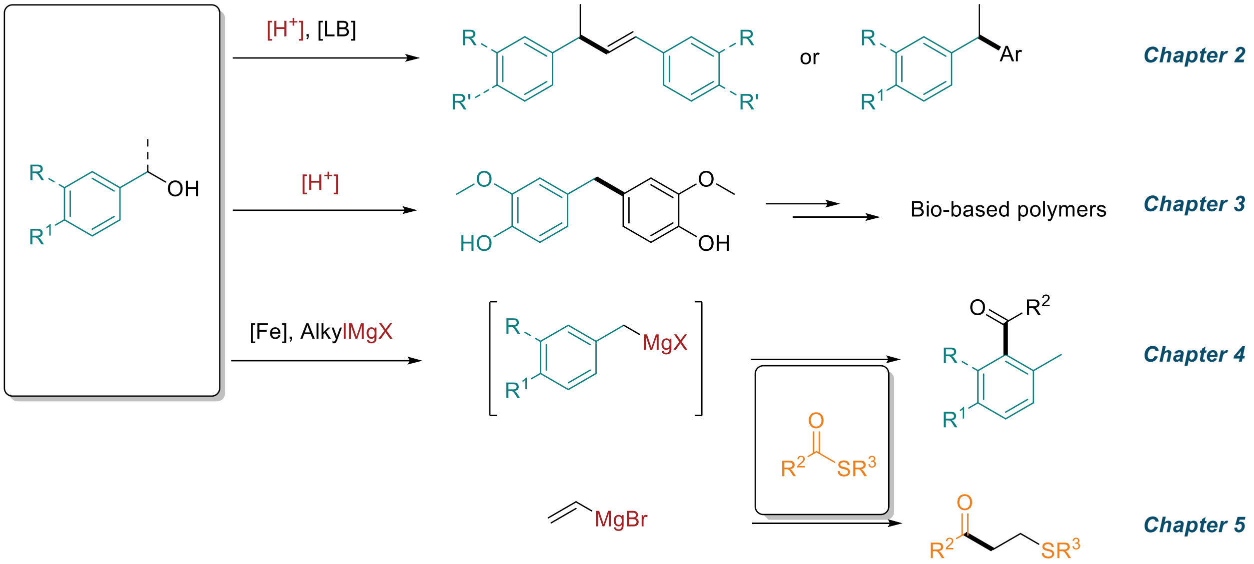
Grignard reagents are used in transition-metal cross-coupling reactions as transmetalation reagent.[54] Further information on this topic will be outlined in chapter 4.



Scheme 11: Overview of possible nucleophilic reactions of Grignard reagents.

1.3. Aim of this Thesis

The overall aim of this thesis is to find new and more sustainable routes to form C-C bonds, which can be conducted under mild reaction conditions with simple, abundant and inexpensive reagents. Therefore, benzylic alcohols were envisioned as main starting material due to their low toxicity and easy availability. Hydroxygroups however, are intrinsically bad leaving groups and have to be activated. In this work, acid catalysis and iron catalyzed magnesiation are shown as possible activation patterns (Scheme 12).



Scheme 12: Overview of the work on C-C-bond forming coupling reactions of benzylic alcohols and thioesters with Grignard reagents and acid catalysts. Benzylic alcohols were activated either by acid catalysis or by magnesiation and coupled with benzylic or arylic reagents and thioesters. Thioesters were additionally applied in a tandem reaction with vinylmagesium bromide.

An acid catalyzed dehydrative coupling is presented in chapter 2, describing an interesting effect of a Lewis base co-catalyst. Building on this, the acid catalyzed dehydrative coupling of lignin-derived vanillin alcohol with guaiacol is used as first step in the synthesis of bio-based polymers, shown in chapter 3. Chapter 4 and 5 are based on the extraordinary reactivity of thioesters as electrophile with a good leaving group. For the formation of the carbon-carbon bonds an alkyl Grignard reagent is used in chapter 4 to activate the alcohol for a subsequent carbonyl transfer reaction. In Chapter 5 a tandem acyl substitution/Michael addition with vinylmagensium bromide and a thioester is described.

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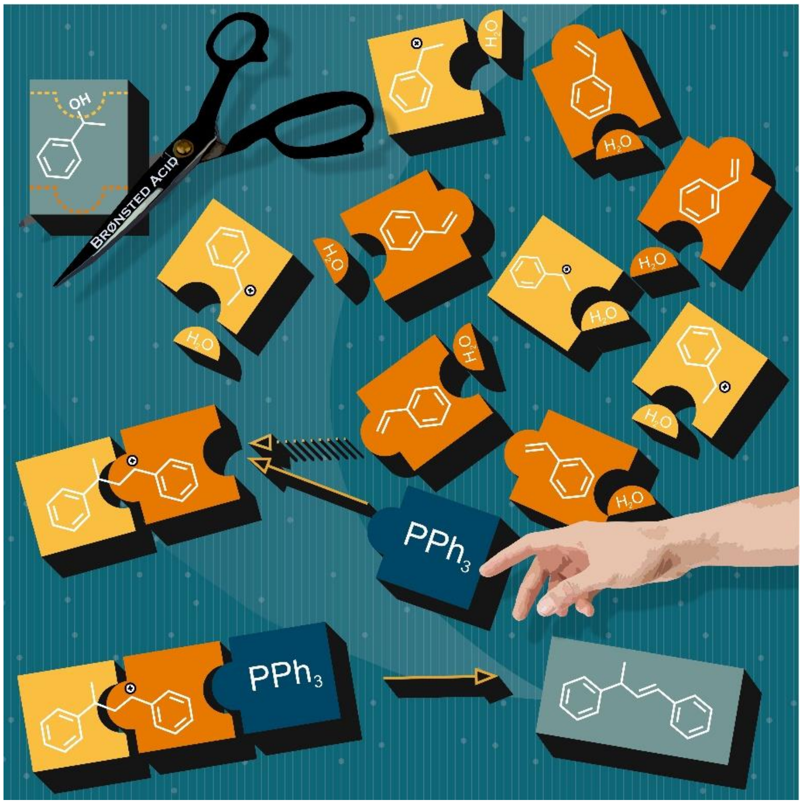
2. Dehydrative Coupling of Benzylic Alcohols Catalyzed by Brønsted Acid/Lewis Base



Abstract: Traditional cross-coupling reactions show some disadvantages like the use of organohalides or the production of stoichiometric amounts of waste. The dehydrative homo- or heterocoupling of alcohols therefore arises as interesting approach for a highly atom-economical formation of carbon-carbon bonds, since water is produced as only byproduct. We herein report a simple and direct, metal-free protocol for the synthesis of olefins by applying catalytic amounts of a sulfonic acid and triphenylphosphine under air. A variety of olefins could be synthesized from benzylic alcohols under relatively mild conditions. Additionally, dehydrative hydroarylation of benzylic alcohols with electronrich arenes was possible by using only Brønsted acid under otherwise identicL reaction conditions. We could show that phosphine additives are essential to overcome oligomerization as main side reaction by occupancy of the reactive carbocation intermediate.

Chapter 2

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Author contribution:

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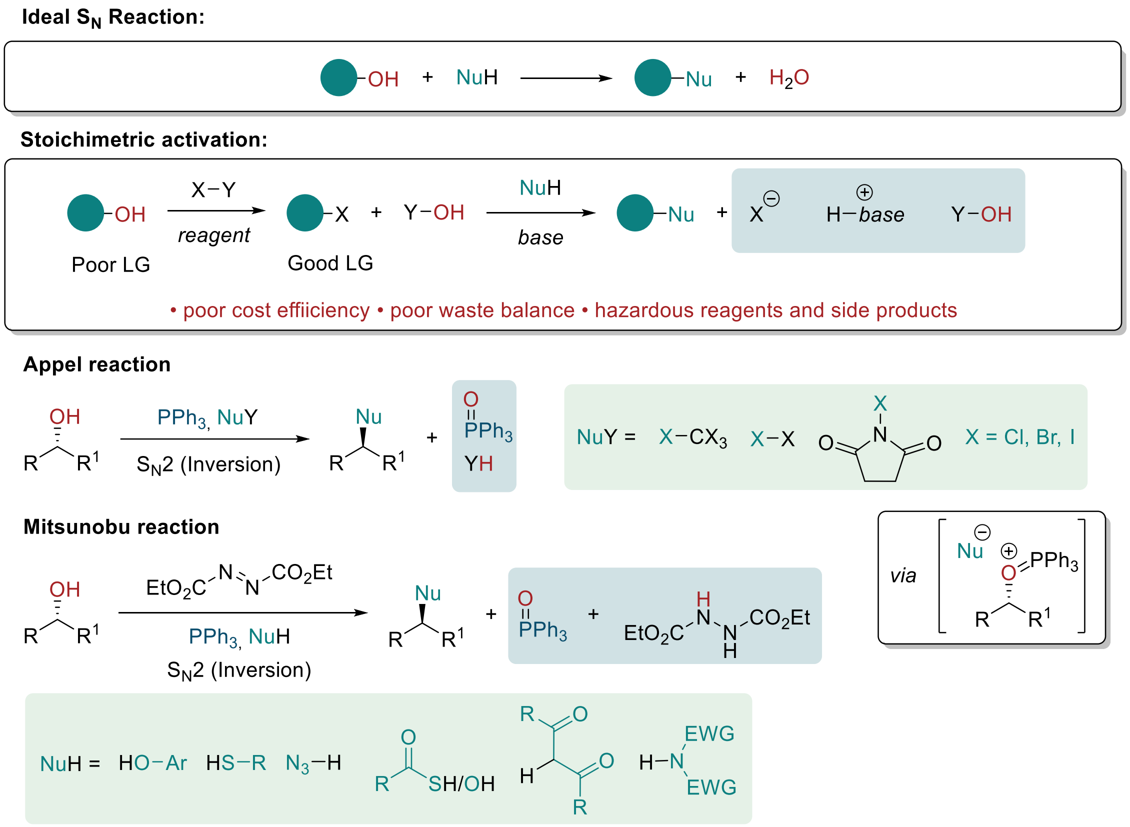
Ivana Fleischer: corresponding author.

2.1. Introduction

2.1.1. C-C Bond Formation by Nucleophilic Substitutions of Alcohols

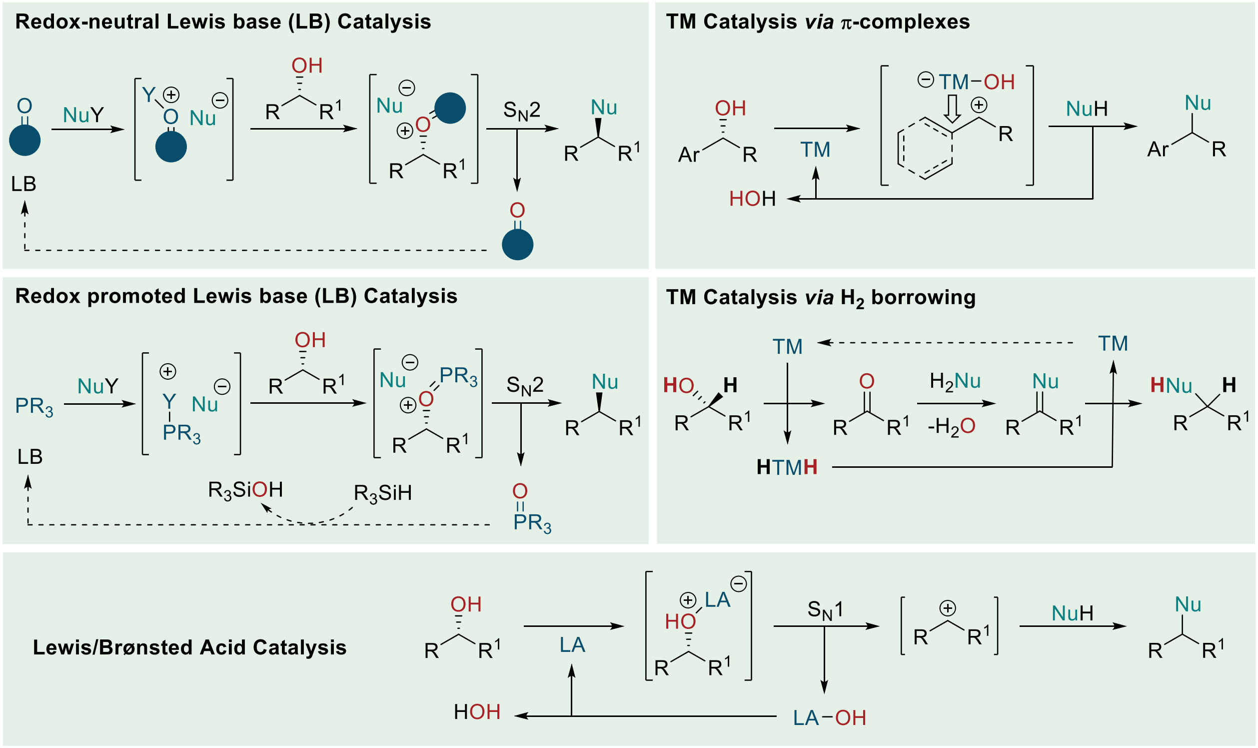
One of the most fundamental subjects in organic chemistry is the efficient and selective formation of carbon–carbon bonds. Especially transition-metal catalyzed cross-coupling reactions emerged as an important tool for the construction of sp^3-sp^2 C-C bonds and have been widely investigated and developed.[2] Nevertheless, most of these protocols show disadvantages in respect to the aspects of green chemistry.[3] Often, additional preparative steps are necessary, as well as the application of hazardous reagents and noble metal catalysts. Also, the production of stoichiometric amounts of waste is unattractive. Nucleophilic substitution with hydroxyl containing starting materials therefore is an important alternative for the formation of C-C bonds. Especially alcohols exhibit a high natural abundance and can be derived from renewable resources.

When alcohols are employed in an ideal S_N reaction, water is formed as by-product, which makes this protocol advantageous (Scheme 1). However, since hydroxy groups in alcohols are intrinsically poor leaving groups (LG), an activation by transforming them in better ones has to occur.[5,6] This dehydroxylation can be conducted indirectly by conversion into good leaving groups like tosylates,[7] triflates,[8] mesylates,[9] acetates[10] and halides.[11] For this step, at least one stoichiometric reagent (X-Y) is necessary, resulting in the generation of critical by-products. Direct substitution of the hydroxyl group is generally more attractive and can be achieved in S_N2 reactions by generating oxyphosphonium intermediates, as in the Mitsunobu[12,13,14] or Appel reaction.[14,15,16] In the Appel reaction, triphenylphosphine acts as promotor for the substitution with an electrophilic halogenation reagent like carbon tetrachloride or *N*-halosuccinimides.[15] In the Mitsunobu reaction, alcohols are converted into ester, ether, amines or thioester by application of triphenylphosphine and a diazodicarboxylate as reagent.[13] In both reactions $O{=}PPh_3$ is generated as leaving group, forming the product under a stereochemical Walden inversion.



Scheme 1: Ideal and conventional nucleophilic subsitution reactions of alcohols.[4]

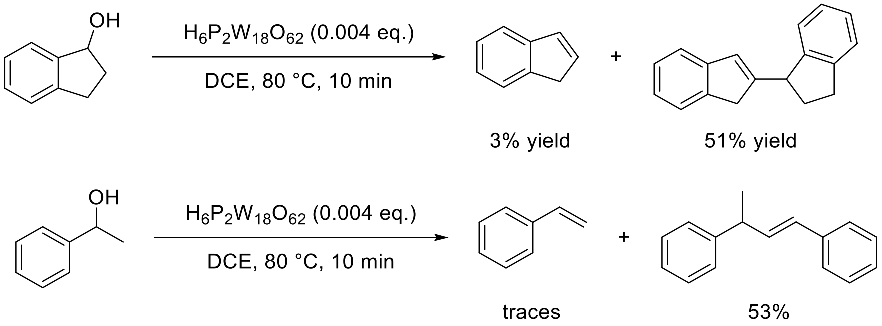
Based on these fundamental substitution reactions, many catalytic methods have been evolved with the intention for more efficient and sustainable nucleophilic substitution protocols for alcohols.[4,17,18] In Scheme 2 simplified concepts are depicted. In particular Lewis base (LB) catalysis is inspired by the reports of Mitsunobu and Appel.[6,19] Thereby redox-neutral, as well as redox promoted strategies are known. In either way, a one-step bimolecular S_N2 like mechanism is responsible for the inversion of configuration. Transition metal (TM) catalysis is another possible strategy for catalytic nucleophilic substitution of alcohols and can either be performed *via* the generation of metal π-complexes[20,21,22] or *via* a hydrogen borrowing mechanism,[23] which is based on an initial dehydrogenation, subsequent imine or aldol condensation and conclusive returning of the hydrogen. The most commonly known strategy however, is Lewis and Brønsted acid catalysis.[24] The alcohol is activated by the acid, forming a reactive intermediate, which undergoes a two-step S_N1 reaction *via* an achiral carbocationic transition state.[25] The major advantage of this reaction is the generation of water as the only byproduct. This principle is for example used in the direct dehydrative coupling of alcohols, forming new sp_3-sp_2 C-C bonds.[21,22,26] Mostly benzylic alcohols are employed in these S_N1 reactions, due to easy ionization to generate the stabilized carbocation.



Scheme 2: Different direct nucleophilic substitution reaction pathways for alcohols.[4]

2.1.2. Direct Dehydrative Coupling of Benzylic Alcohols to New sp_3-sp_2 C-C bonds

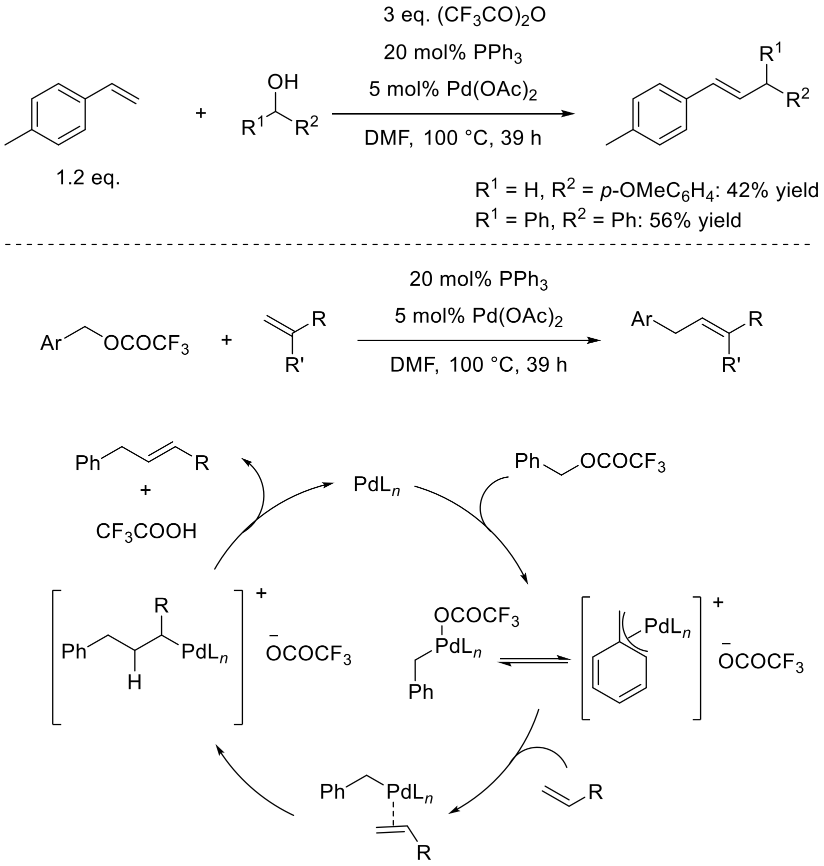
2.1.2.1. Metal-Catalyzed Dehydrative Coupling



Scheme 3: Dehydrative coupling of benzylic alcohols with a Wells-Dawson tungston heteropolyacid by Muzart *et al.*.[27]

When looking on the history of direct dehydrative coupling of benzylic alcohols, metal catalysts are mainly represented as activating agents in earlier reports. In 2006, Muzart and coworkers reported the application of the Wells–Dawson tungsten heteropolyacid $H_2P_2W_{18}O_{62}$ as a catalyst for the homocoupling of 1-indanol and of 1-phenylethanol in 1,2-dichloroethane.The reaction, however, suffered from low yields (Scheme 3).[27]

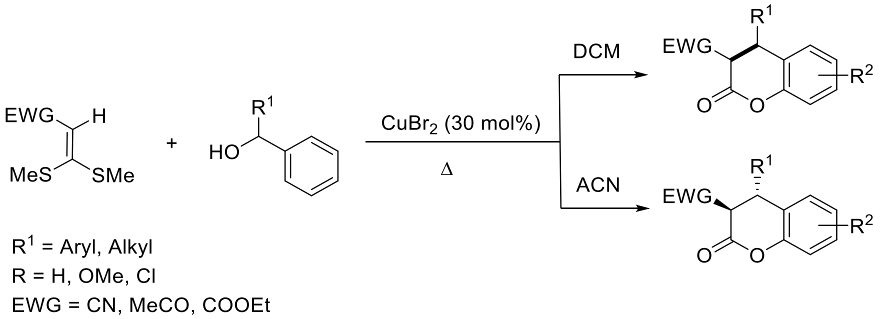
In 2008, Yamamoto *et al*. disclosed a Pd(II)-catalyzed heterocoupling of benzylic alcohols with styrene derivatives shortly afterward (Scheme 4).[28] The desired substituted olefins were obtained in moderate yields by applying three equivalents of $(CF_3CO)_2O$ as additive and PPh_3 as a ligand. In the proposed mechanism, a benzylpalladium (II) carboxylate complex is formed after oxidative addition with C-O bond cleavage. Subsequent olefin insertion to the alkyl palladium complex and β-hydrogen elimination generates the product and CF_3COOH. The direct conversion of carboxylic acids into aldehydes and ketones was accomplished by addition of an external anhydride or dicarbonate.



Scheme 4: Pd(II)-catalyzed heterocoupling of benzylic alcohos with trifluoroacetic anhydride or trifluoroacetic acid.[28]

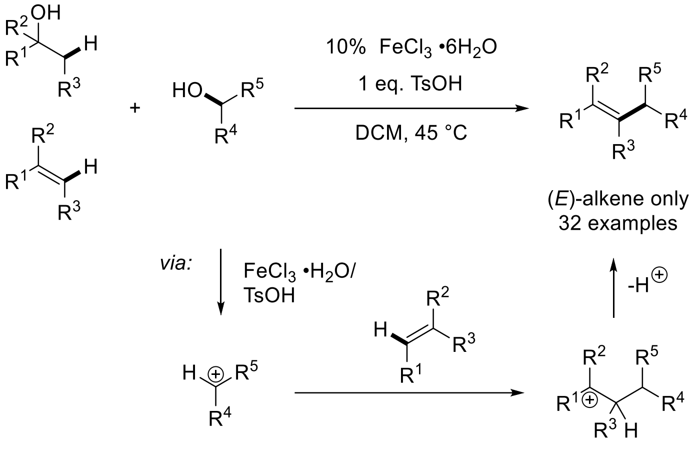
Liu *et al.* reported a C-C coupling of benzylic alcohols and ketene dithioacetals as alkene coupling partners to furnish 4*H*-chromenes *via* a Cu(II)-catalyzed one pot-synthesis (Scheme 5).[29] With $CuBr_2$ in dichloromethane (DCM), a tandem benzylation/cyclization reaction was performed.

Interestingly, a high diastereoselectivity could be achieved by exchanging dichloromethane with acetonitrile (ACN) and the application of other copperhalides did not provide the desired products.



Scheme 5: The synthesis of 4*H*-chromenes *via* copper-catalyzed dehydrative coupling.

In 2011, Wu and coworkers developed an iron-catalyzed coupling of benzylic alcohols with styrenes and alcohols by applying 10 mol% $FeCl_3 \bullet H_2O$ and stoichiometric amounts of *p*-toluenesulfonic acid (1 eq., TsOH) in dichloromethane (Scheme 6).[30] Substituted (*E*)-alkenes were obtained selectively under mild conditions in good yields. Based on kinetic isotope studies, a k_H/k_D value of 1.19 was determined, hinting towards a mechanism involving a carbocationic intermediate. In a mechanistic proposal, this intermediate is formed by the iron catalyst and the acid, which further reacts with the styrene derivative in an electrophilic addition. Deprotonation of the newly formed cationic intermediate provides the heterocoupled product. Additionally, they were able to couple two different benzylic alcohols *via in situ* styrene formation and dehydration.

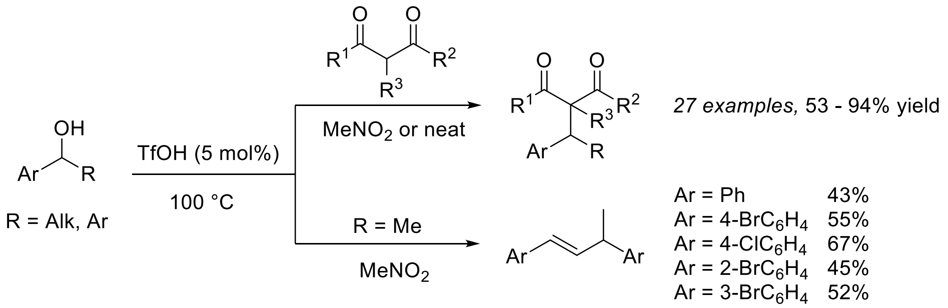


Scheme 6: Iron-catalyzed dehydrative coupling with stoichiometric amounts of a Brønsted acid reported by Wu.[30]

Yi *et al.* published a selective catalytic C-H alkylation of alkenes with aliphatic alcohols with the cationic ruthenium complex as$[(C_6H_6)(PCy_3)(CO)RuH]^+BF_4^-$ catalyst.[31] In 2016, a regioselective calcium-catalyzed dehydrative coupling was established by Yaragorla and co-workers.[32] They were able to synthesize internal alkenes from benzhydrols and styrene derivatives as well as indole derivatives. In addition, arenes and heteroarenes as substrates were employed in sp_3-sp_2 C-C bond forming direct dehydrative coupling reactions similar to a Friedel-Crafts reaction.[21,22]

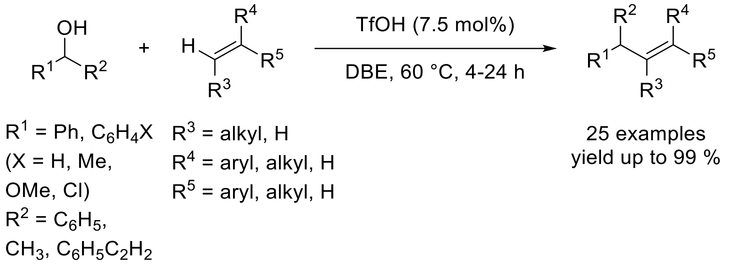
2.1.2.2. Acid-Catalyzed Dehydrative Coupling

Among the metal-free protocols of dehydrative coupling of benzylic alcohols, Sanz *et al.* briefly described dehydrative sp_3-sp_2 C-C bond formation with trifluoromethanesulfonic (TfOH) acid as catalyst in the context of the Brønsted acid-catalyzed benzylation of 1,3-dicarbonyl compounds (Scheme 7).[33] Nevertheless, the use of nitromethane is fairly unattractive due to its explosive properties and only a limited substrate scope and moderate yields could be obtained.



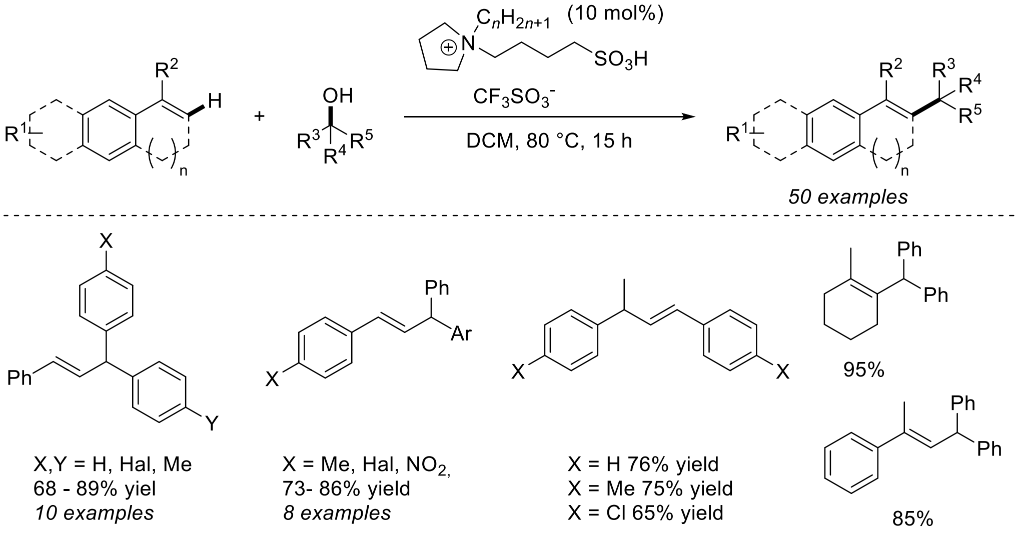
Scheme 7: Brønsted acid-catalyzed dehydrative heterocoupling with β-dicarbonyl compounds and homocoupling of 1-arylethanols.[33]

Ji and co-workers published a metal-free route to substituted olefins by direct heterocoupling of benzylic alcohols with alkenes with TfOH as catalyst a few years later (Scheme 8).[34] Substituted benzhydrols, propargylic, allylic and benzylic alcohols were suitable for the generation of the sp_3-sp_2 C-C bond in good to excellent yields. Interestingly, the reaction was only successful in 1,2-dibromoethane (DBE) and chloroform but not in 1,2-dichloroethane (DCE). Other strong acids such as *para*-toluenesulfonic acid (TsOH), trifluoroacetic acid (TFA), or lewis acids did not lead to any product formation.



Scheme 8: Trifluoromethanesulfonic acid catalyzed coupling of benzylic alcohols with alkenes in 1,2-dibromoethane.[34]

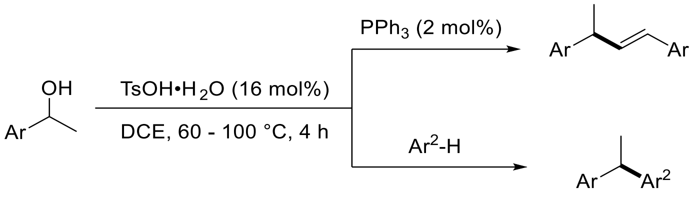
In 2014, this report was followed by a comprehensive publication on metal-free dehydrative homocoupling of benzylic alcohols from Xia *et al.* by applying previously prepared sulfonic acid-functionalized ionic liquids (Scheme 9).[35] The ionic liquids were derived from pyrrolidine, imidazole, pyridine and guanidine, whereas the ionic liquid with a pyrrolidine scaffold was most effective. The extensive substrate scope was mainly based on benzhydrols and benzylic alcohols substituted with halides and yielded the products in good to excellent yields. Employment of TsOH as Brønsted acid instead of an ionic liquid yielded the products only in traces.



Scheme 9: Direct dehydrative coupling with ionic liquids reported by Xia.[35]

Nama and co-workers additionally showed the application of heterogeneous catalysis on dehydrative coupling reactions of benzylic alcohols by using Zeolithes.[36] Generally, in many reports on the topic of direct metal-free dehydrative coupling of benzylic alcohols, the limitations and possible side reaction were not discussed.

2.2. Aim



Scheme 10: direct dehydrative homocoupling of benyzlic alcohols with involvement of a Lewis base and heterocoupling with electron-rich arened under mild reaction conditions.

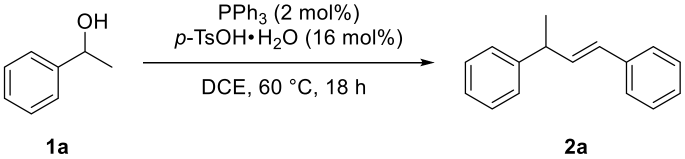
We developed a simple, direct metal-free dehydrative coupling starting from widely available and tractable alcohols by using easy-to-handle and commercially available catalysts under mild conditions (Scheme 10). The protocol was envisioned to overcome previous issues like the use of transition metals, additional preparative steps, side reactions, stoichiometric amounts of acid or additives. The reactions are performed with weaker sulfonic acid and triphenylphosphine as a Lewis base co-catalyst, which was not reported before. We focused on the investigation of the homocoupling of benzylic alcohols and the role of the catalyst components in this reaction.

2.3. Results and Discussion

2.3.1. Optimization Experiments

In a series of initial experiments TsOH•H_2O and 1-phenylethanol (**1a**) were heated to 60 °C in DCE for 18 h, affording dimer **2a** in 26% (Table 1, entry 1). Application of 2 mol% of triphenylphosphane (PPh_3) as additive showed the formation of **2a** in 76 % yield (entry 2). This was surprising since, in previous reports, the application of triphenylposphine as an additive in substitutions of alcohols was mainly shown in Mitsunobu or Appel-type reactions in stoichiometric amounts.[18,37] However, full conversion in both cases indicates oligomerization as main side reaction. Without an acid, low conversion and no formation of the product occurred.

Table 1 Excluding experiments

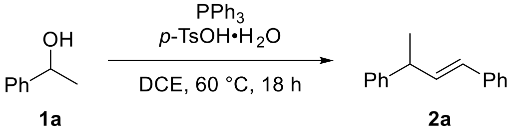


Entry	PPh_3	*p*-TsOH•H_2O	Conversion [%][a]	Yield of 2a [%][a]
1	–	x	100	26
2	x	x	100	76
3	x	–	13	–

General reaction conditions: **1a** (121 µL, 1.0 mmol), *p*-TsOH•H_2O (30 mg, 16 mol%), PPh_3 (5 mg, 2 mol%), 1,2-dichloroethane (3 mL), 60 °C, 18 h; [a] Yields and conversions were determined *via* quantitative GC-FID.

Further investigations of the ratio of acid catalyst to additive showed that 2 mol% of triphenylphosphine to 16 mol% *p*-toluenesulfonic acid gave the best results (Table 2, entry 3). Both increase and decrease of the amounts did not enhance the yield of **2a**. Stoichiometric amounts of triphenylphosphine prevented the formation of **2a** (entry 10 and entry 11), whereas stoichiometric amounts of *p*-toluenesulfonic acid only gave a diminished yield of 60% (entry 5).

Table 2: Variation of the ratio of PPh_3 to acid

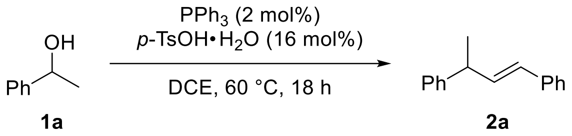


Entry	PPh_3	*p*-TsOH•H_2O	Yield of 2a [%][a]
1	2 mol%	5 mol%	4
2	2 mol%	10 mol%	52
3	2 mol%	16 mol%	76
4	2 mol%	20 mol%	61
5	2 mol%	1 eq	60
6	0.5 mol%	16 mol%	66
7	1 mol%	16 mol%	72
8	5 mol%	16 mol%	27
9	10 mol%	16 mol%	3
10	1 eq	16 mol%	–
11	1 eq	1 eq	–

General reaction conditions: **1a** (121 µL, 1.0 mmol), *p*-TsOH•H_2O (30 mg, 16 mol%), PPh_3 (5 mg, 2 mol%), 1,2-dichloroethane (3 mL), 60 °C, 18 h; [a] Yields and conversions were determined *via* quantitative GC-FID.

Investigations on the concentration showed, that the best result is obtained by applying a 0.33 M solution of **1a** in 1,2-dichloroethane (Table 3, entry 3). Lowering the concentration to 0.08 or 0.04 M (entries 1 and 2) showed only styrene formation which indicates that the reaction proceeds much slower than in the model reaction. On the other hand, increasing the concentration of **1a** to 1 M (entry 4) gave the desired product in a slightly diminished yield of 66% but with quantitative conversion of **1a**. Hence, higher concentration leads to a faster oligomerization, whereas lower concentrations reduce the reaction rate.

Table 3: Investigation on the concentration

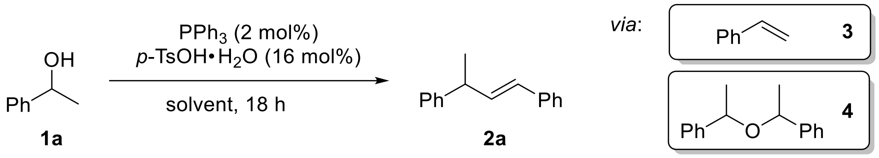


Entry	**Concentration [M]**	**Yield of 2a [%][a]**
1[b]	0.04	–
2	0.08	–
3	0.33	73
4	1.00	66

General reaction conditions: **1a** (60 µL, 0.5 mmol), *p*-TsOH•H_2O (15 mg, 16 mol%), PPh_3 (3 mg, 2 mol%), 1,2-dichloroethane, 60 °C, 18 h; [a] Yields were determined *via* quantitative GC-FID; [b] **1a** (30 µL, 0.25 mmol), *p*-TsOH•H_2O (15 mg, 16 mol%), PPh_3 (3 mg, 2 mol%).

The screening of a range of solvents was conducted under optimized reaction conditions and showed that the reaction proceeded best in polar aprotic, halogenated solvents (Table 4). The reaction worked especially well in in 1,2-dichloroethane. Application of degassed solvents (entries 2 and 6) did not clearly improve the yield, but a reaction temperature of 100 °C showed an increase to 80% yields (entries 3 and 4). The reaction worked also in other halogenated solvents as dichloromethane and chloroform. However, longer reaction times were necessary (entries 5, 7, 8 and 9). Yields decreased significantly when the reaction was carried out in nitrobenzene, trifluorotoluene, toluene, cyclohexane or ethyl acetate (entries 10 – 15). In other polar solvents, such as dimethylformamide, methanol, acetonitrile, acetone or THF, **2a** could not be obtained at all (entries 16 –20).

Table 4: Solvent screening

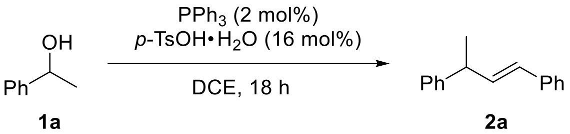


Entry	Solvents	T [°C]	Yield of **2a** [%][a]
1	1,2-dichloroethane	60	73
2[b]	1,2-dichloroethane	60	76
3[c.d]	1,2-dichloroethane	100	80
4[c,d]	1,2-dichloroethane	100	80
5	CH_2Cl_2	60	70
6[b]	CH_2Cl	60	74
7[c,d]	CH_2Cl_2	100	51
8[c]	$CHCl_3$	100	80
9[c,d]]	$CHCl_3$	100	5
10	PhCl	60	77
11	$PhNO_2$	60	57
12	$PhCF_3$	60	70
13	Toluene	60	37
14	Cyclohexane	60	13
15	Ethyl acetate	60	1
16	DMF	60	–
17	MeOH	60	–
18	Acetonitrile	60	–
19	Acetone	60	–
20	THF	60	–

General reaction conditions: **1a** (60 µL, 0.5 mmol), *p*-TsOH•H_2O (15 mg, 16 mol%), PPh_3 (3 mg, 2 mol%) solvent (1.5 mL), 60 °C, 18 h; [a] Yields were determined *via* quantitative GC-FID; [b] reaction was conducted under inert conditions in the respective degassed solvents; [c] **1a** (60 µL, 1.0 mmol), *p*-TsOH•H_2O (15 mg, 16 mol%), PPh_3 (3 mg, 2 mol%), solvent (3 mL); [d] reaction was conducted within 4 h.

As already seen in the solvent screening, higher reaction temperatures generated **2a** in better yields up to 80% (Table 5, entries 4 and 5). Full conversion of **1a** and generation of reaction intermediates **3** and **4** and 16% of **2a** at 40 °C show that the reaction is slowed down at lower reaction temperatures. At room temperature low conversion and no product formation was obtained.

Table 5: Investigation on the temperature.

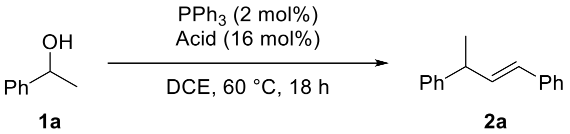


Entry	T [°C]	Conversion of 1a [%]	Yield of 2a [%][a]
1	r.t.	40	–
2	40	97	16
3	60	100	73
4	80	100	77
5	100	100	80

General reaction conditions: **1a** (60 µL, 0.5 mmol), *p*-TsOH•H_2O (15 mg, 16 mol%), PPh_3 (3 g, 2 mol%) solvent (1.5 mL), 60 °C, 18 h, under air; [a] Yields were determined *via* quantitative GC-FID.

Besides *p*-toluenesulfonic acid, also other acids were tested (Table 6). It turned out that sulfonic acids as methanesulfonic acid and trifluoromethanesulfonic acid were also able to catalyze the reaction (entries 2 and 3), whereas other Brønsted acids like trifluoroacetic acid, diphenylphosphate and benzoic acid were not suitable in this reaction and showed only low conversion (entries 4 – 6). Interestingly, also the application of HCl did not furnish **2a** (entry 7).

Table 6: Screening of various acids



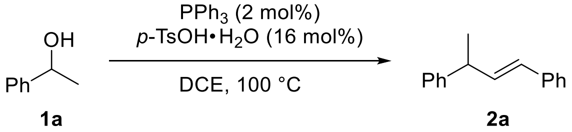
Entry	Acid (16 mol%)	Yield of 2a [%][a]
1	*p*-TsOH•H_2O	73
2	MsOH	71
3	TfOH	39
4	TFA	–
5	Diphenylphosphine	–
6	Benzoic acid	–
7	HCl	–
8	–	–

General reaction conditions: 1a (60 µL, 0.5 mmol), acid (16 mol%), PPh_3 (3 mg, 2 mol%) 1,2-dichloromethane (1.5 mL), 60 °C, 18 h, under air; [a] Yields were determined *via* quantitative GC-FID.

It was then found that the model reaction is already completed after 4 hours instead of 18 at 100 °C. Since the application of a phosphane conversely appears to be a necessity for avoiding oligomerization reactions, other phosphane additives were tested under previously determined optimal reaction conditions (Table 7).

It could be shown that an electron-donating substituent on the phenyl ring of triphenylphosphane decreased the yield from 80% to 70% (entry 3). Electron-withdrawing CF_3 groups on the phenyl ring instead led to quantitative formation of **2a** (entry 4). Beside phenyl-substituted monophosphanes, also alkanesubstituted phosphanes gave **2a** in good yields (74%, entry 5) and heterocyclic tri(2-furyl)phosphane (TFP) showed similar results (75%, entry 6). Bidentate phosphanes like BINAP were as well applicable to this kind of reaction providing good yields (70%, entry 7). Interestingly, also triphenylphosphane oxide worked as a suitable additive, however, the yield dropped from 80% to 63% (entry 8). Nevertheless, PPh_3 was chosen as an additive for subsequent reactions, due to its low cost and high stability.

Table 7: Additive screening



Entry	Additive	t [h]	Yield of 2a [%][a]
1	PPh_3	18	80
2	PPh_3	4	80
3	$P(4\text{-}MeC_6H_4)_3$	4	70
4	$P(4\text{-}CF_3C_6H_4)_3$	4	Quant.
5[b]	PCy_3	4	74
6	TFP	4	75
7	BINAP	4	70
8	$O{=}PPh_3$	4	64

General reaction conditions: **1a** (60 µL, 0.5 mmol), *p*-TsOH•H_2O (15 mg, 16 mol%), PPh_3 (3 mg, 2 mol%), 1,2-dichloroethane (1.5 mL), 100 °C, 18 h, under air; [a] Yields were determined *via* quantitative GC-FID; [b] Under inert conditions in degassed 1,2-dichloroethane.

2.3.2. Mechanistic Investigations

Quantitative conversion in the optimization experiments and observation of styrene as intermediate on GC-MS, indicated *in situ* dehydration of **1a**. The formed styrene can undergo oligomerization as the main side reaction. Addition of 4-*tert*-butylcatechol as inhibitor could not prevent the oligomerization nor the homocoupling, which excludes the possibility of a radical reaction pathway.

For further mechanistic insights, the reaction progress under optimized reaction conditions was evaluated (Figure 1). As already observed, styrene (**3**) was formed *in situ* from **1a** and reached a maximum yield of 84 % after 20 minutes and was then continuously converted to dimer **2a**. Additionally, an ether formation from **1a** to (oxybis(ethane-1,1-diyl))dibenzene (**4**) took place within the first 15 minutes. Compound **4** however, was consumed quite rapidly within the first 30 minutes. This also explains the sigmoidal curve of the formation of **2a**, which reached a maximum yield of 80 % after 4 h. Leftover styrene was further consumed, but it did not enhance the yield of **2a**.

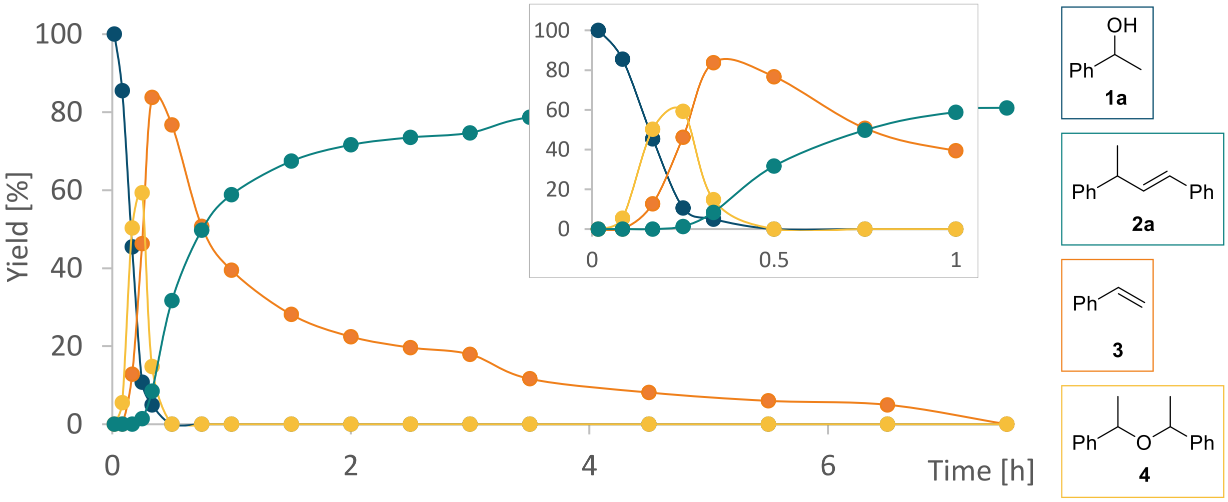
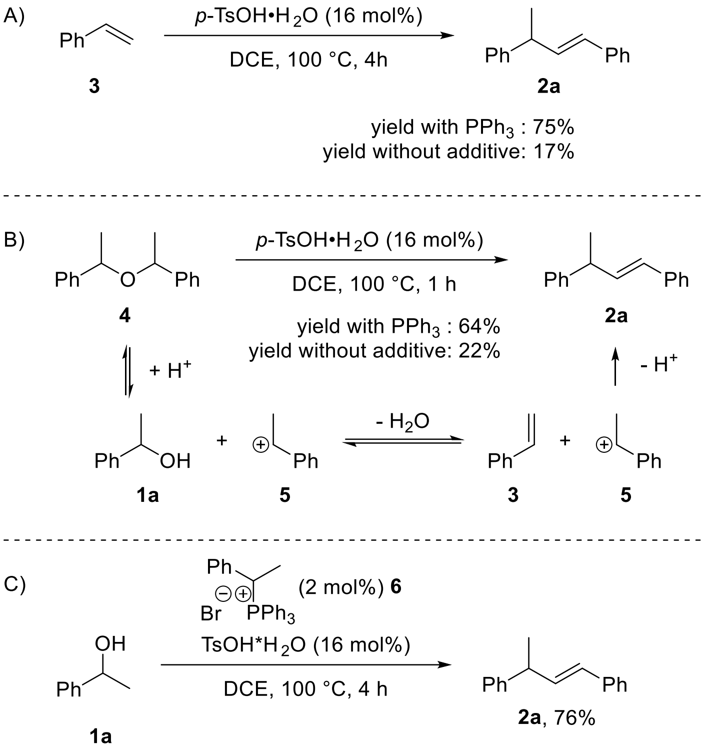


Figure 1: Reaction progress of the dehydrative coupling of **1a**. *General reaction conditions*: **1a** (1.0 mmol, 121 µL), *p*-TsOH·H₂O (16 mol%), PPh_3 (2 mol%), 1,2-dichloroethane (3 mL), 100 °C; yields were determined via quantitative GC-FID.

In order to clarify the influence of PPh_3 as additive, several mechanistic investigations were conducted (Scheme 11). Firstly, it was observed, that styrene (**3**) reacts like **1a** smoothly to **2a** under the optimized reaction conditions (Scheme 11A). Without the addition of PPh_3, **2a** was only obtained in poor yields (17 %), while **3** was fully converted. Hence, in the model reaction of **1a**

(Figure 1), the additive must have the most impact on the transformation of **3** to **2a**. Full conversion in both reactions provides another hint for the role of PPh_3 as inhibitor for the oligomerization.

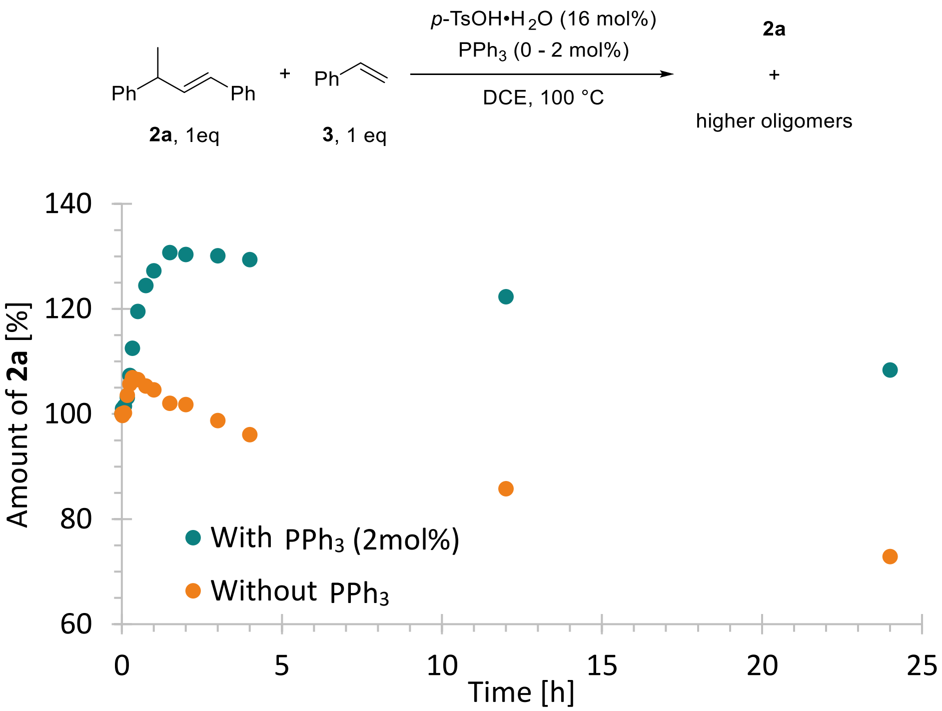


Scheme 11: Mechanistic investigations. *General reaction conditions*: A) **3** (1.0 mmol, 115 µL), *p*-TsOH·H_2O (16 mol%), PPh_3 (2 mol%), 1,2-dichloroethane (3 mL), 100 °C; B) **4** (1.0 mmol, 113 mg), *p*-TsOH·H_2O (16 mol%), PPh_3 (2 mol%), 1,2 dichloroethane (3 mL), 100 °C; C) **1a** (0.5 mmol, 61 µL), *p*-TsOH·H_2O (16 mol%), **6** (2 mol%), 1,2-dichloroethane (1.5 mL); yields were determined via quantitative GC-FID.

A similar observation was made when looking at the transformation of **4** (Scheme 11B). Since **4** is acid labile, **2a** was obtained in 22 % yield in the absence of PPh_3, with 82 % conversion of **4** and formation of **3** in 10 %. This leads to the assumption that in the model reaction, the formation of **4** is reversible and reformation of **1a**, dehydration and subsequent attack on the benzylic carbocation (**5**) generates **2a**. As observed before, the employment of PPh_3 resulted in an increase of yield. With this result in hand, we concluded that PPh_3 has to interact with carbocation **5** by catalytically forming a phosphonium salt, which allows the attack of a single nucleophile but sterically prevents the attack of a further one and consequently suppresses the formation of oligomers. In a subsequent experiment, phosphonium salt **6** was applied in the reaction of **1a** to

2a (Scheme 11C). As the yield is comparable to the model reaction (Table 7, entry 1), it supports the conclusion we have made before.

Furthermore, we followed the progress of the reaction of product **2a** with styrene (**3**, Scheme 12). Since the product itself is stable for at least 18 h under the given reaction conditions, we were wondering, if the addition of **3** would lead to oligomerization. In the experiment without additive, the amount of **2a** initially increased to 107 % of the initially applied **2a** due to the dimerization of **3**. Nevertheless, after only 15 minutes the amount of **2a** started to decline. After 24 h, the amount of **2a** was 30 % lower than in the beginning. This means that vinyl arene **3** indeed undergoes dimerization to **2a** within the first 15 minutes, but subsequently reacts with **2a** to generate higher oligomers. Contrary to that, **3** was consumed much slower in the presence of PPh_3 and 130 % of **2a** was obtained after 4 hours.



Scheme 12: Investigation of the oligomerization of **2a** with **3**. *General reaction conditions*: **2a** (0.5 mmol, 61 μL), **3** (0.5 mmol, 57 μL), p-TsOH·H_2O (16 mol%), PPh_3 (2 mol%), 1,2-dichloroethane (3 mL), 100 °C; yields were determined via quantitative GC-FID.

Even after 24 hours the amount of **2a** was not lower than at the start of the reaction. This proves that **3** is directly converted to **2a** and PPh_3 inhibits the further reaction of **2a** and **3**. Slow decrease in the amount of **2a** indicates, that the additive cannot completely suppress oligomerization over a longer period of time.

To investigate the effect of triphenylphosphine as additive, $^{31}P\{H\}$-NMR studies (NS = 256) were conducted in $CDCl_3$ with phosphoric acid as additional internal standard (δ = –0.63 ppm). An initial $^{31}P\{H\}$-NMR measurement of the used PPh_3 shows minor impurities of triphenylphosphine oxide (5%,Figure 2)

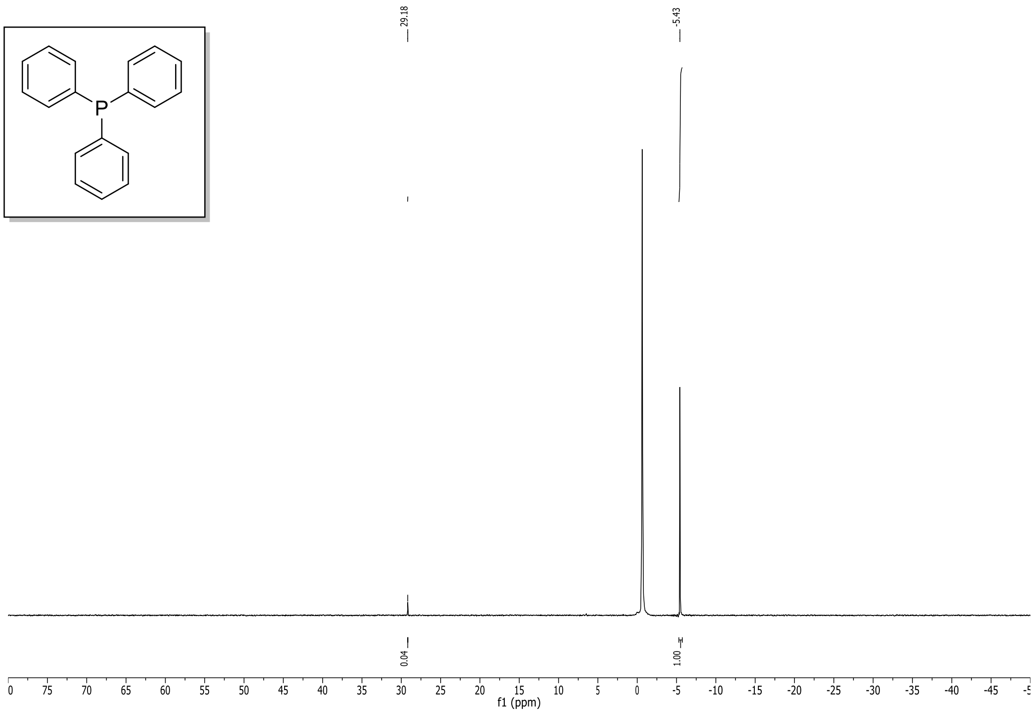


Figure 2 $^{31}P\{H\}$-NMR (400 MHz, $CDCl_3$) δ/ppm = 29.18 ($OPPh_3$), –5.43 (PPh_3); Internal standard: δ/ppm = –0.63 (H_3PO_4).

It is known that triphenylphosphine as well as the oxide forms salts with sulfonic acids at room temperature.[38] The formation of the triphenylphosphine salt with *p*-toluenesulfonic acid was also observed under the optimized reaction conditions of the model reaction, when **1a** was not present in the reaction mixture (δ = 3.45 ppm, Figure 3). Impurities of 4% visible at δ = 39.02 ppm show the salt formation of triphenylphosphine oxide with *p*-toluenesulfonic acid.

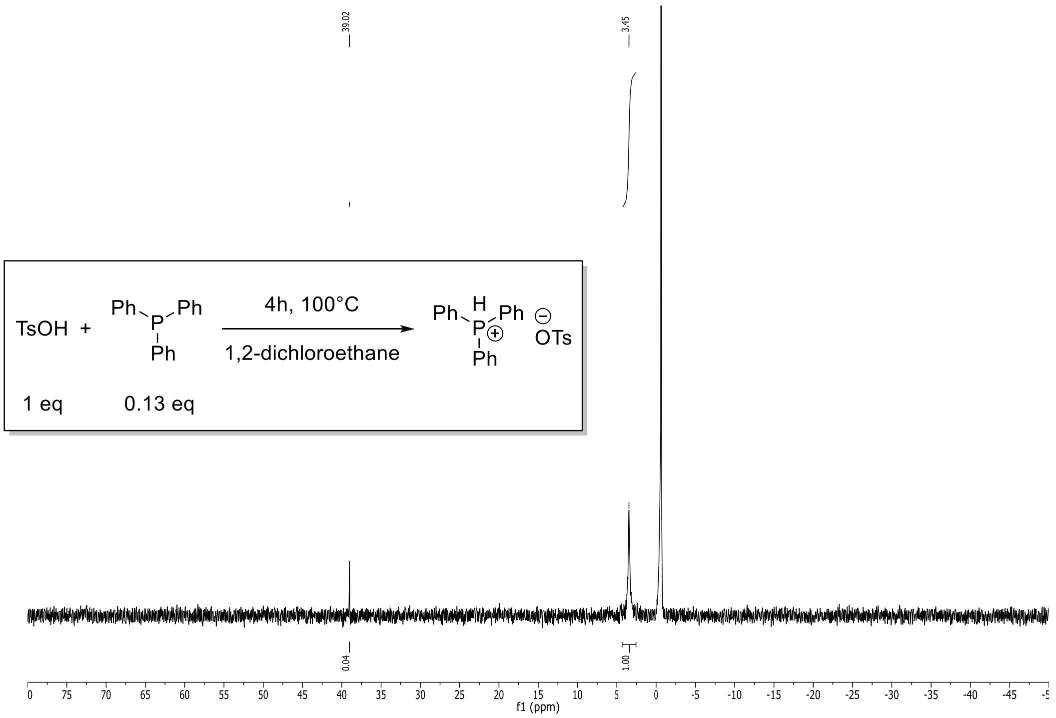


Figure 3 ^{31}P{H}-NMR (400 MHz, $CDCl_3$) δ/ppm = 39.02 (TsO-$HOPPh_3$), 3.45 (TsO-$HPPh_3$); Internal standard: δ/ppm = –0.63 (H_3PO_4).

Also in the model reaction of **1a** with triphenyl phosphine and toluenesulfonic acid under optimized conditions, this salt formation was visible. However, one additional phosphorous species was observed at δ = 26.39 ppm (Figure 4). Since we postulated a coordination of the formed carbocation of **1a**, we synthesized the corresponding salt (1-phenylethyl)triphenylphosphonium bromide (**6**, Figure 5) by standard procedures.[39]

Chemical shift of **6** and of the unknown species in Figure 3 are very close and hence, the formation of a phosphine salt with the carbocation in the model reaction is very likely. Nonetheless, it is not sure whether compound **6** or the corresponding dimer salt **7** is the main species in the ^{31}P{H}-NMR spectrum of Figure 4.

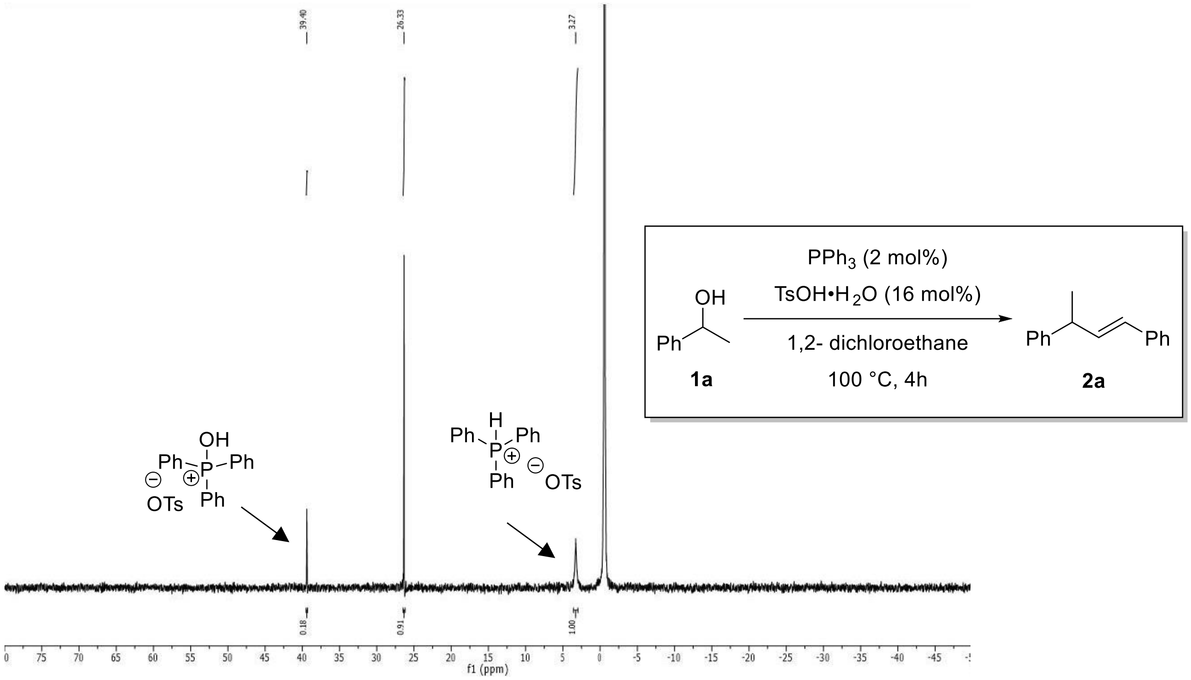


Figure 4 $^{31}P\{H\}$-NMR (400 MHz, $CDCl_3$) δ/ppm = 39.83 (TsO-HOPPh$_3$), 26.39, 3.40 (TsO-HPPh$_3$); Internal standard: δ/ppm = –0.63 (H_3PO_4).

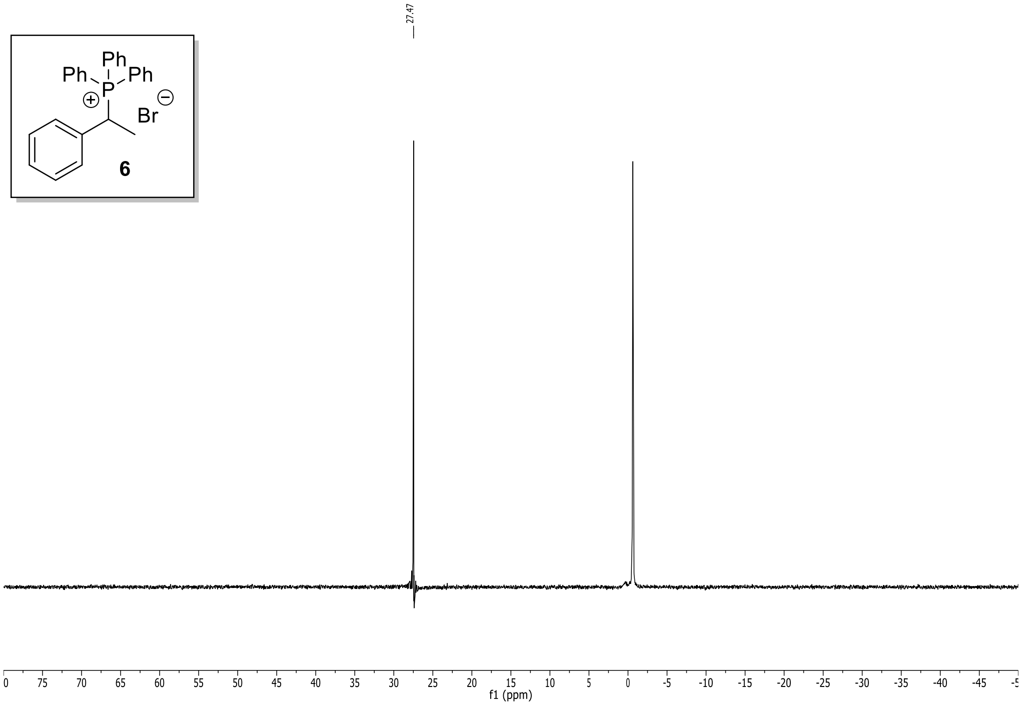
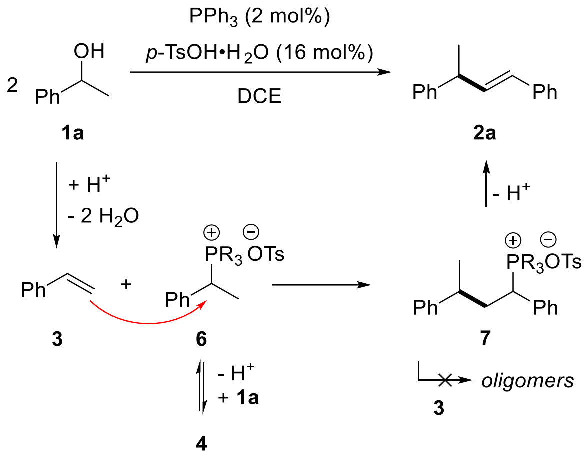


Figure 5 $^{31}P\{H\}$-NMR (400 MHz, $CDCl_3$) δ/ppm = 22.47 (**6**); Internal standard: δ/ppm = –0.63 (H_3PO_4).

Based on these observations, a plausible mechanism of the dehydrative coupling is depicted in Scheme 4. Unlike shown in previous publications,[33,34] we exclude the direct formation of **2a** from

4 by reaction with **3** since we could show the reversibility of the formation of **4** in acidic medium (Scheme 11B). Hence, we propose that dehydration of **1a** provides vinyl arene **3** and carbocation **5** *in situ*, while **5** is stabilized by phosphane to give salt **6**. This carbocation stabilization constitutes a plausible explanation for the reactivity in this reaction. **7** is considered as the determining cause for the prevention of oligomerization due to steric reasons. Proton abstraction from **7** then generates product **2a**.

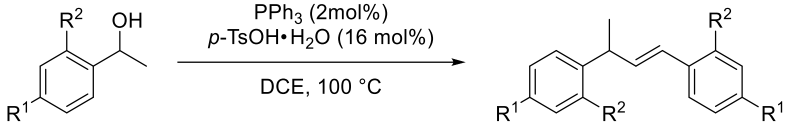


Scheme 4. Proposed mechanism for the dehydrative coupling.

With the proposed mechanism, it is also possible to explain the trend in the phosphane screening (Table 7). More electron-rich phosphanes generally show slightly lower yields after 4 h but also higher amounts of **3** (entries 3 and 5), whereas electron-deficient phosphanes show higher product formation (entry 4). This leads to the assumption that a stronger C-P bond in intermediate **6** slows the reaction with **3**. Application of triphenylphosphane oxide (Table 7, entry 7) shows a faster oligomerization since styrene (**3**) is completely consumed. However, weak coordination to the carbocation is also possible with the oxide and allows to generate **2a** in lower amounts.

2.3.3. Substrate Screening

Table 8: Substrate screening



1

2

Entry	R^1	R^2	Product	t [h]	Yield of 2a [%][a]
1	H	H	**2a**	4	80
2	Ph	H	**2b**	4	77
3	Br	H	**2c**	18	63
4	F	H	**2d**	4	75
5	I	H	**2e**	18	91
6	Cl	H	**2f**	12	77
7	H	Cl	**2g**	18	27
8	Me	H	**2h**	4	75
9	H	Me	**2i**	4	81
10	CF_3	H	**2j**	4	0
11	NO_2	H	**2k**	4	0

General reaction conditions: substrate (1 mmol), *p*-TsOH•H_2O (30 mg, 16 mol%), PPh_3 (5 mg, 2 mol%), 1,2-dichloroethane (3.0 mL), 100 °C, [a] isolated yields.

In subsequent investigations, substrate scope and limitations of the reactions were studied (Table 8). In general, electron donating substituents like methoxy groups in ortho-, meta- and para-position of phenyl, as well as 1-(2-naphthyl)ethanol and heteroaromatic compounds led to inseparable mixtures of various regioisomeric C-C coupling products (Figure 6). This can be explained by the fact that due to the higher electron density, the carbo cation (**6**) is formed faster and a more reactive styrene derivative (**3**) is generated, which cannot provide the desired head-to-tail dimer selectively. On the other hand, strongly electron withdrawing substituents as trifluoromethyl (entry 10) or nitro-groups (entry 11) deactivate the benzylic position and no product formation takes place.

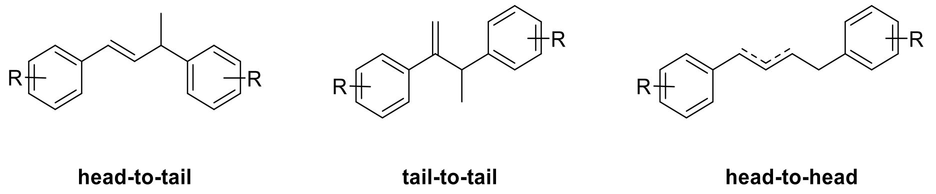


Figure 6: Possible regioisomers generated with electron-rich benzylic alcohols.

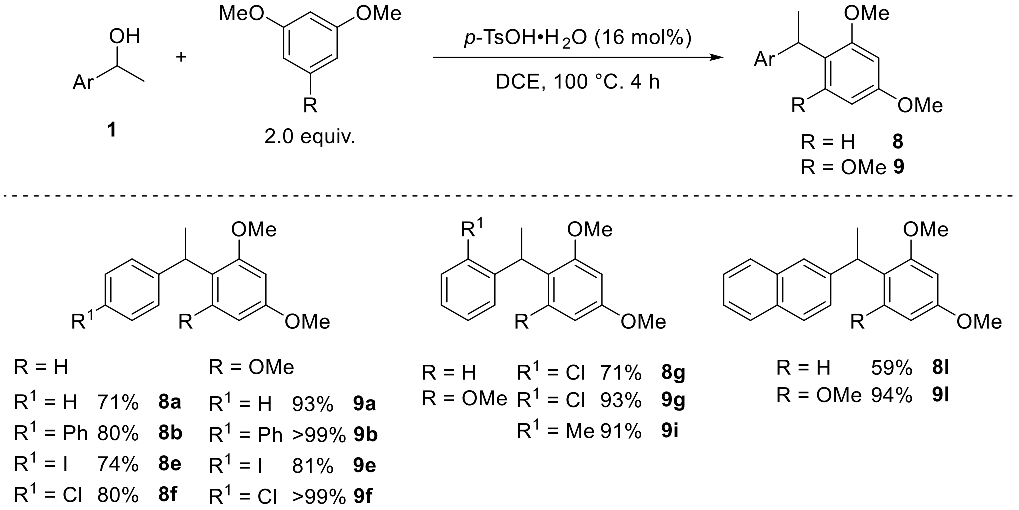
Nevertheless, halogenated substrates were suitable for this protocol, due to their “chameleon-like” inductive electron withdrawing (–I) and mesomeric electron donating (+M) effects. Halides in para-position gave good to excellent yields (entries 3–6). A chloro-substituent in ortho-position yet only provided 27 % yield of **2g** (entry 7). Interestingly, also 1-(4-biphenyl) ethanol (**1b**) as well as ortho- and para-methyl-substituted phenylethanols (**1h**, **1i**) appear to be reactive and selective enough to generate the C–C coupling products (entries 2, 8 and 9). Thus, the reactivity of benzylic alcohols in the homocoupling seems to correlate to substituents constants, however, a precise kinetic analysis is beyond the scope of this work.

2.3.4. C-C Heterocoupling with Electron-rich Arenes

The scope of this reaction was further expanded to C–C heterocoupling with electron-rich arenes. Similar hydroarylations of benzylic alcohols and vinyl arenes have been shown with catalysts like gold,[40]calcium,[41] zinc,[42] graphene oxide[43] and iron(III) porphyrin complexes.[44] In the past, the main focus in the acid-catalyzed heterocoupling of benzylic alcohols was put on vinyl arenes or 1,3-dicarbonyl compounds as nucleophiles.

Nevertheless, acid-catalyzed dehydrative hydroarylation of benzylic alcohols with electron-rich arenes is rare. For example, fluorinated aryl boronic acids were developed as catalysts for this transformation.[45] In a few reports using simple and available sulfonic acids, either the scope was narrow or a large excess of nucleophile was used.[46] On the other hand, the Brønsted-acid catalyzed hydroarylation of vinyl arenes with electron-rich arenes was reported.[47]

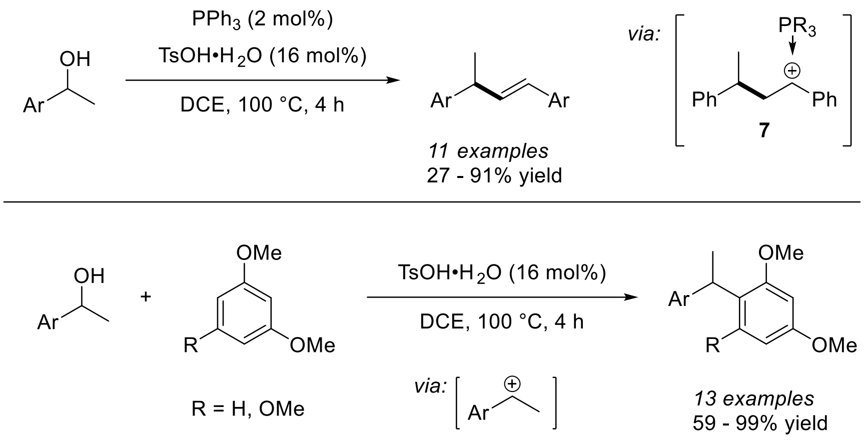
Thus, electron rich 1,3-dimethoxybenzene (DMB) and 1,3,5-trimethoxybenzene (TMB) were used as nucleophiles to react with benzylic alcohols. As expected and also as shown in literature, it is not necessary to add a phosphane or any other additive. This is due to the fact that TMB and DMB are both very good C-nucleophiles, which react much faster with the generated carbocation, than with an *in situ* formed vinyl arene. This inhibits the oligomerization as side reaction kinetically. Hence, the aryl compounds were added in excess under the reaction conditions applied in the previously described homocoupling reactions just without the additive (Scheme 13).



Scheme 13: Dehydrative hydroarylation. General reaction conditions: alcohol (0.5 mmol), arene (1 mmol) *p*-TsOH·H2O (16 mol%, 15 mg), DCE (3.0 mL), 100 °C, 4 h, isolated yields.

Dehydrative hydroarylation starting from 1-phenylethanol (**1a**) with TMB yielded the respective product **9a** in very good yield (93 %), whereas coupling with DMB gave product **8a** in 71 % yield (entry 2), which could be explained by the higher nucleophilicity of TMB provided by the three electron donating methoxy groups. This is a general trend, which is also visible when applying benzylic alcohols substituted on the aryl ring. In contrast to the homocoupling, the hydroarylation of 1-(2-naphthyl)ethanol (**1l**) to **8l** and **9l** was carried out in moderate to very good yields, even though **1l** was too reactive in the homodimerization. On the other hand, methoxy-substituted substrates still underwent various side reactions due to their higher electron density. Halogenated substrates worked well, generating the products in good to excellent yields (**8e**-**g** and **9e**-**g**). Unfortunately, other C–C-heterocoupling approaches with C-nucleophiles like indoles, *N*-methylpyrroles, norbornene or vinyl arenes, could not yield the respective products selectively under these reaction conditions.

2.4. Conclusion



Scheme 14: Overview of conducted dehydrative coupling exeriments in this chapter.

In conclusion, we developed a simple, direct pathway to substituted olefins from benzylic alcohols *via* an acid catalyzed dehydrative homocoupling (Scheme 14). Optimized reaction conditions were investigated, leading to the best yields with 16 mol% of *p*-toluene sulfonic acid, 2 mol% of PPh_3 in 1,2-dchloroethane and a reaction temperature of 100 °C. An interesting promotive effect of phosphane as Lewis basic co-catalyst was observed and mechanistic investigations were conducted. A plausible explanation for the necessity of a co-catalyst is interaction with carbo-cationic intermediates (**7**) to inhibit oligomerization. The use of easy to handle and commercially available, inexpensive reagents, relatively low catalyst loadings and the avoidance of toxic waste provided an attractive route for the formation of new sp_3-sp_2 C-C bonds. Furthermore, the dehydrative hydroarylation of benzylic alcohols with electron-rich arenes led to a variety of substituted 1,1-diarylethanes. It was shown that a co-catalyst is not necessary in this reaction, since nucleophilic addition of the electron-rich arenes is much faster than the formation and nucleophilic attack of *in situ* formed styrene.

2.5. Experimental Section

2.5.1. General Information

Starting materials and reagents were purchased from ABCR, Acros, Alfa Aesar, Fluka, Merck, Sigma Aldrich or TCI and used without further purification unless otherwise noted. Phosphine salts were synthesized from known synthetic routes[39,48] and ^{31}P-NMRs were taken without previous purification. Solvents were used in p.a. grade for reaction mixtures and column chromatography. Degassing of solvents was performed by bubbling argon through the respective liquid. Dry solvents were prepared according to standard procedures. Air sensitive syntheses were performed under an atmosphere of dry argon. Glassware used for these reactions was dried by heating under vacuum (flame) and subsequent cooling under dry Argon.

Chromatography:

Column chromatography was carried out using Silica gel (60 Å) as stationary phase, either using gravity flow or air overpressure flow conditions with puri Flash XS420 (interchim). Mobile phases are outlined for each experiment.

Thin layer chromatography (TLC) was performed on aluminum plates, pre-coated with silica gel 60 F254 (ALUGRAM Xtra SIL G/UV 254 layer thickness: 0.2 mm) and analyzed by fluorescence quenching under UV-light (254 nm).

2.5.2. Analytical Techniques

Nuclear magnetic resonance spectroscopy (NMR)

NMR spectra were recorded at ambient temperature on Bruker Avance 400 (^{1}H: 400.13 MHz, ^{13}C: 101 MHz, ^{31}P: 121 MHz) or Bruker Avance 300 (^{1}H: 300.13 MHz, ^{13}C: 75 MHz, ^{31}P: 162 MHz) instruments. All chemical shifts δ are reported in parts per million [ppm] relative to the solvent signal as internal standard (^{1}H: $CDCl_3$: $\delta = 7.26$ ppm; ^{13}C: $CDCl_3$: $\delta = 77.1$ ppm). Coupling constants across bonds are given in J (Hz). ^{13}C-NMR spectra were acquired on a broad band decoupled mode. ^{1}H-NMR splitting patterns are assigned as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). ^{13}C signals are assigned as C_q (quaternary carbon), + (primary and tertiary carbon), − (secondary carbon).

Melting points (mp)

Melting points were determined using a Schorpp MPM-HV3 and are uncorrected (heating rate 1 °C/min).

Mass spectrometry

GC-MS was recorded on an Agilent 7820A GC system with Quadrupole MS Agilent 7820A (EI) by using dry hydrogen as carrier gas. Agilent 190915-433UI column (30 m x 250 µm x 0.25 µm) was used. Program: Heating from 50 °C to 280 °C within 15 minutes.

HR-MS was recorded on an Agilent 5977A MSD (EI) instrument at the MS-department of the University of Tübingen.

Infrared spectroscopy (IR)

Infrared spectra were recorded on an Agilent Technologies Cary 630 FTIR spectrometer, equipped with an ATR-System. Absorption bands are given in wave numbers $\tilde{\nu}$ (cm^{-1}) and peak intensities are indicated as follows: s = strong, m = medium, w = weak and peak forms as: br = broad, sh = sharp.

Gas Chromatography (GC)

GC-FID (flame ionization detection) analysis was carried out on an Agilent 7820A system using dry hydrogen as carrier gas. Agilent 19091J-431 column (30 m x 320 µm x 0.25 µm) was used. Program 50-280M12: Heating from 50 °C to 280 °C within 12 minutes.

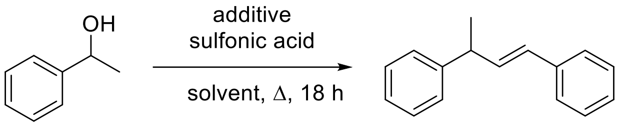
For GC sample preparation, an internal standard (*n*-pentadecane) was added to the reaction mixture in advance of the catalyst. After completion of the reaction, the mixture was filtered over celite 281 and basic alumina “super I”. The resulting filtrate was diluted with dichloromethane or ethyl acetate before performing GC analysis.

In order to determine yields and conversions the internal standard method was used for quantitative GC-FID. Therefore, calibration was conducted by variation of mass ratio of substrate and standard and analyzing the different samples by GC-FID. From the obtained data the peak area ratio was plotted against the mass ratio of substrate to standard. Linear regression led to the determination of the regression factor R.

$$\frac{m_{sub}}{m_{std}} \cdot R = \frac{A_{sub}}{A_{std}}$$

2.5.3. Optimization Experiments

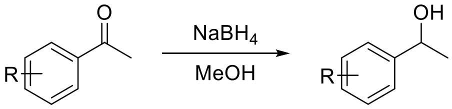
General procedure:



A 9 mL tube with screw cap was charged with 1-phenylethanol (**1a**, 121 µL, 1.0 mmol), *n*-pentadecane (50 µL, 0.18 mmol) as internal standard and dissolved in the desired solvent. An additive and a sulfonic acid were added subsequently, and the reaction mixture was heated and stirred for 18 h. After cooling down to r.t., the reaction mixture was filtered over basic alumina and celite and analyzed by GC-FID.

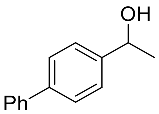
2.5.4. Synthesis of Benzylic Alcohols

General procedure:



In a round bottom flask (100 mL) the respective acetophenone (10 mmol, 1.0 eq.) was dissolved in MeOH (40 mL) and cooled to 0 °C with an ice bath. $NaBH_4$ (757 mg, 20 mmol, 2.0 eq.) was added slowly. After the addition, the reaction mixture was allowed to warm to r.t.. TLC analysis showed completion of the reduction. The reaction was subsequently quenched with a sat. aq. solution of NH_4Cl (20 mL). *p*H was adjusted to 3 and methanol was removed on the rotary evaporator. The mixture was extracted with DCM (3 x 10 mL). There collected organic phases were dried over Na_2SO_4 and filtered. Evaporation of solvent afforded the pure product.

1-([1,1'-Biphenyl]-4-yl)ethan-1-ol **1b**



The compound **1b** was obtained from the respective acetophenone applying the general procedure as a white solid (1.81 g, 9.1 mmol, 91%).

$C_{14}H_{12}O$ (MW: 198.27 g/mol)

R*f* = 0.71 (Cyclohexane/Ethyl acetate 60:40)

m.p.: 90 °C

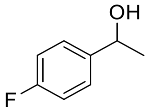
^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm = 7.67 – 7.53 (m, 4 H, C*H*$_{arom}$), 7.57 – 7.24 (m, 4 H, C*H*$_{arom}$), 7.38 – 7.31 (m, 1 H, C*H*$_{arom}$), 4.96 (q, *J* = 6.5 Hz, 1 H, C*H*CH_3), 1.75 (s, 1 H, O*H*), 1.55 (d, *J* = 6.5 Hz, 3 H, CH_2C*H*$_3$).

^{13}C-NMR (121 MHz, $CDCl_3$) δ/ppm = 144.6 (C_q), 140.7 (C_q), 140.30 (C_q), 128.6 (+), 127.1 (+), 126.9 (+), 125.7 (+), 70.0 (+), 25.0 (+).

GC-MS (EI) m/z = 198 (43, $[M^{+\bullet}]$), 183 (77, $[M^{+\bullet}]$-$[CH_3^\bullet]$), 181 (15, $[M^{+\bullet}]$-$[OH^\bullet]$), 155 (100, $[M^{+\bullet}]$-$[C_2H_2^{2\bullet}]$-$[OH^\bullet]$), 153 (39, $[M^{+\bullet}]$-$[C_2H_5O^\bullet]$).

The analytical data is in agreement with the literature.[49]

1-(4-Fluorophenyl)ethan-1-ol **1d**



The compound **1d** was obtained from the respective acetophenone using the general procedure as a colorless oil (448 mg, 3.2 mmol 32% yield).

C_8H_9FO (140.16 g/mol)

***R*f** = 0.20 (Cyclohexane/Ethyl acetate 80:20)

m.p.: Ambient temperature

^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm = 7.40 – 7.29 (m, 2H, C*H*$_{arom}$), 7.08 – 6.98 (m, 2H, C*H*$_{arom}$), 4.90 (q, *J* = 6.4 Hz, 1H, C*H*OH), 1.72 (bs, 1H, O*H*), 1.48 (d, *J* = 6.4 Hz, 3H, C*H*$_3$).

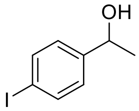
^{13}C-NMR (75 MHz, $CDCl_3$) δ/ppm = 163.3 (C_q), 160.9 (C_q), 141.5 (+, d, *J* = 3.1 Hz), 127.1 (+, d, *J* = 8.0 Hz), 115.2 (+, d, *J* = 21.3 Hz), 69.7 (+), 25.2 (+).

^{19}F-NMR (282 MHz, $CDCl_3$) δ/ppm = -115.8.

GC-MS (EI) m/z = 140.1 (6, [$M^{+\bullet}$]), 125.0 (27, [$M^{+\bullet}$]-[$CH_3^\bullet$]), 123.1 (13, [$M^{+\bullet}$]-[$OH^\bullet$]), 122.0 (100, [$M^{+\bullet}$]-[$F^\bullet$]), 95.0 (8, [$M^{+\bullet}$]-($CH_3CH_2OH^\bullet$].

The analytical data is in agreement with the literature.[50]

1–(4–Iodophenyl)ethan-1-ol **1e**



The compound **1e** was obtained from the respective acetophenone using the general procedure as a yellow solid (2.26 g, 9.1 mmol, 91%).

C_8H_9IO (248.06 g/mol)

***R*$_f$** = 0.19 (Cyclohexane/Ethylacetate 80:20)

m.p.: 49.2 °C

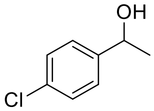
^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm = 7.71 – 7.65 (m, 2H, C*H*$_{arom}$), 7.16 – 7.10 (m, 2H, C*H*$_{arom}$), 4.86 (q, *J* = 6.5 Hz, 1H, C*H*OH), 1.58 (bs, 1H, O*H*), 1.47 (d, *J* = 6.5 Hz, 3H, C*H*$_3$).

^{13}C-NMR (101 MHz, $CDCl_3$) δ/ppm = 145.5 (C_q), 137.6 (+), 127.4(+), 92.7(+), 69.9(+), (+), 25.3 (+).

GC-MS (EI) m/z = 248.0 (13, [$M^{+\bullet}$]), 229.9 (76, [$M^{+\bullet}$]-[H_2O]), 216.9 (15, [$M^{+\bullet}$]-[$OH^\bullet$]-[$CH_3^\bullet$]), 203.9 (4, [$M^{+\bullet}$]-[$CH_2(OH)CH_3^\bullet$]), 121.1 (6, [$M^{+\bullet}$]-[$I^\bullet$]), 104.1 (100, [$M^{+\bullet}$]-[$OH^\bullet$]-[$I^\bullet$]).

The analytical data is in agreement with the literature.[51]

1-(4-Chlorophenyl)ethan-1-ol **1f**



The compound **1f** was obtained from the respective acetophenone using the general procedure as a yellowish oil (1.33 g, 8.5 mmol, 85%).

C_8H_9ClO (156.61 g/mol)

***R*$_f$** = 0.21 (Cyclohexane/ Ethyl acetate 80:20)

m.p.: Ambient temperature

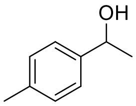
^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm = 7.35 – 7.27 (m, 4H, C*H*$_{arom}$), 4.88 (q, *J* = 6.5 Hz, 1H, C*H*OH), 1.78 (bs, 1H, O*H*), 1.47 (d, *J* = 6.5 Hz, 3H, C*H*$_3$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ/ppm = 144.3 (C_q), 133.1 (C_q), 128.6 (+), 126.8 (+), 69.8 (+), 25.3 (+).

GC-MS (EI) m/z = 156.0 [21, $M^{+\bullet}$], 141.0 (100, [$M^{+\bullet}$]-[$CH_3^\bullet$]), 121.1 (15, [$M^{+\bullet}$]-[$Cl^\bullet$]), 113.0 (48, [$M^{+\bullet}$]-[$CHOHCH_3^\bullet$]), 103.0 (21, [$M^{+\bullet}$]-[$OH^\bullet$]-[$Cl^\bullet$]).

The analytical data is in agreement with the literature.[52,53]

1–(*p*–Tolyl)ethan-1-ol **1h**



The compound **1h** was obtained from the respective acetophenone using the general procedure as a colorless oil (1.17 g, 8.6 mmol, 86%).

$C_9H_{12}O$ (136.19 g/mol)

***R*$_f$** = 0.19 (Cyclohexane/Ethyl acetate 80:20)

m.p.: Ambient temperature

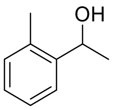
^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm = 7.30 – 7.25 (m, 2H, C*H*$_{arom}$), 7.19 – 7.14 (m, 2H, C*H*$_{arom}$), 4.87 (q, *J* = 6.4 Hz, 1H, C*H*OH), 2.35 (s, 3H, C*H*$_3$), 1.77 (bs, 1H, C), 1.49 (d, *J* = 6.5 Hz, 3H, CH(OH)C*H*$_3$).

^{13}C-NMR (75 MHz, CDCl3) δ/ppm = 142.9 (C_q), 137.2 (C_q), 129.2 (+), 125.4 (+), 70.3 (+), 25.1 (+), 21.1 (+).

GC-MS (EI) m/z = 136.1 (31, [$M^{+\bullet}$]), 121.1 (100, [$M^{+\bullet}$]-[$CH_3^\bullet$]), 103.1 (6, [$M^{+\bullet}$]-[$CH_3^\bullet$]-[$OH^\bullet$]).

The analytical data is in agreement with the literature.[52,54]

1-(*o*-Tolyl)ethan-1-ol **1i**



The compound **1i** was obtained from the respective acetophenone using the general procedure as a colorless oil (694 mg, 5.1 mmol, 51%).

$C_9H_{12}O_2$ (MW: 136.19 g/mol)

***R**f* = 0.33 (Cyclohexane/Ethyl acetate 80:20)

m.p.: Ambient temperature

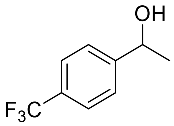
^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm = 7.52 (d, *J* = 7.4 Hz, 1H, C*H*$_{arom}$), 7.28 – 7.11 (m, 3H, C*H*$_{arom}$), 5.14 (q, *J* = 6.4 Hz, 1H, C*H*CH$_3$), 2.35 (s, 3H, C*H*$_3$), 1.69 (bs, 1H, O*H*), 1.47 (d, *J* = 6.4 Hz, 3H, CHC*H*$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 144.0 (C_q), 134.2(C_q), 130.4 (+), 127.1 (+), 126.4 (+), 124.6 (+), 66.7 (+), 24.0 (+), 19.0 (+).

GC-MS (EI) m/z = 136 (19, [$M^{+\bullet}$]), 121 (100, [$M^{+\bullet}$]-[$CH_3^\bullet$]), 91 (100, [$M^{+\bullet}$]-[$C_2H_5O^\bullet$]), 77 (91, [$M^{+\bullet}$]-[$C_2H_5O^\bullet$]-[CH_3]).

The analytical data is in agreement with the literature.[55]

1-(4-(Trifluoromethyl)phenyl)ethan-1-ol **1j**



The compound **1j** was obtained from the respective acetophenone using the general procedure as a yellowish oil in (1.40 g, 9.2 mmol, 92%).

$C_9H_9F_3O$ (190.17 g/mol)

***R*$_f$:** 0.21 (cyclohexane/ethyl acetate 80:20).

m.p.: Ambient temperature

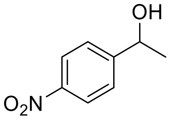
^{1}H-NMR (300 MHz, $CDCl_3$) δ/ppm = 7.61 (d, *J* = 8.2 Hz, 2H, C*H*$_{arom}$), 7.58 (d, *J* = 8.2 Hz, 2H, C*H*$_{arom}$), 4.97 (q, *J* = 6.1 Hz, 1H, C*H*CH$_3$), 1.87 (bs, 1H, O*H*), 1.50 (d, *J* = 6.5 Hz, 3H, CHC*H*$_3$).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 149.7 (C_q), 125.7 (+), 125.5 (+), 125.4 (+), 125.4 (+), 70.0 (+), 25.4 (+).

GC-MS (EI) m/z = 190.1 (8, [$M^{+\bullet}$]), 175.0 (100, [$M^{+\bullet}$]-[$CH_3^\bullet$]), 147.1 (37, [$M^{+\bullet}$]-[$C_2H_5O^\bullet$]), 127.0 (23, [$M^{+\bullet}$]-[$F^\bullet$]-[$C_2H_5O^\bullet$]).

The analytical data is in agreement with the literature.[56]

1–(4–Nitrophenyl)ethan-1-ol **1k**



The compound **1k** was obtained from the respective acetophenone using the general procedure as a yellow oil (1.50 g, 9.0 mmol, 90%).

$C_8H_9NO_3$ (167.16 g/mol)

***R*f** = 0.10 (cyclohexane/ethyl acetate 80:20).

m.p.: ambient temperature.

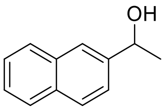
^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm = 8.30 – 8.01 (m, 2H, C*H*arom), 7.63 – 7.39 (m, 2H, C*H*arom)), 5.02 (q, *J* = 6.5 Hz, 1H, C*H*OH), 1.85 (bs, 1H, O*H*), 1.52 (d, *J* = 6.5 Hz, 3H, C*H*$_3$).

^{13}C-NMR (101 MHz, $CDCl_3$): δ/ppm = 153.1 (C_q), 126.1 (+), 123.8 (+), 69.5 (+), 25.6 (+).

GC-MS (EI) m/z = 167.0 (2, [$M^{+\bullet}$]), 152.0 (100, [$M^{+\bullet}$]-[$CH_3^\bullet$]), 121.1 (60, [$M^{+\bullet}$]-[$NO_2^\bullet$]), 107.0 (63, [$M^{+\bullet}$]-[$NO_2^\bullet$]-[$CH_3^\bullet$]).

The analytical data is in agreement with the literature.[51]

1-(Naphthalen-2-yl)ethan-1-ol **1l**



The compound **1l** was obtained from the respective acetophenone using the general procedure as a white solid (1.62 g, 9.4 mmol, 94%).

$C_{12}H_{12}O$ (MW: 172.23 g/mol)

R_f = 0.34 (Cyclohexane/Ethyl acetate 60:40)

m.p.: 74.4 °C

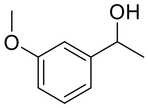
^{1}H-NMR (300 MHz, $CDCl_3$) δ/ppm = 7.91 – 7.75 (m, 4 H, C*H*$_{arom}$), 7.57 – 7.37 (m, 3 H, C*H*$_{arom}$), 5.08 (q, *J* = 6.4 Hz, 1 H, C*H*CH_3), 1.73 (s, 1 H, O*H*), 1.59 (d, *J* = 6.5 Hz, 3 H, CHC*H*$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 143.2 (C_q), 133.3 (C_q), 132.9 (+), 128.4 (+), 128.0 (+), 127.7 (+), 126.19 (+), 125.8 (+), 123.8(+), 70.6 (+), 25.2 (+).

GC-MS (EI) m/z = 172 (31, [$M^{+\bullet}$]-[$H^\bullet$]), 157 (32, [$M^{+\bullet}$]-[$CH_3^\bullet$]), 127 (35, [$M^{+\bullet}$]-[$C_2H_5O^\bullet$]).

The analytical data is in agreement with the literature.[57,58]

<u>1-(3-Methoxyphenyl)ethan-1-ol</u>



The compound was obtained from the respective acetophenone using the general procedure as a yellowish oil in (1.40 g, 9.2 mmol, 92%).

$C_9H_{12}O_2$ (MW: 152.08 g/mol)

R_f = 0.37 (Cyclohexane/Ethyl acetate 80:20)

m.p.: Ambient temperature

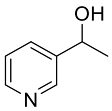
^{1}H-NMR (300 MHz, $CDCl_3$) δ/ppm = 7.27 (t, *J* = 8.1 Hz, 1H, C*H*$_{arom}$), 6.95 (m, 2H, C*H*$_{arom}$), 6.82 (m, 1H, C*H*$_{arom}$), 4.88 (q, *J* = 6.4 Hz, 1H, C*H*CH_3), 3.82 (s, 3H, OC*H*$_3$), 1.82 (bs, 1H, O*H*), 1.49 (d, *J* = 6.5 Hz, 3H, CHC*H*$_3$).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 159.8 (C_q), 147.6 (C_q), 129.6 (+), 117.7 (+), 112.9 (+), 110.9 (+), 70.4 (+), 55.3 (+), 25.2 (+).

GC-MS (EI) m/z = 152.0 (39, [$M^{+\bullet}$]), 137.1 (36, [$M^{+\bullet}$]-[$CH_3^\bullet$]), 121.0 (4, [$M^{+\bullet}$]-[$CH_3O^\bullet$]), 108.1 (100, [$M^{+\bullet}$]-[$C_2H_5O^\bullet$]), 77.1 (33, [$M^{+\bullet}$]-[$C_2H_5O^\bullet$]-[$CH_3O^\bullet$]).

The analytical data is in agreement with the literature.[57,59]

1–(3'–Pyridyl)ethanol



The compound was obtained from the respective ketone using the general procedure as a colorless oil (1.08 g, 8.8 mmol, 88%).

C_7H_9NO (123.16 g/mol)

***R*f:** 0.18 (Cyclohexane/Ethyl acetate 80:20)

m.p.: Ambient temperature.

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 8.55 (d, *J* = 1.5 Hz, 1H, CH_{arom}), 8.51 – 8.44 (m, 1H, CH_{arom}), 7.74 (dt, *J* = 7.9, 1.8 Hz, 1H, CH_{arom}), 7.31 – 7.24 (m, 1H, CH_{arom}), 4.95 (q, *J* = 6.5 Hz, 1H, $CHCH_3$), 2.59 (bs, 1H, O*H*), 1.52 (d, *J* = 6.5 Hz, 3H, $CHCH_3$).

^{13}C-NMR (75 MHz, $CDCl_3$): δ/ppm = 148.6 (+), 147.3 (+), 141.2, 133.3 (+), 123.6 (+), 68.0 (+), 25.3 (+).

GC-MS (EI) m/z = 123.1 (29, $[M^{+\bullet}]$), 108.0 (100, $[M^{+\bullet}]$-$[CH_3^{\bullet}]$).

The analytical data is in agreement with the literature.[60]

2.5.5. Substrate Screening: Homocoupling

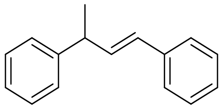
General procedure:

A pressure tube with screw-cap was charged with *p*-toluenesulfonic acid (0.16 eq., 30 mg, 160 µmol) and triphenyl phosphine (0.02 eq., 5 mg, 20 µmol). The components were dissolved in 1,2-dichloroethane (3 mL) and subsequently, the substrate (1.0 eq, 1.0 mmol) was added and the reaction mixture was stirred at 100 °C. The reaction was quenched by addition of sat. aq. solution of $NaHCO_3$. Extraction with dichloromethane gave the crude product. Purification was conducted *via* flash column chromatography.

No dimer formation was observed when applying 1-(4-(trifluoromethyl)phenyl)ethan-1-ol, 4-(1-hydroxyethyl)phenyl acetate, 1-(4-nitrophenyl)ethan-1-ol, 1-(4-aminophenyl) ethan-1-ol, 1-(2-methoxyphenyl)ethan-1-ol and 1-(pyridin-3-yl)ethan-1-ol.

A mixture of dimers, which could not be purified was obtained when applying 1-(naphthalene-2-yl)ethan-1-ol, 4-(1-Hydroxyethyl)benzonitrile, 1-(3-methoxyphenyl) ethan-1-ol, 1-(2-methoxyphenyl)ethan-1-ol, 1-(4-methoxyphenyl)ethan-1-ol.

(*E*)-But-1-ene-1,3-diyldibenzene **2a**



The compound **2a** was obtained from the respective benzylic alcohol using the general procedure within 4 h reaction time and purification by column chromatography (Petroleum ether) as a colorless oil (83 mg, 0.4 mmol, 80%).

$C_{16}H_{16}$ (MW: 208.30 g/mol)

$\mathbf{R}_{\boldsymbol{f}}$ = 0.72 (Petroleum ether /Ethyl acetate 97.5:2.5)

m.p.: Ambient temperature

^{1}H-NMR (400 MHz, CDCl3) δ/ppm = 7.38 – 7.21 (m, 8H, $\mathrm{C}H_{\mathrm{arom}}$), 7.20 – 7.07 (m, 2H, $\mathrm{C}H_{\mathrm{arom}}$), 6.36 (m, 2H, C*H*=C*H*), 3.60 (m, 1H, $\mathrm{C}H\mathrm{CH_3}$), 1.43 (d, J = 7.0 Hz, 3H, $\mathrm{CHC}H_3$).

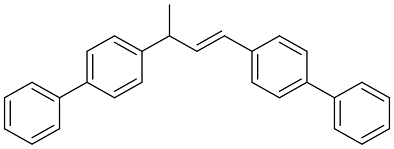
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = δ 145.7 (C_q), 137.7(C_q), 135.4 (+), 128.7 (+), 128.6 (+), 127.4 (+), 127.2 (+), 126.4 (+), 126.3 (+), 42.7 (+), 21.4 (+).

GC-FID (50-280M12): t_R = 9.67 min

GC-MS (EI) m/z = 208.2 (97, $[M^{+\bullet}]$),193.2 (92, $[M^{+\bullet}]$-$[CH_3^{\bullet}]$), 178.2 (41.8, $[M^{+\bullet}]$-$[CH_3^{\bullet}]$-$[CH^{2\bullet}]$), 165.1 (14, $[M^{+\bullet}]$-$[C_2H_2^{\bullet}]$-$[CH_3^{\bullet}]$), 130.1 (31, $[M^{+\bullet}]$-$[H^{\bullet}]$-$[C_6H_5^{\bullet}]$), 115.1 (100, $[M^{+\bullet}]$-$[H^{\bullet}]$-$[CH_3^{\bullet}]$- $[C_6H_4^{\bullet}]$), 105.1 (13, $[M^{+\bullet}]$-$[C_8H_7^{\bullet}]$).

The analytical data is in agreement with the literature.[61]

(*E*)-4,4''-(But-1-ene-1,3-diyl)di-1,1'-biphenyl **2b**



The compound **2b** was obtained from the respective benzylic alcohol using the general procedure within 4 h reaction time and purification by column chromatography (Petroleum ether) as a white solid (137 mg 0.4 mmol, 77%).

$C_{28}H_{24}$ (MW: 360.50 g/mol)

R*f* = 0.57 (Petroleum ether /Ethyl acetate 97.5:2.5)

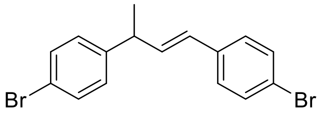
m.p.: 125.7 °C

^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm = 7.63 – 7.52 (m, 8H, C*H*$_{arom}$), 7.49 – 7.40 (m, 6H, C*H*$_{arom}$), 7.40 – 7.30 (m, 4H, C*H*$_{arom}$), 6.56 – 6.39 (m, 2H, C*H*=C*H*), 3.72 (m, 1H, C*H*CH_3), 1.53 (d, J = 7.0 Hz, 3H, CHC*H*$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 144.7 (C_q), 141.0 (C_q), 140.8 (C_q), 139.9 (C_q), 139.3 (C_q), 136.6 (C_q), 135.3 (+), 128.76 (+), 128.7 (+), 128.2 (+), 127.7 (+), 127.3 (+), 127.2 (+), 127.1 (+), 127.1 (+), 126.9 (+), 126.6 (+), 42.3 (+), 21.2 (+).

HRMS (EI) m/z = [$M^{+\bullet}$] calc. for $C_{28}H_{24}$ 360.1873, found 360.1863.

(*E*)-4,4'-(but-1-ene-1,3-diyl)bis(chlorobenzene) **2c**



The compound **2c** was obtained from the respective benzylic alcohol using the general procedure within 18 h reaction time and purification by column chromatography (Petroleum ether) as a white solid (116 mg, 0.3 mmol, 63%).

$C_{16}H_{14}Br_2$ (MW: 366.10 g/mol)

R*f* = 0.86 (Petroleum ether /Ethyl acetate 97.5:2.5)

m.p.: 64.9 °C

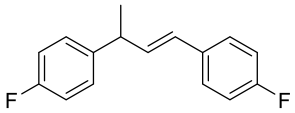
^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm = 7.51 – 7.38 (m, 4H, CH_{arom}), 7.24 – 7.17 (m, 2H, CH_{arom}), 7.16 – 7.09 (m, 2H, CH_{arom}), 6.32 (d, J = 2.6 Hz, 2H, C*H*=C*H*), 3.66 – 3.49 (m, 1H, C*H*CH_3),), 1.44 (d, J = 7.0 Hz, 3H, CHCH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 144.7 (C_q), 136.7 (C_q), 135.8 (+), 132.1 (+), 129.5 (+), 128.3 (+), 128.16 (+), 121.4 (C_q), 120.5 (C_q), 42.5 (+), 21.5 (+).

GC-MS (EI) m/z = 365.9 (5, [$M^{+\bullet}$]), 350.9 (2, [$M^{+\bullet}$]-[$CH_3^\bullet$]), 285.0 (8, [$M^{+\bullet}$]-[$Br^\bullet$]), 272.0 (7, [$M^{+\bullet}$]-[$CH_3^\bullet$]-[$Br^\bullet$]), 210.1 (51, [$M^{+\bullet}$]-[$C_6H_4Br^\bullet$]), 193.1 (28, [$M^{+\bullet}$]-[$C_6H_4Br^\bullet$]-[$CH_3^\bullet$]), 130.1 (11, [$M^{+\bullet}$]-[$C_6H_4Br^\bullet$]-[$Br^\bullet$]), 115.1 (31, [$M^{+\bullet}$]-[$C_7H_5Br^{2\bullet}$]-[$Br^\bullet$]), 105.1 (100, [$M^{+\bullet}$]-[$C_8H_6Br^\bullet$]-[$Br^\bullet$]), 91.1 (70, [$M^{+\bullet}$]-[$C_8H_6Br^{2\bullet}$]-[$Br^\bullet$]).

The analytical data is in agreement with the literature.[30]

(*E*)-4,4'-(but-1-ene-1,3-diyl)bis(fluorobenzene) **2d**



The compound **2d** was obtained from the respective benzylic alcohol using the general procedure within 4 h reaction time and purification by column chromatography (Petroleum ether) as a colorless oil (92 mg, 0.4 mmol, 75%).

$C_{16}H_{14}F_2$ (244.28 g/mol)

R*f* = 0.70 (Petroleum ether/Ethyl acetate 97.5:2.5)

m.p.: Ambient temperature

^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm = 7.29 – 7.17 (m, 2H, CH_{arom}), 7.17 – 7.08 (m, 2H, CH_{arom}), 7.00 – 6.83 (m, 4H, CH_{arom}), 6.26 (d, *J* = 16.0 Hz, 1H, CHCH=C*H*), 6.16 (dd, *J* = 15.9, 6.5 Hz, 1H, CHC*H*=CH), 3.60 – 3.42 (m, 1H, C*H*CH_3), 1.35 (d, *J* = 7.0 Hz, 3H, CHCH_3).

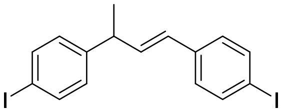
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 163.1 (d, *J* = 65.5 Hz, C_q), 160.6 (d, *J* = 63.4 Hz, C_q), 141.3 (d, *J* = 3.2 Hz, C_q), 134.9 (d, *J* = 2.2 Hz, +), 133.7 (d, *J* = 3.3 Hz, C_q), 128.8 (d, *J* = 7.8 Hz, +), 127.7 (d, *J* = 8.0 Hz, +) , 127.7 (+), 115.4 (dd, *J* = 21.3, 14.7 Hz, +), 41.9 (+), 21.4 (+).

^{19}F-NMR (376 MHz, $CDCl_3$) δ/ppm = –115.3 (m), –117.1 (m).

GC-MS (EI) m/z = 244.2 (66, [M$^{+\bullet}$]), 229.2 (100, [M$^{+\bullet}$]-[CH$_3^\bullet$]), 214.1 (22, [M$^{+\bullet}$]-[CF$^\bullet$]), 209.1 (6, [M$^{+\bullet}$]-[CH$_3^\bullet$]-[F$^\bullet$]), 201.1 (5, [M$^{+\bullet}$]-[C$_2$HF$^\bullet$]), 147.1 (9, [M$^{+\bullet}$]-[C$_6$H$_4$F$^\bullet$]), 133.1 (73, [M$^{+\bullet}$]-[CH$_3^\bullet$]-[C$_6$H$_4$F$^\bullet$]), 123.1 (13, [M$^{+\bullet}$]-[C$_8$H$_8$F$^\bullet$]), 109.1 (44, [M$^{+\bullet}$]-[C$_{10}$H$_{10}$F$^\bullet$]).

The analytical data is in agreement with the literature.[62]

(*E*)-4,4'-(but-1-ene-1,3-diyl)bis(iodobenzene) **2e**



The compound **2e** was obtained from the respective benzylic alcohol using the general procedure within 18 h reaction time and purification by column chromatography (Petroleum ether) as a white solid (209 mg, 0.5 mmol, 91%).

$C_{16}H_{14}I_2$ (460.10 g/mol)

R$_f$ = 0.80 (*n*-hexane)

m.p.: 104.1 °C

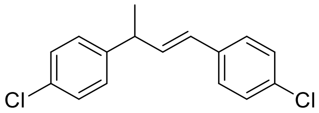
^{1}H-NMR (400 MHz, CDCl$_3$) δ/ppm = 7.77 – 7.52 (m, 4H, C*H*$_{\text{arom}}$), 7.14 – 7.03 (m, 2H, C*H*$_{\text{arom}}$), 7.05 – 6.90 (m, 2H, C*H*$_{\text{arom}}$), 6.39 – 6.15 (m, 2H, C*H*=C*H*), 3.85 – 3.33 (m, 1H, C*H*CH$_3$), 1.43 (d, *J* = 7.0 Hz, 1H, CHC*H*$_3$).

^{13}C NMR (101 MHz, CDCl$_3$) δ/ppm = 145.4 (C$_q$) , 138.0 (+), 138.0 (+), 137.3 (C$_q$), 135.9 (+), 129.9 (+), 128.5 (+), 128.4 (+), 92.8 (C$_q$), 91.9 (C$_q$), 42.6 (+), 21.4 (+).

GC-MS (EI) m/z = 459.9 (15, [M$^{+\bullet}$]), 444.9 (3, [M$^{+\bullet}$]-[CH$_3^\bullet$]), 333.0 (34, [M$^{+\bullet}$]-[I$^\bullet$]), 318.0 (26, [M$^{+\bullet}$]-[CH$_3^\bullet$]-[I$^\bullet$]), 208.2 (99, [M$^{+\bullet}$]-2[I$^\bullet$]), 193.1 (93, [M$^{+\bullet}$]-[CH$_3^\bullet$]-2[I$^\bullet$]), 178.1 (42, [M$^{+\bullet}$]-[C$_{12}$H$_{11}$I$^{2\bullet}$]), 165.1 (20, [M$^{+\bullet}$]-[C$_{13}$H$_{12}$I$^{2\bullet}$]), 129.1 (37, [M$^{+\bullet}$]-[C$_6$H$_4$I$^\bullet$]-[I$^\bullet$]), 115.1 (100, [M$^{+\bullet}$]-[CH$_3^\bullet$]-[I$^\bullet$]-[C$_6$H$_4$I$^\bullet$]).

HRMS (EI) m/z = [M$^{+\bullet}$] calc. for $C_{16}H_{14}I_2$ 459.9179, found 459.9164.

(*E*)-4,4'-(but-1-ene-1,3-diyl)bis(chlorobenzene) **2f**



The compound **2f** was obtained from the respective benzylic alcohol using the general procedure within 12 h reaction time and purification by column chromatography (Petroleum ether) as a colorless oil (48 mg, 0.4 mmol, 77%).

$C_{16}H_{14}Cl_2$ (277.19 g/mol)

R*f* = 0.73 (Cyclohaxane/Ethyl acetate 95:5)

m.p.: Ambient temperature

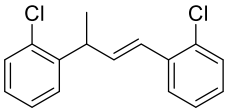
^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm = 7.28 (m, 6H, C*H*$_{arom}$), 7.18 (m, 2H, C*H*$_{arom}$), 6.41 – 6.26 (m, 2H, C*H*=C*H*), 3.67 – 3.55 (m, 1H, C*H*CH_3), 1.44 (d, J = 7.1 Hz, 3H, CHC*H*$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 143.9 (C_q), 136.0 (C_q), 135.5 (+), 132.9 (C_q), 132.2 (C_q), 128.8 (+), 128.8 (+), 127.9 (+), 127.5 (+), 42.1 (+), 21.2 (+).

GC-MS (EI) m/z = 276.1 (37, [$M^{+\bullet}$]), 261.0 (55, [$M^{+\bullet}$]-[$CH_3^\bullet$]), 241.1 (100, [$M^{+\bullet}$]-[$Cl^\bullet$]), 226.1 (41, [$M^{+\bullet}$]-[$CH_3^\bullet$]-[$Cl^\bullet$]), 206.1 (10, [$M^{+\bullet}$]-2[$Cl^\bullet$]), 191.1 (33, [$M^{+\bullet}$]-[$CH_3^\bullet$]-2[$Cl^\bullet$]), 165.1 (13, [$M^{+\bullet}$]-[$C_6H_4Cl^\bullet$]), 149.0 (52, [$M^{+\bullet}$]-[$C_6H_4Cl^\bullet$]-[$CH_3^\bullet$]), 139.1 (33, [$M^{+\bullet}$]-[$C_8H_6Cl^\bullet$], 125.0 (43, [$M^{+\bullet}$]-[$C_8H_6Cl^\bullet$]-[$CH_3^\bullet$]) 115.1 (18, [$M^{+\bullet}$]-[$C_6H_4Cl^\bullet$]-[$CH_3^\bullet$]-[$Cl^\bullet$]).

The analytical data is in agreement with the literature.[30]

(*E*)-2,2'-(but-1-ene-1,3-diyl)bis(chlorobenzene) **2g**



The compound **2g** was obtained from the respective benzylic alcohol using the general procedure within 18 h reaction time and purification by column chromatography (Petroleum ether) as a yellow oil (37 mg, 0.1 mmol, 27%).

$C_{16}H_{14}Cl_2$ (277.19 g/mol)

R*f* = 0.62 (Cyclohexane/Ethyl acetate 97.5:2.5)

m.p.: Ambient temperature

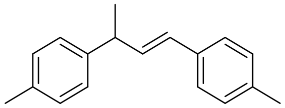
^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm = 7.51 (dd, *J* = 7.6, 1H, C*H*$_{arom}$), 7.42 – 7.28 (m, 3H, C*H*$_{arom}$), 7.28 – 7.12 (m, 4H, C*H*$_{arom}$), 6.87 (dd, *J* = 16.0, 1.6 Hz, 1H, CHCH=C*H*), 6.35 (dd, *J* = 16.0, 6.2 Hz, 1H, CHC*H*=CH), 4.36 – 4.05 (m, 1H, C*H*CH_3), 1.49 (d, *J* = 7.0 Hz, 3H, CHC*H*$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 142.4 (C_q), 136.1 (+), 135.5 (C_q), 133.4 (C_q), 132.7 (C_q), 129.5 (+), 129.4 (+), 128.0 (+), 127.3 (+), 126.9 (+), 126.6 (+), 125.4 (+), 38.4 (+), 19.6 (+).

GC-MS (EI) m/z = 276.1 (23, $[M^{+\bullet}]$), 261.0 (42, $[M^{+\bullet}]$-$[CH_3^\bullet]$), 241.1 (100,$[M^{+\bullet}]$-$[Cl^\bullet]$), 226.1 (34, $[M^{+\bullet}]$-$[CH_3^\bullet]$-$[Cl^\bullet]$), 206.1 (12, $[M^{+\bullet}]$-2$[Cl^\bullet]$), 191.1 (27, $[M^{+\bullet}]$-$[CH_3^\bullet]$-2$[Cl^\bullet]$), 165.1 (12, $[M^{+\bullet}]$-$[C_6H_4Cl^\bullet]$), 149.0 (39, $[M^{+\bullet}]$-$[C_6H_4Cl^\bullet]$-$[CH_3^\bullet]$), 139.1 (20, $[M^{+\bullet}]$-$[C_8H_6Cl^\bullet]$, 125.0 (43, $[M^{+\bullet}]$-$[C_8H_6Cl^\bullet]$-$[CH_3^\bullet]$) 115.1 (17, $[M^{+\bullet}]$-$[C_6H_4Cl^\bullet]$-$[CH_3^\bullet]$-$[Cl^\bullet]$).

HRMS (EI) $[M^{+\bullet}]$ calc. for $C_{16}H_{14}Cl_2$ 276.0467, found 276.0454.

(*E*)-4,4'-(but-1-ene-1,3-diyl)bis(methylbenzene) **2h**



The compound **2h** was obtained from the respective benzylic alcohol using the general procedure within 4 h reaction time and purification by column chromatography (Petroleum ether) as a colorless oil (89 mg, 0.4 mmol, 75%).

$C_{18}H_{20}$ (236.16 g/mol)

R*f* = 0.53 (*n*-hexane/Ethyl acetate 99:1)

m.p.: Ambient temperature

^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm = 7.25 – 7.06 (m, 8H, C*H*$_{arom}$), 6.42 – 6.27 (m, 2H, CHC*H*=C*H*), 3.60 (p, J = 6.8 Hz, 1H, C*H*CH_3), 2.33 (s, 3H, C*H*$_3$), 2.32 (s, 3H, C*H*$_3$), 1.44 (d, J = 7.0 Hz, 3H, CHC*H*$_3$).

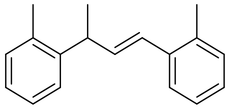
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 142.8 (C_q), 136.7 (C_q), 135.7 (C_q), 134.9 (C_q), 134.4 (+), 129.2 (+), 129.1 (+), 128.2 (+), 127.2 (+), 126.0 (+), 42.1 (+), 21.3 (+), 21.2 (+), 21.0 (+).

GC-MS (EI) m/z = 236.1 (50, $[M^{+\bullet}]$), 221.1 (75, $[M^{+\bullet}]$-$[^\bullet CH^3]$), 129.1 (100, $[M^{+\bullet}]$-$[^\bullet CH_3]$-$[^\bullet C_6H_4CH_3]$, 105.1 (37, $[M^{+\bullet}]$-$[^{2\bullet}CHCHCH_3C_6H_4CH_3]$), 91.1 (55, $[M^{+\bullet}]$-$[^\bullet CH(CH)_2CH_3C_6H_4CH_3]$).

HRMS (EI) $[M^{+\bullet}]$ calc. for $C_{18}H_{20}$ 236.1560, found 236,1526.

The analytical data is in agreement with the literature.[30]

(*E*)-2,2'-(but-1-ene-1,3-diyl)bis(methylbenzene) **2i**



The compound **2xxx** was obtained from the respective benzylic alcohol using the general procedure within 4 h reaction time and purification by column chromatography (Petroleum ether) as a yellow oil (96 mg, 0.4 mmol, 81%).

$C_{18}H_{20}$ (236.16 g/mol)

R*f* = (Cyclohexane/Ethyl acetate 97.5:2.5)

m.p.: Ambient temperature

^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm = 7.44 – 7.38 (m, 1H, CH_{arom}), 7.28 (m, J = 1.4 Hz, 2H, CH_{arom}), 7.23 – 7.10 (m, 6H, CH_{arom}), 6.57 (dd, J = 15.8, 1.5 Hz, 1H, CHCH=C*H*), 6.22 (dd, J = 15.8, 6.5 Hz, 1H, CHC*H*=CH), 3.89 (pd, J = 6.9, 1.5 Hz, 1H, C*H*CH_3), 2.40 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 1.46 (d, J = 7.0 Hz, 3H, CHCH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 143.7 (C_q), 137.0 (C_q), 136.4 (+), 135.7 (C_q), 135.2 (C_q), 130.5 (+), 130.3 (+), 127.1 (+), 126.5 (+), 126.4 (+), 126.2 (+), 126.2 (+), 125.7 (+), 38.6 (+), 20.7 (+), 20.0 (+), 19.6 (+).

GC-MS (EI) m/z = 236.1 (38, $[M^{+\bullet}]$), 221.1 (61, $[M^{+\bullet}]$-$[^{\bullet}CH^3]$), 129.1 (100, $[M^{+\bullet}]$-$[^{\bullet}CH_3]$-$[^{\bullet}C_6H_4CH_3]$, 105.1 (42, $[M^{+\bullet}]$-$[^{2\bullet}CHCHCH_3C_6H_4CH_3]$), 91.1 (35, $[M^{+\bullet}]$-$[^{\bullet}CH(CH)_2CH_3C_6H_4CH_3]$).

HRMS (EI)**:** $[M^{+\bullet}]$ calc. for $C_{18}H_{20}$ 236.1560, found 236.1516

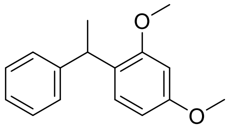
2.5.6. Substrate Screening: Heterocoupling

General procedure:

A 10 mL tube with screw cap was charged with a nucleophile (2.0 eq, 1 mmol). The substrate (1.0 eq, 0.5 mmol) was added and dissolved in 1,2-dichloroethane (3 mL). Subsequently, toluene sulfonic acid (0.16 eq., 15 mg, 80 µmol) was added and the reaction mixture was stirred for 4 h at

100 °C. The reaction was quenched with $NaHCO_3$, extracted with DCM and dried over $MgSO_4$. Purification was conducted *via* flash column chromatography and Kugelrohr distillation.

2,4-Dimethoxy-1-(1-phenylethyl)benzene **8a**



The compound **8a** was obtained from the respective benzylic alcohol and 1,3-dimethoxybenzene by using the general procedure and purification by column chromatography (Cyclohexane/Ethyl acetate) as a colorless oil (86 mg, 0.4 mmol, 71%, containing 5% of 1,3-dimethoxy-2-(1-phenylethyl)benzene).

$C_{16}H_{18}O_2$ (242.32 g/mol)

R*f* = 0.24 (Cyclohexane/Ethyl acetate 97.5:2.5)

m.p.: Ambient temperature

^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm = 7.33 – 7.11 (m, 5H, CH_{arom}), 7.09 – 6.97 (m, 1H, CH_{arom}), 6.49 – 6.40 (m, 2H, CH_{arom}), 4.50 (q, *J* = 7.3 Hz, 1H, $CHCH_3$), 3.80 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 1.58 (d, *J* = 7.3 Hz, 3H, $CHCH_3$).

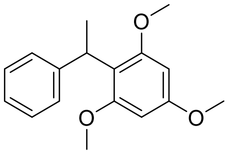
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 159.2 (C_q), 157.9 (C_q), 146.9 (C_q), 128.2 (+), 128.1 (+), 127.7 (+), 127.6 (+), 125.7 (+), 104.1 (+), 98.8 (+), 55.6 (+), 55.4 (+), 37.1 (+), 21.2 (+).

GC-MS (EI) m/z = 242.2 (58, $[M^{+\bullet}]$), 227.1 (100, $[M^{+\bullet}]$-$[CH_3^{\bullet}]$), 195.1 (3, $[M^{+\bullet}]$-$[CH_3^{\bullet}]$-$[OCH_3^{\bullet}]$), 165.1 (16, $[M^{+\bullet}]$-$[C_6H_5^{\bullet}]$), 152.1 (6, $[M^{+\bullet}]$-$[CH_3^{\bullet}]$-2$[OCH_3^{\bullet}]$-$[CH^{3\bullet}]$), 103.1 (4, $[M^{+\bullet}]$-$[C_6H_5^{\bullet}]$-2$[OCH_3^{\bullet}]$), 91.1 (55, $[M^{+\bullet}]$-$[CH_3^{\bullet}]$-$[C_8H_9O_2^{\bullet}]$).

HRMS (EI)**:** $[M^{+\bullet}]$ calc. for $C_{16}H_{18}O_2$ 242.1301, found 242.1312.

The analytical data is in agreement with the literature.[63]

1,3,5-Trimethoxy-2-(1-phenylethyl)benzene **9a**



The compound **9a** was obtained from the respective benzylic alcohol and 1,3,5-trimethoxybenzene by using the general procedure and purification by column chromatography (Cyclohexane/Ethyl acetate) as a white solid (127 mg, 0.5 mmol, 93%).

$C_{17}H_{20}O_3$ (272.34 g/mol)

R*f* = 0.21 (Cyclohexane/Ethyl acetate)

m.p.: 67.3 °C

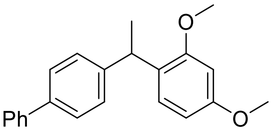
^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm = 7.36 – 7.16 (m, 4H, C*H*$_{arom}$), 7.17 – 7.07 (m, 1H, C*H*$_{arom}$), 6.14 (s, 2H, C*H*$_{arom}$), 4.76 (q, *J* = 7.3 Hz, 1H, C*H*CH_3), 3.80 (s, 3H, OC*H*$_3$), 3.70 (s, 2H, OC*H*$_3$), 1.66 (d, *J* = 7.3 Hz, 3H, CHC*H*$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 159.4 (C_q), 159.1 (C_q), 146.7 (C_q), 127.6 (+), 127.4 (+), 125.0 (+), 116.0 (C_q), 91.5 (+), 55.9 (+), 55.4 (+), 33.1 (+), 17.9 (+).

GC-MS (EI) m/z = 272.2 (61, [$M^{+\bullet}$]), 257.2 (100, [$M^{+\bullet}$]-[$CH_3^\bullet$]), 195.1 (19, [$M^{+\bullet}$]-[$C_6H_5^\bullet$]), 165.1 (6, [$M^{+\bullet}$]-[$CH_3^\bullet$]-[$C_6H_5^\bullet$]), 91.1 (52, [$M^{+\bullet}$]-[$CH_3^\bullet$]-[$C_9H_{11}O_3^\bullet$]).

The analytical data is in agreement with the literature.[64]

4-(1-(2,4-Dimethoxyphenyl)ethyl)-1,1'-biphenyl **8b**



The compound **8b** was obtained from the respective benzylic alcohol and 1,3-dimethoxybenzene by using the general procedure and purification by column chromatography (Cyclohexane/Ethyl acetate) as a yellow oil (137 mg, 0.5 mmol, 99%)

$C_{22}H_{22}O_2$ (318.42 g/mol)

R*f* = 0.49 (Cyclohexane/Ethyl acetate 97.5:2.5)

m.p.: Ambient temperature

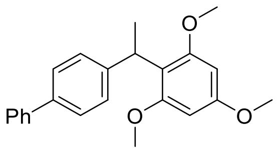
^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm = 7.61 – 7.55 (m, 2H, CH_{arom}), 7.52 – 7.47 (m, 2H, CH_{arom}), 7.41 (t, *J* = 7.5 Hz 2H, CH_{arom}), 7.34 – 7.28 (m, 3H, CH_{arom}), 7.13 – 7.06 (m, 1H, CH_{arom}), 6.48 – 6.44 (m, 2H, CH_{arom}), 4.52 (q, *J* = 7.3 Hz, 1H, $CHCH_3$), 3.80 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 1.58 (d, *J* = 7.3 Hz, 3H, $CHCH_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 159.3 (C_q), 157.9 (C_q), 146.1 (C_q), 141.3 (C_q), 138.6 (C_q), 128.8 (+), 128.1(+), 128.1 (+), 127.5 (C_q), 127.1 (+), 127.0(+), 127.0(+),104.1 (+),98.8 (+), 55.6 (+), 55.5 (+), 36.8 (+), 21.2 (+).

GC-MS (EI) m/z = 318.2 (36, $[M^{+\bullet}]$) 303.1 (33, $[M^{+\bullet}]$-$[CH_3^{\bullet}]$), 287.1 (2, $[M^{+\bullet}]$-$[OCH_3^{\bullet}]$), 272.1 (2, $[M^{+\bullet}]$-$[CH_3^{\bullet}]$-$[OCH_3^{\bullet}]$), 241.1 (2, $[M^{+\bullet}]$-$[CH_3^{\bullet}]$-2$[OCH_3^{\bullet}]$), 180.1 (11, $[M^{+\bullet}]$-$[C_8H_9O_2^{\bullet}]$), 167.1 (100, $[M^{+\bullet}]$-$[CH_3^{\bullet}]$-$[C_8H_9O_2^{\bullet}]$), 153.1 (9, $[M^{+\bullet}]$-$[C_{10}H_{13}O_2^{\bullet}]$), 138.1 (8, $[M^{+\bullet}]$-$[C_{14}H_{13}^{\bullet}]$), 115 (3, $[M^{+\bullet}]$-$[C_{13}H_{15}O_2^{3\bullet}]$).

HRMS (EI)**:** $[M^{+\bullet}]$ calc. for $C_{22}H_{22}O_2$ 318.1614, found 318.1611.

<u>4-(1-(2,4,6-trimethoxyphenyl)ethyl)-1,1'-biphenyl **9b**</u>



The compound **9b** was obtained from the respective benzylic alcohol and 1,3,5-trimethoxybenzene by using the general procedure and purification by column chromatography (Cyclohexane/Ethyl acetate) as a colorless oil (174 mg, 0.5 mmol, 100%).

$C_{23}H_{24}O_3$ (348.44 g/mol)

R*f* = 0.34 (Petroleum ether/Ethyl acetate 9:1)

m.p.: Ambient temperature

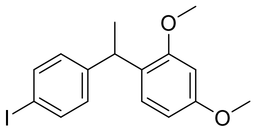
^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm = 7.62 – 7.56 (m, 2H, CH_{arom}), 7.50 – 7.46 (m, 2H, CH_{arom}), 7.44 – 7.39 (m, 2H, CH_{arom}), 7.39 – 7.34 (m, 2H, CH_{arom}), 7.33 – 7.28 (m, 1H, CH_{arom}), 6.16 (s, 2H, CH_{arom}), 4.81 (q, *J* = 7.3 Hz, 1H, $CHCH_3$), 3.81 (s, 3H, OCH_3), 3.73 (s, 6H, OCH_3), 1.70 (d, *J* = 7.3 Hz, 3H, $CHCH_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 159.6 (C_q), 159.2 (C_q), 146.0 (C_q), 141.6 (C_q), 137.8 (C_q), 128.8 (+), 127.8 (+), 127.1 (+), 126.9 (+), 126.4 (+), 115.8 (C_q), 91.6 (+), 55.9 (+), 55.4 (+), 32.9 (+), 18.0 (+).

GC-MS (EI) m/z = 348.2 (55, [$M^{+\bullet}$]), 333.2 (100, [$M^{+\bullet}$]-[$CH_3^\bullet$]), 317.1 (3, [$M^{+\bullet}$]-[$OCH_3^\bullet$]), 303.1 (2, [$M^{+\bullet}$]-[$CH_3^\bullet$]-[$OCH_3^\bullet$]), 241.1 (2, [$M^{+\bullet}$]-[$CH_3^\bullet$]-3[$OCH_3^\bullet$]), 195.1 (8, [$M^{+\bullet}$]-[$C_{12}H_9^\bullet$]), 181.1 (10, [$M^{+\bullet}$]-[$C_9H_{11}O_3^\bullet$]), 180.1 (38, [$M^{+\bullet}$]-[$CH_3^\bullet$] -[$C_{12}H_9^\bullet$]), 167.1 (99, [$M^{+\bullet}$]-[$C_{14}H_{13}^\bullet$]), 153.1 (4, [$M^{+\bullet}$]-[$C_{11}H_{15}O_3^\bullet$]).

HRMS (EI)**:** [$M^{+\bullet}$] calc. for $C_{23}H_{24}O_3$ 348.1720, found 348.1703.

<u>1-(1-(4-Iodophenyl)ethyl)-2,4-dimethoxybenzene **8e**</u>



The compound **8e** was obtained from the respective benzylic alcohol and 1,3-dimethoxybenzene by using the general procedure and purification by column chromatography (Cyclohexane/Ethyl acetate) as a yellow oil (136 mg, 0.4 mmol, 74%).

$C_{16}H_{17}O_2I$ (368.21 g/mol)

R*f* = 0.58 (Petroleum ether/Ethyl acetate 9:1)

m.p.: Ambient temperature

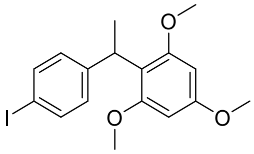
^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm = 7.57 – 7.52 (m, 2H, C*H*$_{arom}$), 7.09 – 6.85 (m, 3H, C*H*$_{arom}$), 6.56 – 6.40 (m, 2H, C*H*$_{arom}$), 4.39 (q, *J* = 7.3 Hz, 1H, C*H*CH$_3$), 3.79 (s, 3H, OC*H*$_3$), 3.73 (s, 3H, OC*H*$_3$), 1.52 (d, *J* = 7.2 Hz, 3H, CHC*H*$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 160.7 (C_q), 159.1 (C_q), 157.5 (C_q), 146.5 (C_q), 136.9 (+), 129.6 (+), 127.3 (+),106.0 (+), 103.8 (+), 100.3 (+), 98.5 (+), 90.5 (C_q), 55.2 (+), 55.2 (+), 36.6 (+), 20.7 (+).

GC-MS (EI) m/z = 368.0 (19, [$M^{+\bullet}$]), 353.0 (29, [$M^{+\bullet}$]-[$CH_3^\bullet$]), 242.2 (59, [$M^{+\bullet}$]-[$I^\bullet$]), 227.2 (100, [$M^{+\bullet}$]-[$I^\bullet$]-[$CH_3^\bullet$]), 217.0 (18, [$M^{+\bullet}$]-[$CH_3^\bullet$]-[$C_8H_9O_2^\bullet$]), 165.1 (22, [$M^{+\bullet}$]-[$C_6H_4I^\bullet$]), 91.1 (57, [$M^{+\bullet}$]-[$I^\bullet$]-[$C_8H_9O_2^\bullet$]).

HRMS (EI)**:** [$M^{+\bullet}$] calc. for $C_{16}H_{17}O_2I$ 368.0268, found 368.0260.

2-(1-(4-Iodophenyl)ethyl)-1,3,5-trimethoxybenzene **9e**



The compound **xxx** was obtained from the respective benzylic alcohol and 1,3,5-trimethoxybenzene by using the general procedure and purification by column chromatography (Cyclohexane/Ethyl acetate) as a colorless oil (161 mg, 0.4 mmol, 81%).

$C_{17}H_{19}O_3I$ (398.24 g/mol)

R*f* = 0.31 (Cyclohexane/Ethyl acetate 97.5:2.5)

m.p.: Ambient temperature

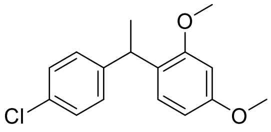
^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm = 7.64 – 7.45 (m, 2H, C*H*$_{arom}$), 7.11 – 6.90 (m, 2H, C*H*$_{arom}$), 6.13 (s, 2H, C*H*$_{arom}$), 4.68 (q, *J* = 7.3 Hz, 1H, C*H*CH$_3$), 3.80 (s, 3H, OC*H*$_3$), 3.70 (s, 6H, OC*H*$_3$), 1.60 (d, *J* = 7.3 Hz, 3H, CHC*H*$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 159.7 (C$_q$), 159.0 (C$_q$), 146.6 (C$_q$), 136.6 (+), 129.7 (+), 115.2 (C$_q$), 91.4 (+), 90.0 (C$_q$), 55.8 (+), 55.4 (+), 32.7 (+), 17.7 (+).

GC-MS (EI) m/z = 398.1 (28, [$M^{+\bullet}$]), 383.1 (41, [$M^{+\bullet}$]-[$CH_3^\bullet$]), 272.2 (61, [$M^{+\bullet}$]-[$I^\bullet$]), 257.2 (100, [$M^{+\bullet}$]-[$I^\bullet$]-[$CH_3^\bullet$]), 217.0 (20, [$M^{+\bullet}$]-[$CH_3^\bullet$]-[$C_9H_{11}O_3^\bullet$]), 195.1 (21, [$M^{+\bullet}$]-[$C_6H_4I^\bullet$]), 91.1 (46, [$M^{+\bullet}$]-[$I^\bullet$]-[$C_9H_{11}O_3^\bullet$]).

HRMS (EI)**:** [$M^{+\bullet}$] calc. for $C_{17}H_{19}O_3I$ 398.0373, found 398.0399.

1-(1-(4-Chlorophenyl)ethyl)-2,4-dimethoxybenzene **8f**



The compound **8f** was obtained from the respective benzylic alcohol and 1,3-dimethoxybenzene by using the general procedure and purification by column chromatography (Cyclohexane/Ethyl acetate) as a colorless oil (111 mg, 0.4 mmol, 80%, containing 12% of 2-(1-(4-chlorophenyl)ethyl)-1,3-dimethoxybenzene.

$C_{16}H_{17}O_2Cl$ (276.76 g/mol)

R*f* = 0.50 (Petroleum ether/Ethyl acetate 9:1)

m.p.: Ambient temperature

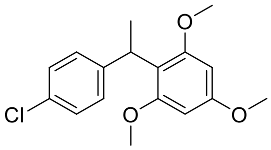
^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm = 7.22 – 7.13 (m, 4H, CH_{arom}), 6.12 (s, 2H, CH_{arom}), 4.70 (q, *J* = 7.3 Hz, 1H, C*H*CH_3), 3.79 (s, 3H, OCH_3), 3.69 (s, 6H, OCH_3), 1.60 (d, *J* = 7.3 Hz, 3H, CHCH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 159.4 (C_q), 158.7 (C_q), 145.0 (C_q), 130.2 (C_q), 128.5 (+), 127.3 (+), 115.1 (C_q), 91.1, 55.5 (+), 55.1 (+), 32.3 (+), 17.5 (+).

GC-MS (EI) m/z = 276.1 (54, [$M^{+\bullet}$]), 261.1 (100, [$M^{+\bullet}$]-[$CH_3^\bullet$]), 242.2 (10, [$M^{+\bullet}$]-[$Cl^\bullet$]), 227.2 (17, [$M^{+\bullet}$]-[$CH_3^\bullet$]-[$Cl^\bullet$]), 211.1 (4, [$M^{+\bullet}$]-2[$CH_3^\bullet$]-[$Cl^\bullet$]), 165.1 (17, [$M^{+\bullet}$]-[$C_6H_4Cl^\bullet$]), 125.1 (60, [$M^{+\bullet}$]-[$CH_3^\bullet$]-[$C_8H_9O_2^\bullet$]), 103.1 (4, [$M^{+\bullet}$]-[$C_6H_4Cl^\bullet$]-2[$OCH_3^\bullet$]).

HRMS (EI)**:** [$M^{+\bullet}$] calc. for $C_{16}H_{17}O_2Cl$ 276.0912, found 276.0888.

2-(1-(4-Chlorophenyl)ethyl)-1,3,5-trimethoxybenzene **9f**



The compound **9f** was obtained from the respective benzylic alcohol and 1,3,5-trimethoxybenzene by using the general procedure and purification by column chromatography (Cyclohexane/Ethyl acetate) as a colorless oil (153 mg, 0.5 mmol, 100%).

$C_{17}H_{19}O_3Cl$ (306.79 g/mol)

R*f* = 0.19 (Cyclohexane/Ethyl acetate 97.5:2.5)

m.p.: Ambient temperature

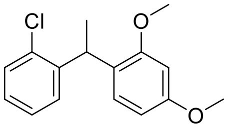
^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm = 7.22 – 7.13 (m, 4H, CH_{arom}), 6.12 (s, 2H, CH_{arom}), 4.70 (q, *J* = 7.3 Hz, 1H, C*H*CH_3), 3.79 (s, 3H, OCH_3), 3.69 (s, 6H, OCH_3), 1.60 (d, *J* = 7.3 Hz, 3H, CHCH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 159.4 (C_q), 158.7 (C_q), 145.0 (C_q), 130.2 (C_q), 128.5 (+), 127.3 (+), 115.1 (C_q), 91.1, 55.5 (+), 55.1 (+), 32.3 (+), 17.5 (+).

GC-MS (EI) m/z = 306.2 (53, [$M^{+\bullet}$]), 293.1 (35, [$M^{+\bullet}$]-[$CH^{3\bullet}$]), 291.2 (100, [$M^{+\bullet}$]-[$CH_3^\bullet$]), 272.2 (14, [$M^{\bullet+}$]-[$Cl^\bullet$]), 257.2 (24, [$M^{\bullet+}$]-[$Cl^\bullet$]-[$CH_3^\bullet$]), 195.1 (18, [$M^{+\bullet}$]-[$C_6H_4Cl^\bullet$]), 165.1 (, [$M^{+\bullet}$]-[$C_6H_4Cl^\bullet$]-2[$CH_3^\bullet$]), 125.1 (61, [$M^{+\bullet}$]-[$CH_3^\bullet$]-[$C_9H_{11}O_3^\bullet$]), 103.1 (5, [$M^{+\bullet}$]-[$C_6H_4Cl^\bullet$]-3[$OCH_3^\bullet$]).

HRMS (EI)**:** [$M^{+\bullet}$] calc. for $C_{17}H_{19}O_3Cl$ 306.1017, found 306.0997.

1-(1-(2-Chlorophenyl)ethyl)-2,4-dimethoxybenzene **8g**



The compound **8g** was obtained from the respective benzylic alcohol and 1,3-dimethoxybenzene by using the general procedure and purification by distillation and column chromatography (*n*-hexane/Ethyl acetate 99:1) as a colorless oil (60 mg, 0.2 mmol, 43% containing 11 % 1-(1-(2-Chlorophenyl)ethyl)-2,6-dimethoxybenzene)

$C_{16}H_{17}O_2Cl$ (276.76 g/mol)

R*f* = 0.63 (*n*-hexane/Ethyl acetate 99:1)

m.p.: Ambient temperature

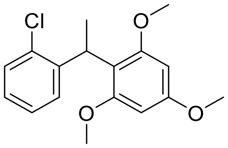
^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm = 7.35 – 7.28 (m, 1H, C*H*$_{arom}$), 7.18 – 6.96 (m, 4H, C*H*$_{arom}$), 6.54 – 6.36 (m, 2H, C*H*$_{arom}$), 4.82 (q, *J* = 7.2 Hz, 1H, C*H*CH_3), 3.76 (2 x s, 2 x 3H, OC*H*$_3$), 1.51 (d, *J* = 7.2 Hz, 3H, CHC*H*$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 159.3 (C_q), 158.0 (C_q), 144.2 (C_q), 134.0 (C_q), 129.4 (+), 128.3 (+), 127.7 (+), 126.9 (+), 126.5 (+), 126.1 (C_q), 103.7 (+), 98.7 (+), 55.5 (+), 55.3 (+), 34.41 (+), 20.05 (+).

GC-MS (EI) m/z = 276.1 (43, [$M^{+\bullet}$]), 261.1 (68, [$M^{+\bullet}$]-[$CH_3^\bullet$]), 227.2 (5, [$M^{+\bullet}$]-[$CH_3^\bullet$]-[$Cl^\bullet$]), 211.1 (7, [$M^{+\bullet}$]-2[$CH_3^\bullet$]-[$Cl^\bullet$]), 165.1 (34, [$M^{+\bullet}$]-[$C_6H_4Cl^\bullet$]), 125.0 (100, [$M^{+\bullet}$]-[$CH_3^\bullet$]-[$C_8H_9O_2^\bullet$]), 103.1 (11, [$M^{+\bullet}$]-[$C_6H_4Cl^\bullet$]-2[$OCH_3^\bullet$]).

HRMS (EI)**:** [$M^{+\bullet}$] calc. for $C_{16}H_{17}O_2Cl$ 276.0912, found 276.0919.

2-(1-(2-Chlorophenyl)ethyl)-1,3,5-trimethoxybenzene **9g**



The compound **9g** was obtained from the respective benzylic alcohol and 1,3,5-trimethoxybenzene by using the general procedure and purification by distillation as a white solid (112 mg, 0.4 mmol, 73%).

$C_{17}H_{19}O_3Cl$ (306.79 g/mol)

R*f* = 0.61 (Cyclohexane/Ethyl acetate 95:5)

m.p.: 93 – 95 °C

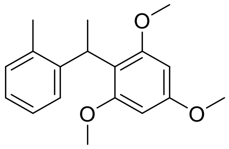
^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm = 7.45 (dd, *J* = 7.9, 1.7 Hz, 1H, CH_{arom}), 7.18 – 7.05 (m, 2H, CH_{arom}), 6.99 (td, *J* = 7.6, 1.7 Hz, 1H, CH_{arom}), 6.03 (s, 2H, CH_{arom}), 4.82 (q, *J* = 7.2 Hz, 1H, $CHCH_3$), 3.71 (s, 3H, OCH_3), 3.60 (s, 2 x 3H, OCH_3), 1.52 (d, *J* = 7.3 Hz, 3H, $CHCH_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 159.5 (C_q), 159.1 (C_q), 143.8 (C_q), 133.9 (C_q), 129.8 (+), 129.0 (+), 126.4 (+), 125.6 (+), 114.1 (C_q), 91.4 (+), 55.7 (+), 55.2 (+), 32.00 (+), 18.46 (+).

GC-MS (EI) m/z = 306.1 (51, $[M^{+\bullet}]$), 291.2 (78, $[M^{+\bullet}]$-$[CH_3^\bullet]$), 272.2 (4, $[M^{\bullet+}]$-$[Cl^\bullet]$), 257.2 (5, $[M^{\bullet+}]$-$[Cl^\bullet]$-$[CH_3^\bullet]$), 195.1 (27, $[M^{+\bullet}]$-$[C_6H_4Cl^\bullet]$), 165.1 (11, $[M^{+\bullet}]$-$[C_6H_4Cl^\bullet]$-2$[CH_3^\bullet]$), 125.1 (100, $[M^{+\bullet}]$-$[CH_3^\bullet]$-$[C_9H_{11}O_3^\bullet]$), 103.1 (10, $[M^{+\bullet}]$-$[C_6H_4Cl^\bullet]$-3$[OCH_3^\bullet]$).

HRMS (EI)**:** $[M^{+\bullet}]$ calc. for $C_{17}H_{19}O_3Cl$ 306.1017, found 306.1048.

1,3,5-Trimethoxy-2-(1-(o-tolyl)ethyl)benzene **9i**



The compound **9i** was obtained from the respective benzylic alcohol and 1,3,5-trimethoxybenzene by using the general procedure and purification by column chromatography (Cyclohexane/Ethyl acetate) as a white solid (130 mg, 0.5 mmol, 91%).

$C_{18}H_{22}O_3$ (286.37 g/mol)

R*f* = 0.27 (Cyclohexane/Ethyl acetate 97.5:2.5)

m.p.: 93.2 °C

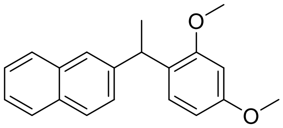
^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm = 7.52 (d, *J* = 7.8 Hz, 1H, CH_{arom}), 7.20 – 7.10 (m, 1H, CH_{arom}), 7.09 – 6.98 (m, 2H, CH_{arom}), 6.09 (s, 2H, CH_{arom}), 4.68 (q, *J* = 7.2 Hz, 1H, $CHCH_3$), 3.77 (s, 3H, OCH_3), 3.64 (s, 6H, OCH_3), 2.12 (s, 3H, CCH_3), 1.59 (d, *J* = 7.2 Hz, 3H, $CHCH_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 159.8 (C_q), 159.4 (C_q), 144.9 (C_q), 136.7 (C_q), 130.1 (+), 128.3 (+), 125.4 (+), 125.2 (+), 115.4 (C_q), 92.0 (+), 56.1 (+), 55.7 (+), 31.7 (+), 19.7 (+), 19.1 (+).

GC-MS (EI) m/z = 286.2 (74, [$M^{+•}$]), 271.2 (39, [$M^{+•}$]-[$CH_3^•$]), 195.1 (21, [$M^{+•}$]-[$C_7H_7^•$]), 168.1 (10, [$M^{+•}$]-[$C_9H_{11}^•$]), 118.2 (100, [$M^{+•}$]-[$C_9H_{11}O_3^•$]), 105.1 (57, [$M^{+•}$]-[$C_9H_{11}O_3^•$]-[$CH_3^•$]).

HRMS (EI)**:** [$M^{+•}$] calc. for $C_{18}H_{22}O_3$ 286.1563, found 286.1553.

2-(1-(2,4-Dimethoxyphenyl)ethyl)naphthalene **8l**



The compound **8l** was obtained from the respective benzylic alcohol and 1,3-dimethoxybenzene by using the general procedure and purification by Kugelrohr distillation as a yellow oil in (127 mg, 0.4 mmol, 87%, containing 10% of 2-(1-(2,6-dimethoxyphenyl)ethyl)naphthalene).

$C_{20}H_{20}O_2$ (292.38 g/mol)

R*f* = 0.34 (Petroleum ether/Ethyl acetate 9:1)

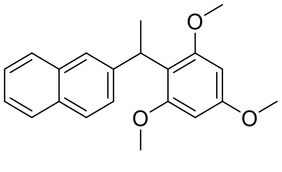
m.p.: Ambient temperature

^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm = 7.82 – 7.67 (m, 4H, C*H*$_{arom}$), 7.46 – 7.32 (m, 3H, C*H*$_{arom}$), 7.05 (m, 2H, C*H*$_{arom}$), 6.61 – 6.39 (m, 2H, C*H*$_{arom}$), 4.65 (q, *J* = 7.1 Hz, 1H, C*H*CH_3), 3.79 (s, 3H, OC*H*$_3$), 3.77 (s, 3H, OC*H*$_3$), 1.65 (d, *J* = 7.2 Hz, 3H, CHC*H*$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 159.3 (C_q), 158.0 (C_q), 144.4 (C_q), 133.7 (C_q), 132.1 (C_q), 128.3 (+), 127.8 (+), 127.7 (+), 127.6 (+), 127.5 (C_q), 127.4 (+), 125.8 (+), 125.3 (+), 125.2 (+), 104.1 (+), 98.8 (+), 55.6 (+), 55.5 (+), 37.2 (+), 21.1 (+).

HRMS (EI)**:** [$M^{+•}$] calc. for $C_{20}H_{20}O_2$ 292.1458, found 292.1471.

2-(1-(2,4,6-Trimethoxyphenyl)ethyl)naphthalene **9l**



The compound **9l** was obtained from the respective benzylic alcohol and 1,3,5-trimethoxybenzene by using the general procedure and purification by Kugelrohr distillation as a white solid (151 mg, 0.5 mmol, 94%).

$C_{21}H_{20}$ O_3 (322.40 g/mol)

R*f* = 0.25 (Petroleum ether/Ethyl acetate 9:1)

m.p.: 66.3 °C

^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm = 7.85 – 7.66 (m, 4H, C*H*$_{arom}$), 7.48 – 7.34 (m, 3H, C*H*$_{arom}$), 6.16 (s, 2H, C*H*$_{arom}$), 4.92 (q, *J* = 7.2 Hz, 1H, C*H*CH_3), 3.81 (s, 3H, OC*H*$_3$), 3.69 (s, 6H, OC*H*$_3$), 1.76 (d, *J* = 7.2 Hz, 3H, CHC*H*$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 159.7 (C_q), 159.2 (C_q), 144.3 (C_q), 133.6 (C_q), 131.8 (C_q), 127.8 (+), 127.5 (+), 127.2 (+), 126.9 (+), 125.5 (+), 124.8 (+), 124.7 (+), 115.8 (C_q), 91.6 (+), 55.9 (+), 55.4 (+), 33.3 (+), 17.9 (+).

GC-MS (EI) m/z = 322.2 (60, [$M^{+\bullet}$]), 307 (100, [$M^{+\bullet}$]-[$CH_3^\bullet$]), 195.1 (10, [$M^{+\bullet}$]-[$C_{10}H_7^\bullet$]), 168.1 (12, [$M^{+\bullet}$]-[$C_{12}H_{11}^\bullet$]), 154.1 (20, [$M^{+\bullet}$]-[$C_9H_{11}O_3^\bullet$]), 141.1 (88, [$M^{+\bullet}$]-[$CH_3^\bullet$]-[C9$H_{11}O_3^\bullet$]).

HRMS (EI)**:** [$M^{+\bullet}$] calc. for $C_{21}H_{20}O_3$ 322.1563, found 322.1554.

2.6. Literature

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3. Development of a New Route to Lignin-based Biopolymers Starting from Benzylic Alcohols

Author contribution:

Marlene Böldl: 90% of reproduced part.

Xianyuan Wu contributed to this chapter in 10% with scientific ideas, data generation, analysis and interpretation of results shown in Table 8 and Figure 7.

3.1. Introduction

The basis of our modern life is depleting. The resources for most of our goods are based on fossil fuels. They are not only decreasing while the demand is continuously increasing, but are also long time buried CO_2 deposits, which have a huge impact on the world’s climate, when released.[1] However, the things humanity made from petrochemicals changed the way of living completely. Especially polymer production increased our quality of life. These materials can be found in every aspect of our life; in our homes, in everything that includes mobility, in electronic devices and medicine, where plastic is irreplaceable. And even tough plastic packaging should be reduced as far as possible, concerning the near-permanent pollution of the natural environment with plastic waste, it still has positive effects on our climate when thinking of transportation. Also packaging decreased the spoilage of food to 75% and is therefore a central issue in conservation of natural resources.[2]

Environmental issues are very complex and there will be no panacea, but there are multiple options towards a more sustainable world. The generation of bio-mass derived platform chemicals is probably one of the most crucial steps.[3] The most known valorizations of biomass from vegetable oil, starch or sugars are important to evolve greenhouse gas neutrality, however, the sources have a huge downside. Food and fuel have to compete for agricultural land. Therefore, it is much more attractive to valorize a renewable feedstock that does not compete with food especially in view of the rising global population.[4,5]

3.1.1. Valorization of Lignin as Renewable Resource

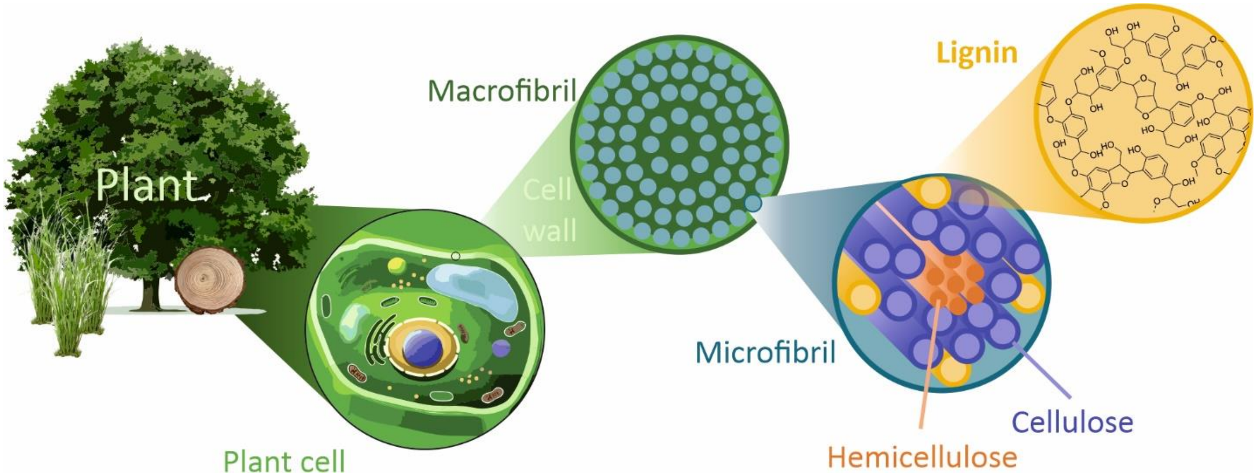


Figure 1: Origin of lignin from plants.

Production of bio-based products only makes sense when coming from a inexpensive and available biomass feedstock. Lignocellulose is the cheapest and most abundant source of biomass worldwide, derived from wood, wood wastes, corn stover, switch grass or agricultural and food waste.[4,6,7] Lignocellulosic biomass is mainly composed of 40-80%wt cellulose, 15-30 wt% hemicellulose and 10-25 wt% lignin.[7] Cellulose is a crystalline, linear glucose polymer with β-1,4-linkages of D-glucopyranose monomers. Hemicellulose, in contrast, is a polymer of five different sugars including five and six-carbon sugars and hence it is branched and amorphous and relatively easy to hydrolyze.

The cell wall of plants mainly contains lignin, a highly branched and substituted aromatic polymer consisting of complex methoxylated phenol units (Figure 1).[8] Lignin is the only large-volume bio-source of aromatic building blocks and bears therefore a tremendous potential for the production of bio-based aromatic bulk chemicals, especially as alternative for petroleum-derived BTX (benzene, toluene and xylene).[9,10] Nevertheless, its valorization often faces difficulties mainly because it is irregularly formed by an enzyme-initiated free-radical polymerization of the alcohol precursors.[11,12] Hence, lignin shows various structural linkages with strong C-C and C-O bonds, which differ with every plant source.[11] Generally, the majority of all linkages is the β-O-4 linkage, upon which most research is focused regarding depolymerization strategies for valorization (Figure 2, highlighted in red).[8]

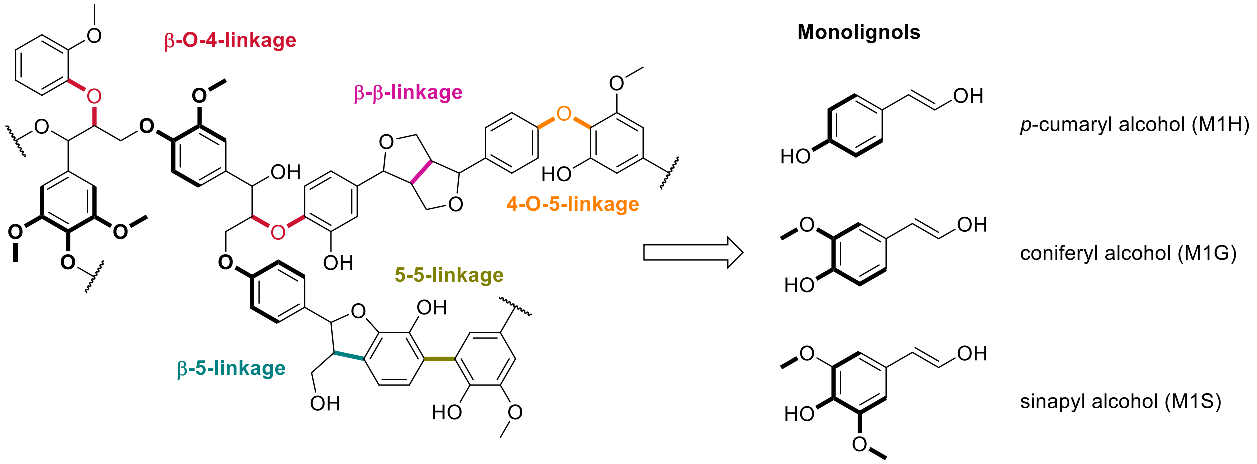
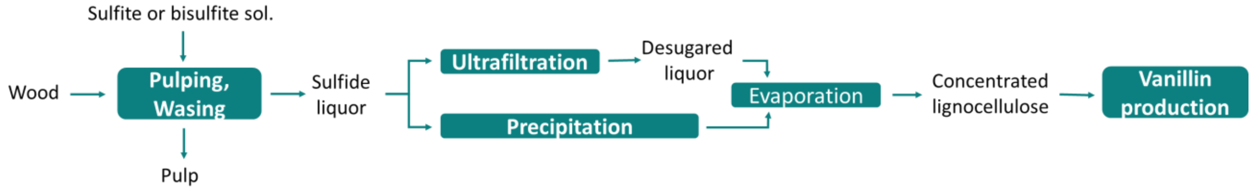


Figure 2: A representative lignin structure with highlighted most common linkages, which is derived from the three depicted monolignols[8,10]

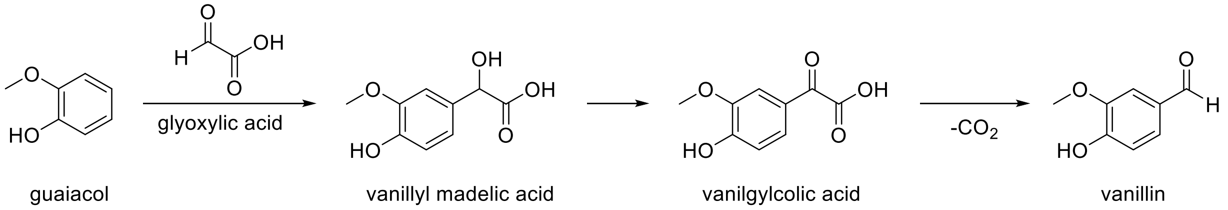
The main industrial sources for lignin are the pulp and paper industry[13] as well as the production of cellulosic ethanol,[14] which both generate lignin as main waste product. The majority is then burned to produce energy. The production of renewable energy, can yet also be covered by wind and solar radiation which is why the chemical valorization of lignin is much more attractive than its energetic use.[12]

To generate aromatic products from lignocellulose several pathways are possible.[15] One common strategy is the oxidative depolymerization of lignin, employing hydrogen peroxide, peroxyacids or oxygen.[16] The main advantages of these delignification processes are the possible economic feasibility, because they are already widely applied for pulp bleaching in the paper industry, and the mild conditions under which fractionation and separation is generally conducted. Overoxidation, formation of isomers and oxidative polymerizations however, could lead to more complex lignin structures, as well as a decrease in yield.[16] One of the oldest and most important processes in lignin valorization is the oxidative cleavage to vanillin as fine chemical product from the pulping process.[17]



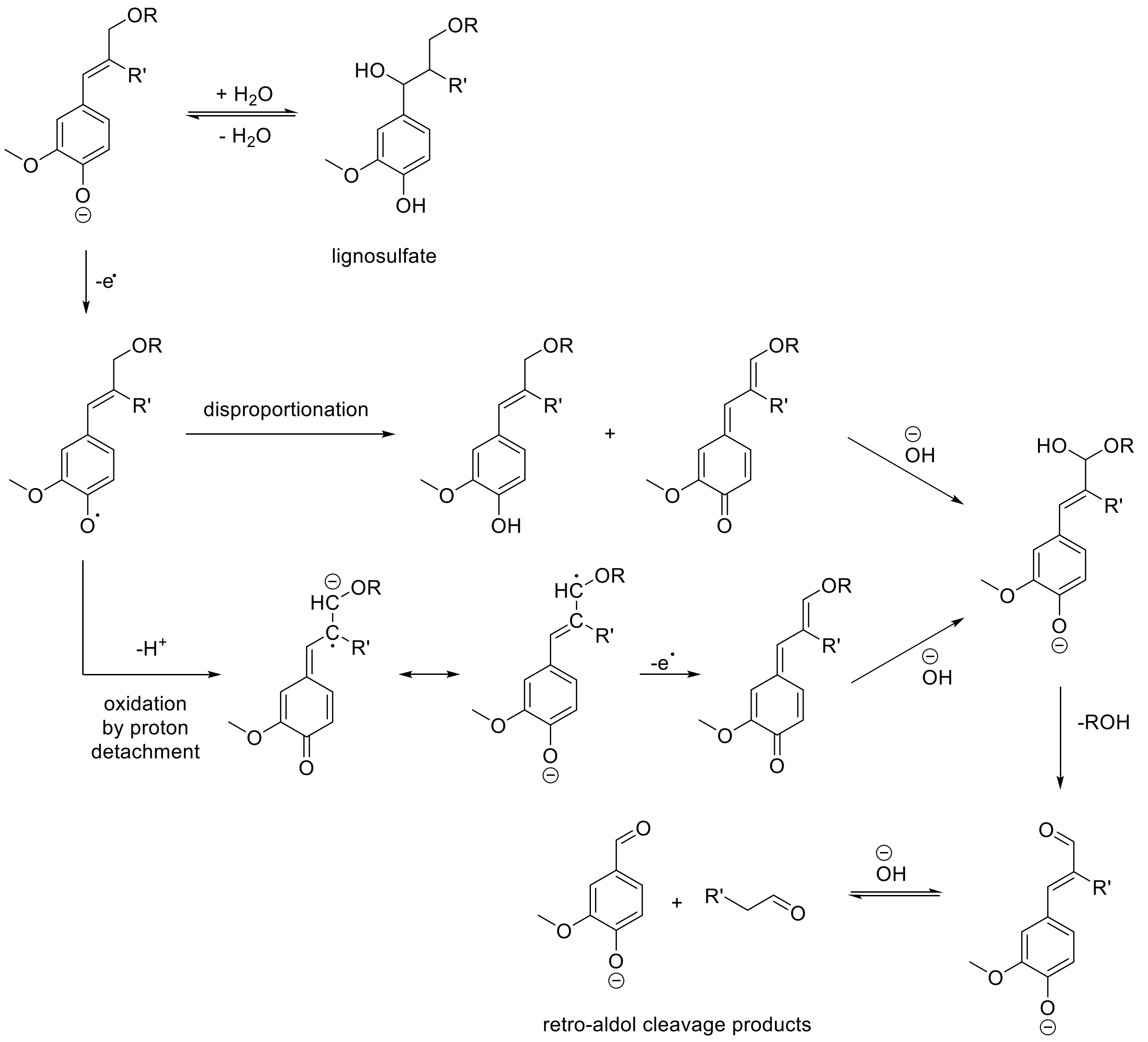
Scheme 1: Schematic lignin-to-vanillin process starting from wood, with production of lignosulfonate-rich sulfite liquor as by-product.[17]

Vanillin is the highest volume aroma chemical produced worldwide and has a wide application in the food and beverage industry as flavoring agent.[10,18] Due to the high demand of vanillin, its synthetic production from lignin started in 1936.[19] Until the 1980s, oxidation of lignin from sulfite pulping was the main process for vanillin production (Scheme *1*). Then, this process faced constrains that forced the industry to change the vanillin source. Now, 85% of the world supply of synthetic vanillin is generated from cheap petroleum-based guaiacol (Scheme 2).[20] Nevertheless, vanillin is the most available pure monoaromatic phenol currently produced at an industrial scale from lignin and the process is still gaining a lot of attention in research, especially in aspect of depleting oil reserves and valorization of vanillin to bio-based materials.[17] The fact that vanillin is a safe and non-hazardous compound and that it is available on an industrial scale as well as the availability of two reactive functionalities make vanillin a key renewable aromatic building block.



Scheme 2: Outlines of the main petrochemical synthesis of vanillin.[21]

The mechanism of oxidative depolymerization of lignin to vanillin was intensively studied with various lignin model compounds and due to the complexity of lignin the mechanism is still subject of debate and not fully understood yet.[16,22] In 2000 and 2004, Tarabanko and co-workers studied the mechanism involving lignosulfonates and other model compounds in alkaline media, suggesting that the vanillin formation proceeds *via* formation of a phenoxyl radical and a range of unsaturated intermediates with a retro-alcohol condensation as the final step (Scheme 3).[23,24]



Scheme 3: Mechanism of the vanillin formation from lignosulfates by Tarabanko and co-workers.[23,24]

Obtaining high vanillin yields from lignin is still a challenge, because oxidative depolymerization generally produces a complex mixture of monomers like vanillin, vanillic acid, syringaldehyde, syringic acid or 4-hydroxybenzaldehyde (Figure 3). The product distribution and the vanillin yield are highly dependent on the source of the lignin source and the reaction conditions as well as on the separation process.[17,25] A possible way to selectively isolate vanillin from the mixture is the bisulfitation in which $NaHSO_3$ is used to generate a vanillin bisulfite by selective reaction of the hydrosulfite anion with the aldehyde moiety, and subsequent extraction in water and acidification of the aqueous layer.[26] Current techniques generate vanillin in about 6 – 12% overall yield from softwood.[17] In 2017, Tarabanko *et al.* published a one-step oxidation, catalyzed by copper sulfate pentahydrate with O_2 as oxidant and sodium hydroxide as additive, generating vanillin in 18% wt from extractive-free pine wood.[27]

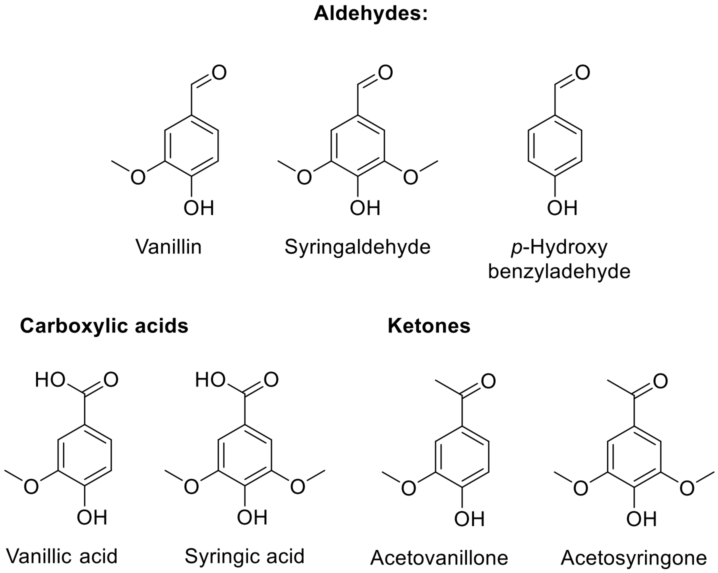


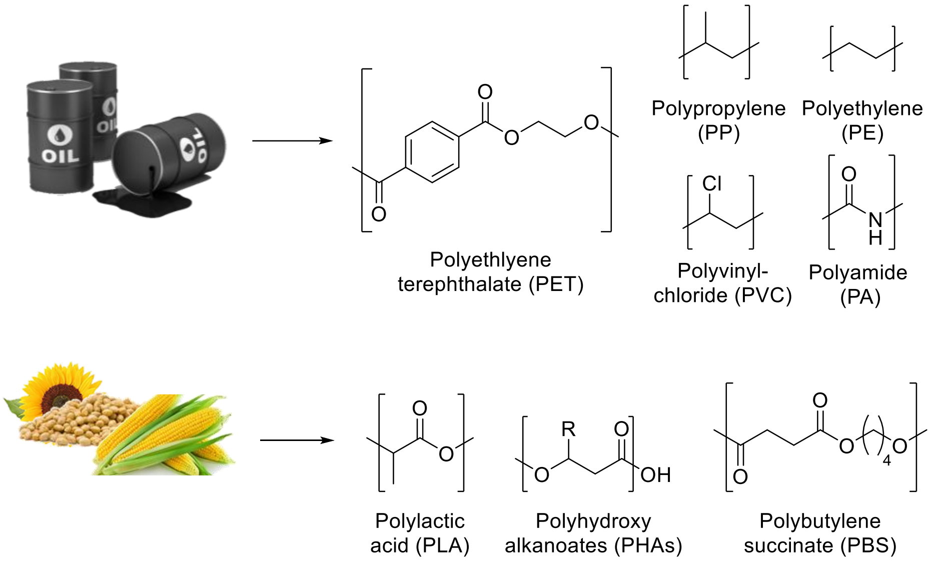
Figure 3: Main products of the alkaline oxidative depolymerization of lignin.[17,21]

Fractionation and separation methods as used in paper and ethanol production, are generally product target approaches, which consider only pathways that generate one specific product. Nevertheless, these methods have the main disadvantage that they lead to different structurally modified lignin species with less C-O linkages depending on the lignocellulose fraction conditions.[28] However, it is crucial to efficiently generate high product yields in following catalytic processing, in order to sustain the native structure of lignin. This leads to a platform-molecule strategy that has the goal to derive multiple high-value chemicals from one platform chemical.[5] Hence, one other way to generate lignin monomers is the reductive catalytic fractionation (RCF), in which lignocellulose is extracted and catalytically converted under reductive conditions in a one-pot process by using commercial redox catalysts like Ru/C, Pd/C or Ni/C.[29] With this method a solid carbohydrate pulp and a mixture of aromatic compounds is obtained with aromatic compounds in higher yields compared oxidative depolymerization processes. These monomers can be successfully converted into fuels,[30] high performance materials[21,31,32] and commercially available chemicals.[33] In 2018 for example, Epps and co-workers extracted high-purity **3S** and **3G** monomers from popular wood with cyclohexane from lignin oil by using RCF over a Ru/C catalyst.[34] Functionalization with acrylate or methacrylate and polymerization generated thermally stable and pressure sensitive adhesives (PSAs), which had similar properties to commercial available PSAs like adhesion to stainless steel. Barta and co-workers published a sustainable *LignoFlex* process in the same year, showing the complete conversion of pine lignocellulose over copper-doped porous metal oxide (Cu2-PMO) predominantly to 4-*n*-propansyringol and 4-*n*-propanolguaiacol from lignin and aliphatic alcohols from hemicellulose in high selectivity.[35] Generally, oxidative depolymerization, as well as reductive catalytic fractionations are powerful tools to generate various monomers from lignin.

Beside these two methods, also reductive depolymerization, acid-catalyzed depolymerization, biochemical transformations and other catalytic fractionations play a role in lignin valorization but will not be discussed in this work.[15] Generally, various defined building blocks can be yielded from lignin and since the interest in lignin valorization is still rising, with more insights and better separation methods, novel industrially applicable processes for lignin depolymerization are becoming increasingly probable. Therefore, also processing of lignin-based monomers into new materials like bio-polymers has an immense potential for the future.

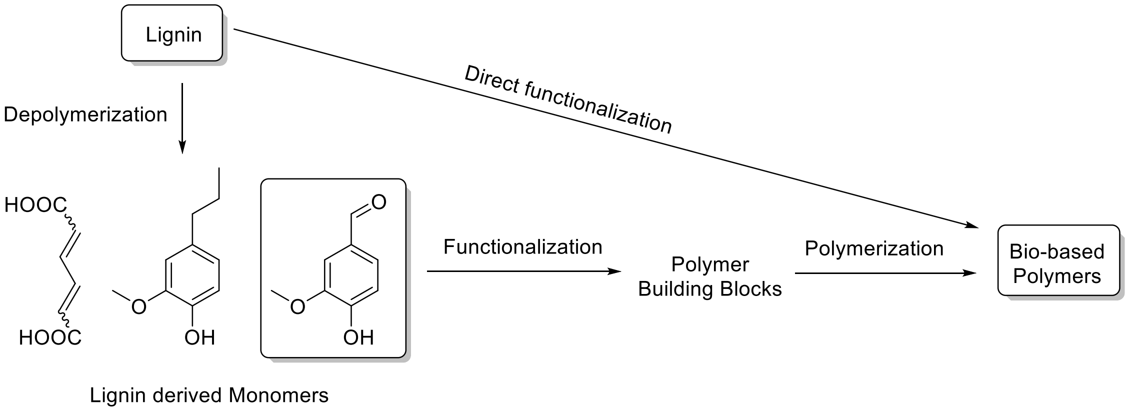
3.1.2. Biomass-based Polymers from Functionalized Lignin Monomers

Worldwide, 6% of the oil produced is used in the manufacture of polymers.[36] That were almost 350 million tons in 2018, tendency increasing.[2] Nonetheless, the production of sustainable polymers is very small in comparison to petroleum-based polymers. In 2014 for example, globally only 0.6% of the produced polymers originated from biomass.[36] The production of synthetic polymers is globally determined by polyethylene (PE), polypropylene and polyamide (PP&A), polyvinylchloride (PVC) and polyethylene terephthalate (PET) (Scheme 4).[37] Industrially available biopolymers, are yet mainly derived from cellulose, starch and or triglycerides.[38] From these raw materials aliphatic or cycloaliphatic polymers can be produced, mostly polylactide (PLA), polyhydroxy alkanoates (PHAs) or polybutylene succinate (PBS) (Scheme 4).[39]



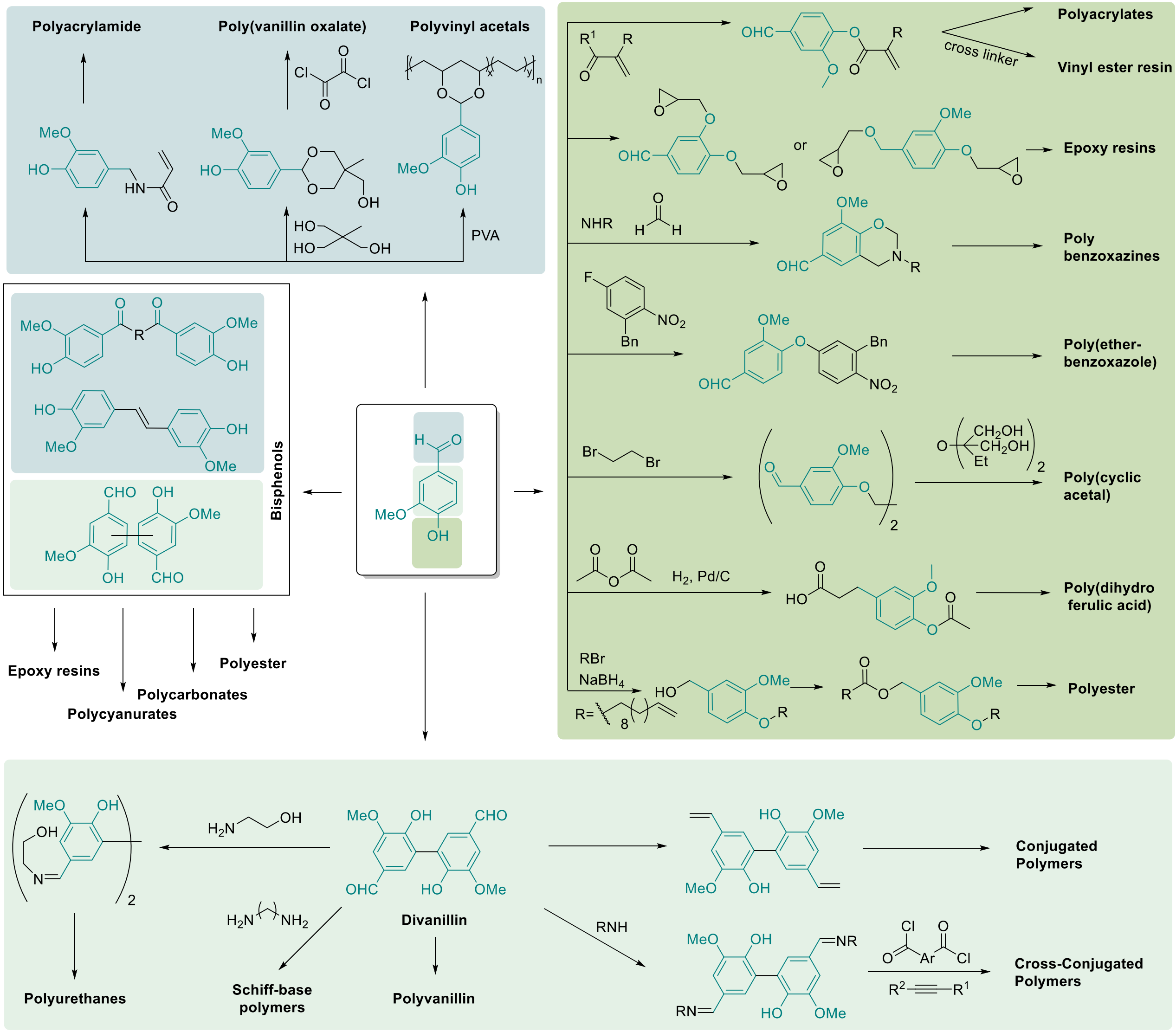
Scheme 4: Most prominent synthetic industrial polymers from petroleum sources and plant sources.

Also direct functionalization of lignin to polymers has been reported in recent years.[13] To generate industrially more variable and applicable polymers however, the production of biopolymers from lignin based monomers like vanillin arises as attractive alternative (Scheme 5). In the last years, this approach has therefore generated significant advances in polymer science.[15,31]



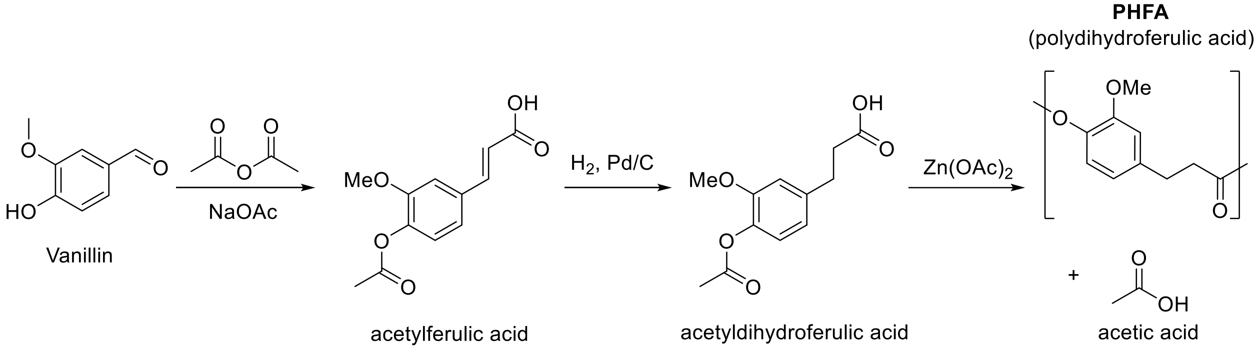
Scheme 5: General strategies for the production of lignin-based polymers.[15]

There are plenty of lignin and lignocellulose-based monomers, which could be applied for further functionalization to polymer building blocks. Due to the scope of this work, only vanillin functionalization will be discussed here. On an industrial scale, vanillin is the most manufactured lignin monomer and has therefore the potential to be a key-intermediate in the biopolymer production (Scheme 6). Vanillin and its derivatives have already been widely applied in the biopolymer production: functionalization on the hydroxyl group can produce vinyl ester resins,[40] polyacrylates,[41] epoxy resins,[17,21,42,43] polybenzoxazines,[44,45] poly(ether-benzoxazoles),[46] poly(cyclic acetals),[47] poly(dihydroferulic acids)[48] and polyesters,[49] whereas functionalization of the aldehyde functionality generates polyvinyl acetals,[50] poly(vanillin oxalate)[51] and polyacrylamine.[52]



Scheme 6: Polymers derived from lignin-based vanillin by functionalization of the aldehyde moiety, the aromatic ring or the alcohol moiety.[15]

One interesting example of hydroxyl- and aldehyde functionalization of vanillin was shown by Mialon *et al.* in 2012 (Scheme 7).[48] They synthesized the first wholly bio-polymer that successfully mimics PET, which is petroleum-based and the third most common synthetic polymer. The approach was to use one bio-based monomer instead of two co-monomers that would need a stoichiometric balance to achieve high molecular weights. Therefore, a Perkin reaction on the acetyl group as well as acetylation of the hydroxyl group of vanillin with acetic anhydride and sodium acetate was conducted as first step. A hydrogenation of the double bond and condensation polymerization at 200-220 °C with Sb_2O_3 or $Zn(OAc)_2•H_2O$ as catalyst gave poly(dihydroferulic acid) with loss of acetic acid.[48]

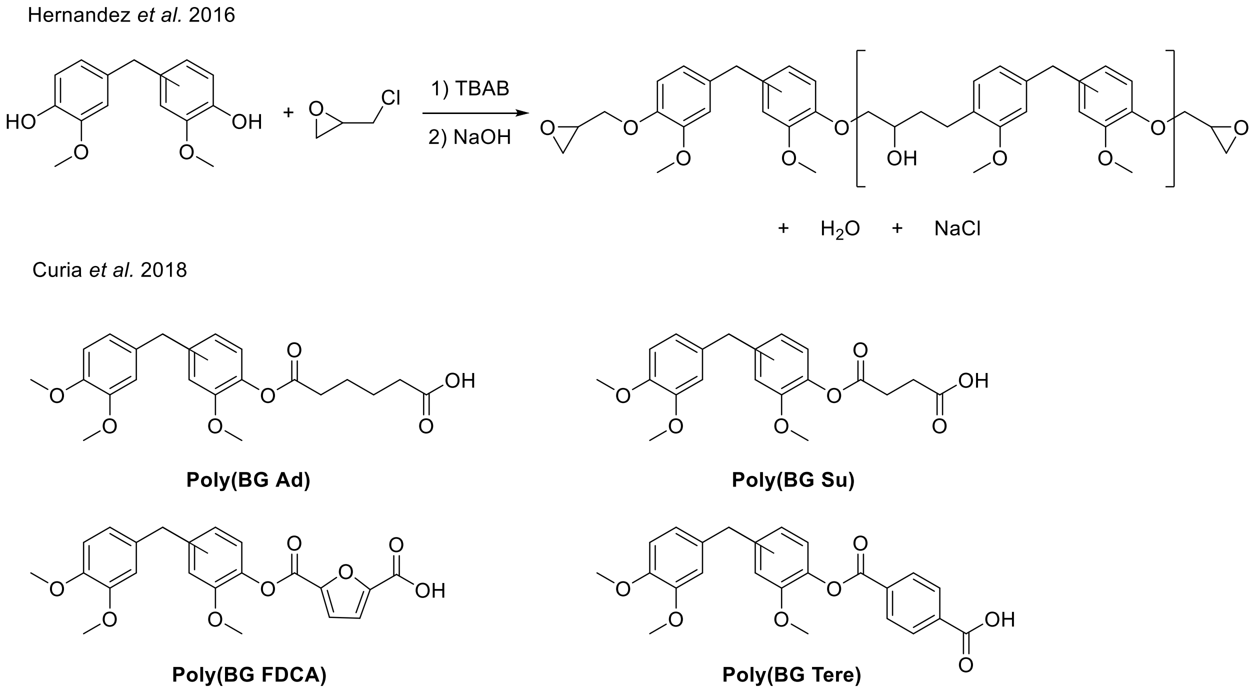


Scheme 7: Synthetic procedure to PHFA(polydihydroferulic acid) from bio renewable compounds acetic acid and vanillin.[48]

Beside functionalization of the alcohol and aldehyde moiety, also transformation on the aromatic ring can be conducted, leading to divanillin,[53] which can be further polymerized to polyvanillin,[54] conjugated polymers,[55] cross-conjugated polymers,[56] polyurethanes[57] and Schiff-base polymers.[58] Also bisphenols can be synthesized from functionalizing the aromatic ring of vanillin either by transformation of the side chain to stilbenes,[59] or with crosslinkers,[60] by enzymatic dimerization,[55,61] electrophilic aromatic condensation[62,63] or coupling with formaldehyde[64] (Scheme 6). These bisphenols are then applicable for various polymers like polyester,[61,63] epoxy resins,[60,65] polycarbonates or polycyanurates.[59]

The application of bisguaiacols for bio-based polymers for example, was shown by Herandez *et al* in 2016 (Scheme *8*).[62] They synthesized them from vanillin alcohol and guaiacol *via* electrophilic aromatic condensation with a heterogeneous acid and avoided thereby the use of carcinogenic formaldehyde, which is mostly used for bisphenol formation, since the methylene bridge is derived from vanillin alcohol. Epichlorohydrin was then used for the generation of diglycidyl ethers. With cycloaliphatic diamine as curing agent, the resulting epoxy amine thermoset had positive thermomechanical properties. Mauck *et al.* subsequently reported diglycidyl ethers of vanillin alcohol, which were cured with bio-based 5,5'-methylenedifurfurylamine.[66] Compared to commercial BPA, the obtained thermosets had good thermomechanical and thermogravimetric properties, which could possibly lead to replacement of BPA.

Recently, Curia *et al.* reported the synthesis of bisguaiacol-based polyesters by applying four diacid derivatives (Scheme *8*).[63] The resulting polymers showed a high thermal stability (T_{max}) up to 300 °C in air and glass-transition temperatures (T_g) higher than PET or other commercially relevant polyesters.



Scheme 8: Bisguaiacol-based polymers from Curia et al. and Hernandez et al.[62,63]

3.1.3. Deep Eutective Solvents as Green Solvents

In every case of lignin monomer functionalization it is important to target a pathway that meets green chemistry goals.[67] Hence, reactions should be as atom efficient and waste-free as possible. In most organic reactions, large quantities of solvent are used relatively to the reagents. Moreover, a large excess of solvent is necessary for extractions and purifications, which is why solvents are responsible for 80% of the waste in chemical synthetic procedures.[68] Conventional solvents however, are mostly non-renewable, non-biodegradable, volatile, flammable and/ or explosive, often hazardous and the main environmental drawback in organic chemistry. Nevertheless, solvent effects in organic chemistry are not negligible.[69] The choice of the solvent system is therefore an essential factor towards sustainable organic chemistry.

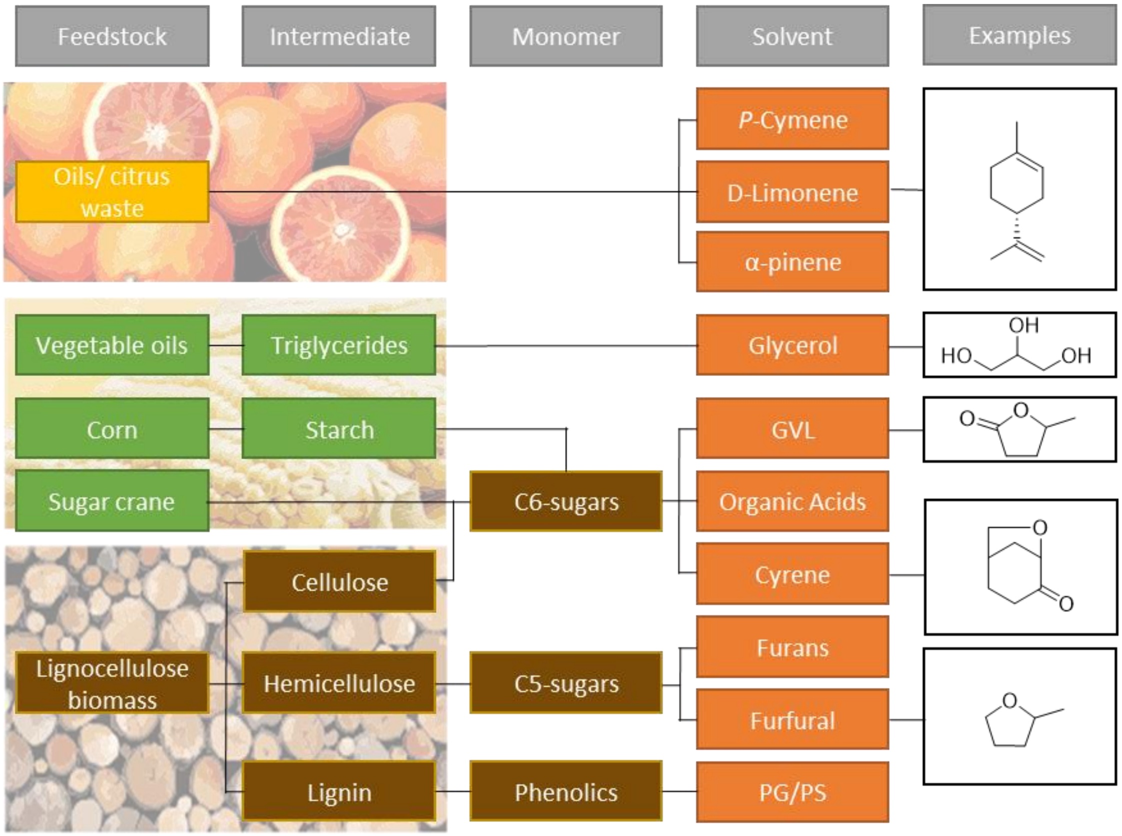


Figure 4*:* Some examples of sustainable solvents from renewable plant sources.[70]

According to Gu and Jérôme sustainable solvents have to fulfill 12 criteria related to toxicity, flammability, price, availability, recyclability, renewability, synthesis, biodegradability, performance, storage and stability.[71] In order to evaluate the environmental impact, the whole life cycle of a chemical process, including energy intensive procedures like distillations, isolation and purifications, has to be considered. Most commonly known and used green solvents that are derived from plant biomass and are safe, non-toxic, bio-renewable and cheap, due to the high abundance.[70] The most popular green solvents 2-MeTHF and γ-valerolactone (GVL) are synthesized from starch and cellulose, whereas glycerol is produced from triglycerols (Figure 4).

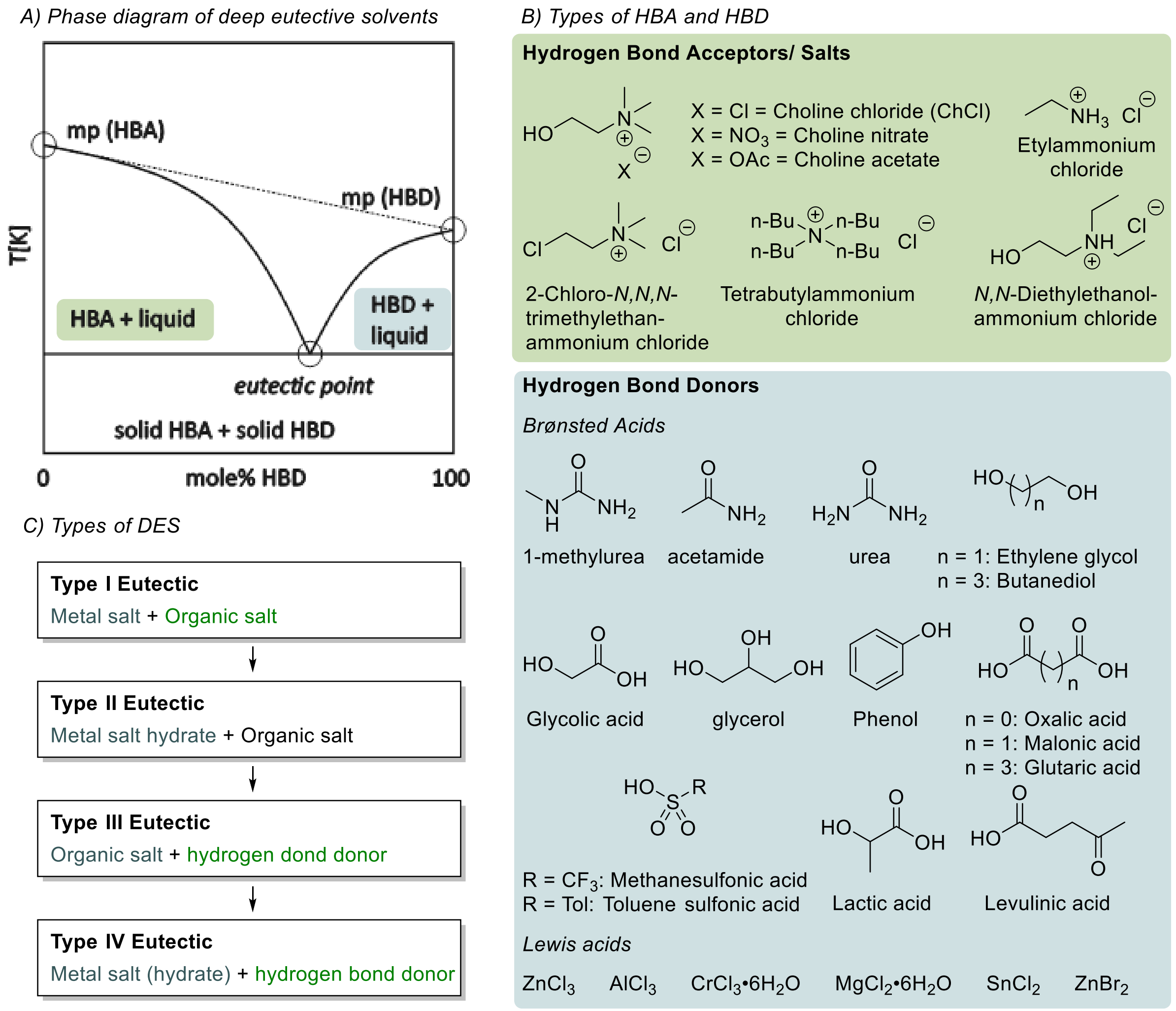


Figure 5: A) Schematic solid-liquid phase diagram for a binary mixture between a hydrogen bond donor (HBD) and a hydrogen bond acceptor (HBA) at a specific mixture composition and temperature (mp = melting point) and B) typical hydrogen bond donors and acceptors; C) the four types of DES proposed by Smith et al.[72]

In industry, conventional solvents are mostly used. First sustainable big scale approaches use neoteric solvents including supercritical carbon dioxide, gas expanded solvents, liquid polymers (e.g. Polyethylene glycol, PEG), switchable solvents ,ionic liquids (ILS) and deep eutectic solvents (DES).[73] ILS exhibit similar properties like DES but have some major drawbacks such as eco-toxicity, high-costs and complex synthesis and preparation.[74] DES instead, are gained by simply mixing two or three components, of which one is usually an organic salt, at elevated temperature. The interaction of a strong hydrogen bond donor (HBD) and a hydrogen bond acceptor (HBA) leads to an extreme depression of the freezing points compared to those of the staring individual components and therefore generates a homogeneous liquid (Figure 5A). This has the advantage that inexpensive and biocompatible compounds with a low toxicity also generate nontoxic, biodegradable solvents. Additionally, DES systems have highly tunable properties depending on the nature and the ratio of the components. Typical HBDs are urea, carboxylic acids or polyols, typical HBAs are quaternary halide salts like choline chloride (ChCl) (Figure 5B). [70]

First investigations on the properties of choline chloride based deep eutectic solvents were published in the early 2000's by Abbot and co-workers.[75,76] They measured the viscosity and a general high conductivity, which means that ionic species can move independently. DES are not reactive with water and miscible with other polar solvents like ethanol and methanol. Less polar solvents like acetone, Et_2O, ethyl acetate, hexane, 1,2-dichloroethane or toluene form biphasic systems due to immiscibility. It was also shown that inorganic salts, aromatic acids, amino acids and metal oxides are easily dissolvable in these systems and therefore new possible green solvents.[75,76] Later, more structural studies were published, showing that in DES of choline chloride and urea, a 1:2 molar ratio is necessary to ensure reasonable hydrogen bond interactions.[77] For this ratio, Hammond *et al.* determined the liquid structure in 2016.[78] Other advantages of DES were also shown recently, such as a high thermal stability,[79] a wide liquid range,[80] a negligible vapor pressure[81] and non-flammability.[82] Yet, reports on the polarity of DES systems are rare. In a work of Abbot *et al.* on glycerol/ChCl based DES, a linear relation of increasing ChCl concentration and a higher polarity was. Additionally, the calculated values exhibit a polarity similar to $RNH_3^+X^-$ and $R_2NH_2^+X^-$ ionic liquids with discrete anions [83] In 2011, Pandey and co-workers complemented these findings. They could show that 1:2 rations of choline chloride with glycerol, ethane diol and urea were more polar than methanol but less polar than water and fluorinated alcohols (Table 1).[84]

Table 1: Some examples for deep eutective solvents with solvent polarity parameter (electronic transition energy of dye 30).

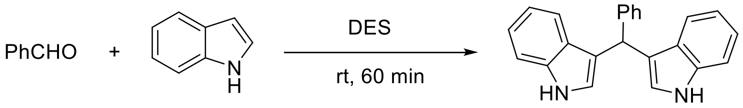
DES	E_T (30) [kcal mol^{-1}]
ChCl/Glycerol 1:2	58.0
Glycerol	57.9
ChCl/Ethane diol 1:2	57.3
1,2-Ethandiol	57.1
ChCl/Urea 1:2	57.0
MeOH	55.5
2,2,2-Triflouroethanol	59.9
H_2O	63.1

Nowadays, there are already plenty of applications for DES known, as in biotransformations,[85] polymerizations,[86] biodiesel production,[87] nanotechnology,[88] biomass processing,[89,90] electrochemistry,[91] material chemistry,[92] CO_2 capture,[93] separation and extraction[94] and in organic synthesis. In the latter, it is mostly known as solvent for reactants and catalysts in cyclization, addition, replacement, oxidation, reduction and condensation reactions.[95] In recent years, multiple reviews have also been published on the application of DES in metal-catalyzed and -mediated organic reactions in general,[96] transition-metal catalysis [68,97] and organometallic chemistry.[98]

DES in organic chemistry, however, are not only known to act as solvents but also as catalysts. In a one-pot four-component reaction of 1,3-dicarbonyl compounds, nitromethane, aldehydes and amines reported by Zhang *et al.,* ChCl-MA was applied as a catalyst and a reaction media to gain substituted pyrroles.[99] Other examples for DES-systems as catalysts and solvents were shown by Shankarling and co-workers on mono *N*-alkylation or aromatic amines.[100]

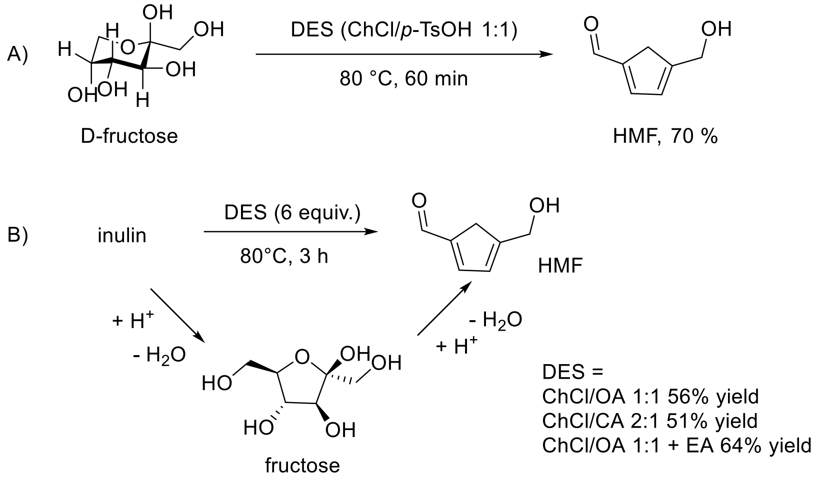
In 2013, Phadtare and Shankarling investigated the bromination of substituted 1-aminoanthra-9,10-quinone with ChCl-U as catalyst.[101] The same catalyst was used for the synthesis of cinnamic acid *via* a base-catalyzed Perkin reaction, shown by Pawar *et al.*,[102] and for the synthesis of diphenylamine-based chromophores *via* a Knoevenagel reaction.[103] The Lewis acid DES (LADES) ChCl-$SnCl_2$ was applied in the acid-catalyzed synthesis of bis(indolyl)methane (Table *2*).[104] Other applications of LADES have been recently shown in a review of Qi and co-workers.[105]

Table 2: Synthesis of bis(indolyl)methane in LADES.[104]



DES	ChCl/$SnCl_2$	ChCl/$SnCl_2$/PE	ChCl/$SnCl_2$/H_2O	ChCl/ $ZnCl_2$, $SnCl_2$
Molar ratio	1:2	1:2:3	1:2:3	1:1:1
Yields [%]	80	97	85	70

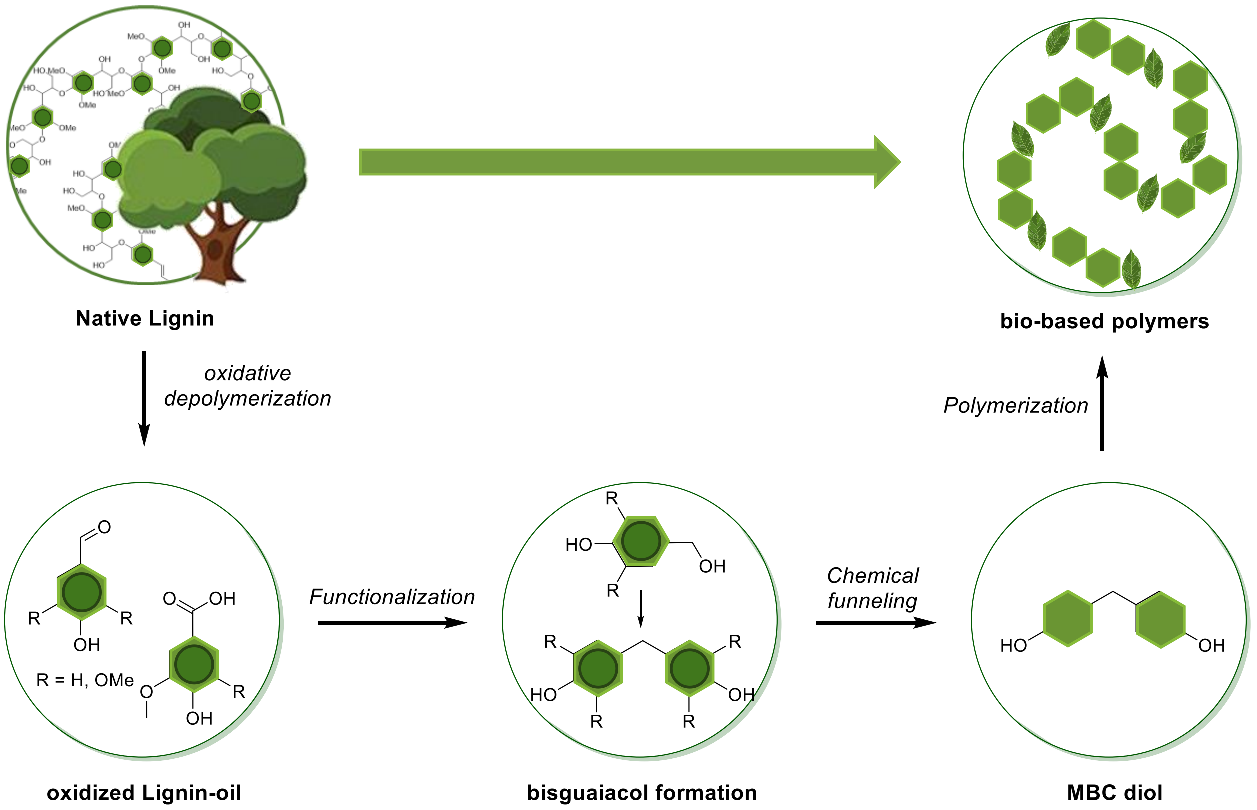
Besides LADES, there are also Brønsted acid DES known to act as acid catalysts: The synthesis of 5-hydroxymethylfurfural as important building block from the dehydration of fructose for example, was reported to be catalyzed by DES of ChCl and *p*-toluenesulfonic acid (TsOH)(Scheme *9*A).[106] The synthesis of 5-HMF from inulin catalyzed by ChCl/citric acid (CA)was shown by Hue *et al*, yielding the product in 57% yield. Application of a biphasic system of ChCl/oxalic acid (OA) and ethyl acetate increased the yield to 64% (Scheme *9*B).[107]



Scheme 9: Dehydration reaction of D-fructose and inulin to 5-hydroxymethylfurfural (HMF) with deep eutective solvents; CA = citric acid, OA = oxalic acid.[106,107]

Very recently, a new term for DES containing primary metabolites such as amino acids, organic acids, sugars or choline derivatives arose. Natural deep eutectic solvents (NADES) could be involved in the biosynthesis, transportation and storage of poorly water-soluble compounds in cells and show some noteworthy advantages in respect to sustainability and biodegradability.[108]

3.2. Aim



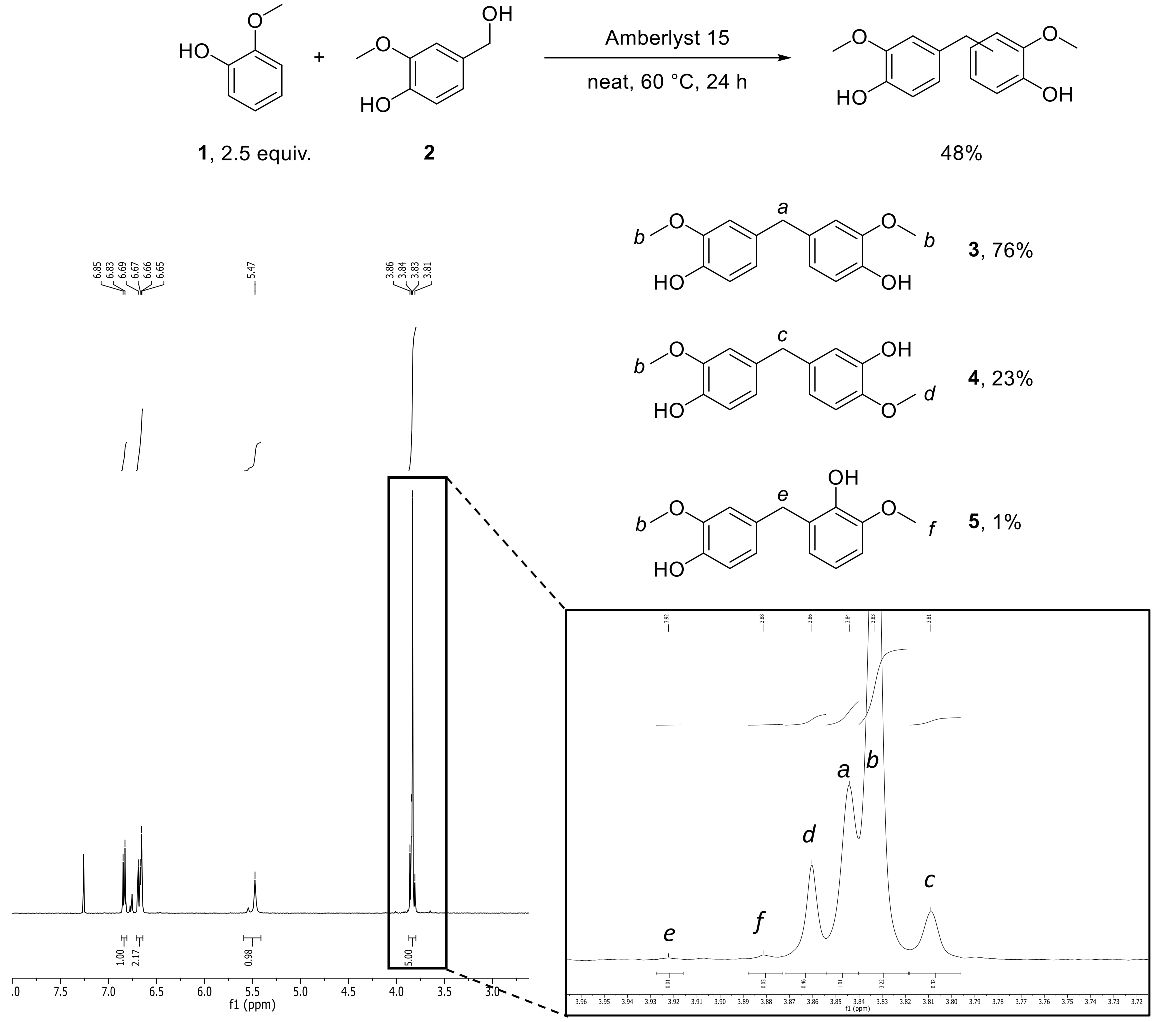
Scheme 10: General route from lignin to benzylic alcohols to generate bio-based polymers.

The idea of this project was to selectively design a new pathway for the conversion of raw biomass to fully renewable diol-based biopolymers, with potential characteristics similar to styrene-containing polymers. We herein generated bisguaiacols as potential monomer building block from lignin-based starting materials like vanillin by applying the principles of green chemistry.[67] Additionally, deep eutective solvents (DES) were prepared and used for the conversion of vanillin alcohol under very mild reaction conditions. The generated bisguaiacols were then hydrogenated to aliphatic diols, for further transesterification and condensation polymerization to polyesters. This protocol hence shows a highly favorable way to a broad range of potentially industrially applicable polymers and is the first reported use of lignin derived symmetric diols fur successful production of polymers in atmospheric pressure.

3.3. Results and Discussion

3.3.1. Synthesis of Bisguaiacols

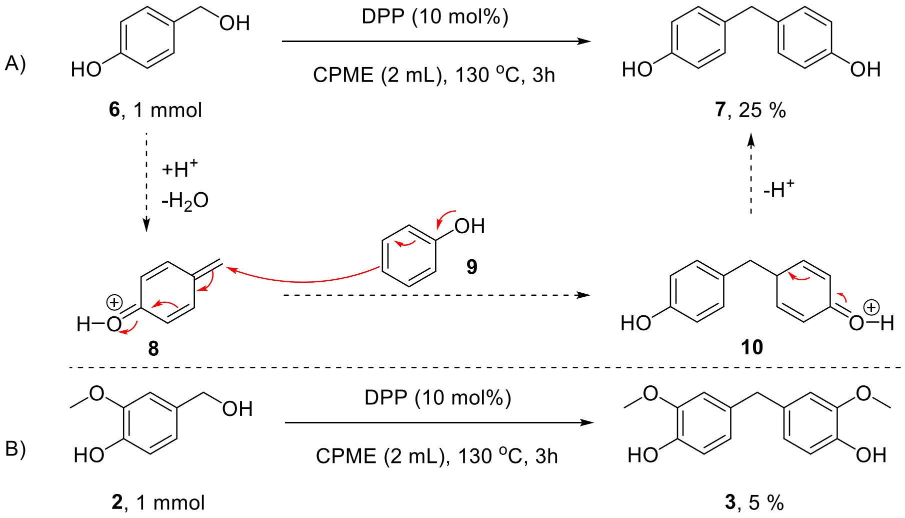
For the formation of a bisphenolic species, an electrophilic aromatic condensation reaction to bisguaiacol starting from vanillin alcohol (**2**) was conducted as starting point of this work. Therefore, a literature synthesis from Stanzione and Epps[62,109] was applied by using the heterogeneous acid catalyst Amberlyst 15 (*Scheme 11*). The reaction was conducted under neat reaction conditions by applying Guaiacol (**1**) in excess. The Friedel-Crafts reaction generated mainly Bisguaiacol F (**3**). However, it was not possible to separate it from side products **4** and **5** by column chromatography.



Scheme 11: Synthesis of Bisguaiacol F by Epps and co-workers; *reaction conditions:* **1** (4.0 mL, 4.4 g, 35.8 mmol, 2.5 equiv.), **2** (1.1 g, 7.2 mmol, 1.0 equiv.), Amberlyst 15 (1.2 g), 60 °C, 24 h.[62]

In prior to this work, it was observed that methylenediphenol (7) was generated solely from *p*-phenylmethanol (**6**) in cyclopentyl methyl ether (CPME) as green solvent and with diphenylphosphate (DPP) as catalyst. Hence, a reaction with 10 mol% DPP at 130 °C was carried out (Scheme 12A). After 3 h, **5** was fully converted and 25% of the desired product **6** was isolated in 25% yield. Interestingly, the formation of phenol (**9**), but no formation of 1,1-diphenylethane or 4,4'-Dihydroxydibenzyl ether were observed *via* GC-MS. This leads to the assumption that a Friedel-Crafts reaction of **5** with *in situ* generated **9** and *p*-quinone methide **8** takes place at higher temperatures. The main side product is yet a yellow precipitate which is not dissolvable in any common solvent and may therefore be a polymeric species of **6** and **7**.

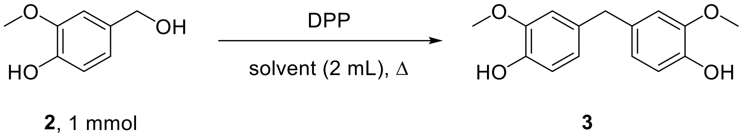
Since the idea of this project was, to generate polymers from renewable resources, vanillin alcohol (**2**) was then tested as starting material under the given reaction conditions. Nevertheless, Bisguaiacol F (**3**) was only isolated in 5% yield. The main side products observed on GC-MS were trimeric species, which hint towards an oligomerization of vanillin alcohol as main reaction pathway.



Scheme 12: Initial acid catalyzed conversion of benzylic alcohols in CPME. *Reaction conditions:* A) **5** (124 mg, 1.0 mmol, 1.0 equiv.), DPP (25 mg, 0.1 mmol, 10 mol%), CPME (2 mL), 130 °C, 3 h; B) **2** (154 mg, 1.0 mmol, 1.0 equiv.), DPP (25 mg, 0.1 mmol, 10 mol%), CPME (2 mL), 130 °C, 3 h.

Further tests with various solvents, temperatures and acid catalysts did not lead to yields over 6% (Table 3). Also, only small amounts of other species were observed with GC-FID, which supports the hypothesis of vanillin alcohol oligomerization. Addition of Lewis bases to acid-catalyzed homocoupling reactions of benzylic alcohols was recently shown to be advantageous to prevent oligomerization.[110] However, in this reaction the addition of triphenylphosphine as Lewis base was not successful (Table 3, Entry 12).

Table 3: Acid-catalyzed bisguaiacol formation from vanillin alcohol.

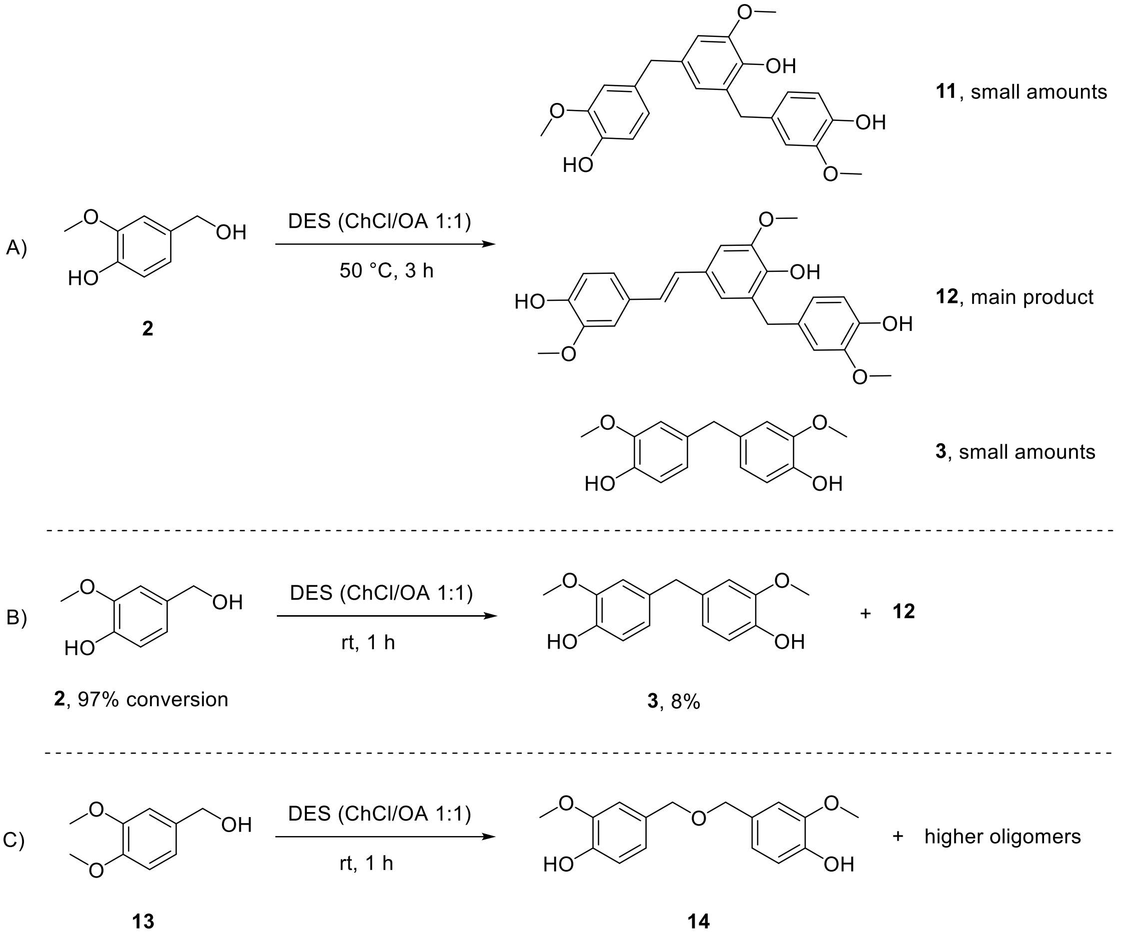


Entry[a]	Solvent	T [°C]	Yield of 3[%][b]
1	CPME	130	6[c]
2	CPME	rt	0
4	CPME	100	3
5[d]	CPME	100	2
6	EtOH	100	0
7	MeCN	100	5
8	Dioxane	100	3
9	Acetone	100	2
10[e]	CPME	100	2
11[f]	CPME	100	3
12[g]	CPME	100	4
13[h]	MeCN	80	5

[a] *General reaction conditions:* **2** (154 mg, 1.0 mmol, 1.0 equiv.), DPP (25 mg, 0.1 mmol, 10 mol%), CPME (2 mL), 130 °C, 3 h; [b] Yield determined by quantitative GC-FID; [c] isolated yield; [d] CPME (4 mL); [e] DPP (50 mg, 0.2 mmol, 20 mol%); [f] TsOH (17 mg, 0.1 mmol, 10 mol%) instead of DPP; [g] DPP (41 mg, 0.2 mmol, 16 mol%), PPh_3 (5 mg, 0.02 mmol, 2 mol%); [h] Oxalic acid (18 mg, 0.2 mmol, 20 mol%).

3.3.2. Bisguaiacol Formation in Deep Eutectic Solvents

To overcome polymerization issues, the application of DES was envisioned to improve the selectivity of vanillin alcohol towards the formation of **3** rather than oligomerization. In a first approach, a DES was formed from oxalic acid (OA) and choline chloride (ChCl) in a 1:1 ratio by stirring both components for 15 min at 60 °C. Vanillin alcohol (**2**) was added to the DES and heated to 90 °C. GC-MS analysis showed full conversion of **2** into higher oligomers. At 50 °C small amounts of **3**, and **11** were observed and trimeric species **12** was formed as main product after 3 h (Scheme *13*:Scheme 13A). This led to the assumption that **3** as well as the trimeric species could be intermediates of oligomerization reactions. Hence, lowering the temperature could decrease the amount of oligomer formation by stopping the oligomerization reaction after formation of **3**.

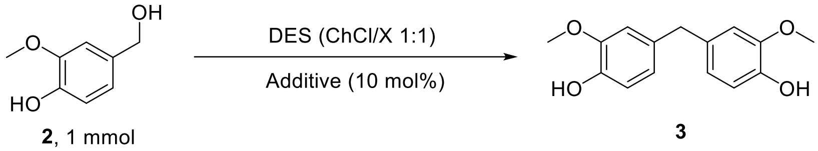


Scheme 13: Initial reaction of vanillin alcohol in deep eutectic solvent of OA and ChCl; yield and conversions were determined by quantitative GC-FID; *reaction conditions:* A) **2** (154 mg, 1.0 mmol, 1.0 equiv.), DES (OA: 10 mmol, ChCl: 10 mmol), 50 °C, 3 h; B) rt, 1 h; C) **13** (166 mg, 1.0 mmol, 1 equiv.), DES (OA 10 mmol, ChCl 10 mmol), rt, 1 h.

When the reaction was performed at room temperature, the starting material was only dissolved fully after one hour, which is why vanillin alcohol could still be observed in the chromatogram (Scheme 13B). After 3 h, **2** is fully converted, however, the amount of **3** did not rise over 8%. In conclusion, lowering the temperature did not lead to a significant decrease of oligomerization or to a higher yield of the desired product. When veratryl alcohol (**13**) is used as starting material, generation of a quinone methide is not possible and hence, only low conversion and no methylated bisguaiacol formation is observed (Scheme 13C). Nonetheless, small amounts of ether **14** are produced. Overnight, **13** gets fully converted to higher oligomers.

The reason for the tendency of oligomerization of vanillin alcohol is most likely due to the high acidity in this DES system, which is depending on the pH of the hydrogenbond donor.[105] This was already demonstrated, when oxalic acid was applied solely in acetonitrile for the dimerization of vanillin alcohol (Table *3*, Entry 13). In the reaction, the formation of bisguaiacol F was as well minor compared to the formation of higher oligomers. Thereupon, less acidic DES systems were prepared (Table 4).

Table 4: Reaction of vanillin alcohol **2** in deep eutectic solvents.



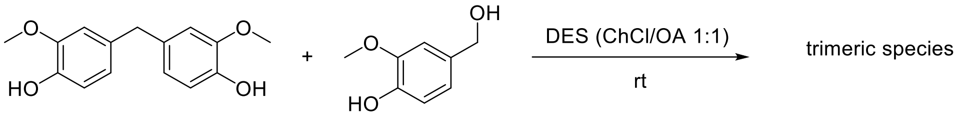
Entry[a]	X	Additive	T [°C]	t [h]	Conversion	Yield of 3[%]
1	Urea	$AlCl_3$	90	20	Low	0
2	Urea	DPP	50	20	69	0
3	Lactic Acid	-	50	1	86	4
4	Lactic Acid	-	50	18	95	6
5	Glycerol	-	50	20	43	0

General reaction conditions: **2** (154 mg, 1.0 mmol, 1.0 equiv.), DES (ChCl: 10 mmol, **X:** 10 mmol), additive (10 mol%); [a] yields and conversions were determined *via* quantitative GC-FID.

First attempts showed, that systems based on basic urea and ChCl with the addition of catalytic amounts of Lewis are not suitable for the conversion of **2** (Table 4, Entry 1). Interestingly, **2** was 69% converted into higher oligomers when applying DPP as Brønsted acidic additive in 10 mol% at lower reaction temperatures (Table 4, Entry 2). When lactic acid as used as second DES component, the desired product was generated in 4% after one hour but did not increase substantially after 18 h (Table 4, Entries 3 – 4). Since the conversion of **2** is relatively high, a similar reaction pathway as with oxalic acid can be assumed. The application of less acidic glycerol instead of oxalic acid at lower temperatures, showed a low conversion of 43% after 20 h, but no formation of significant amounts of low molecular weight molecules were visible on GC-data.

To get a closer insight in the reaction of **2** in DES of OA and ChCl, **2** and **3** were added to the previously formed DES and stirred at 50 °C (Table 5). After 1.5 h, **2** was completely converted, but the amount of bisguaiacol **3** did not rise over the initially applied amount (Table 5, Entry 1). Instead, trimeric species were formed from **2**. After 4.5 h, these trimeric species were also completely converted. **3** shows a conversion of 25% after 4.5 h, which means that **2** is converted to trimers and eventually to higher oligomers very fast, whereas Bisguaiacol F (**3**) reacts far slower and rather with already generated oligomers from **2** than with the vanillin alcohol monomer (Table 5, Entry 2). Without **2**, Bisguaiacol F (**3**) is stable for at least 24 h in the reaction media. Hence, it can be concluded that **2** is probably not converted to the respective bisguaiacol in suitable amounts and that the formed trimers and oligomers are generated directly from **2** without or with minor interference of **3**.

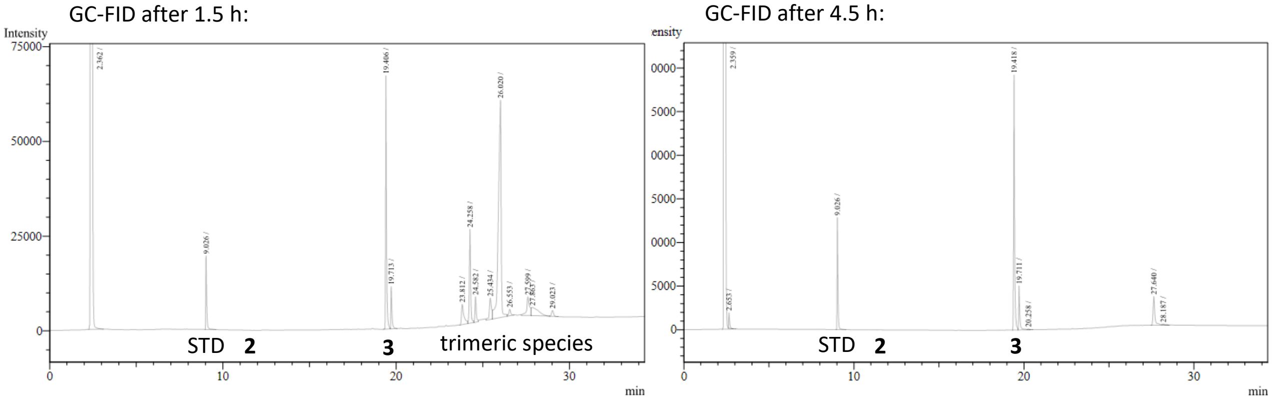
Table 5: Conversion of Bisguaiacol F **3** and vanillin alcohol in deep eutectic solvents.



3, 0.3 mmol

2, 0.3 mmol

Entry	t [h]	Conversion **3** [%]	Conversion **2** [%]
1	1.5	0	100
2	4.5	25	100

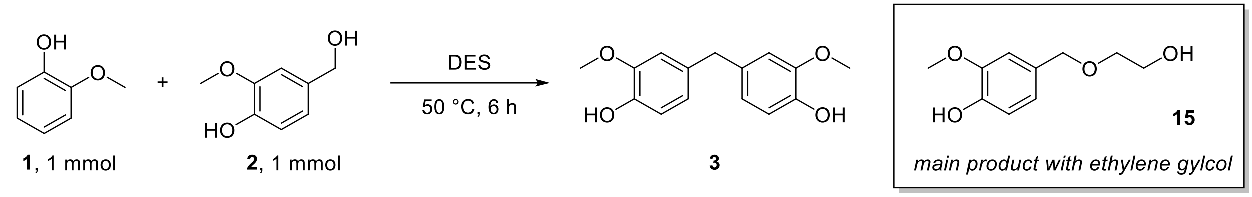


General reaction condition: **3** (86 mg, 0.3 mmol, 1.0 equiv.), **2** (51 mg, 0.3 mmol, 1.0 equiv.), DES (ChCl: 10 mmol, OA: 10 mmol), rt; [a] conversions were determined *via* quantitative GC-FID.

3.3.2.1. Friedel-Crafts Reactions in DES

Besides the fact, that vanillin alcohol oligomerization is very fast in acidic media, Friedel-Crafts reactions, which was previously performed with Amberlyst 15 as catalyst, could profit from the fast activation of **2**. Hence, the synthesis of Bisguaiacol F (**3**) from **2** and lignin-based guaiacol (**1**)[111] was tested in DES consisting of choline chloride and oxalic acid (Table 6, Entry 1). At 50 °C, the starting materials are easily dissolvable and after 30 min **2** is completely converted. Bisguaiacol F however, could only be generated in 19% yield. It can be assumed that oligomerization due to the high acidity is also the main issue here. Therefore, the amount of oxalic acid was halved and glycerol was added to ensure the formation of a deep eutectic solvent (Table 6, Entry 2). Indeed, the product yield rose to 34% yield after 6 h reaction time. With glycerol as well as solely with oxalic acid as DES component, **2** was completely converted, whereas **1** was still present in the reaction mixture. When ethylene glycol was used as third DES component beside oxalic acid and choline chloride, formation of ether **15** was observed (Table 6, Entry 3). Sadly, longer reaction times and higher temperatures could not lead to a significant improvement in yield.

Table 6: Friedel-Crafts reaction of guaiacol (**1**) and vanillin alcohol (**2**) in DES.



Entry	DES composition [mmol]				Yield of **3** [%][a]
	ChCl	OA	Glycerol	Ethylene glycol	
1	10	10	0	0	19
2	10	5	5	0	34[b]
3	10	5	0	5	0

General reaction conditions: **1** (124 mg, 1.0 mmol, 1.0 equiv.), **2** (154 mg, 1.0 mmol, 1.0 equiv), DES, 50 °C, 6 h; [a] yields were determined *via* quantitative GC-FID; [b] isolated yield.

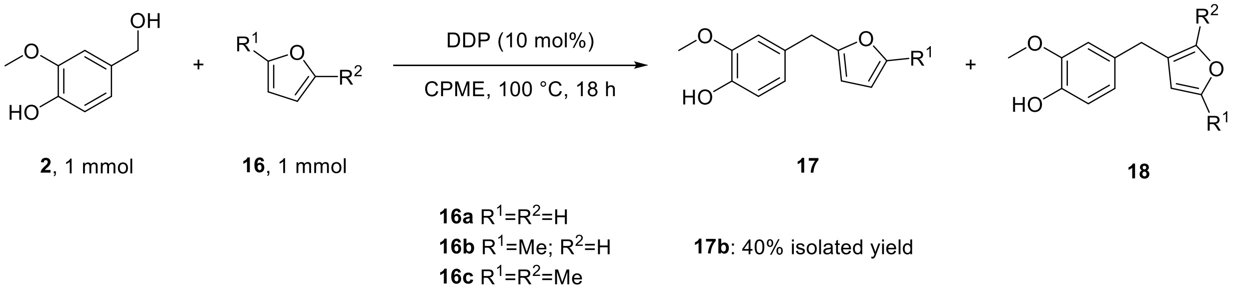
In conclusion, the application of DES for bisguaiacol formation from vanillin appears to be quite challenging. This is due to the fact that DESs not only act as solvents or catalysts but as complex all-in-one solvent-template-reactant systems and the fundamental principles behind DES formation are difficult to be established. Therefore it could be possible, that the acidity of the DES system is the reason why vanillin is polymerizing, but it is also possible, that the DES is forming polymers with the alcoholic starting materials *via* a condensation reaction. Polymerization reactions with DESs have already been reported in the literature.[112] Additionally, the reactants could become a part of the DES system because of their ability to form hydrogen bonds with ChCl. Singh and co-workers recently reported the partial formation of DESs with hydroxylbenzoic acid, ferulic acid and vanillic acid.[90] They claim that the phenolic hydroxyl group plays an important role in the hydrogen bond formation with ChCl, and that *ortho*-methoxygroups can sterically hinder the interaction.

2 not only bears a phenolic but also a benzylic alcohol moiety, which leads to the assumption that it is even more likely to form a DES or polymers than guaiacol, which would also explain the full conversion of vanillin and the poor conversion of guaiacol. To perform condensation reactions like the synthesis of bisguaiacols in DES, a detailed understanding in DES formation hence is essential for further investigations.

3.3.3. Friedel-Crafts Reaction of Vanillin Alcohol with Other Nucleophiles

Additional to guaiacol (**1**), also other molecules were envisioned to act as nucleophiles in Friedel-Crafts reactions with vanillin alcohol. Since they can also be obtained from lignocellulose , furans appear to be very interesting nucleophiles for biopolymer production like polyethylene 2,5-furandicarcoxylate (PEF) as alternative for polyethylene terephthalate (PET).[31,113] Additionally, the copolymerization with vanillin derivatives appears to be a very attractive route to all lignocellulose-based polymers.[45,114]

In course of this work, furan, 2-methylfuran and 2,5-dimethylfuran were used as nucleophiles in the Friedel-Crafts reaction with vanillin alcohol under acidic conditions (Scheme 14). The products could eventually lead to novel monomers or furan-linked bisphenols, which are also interesting for further hydrogenation to aliphatic diol monomers.



Scheme 14: Friedel-Crafts reaction of **2** with furans as nucleophiles; *general reaction conditions:* **2** (154 mg, 1.0 mmol, 1.0 equiv.), furan **16a**, **16b** or **16c** (1.0 mmol, 1 equiv.), DPP (25 mg, 0.1 mmol, 10 mol%), CPME (2 mL), 100 °C, 18 h).

At 100 °C; application of furan **16a** showed the formation of product **16b** after 3 h as main product on the GC-MS spectra. Nevertheless, after 18 h only impurities of the starting material are visible, which leads to the assumption that furan also forms oligomers with the electron-rich vanillin alcohol (**2**). Additionally, no generation of the double addition product were observed at 3 h and 18 h, which could have been interesting for further hydrogenation and polymerization. When **16a** and **2** were mixed in DES (ChCl/OA 1:1) at rt, low amounts of product were generated after stirring for one hour, but after 16 h, **17a** is completely converted.

Interestingly, 2-methylfuran (**16b**) generates product **17b** in 40% after 18 h. This may be due to the additional methyl group, which sterically hinders multiple attacks of the nucleophile, generating oligomers in lower amounts than with unsubstituted furan. Beside the product peak, various peaks containing the mass fragment of the vanillin alcohol moiety are observed on the GC-MS chromatogram. These compounds could be generated by decomposition of the furan moiety to the corresponding 1,4-diketones, which is well known for furans with electron-donating substituents under acidic conditions and could explain the moderate yield of product **17b**.[115]

Dimethylated furan **16c** however, did not show any Friedel-Crafts product formation, but a large range of diverse products on the GC-MS chromatogram, which could not be assigned to any envisioned product and is most likely based on the fact that **16c** decomposes due to the additional electron-donating methyl group. Obviously, substitution of the most nucleophilic 2- and 5-position of furan is not suitable for these kind of reactivities. Product **18** was also never observed with any other starting material outlined in Scheme 14.

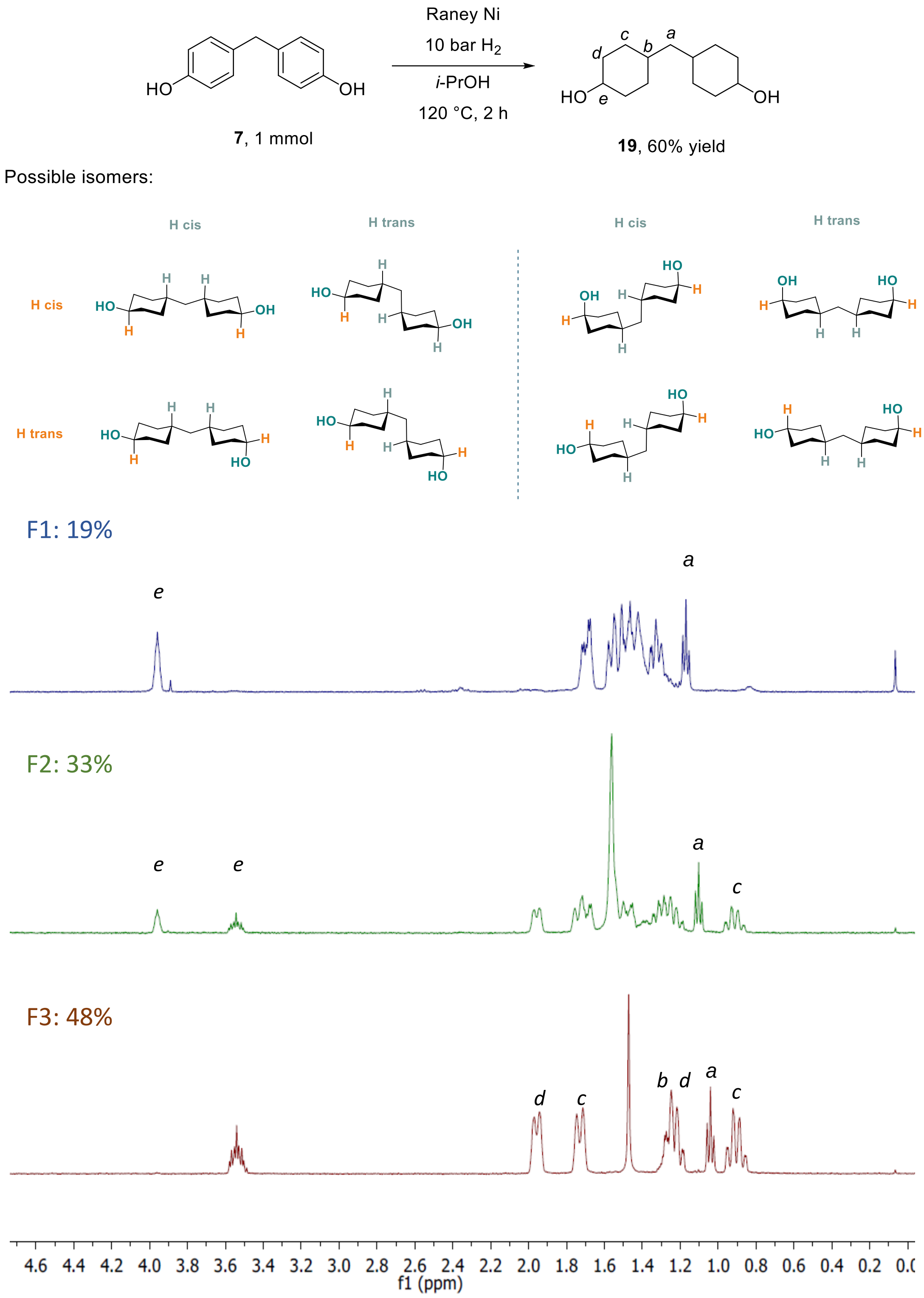
3.3.4. Hydrogenation of Bisguaiacol

Lignin-based monomers have been extensively investigated in defunctionalization strategies.[15] Recently, Vriamont *et al.* for example, reported a ruthenium on carbon catalyzed hydrogenation of lignin-monomers like guaiacol **1** with simultaneous demethoxylation, when applying acetic acid as solvent.[116] Prior to this work, Barta and co-workers were investigating efficient and selective catalytic dearomatization and simultaneous demethoxylation of lignin-derived phenolic monomers to single 4-*n*-propanolcyclohexanols in high selectivity *via* a homogeneous Raney Ni catalyst. Since Raney Nickel is one of the most known and active metal catalysts for the cleavage of C-O bonds and hydrogenation of unsaturated benzene rings,[30,117,118] it was also applied for the hydrogenation of bio-based bisguaiacols to symmetrical aliphatic diols in course of this work. The hydrogenation of bisphenols is very rarely reported and was never conducted with non-noble metals as catalyst before.[119]

In an initial experiment, previously generated 4,4'-methylenediphenol (**7**) was hydrogenated with a pressure of 20 bar at 160 °C for 4 h (Scheme 15). Isopropanol was used as a solvent, since it turned out to very effective in Raney-Ni-catalyzed H-transfer reactions.[118,120] *p,p'*-Methylene biscyclohexanol (MBC, **19**) was generated in 60% isolated yield. TLC showed the occurrence of three isomers (F1-3) with F3 being the major isomer (48% of **19**), which could all be isolated *via* column chromatography. Possible isomers are outlined in Scheme 15. To identify the exact isomers, extended NMR studies have to be conducted but were not part of this work.

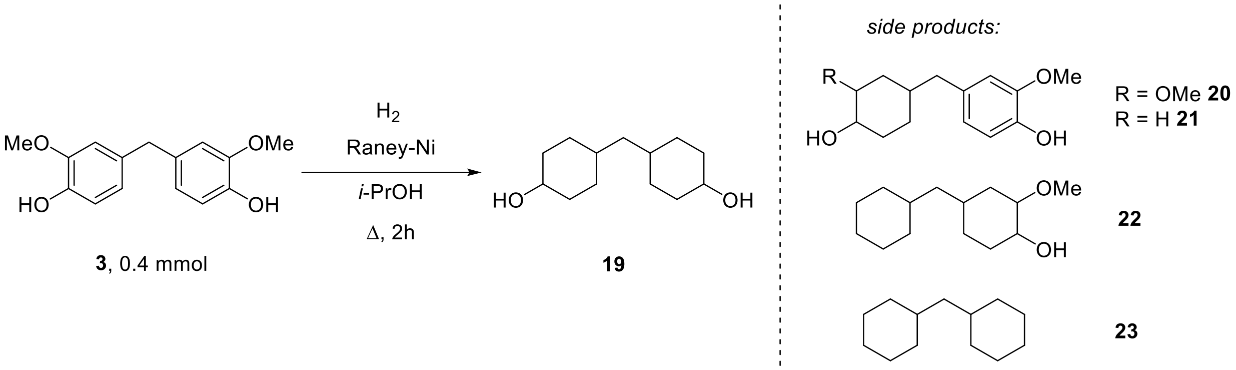
For hydrogenation and demethoxylation of **3** at 20 bar, Raney-Ni was applied under various temperatures (Table 7, Entries 2 – 5). When the reaction was heated to 120 °C for 2 h, **3** was only converted in 66% and generated **19** in low amounts (Table 7, Entry 1). Increasing of the temperature to 140 °C and 160 °C led to full conversion and the formation of the product in 60% yield (Table 7, Entries 2 and 4), whereby less side products are observed at higher temperatures. At 180 °C the yield drops again (Table 7, Entry 5). In a control experiment, the reaction was conducted in the autoclave, without the Ni-catalyst to ensure the absence of catalytically active noble metal residues (Table 7, Entry 3).

Interestingly, at 30 bar H_2-pressure, the highest yield of 58% was obtained at 180 °C, whereas the yield decreased with lowering the temperature to 140 °C (Table 7, Entries 6 – 8). Also, increasing the pressure from 30 to 40 and 50 bar did only lead to a significant drop in yield compared to the reactions at 20 bar (Table 7, Entries 6, 9 and 10).



Scheme 15: hydrogenation of **7** with Raney-Nickel catalysis; *general reaction conditions*: **7** (0.2 g, 1 mmol), Raney Ni@2400 (1.0 g), *i*-PrOH (15 mL), 120 °C, 2 h; isolated yields.

Table 7: Hydrogenation of Biguaiacol F (**3**) with Raney-Ni as catalyst.



Entry[a]	T [°C]	H_2-pressure [bar]	Conversion of 3 [%]	Yield of 19[%]	Side products
1	120	20	66	13	**20**, **21**, **22**
2	140	20	100	60	**20**, **21**, **22**
3[b]	140	20	0	0	-
4	160	20	100	60	**22**
5	180	20	100	48	**22**,**23**
6	140	30	100	40	**22**, **21**
7	160	30	100	48	**22**, **23**
8	180	30	100	58	**22**, **23**
9	140	40	100	36	**22**, **21**
10	140	50	100	34	**22**

General reaction conditions: **3** (0.1 g, 4 mmol), Raney Ni@3202 (1.0 g), i-PrOH (15 mL), 2 h; yields determined *via* quantitative GC-FID; [b] no Ni-catalyst used.

Further investigations on the optimal reaction time were therefore conducted at 20 bar H_2 pressure and at 160 °C (Figure 6). The maximum yield of 80% is already reached after one hour and slightly decreases over time.

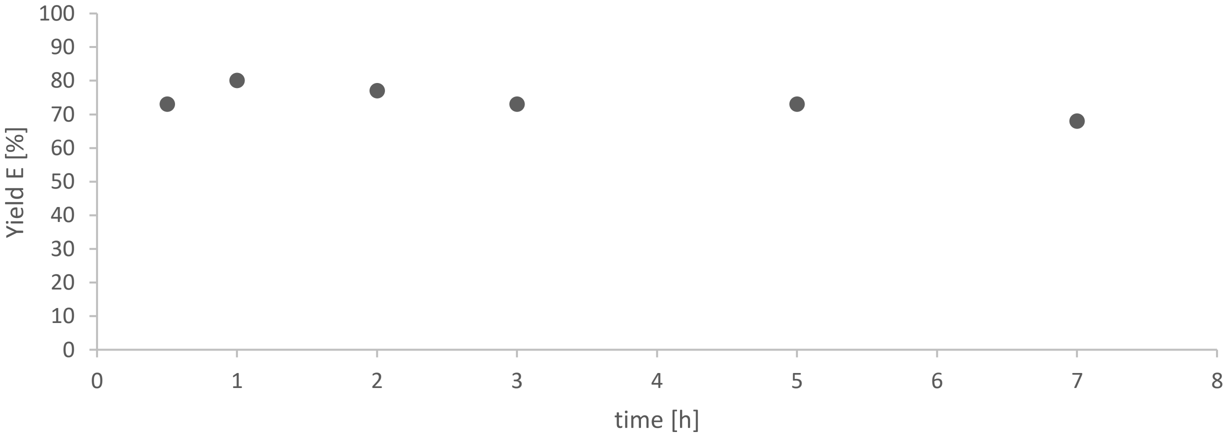
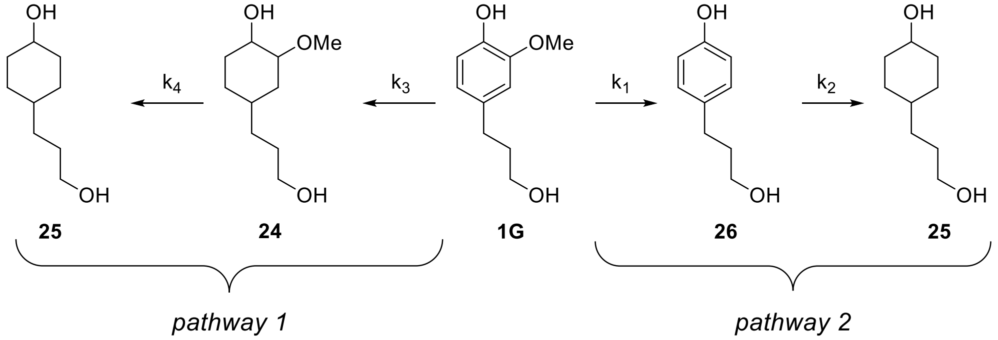


Figure 6: Reaction control over time; general reaction conditions: **3** (0.1 g, 4 mmol), Raney Ni@2400 (1.0 g), i-PrOH (15 mL), 160 °C; yields determined *via* quantitative GC-FID.

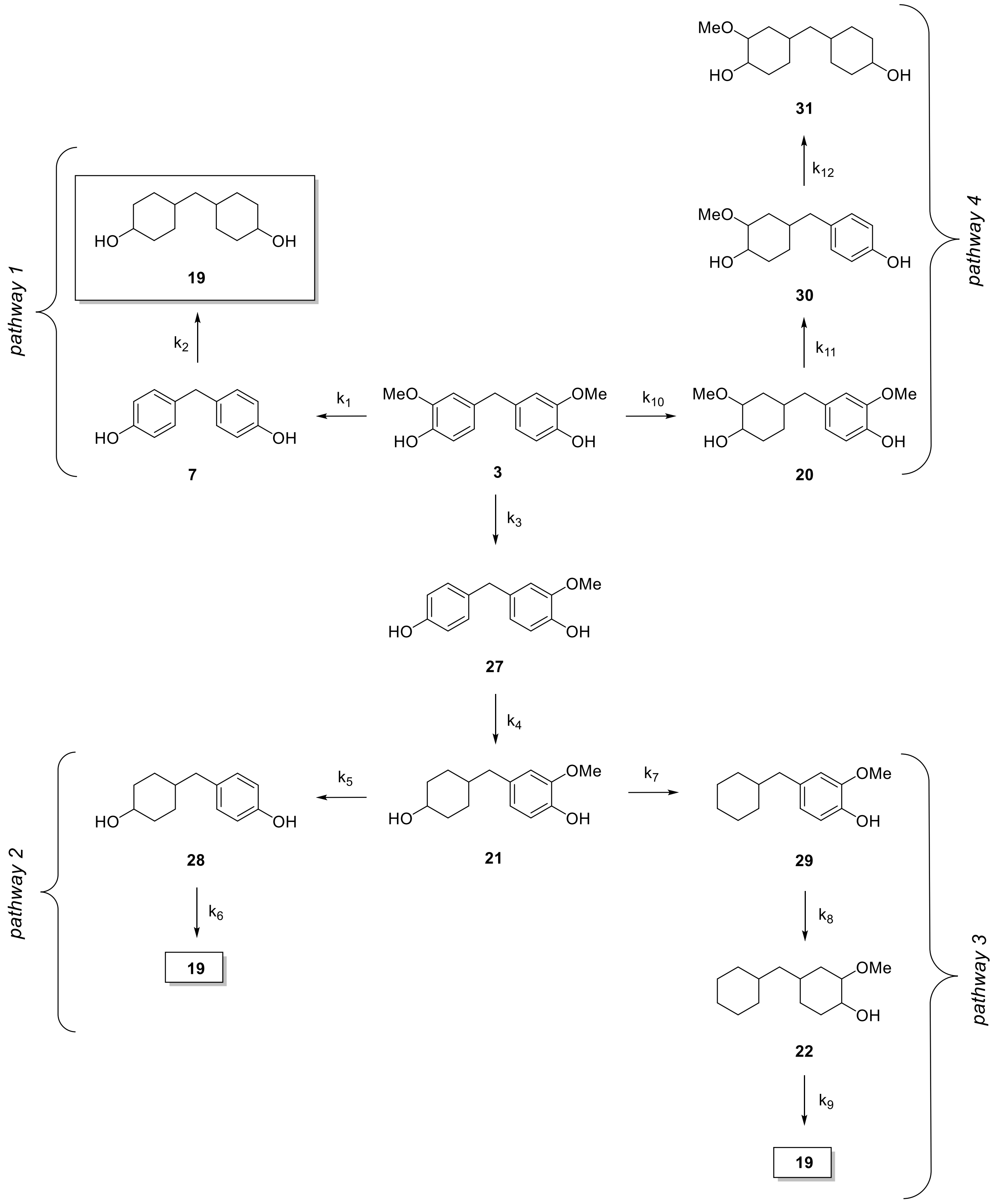
In general, side products **20** and **21** were generated in minor amounts at lower temperatures of 120 – 140 °C, resulting from unfinished hydrogenation. Dehydration to compound **23** occurred only at high temperatures and with elongated reaction time, also explaining why the yield of **19** deceases with temperature and time. Partly dehydrated product **22** was observed as main side product in all cases, where Raney-Ni was used as catalyst.

Earlier studies of the Barta group on **1G** already showed dehydration of the product (**25**) is a possible side reaction. However, they could not detect a dehydration of the hydrogenated starting material, which still bears the methoxy group. They also observed, that demethoxylation of hydrogenated species **24** has a very low reaction rate (k_4), whereas the reaction rate of the hydrogenation of demethoxylated compound **26** is much higher and hence, determined as rate limiting step (Scheme 16, $k_2 = 0.44$ min^{-1} > $k_1 = 0.0082$ min^{-1} > $k_3 = 0.0017$ min^{-1} > $k_4 = 10^{-7}$ min^{-1}). The reaction mechanism is therefore proposed to run *via* pathway 2 with minor formation of intermediate **24**, which is not further converted to the product **26**.



Scheme 16: Possible reaction pathways for the defunctionalization of **1G** investigated by Barta and co-workers.

The appearance of **20**, **21** and **22** in the hydrogenation of **3** leads to the proposal of various possible mechanistic pathways depicted in Scheme 17. Since the starting material has two aromatic rings, demethoxylation and subsequent hydrogenation can occur simultaneously on both sides or one after another. The hydrogenation of non-methoxylated bisphenol 7 was already proven to be conducted easily at 120 °C (Scheme 15), leading to the conclusion that **7** is most likely an intermediate of the reaction, where the demethoxylation has a higher reaction rate than the hydrogenation (k_2> k_1).



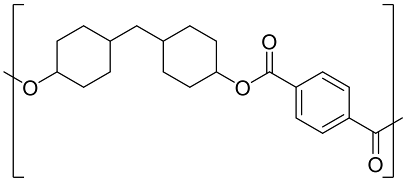
Scheme 17: Possible reaction pathways for the Raney-Ni catalyzed defunctionalization of **3**.

Another possible pathway to **19** would be an alternating demethoxylation-hydrogenation, defunctionalizing first one aromatic ring to intermediate **21**, which can then be converted to **19** after a second demethoxylation and hydrogenation. Compounds **27** and **18** were not observed as intermediates in the reaction, most likely because of the fast hydrogenation (k_6, k_8 > k_5, k_7). **22** could be generated from an aliphatic dehydration of **21** and fast hydrogenation of intermediate **29** (pathway 3). Since aliphatic demethoxylation has already been proven to have a very low reaction rate (k_4, Scheme 16), conversion of **22** is very unlikely ($k_8 >> k_9$) and hence an explanation why this compound is formed as main byproduct at every temperature tested (Table 7). A forth minor reaction pathway could be a hydrogenation of one aromatic ring to **20** at first, and then demethoxylation and dearomatization as second and third step ($k_{12} > k_{11}$). Nevertheless, **31** was never observed as side product. For further investigation and determining the reaction rates, intermediates have to be applied separately in the hydrogenation.

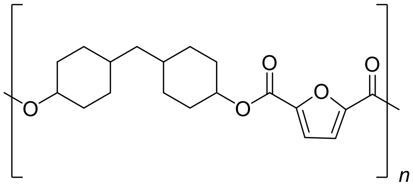
3.3.5. Polymerization of Bisguaiacol derived Diols

Aliphatic and cyclic diols are generally critical intermediates for the production of commercially important products like perfumes, pharmaceutical active compounds, fuels or surfactant in petrochemical industry. But they are also quite common monomers for polyester, polycarbonate and polyurethane synthesis.[31,121] The main bio-source is hemi(cellulose), from which aliphatic diols like ethylene glycol, 1,4-butanediol or 1,6-hexanediol can be derived. Current research is predominantly focused on co-polymerization of these diols with renewable 2,5-furan dicarboxylic acid (FDCA) and terephthalic acid (TPA). However, the obtained polyesters show weak heat resistance and glass-transition temperatures (T_g) lover than 90 °C.[31,32] Therefore, we investigated the previously generated cyclic diol MBC (**19**) in polymerization reactions, to improve heat resistance properties.

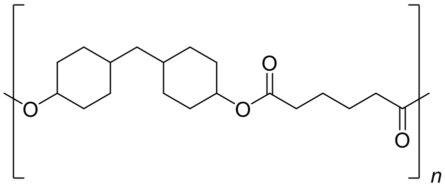
Table 8: Polymerization of aliphatic diol ***19*** *with different substrates.*



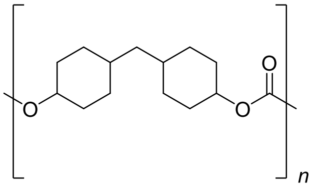
MBC, DTP (**32**)



MBC, DFDC (**33**)



MBC, AD (**34**)



MBC, DP (**35**)

Entry	**Product**	**Yield [wt%]**	**M_n [g/mol]**	**Đ**	T_{cc} [°C]	T_m [°C]	$T_{5\%}d_{N2}$ [°C]	$T_{max}d_{N2}$ [°C]	T_g [°C]
1	**32**	94			n.d	n.d.	337.5	373.8	127.5
2	**33**	85	6494	1.54	153.6	202.3	306.2	330.3	116.4
3	**34**	76	15170	1.79	61.5	n.d.	360.6	415.1	35.5
4	**35**	84	6763	1.61	n.d.	220.2	313.4	362.6	110.6

General reaction conditions: **19** (3.4 mmol, 1 equiv.), substrate (3.4 mmol, 1 equiv), $Zn(OAc)_2$ (1 mol%), 190 °C, N_2/1 h, then 230 °C, vacuum (1mPa)/1h; M_n = Numer average molar mass, Đ = M_w/M_n = molar dispersitiy, T_{cc} = cold crystallization temperature, T_m = melting temperature, $T_{5\%}d_{N2}$ = thermal decomposition temperature T5 (5%wt weight loss), $T_{max}d_{N2}$ = maximum thermal decomposition temperature, T_g = glass transition temperature.

For the synthesis, transesterification with diphenyl carbonate (DP), adipic acid (AD), Dimethyl terephthalate (DTP), dimethylfuran-2,5-dicarboxylate (DFDC) was conducted at 190 °C (Table 8). Dimethylated substrates were used to provide a faster subsequent polycondensation, in which generated methanol was easier to remove under reduced pressure than water.[122] The solid state polymerization was performed without the use of solvents. The resulting polymers were generated in yields over 80% with molecular weights over 10,000 and the structures were determined by ^{1}H-NMR, ^{13}C-NMR 2D-NMR (COSY; HSQC) and FTIR-analysis. Thermal analysis (TGA and DSC) showed that all products exhibit good thermal stability with decomposition temperature (Td) between 300 and 400 °C. For **34**, the lowest glass transition temperature (T_g) of 35 °C was measured, whereas **32, 33** and **35** were highly thermally resistant with T_gs over 100 °C. To the best of our knowledge, bio-mass derived polyesters and polycarbonated of aliphatic and cyclic diols scarcely reach these high T_gs. Hence, this procedure to bio-mass derived rigid cyclic diols harbours great potential for the production of highly thermally resistant engineering thermoplastics in the future biorefinery practices.

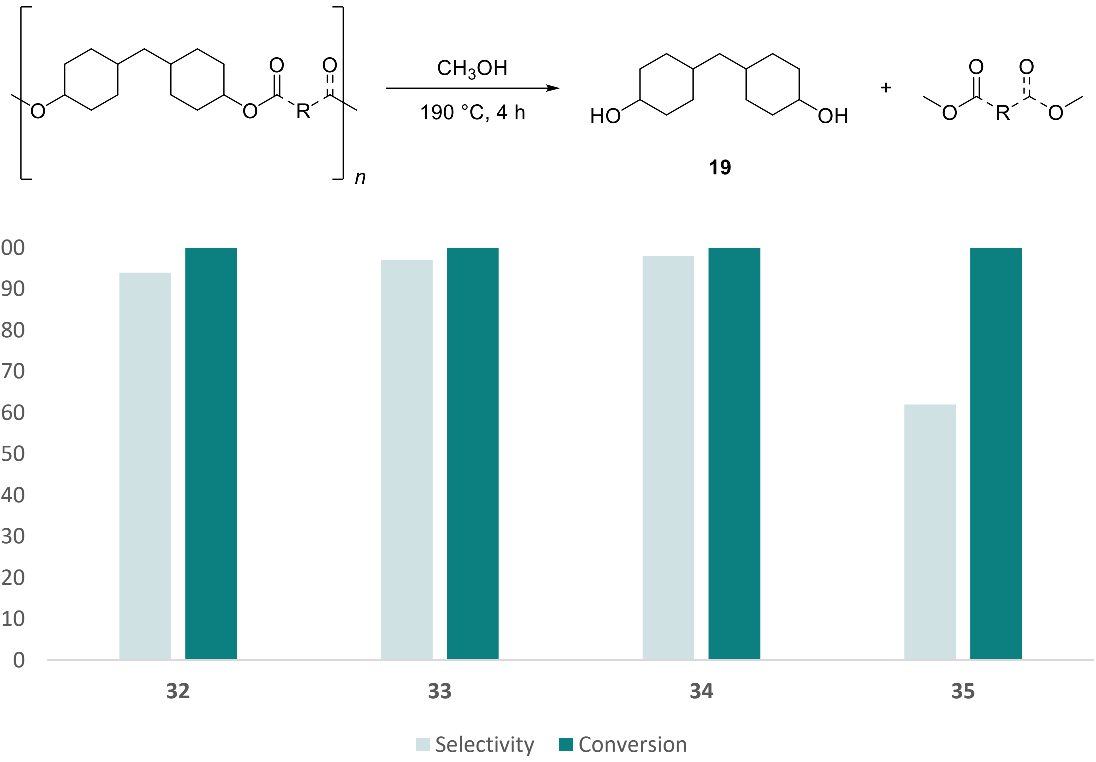
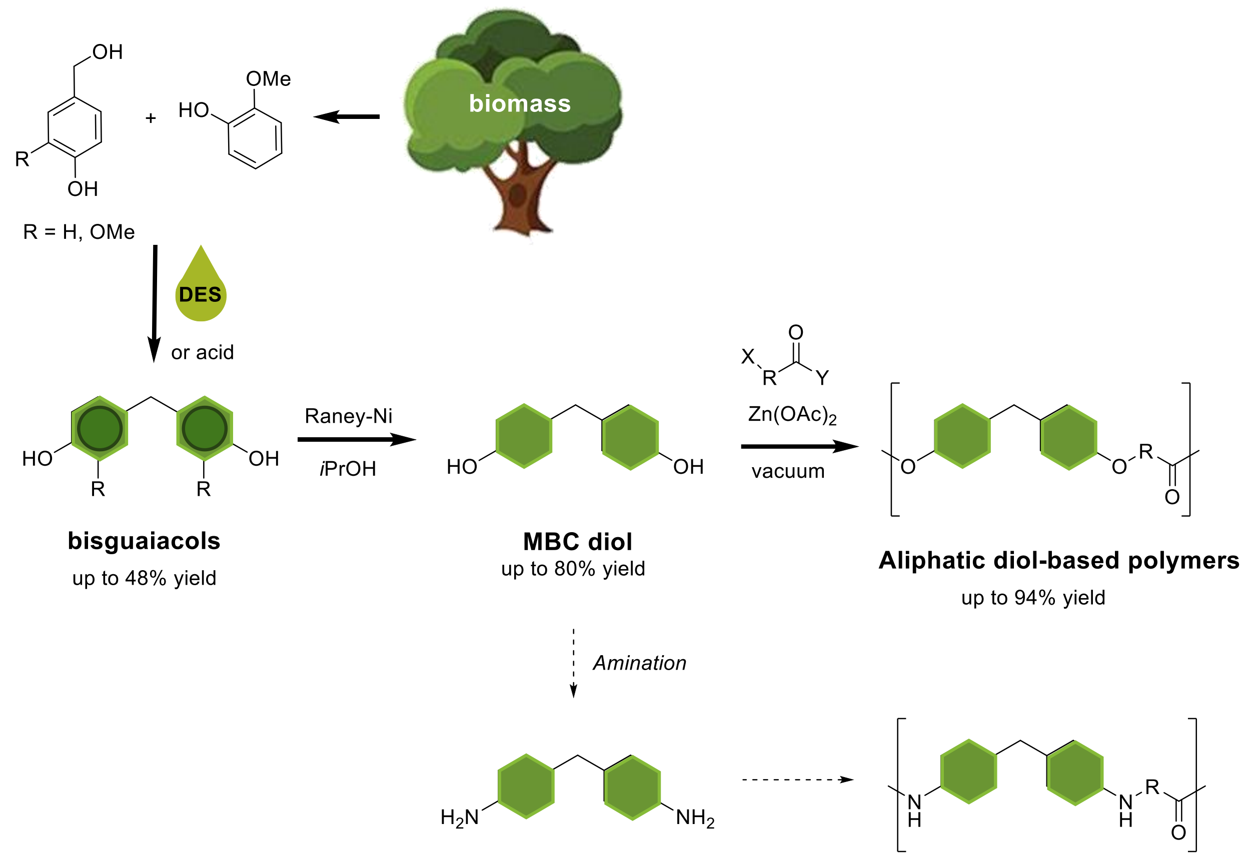


Figure 7: One pot-methanol alcoholysis of polymers **32**. **33**, **34** and **35**; *general reaction conditions*: 0.1 g polymer, 30 mL methanol, 190 °C, 4 h¸ Selectivity was determined by quantitative GC-FID.

In respect to more environmental and economical sustainability, efficient degradation and utilization of waste plastics for the reproduction of plastics or production of other fuels and chemicals are increasingly receiving great attention. We therefore completely depolymerized and degraded polymers **32**. **33**, **34** and **35** with the conversion of 100 % by one-pot methanol alcoholysis in the absence of any catalyst, acid and base additives by literature known procedures (Figure *7*).[123,124] This enables a complete chemical recyclability of diol **19** and offers therefore a great potential in the development of sustainable bio-based polyesters.

3.4. Conclusion and Outlook

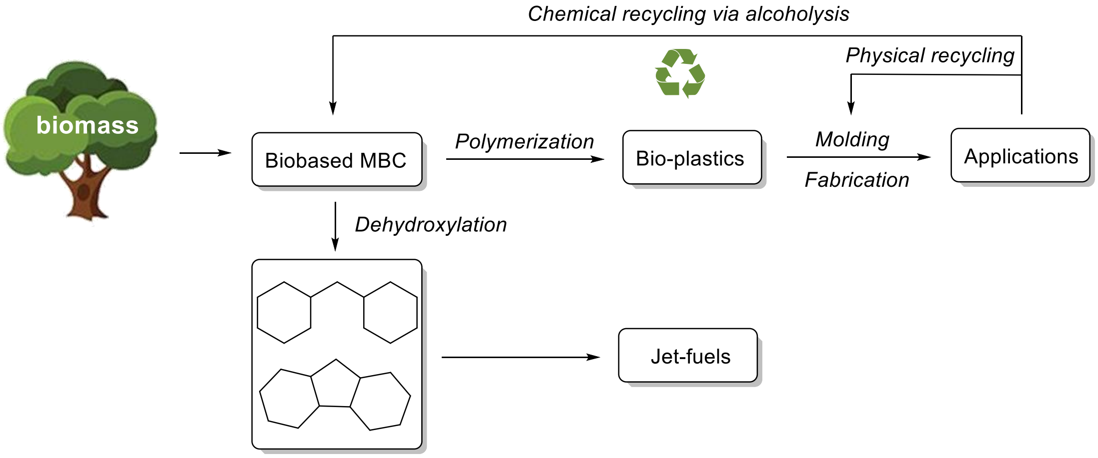


Scheme 18: Established route to aliphatic diol-based bio-polymers starting from vanillin and guaiacol to generate bisguaiacols and MBC diol subsequently *via* hydrogenation. Dashed arrows show a possible route to diamine-based io-polymers.

In this chapter, a successful, green route to novel bio-based polymers was described (Scheme 18). Thereby, the industrial production process of vanillin was modified by generation of bisguaiacols from vanillin alcohol, which were subsequently hydrogenated and demethoxylated to a symmetrical aliphatic diol, which acts as polymer building block. For the generation of bisguaiacol, vanillin alcohol and guaiacol underwent a Friedel-Crafts reaction in deep eutective solvents, which are easy to prepare, biocompatible, low in toxicity and non-flammable. However, **23** could only be generated in yields up to 34%, since vanillin alcohol tends to undergo oligomerization under acidic condition and may as well play a role in the DES formation.

The bisphenols were subsequently funneled into polymer building blocks by selective hydrogenation with Raney-Ni as catalyst at pressures of 20 – 30 bar H_2, generating diol **19** in yields up to 80%. To show the application of these compounds in polymer science, **19** was converted with various esters and a carboxylic acid in a transesterification reaction with $Zn(OAc)_2$ as catalyst. Condensation under reduced pressure generated polymers which showed significant heat resistance with T_gs up to 110 °C and Tds >300 °C. The thermoplastics were additionally chemically degraded by a one-pot methanol alcoholysis in the absence of a catalyst, showing the potential recyclability of these novel materials.

Since amines also play a central role in the chemical industry, especially in polymers and surfactants, and since catalytic approaches to lignin-derived amines are very rarely reported,[35] the amination of **19** to a diamine appear as an interesting approach for future pathways to lignin-based thermosets.[43] Additionally to that, aliphatic diol **19** could also be continuously used for reproduction of bioplastics or for production of high density bio-based jet fuel like dicyclohexylmethane and dodecahydrofluorene by complete dehydroxylation of **19**. The C13 cycloalkanes have higher energy density (0.88 g mL-1 and 0.96 g mL-1) than current jet fuels (0.76-0.78 g mL-1) that are rich in straight-chain alkanes. Therefore these products are also promising aviation fuels or fuel additives to current jet fuel.·[30,123] Hence, a full recycling pathway of renewable diols for bio-plastic production could be established (Scheme 19).



Scheme 19: A proposed recycling pathway of the generated thermoplastics.

3.5. Experimental Section

3.5.1. General Information

Starting materials and reagents were purchased from Sigma Aldrich, Acros and TCI in reagent or higher grade and used without further purification unless otherwise noted. Solvents were used in p.a. grade for reaction mixtures and column chromatography. Autoclave reactions were performed in a Parr reactor, series 4598 bench top reactor system.

Chromatography

Column chromatography was carried out using Merck silica gel type 9385 230-400 mesh as stationary phase, using gravity flow. Thin layer chromatography (TLC) was performed on Merck silica gel 60, 0.25 mm. and analyzed by fluorescence quenching under UV-light (254 nm) or stained with a potassium permanganate solution.

3.5.2. Analytical Techniques

Nuclear magnetic resonance spectroscopy (NMR)

NMR spectra were recorded at ambient temperature on a Varian Mercury Plus 400, Agilent MR 400 (^{1}H: 400 MHz, ^{13}C: 101 MHz) instrument. Chemical shifts δ are reported in parts per million [ppm] relative to the solvent signal as internal standard (^{1}H: $CDCl_3$: δ = 7.26 ppm; ^{13}C: $CDCl_3$: δ = 77.1 ppm). Coupling constants across bonds are given in J (Hz). ^{13}C-NMR spectra were acquired on a broad band decoupled mode. ^{1}H-NMR splitting patterns are assigned as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). ^{13}C signals are assigned as C_q (quaternary carbon), + (primary and tertiary carbon), − (secondary carbon). The assignment resulted from COSY, DEPT-135°, HMBC or HSQC experiments.

Mass spectrometry

GC-MS was recorded on an Shimadzu QP210 Ultra system with an HP-1MS column (30 x 0.25 mm x 0.25 µm) by using dry helium as carrier gas. Program: Heating from 40 °C to 250 °C with 10 °C/min and holding the final temperature for 5 min.

Gas Chromatography (GC)

GC-FID (flame ionization detection) analysis was carried out on an Agilent 6890system using dry hydrogen as carrier gas. HP-5MS column (30 m x 0.25 mm x 0.25 µm) was used. Program: Heating from 50 °C to 300 °C with10 °C/min and holding the final temperature for 5 min. For GC sample preparation, an internal standard (*n*-dodecane) was added to the reaction mixture before heating.

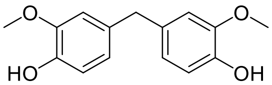
In order to determine yields and conversions the internal standard method was used for quantitative GC-FID. Therefore, calibration was conducted by variation of mass ratio of substrate and standard and analyzing the different samples by GC-FID. From the obtained data the peak area ratio was plotted against the mass ratio of substrate to standard. Linear regression led to the determination of the regression factor R.

$$\frac{m_{sub}}{m_{std}} \cdot R = \frac{A_{sub}}{A_{std}}$$

3.5.3. Experimental Procedures

3.5.3.1. Vanillin Alcohol as Starting Material in the Synthesis of Bisguaiacols

4,4'-Methylenebis(2-methoxyphenol) (**3**)



Amberlyst-catalyzed procedure:

3 was synthesized from vanillin alcohol (**2**, 1.1 g, 7.2 mmol, 1.0 equiv.) which was dissolved in guaiacol (**1**, 4.0 mL, 4.4 g, 35.8 mmol, 2.5 equiv.) in a pre-heated screw cap schlenk tube. Amberlyst 15 (1.2 g was added and the mixture was heated to 60 °C for 24 h under N_2 atmosphere. After cooling to rt, the mixture was dissolved in dichloromethane (25 mL) the organic solution was filtered to remove the catalyst and then washed with water (3 x 10 mL) and dried over Na_2So_4. **1** was removed under reduced pressure and the product was purified *via* column chromatography (Hex/EA 8:2) to give the product as white solid (0.9 mg, 3.4 mmol, 48%, containing 23% of **4**).

DPP-catalyzed procedure:

2 (154 mg, 1.0 mmol, 1.0 equiv.) and diphenylphosphate (25 mg, 0.1 mmol, 10 mol%) were added in a screw capped schlenk tube, subsequently dissolved in CPME (2 mL) and heated to 130 °C for 3 h. the reaction was quenched with H_2O, extracted with EtOAc. The organic phase was dried over Na_2SO_4. After evaporation of solvent column chromatography (Hept/EA 6:4) the product was obtained (8 mg, 0,03 mmol, 6%).

$C_{15}H_{16}O_4$ (260.3 g/mol)

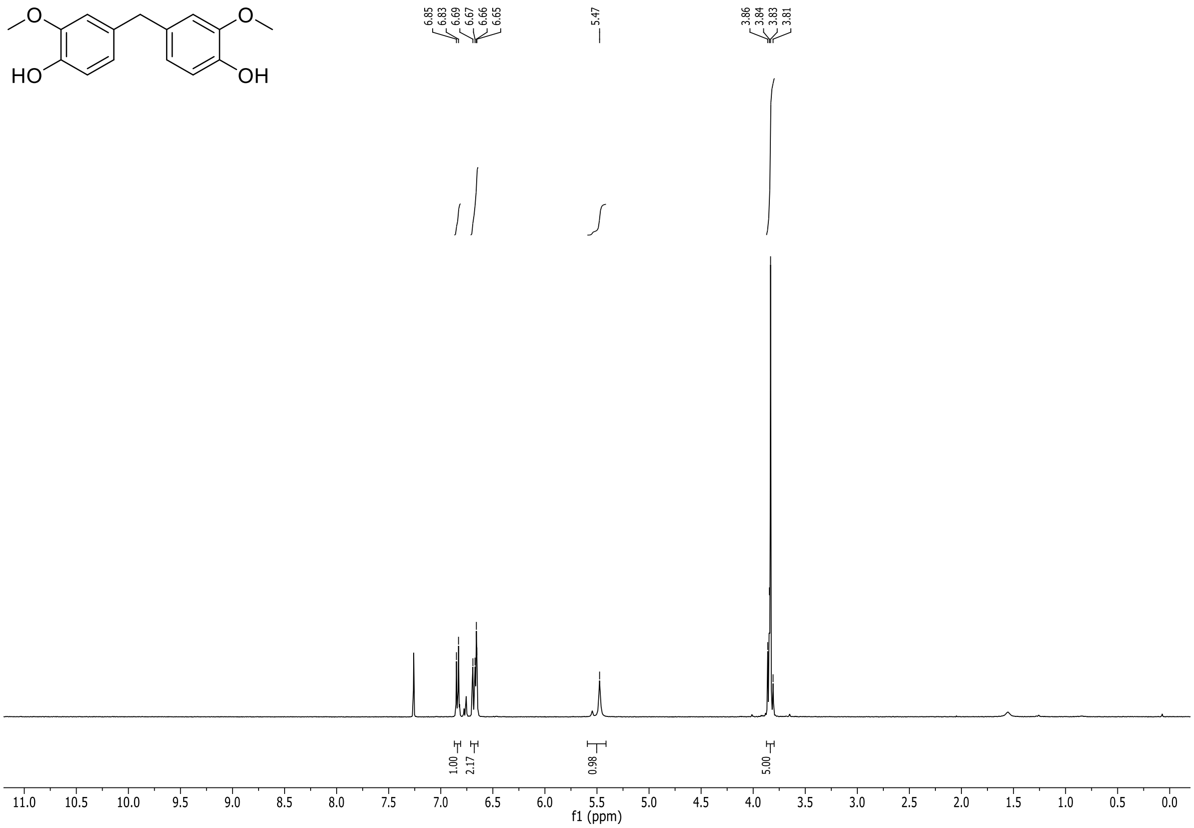
R_f: 0.32 (Hept/EA:8/2)

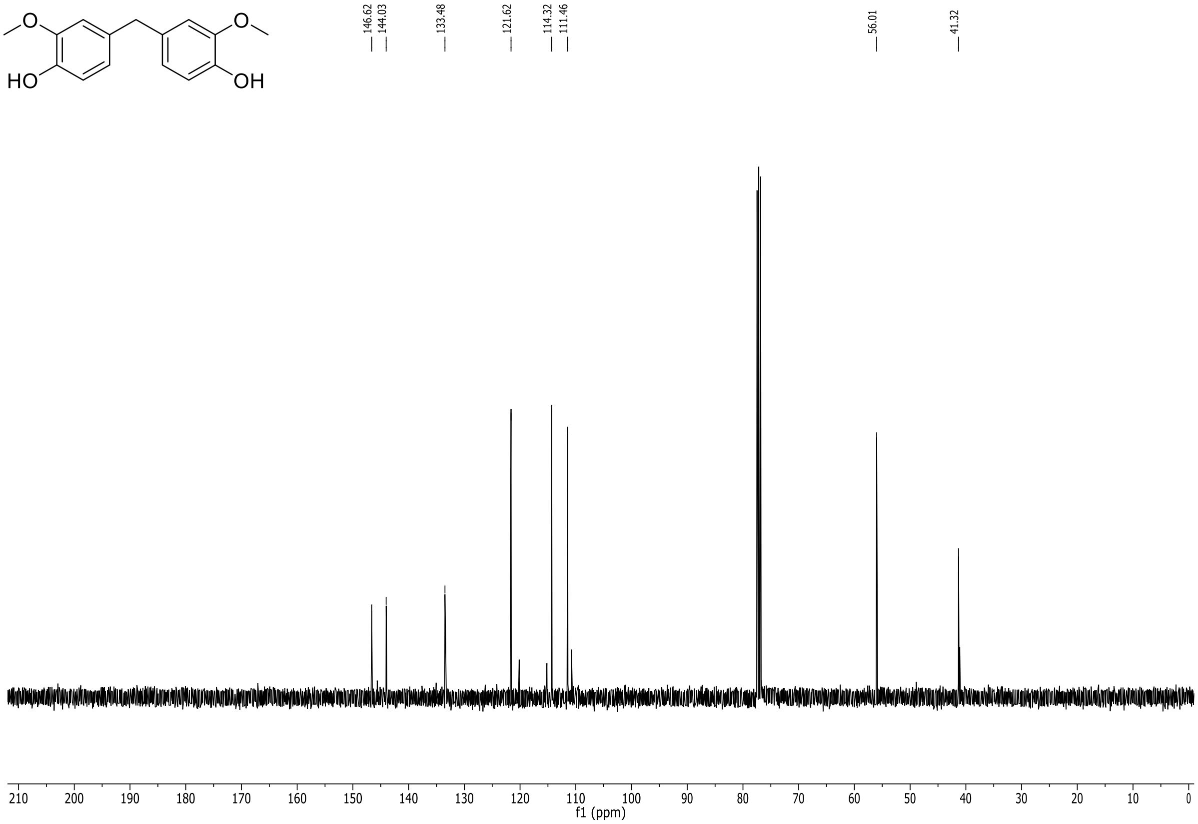
^{1}H-NMR (400 MHz, $CDCl_3$) δH/ppm: 6.84 (d, J = 8.0 Hz, 2H, Ar*H*), 6.71 – 6.63 (m, 4H, Ar*H*), 5.47 (s, 2H, O*H*), 3.80 – 3.87 (m, 8H, C*H*$_3$, C*H*$_2$).

^{13}C-NMR (101 MHz, $CDCl_3$) δ_C/ppm: 146.6 (C_q), 144.0 (C_q), 133.5 (C_q), 121.6 (+), 114.3 (+), 111.5 (+), 56.0 (+), 41.3 (–).

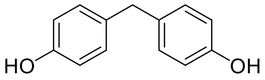
GC-MS (EI): m/z = 260 (100, [$M^{+\bullet}$]), 243 (14, [$M^{+\bullet}$]-[$^\bullet$OH]), 229 (43, [$M^{+\bullet}$]-[$^\bullet OCH_3$]), 137 (33, [$M^{+\bullet}$]-[$^\bullet(C_6H_3)_4(OH)(OCH_3)$]).

The analytical data was in accordance with the literature.[109]


HO
OH
6.85
6.83
6.69
6.67
6.66
6.65
5.47
3.86
3.84
3.83
3.81
1.00
2.17
0.98
5.00
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


HO
OH
146.62
144.03
133.48
121.62
114.32
111.46
56.01
41.32
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

4,4'-Methylenediphenol (**7**)



4-(Hydroxymethyl)phenol (**6**, 124 mg, 1.0 mmol, 1.0 equiv.) and diphenylphosphate (25 mg, 0.1 mmol, 10 mol%) were added in a screw capped schlenk tube, subsequently dissolved in CPME (2 mL) and heated to 130 °C for 3 h. the reaction was quenched with H_2O, extracted with EtOAc. The organic phase was dried over Na_2SO_4. After evaporation of solvent column chromatography (Hept/EA 6:4) the product was obtained as yellow solid (25 mg, 0,3 mmol, 25%).

$C_{15}H_{16}O_4$ (200.2 g/mol)

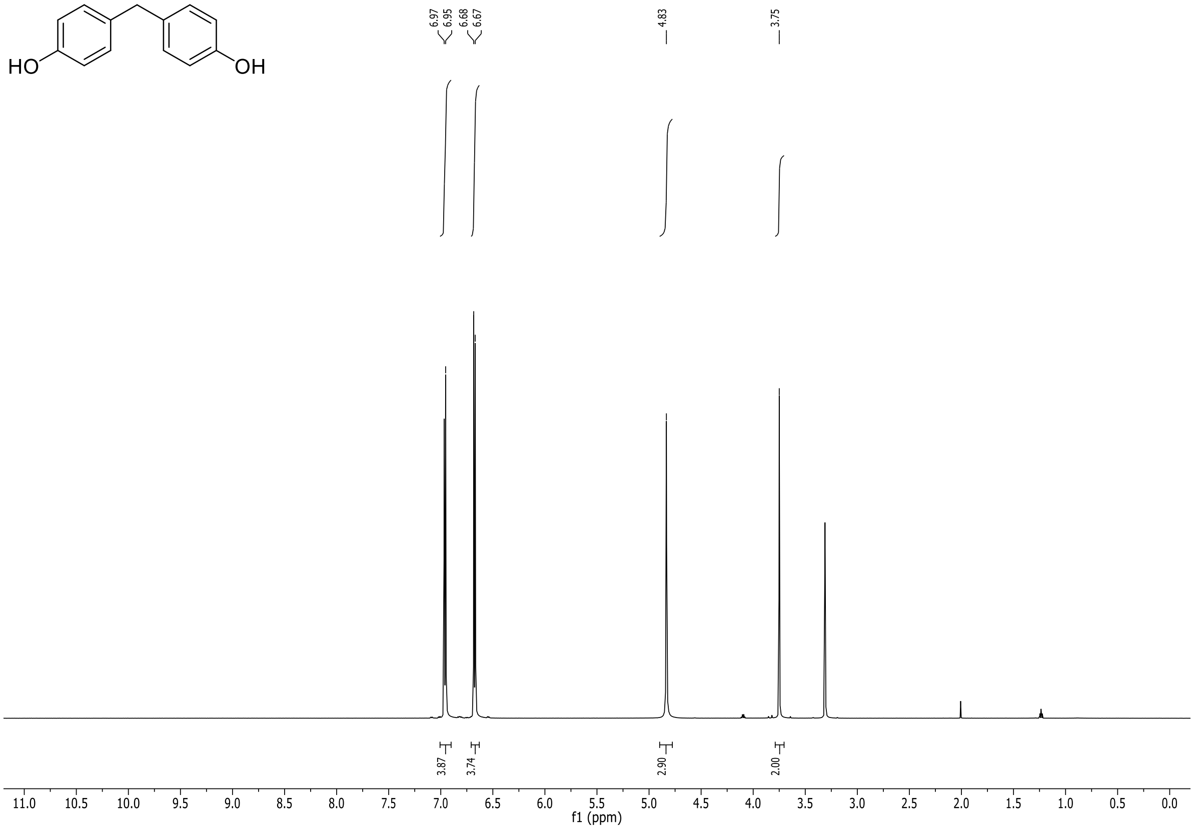
R_f: 0.62 (Hept/EA: 4/6)

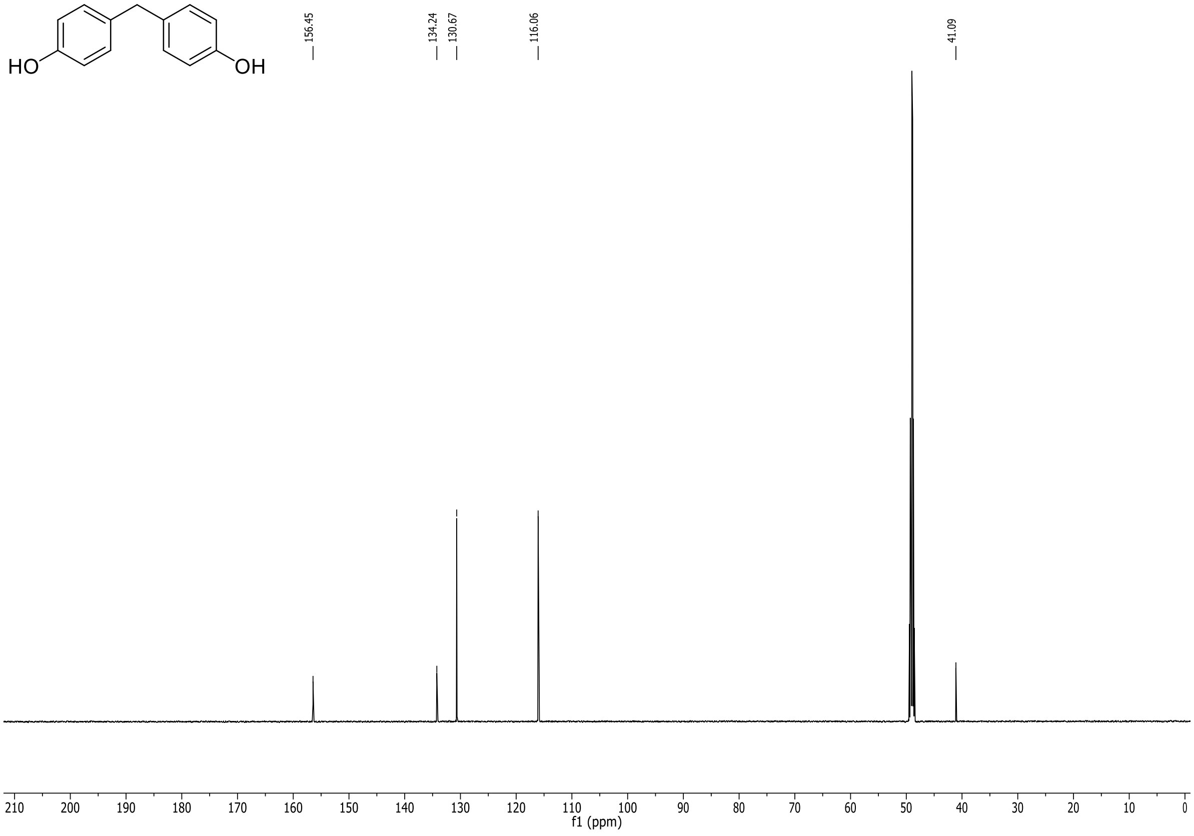
^{1}H-NMR (400 MHz, MeOD) δH/ppm: 7.03 (d, *J* = 8.1 Hz, 4H, Ar*H*), 6.75 (d, *J* = 8.2 Hz, 4H, Ar*H*), 3.84 (s, 2H, C*H*$_2$).

^{13}C-NMR (101 MHz, MeOD) δ_C/ppm: 156.45 (C_q), 134.24 (C_q), 130.67 (+), 116.06 (+), 41.09 (–).

GC-MS (EI): m/z = 200 (67, [$M^{+\bullet}$]), 107 (100, [$M^{+\bullet}$]-[$^\bullet C_6H_4OH$]), 94 (23, [$M^{+\bullet}$]-[$^\bullet CH_2C_6H_4OH$]).

The analytical data was in accordance with the literature.[125]


HO
OH
6.97
6.95
6.68
6.67
4.83
3.75
3.87
3.74
2.90
2.00
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


HO
OH
156.45
134.24
130.67
116.06
41.09
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

3.5.3.2. Reactions in DES

General procedure for the preparation of deep eutectic solvents:

A reactor tube was charded with a stirring bar, oxalic acid (0.9 g, 10 mmol, 1.0 equiv.) and choline chloride (1.4 g, 10 mmol, 1.0 equiv.) and heated to 60 °C. After 10 min the reaction mixture was cooled to rt and a colorless solution was obtained. Further additives and substrates were added directly to the solution.

General procedure for reactions of vanillin alcohol (**2**) in DES:

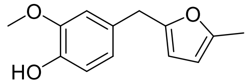
Vanillin alcohols (**2**, 154 mg, 1.0 mmol, 1.0 equiv) was added to the respective DES and stirred at 50 °C. After cooling to rt, the reaction mixture was washed with H_2O and extracted with DCM. The combined organic phases were washed with brine and dried over $MgSO_4$. The product was purified *via* column chromatography (Hept/EA 8:2 → 6:4).

General procedure for reactions of vanillin alcohol (**2**) and guaiacol (**1**) in DES:

Vanillin alcohol (**2**, 154 mg, 1.0 mmol, 1.0 equiv) and guaiacol (**1**, 112 µL, 124 mg, 1.0 mmol, 1.0 equiv.) were added to the respective DES and stirred for 50 °C. After cooling to rt, the reaction mixture was washed with H_2O and extracted with DCM (2 x 20 mL). The combined organic phases were washed with brine and dried over $MgSO_4$. The product was purified *via* column chromatography (Hept/EA 8:2 → 6:4).

3.5.3.3. Friedel-Crafts Reaction with Furanes

2-Methoxy-4-((5-methylfuran-2-yl)methyl)phenol (**18b**)



2 (154 mg, 1.0 mmol, 1.0 equiv), 2-methylfuran (82 mg, 1.0 mmol, 1.0 equiv.) and diphenylphosphate (25 mg, 0.1 mmol, 10 mol%) were dissolved in CPME (2 mL) and the mixture was heated at 100 °C for 18 h. The reaction was quenched with H_2O and extracted with EtOAc. The organic phase was dried over $MgSO_4$. After filtration and evaporation of solvent, purification *via* column chromatography (Hept/EA 8:2) yielded the product as yellow oil (86.4 mg, 0.4 mmol, 40%).

$C_{13}H_{14}O_3$ (218.3 g/mol)

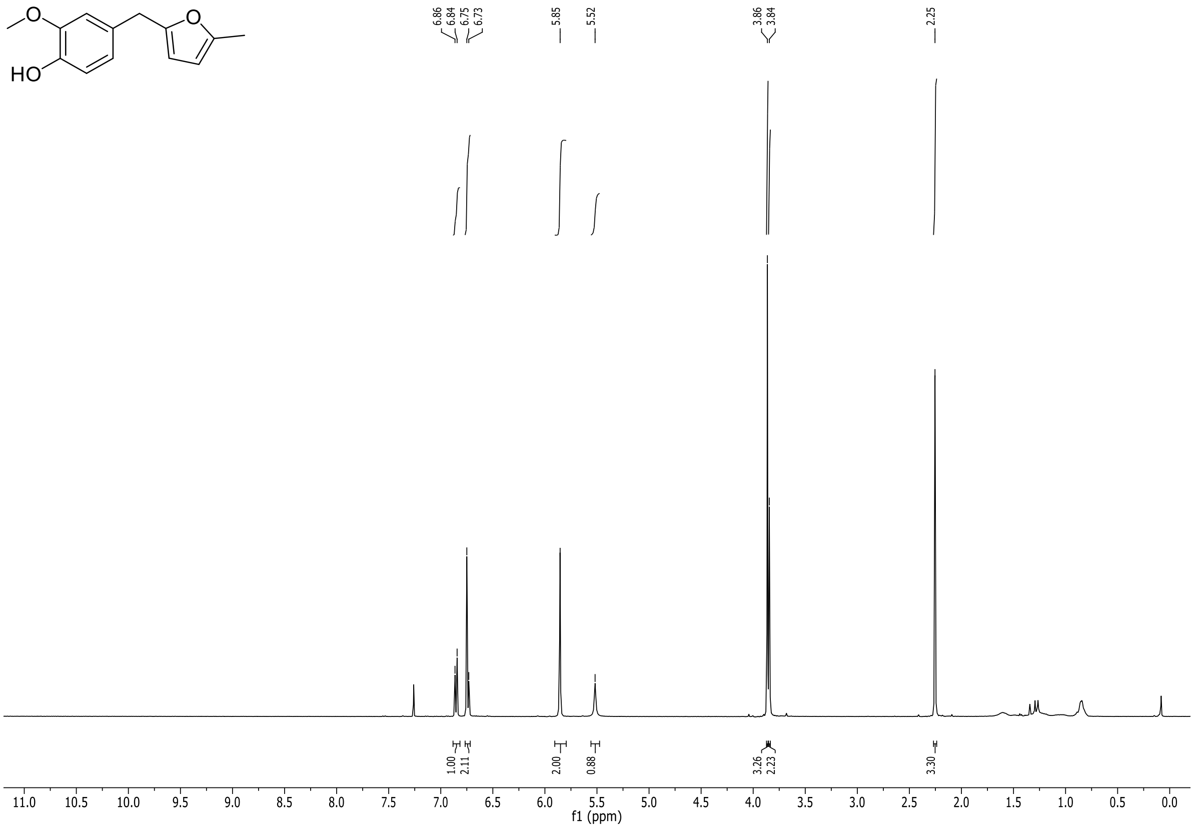
R_f: 0.46 (Hept/EA: 8/2)

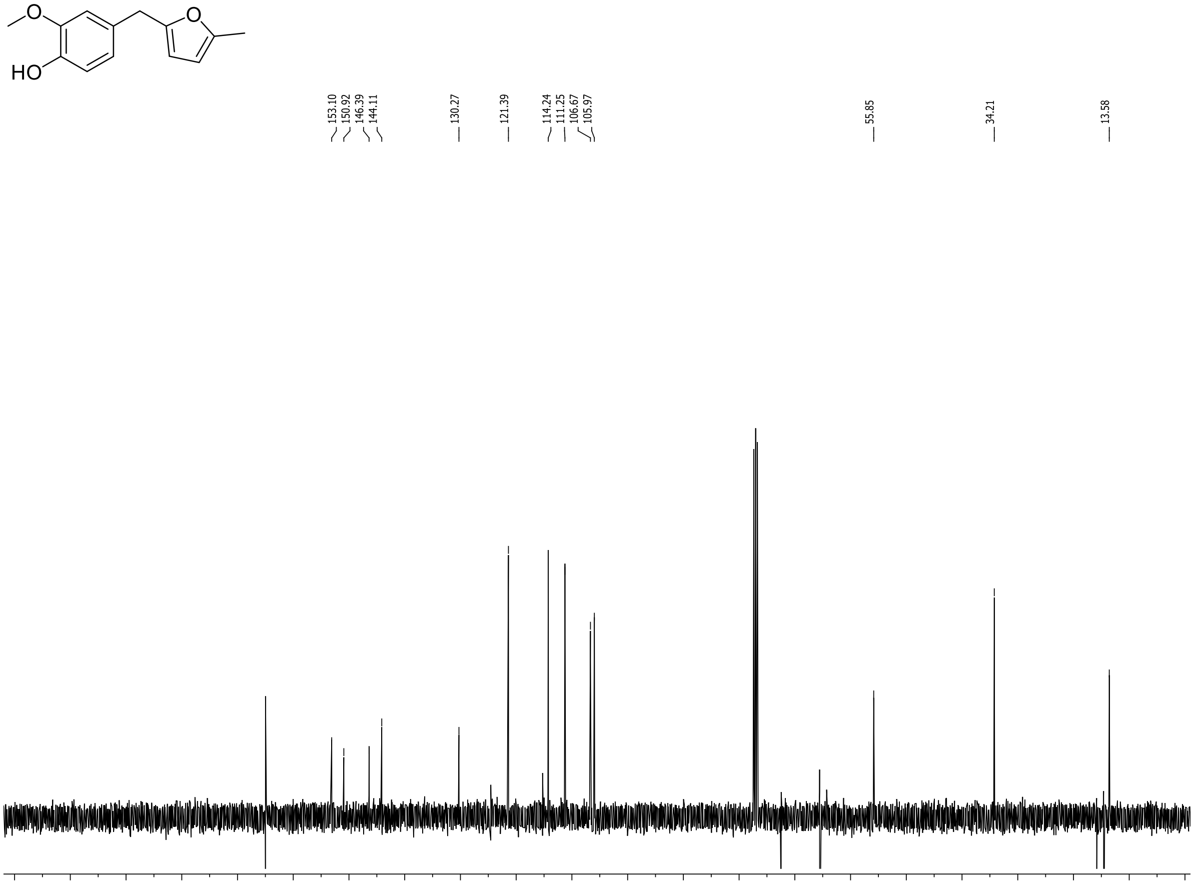
^{1}H-NMR (400 MHz, $CDCl_3$) δH/ppm: 6.85 (d, J = 8.0 Hz, 1H, Ar*H*), 6.74 (d, J = 7.5 Hz, 2H, Ar*H*), 5.85 (s, 2H, Ar*H*), 5.52 (s, 1H, O*H*), 3.86 (s, 3H, OC*H*$_3$), 3.84 (s, 2H, C*H*$_2$), 2.25 (s, 3H, C*H*$_3$).

^{13}C-NMR (101 MHz, $CDCl_3$) δ_C/ppm: 153.1 (C_q), 150.9 (C_q), 146.4 (C_q), 144.1 (C_q), 130.3 (C_q), 121.4 (+), 114.2 (+), 111.3 (+), 106.7 (+), 106.0 (+), 55.9 (+), 34.2 (−), 13.6 (+).

GC-MS (EI): m/z = 218 (100, $[M^{+\bullet}]$), 203 (20, $[M^{+\bullet}]$-$[^\bullet CH_3]$), 187 (31, $[M^{+\bullet}]$-$[^\bullet OCH_3]$), 175 (42, $[M^{+\bullet}]$-$[^{3\bullet}C_2H_3O]$), 95 (24, $[M^{+\bullet}]$-$[^\bullet CH_2C_6H_3(OCH_3)(OH)]$).

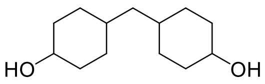
The analytical data was in accordance with the literature.[126]


HO
6.86
6.84
6.75
6.73
5.85
5.52
3.86
3.84
2.25
1.00
2.11
2.00
0.88
3.26
2.23
3.30
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


HO
153.10
150.92
146.39
144.11
130.27
121.39
114.24
111.25
106.67
105.97
55.85
34.21
13.58
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

3.5.3.4. Hydrogenation of Bisguaiacols

4,4'-Methylenebis(cyclohexan-1-ol) (**19**)



7 (200 mg, 1 mmol, 1 equiv.) was dissolved in *i*-PrOH (15 mL) in an autoclave reaction vial. Raney-Ni@2400 (1.0 g) was added and the reaction was set up in an autoclave at 10 bar and heated at 100 °C for 2 h. After cooling to rt, the catalyst was removed by filtration and the solvent was evaporated. Purification was conducted *via* column chromatography (Hept/EA 8:2 → 4:6) obtaining product **19** as white powder as three different isomers (120 mg, 0.6 mmol, 60% containing 48% F3, 33% F2 and 19% F1).

$C_{13}H_{24}O_2$ (212.3 g/mol)

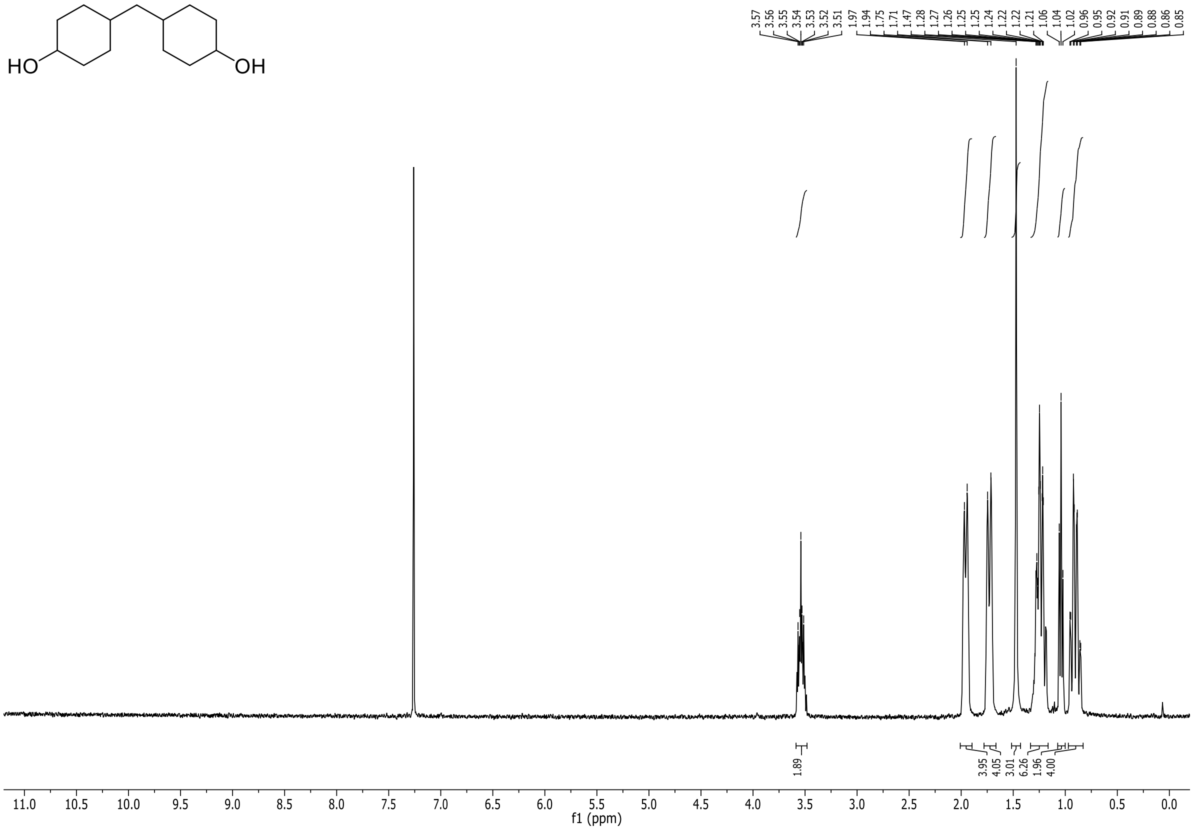
R$_f$: 0.45(F1), 0.33 (F2), 0.24 (F3) (Hept/EA: 6/4)

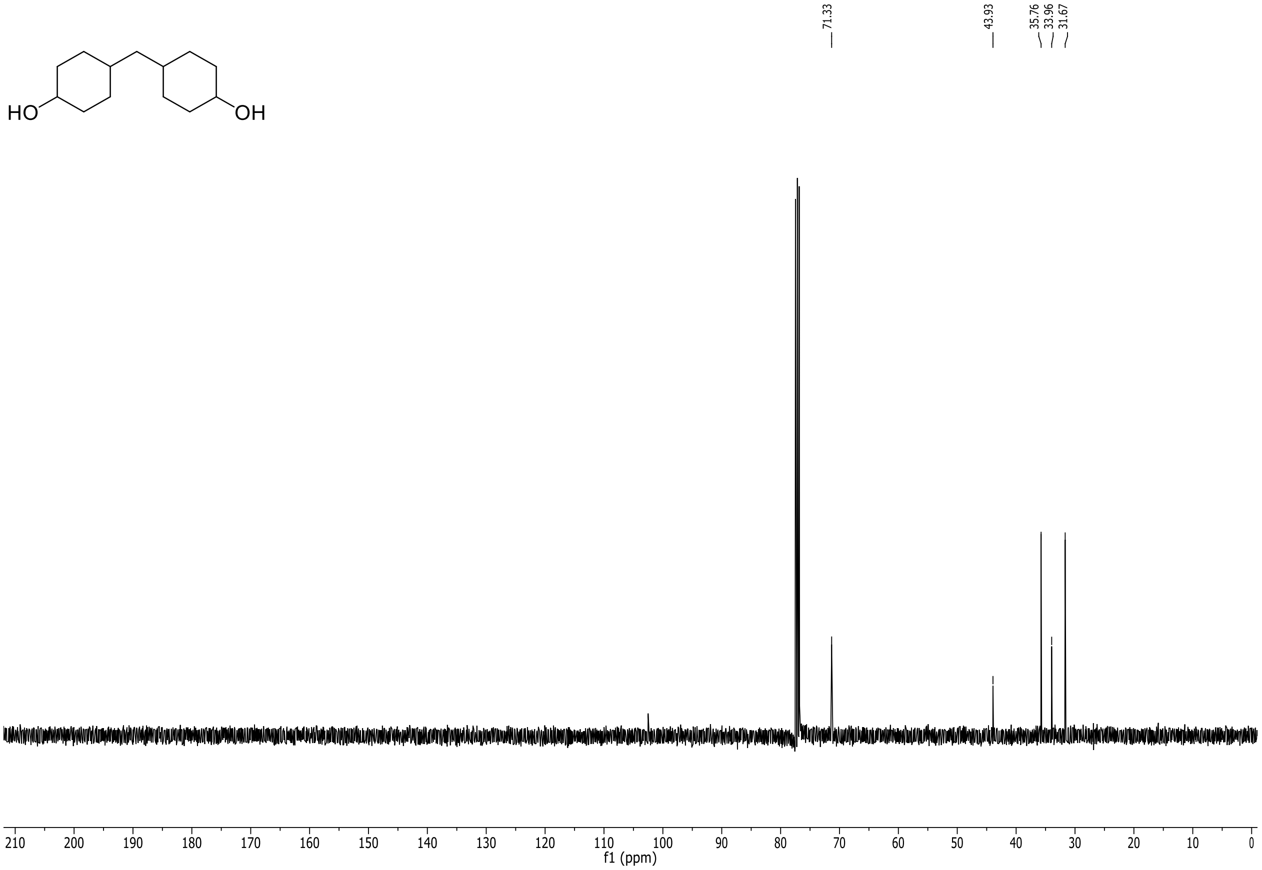
^{1}H-NMR (400 MHz, $CDCl_3$) δH/ppm (F3): 3.54 (ddd, J = 10.9, 6.5, 4.3 Hz, 2H, C*H*OH), 1.96 (d, J = 10.7 Hz, 4H, $CH_2CHCH_2C\textit{H}_2CHOH$), 1.73 (d, J = 12.5 Hz, 4H, $CH_2CHC\textit{H}_2CH_2CHOH$), 1.47 (s, 2H, O*H*), 1.15 – 1.34 (m, 6H, $CH_2C\textit{H}CH_2C\textit{H}_2CHOH$), 1.04 (t, J = 7.0 Hz, 2H, $C\textit{H}_2CH(CH_2)_2CHOH$), 0.85 – 0.96 (m, 4H, $CH_2CHC\textit{H}_2CH_2CHOH$).

^{13}C-NMR (101 MHz, $CDCl_3$) δ_C/ppm (F3): 71.3 (+), 43.9 (−), 35.8 (−), 34.0(+), 31.7 (−).

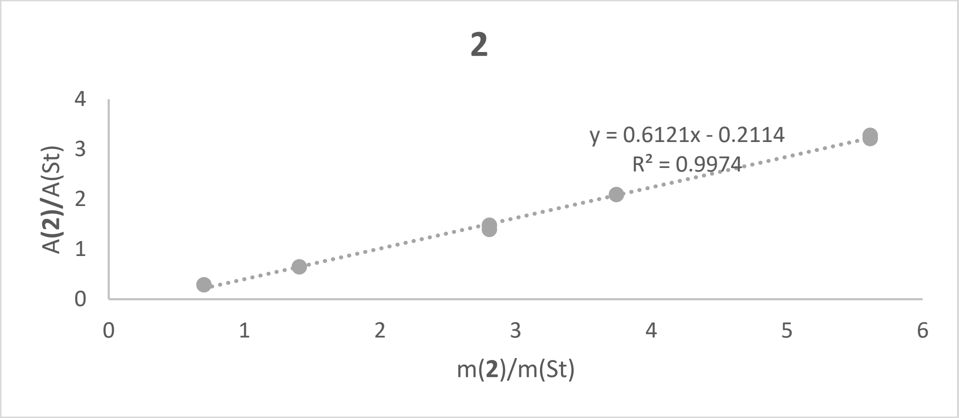
GC-MS (EI): m/z = 138 (8, $[M^{+\bullet}]$-[OH]-$[^{2\bullet}C_3H_5OH]$), 94 (62, $[^{2\bullet}C_7H_{12}]$), 81 (100, $[^{2\bullet}C_6H_{10}]$-$[^{\bullet}H]$), 67 (40, $[^{3\bullet}C_4H_7]$-$[2^{\bullet}H]$), 55 (48, $[^{3\bullet}C_4H_7]$), 41 (40, $[^{3\bullet}C_3H_5]$).

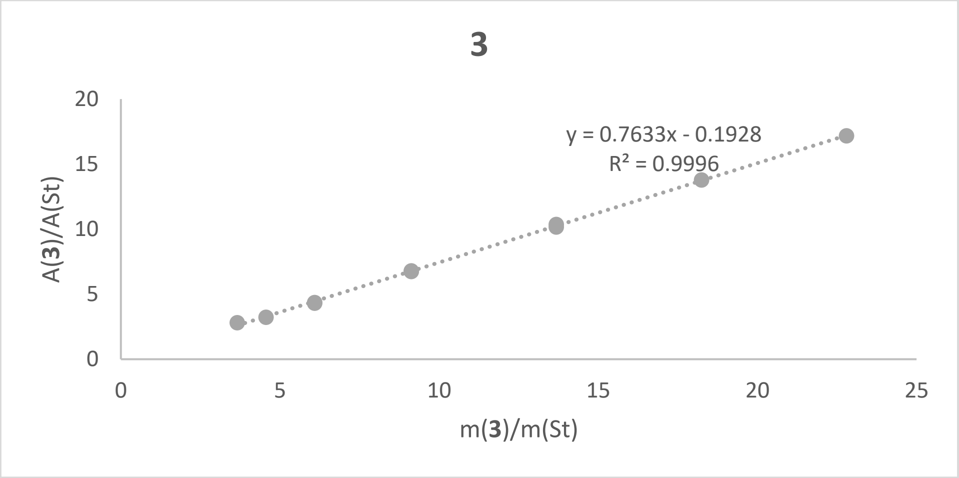
FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3260 (w, br), 2950 (m, sh), 2800(m, sh), 1450 (w, sh), 1300 (w, sh), 1105 (m, sh).

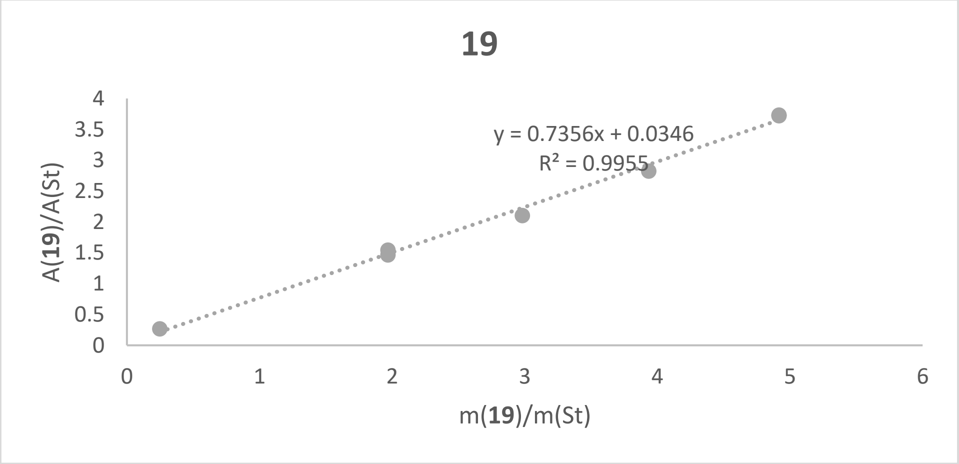

HO
OH
3.57
3.56
3.55
3.54
3.53
3.52
3.51
1.97
1.94
1.75
1.71
1.47
1.28
1.27
1.26
1.25
1.25
1.24
1.22
1.22
1.21
1.06
1.04
1.02
0.96
0.95
0.92
0.91
0.89
0.88
0.86
0.85
1.89
3.95
4.05
3.01
6.26
1.96
4.00
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


HO
OH
71.33
43.93
35.76
33.96
31.67
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

3.5.4. GC-FID Calibration data







3.6. Literature

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4. One-pot Magnesiation/Carbonylation of Benzylic Alcohols

Author contribution:

Marlene Böldl: 80% of reproduced part.

Vera Hirschbeck contributed to this chapter in 20% with scientific ideas, data generation, analysis and interpretation of results shown in Scheme 10, 11, 12 and 14.

4.1. Introduction

4.1.1. C-C bond Formation by Transition Metal-Catalyzed Cross-Coupling Reactions

The most prominent way to form C-C bonds are cross-coupling reactions, in which organic halides or related electrophiles react with organometallic compounds catalyzed by transition metals (Scheme 1).[2] Its development has profoundly changed the logic of chemical synthesis and revolutionized the protocols for the formation of natural products, pharmaceuticals, agrochemicals and building blocks for polymers, self-assembly, organic materials and supramolecular chemistry.[3,4] Cross-coupling reactions were an elemental part of the work of the chemists Ei-ichi Negishi, Richard Fred Heck and Akira Suzuki. For their attribution to this topic, they were awarded with the Nobel Prize in 2010.[5]

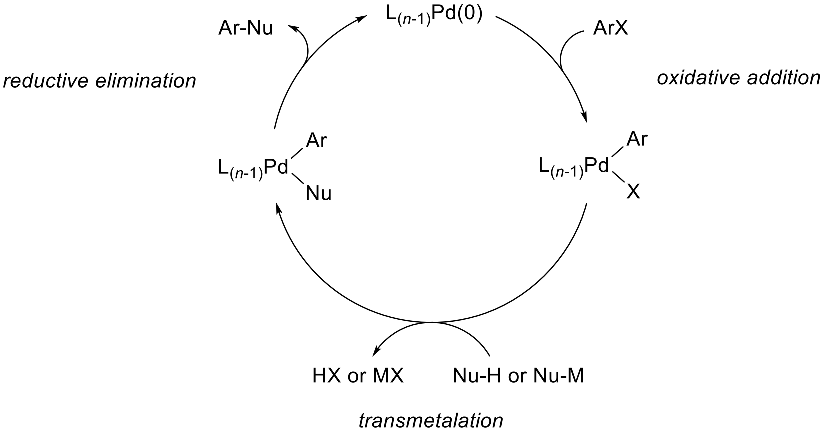
$$R-X \quad + \quad R^{1}\text{-}M \quad \xrightarrow{[cat.]} \quad R-R \quad + \quad M-X$$

M = B: Suzuki-Miyaura
M = Sn: Stille
M = Si: Hiyama
M = Zn: Negishi
M = Mg: Kumada-Corriu

Scheme 1: Most common cross-coupling reactions.

Modern cross-coupling chemistry is based a series of simultaneous contributions reported in the early 1970's.[6,7] One of the first investigations during that time were performed by Kumada and Corriu in 1972, showing the coupling of aryl halides with Grignard reagents and Ni catalysts.[8,9] Five years later, Negishi reported the application of organozinc reagents as coupling partners of aryl halides in the presence of Pd and Ni catalysts, which is now known as Negishi coupling.[10] The application of organotin reagents in cross-coupling reaction with aryl halides is commonly called Stille reaction and was fist investigated 1986.[11] But also organosilicium reagents are applicable in presence of fluoride, which generates a more nucleophilic, anionic hypervalent silicon reagent. This reaction is called Hiyama(-Tamao) coupling.[12] Other prominent C-C bond forming cross-coupling reactions discovered in the 1970's are Suzuki coupling reactions, which represent the reaction of organoboron reagents under basic conditions and a Pd catalyst,[13] the Heck reaction[14] and the Sonogashira reaction, in which an aryl halide forms an alkynylarene with a terminal alkyne under Pd catalysis.[15]

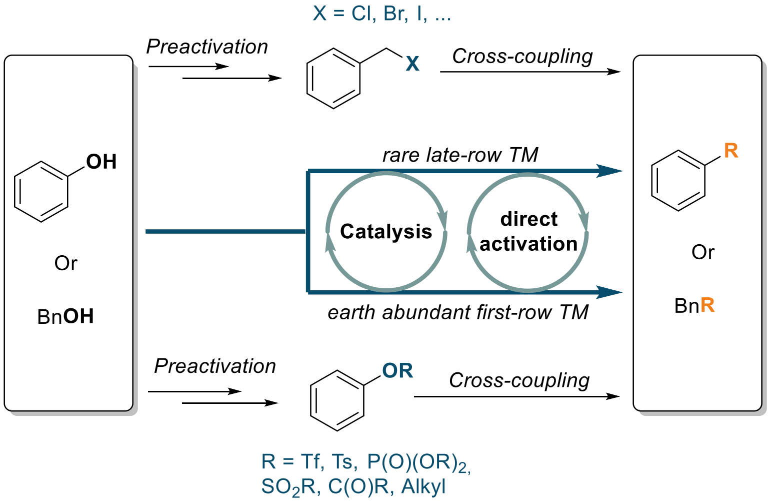
With exception of the Heck reaction, a general mechanism for Pd-catalyzed cross-coupling reactions with main group organometallic nucleophiles can be summarized as three step process with an oxidative addition of the halide to the active catalyst as first step, transmetalation with the organometallic species as key step and reductive elimination as final step to form the C-C bond and to release the product (Scheme 2).[7]



Scheme 2: General mechanism for Pd-catalyzed cross-coupling reaction with main group organometallic nucleophiles.

Cross-coupling reactions evolved to a fundamental tool in organic chemistry with an impressive application profile over the last decades. In recent years, chemists were looking for cheaper and more sustainable procedures to conduct cross-coupling reactions either by replacing less abundant and expensive late transition metals like Pd with early transition metals or by replacing toxic starting materials. Iron-catalyzed cross-coupling for example, arose around the turn of the millennium based on the early investigations by Kochi *et al*.[16] Beside the economical factor, iron exhibits chemical advantages compared to late row transition metals, since it enables to couple alkyl electrophiles with Grignard reagents. This is challenging with late transition metals, because alkyl palladium complexes tend to undergo β-hydrogen elimination faster than transmetalation.[7] Iron complexes however, were shown to be efficient catalysts for these reactions.[17] Replacement of halides as starting material is also a matter of interest for more sustainable cross-coupling reactions due to their negative environmental impact. Not only the toxicity of halides is disadvantageous but also the production of environmentally polluting halide byproducts from coupling reactions and the difficult synthesis which includes tedious steps, harsh reaction conditions and waste generation.[18] Hence, electrophiles with C-C, C-H, C-O, C-S or C-N bonds are more attractive than C-X bonds.

4.1.2. C-O Bond Activation in Cross-Coupling Reactions



Scheme 3: Inert chemical bond activation logic shown in the figure.[19]

C-C, C-H, and C-O bonds are fundamental structural units in organic chemistry but are also so called “inert” bonds, due to their high bond dissociation energy. Hence, functionalization of these bonds is still a challenging issue. Especially direct C-H activation has gained considerable attention.[20] The spotlight on carbon-oxygen bond activation was significantly lower, even though carbon-oxygen bonds extensively exist in a variety of organic and biologic structures like lignin.[21] In Scheme 3, possible pathways for cleavage of C-O bond of alcohols and subsequent coupling reaction are depicted.[19] Generally, most publications on C-O bond activation for coupling reactions are based on indirect activation by formation of better leaving groups like halides or active ethers and esters.[22,23,24] Phenols and ketones for example are usually transformed into active sulfonates and phosphates.[22,24] Especially aryl sulfonates have a low activation barrier for C-O bond cleavage and are therefore the most widely applied C-O electrophiles in cross-coupling.[4,25] But high costs and a bad atom economy diminish their application profile.

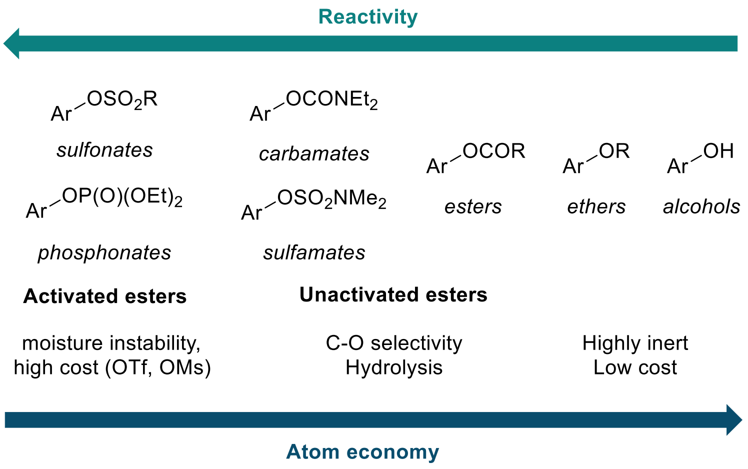


Figure 1: Reactivity vs. atom economy of C-O based electrophiles.[26]

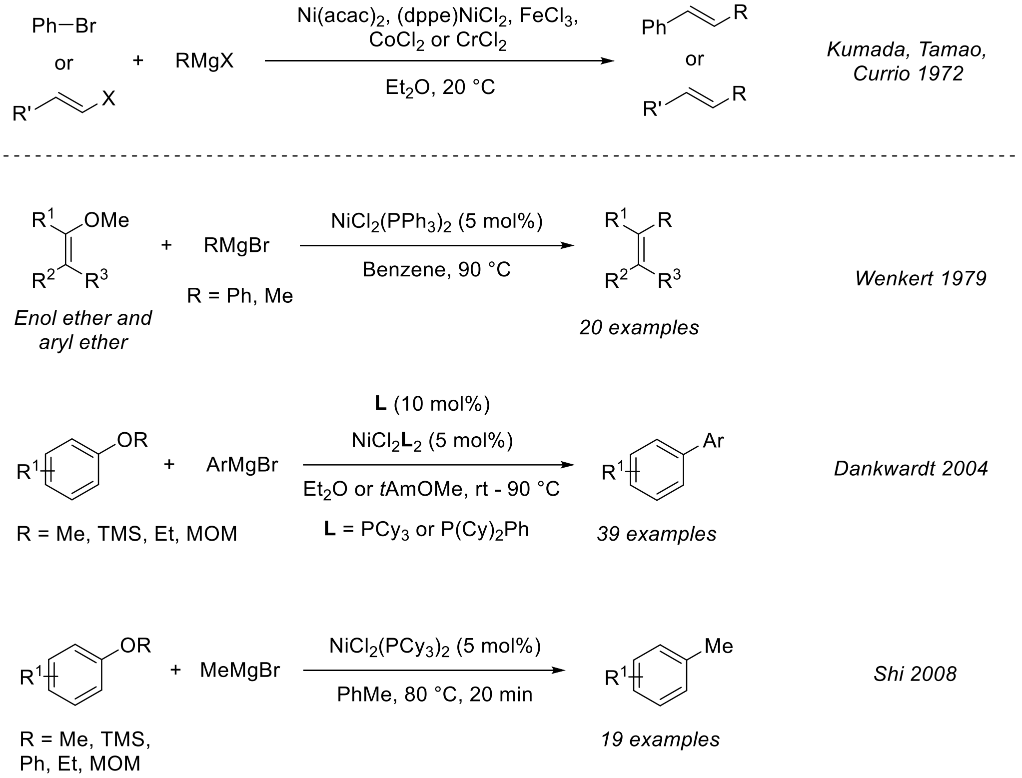
Since increased number of steps in indirect transformation also results in a larger waste emission and due to the higher abundancy and lower toxicity of phenol derivatives compared to their halide counterparts, selective and direct C-O bond activation is a more favorable way to achieve sustainable catalytic protocols. The use of C-O based electrophiles additionally expands the pool of substrates available for cross-coupling, because these electrophiles originate from different precursors than traditional halide electrophiles.[26] And also despite the advantageous economic properties, like easy accessibility and generally low prizes, especially ethers and non-preactivated phenols and alcohols have rarely been used as direct coupling partners in traditional cross-coupling reactions because of their high activation energy.

However, within the last two decades, progress has been made in the development of selective C-O bond cleavage and application of these compounds as electrophiles in cross-coupling reactions.[25–27] To improve the sustainability of these reactions, the application of first –row transition metals (TM) catalysts is highly favored. Ni, Fe and Co for example are highly versatile, more abundant and environmentally friendly as well as less expensive than noble metal catalysts like Pd, Pt, Ru or Rh.

Abundant first-row TM-catalyzed C-O bond activation was shown to be conducted in Negishi type reactions,[28] Suzuki-Miyaura type reactions,[29,30] Mizoroki-Heck type reactions.[31] But the vast majority of C-O bond activation in coupling reactions was reported under Kumada-Tamao-Currio reaction conditions with Grignard reagents as transmetalation agents.[32]

4.1.2.1. Iron- and Nickel-catalyzed Kumada-Tamao-Currio Coupling of Ethers

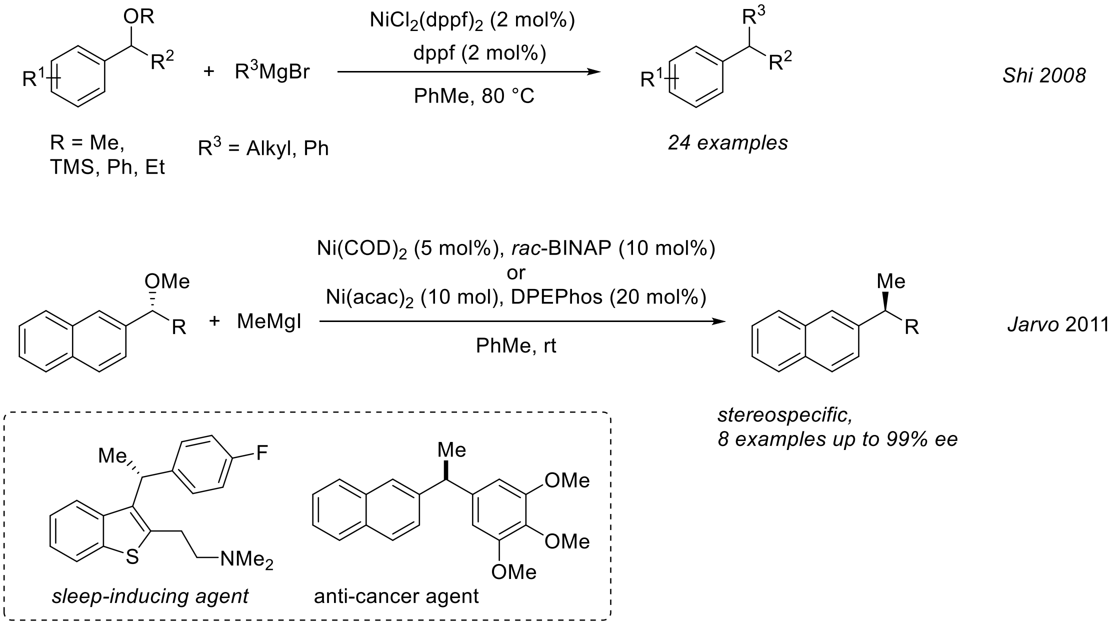
First investigations on C-O bond activation in Kumada-Tamao-Currio coupling reactions were already done in 1979 by Wenkert, who published a [$NiCl_2(PPh_3)_2$] mediated coupling of Grignard reagents with aryl and vinyl ethers as coupling partners *via* C-O bond cleavage (Scheme 4).[33,34] Nevertheless, the scope was rather limited to activate extended π-systems and only 1- and 2- methoxynaphthalene derivatives were generated in synthetically useful yields. Noteworthy, alkyl Grignard reagents, which exhibit a β-hydrogen were significantly less effective.



Scheme 4: Kumada-Tamao-Currio coupling and early reports on C-O bond activation of ethers in cross-coupling reactions with Grignard reagents.[8,33,35,36]

In 2004, Dankwardt extended the substrate scope of Wenkert by aryl alkyl ethers without an extended naphtalene π-conjugation and laid the foundation for following research in C-O bond activation (Scheme 4). The key contributory factor for the successful synthesis of biaryl compounds was the use of an electron-rich phosphine ligand with a large cone angle in etheric solvent. However, methylation of aryl ethers still seemed to fail.[35] Only in 2008, Shi could show that it is possible to generate aryl methyl ethers by applying $NiCl_2(PCy_3)_2$ as catalyst (Scheme 4).[36] Beside π-extended napthylene systems, less activated aryl ethers or biaryl ethers were applicable, even though the latter reacted much slower, which shows the important role of the π-extended system. Employment of other alkyl Grignard reagents resulted in complex mixtures, which led to the conclusion that the high nucleophilicity of the Grignard reagent was necessary to maintain reductive conditions to stabilize the low-valent Ni species.

In the same year, the same group reported the first C(sp3)-O bond activation of benzylic ethers (Scheme 5).[37] In cross-coupling, the selective C-O bond cleavage in dialkyl ethers is generally more difficult due to the presence of two differentiating C(sp3) centers on the oxygen atom. It was shown that dppf (1,1'-bis(diphenylphosphino)ferrocene) was an efficient ligand in the nickel-catalyzed reaction to generate C-C coupling products from primary and secondary benzyl alkyl ethers at room temperature.[37]

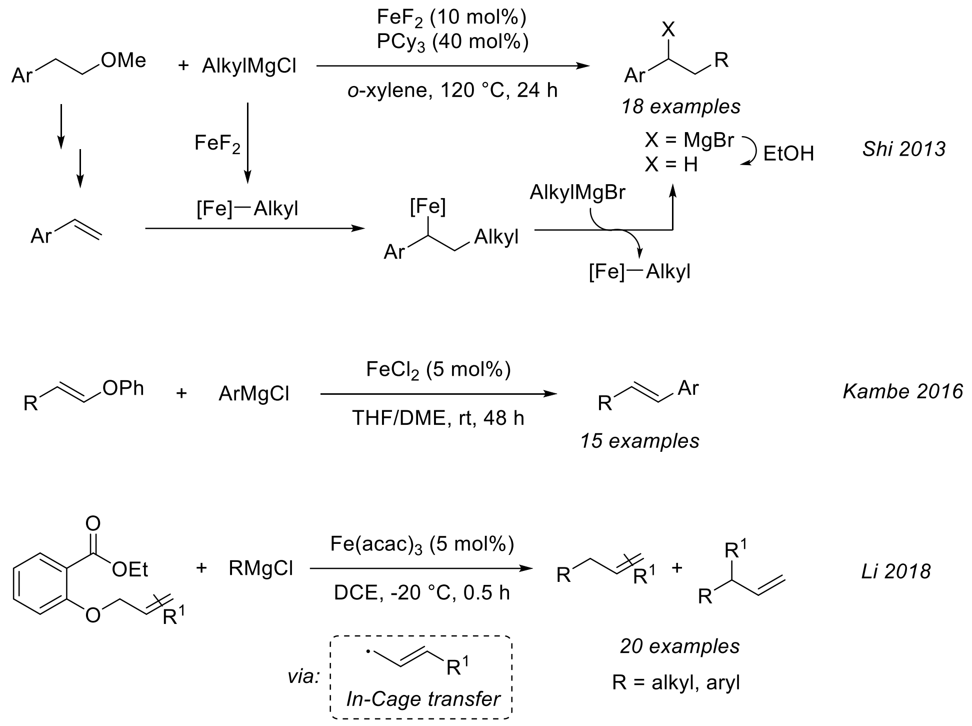


Scheme 5: Kumada-Tamao-Currio coupling of not previously activated ethers.[37,38]

Later on, Watson and Jarvo improved the reaction by synthesizing chiral diarylethanes *via* enantioselective cross-coupling with inversion of configuration (Scheme 5).[38,39] Interestingly, the extension of the aromatic π-system was crucial for success. Regular benzyl methyl ether derivatives were only suitable for this reaction when directing groups were introduced on the ether motif to facilitate the oxidative addition.[38] When diaryl benzyl ethers and ArMgBr were employed in the cross-coupling with $Ni(dppe)Cl_2$ (dppe = 1,2-bis(diphenylphosphino)ethane) as catalyst or a Ni(acac)$_2$ (acac = acetylacetonate) catalytic system with bidentate ligands with large bite angle, triarylmethanes were generated stereoselectively.[39] A bimolecular reaction of low valent Ni species with π-benzyl Ni oxidative addition intermediates was proposed.

The C-O bond activation of alkyl ethers with alkyl Grignard reagents possessing a β-hydrogen was reported by the group of Shi in 2013 (Scheme 6).[40] With the application of FeF$_2$ as catalyst and PCy$_3$ as ligand a broad substrate scope was accomplished. Yet, substituents in β-position emerged as limitation of this reaction. They proposed the *in situ* generation of styrene derivatives of the staring material, carbometalation of the double bond by the organoiron species and subsequent transmetalation with the organogrignard reagents. The magnesiation was followed by hydrolytic workup with EtOH. Another iron-catalyzed coupling reaction of styrene derivatives and vinylic ethers was reported by Kambe and co-workers in 2016 (Scheme 6).[41] Contrary to the high temperatures used in Shi's work, Kambes group enabled the cross-coupling at room temperature and without the use of ligands. However, sterically hindered *ortho*-substituted aryl Grignard reagents were necessary for successful conversion. Like Shi's work, they propose a carbometalation to Fe (I) or Fe (0) prior to the transmetalation and β-oxygen elimination.

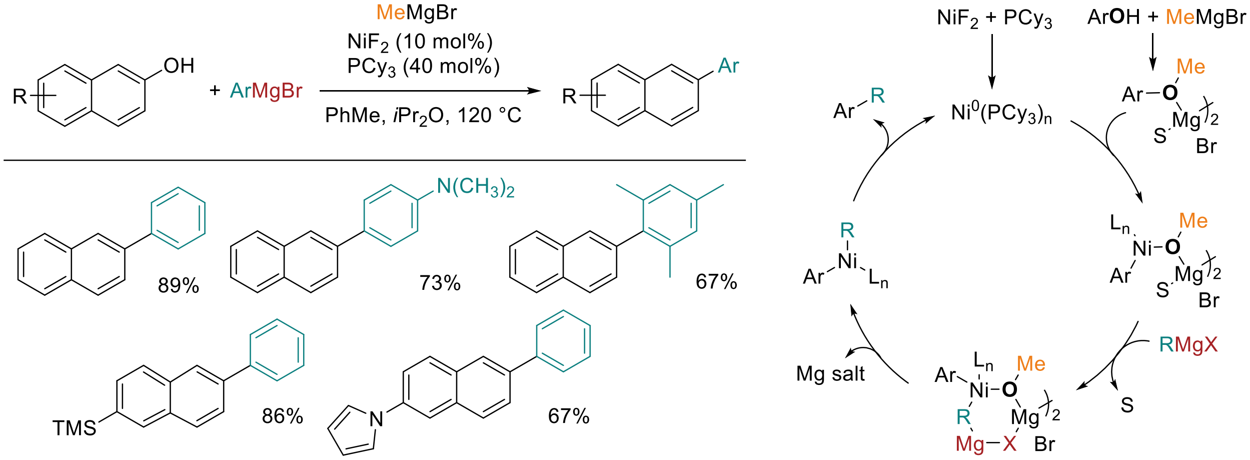
In the same Year, Li *et al.* reported an iron-catalyzed coupling of allylic ethers with aryl Grignard reagents. They used 2.5 mol% of Fe(acac)$_3$ in 1,2-dichloroethane and *N*-methyl-2-pyrrolidone at -15 °C.[42] Recently, they extended the substrate scope by introducing ester moieties as *ortho*-substituents on the phenolic leaving group, leading to chelation of the ester with the iron catalyst (Scheme 6).[43] The beneficial properties of *ortho*-directing groups in cross-coupling reactions with C-O bond activation have also been reported earlier with other precious and non-precious transition metals.[27,30,44] In this publication, they proposed the generation of an allyl radical which reacts with the transmetalated organo-iron species to form a π-allyl iron intermediate. Aromatic and alkyl Grignard reagents were applicable for reaction with phenolic allyl ethers. Nevertheless, most products were found as mixture of linear and branched regioisomers. Hashimoto *et al*. were able to improve the regioselectivity of this reaction by using a β-amioketonato Ni (II)-pincer complex bearing a diphenylphosphino group.[45] They generated the linear products of cinnamyl ethers, yet α- and γ-alkyl substituted allylic ethers generated a mixture of isomers, leading to the proposal of a π-allyl nickel intermediate.



Scheme 6: C-O bond activation of alkyl ethers with Grignard reagents.[40,41,43]

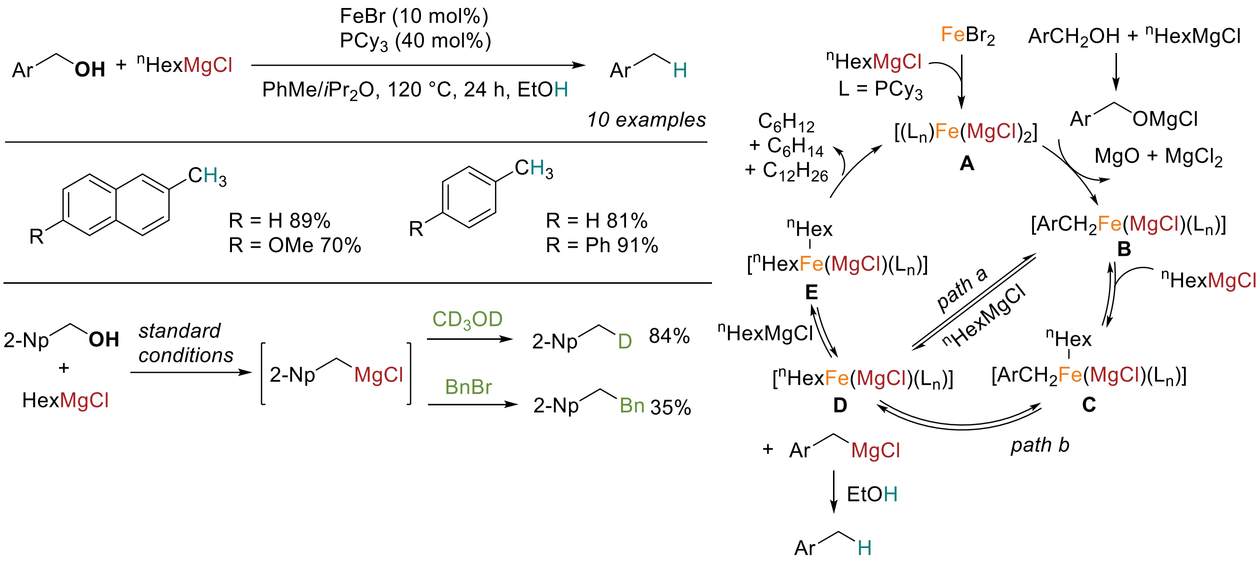
4.1.2.2. Iron- and nickel-catalyzed Kumada-Tamao-Currio Coupling of Alcohols

The direct C-O bond cleavage of phenols and other alcohols is an ideal way to convert a broad range of abundant, cheap and mostly non-toxic organic compounds and is hence the major goal in C-O bond activation. For a long time, this was quite illusory due to the fact that alcohols have a high bond dissociation energy.[46] Hence, conversion into more reactive compounds with mostly toxic reagents and radical activation pathways like in the Barton-McCombie desoxygenation are traditional methods to overcome the strong C-O bond.[47] In cross-coupling reactions, the direct C-O bond activation of alcohols, especially without the addition of stoichiometric amounts of an *in situ* activating agent, is only poorly developed.[48] Samec and co-workers only recently published a short review on the C-O-bond activation of alcohols in Suzuki-Miyaura-type cross-coupling reactions.[49] Kumada-Tamao-Currio type coupling reactions with direct alcohol activation yet are only reported by the group of Shi.[50,51] In an initial report from 2010 they showed the formation of a naphtolate from 2-napthol with MeMgBr in a THF/toluene solvent mixture. They envisioned a tight coordination of the magnesium ions to the oxygen which induces an electronic reorganization to activate the C-O bond. Indeed, a dimeric structure was observed in single crystals of 2-naphthylOMgBr, in which the oxygen atom coordinates to two magnesium ions that each coordinate to a second 2-naphthylO$^-$ molecule to form a four membered ring. To couple the naphthol derivative with different aryl Grignard reagents, 2-NaphOMgBr was first generated *in situ* by addition of MeMgBr in THF. The salt formation was conducted in presence of NiF_2 as catalyst and PCy_3 as ligand for the subsequent coupling reaction with ArMgBr in a PhMe/*i*PrO_2 solvent mixture at 120 °C. Interestingly, the reaction only proceeds with 2-naphthol derivatives generating the cross-coupling products in 67-92% yield (Scheme 7). Additionally, bulky substituents were shown to decrease the reaction rate and yields. It was proposed that the magnesium-naphtholate-complex undergoes oxidative addition with an catalytically active Ni(0) species, followed by transmetallation which leads to the formation of a six-membered ring transition-state and subsequently to the biaryl product *via* reductive elimination. An important correlation of halide source to reaction outcome was found, with bromide generating the best results.



Scheme 7: Cross-coupling of benzylic alcohols with Grignard reagents by Shi (S = solvent).[50]

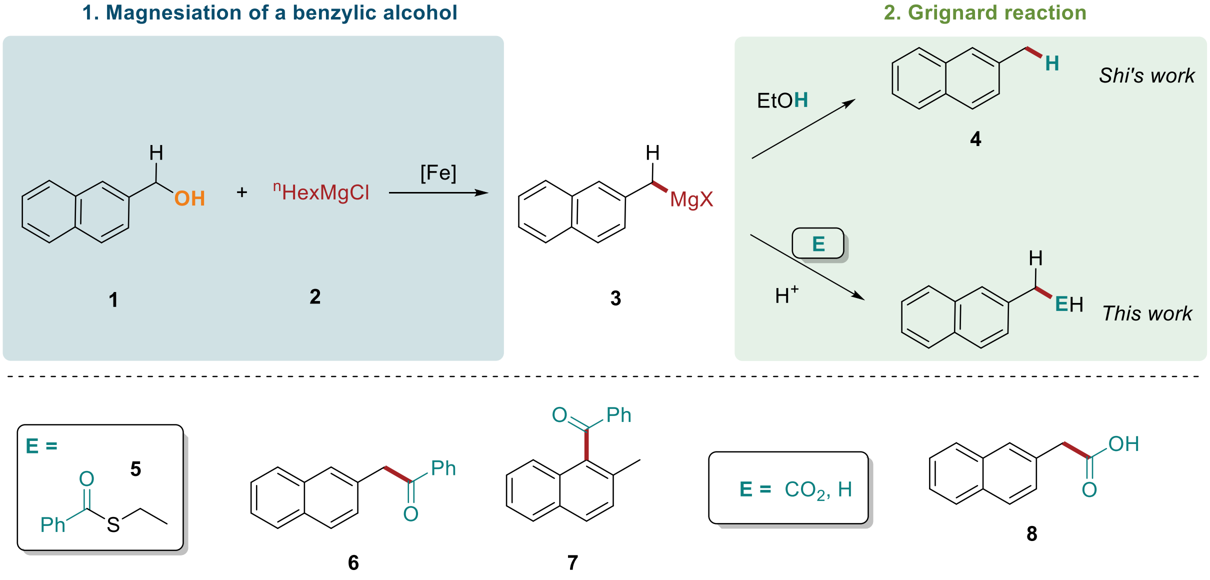
Based on these investigations, the group of Shi reported in 2012 the first cross-coupling of benzylic alcohols with Grignard reagents by a sequential *in situ* formation of a magnesium benzylate-complex and addition of an aryl magnesium bromide or halide in presence of a nickel-phosphine catalyst system.[51] Interestingly, they found out that the application of an alkyl Grignard reagent generated reduced benzylic alcohol products (Scheme 8). Beside nickel, the reaction turned out to work also with cobalt and less cost intensive iron-catalysts. Hence, a $FeBr_2$ and PCy_3 catalytic system was able to convert ten substrates selectively to the respective reduced form after a reaction time of 24 h at 120 °C and hydrolytic quenching with EtOH. In deuterium labelling experiments with CD_3OD instead of EtOH they could observe a mono-deuterium-labeled product in 84% yield. Hence, the new introduced hydrogen in the "reduction" derives from the protic solvent, which strongly supports the formation of a benzylic C-M bond. Additionally, BnBr was used as carbon-based electrophile to trap the proposed benzyl Grignard intermediate. Indeed, the desired C-C bond was formed, however, the product was only generated in 35% yield.



Scheme 8: Iron-catalyzed magensiation and subsequent "reduction" with a protic solvent reported by Shi *et al*.[51]

In a proposed mechanism, the active Grignard reagent is formed *in situ* from the alkyl Grignard, the iron catalyst and the ligand. After an oxidative addition of the prior formed magnesium benzylate (**A**) and release of a magnesium salt, a transmetalation with another Grignard molecule to a more stable iron complex occurs (**D**), releasing the benzyl Grignard reagent, which can be quenched by EtOH. To close the catalytic cycle, the addition of a third alkyl Grignard compound to **E** and β-hydrogen elimination or reductive elimination regenerates the active catalyst. Up until today, this protocol is the only example of transition metal-catalyzed magnesiation of benzylic alcohol. With this protocol however, new opportunities open up. The generation of a benzyl Grignard reagent from a benzylic alcohol has tremendous potential in C-O bond activation and can lead to a vast variety of coupling products, when applying other electrophiles than H^+. Eventually, common coupling products which have only been derived from halogenated starting materials could be synthesized.

4.2. Aim

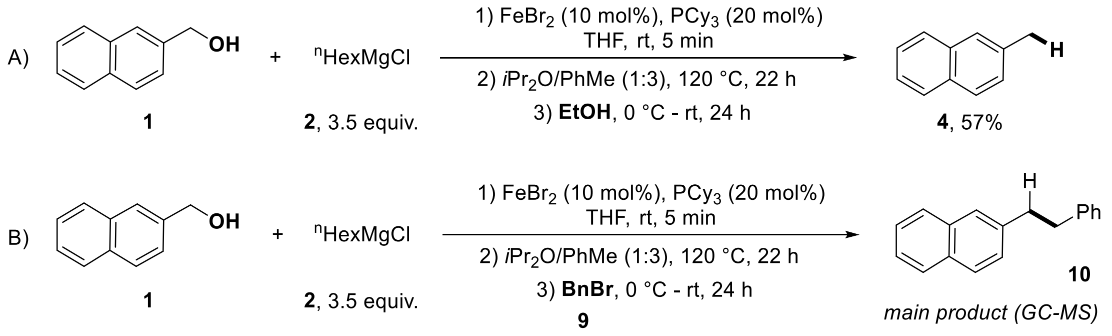


Scheme 9: Iron-catalyzed magnesiation and subsequent reaction with a carbonyl containing electrophile based on prior investigations by Shi.[51]

The aim of this project was to synthesize a ketone from the cross-coupling of a benzylic alcohol (**1**) and an carbonyl electrophile by an *in situ* generation of a benzyl magnesium intermediate (**3**) based on the work of Shi (Scheme 9).[51] Thereby, we took a closer look into the reactivity of 2-napthylmethanol (**1**) in presence of an alkyl Grignard reagent (**2**) and iron catalysts, as well as the direct reactivity of 2-naphylmethyl Grignard reagent (**3**) with different electrophiles. Interestingly, the one-pot magnesiation/acylation with a thioester (**5**) leads to a substitution of 2-methylnaphthalene in *ortho*-position (**7**) instead of a substitution in benzylic position (**6**). This reaction was further investigated by varying reaction conditions, reagents and additives. Eventually, carbon dioxide was envisioned to act as electrophile in a similar way as thioester **5** to generate **8**.

4.3. Results and Discussion

Initial experiments were conducted to reproduce the work of Shi (Scheme 10).[51] In a fist reaction step, iron(II) bromide was added as catalyst in 10 mol% to 2-naphtylmethanol (**1**) together with PCy_3 as ligand in THF. After addition of *n*-hexylMgCl (**2**) and stirring for 5 min to generate a magnesium benzylate (**3**), the solvent system was exchanged by *i*Pr_2O and toluene and heated to 120 °C. Shi and co-workers claimed in their work that this non-polar solvent system might retain the core framework of the dimeric magnesium benzylate due to its low coordination ability.[50] Quenching with EtOH for 24 h yielded **4** in 57% (Scheme 10A).This constitutes a decline compared to the very good yield of 89% by Shi.[51] Additionally, we tested the application of benzyl bromide (**9**, Scheme 10B) as electrophile in the third step and were able to detect **10** as main product on the GC-MS chromatogram.



Scheme 10: Reproduction of Shi's work;[51] *General reaction conditions*: **1** (31 mg, 0.20 mmol, 1.0 equiv.), **2** (400 µL, 1.75 M in THF, 0.70 mmol, 3.5 equiv.), $FeBr_2$ (4 mg, 0.20 mmol, 10 mol%), PCy_3 (11 mg, 0.04 mmol, 20 mol%), THF (1 mL), rt, 5 min, then: *i*Pr_2O (0.25 mL), toluene (0.75 mL), 120 °C, 22 h, quenching with EtOH or **9** (0.04 mmol, 2.0 equiv.), 0°C – rt, 24 h.

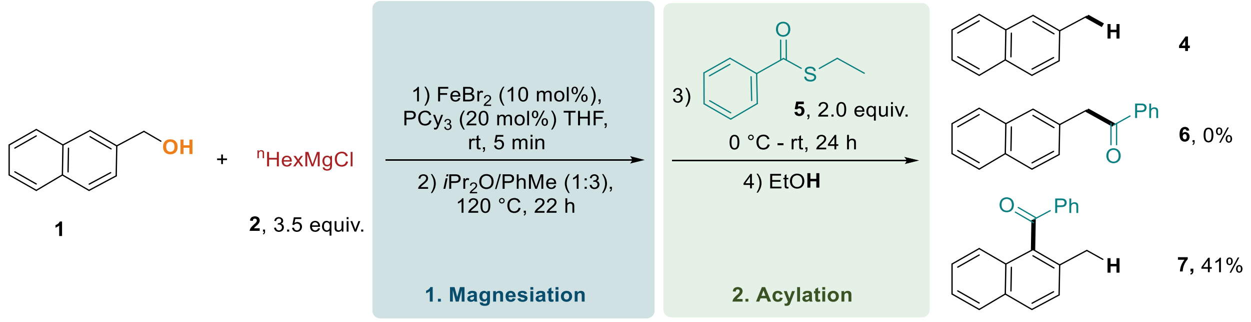
Even though we could not isolate the products in equal amounts as reported in the literature, we decided to investigate this reaction further by adding carbonyl electrophiles for the synthesis of ketones from alcohols. Transition metal-catalyzed carbonylative coupling reactions with organometallic reagents are quite well known for the synthesis of diarylketones, which have an important and versatile structure and are present in various natural products.[52] Nonetheless, to the best of our knowledge, there is no report of a one pot C-O bond activation/acylation of alcohols to ketones.

One way to generate ketones *via* transition-metal cross-coupling reaction is the application of thioesters as electrophiles, which has been shown by Fukuyama, Marchese, Liebeskind, Srogl and others.[53] Thioesters show some major advantages to normal oxo-esters (see also chapter 5). Due to their poorer orbital overlap between the p-orbital of the sulfur atom and the carbonyl π*-orbital to the oxygen-carbonyl orbital overlap, thioesters are more easily converted and contain a better leaving group ($RS^- > RO^-$).[54] Additionally, sulfur electrophiles exhibit a high abundance in natural products, pharmaceuticals and biological molecules.[55] Hence, we subsequently used thioesters as electrophiles instead of ethanol in the reaction of 2-naphthylmethanol (**1**) with *n*-hexyl MgCl (**2**) under reaction conditions of Shi and co-workers.

4.3.1. Thioester as Electrophile

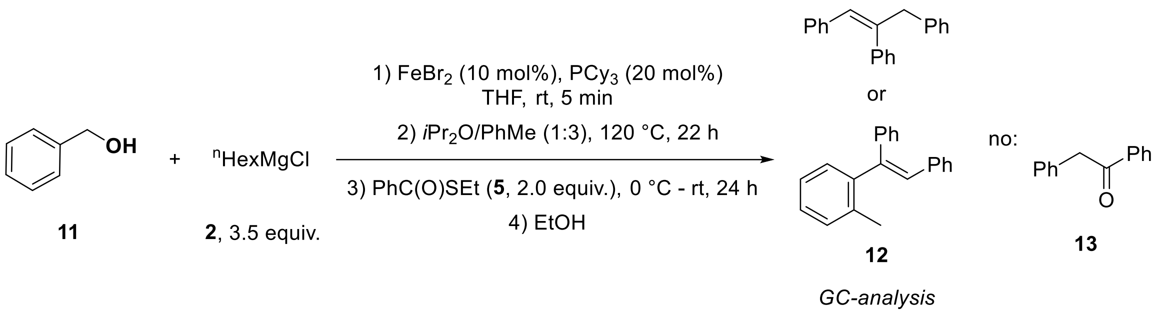
4.3.1.1. One-pot Magnesiation/Acylation

In an initial investigation, **1** was dissolved in THF together with 10 mol% of iron(II) bromide and 20 mol% of tricyclohexyl phosphine. Addition of the alkyl Grignard reagent **2**, change of the solvent system and heating to 120 °C for 22 h was followed by the addition of two equivalents of thioester **5** at 0 °C (Scheme 11). The reaction was eventually quenched with EtOH. GC-MS analysis showed the formation of **4** and of the desired product **6**. After isolation, NMR analysis however, revealed that an unexpected *ortho*-acylated regioisomer (**7**) is formed in 41% yield instead **6**.



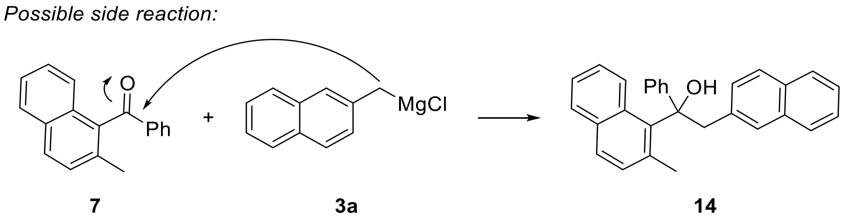
Scheme 11: One-pot Magnesiation/acylation of benzylic alcohol **1** with thioester **5**; *Reaction conditions*: **1** (31 mg, 0.20 mmol, 1.0 equiv.), **2** (1.98 M in THF, 0.70 mmol, 3.5 equiv.), $FeBr_2$ (4 mg, 0.20 mmol, 10 mol%), PCy_3 (11 mg, 0.04 mmol, 20 mol%), THF (1 mL), rt, 5 min, then: *i*Pr_2O (0.25 mL), toluene (0.75 mL), 120 °C, 22 h, then: **5** (67 mg, 0.04 mmol, 2.0 equiv.), 0°C – rt, 24 h.

When the same reaction was conducted with benzyl alcohol (**11**) instead of **1**, generation of product **12** was observed on GC-MS, which is presumably derived from a second attack of the *in* *situ* formed Grignard reagent from **11** onto the desired product **13**, which was not observed on the chromatogram, and subsequent water elimination. Therefore, it can be assumed that the cross-coupling succeeded but that ketone **13** is too reactive in presence of Grignard reagents. An extended π-system as in **1** seems to be crucial for the reaction since it could donate more electrons into the C=O bond of **7**, making it less electropositive and therefore less reactive towards a second Grignard attack.



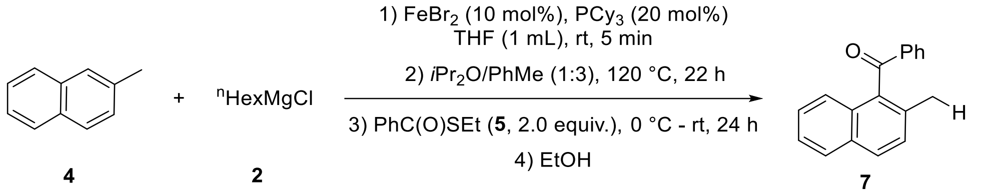
Scheme 12: One-pot reaction of benzyl alcohol (**11**); *Reaction conditions*: **11** (22 mg, 0.20 mmol, 1.0 equiv.), **2** (1.75 M in THF, 0.70 mmol, 3.5 equiv.), $FeBr_2$ (4 mg, 0.20 mmol, 10 mol%), PCy_3 (11 mg, 0.04 mmol, 20 mol%), THF (1 mL), rt, 5 min, $i$$Pr_2O$ (0.25 mL), then: toluene (0.75 mL), 120 °C, 22 h, **5** (67 mg, 0.04 mmol, 2.0 equiv.), 0°C – rt, 24 h.

It should be mentioned, that in following reactions with **1** no formation of the respective secondly attacked product (**14**) is observed (Scheme 13). This can be based on the fact that either **14** is not formed at all or that **14** is formed but has a high boiling point and is therefore not measurable with the common GC-methods used in following analyses. Nevertheless, it should not be forgotten that **14** might be a possible side product.



Scheme 13: Possible side reaction of the one-pot magnesiation/acylation of **1** with **5**.

For the reaction of **1** quenched with benzyl bromide (**9**) shown in Scheme 10B*,* a detailed structural analysis was not conducted. Fragmentation of GC-MS shows a free CH_3 fragment, which would exclude alkylation in benzylic position to **10** and imply aromatic alkylation. From the occurrence of aromatic acylation, the question arises, if a Friedel-Crafts reaction of *in situ* generated compound **4** with **2** to **7** is the main reaction. Hence, **4** was employed as starting material (Scheme 14). Interestingly, **7** was not formed in presence of alkyl Grignard reagent **2**, excluding a Friedel-Crafts reaction, but in absence of **2**, **7** was formed in 8% yield. From these results it can be concluded that Friedel-Crafts reaction plays a minor role in the absence of an alkyl Grignard reagent. The main reaction pathway from **1** to **7** does neither include a Friedel-Crafts reaction, nor the formation of **4** as intermediate. Therefore, it can be assumed that a 2-naphthylmethyl Grignard reagent (**3a**) is generated as proposed in Shi's work, which undergoes a rearrangement reaction with **2**.

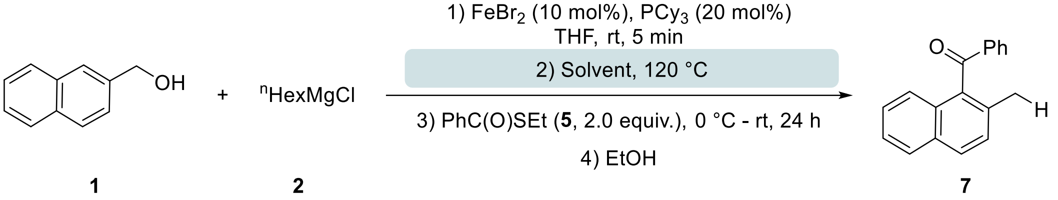


2	Yield **7**
3.5 equiv.	0%
-	8%

Scheme 14: One-pot reaction of 2-Methyl naphthalene (**4**); *Reaction conditions*: **4** (28 mg, 0.20 mmol, 1.0 equiv.), **2** (1.98 M in THF, 0.70 mmol, 3.5 equiv.), $FeBr_2$ (4 mg, 0.20 mmol, 10 mol%), PCy_3 (11 mg, 0.04 mmol, 20 mol%), THF (1 mL), rt, 5 min, then: *i*Pr_2O (0.25 mL), toluene (0.75 mL), 120 °C, 22 h, then: **5** (67 mg, 0.04 mmol, 2.0 equiv.), 0°C – rt, 24 h; yields determined *via* quantitative GC-FID.

With these observations in hand, screening experiments were performed to determine optimal reaction conditions. For this purpose, the reaction conditions of the first step were examined first (Table 1). It was shown that the reaction is difficult to reproduce, because **7** could be isolated in 41% yield as shown in Scheme 11, but GC-FID analysis of other batches never showed higher yields than 30% under the same reaction conditions (Table 1, entry 1). When the reaction was conducted in a higher concentration of 1 M, a dense suspension is formed during the reaction, providing the product in 6% yield (entry 2). The yield also dropped significantly, when the reaction time of the first step was diminished to 4 h (entry 3), leading to the conclusion, that an overnight reaction is necessary. However, further investigations on the reaction time of the first step should be conducted to vary this hypothesis.

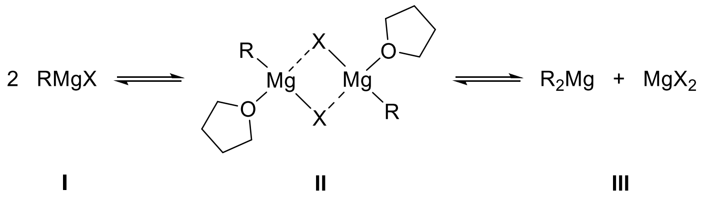
Table 1: Screening of solvent system and reaction time for the magnesiation step.



Entry	Solvent	t	Yield **7** [%][a]
1	*i*Pr$_2$O/PhMe (1:3)	22 h	30 (41)
2[b]	*i*Pr$_2$O/PhMe (1:3)	22 h	6
3	*i*Pr$_2$O/PhMe (1:3)	**4 h**	9
4	*i*Pr$_2$O/PhMe (1:2)	22 h	26
5	*i*Pr$_2$O/PhMe (1:1)	22 h	23
6	Et$_2$O/PhMe (1:3)	22 h	**39**
7[c]	Et$_2$O/PhMe (1:2)	22 h	23
8[c]	Et$_2$O/PhMe (1:1)	22 h	11
9	THF/PhMe (1:3)	22 h	36
10	PhMe	22 h	33
11	*i*Pr$_2$O	22 h	18
12	THF	22 h	13
13	1,4-dioxane	22 h	6
14	DCM	22 h	0

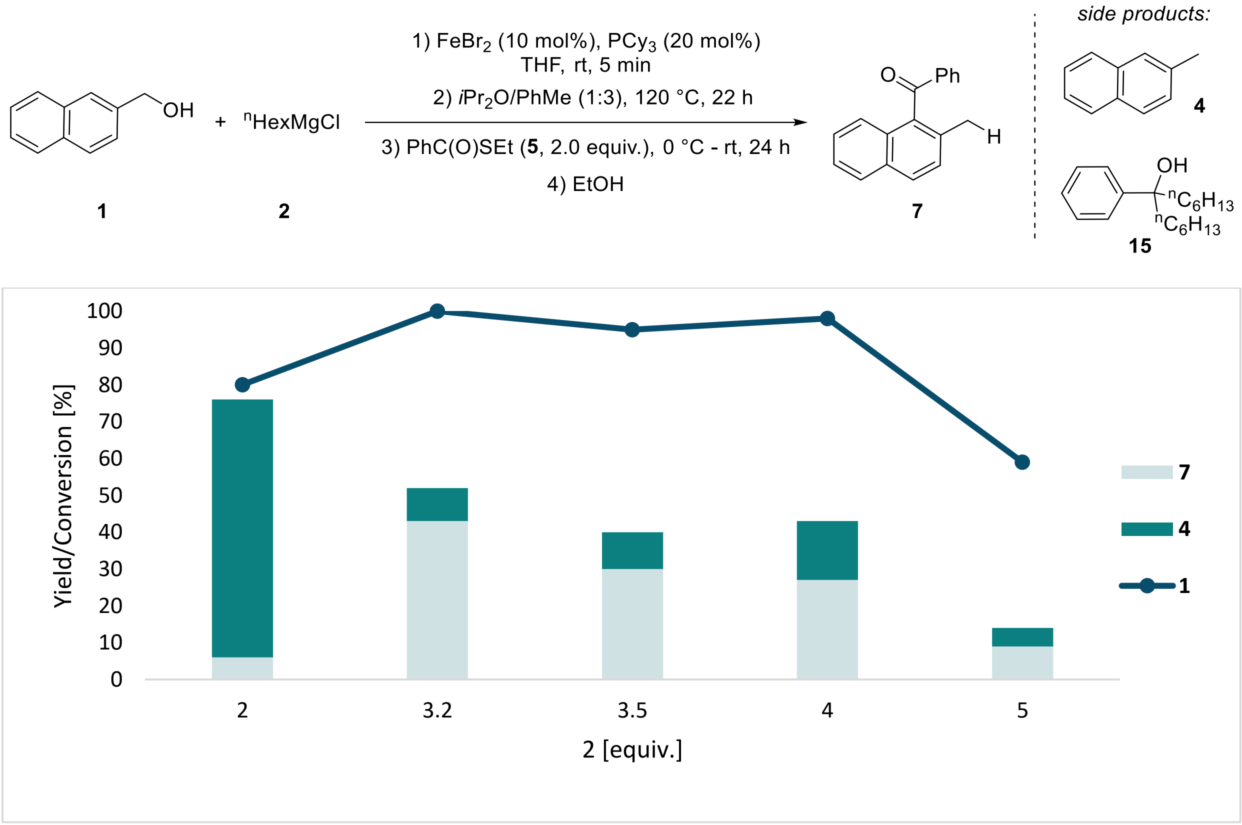
General reaction conditions: **1** (32 mg, 0.20 mmol, 1.0 equiv.), **2** (1.75 M in THF, 0.37 mL, 0.70 mmol, 3.5 equiv.), FeBr$_2$ (4.3 mg, 0.02 mmol, 10 mol%), PCy$_3$ (11 mg, 0.04 mmol, 20 mol%), THF (0.5 mL), 5 min, then: solvent (1.0 mL), 120 °C, then: **5** (67 mg, 0.40 mmol, 2.0 equiv.), 0 °C – rt, 24 h; [a] yields determined *via* quantitative GC-FID, number in brackets displays isolated yields; [b] **1** (1.00 mmol), solvent (1.0 mL); [c] **2** (3.2 equiv.).

When the ratio of the non-polar (toluene) to the etheric solvent (*i*PrO$_2$ and Et$_2$O) was changed to a more polar binary solvent system, yields generally decreased (entries 1 – 8). Application of diethyl ether and THF in the bisolvent system with a ratio of 1:3 showed the highest yields of 36 – 39% (entries 6 and 9). Interestingly, the yield in these solvent systems was even higher than when pure toluene was used (entry 10). Etheric solvents on the other hand, showed only low product formation and the application of dichloromethane results in low conversion and no generation of **6a** (entries 11 – 14).



Scheme 15: Schlenk equilibrium: In low concentrations in etheric solvents, **I** is the main constitution of the Grignard reagent; **II** is formed in THF; in dioxane, insoluble magnesium halide is precipitating and dialkylmagnesium is present in the solution (**III**).

This leads to the conclusion that the addition of etheric solvents to the non-polar aprotic reaction mixture can increase the yield, probably based on the Schlenk equilibrium of the organomagnesium reagent (Scheme 15).[56] However, a detailed explanation for the effect of the ratio and the difference in the application of diethyl ether and diisopropyl ether is still pending.

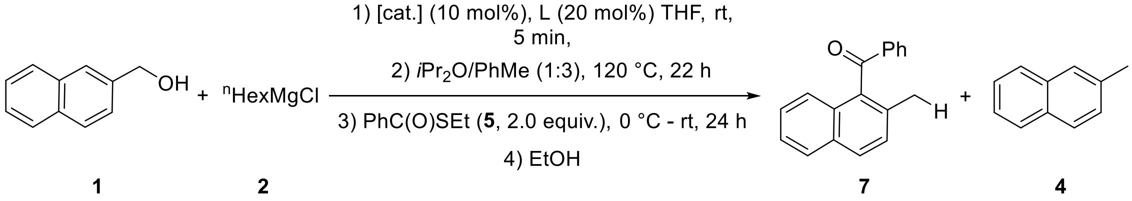


Scheme 16: Variation of the amount of 2; *General reaction conditions:* 1 (32 mg, 0.20 mmol, 1.0 equiv.), 2 (1.98 M in THF), FeBr2 (4 mg, 0.20 mmol, 10 mol%), PCy3 (11 mg, 0.04 mmol, 20 mol%), THF (1 mL), rt, 5 min, then: *i*Pr2O (0.25 mL), toluene (0.75 mL), 120 °C, 22 h, 5 (67 mg, 0.04 mmol, 2.0 equiv.), 0°C – rt, 24 h; yields determined *via* quantitative GC-FID.

For determining the optimal amount of **2** in the reaction, 2 equivalents of alkyl Grignard reagent **2** were used, generating 70% of 2-methylnaphthalene (**4**), whereas **7** was only formed in 6%.

A noteworthy difference in yield of **7** was observed when 3.2 or 3.5 equivalents of **2** were added (Scheme 16). **7** was formed in 43% yield with 3.2 equivalents but only in 30% with 3.5 equivalents. Larger amounts of **2** only led to a decrease in yield. In all cases with a higher amount of 3.2 equivalents of **2**, the conversion of **1** was much higher than the overall yield of products determined *via* quantitative GC-FID. It was additionally observed that alkyl Grignard reagent **2** undergoes a nucleophilic attack on thioester **5** twice, forming **15** as main product when the reaction was carried out in absence of the starting material **1**. Hence, large amounts of **2** decreased not only the yield of **7** but also of **4** due to more formation of side products, which were not further quantified. However, since the difference in product yield for 3.5 to 3.2 equivalents is so drastic for so little variation and because this result is difficult to reproduce, it might rather be a question of Grignard concentration than of its amount. This can be included in future studies, as well as the influence of the alkyl rest of the Grignard reagent on the outcome of the reaction.

Table 2: Catalyst and ligand screening.



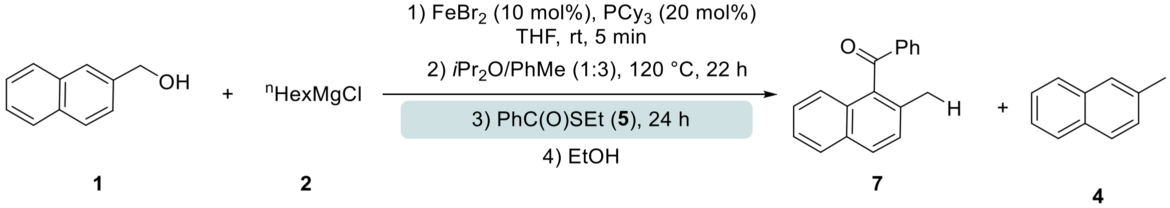
Entry	[cat.]	L	Conv. 1 [%][a]	Yield 7 [%][a]	Yield 4 [%][a]
1	$FeBr_2$	PCy_3	100	43	9
2[b]	$FeBr_2$	PCy_3	95	42	27
3	$NiBr_2$	PCy_3	100	7	65
4	$Ni(acac)_2$	PCy_3	75	4	58
5	$FeBr_2$	PPh_3	94	5	27
6	$FeBr_2$	$P(4\text{-}CF_3\text{-}C_5H_4)_3$	42	0	11
7	$FeBr_2$	$P(2\text{-}C_4H_3O)_3$	53	6	6

General reaction conditions: **1** (32 mg, 0.20 mmol, 1.0 equiv.), catalyst (0.02 mmol, 10 mol%), ligand (0.04 mmol, 20 mol%), **2** (1.98 M in THF, 0.64 mmol, 3.2 equiv.),THF (0.50 mL), rt, 5 min, then: *i*Pr_2O (0.25 mL), toluene (0.75 mL), 120 °C, 22 h, then: **5** (67 mg, 0.40 mmol, 2.0 equiv.), 0 °C – rt, 24 h; [a]: yields determined *via* quantitative GC-FID, [b] PCy_3 (0.08 mmol, 40 mol%).

In further investigation of the optimal reaction conditions, various catalysts and ligands were tested (Table 2). When iron(II) bromide was used and the amount of ligand was increased from

20 to 40 mol%, no significant change in yield of **7** was observed. The yield of **4** interestingly rose while the conversion was almost quantitative, which indicates lower formation of side products like **15** (entries 1 – 2). The application of the nickel catalysts $NiBr_2$ and $Ni(acac)_2$ in combination with tricyclohexyl phosphine as ligand could not lead to the formation of **7** but notably higher amounts of **4** were generated compared to the reactions catalyzed by iron complexes (entries 3 – 4). The use of these Ni catalysts has already been reported by Shi for the formation of **4** from **1**, when quenching with ethanol. Hence, a different reaction mechanism for the iron-catalyzed cross-coupling with **5**, than for the nickel-catalyzed cross-coupling reactions reported by Shi (Scheme 8) can be expected. When the reaction was performed with iron(II) bromide with different phosphines, it was observed that with the use of sterically less hindered PPh_3, which has also a lower Tolman cone angle than PCy_3 (145 ° to 179 °),[57] far lower yields of **7** were received (entry 5). Electron-poor ligand tis(trifluoromethylphenyl) phosphine and heterocyclic Tris(2-furyl)phosphine only showed low conversion and yields (entries 6 – 7).

Table 3: Screening the effect of reaction temperature and amount of thioester (**5**) in the acylation reaction.



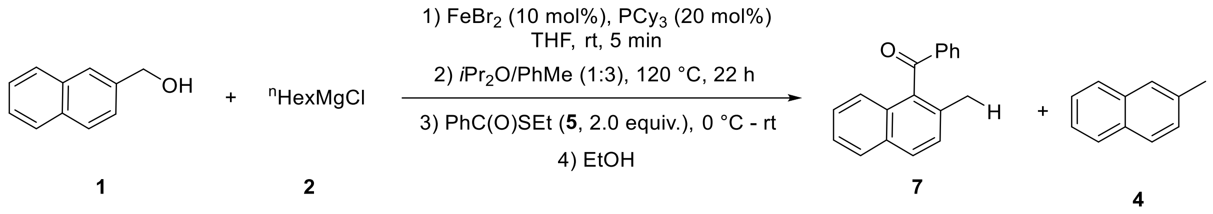
Entry	5 [equiv.]	T [°C]	Yield 7 [%][a]	Yield 4 [%][a]
1	1	0	4	12
2	2	0	**30**	10
3	2	–20	11	4
4	2	rt	19	6
5	2	40	8	5
6	5	0	29	14

General reaction conditions: **1** (32 mg, 0.20 mmol, 1.0 equiv.), **2** (1.98 M in THF, 0.64 mmol, 3.2 equiv.), $FeBr_2$ (4 mg, 0.02 mmol, 10 mol%), PCy_3 (11 mg, 0.04 mmol, 20 mol%), THF (0.5 mL), rt, 5 min, then: *i*Pr_2O (0.25 mL), toluene (0.75 mL), 120 °C, 22 h,, 24 h; [a]: yields determined *via* quantitative GC-FID.

To conclude the observations based on the investigation of the first reaction step, it was not possible to increase the yield substantially by changing the solvent system, the amount of alkyl Grignard added or by changing the catalytic system. However, it became clear that the concentration of the Grignard reagent could play a major part in the success of the reaction and that iron catalysts selectively generate the desired product, which cannot be found in considerable extent when using nickel catalysts. This, in turn, leads to the assumption that the mechanism of the reaction differs from the one proposed by Shi *et al.*.[51]

Further conducted experiments concern the second step of the one pot magnesiation/acylation with thioester **5** (Table 3). When adding one equivalent of **5** instead of two to the reaction in the second step, **7** was received in only 4% (entry 1). An increase to five equivalents of **5** yet did not show any change in the yield of **7** (entry 6). Changing the temperature for the addition of **5** from 0 °C to −20 °C, lowered the outcome to 11% instead of 30% (entry 3). Also, a rise in temperature diminished the yield (entries 4 – 5). Consequently, **5** was further added in two equivalents at 0 °C to the reaction mixture after the proposed magnesiation step.

Table 4: Investigation of the reaction time in the acylation step.

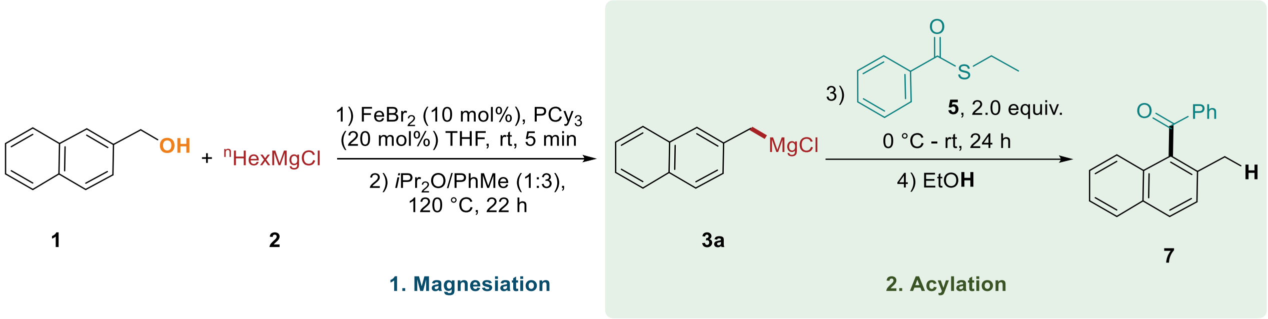


Entry	t [h]	Conv. 1 [%][a]	Yield 7 [%][a]	Yield 4 [%][a]
1	1	100	20	19
2	4	96	27	16
3	24	95	30	10
4	48	100	34	7

General reaction conditions: **1** (32 mg, 0.20 mmol, 1.0 equiv.), **2** (1.98 M in THF, 0.64 mmol, 3.2 equiv.), $FeBr_2$ (4 mg, 0.02 mmol, 10 mol%), PCy_3 (11 mg, 0.04 mmol, 20 mol%), THF (0.5 mL), rt, 5 min, then: $i Pr_2O$ (0.25 mL), toluene (0.75 mL), 120 °C, 22 h, then: **5** (67 mg, 0.40 mmol, 2.0 equiv.), 0 °C – rt.

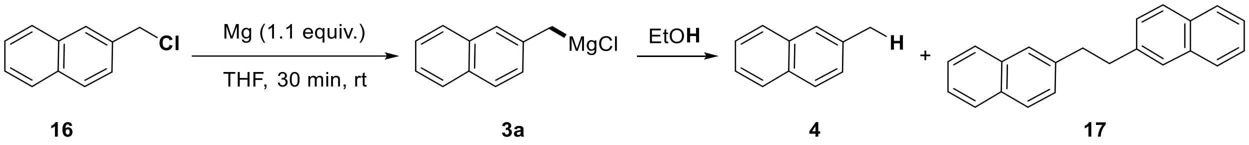
When looking into the yield of **7** over time after the addition of **5**, only a slow rising is observed between 4 h (27%) and 48 h (34%, Table 4). It is noteworthy to mention, that **1** is completely converted after the first reaction step, whereas the yield of side product **4** slowly decreases from 19% after 1 h to 7% after 48 h. Additionally, we conducted a reaction control experiment over time in only one batch by quenching small portions of the reaction mixture with ethanol in certain time frames and measuring the derived samples *via* quantitative GC-FID. However, in this experiment there was no trend observable. After one minute already 22% of **7** were formed, but after that the measured yields fluctuated and never exceeded 26%.

In summary, we struggled a lot with general reproducibility problems and with the lack of specific trends or increase in yield by varying the reaction conditions in the first and in the second step. Therefore, we hypothesized that reducing the complexity of the system by starting directly with the proposed benzyl Grignard intermediate, optimal reaction conditions for the second step could be found independently from the first one (Scheme 17).



Scheme 17: Starting the reaction from **3a** as possible way to investigate the optimal conditions of the second reaction step (Acylation).

4.3.1.2. Direct Coupling of Benzyl Grignard Reagents



Scheme 18: Grignard formation of halide **16** and subsequent quenching eith EtOH; *reaction conditions:* **16** (70.7 mg, 400 µmol, 1.0 equiv.), Mg (11 mg, 440 µmol, 1.1 equiv.), THF (1.2 mL), rt, 30 min, then: EtOH.

Initially, the optimal conditions for the preparation of benzyl Grignard **3a** were investigated. In the literature it was described that the preparation of benzylic Grignard reagents from their halides can be difficult. This is due to the fact that benzyl Grignard reagents are quite reactive[58] and undergo side reactions like metathesis of the Grignard reagent and the halide to the homo-coupling product[59,60] or reactions to other side products.[61,62] Indeed, when we prepared **3a** from benzyl halide **16** and quenched it with ethanol, the main product was dimer **17**, which precipitated as white solid and was determined by NMR analysis (Scheme 18). Interestingly, it was not possible to determine the concentration of the resulting Grignard solution *via* titration against iodine based on Knochel's work.[63] Therefore, all concentrations and yields were identified by quenching the Grignard solution with ethanol to **4** and subsequent measurement *via* quantitative GC-FID by using *n*-pentadecane as internal standard.

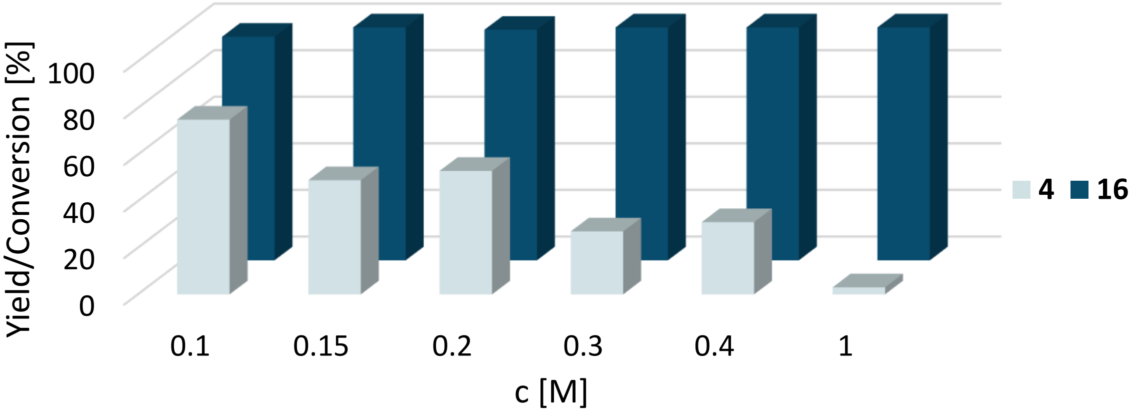
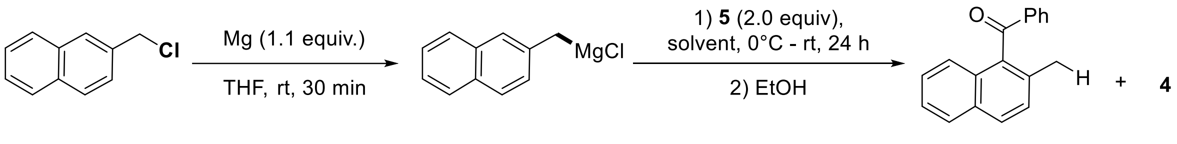


Figure 2: Investigation on the concentration; *General reaction conditions:* **16** (70.7 mg, 400 µmol, 1.0 equiv.), Mg (11 mg, 440 µmol, 1.1 equiv.), rt, 30 min, EtOH.

As depicted in Figure 2, a high dependency of the Grignard formation to the concentration of the starting material is observed. When 0.1 mmol of **16** were used in a concentration of 0.1 M in THF, **4** is generated in 75% yield, which implies that also the Grignard reagent (**3a**) was formed in 75%. Unfortunately, in scale-up reactions to 0.2 – 3 mmol **4** was only detected in around 50% yield instead of 75%. Higher concentrations also led to lower yields. When **16** was applied in concentrations below 0.2 M, the yield of **4** was always above 50%. A concentration of 1 M even inhibits the formation of **4** almost completely. As we see precipitation and full conversion of **16** in all reactions, one can conclude that the occurrence of side reactions as formation of **17** increases with higher concentration. Therefore, a concentration of 0.1 M was used for further reactions of **3a** with thioester **5** (Table 5).

Table 5: Varation of the solvent system and addition of catalysts and additives.



16 **3a** **7**

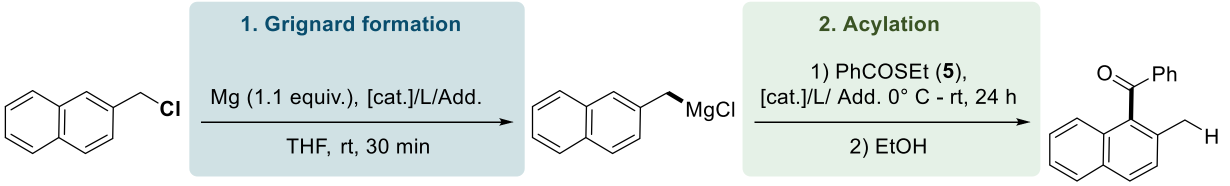
Entry	Solvent	Additive (mol%)	Yield 7 [%][a]	Yield 4 [%][a]
1	THF	-	0	40
2[b]	*i*Pr$_2$O/PhMe 1:3	-	0	0
3	*i*Pr$_2$O/PhMe1:3	-	0	15
4	*i*Pr$_2$O/PhMe 1:3	FeBr$_2$ (10), PCy$_3$ (20)	0	14
5	THF	FeBr$_2$ (10), PCy$_3$ (20)	6	16
6	THF	FeBr$_2$ (10)	0	21
7	THF	FeBr$_2$ (10), PCy$_3$ (20), **1** (5)	0	0

General reaction conditions: **16** (70.7 mg, 0.4 mmol, 1.0 equiv.), Mg (11 mg, 0.4 mmol, 1.1 equiv.), rt, 30 min, **5** (134 mg, 0.8 mmol, 2.0 equiv.), solvent (4 mL), 0 °C – rt, 24 h, EtOH; [a] Yields were determined *via* quantitative GC-FID; [b] Grignard formation and Grignard reaction were carried out in the same solvent system.

For this purpose, Grignard reagent **3a** was freshly generated from halide **16** without subsequent determination of the yield. When the reaction was carried out in pure THF without changing the solvent, no formation of the desired product (**7**) was observed, but 40% of **4** (Table 5, entry 1). If the reaction runs *via* the mechanism of Shi and co-workers, Grignard reaction of thioester (**5**) with **3a** should be conducted without further addition of catalysts or additives in an *i*Pr$_2$O/PhMe (1:3) solvent system. When Grignard formation and Grignard reaction were performed in *i*Pr$_2$O and

PhMe, **16** was only converted in 30 to 40% and no product formation was observed (entry 2). Consequently, the Grignard formation must be conducted in a different solvent system. Nevertheless, with the use of THF for the Grignard formation and *i*Pr_2O/PhMe for the Grignard reaction, no conversion of thioester **5** was observed (entry 3). Addition of $FeBr_2$ and PCy_3 did not change the outcome of the reaction (entry 4). Interestingly, when $FeBr_2$ and PCy_3 were both employed in THF, **7** could be yielded in 6% (entry 5). But since the yield is very low, it is not clear if the catalytic system acts catalytically or stoichiometrically. But when $FeBr_2$ was used without PCy_3, no product was generated (entry 6). Additionally, benzylic alcohol **1** was added in catalytical amounts, to see if remaining starting material could influence the outcome of the reaction shown in Scheme 11 (entry 7). Indeed, addition of **1** could inhibit the formation of **7** from **1** since it is also not formed when starting from **16** in presence of **1**. Yet, the yields are very low and the nonexistence of **7** could also be based on other effects, like varying Grignard concentrations, which is supported by the lack of consistency in the color change during the Grignard formation, or the formation of side products in different amounts.

Table 6: Investigation on order of the catalyst ([cat.]), ligand (L) and additive (Add.) addition.



16 **3a** **7**

Entry	[cat.]/Lig./Add. (mol%)	5 [equiv.]	[cat.]/L/Add.(mol%)	Conv 16 [%][a]	Yield 7 [%][a]
2	-	2	$FeBr_2$ (10), PCy_3 (20)	98	6 (6)
3	$FeBr_2$ (10), PCy_3 (20)		-	90	8
4	-	0.5	$FeBr_2$ (10), PCy_3 (20)	96	12
5[b}			$FeBr_2$ (10), PCy_3 (20)	100	11
6			$FeBr_2$ (**20**), PCy_3 (20)	100	15 (20)
7			**$Fe(acac)_3$** (10), PCy_3 (20)	90	5
8	**2** (1 equiv.)		$FeBr_2$ (10), PCy_3 (20)	100	1

General reaction conditions: **16** (70.7 mg, 400 µmol, 1.0 equiv.), Mg (11 mg, 440 µmol, 1.1 equiv.), THF (4 mL), rt, 30 min, $FeBr_2$ (8 mg, 0.04 mmol, 10 mol%), PCy_3 (22 mg, 0.08 mmol, 20 mol%), then: **5**, 0 °C – rt, 24 h, then: EtOH; [a] Yields were determined *via* quantitative GC-FID; [b] THF (8 mL).

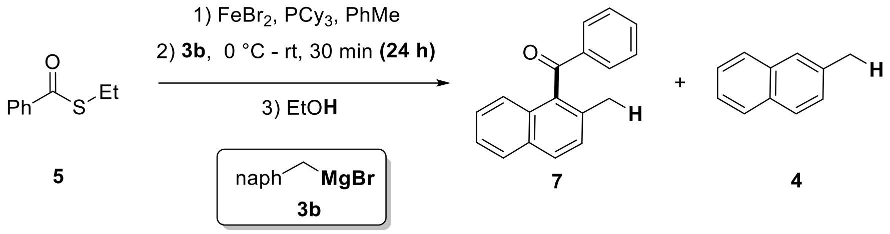
It was then examined whether it is important for the outcome of the reaction in which reaction step the catalyst and ligand are added. It turned out, that the yield of **7** slightly increased from 6 to 8% when $FeBr_2$ and PCy_3 were added before the Grignard formation instead of after (Table 6, entries 1 – 2). Yet, these changes are too insignificant to draw mechanistic conclusions. Hence, the catalytic system was further added after formation of the Grignard reagent. When thioester **5** was added in only quarter the amount, implying a theoretical excess of Grignard reagent **3a**, **7** was found in 12% yield (entry 4). A lower concentration of 0.05 M was envisioned to decrease the formation of the homo-coupled side product, but it resulted in similar yields to a 0.1 M reaction mixture (entry 5). With 20 mol% of $FeBr_2$ instead of 10 mol%, a small improvement of 3% was observed (entry 6). Interestingly, the yield could rise to 20% after 24 h. Additional $Fe(acac)_3$ or Grignard reagent **2** only inhibited the formation of **7** (entries 7 – 8).

Although the yield could be increased from 6 to 20%, it is not possible to exclude stoichiometric influence of iron bromide in this reaction. Also, a reproducible protocol for the Grignard formation is necessary to produce meaningful results for comparison. A possible procedure for benzylic alcohols might be the application of [Mg(anthracene)(thf)$_3$] in the formation of Grignard reagents as reported by Gallghaer *et al.*.[59] Another possibility to provide more comparable results, is to use commercially available 2-napthylmethyl magnesium bromide (**3b**). However, it is important to mention that the nature of the halide in Grignard reagents can significantly influence the feasibility of reactions.[64] Therefore, a direct mechanistic conclusion for the one pot reaction depicted in Scheme 11 should be drawn with caution.

Based on the prior investigations, commercial **3b** in diethyl ether was added dropwise in an excess of two equivalents to thioester **5** in toluene, generating a 1:3 diethylether toluene solvent mixture. Quenching with ethanol after 30 minutes yielded **7** in 41% (Table 7, entry 1). Since **5** is generated in 51%, one can conclude that **3b** is active enough to react with thioester **4** but is not so reactive that it undergoes side reactions to a large extent. Sadly, elongation of the reaction time did not lead to higher yields. The addition of iron bromide decreased the formation of **7** a little, which seems to refute the hypothesis of a stoichiometric influence of iron (entry 2). When iron bromide and PCy_3 were added, no major change in yield was observed compared to the non-catalyzed reaction (entry 3). Interestingly, after 24 h an increase in yield of **7** to 50% occurred, which has not been seen earlier. The addition of 3 equivalents of Grignard reagent **3b** led to 1%

of **7** and 46% of **4** and more than 3 equivalents led to no formation of the product (entry 4). This brings us to the conclusion that **3b** rather forms side products in higher concentrations than reacting with thioester **5**.

Table 7: Acylation with commercial Grignard reagent **3b**.



Entry	FeBr$_2$	PCy$_3$	3b [equiv]	Yield 7 [%][a]	Yield 4 [%][a]
1	-	-	2	41 (41)	51 (54)
2	10 mol%	-	2	30 (27)	51 (50)
3	10 mol%	20 mol%	2	44 (50)	51 (51)
4	10 mol%	20 mol%	3	1	46

General reaction conditions: **5** (134 mg, 0.4mmol, 1.0 equiv), **3b** (0.25 M in Et$_2$O, 1.6 mL, 0.8 mmol, 2 equiv.), toluene (3.2 mL), 0 °C – rt, 30 min, FeBr$_2$ (8 mg, 0.04 mmol, 10 mol%), PCy$_3$ (22 mg, 0.08 mmol, 20 mol%), **5** (134 mg, 0.8 mmol, 2.0 equiv.), 0 °C – rt, 24 h, EtOH; [a] Yields were determined *via* quantitative GC-FID; numbers in brackets are yields determined after 24 h reaction time.

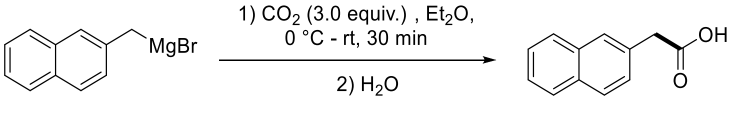
To sum up, Grignard reagent **3b** reacts with thioester **5** just partially and without the need of a catalyst. So, the main problem of this reaction is the full conversion of **3** with **5**, which cannot be activated by iron bromide or the phosphine. This could also explain the moderate yield in the one-pot magnesiation/acylation which never exceeded 41%. Other possibilities to improve the yield would be to find other activation agents or try different solvent systems. When optimized reaction conditions are found, these can be applied in the one-pot magnesiation/acylation reaction to see, if there is any enhancement.

4.3.2. Carbondioxide as Electrophile

Beside the application of thioesters as acylation reagents, insertion of CO$_2$ appears to be an interesting approach for the one-pot magnesiation/acylation reaction of benzylic alcohols. Carbon dioxide is a highly abundant C1-building block, which is characterized by its low toxicity and tremendous potential as a renewable carbon source.[65] Nevertheless, most carboxylation reactions are performed on aryl or benzyl halides, which are either toxic itself or generate toxic waste.[66] Replacement by less harmful and readily available C-O electrophiles is therefore a sustainable alternative to common carboxylation routes. The use of cost-efficient alcohols in cross-coupling reactions with CO_2 *via* C-O bond cleavage, however, is only poorly reported even though this protocol would bear a huge potential of synergetic activation of inert C=O bonds and CO_2.

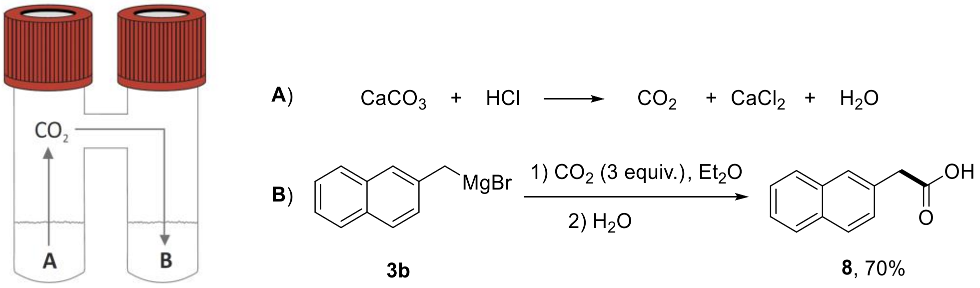
The application of benzylic alcohols in carboxylation reactions with CO_2 was only shown by Senboku *et al.* in 2015 describing an electrochemical carboxylation of benzyl alcohols with electron withdrawing group by using a platinum plate cathode and a magnesium rod anode.[67] The transition-metal cross-coupling reaction with CO_2 *via* benzylic C-O bond activation has been reported 2014 by Correa *et al*[68] and 2015 by Tsuji and co-workers[69] by using Ni catalysis on activated alcohols. In 2019, Mei and coworkers established a nickel-catalyzed carboxylation of phenols by *in situ* activation to aryl fluorosulfates for the generation of benzoic acids.[70] Other direct approaches are not known so far.

For this chapter, a one-pot magnesiation/carboxylation of benzylic alcohols with CO_2 as electrophile was envisioned. As already shown earlier, Grignard reagent **3b** can be used as model compound mimicking the start of the second reaction step in the one-pot reaction. Carbon dioxide can thereby be used in various forms. Besides the common use of a CO_2 gas bottle, the use of dry ice is possible, but also an *ex situ* CO_2 generation from a carbonate and an acid in a two chamber system is a cost-efficient and easy to handle alternative, similar to the *ex situ* CO generation reported by Skrydstrup.[72] Regarding the reactivity of benzylic Grignard reagents, it is known that carbon dioxide as an electrophile does not tend to undergo a rearrangement to the *ortho*-position.[71]



Scheme 19: Carboxylation of Grignard reagent **3b** by addition of dry ice; *reaction conditions:* **3b** (0.15 M in Et_2O, 6.6 mL, 1.0 mmol, 1.0 equiv.), dry ice (123 mg, 3.0 mmol, 3.0 equiv.), Et_2O (0.5 mL), 0 °C – rt, 30 min.

In an initial approach, dry ice was added directly to Grignard reagent **3b** in diethyl ether (Scheme 19). After 30 minutes and a color change from brown over yellow to colorless, aqueous workup was conducted based on literature reports yielding the expected product **8** in 50% yield without further purification.[71] The product has a high boiling point and is not observed on GC chromatograms. For further optimization of the carboxylation, NMR analysis was conducted with dimethyl sulfone as internal standard. An explanation for the only moderate yield of 50% would be the presence of water in the system caused by addition of the dry ice. Water reacts with the Grignard reagent **3b** to **4** (observed *via* GC-analysis), resulting in lower yields. Therefore, in a subsequent experiment dry ice was added to a Schlenk tube with septum and CO_2 was transferred *via* cannula in a second Schlenk tube filled with the Grignard reagent. Unfortunately, quantitative NMR analysis only showed the formation of 5% of **8**.



Scheme 20: Carboxylation of Grignard reagent **3b** in a two-chamber system with *ex situ* generation of CO_2; *reaction conditions:* A) $CaCO_3$ (100 mg, 1.0 mmol, 3.0 equiv.), HCl (6 M, 333 µL, 2.0 mmol, 6.0 equiv.); B) **3b** (0.15 M in Et_2O, 2.0 mL, 0.3 mmol, 1.0 equiv.), Et_2O (0.5 mL), 0 °C – rt, 30 min

In another approach, CO_2 was generated in a two-chamber system by addition of hydrochloric acid to calcium carbonate in chamber A. Then CO_2 was transferred to chamber B, which already contained the Grignard reagent (**3b**) in diethylether. Even though a color change from yellow to colorless was observed in chamber B, compound **8** was not visible in the NMR spectrum. As in the first reaction with dry ice, we assumed that presence of water could be the reason for this. And indeed, when the CO_2 generation was conducted in a second Schlenk tube and CO_2 transfer happened *via* cannula, **8** was obtained in 70% yield. In all reactions, **4** is generated as main side product, implying an incomplete reaction, which is why the reaction time should be elongated in future investigations. Additionally, concentration of the Grignard reagent should be varied, to find the optimal condition to avoid the formation of the homo-coupled product (**17**, Figure 3).

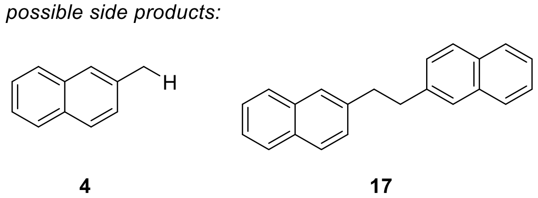
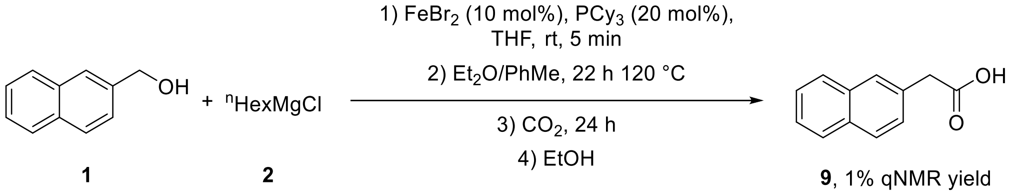


Figure 3: Possible side products of the carboxylation reaction with CO_2.

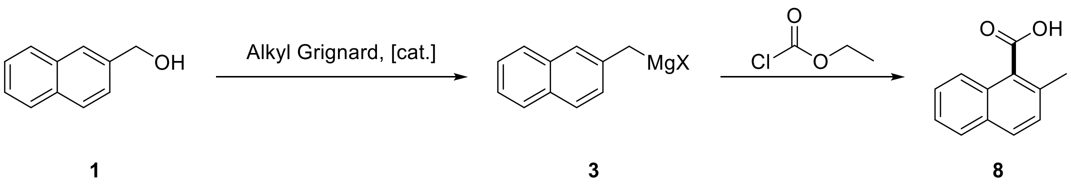
In course of this work it was only once possible to apply these findings in a one-pot magnesiation/carboxylation of **1** with CO_2 similar to the reactions with thioester **5** as shown in chapter 3.1.1.. CO_2 was thereby derived from dry ice and transferred to the reaction mixture after competition of the first reaction step *via* cannula (Scheme 21). Unfortunately, **9** was only observed in traces. However, this is consistent with the reaction starting from **3b** shown in Scheme 19.



Scheme 21: Magensiation and subsequent carbonylation of benzylic alcohol **1** with dry ice; *reaction conditions* **1** (31 mg, 200 µmol, 1.0 equiv.), **2** (1.72 M in THF, 372 µL, 640 µmol, 3.2 equiv.), $FeBr_2$ (4 mg, 20 µmol, 10 mol%), PCy_3 (11 mg, 40 µmol, 20 mol%), THF (1 mL), rt, 5 min, then: Et_2O (0.25 mL), toluene (0.75 mL), 120 °C, 22 h, then: dry ice, 24 h, EtOH.

In following studies on carboxylation of the benzylic position, the reaction should be conducted with pure commercial CO_2 for having a consistent variable. Thereupon, influence of the concentration and the amount of CO_2 can be investigated. With these results in hand, alternative CO_2 generation pathways can be applied and compared.

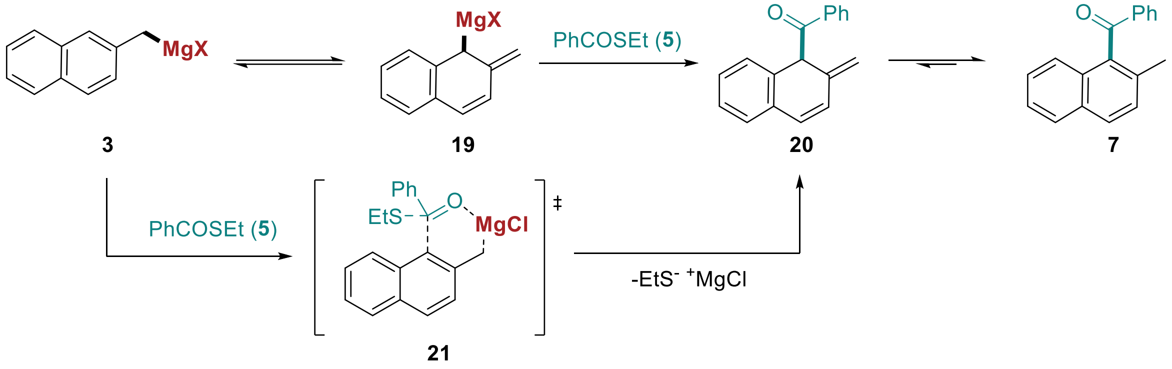
Additionally, new reaction pathways in the C-O bond activations can be addressed by using ethyl chloroformate as electrophile for carboxylation instead of CO_2 (Scheme 22). In 1958, Lawesson *et al.* already reported the use of this compound in the *ortho* carboxylation of benzylic Grignard reagents.[71]



Scheme 22: Acetylchloride as carboxylation agent in the one-pot magnesiation/carbonylation reaction.

4.3.3. Mechanistic Aspects of the Reaction

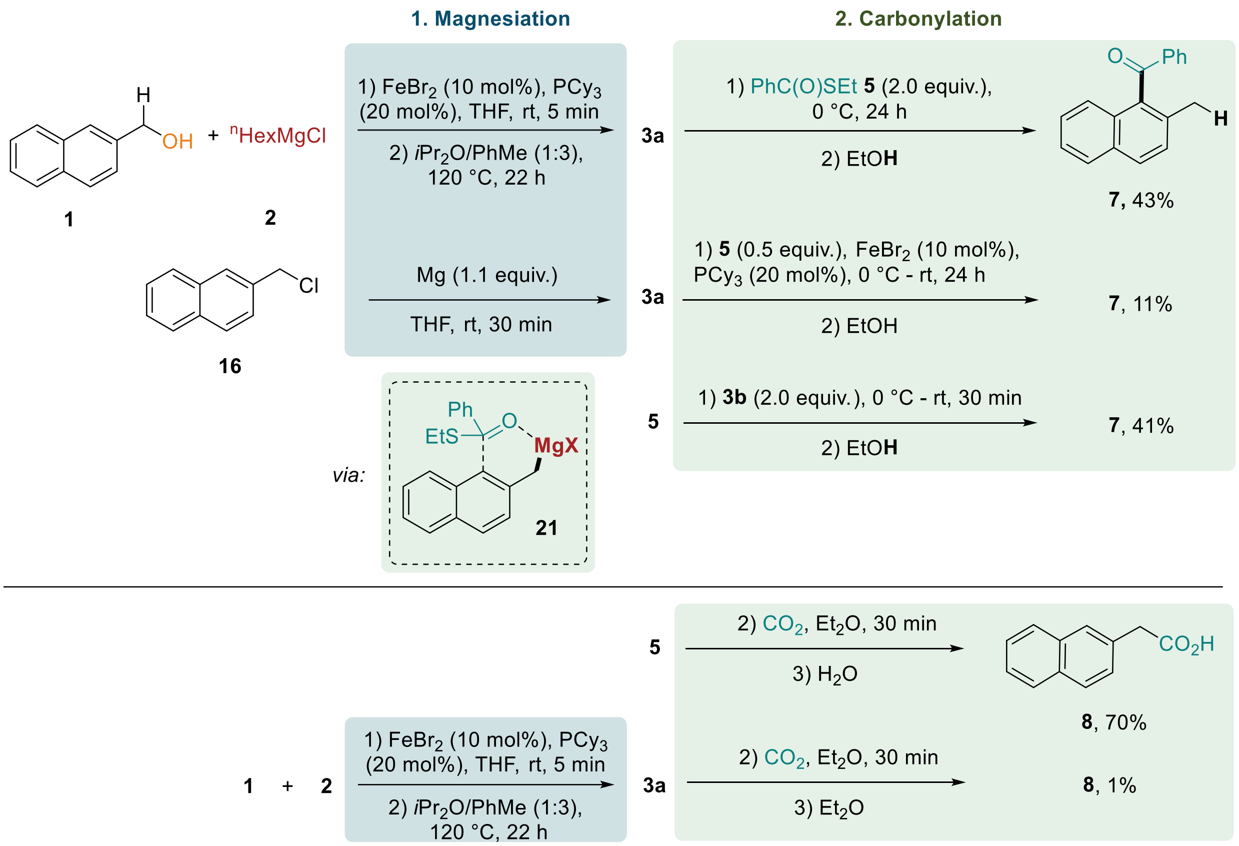
The *ortho*-selective substitution of benzyl Grignard reagent has been reported in a few publications between the 1930's and 1950's[71,73,74] and in two reports from the early 1980's.[61,62] Lawesson *et al.* reported "anomalous" reactions of 2-naphthylmethylmagnesium bromide (**3b**), generated from 2-naphthylmethyl bromide, with various carbon electrophiles.[71] Carbon dioxide and tributyl borate yielded the desired benzylic substitution products, whereas other carbon electrophiles led to substitution in *ortho* position. Sadly, no further explanation for the selectivity of specific electrophiles was reported. Nevertheless, general rearrangements of organomagnesium reagents are known for a couple of substrates and have been reviewed in the 70's.[75]



Scheme 23: Possbile mechanistic pathways for the acetylation with **5**.

Based on our findings and the literature reports, two reaction pathways starting from Grignard reagent **3** are possible (Scheme 23). There could be a dynamic isomerism of the benzylic (**3**) and the quinoid structure (**19**) of the Grignard reagent, in which the latter attacks the electrophile to generate **20** and leads to product **7** after rearomatization. On the other hand, this dynamic isomerism is unlikely, since it would not explain the relation between the nature of the reactant and the rearrangement.[76] Alternatively, a concerted mechanism with a cyclic transition state (**21**) directly from **3** to **20** could occur, following the proposed mechanism after Johnson from 1933.[74] To prove this hypothesis, it should be investigated if other electrophiles that don't bear carbonyl groups undergo similar reactions. Additionally, presence of radicals should be excluded. Mechanistic investigations in 2015 imply a radical reaction pathway for benzylic halide substrates in iron-catalyzed cross-coupling reactions with Grignard reagents. The authors claim that the transmetalation step occurs in advance of oxidative addition, leading to a three-centered concerted mechanism.[77] It is also known that phenyl groups can stabilize carbon-centered π-radicals, which would explain the necessity of the napthyl moiety.[78] Hence, to exclude a radical mechanism in the reaction shown in this work, radical trapping agents have to be employed under the respective reaction conditions.

4.4. Conclusion



Scheme 24: Overview of reactions performed in this chapter.

In this chapter, a known procedure for C-O activation of benzylic magnesium halides was used for the cross-coupling reaction with carbonyl electrophiles to generate ketones (Scheme 24). Therefore, iron bromide and tricyclohexyl phosphine were used as catalytic system for the *in situ* formation of benzyl Grignard reagent **3a** from 2-naphthylmethanol (**1**) with *n*-hexylmagnesium bromide (**2**). When thioester **5** was added as electrophile in the second step of this one-pot magnesiation/carbonylation reaction, an unusual *ortho*-selectivity was observed, which is most likely based on a six-membered transition state (**21**). Friedel-Crafts reaction of 2-napthylmethane (**4**) could be excluded but possible radical pathways still have to be examined in the future. Unfortunately, the yield of this reaction did not exceed 40%, even though various solvent systems, catalysts and ligands as well as amounts, reaction time and temperature have been investigated. Additionally, reproducibility issues made it difficult to draw conclusions from the obtained results.

Subsequently, only the second reaction step was investigated in order to reduce the complexity of the reaction and to gain information of the optimal conditions. Therefore, Grignard reagent **3a** had to be generated, which turned out to be challenging. This is due to the fact that the Grignard formation is highly dependent on the concentration and that benzyl halides generally tend to undergo side reactions as to the formation of the homo-coupled product (**17**). **6a** could only be generated from benzyl halide **16** by addition of $FeBr_2$ and PCy_3. This leads to the assumption that the catalytic system plays a minor role in the second step of the one-pot magnesiation/acylation reaction. However due to the low yields, a stoichiometric effect of $FeBr_2$ and PCy_3 cannot be excluded. A second approach for investigating the second reaction step, was the use of commercial Grignard reagent **3b**, which was added to thioester **5** in absence and in presence of the catalytic system. **6a** was generated in about 40% to 50%, whereas the addition of the catalyst and ligand only showed a small increase in yield over a longer period. With carbon dioxide as electrophile, benzyl substituted product **8** was obtained from Grignard reagent **3b**. Sadly, an initial approach for carboxylation starting from 2-naphthyl methanol (**1**) did not lead to the respective product.

In future investigations, carbon dioxide can be transferred directly as CO_2 gas to provide more comparable results. Additionally, ethyl chloroformate could be used instead of CO_2 for *ortho*-selective carboxylation.

4.5. Experimental Section

4.5.1. General Information

Starting materials and reagents were purchased from Sigma Aldrich, Acros, ABCR, Merck or TCI in reagent or higher grade and used without further purification unless otherwise noted. Solvents were used in p.a. grade for reaction mixtures and column chromatography. All reactions were carried out under an atmosphere of dry argon. All reactions with oxygen- or moisture-sensitive reagents were carried out in glassware, which was dried by heating under vacuum (flame) and cooled under dry Argon. Furthermore, degassed and dry solvents were used where necessary. Dry solvents were prepared according to standard procedures. *n*-Hexylmagnesium chloride (**2**) was commercially obtained from Sigma Aldrich (2.0 M solution in THF) and effective concentration was determined by titration using I_2.[63]

Chromatography

Column chromatography was carried out using silica gel as stationary phase, using either gravity flow or air overpressure. Mobile phases are outlined for each experiment. Thin layer chromatography (TLC) was performed on aluminum plates, pre-coated with silica gel 60 F254 (ALUGRAM Xtra SIL G/UV 254 layer thickness: 0.2 mm) and analyzed by fluorescence quenching under UV-light (254 nm).

4.5.2. Analytical Techniques

Nuclear magnetic resonance spectroscopy (NMR)

NMR spectra were recorded at ambient temperature on a Bruker Avance 400 (^{1}H: 400.13 MHz, ^{13}C: 101 MHz) instrument. Chemical shifts δ are reported in parts per million [ppm] relative to the solvent signal as internal standard (^{1}H: $CDCl_3$: δ = 7.26 ppm; ^{13}C: $CDCl_3$: δ = 77.1 ppm). Coupling constants across bonds are given in *J* (Hz). ^{13}C-NMR spectra were acquired on a broad band decoupled mode. ^{1}H-NMR splitting patterns are assigned as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). ^{13}C signals are assigned as C_q (quaternary carbon), + (primary and tertiary carbon), − (secondary carbon). The assignment resulted from COSY, DEPT-135°, HMBC or HSQC experiments.

Quantitative NMR experiments were conducted with dimethyl sulfone (DMS) as internal standard (STD) in order to determine the yields. The ratio of the normalized integrals (Eq 1) from the NMR spectrum equals the molar ratio (Eq 2).

$$\frac{\mathrm{I(A)}}{\mathrm{I(STD)}} = \frac{\mathrm{A\ (A)}}{\mathrm{A\ (STD)}} \times \frac{\mathrm{N(STD)}}{\mathrm{N(A)}} \text{ (Eq 1)}$$

$$\frac{\mathrm{n(A)}}{\mathrm{n(STD)}} = \frac{\mathrm{m(A)}}{\mathrm{m(STD)}} \times \frac{\mathrm{M(STD)}}{\mathrm{M(A)}} \text{ (Eq 2)}$$

Mass spectrometry

GC-MS was recorded on an Agilent 7820A GC system with Quadrupole MS Agilent 7820A (EI) by using dry hydrogen as carrier gas. Agilent 190915-433UI column (30 m x 250 µm x 0.25 µm) was used. Program: Heating from 50 °C to 280 °C within 15 minutes.

HR-MS was recorded on an Agilent 5977A MSD (EI) instrument at the MS-department of the University of Tübingen.

Gas Chromatography (GC)

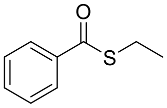
GC-FID (flame ionization detection) analysis was carried out on an Agilent 7820A system using dry hydrogen as carrier gas. Agilent 19091J-431 column (30 m x 320 µm x 0.25 µm) was used. Program 50-280M12: Heating from 50 °C to 280 °C within 12 minutes.

In order to determine yields and conversions the internal standard method was used for quantitative GC-FID. Therefore, calibration was conducted by variation of mass ratio of substrate and standard and analyzing the different samples by GC-FID. From the obtained data the peak area ratio was plotted against the mass ratio of substrate to standard. Linear regression led to the determination of the regression factor R.

$$\frac{m_{sub}}{m_{std}} \cdot R = \frac{A_{sub}}{A_{std}}$$

4.5.3. Experimental Procedures

S-etyl benzothioate (**5**)



The thioester was synthesized *via* Steglich-esterification. A flame-dried 100 mL RBF was charged with benzoic acid (3.7 g, 30 mmol, 1.0 equiv.), which was dissolved in anhydrous CH_2Cl_2 (50 mL). DMAP (366 mg, 3.0 mmol, 0.1 equiv.) and ethanethiol (2.6 mL, 36 mmol, 1.0 equiv.) were added and the reaction mixture was cooled down to 0 °C. After the addition of DCC (6.2 g, 30 mmol, 1.0 equiv.) the mixture was stirred for 30 min at 0 °C and the reaction was completed by stirring overnight at room temperature. Precipitated urea was filtered off and the filtrate was washed with HCl (1 M, 50 mL), saturated solution of $NaHCO_3$ and brine (50 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (gradient CyH → CyH/EtOAc: 95/5) yielding **5** as colorless oil (4.0 g, 24 mmol, 80%).

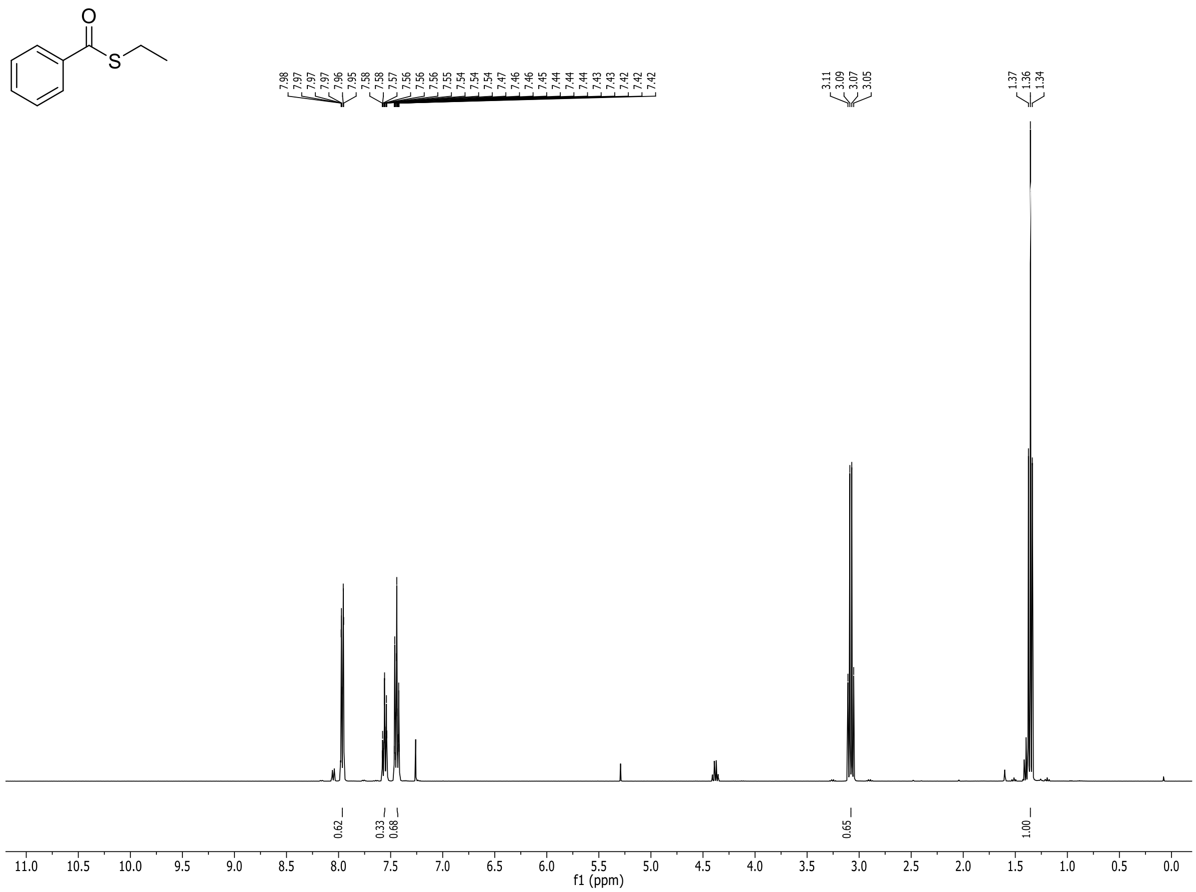
$C_9H_{10}OS$ (166.05 g/mol)

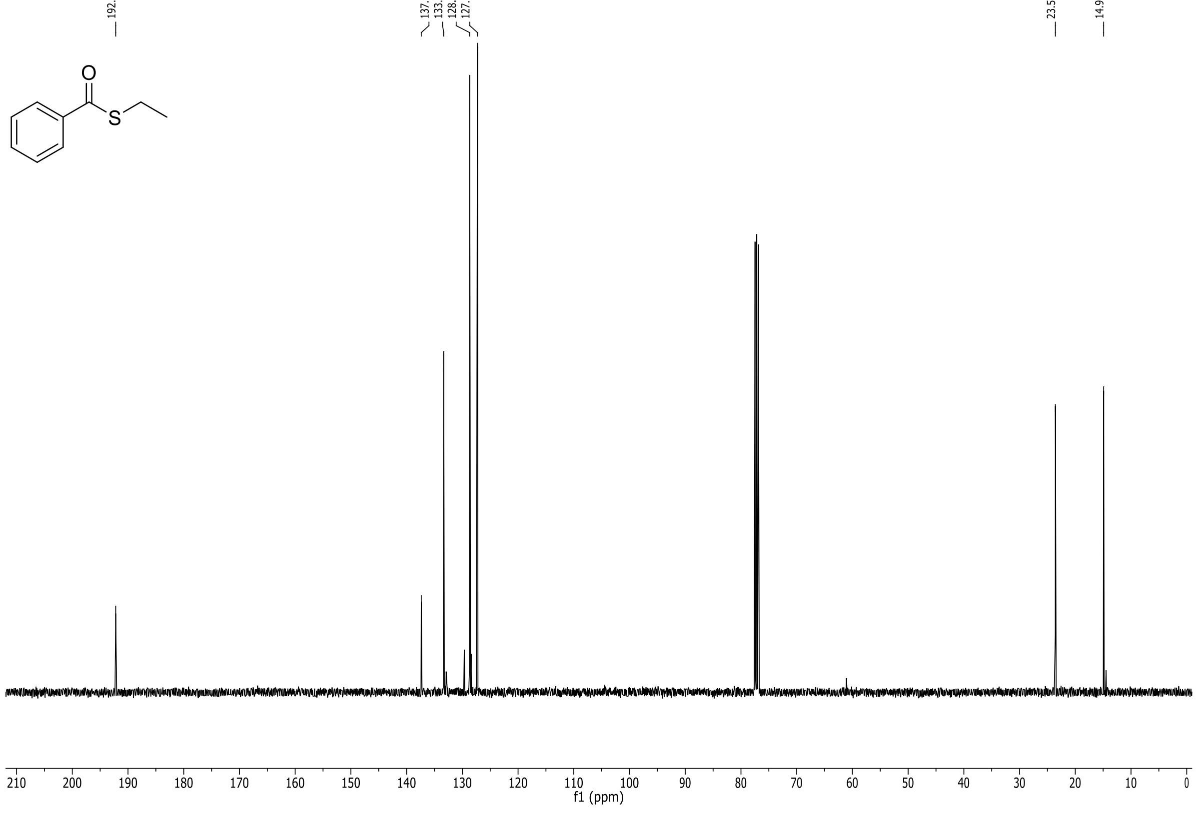
^{1}H-NMR (400 MHz, $CDCl_3$) δ_H/ppm: 8.00 – 7.94 (m, 2H, Ar*H*), 7.60 – 7.54 (m, 1H, Ar*H*), 7.48 – 7.42 (m, 2H, Ar*H*), 3.13 – 3.05 (q, *J* = 7.5 Hz, 2*H*, C*H*$_2$), 1.40 – 1.33 (t, *J* = 7.5 Hz, 3H, C*H*$_3$).

^{13}C-NMR (101 MHz, $CDCl_3$) δ_C/ppm: 192.2 (C_q), 137.4 (C_q), 133.3 (+), 128.7 (+), 127.3 (+), 23.6 (-), 14.9 (+).

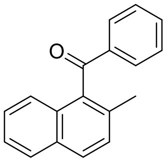
GC-MS (EI): t_R = min, m/z = 166 (4, [$M^{+\bullet}$]), 105 (100, [$M^{+\bullet}$]-[$SEt^\bullet$]), 77 (72, [$M^{+\bullet}$]-[$C_3H_5OS_2^\bullet$]).

The analytical data was in agreement with the literature.[79]


O
S
7.98
7.97
7.97
7.97
7.96
7.95
7.58
7.57
7.56
7.56
7.56
7.55
7.54
7.54
7.54
7.47
7.46
7.46
7.45
7.44
7.44
7.44
7.43
7.42
7.42
7.42
3.11
3.09
3.07
3.05
1.37
1.36
1.34
0.62
0.33
0.68
0.65
1.00
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


192.21
137.37
133.34
128.68
127.28
23.57
14.91
O
S
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

(2-Methylnaphthalen-1-yl)(phenyl)methanone (**6a**)



A flame-dried Schlenk tube was charged with benzoic acid (610.6 mg, 5.0 mmol, 1.0 equiv.) and triflic anhydride (1.0 mL, 6.0 mmol, 1.2 equiv.). Nitromethane (5 mL) was subsequently added *via* syringe and the mixture was heated at 45 °C until all solids were dissolved. Thereupon, 2-napthyl methanol (**1**, 711.0 mg, 6.0 mmol, 1.0 equiv.) was added turning the color red. After the mixture was stirred for 3 min, a saturated solution of $NaHSO_4$ was added. The inorganic layer was extracted with Et_2O (3 × 50 ml) and the combined organic layers where dried over anhydrous $MgSO_4$. The solvent was removed under vacuum. The remaining oil was dissolved in DCM and the solvent was evaporated to remove remaining nitromethane. The crude product was purified *via* flash chromatography (hexane/EtOAc 95:5) providing **5** as yellow oil (810.9 mg, 3.3 mmol, 66%).

$C_{18}H_{14}O$ (246.10 g/mol)

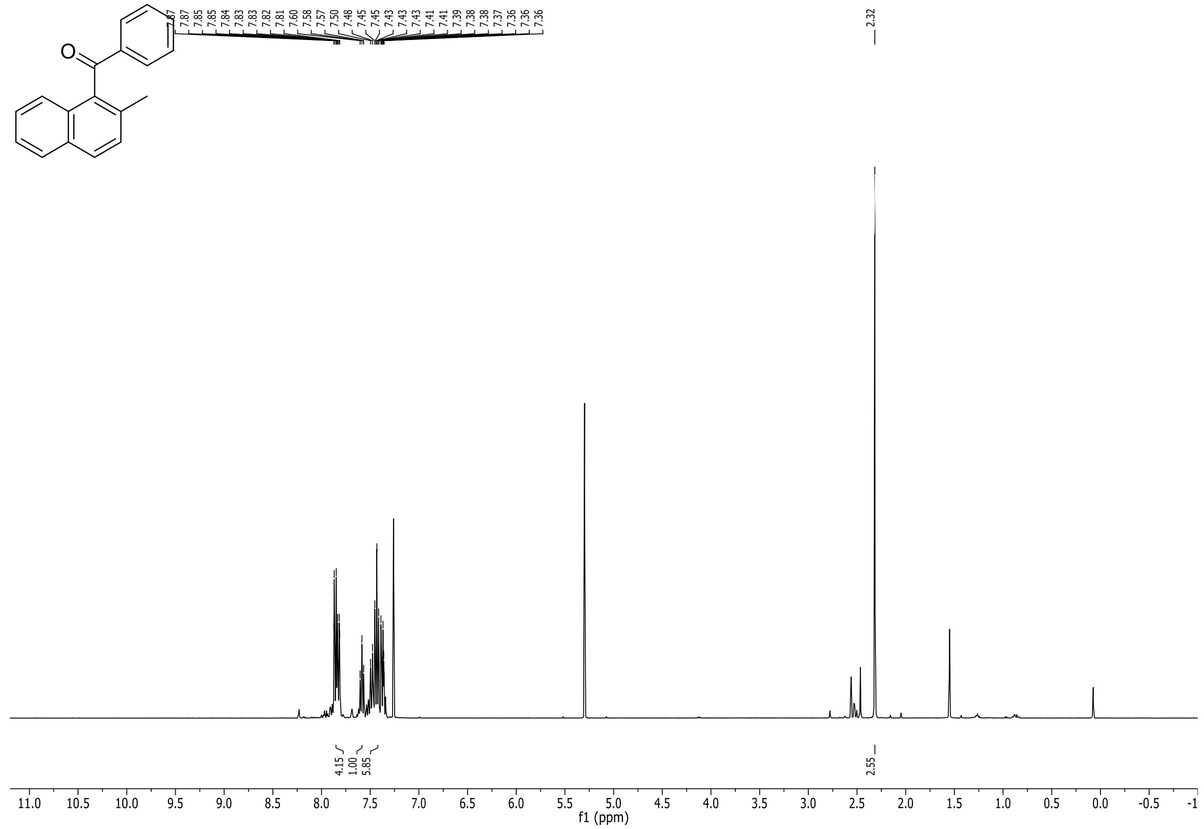
^{1}H-NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.89 – 7.79 (m, 4H, Ar*H*), 7.63-7.55 (m, 1H, Ar*H*), 7.53 – 7.31 (m, 6H, Ar*H*), 2.32 (s, 3H, CH_3).

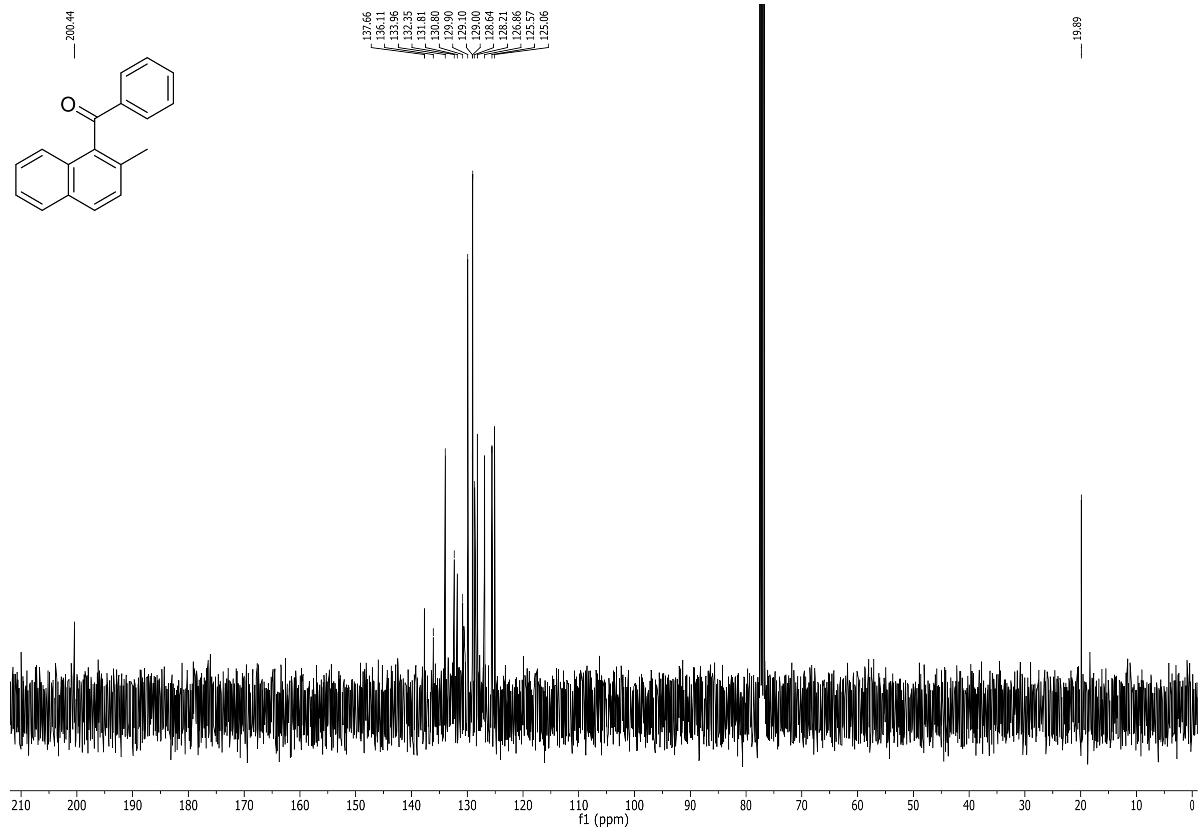
^{13}C-NMR (101 MHz, $CDCl_3$) δ_C/ppm: 200.3 (C_q), 137.7 (C_q), 136.1 (C_q), 134.0 (+), 132.4 (C_q), 131.8 (C_q), 130.8 (C_q), 129.9 (+), 129.1 (+), f129.0 (+), 128.6 (+), 128.2 (+), 126.9 (+), 125.6 (+), 125.0 (+), 19.9 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3052 (w, br), 1662 (s, sh), 1595 (m, sh), 1580 (m, sh), 1505 (m, sh), 1446 (m, sh), 1338 w, sh), 1274 (m, sh), 1244 (s, sh), 1218 (s, sh), 1155 (m, sh), 895 (m, sh), 812 (s, sh), 779 (m, sh), 719 (s,sh).

GC-MS (EI): t_R = 10.08 min, m/z = 246 (87, [$M^{+\bullet}$]), 245 (83,[$M^{+\bullet}$]-[$H^\bullet$]), 229 (19,[$M^{+\bullet}$]-[$O^\bullet$]), 169 (40,[$M^{+\bullet}$]-[$Ar^\bullet$]), 141 (56,[$M^{+\bullet}$]-[$ArCO^\bullet$]), 105 (44,[$M^{+\bullet}$]-[$C_{11}H_9^\bullet$]), 77 (100, [$Ar^\bullet$]).

The analytical data was in accordance with the literature.[80]


O
7.87
7.87
7.85
7.85
7.84
7.83
7.83
7.82
7.81
7.60
7.58
7.57
7.50
7.48
7.45
7.45
7.43
7.43
7.43
7.41
7.41
7.39
7.38
7.38
7.37
7.36
7.36
7.36
2.32
4.15
1.00
5.85
2.55
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1
f1 (ppm)


200.44
137.66
136.11
133.96
132.35
131.81
130.80
129.90
129.10
129.00
128.64
128.21
126.86
125.57
125.06
19.89
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

General Procedure for the one-pot magnesiation/acylation with Thioester **5**:

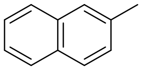
A flame-dried Schlenk tube was charged with **1** (31.6 mg, 200 µmol, 1.0 equiv.). PCy_3 (11.2 mg, 40 µmol, 0.2 equiv.) and $FeBr_2$ (4.3 mg, 20 µmol, 0.1 equiv.) were added in the glovebox. The solids were subsequently dissolved in THF (1 ml) outside of the glovebox and **2** (1.89 M, 372 µL, 640 µmol, 3.2 equiv.) was added, turning the color dark. After stirring for 5 min, the solvent was removed with a cold trap under vacuum at room temperature. The remaining residue was dissolved in *i*Pr_2O (0.25 mL) and toluene (0.75 mL) and afterwards heated to 120 C for 22 h. After the magnesiation step, the mixture was cooled to 0 °C, **5** (66.5 mg, 400 µmol, 2.0 equiv.) was added and then stirred for 24 h. EtOH was added for quenching. For GC-analysis, *n*-pentadecane was added as internal standard and the quenched mixture was filtered over silica gel.

For isolation, EtOH was removed from the quenched reaction mixture and purification by column chromatography (hexane/EtOAc 95:5) yielded the product as yellow oil. Yields and conditions for optimization reactions are outlined in the respective schemes and tables in chapter 3.1.1..

General Procedure for the formation of Grignard **3a** derived from halide **11**:

In a 25 mL pre-heated Schlenk-tube freshly ground Mg (10.7 mg, 440 µmol, 1.1 equiv.) and I_2 for activation were heated for 20 sec with a heat gun, stirred for 10 min and subsequently dissolved in THF (0.2 mL). **11** (70.7 mg, 400 µmol, 1.0 equiv.) was dissolved in THF (1 mL) and added dropwise *via* syringe. When there was no immediate exothermal reaction after the addition of **11**, the flask was additionally heated. The formation of Grignard **3a** is accompanied by a colour change from yellow to colourless to yellow. The mixture was stirred for 30 min at rt and subsequently filtered to remove precipitating magnesium-salts and Mg. The product was obtained as yellow solution in THF and is used without further purification.

For determining the yield of **3a**, the filtered Grignard solution was quenched with ethanol, *n*-pentadecane was added as internal standard and the mixture was analysed by GC-FID. The yield of 2-methyl naphthalene (**4**) was then equate with the yield of **3a**.



$C_{11}H_{10}$ (142.20 g/mol)

GC-MS (EI): t_R = 8.07 min, m/z = 142.1 (38, $[M^{+\bullet}]$), 141.0 (100 ,$[M^{+\bullet}]$-$[H^{\bullet}]$), 126.9 (20, $[M^{+\bullet}]$-$[CH_3^{\bullet}]$), 115.0 (43, $[M^{+\bullet}]$-$[CCH_3^{\bullet}]$).

The analytical data was in accordance with the literature.[36]

General Procedure for the acylation of **3a** with thioester **5**:

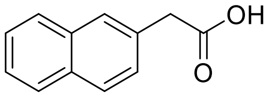
PCy_3 (22.4 mg, 80 µmol, 0.20 equiv.) and $FeBr_2$ (8.6 mg, 40 µmol, 0.10 eq) were added to a pre-heated Schlenk tube in the glovebox. Freshly prepared **3a** Grignard solution (400 µmol, 1.0 equiv.) was added outside of the glovebox and the mixture was cooled to 0 °C. Thioester **5** (133.0 mg, 800 µmol, 2.0 equiv.) and the internal standard were added and the reaction was stirred for 24 h, allowing the mixture to come to rt. Subsequently the reaction was quenched with EtOH and filtered over silica gel for GC-analysis.

Change of the solvent system was conducted before the addition of **5** by removing THF with a cold trap under vacuum at room temperature and following addition of the respective solvents. When **1** was used as additive, it was added before **3a**, whereas additive **2** was added together with **3a**.

General Procedure for the acylation of **3b** with thioester **5**:

PCy_3 (22.4 mg, 80 µmol, 0.20 equiv.) and $FeBr_2$ (8.6 mg, 40 µmol, 0.10 eq) were added to a pre-heated Schlenk tube in the glovebox. The solids were dissolved in toluene (3.2 mL) outside of the glovebox and **3b** (0.25 M in Et_2O, 1.6 mL, 400 µmol, 1.0 equiv.) was added. The mixture was cooled to 0 °C. Thioester **5** (33.3 mg, 200 µmol, 0.5 equiv.) and the internal standard were added, and the reaction was stirred for 24 h, allowing the mixture to come to rt. Subsequently, the reaction was quenched with EtOH and filtered over silica gel for GC-analysis.

2-(Naphthalene-2-yl)acetic acid (**13**)



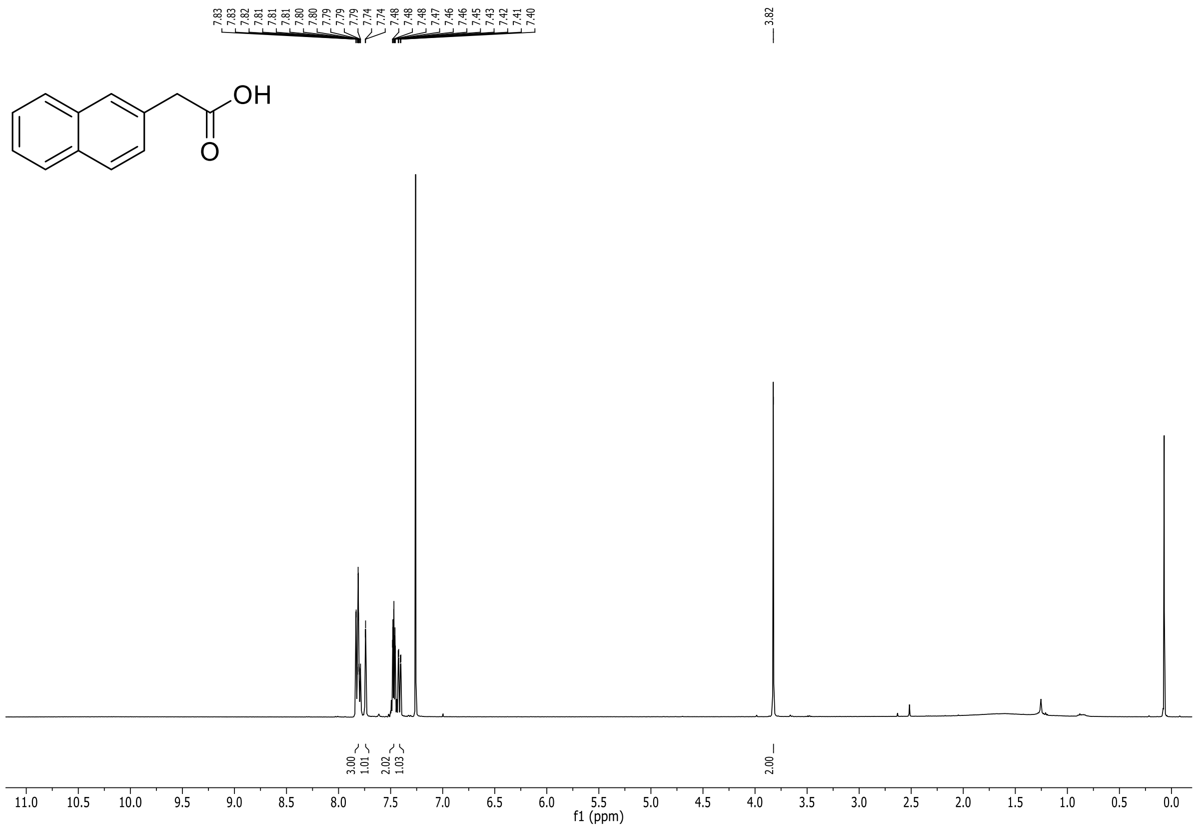
3b (0.15 M in Et_2O, 6.6 mL, 1.0 mmol, 1.0 equiv.) was cooled to 0 °C in a pre-heated Schlenk tube. In a second Schlenk tube dry ice (132 mg, 3.0 mmol, 3.0 equiv.) was added to dry Et_2O (0.5 mL) at 0 °C and the prior cooled **3b** solution was added to the reaction mixture, turning the color from yellow to colorless. The mixture was allowed to come to rt and was subsequently quenched with H_2O. The aqueous phase was extracted three times with Et_2O and combined organic layers were washed with an aqueous saturates solution of NaOH. Acidification with 1 M HCl resulted in a precipitation of the product, which was filtrated, dissolved in Et_2O and dried over $MgSO_4$. Removal of solvent yielded the product as colorless solid (93 mg, 0.5 mmol, 50%).

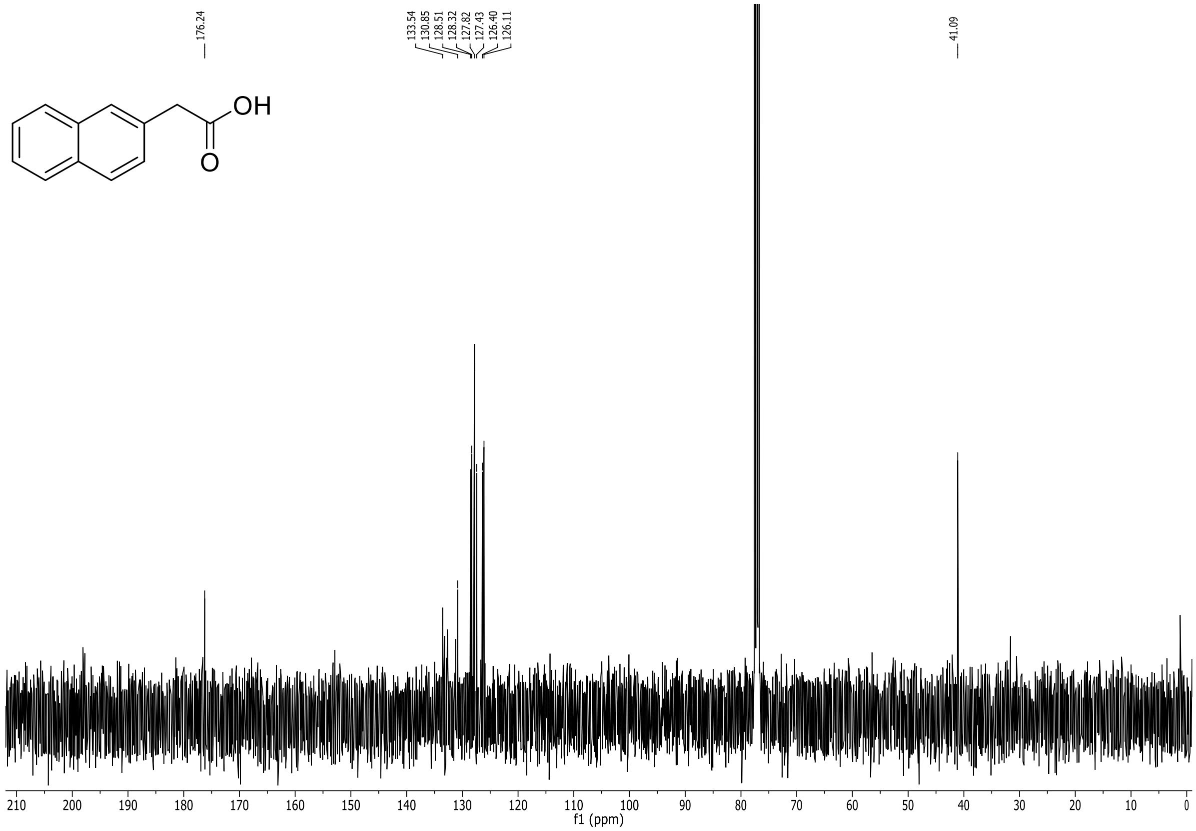
$C_{12}H_{10}O_2$ (186.21 g/mol)

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.85 – 7.77 (m, 3H, Ar*H*), 7.77 – 7.73 (s, br, 1H, Ar*H*), 7.49 – 7.45 (m, 2H, Ar*H*), 7.41 (dd, *J* = 8.4, 1.8 Hz, Ar*H*), 3.82 (s, 3H, C*H*$_3$).

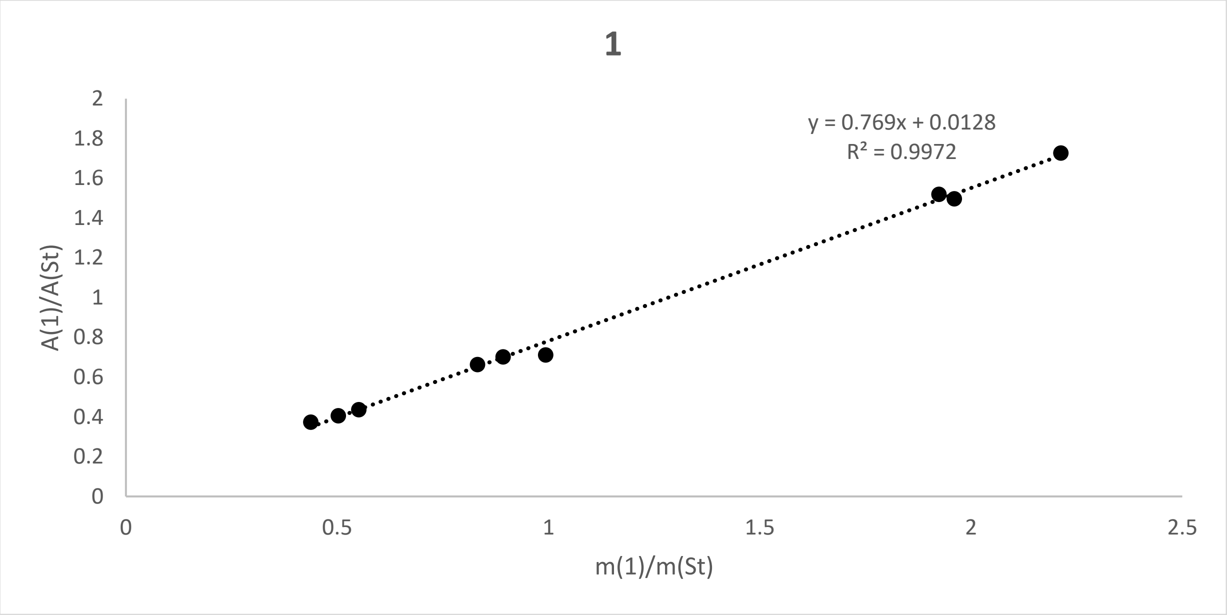
^{13}C-NMR (101 MHz, $CDCl_3$) δ_C/ppm: 176.2 (C_q), 133.5 (C_q), 130.9 (C_q), 128.5 (+), 128.3 (+), 127.8 (+), 127.4 (+), 126.40 (+), 126.11 (+), 41.09 (+).

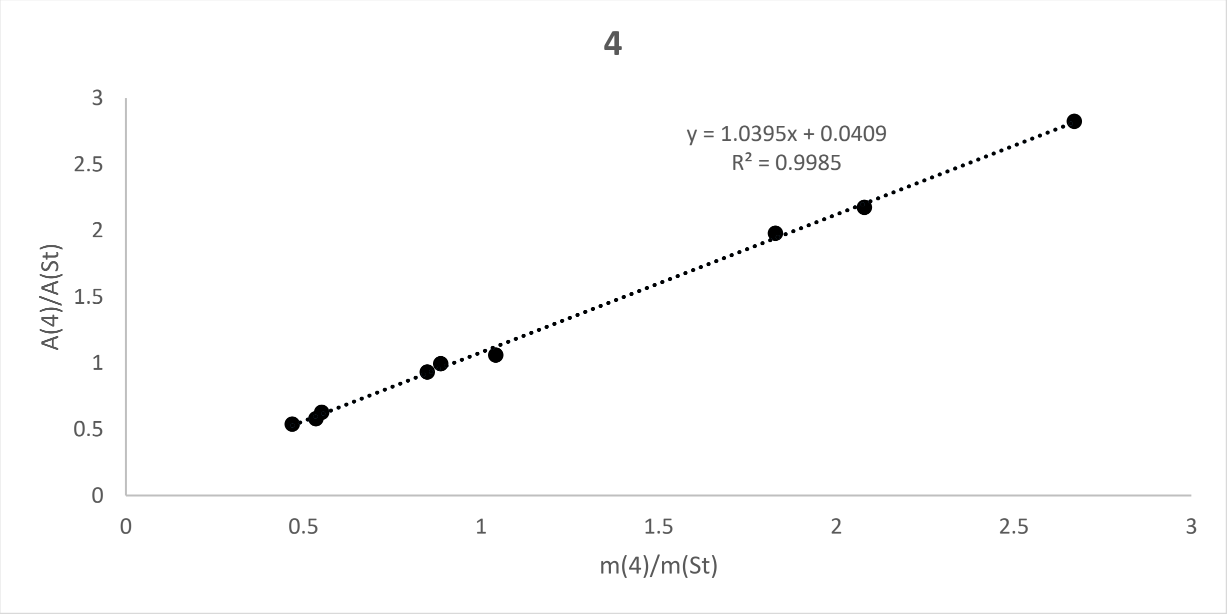
The analytical data was in accordance with the literature.[81]

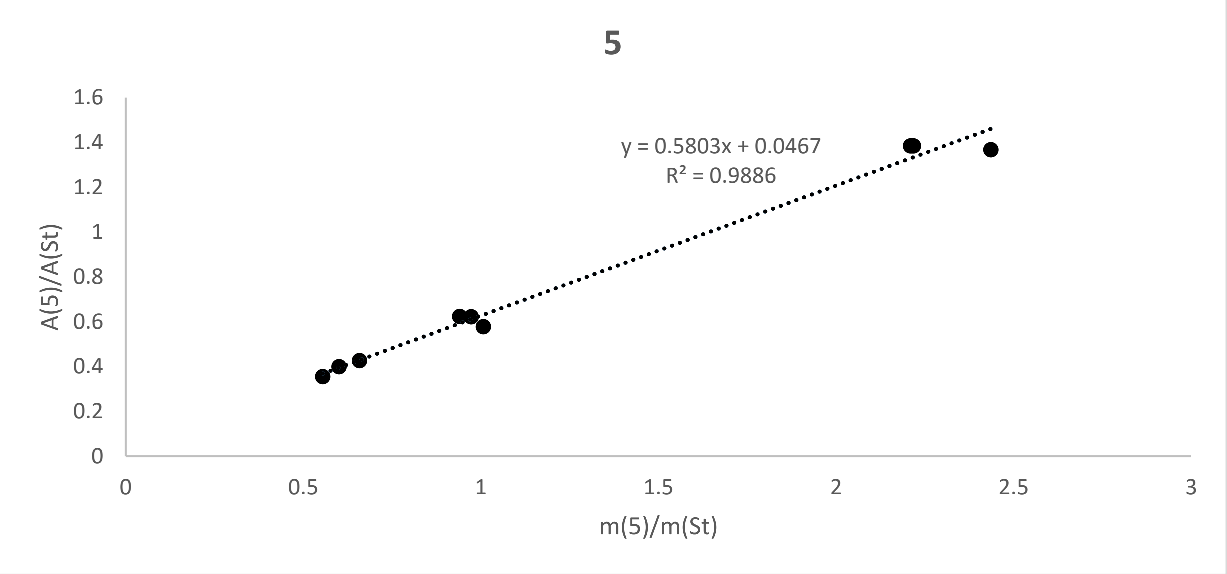

7.83
7.83
7.82
7.81
7.81
7.81
7.80
7.79
7.79
7.79
7.74
7.74
7.48
7.48
7.48
7.47
7.46
7.46
7.45
7.43
7.42
7.41
7.40
3.82
OH
O
3.00
1.01
2.02
1.03
2.00
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

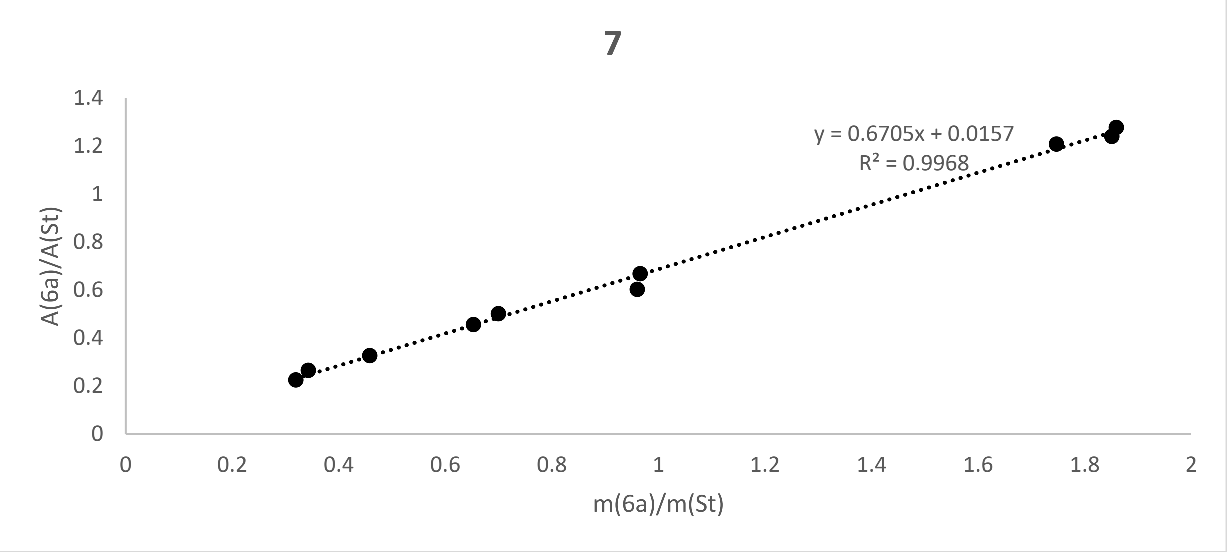

176.24
133.54
130.85
128.51
128.32
127.82
127.43
126.40
126.11
41.09
OH
O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

4.5.4. GC-FID Calibration Data






5
y = 0.5803x + 0.0467
R² = 0.9886
A(5)/A(St)
m(5)/m(St)
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
0
0.5
1
1.5
2
2.5
3


7
y = 0.6705x + 0.0157
R² = 0.9968
A(6a)/A(St)
m(6a)/m(St)
0
0.2
0.4
0.6
0.8
1
1.2
1.4
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
2

4.6. Literature

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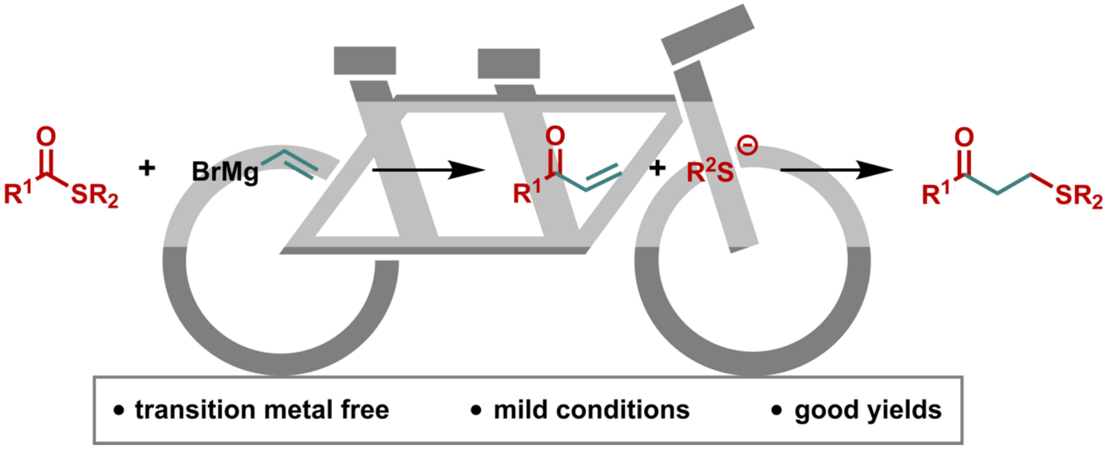
5. Tandem Acyl Substitution/Michael Addition of Thioesters with Vinylmagnesium Bromide



Abstract: A tandem reaction of thioesters with vinylmagnesium bromide is reported. The initial acyl substitution provides an α,β-unsaturated ketone, which further reacts with the liberated thiolate. This transition metal free synthesis of β-sulfanyl ketones is taking place under mild reaction conditions, whereas the addition of a second Grignard molecule is almost completely suppressed. The carefully chosen parameters enabled the transformation of many different substrates in moderate to good yields.

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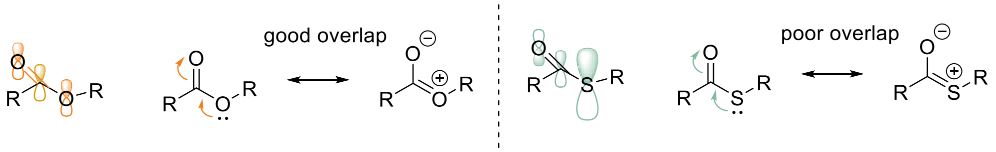
Author contribution:

Dr. Vera Hirschbeck and I equally contributed to the project in terms of scientific ideas, data generation, analysis and interpretation as well as paper writing. Paul Henry Gehrtz was involved in the synthesis of the starting materials (10%) and Jun.-Prof. Ivana Fleischer is corresponding author.

5.1. Introduction

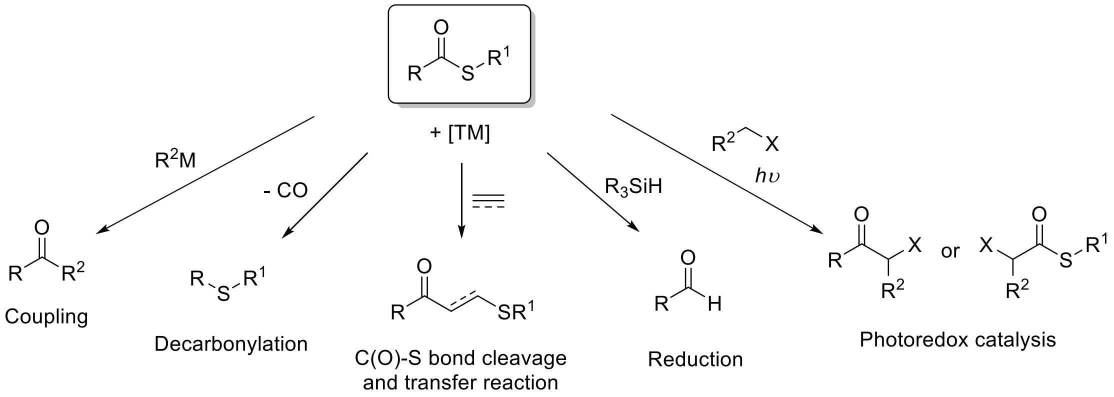
5.1.1. Characteristics and Application of Thioesters

Thioesters are found in many fundamental biochemical processes as in the citric acid cycle[3] and in polyketide biosynthesis[4] and hence constitute an important part for the development of life. They are as reactive as acyl chlorides and therefore in principle more reactive than alcohol-derived esters. This is because of a poorer orbital overlap between the p-orbital of the sulfur atom and the π^*-orbital of the carbonyl group in thioesters (Scheme 1). Therefore, the α-anion is better stabilized and the carbon atom of the carbonyl group is more reactive towards nucleophiles, resulting in a faster enolization of thioesters. In the Claisen ester condensation for example, milder reaction conditions are necessary to generate higher yields compared to oxo-esters based on faster reaction steps.[5]



Scheme 1: Comparison of the reactivity of thioesters and oxoesters.[6]

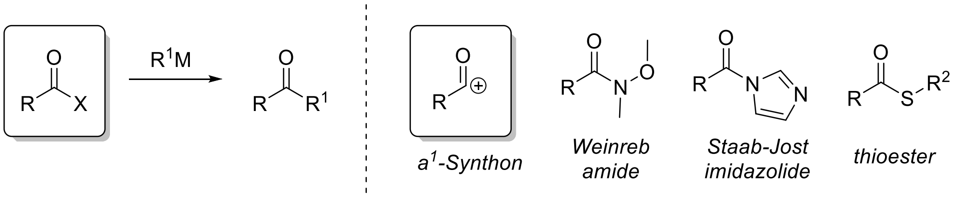
Various procedures based on acylations[7] or metal-catalyzed reactions[8] can be used to synthesize thioesters, which are also bench stable and storable for a long time. Therefore, they are highly significant in manifold synthetic applications.[6,9] One of the most prominent use is the native chemical ligation method for connecting peptides.[10] In organic chemistry, thioesters are typically applied in acyl substitutions and aldol chemistry. But their chemistry is much more diverse especially due to their special reactivity. Especially transition-metal-catalyzed reactions with thioesters are known. Pd-catalyzed CO extrusion of thioesters for example has been reported in the 80's by Yamamoto and co-workers.[11] Other reported decarbonylative reactions were coupled with simultaneous desulfenylation[12] or on simultaneous fragmentation.[13] Beside decarbonylation reactions, the C(O)-S bond of thioesters can be cleaved *via* transition-metal catalysis and the acyl as well as the thiol moieties can be both subsequently transferred to the reaction partner. Functionalized arenes, heterocycles and unsaturated compounds have already been proven as successful reaction partners in these kind of reactions.[14] Thioesters can also be reduced as shown by Fukuyama and co-workers, who used triethylsilane as reducing agent in a Pd-catalyzed synthesis of aldehydes.[15] Additionally, photoredox catalysis in combination with transition metal catalysis can be used for the activation of the C(O)-C or the C(O)-S bond of thioesters.[16] One other application of thioesters are coupling reactions for the formation of ketones (also shown in Chapter 4), which will be discussed in the following.



Scheme 2: Possible metal-catalzed applications of thioesters; [11] Adapted from Hirschbeck *et al*.[6]

5.1.2. Ketone Synthesis from Thioesters

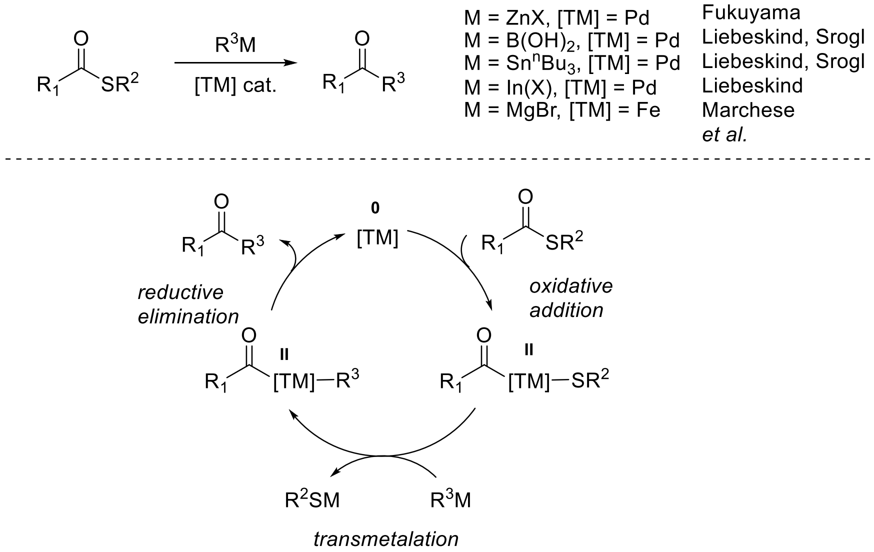
For the synthesis of ketones, nucleophilic substitution with numerous carboxylic acid derivatives and organometallic reagents has been intensively investigated.[17,18] The main issue in these reactions is the control of chemoselectivity. By a second attack of the C-nucleophile to the desired ketone an undesired tertiary alcohol is generated. To overcome the problem of overaddition, the application of Weinreb amides[18] or Staab-Jost imidazolines[19] as a^1-synthons are traditional methods to generate ketones selectively by formation of a chelate intermediate (Scheme 3). Compared to oxoesters, thio-esters are generally less affected by this problem, due to the fact that they are more reactive than the resulting ketones. The second attack of the C-nucleophile can only be inhibited by an inconvenient controlled slow addition of the nucleophile.



Scheme 3: Ketone synthesis from coupling reaction with a¹-synthons. Adapted from Hirschbeck *et al*.[6]

5.1.2.1. Transition-metal Catalyzed Ketone Synthesis

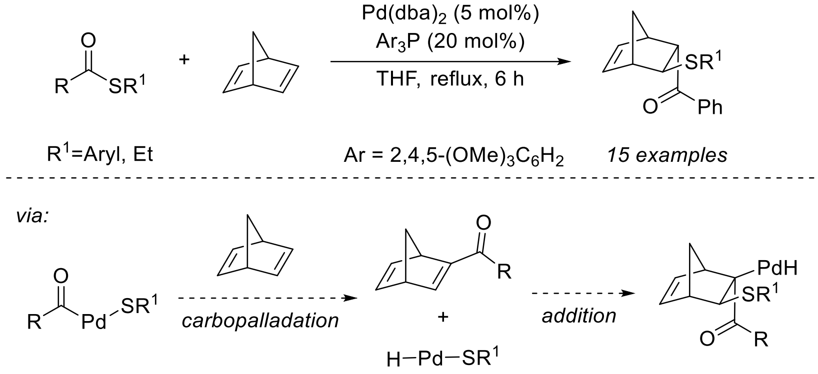
Especially transition-metal catalysis is known to be a selective tool for the synthesis of ketones from thioesters. In the catalytic cycle, after the oxidative addition of the transition metal into the C(O)-S bond, a transmetalation with an organometallic compound occurs. Subsequent reductive elimination furnishes the ketone chemoselectively (Scheme 4). It should be noted, that various effects can influence the success of the ketone synthesis, as for example the thiophilicity of the stoichiometric organometallic species. The thiophilicity increases from boron over silicon, magnesium, lithium and zinc to copper as metal species and can influence the thermodynamics in the transmetalation step.[20] In particular with late, thiophilic transition metals, a poisoning effect with the liberated thiolate can occur.[6]



Scheme 4: Transition-metal-catalyzed cross-coupling reacion.

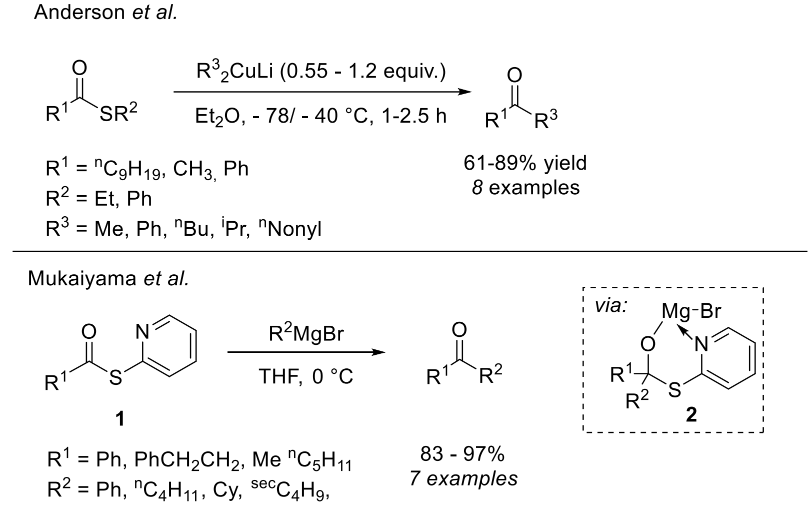
In their pioneering reports, Fukuyama, Liebeskind and Srogl pubished diverse coupling reactions with different organometallic compounds (based on Zn, B, Sn, In) catalyzed by a palladium complex.[21–24] In the initial ketone synthesis of Fukuyama from 1998, which was later named Fukuyama coupling, a *S*-ethyl thioester was converted with excellent functional group tolerance by applying primary alkyl- and aryl zinc reagents in presence of $PdCl_2(PPh_3)$ as catalyst under mild reaction conditions.[23] In the Liebeskind-srogl coupling, which was disclosed two years after Fukuyama's discovery, arylboronic acids were used as organometallic species in the transmetalation mediated by a Cu(I) source to facilitate the Pd-S bond cleavage.[22] Interestingly, this reaction could also be conducted with organostannates[24] and organoindium,[21] whereas with the latter, no copper mediation is needed, which points out the influence of the thiophilicity as described above. Beside palladium-catalyzed ketone synthesis, also nickel-catalyzed versions were reported. In 2002, the use of $Ni(acac)_2$ and a zinc reagent was described by Seki and Shimizu as step in the synthesis of (+)-Biotin.[25] Other Ni-catalyzed ketone synthesis from thioesters are either based on the use of organozinc or organomanganese species.[26,27] Contrary to organozinc and organomanganese species, highly polar organometallc species as RLi or RMgX are generally disfavored in the synthesis of ketones from thioesters. This is due to the fact that they should react with the formed ketone product. Marchese *et al.* however, could show that the application of Grignard reagents is suitable for iron catalysis.[28] They employed $Fe(acac)_3$ as catalyst in 4.2 mol% and 1.4 equiv. of a primary, secondary or aromatic Grignard reagent at 0 °C in THF, generating ketones on good to excellent yields.

Another possible way to generate ketones *via* transition-metal catalysis from thioesters is a C(O)-S bond cleavage and transfer reaction, which are defined as transfer of both the acyl and the thiol moieties to a functionalized arene, heterocycle or unsubsituted compound. In 2015, Yamaguchi and co-workers reported a thioacylation of norbornenes to the respective *trans*-product catalyzed by $Pd_2(dba)_3$ (dba = dibenzylideneacetone) and tris(2,4,6-trimethoxyphenyl)phosphine as ligand (Scheme 5).[29] In a proposed mechanism, oxidative addition of the thioester onto Pd(0) to a Pd(II) intermediate is followed by a carbopalladation generating a thiopalladium(II)hydride and an enone. Subsequent addition and reductive elimination provides the desired ketone and regenerates the Pd catalyst.



Scheme 5: Pd-catalyzed ketone synthesis from thioesters *via* carbopalladiation and addition.[29]

5.1.2.2. Transition-metal-free Ketone Synthesis



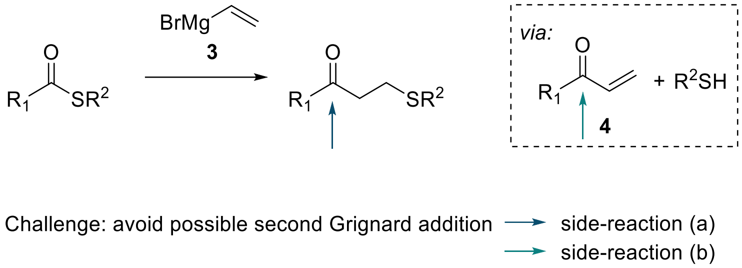
Scheme 6: Uncatalyzed ketone synthesis from thioester.

One disadvantage of transition-metal catalyzed routes to the formation of ketones from thioesters, is the relatively high price of transition metals. Hence, transition-metal free versions of this reactions are of considerable interest. In 1974, Anderson, Henrick and Rosenblum developed a copper mediated ketone synthesis from S-alkyl and S-aryl thioesters (Scheme 6).[30] They initially employed organocopper(I) complexes like (^{n}Bu)$_2$CuLi in 0.55 equiv at –40 °C in Et$_2$O generating the desired ketone in 89% yield after 2 h. The use of 1.0 equiv of ^{n}BuMgBr at 0 °C and ^{n}BuLi at –78 °C however, led to a second nucleophilic attack to the tertiary alcohol, which was formed in equal amounts as the remaining starting material. Interestingly, with the application of

^{n}BuMgBr•CuI and ^{n}BuLi•CuI the desired product was gained in over 78% yield and formation of the tertiary alcohol was completely suppressed.

A successful transition-metal free carbon-carbon bond forming reaction of *S*-(2-pyridyl) thioates (**1**) with Grignard reagents in THF was reported by Mukaiyama *et al.* in 1973 (Scheme 6).[31] They were able to suppress the generation of a tertiary alcohol by the formation of a six-membered complex **2**, due to stabilization by coordination of the nitrogen to the magnesium ion. The resulting complex is reacting with a second Grignard reagent very slowly compared to the starting material, enabling a selective ketone generation. Hence, 2-pyridyl thioesters can be regarded as alternatives to Weinreb amides.[18] The principle was also applied in the synthesis of dihydrojasmone.[31]

5.2. Aim



Scheme 7: Transition metal-free tandem-reaction (nucleophilic substitution and Michael addion.

In this chapter, a transition metal free tandem reaction of thioesters with vinylmagnesium bromide (**3**) under mild reaction conditions is reported (0 °C, 1 h) (Scheme 7). An initial nucleophilic substitution of the thioester with **3** generates the Michael acceptor **4**, followed by a nucleophilic addition of the free thiolate to furnish β-sulfanyl ketones, which show unique synthetic[32] and also potential medical[33]applications. We also proposed the formation of a six-membered complex, which enables a chemoselective formation of ketones, whereas overaddition is almost completely suppressed. This reactivity was also inadvertently observed by Chen *et al.* in the synthesis of (+)-Biotin.[34] In the application of other Grignard reagents no selective ketone formation was observed, which emphasizes the unique reactivity of **3**.[35]

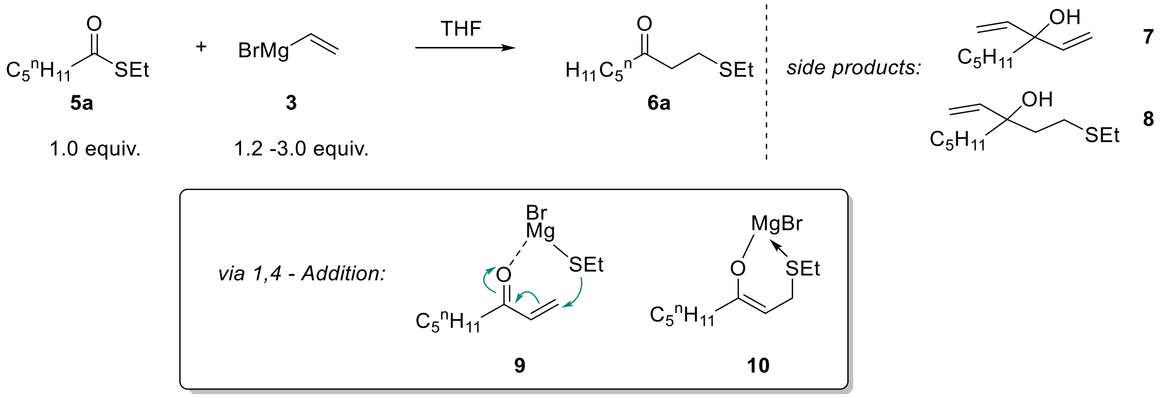
5.3. Results and Discussion

5.3.1. Optimization Experiments

The first experiments were performed using thioester **5a** and vinylmagnesium bromide (**3**) in THF. At the beginning of this project, we struggled with reproducibility problems. We came to the conclusion that crystallization of **3** from the reaction mixture, which can already take place below 25 °C, might be the source of the problem. Since crystallization is strongly influenced by purity and temperature, it is extremely important to ensure the same conditions for each reaction. Therefore, the batch of purchased vinylmagnesium bromide (different purities), cooling system (different cooling capacity of Dewar and crystallizing dish) and reaction flask (different wall thickness and volume of the flask) might influence crystallization and cannot be varied during the comparison of different reaction parameters. Thus, every new batch of **3** was applied in a test reaction in order to see if the yield has changed. If crystallization is taking place, the problem can be overcome by increasing the amount of solvent.

In the initial optimization using **5a** as a test substrate, different temperatures, reaction times, equivalents of Grignard reagents and additives were tested (Table 1). As expected, no reaction was observed at –78 °C, because vinylmagnesium bromide crystallized instantly. On the other hand, side-reactions become more likely at room temperature, resulting in yield of only 51% (Table 1, Entry 4). The best result was observed at 0 °C (Table 1, Entry 3), providing **6a** in 75% yield with almost full conversion of thioester. Since a lower amount of Grignard reagent might prevent a second attack of vinylmagnesium bromide either to product **6a** or to the intermediate **4**, 1.2 equiv. and 2.0 equiv. of **3** were applied. However, the yields dropped significantly (Table 1, Entries 5, 6). The combination of a low concentration of the substrate (0.12 mol/L) and a large excess of the Grignard reagent could facilitate side-reaction (b) (Scheme 7), which might be avoided by the addition of external EtSH (Table 1, Entry 7). Interestingly, lower amounts of the product were formed. Despite the small concentration of free thiolate, the high selectivity for the nucleophilic addition of EtSH instead of **3** to the Michael acceptor **4** is remarkable. Therefore, we suggest the formation of chelate **10** *via* 1,4-addition of intermediate **9**, in which the thiol is not leaving the coordination sphere and is able to attack the Michael-acceptor rapidly.

Table 1: Initial Optimization



Entry	T (°C)	t (h)	3 (equiv.)	additive	Conv. (%)	Yield (%)
1	-78	1	3	-	0	0
2	-10	1	3	-	89	73
3	0	1	3	-	97	75
4	rt	1	3	-	100	51
5	0	1	1.2	-	70	48
6	0	1	2	-	88	64
7	0	1	3	EtSH[a]	92	66
8[b]	0	1	3	-	99	65
9	0	1	3	LiCl[c]	96	74
10	0	2	3	-	100	64
11	0	4	3	-	99	65

Reaction conditions: **5a** (163 mg, 1.02 mmol, 1.0 equiv.), **3** (0.89 M in THF), THF (5 mL), yields and conversions were determined by quant. GC-FID using *n*-pentadecane as an internal standard; [a] EtSH (1.0 equiv.); [b] THF (1 mL); [c] LiCl (0.2 equiv.).

Lowering the amount of solvent and thereby increasing the substrate concentration leads to lower yield due to the partial crystallization of **3**, which was observed during the reaction (Table 1, Entry 8). LiCl might accelerate the nucleophilic attack to **5a** or **4** (Table 1, Entry 9) or modulate the reactivity of **3**,[36] but no effect was observed. Longer reaction time led to decomposition (mainly overaddition) of the product under the reaction conditions. The general difference between conversion and yield can be explained by the formation of small amounts of several different side products, which were observed by GC-MS of the crude mixture, but could not be assigned.

5.3.2. Reaction Profile

Since the reaction time plays an important role, the reaction progress was evaluated, in order to find the optimum between product formation and degradation (Figure 1). Indeed, highest yield and full conversion were observed after one hour. In the further course of the reaction, the side reactions became prevalent. Interestingly, by treatment of isolated **6a** with vinylmagnesium bromide (3.0 equiv.) in THF at 0 °C for 1 h, **8** was generated in 83% (100% conversion). In the reaction progress study only 11% of the product reacted with the remaining Grignard reagent. Therefore it can be assumed that chelate **9** is formed in the reaction mixture, which impedes the attack of the second vinylmagnesium bromide molecule. In conclusion, the best result was observed using 3.0 equiv. of **3** at 0 °C for 1 h. **6a** was generated in a yield of 75%, which is satisfying for a two-step tandem reaction.

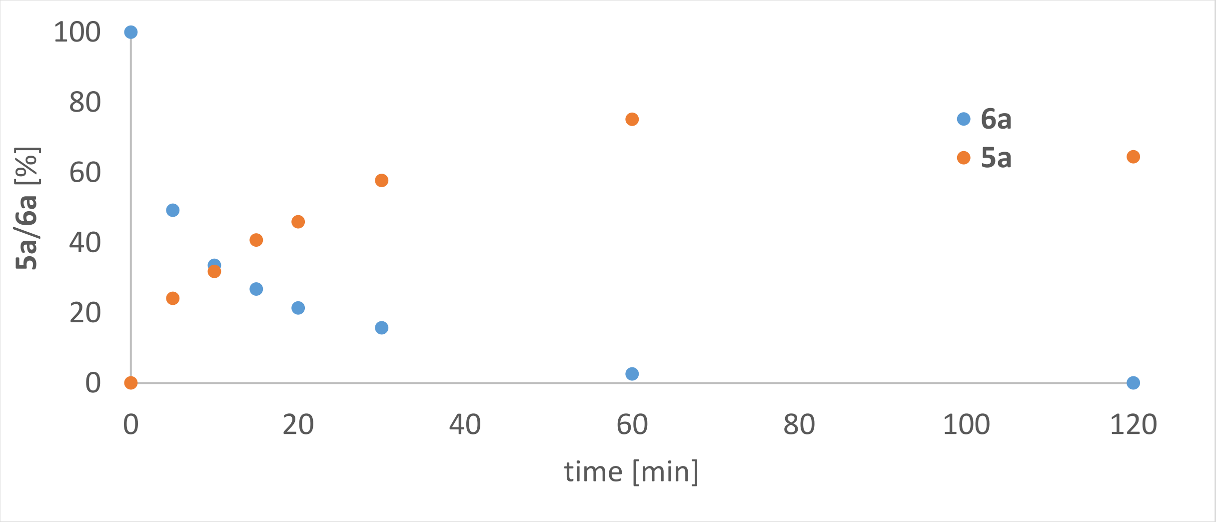
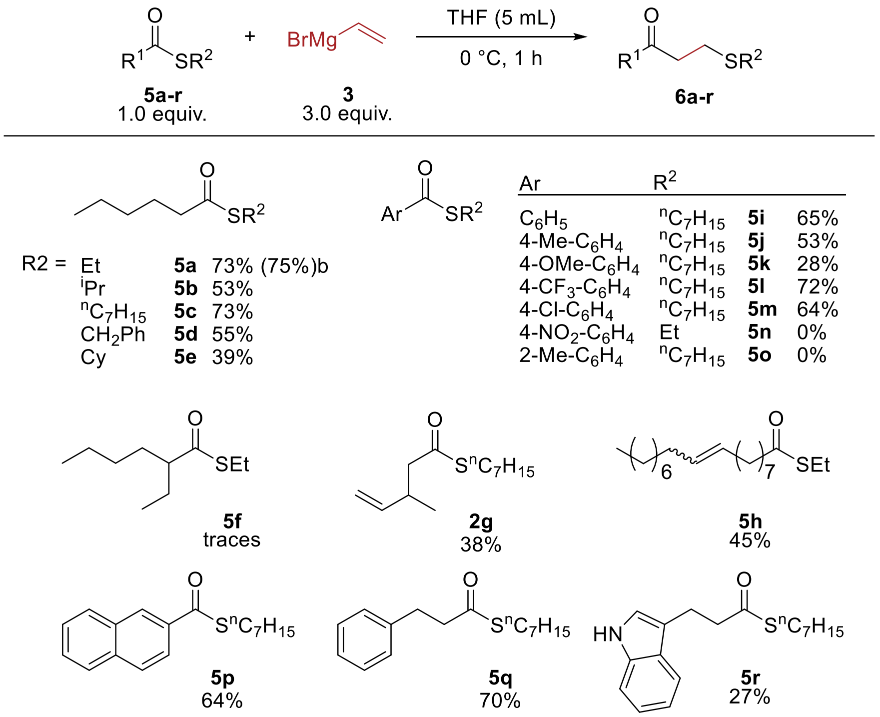


Figure 1: Reaction profile for the conversion of **5a** with vinylmagnesium bromide (**3**). *reaction conditions:* **5a** (160 mg, 998 µmol, 1.0 equiv.), **3** (0.52 – 0.89 M in THF, 3.0 equiv.), THF (5 mL), 0 °C, 1 h. Yields were determined by quant. GC-FID using *n*-pentadecane as an internal standard.

5.3.3. Substrate Screening

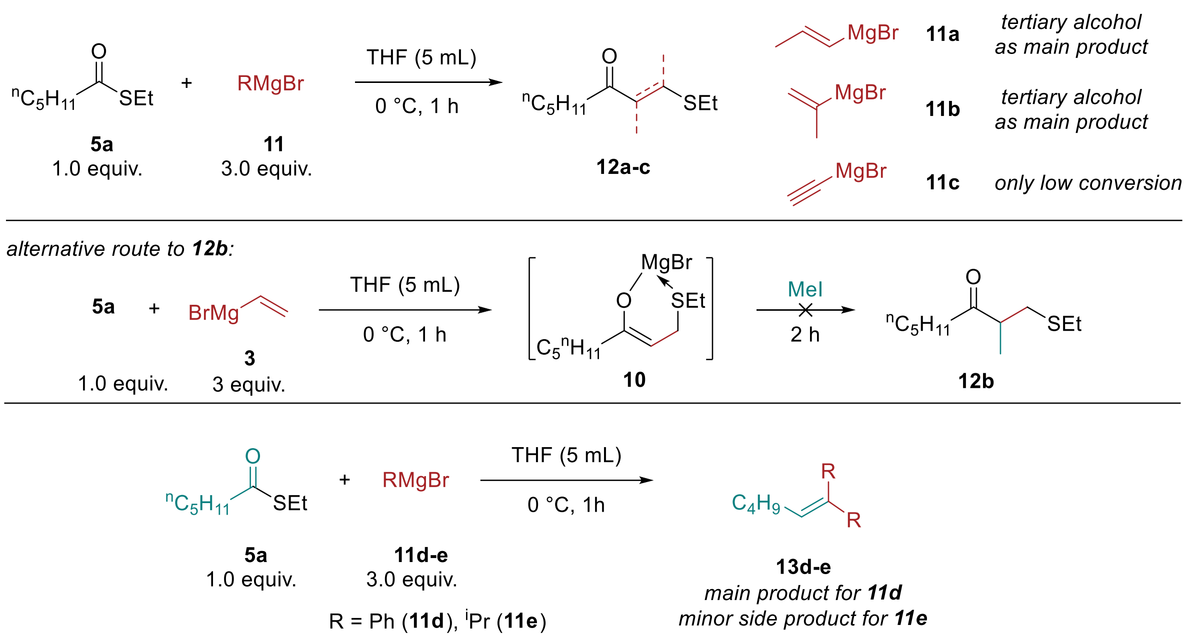
With the optimized conditions in hand, the substrate screening was performed beginning with the investigation of the influence of the S-substituent (Scheme 8). The same yield was observed by using **5c** instead of the ethylthioester **5a**. The sterically more demanding thioesters **5b**, **5d** and **5e** were less reactive, generating a significantly lower yield. Then, the carbonyl substituent was varied. Disappointingly, only traces of the product were observed for the α-substituted **5f**, whereas β-substituted **5g** generated **6g** in 38% yield. The long chain thioester **5h** was also less reactive, furnishing **6h** in 45% yield.

Furthermore, different aryl-substituted benzothioates (**5i** – **5o**) were tested. The unsubstituted **5i** showed a yield of 65%, whereas the electron donating substituents, present in **5j** and **5k** led to lower reactivity. Increasing the electron density at the carbonyl center reduces the electrophilicity of thioester and therefore the nucleophilic attack of **3** is slower. As expected, the electron deficient CF_3 group in *para*-position increased the yield to 72% (**6l**). Chlorinated substrate **5m** showed the same reactivity as the unsubstituted one, which can be explained by "chameleon-like" inductively electron withdrawing (–I) and electron donating mesomeric (+M) effects. The nitro-group was not tolerated, which is not surprising, since reactions of nitroarenes with Grignard reagents are known in the literature.[37] Also substitution in *ortho*-position seems to be a limitation of the catalytic system, since no yield was observed by using **5o**. Moreover, **5p** showed a similar reactivity as **5i**, with a yield of 64%. Whereas, **5q** is more compatible to **5a**. Unfortunately, an indol functionality seems to be a limitation of this reaction, since **5r** was transformed only in a yield of 27%.



Scheme 8: Substrate screening; *reaction conditions:* **5a-r** (1.0 mmol, 1.0 equiv.), **3** (0.52 – 0.89 M in THF, 3.0 equiv.), THF (5 mL), 0 °C, 1 h. Isolated yields.

To enhance the substrate scope, further Grignard reagents were tested in the reaction of S-ethyl hexanethioate (**5a**, Scheme 9). When **11a** and **11b** were applied, the desired product **12** was not generated. Instead, two subsequent nucleophilic additions of **11** generate the tertiary alcohol as main product. This is most likely due to the fact, that the additional methyl group sterically interferes the close proximity of the free thiolate for a 1,4-addition (**9**) and prevents the formation of **12**. Also an alternative route to product **12b** by reaction of **5a** with **3** under optimized reaction conditions and subsequent quenching with methyl iodide for 2 h, unfortunately led to the overaddition product **7**. Interestingly, with the use of sterically less hindered **11c** only starting material was observed on the GC-MS chromatogram. To compare these results with Grignard reagents, which do not generate an electrophilic β-carbon after ketone formation, phenylmagnesium bromide (**11d**) and *iso*-propylmagnesium bromide (**11e**) were applied. Compound **13d** was generated as main product from **11d** by double attack on **5a** and subsequent water elimination. **11e** however, was converted to a more complex, but not fully identified structure and to **13e** as minor side product.

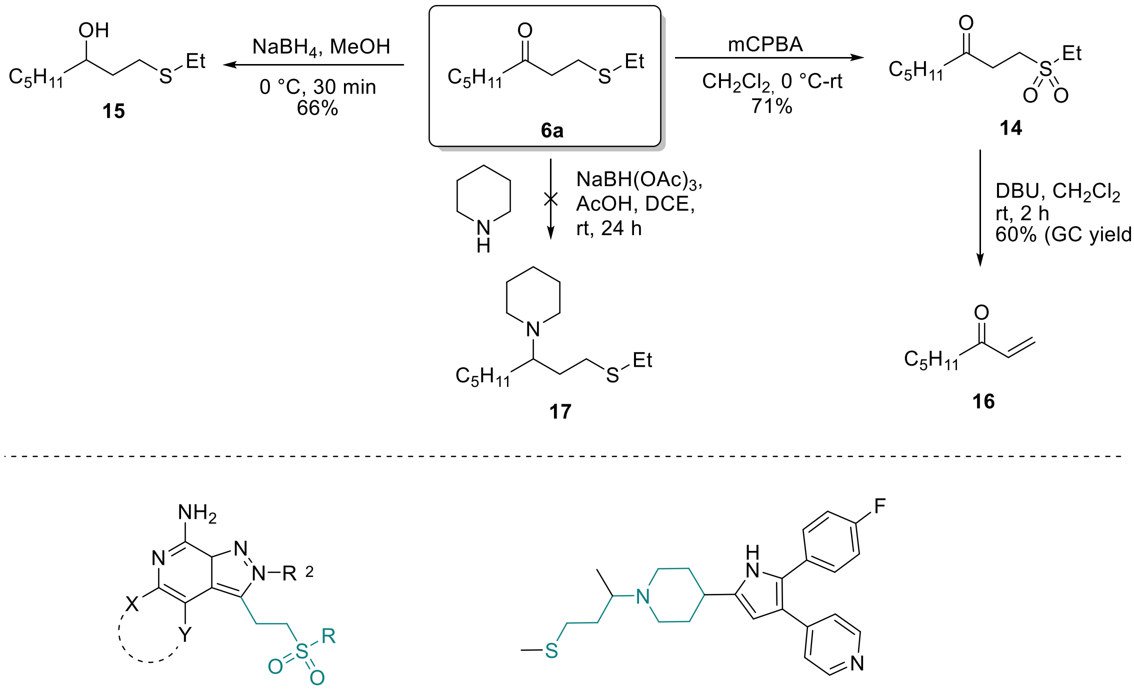


Scheme 9: Application of other Grignard reagents. Determination of products was conducted *via* GC-MS fragmentation analysis.

5.3.4. Application

The synthesized β-sulfanyl ketones can be used to generate β-sulfonyl ketones in one oxidation step with ^{m}CPBA, which was shown in an exemplary way by using **6a** as a substrate (Scheme 10). β-Sulfonyl ketones are important structural motives in biologically active molecules such as pyrazolopyridines which are core compounds for pharmaceuticals and pesticides that inhibit cytokine biosynthesis in animals.[38] Additionally, β-sulfonyl ketones are common in organic synthesis.[39] The treatment of **14** with DBU led to the elimination of the sulfonyl moiety and formation of valuable vinyl ketone **16**. In total, with this procedure a Michael acceptor can be generated from a thioester, which is generally difficult in direct transformations like the Fukuyama coupling, due to further 1,4-addition or overaddition to the tertiary alcohol.

Moreover, **6a** was reduced to the corresponding 3-thio-substituted alcohol **15**. Another promising application would be the transformation into amines as model reaction for synthesizing antiprotozoal agents for the treatment of parasitic diseases.[40] Unfortunately, reductive amination with sodium triacetoxyborohydride to **17** with was not successful.[41]



pyrazolopyridins

antiprotozal agent

Scheme 10: Application of thioester **5a**.

5.4. Conclusion

In conclusion, a transition metal free two-step tandem reaction of thioesters with vinylmagnesium bromide was investigated. The likely formation of a chelate complex hinders the attack of a second Grignard molecule and hence the formation of a tertiary alcohol. Low temperature (0 °C) and short reaction times (1 h) enabled the transformation of various substrates in moderate to good yields. The obtained products can be used as building blocks for other synthetic transformations e.g. the generation of β-sulfonyl ketones.

5.5. Experimental Section

5.5.1. General Information

Chemicals were purchased from ABCR, Acros, Sigma Aldrich, TCI or Merck and used without any further purification unless otherwise noted. Vinylmagnesium bromide (**3**) was commercially obtained from Acros (0.7 M solution in THF, 100 mL, AcroSeal®) and the effective concentration was determined by titration using I_2.[42] All reactions were carried out under an atmosphere of dry nitrogen. All reactions with oxygen- or moisture-sensitive reagents were carried out in glassware, which was dried by heating under vacuum (flame) and cooled under dry N_2. Furthermore, degassed and dry solvents were used where necessary. Dry solvents were obtained by refluxing over Na, followed by distillation under N_2.

Chromatography

Column chromatography was carried out using silica gel (60 Å) as stationary phase, using either gravity flow or air overpressure flow conditions with Puri Flash XS420 (intechim). Mobile phases are outlined for each experiment. Thin layer chromatography (TLC) was performed on aluminum plates, coated with Merck silica gel 60 F254 (layer thickness: 0.2 mm) and analyzed by fluorescence quenching under UV-light (254 nm) or stained with a potassium permanganate solution.

5.5.2. Analytical Techniques

Nuclear magnetic resonance spectroscopy (NMR)

NMR spectra were recorded at ambient temperature on a Bruker Avance 400 (^{1}H: 400 MHz, ^{13}C: 101 MHz) or Bruker Avance 300 (^{1}H: 300 MHz, ^{13}C: 75 MHz) instrument. All measurements were performed at ambient temperature. Chemical shifts δ are reported in parts per million [ppm] relative to the solvent signal as internal standard (^{1}H: $CDCl_3$: δ = 7.26 ppm; ^{13}C: $CDCl_3$: δ = 77.1 ppm). Coupling constants across bonds are given in *J* (Hz). ^{1}H-NMR splitting patterns are assigned as s (singlet), d (doublet), t (triplet), q (quartet), q (quintet), sext (sextet), hept (heptet), m (multiplet). ^{13}C signals are assigned as C_q (quaternary carbon), + (primary and tertiary carbon),

− (secondary carbon). The assignment resulted from COSY, DEPT-135°, HMBC or HSQC experiments.

Infrared spectroscopy (IR)

Infrared spectra were recorded on an Agilent Technologies Cary 630 FTIR spectrometer, equipped with an ATR-System. Absorption bands are given in wave numbers v (cm-1) and peak intensities are indicated as follows: s = strong, m = medium, w = weak and peak forms as: br = broad, sh = sharp.

Melting points (m.p.)

Melting points were determined using either a BÜCHI Melting Point B-545 or a Schorpp MPMHV3 and are uncorrected (heating rate 1-5 °C/min).

Mass spectrometry

HR-MS and GC-MS were recorded on *Agilent* Q-TOF 6540 UHD, *Jeol* AccuTOF GCX, and *Finnigan* MAT SSQ 710 A, *Agilent* 5977A MSD and *Agilent* 7820A GC system with Quadrupole MS *Agilent* 7820A (EI) and Agilent 190915-433UI column.

Gas Chromatography (GC)

GC-FID (flame ionization detection) analysis was carried out on SHIMADZU GC-2010 Plus with SHIMADZU AOC-20i Auto-injector using dry hydrogen as carrier gas. Program 50-280M3: Heating from 50 to 130 °C in 50 °/min followed by heating to 170 °C in 3 °C/min and subsequent heating to 280 °C in 50 °C/min and eventually holding 280 °C for 3 min.

Alternatively, GC_FID analysis was carried out on an Agilent 7820A system using dry hydrogen as carrier gas. Agilent 19091J-431 column (30 m x 320 µm x 0.25 µm) was used. Program 50-280M12: Heating from 50 °C to 280 °C within 12 minutes.

In order to determine yields and conversions the internal standard method was used for quantitative GC-FID. Therefore, calibration was conducted by variation of mass ratio of substrate and standard and analyzing the different samples by GC-FID. From the obtained data the peak area ratio was plotted against the mass ratio of substrate to standard. Linear regression led to the determination of the regression factor R.

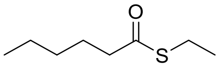
$$\frac{m_{sub}}{m_{std}} \cdot R = \frac{A_{sub}}{A_{std}}$$

5.5.3. Preparation of Starting Materials

General Procedure S1 for the Synthesis of Thioesters

The thioesters were synthesized *via* Steglich-esterification.[43] A flame-dried 25 mL RBF was charged with carboxylic acid (1.0 equiv.), which was dissolved in anhydrous CH_2Cl_2 (10 mL, DMF for less soluble acids). DMAP (0.1 equiv.) and thiol (1.0 equiv.) were added and the reaction mixture was cooled down to 0 °C. After the addition of DCC (1.0 equiv.) the mixture was stirred for 30 min at 0 °C and the reaction was completed by stirring overnight at room temperature. Precipitated urea was filtered off and the filtrate was washed with HCl (1 M), saturated solution of NaHCO3 and brine, dried over MgSO4 and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (gradient CyH → CyH/EtOAc: 95/5). Substrates **5f**, **5g**, **5h**, **5n**, **5p** and **5r** were synthesized for a different project.[26]

S-Ethyl hexanethioate **5a**



According to the general procedure *S1*, **5a** was synthesized from hexanoic acid (1.0 mL, 7.9 mmol, 1.0 equiv.) with EtSH (685 µL, 9.51 mmol, 1.2 equiv.). Purification of the crude product by column chromatography (gradient: CyH → CyH/EtOAc: 95/5) provided **5a** as a colorless liquid (926 mg, 5.8 mmol, 73%).

$C_8H_{16}OS$ (160.28 g/mol), **R_f:** 0.46 (CyH/EtOAc: 95/5).

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H/ppm: 2.87 (q, J = 7.4 Hz, 2 H, SCH_2), 2.53 (t, J = 7.4 Hz, 2 H,$COCH_2(CH_2)_3CH_3$), 1.72 – 1.61 (m, 2 H, $COCH_2CH_2(CH_2)_2CH_3$), 1.36 – 1.27 (m, 4 H, $CO(CH_2)_2(CH_2)_2CH_3$), 1.24 (t, J = 7.4 Hz, 3 H, SCH_2CH_3), 0.89 (t, J = 6.9 Hz, 3 H, $CO(CH_2)_4CH_3$).

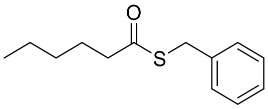
^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 199.9 (q), 44.1 (–), 31.1 (–), 25.4 (–), 23.2 (–), 22.3 (–), 14.8 (+), 13.9 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2960 (m, sh), 2930 (m, sh), 2862 (w, sh), 1689 (s, sh), 1454 (m, sh), 1267 (w, sh), 1122 (m, sh), 1014 (m, br), 962 (m, sh), 738 (w, br).

GC-MS (EI): t_R = 4.82 min, m/z = 131 (27, [$M^{+\bullet}$]-[$^{\bullet}$Et]), 99 (100, [$M^{+\bullet}$]-[$^{\bullet}$SEt]).

HR-MS (EI): [$M^{+\bullet}$] calc. for $C_8H_{16}OS$ 160.0916, found 160.0915.

S-Benzyl hexanethioate **5d**



According to the general procedure *S1*, **5d** was synthesized from hexanoic acid (2.2 g, 10.0 mmol, 1.0 equiv.) with $^{n}C_7H_{15}SH$ (1.2 g, 10.0 mmol, 1.2 equiv.). Purification of the crude product by column chromatography (gradient: hexane/Et_2O: 99/1 → hexane/Et_2O: 95/5) provided **5d** as a colorless liquid (895 mg, 4.0 mmol, 40%).

$C_{13}H_{18}OS$ (222.11 g/mol), **R_f:** 0.62 (PE/Et_2O: 9/1).

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.32 – 7.21 (m, 5 H, Ar*H*), 4.12 (s, 2 H), 2.56 (t, J = 7.4 Hz, 2 H, SC*H*$_2$), 1.68 (p, J = 7.4 Hz, 2 H, SCH_2C*H*$_2$), 1.30 (m, 4 H, SCH_2CH_2(C*H*$_2$)$_2CH_3$), 0.90 (t, J = 6.9 Hz, 3 H, C*H*$_3$).

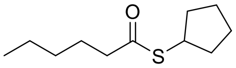
^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 199.1 (q), 137.9 (q), 2 x 129.0 (+, +), 2 x 128.8 (+, +), 127.3 (+), 44.0 (–), 33.3 (–), 31.3 (–), 25.5 (–), 22.5 (–), 14.0 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3064 (w, sh), 3030 (w, sh), 2956 (m, sh), 2930 (m, sh), 2863 (w, sh), 1685 (s, sh), 1495 (w, sh), 1454 (m, sh), 1118 (w, sh), 1029 (m, sh), 962 (m, sh), 697 (s, sh).

GC-MS (EI): t_R = 7.81 min, m/z = 222 (22, [$M^{+\bullet}$]), 131 (11, [M]-[C_7H_7]), 124 (12, [MH]-[$^{\bullet}$COC$_5$H11]), 99 (87, [$M^{+\bullet}$]-[$^{\bullet}SC_7H_7$]), 91 (100, [M]-[$^{\bullet}$SCO$^{n}C_6H_{11}$]).

HR-MS (EI): [$M^{+\bullet}$] calc. for $C_{13}H_{18}OS$ 245.0971, found 245.0973.

S-Cyclopentyl hexanethioate **5e**



According to the general procedure *S1*, **5e** was synthesized from hexanoic acid (2.0 g, 10.0 mmol, 1.0 equiv.) with phenylmethylethiol (1.2 g, 10.0 mmol, 1.0 equiv.). Purification of the crude product by column chromatography (gradient: hexane/Et$_2$O 99/1 → hexane/Et$_2$O: 95/5) provided **5e** as a colorless liquid (1.2 g, 7.1 mmol, 71%).

$C_{11}H_{20}OS$ (200.34 g/mol), **R_f:** 0.89 (PE/Et$_2$O: 9/1).

^{1}H-NMR (400 MHz, CDCl$_3$) δ_H/ppm: 3.70 (p, J =7.3 Hz, 1 H, OCCH(CH$_3$)$_2$), 2.49 (t, J = 7.5 Hz, 2 H, COCH_2), 2.15 – 2.01 (m, 2 H, COCH$_2$CH_2), 1.74 – 1.54 (m, 8 H, SCH(CH_2)$_4$), 1.30 (m, 4 H, COCH$_2$CH$_2$(CH_2)$_2$CH$_3$) 0.90 (t, J = 6.9 Hz, 3 H, CH_3).

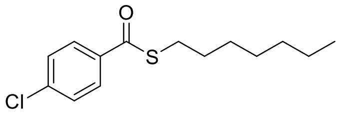
^{13}C-NMR (75 MHz, CDCl$_3$) δ_C/ppm: 200.6 (q), 44.1 (–), 42.4 (+), 33.4 (–), 31.3 (–), 25.5 (–), 24.9 (–), 22.5 (–), 14.0 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2956 (m, sh), 2866 (w, sh), 1685 (s, sh), 1454 (w, sh), 1118 (w, sh), 1013 (m, sh), 962 (w, sh), 924 (w, sh), 734 (w, sh), 697 (w, sh).

GC-MS (EI): t_R = 6.43 min, m/z = 200 (0.2, [M$^{+\bullet}$]), 131 (21, [M$^{+\bullet}$]-[$^\bullet$C5H9]) 99 (100, [M$^{+\bullet}$]-[$^\bullet$SC5H9]), 71 (42, [M$^{+\bullet}$]-[$^\bullet$COSC5H9]).

HR-MS (ESI): [M$^{+\bullet}$] calc. for $C_{11}H_{20}OSNa$ 223.1127, found 223.1130.

S-Heptyl 4-chlorobenzothioate **5n**



According to the general procedure *S1*, **5n** was synthesized from 4-chlorobenzoic acid (1.6 g, 10.0 mmol, 1.0 equiv.) with $^nC_7H_{15}SH$ (1.6 mL, 10.0 mmol, 1.0 equiv.). Purification of the crude product by column chromatography (Hexane/Et$_2$O: 99/5) provided **5n** as a colorless liquid (638.0 mg, 2.28 mmol, 23%).

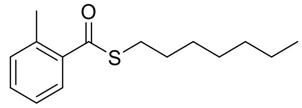
$C_{14}H_{19}ClOS$ (279.8 g/mol), R_f: 0.72 (PE/Et$_2$O: 9/1).

^{1}H-NMR (400 MHz, CDCl$_3$) δ_H/ppm: 7.90 (d, J = 8.6 Hz, 2 H, ArH), 7.41 (d, J = 8.6 Hz, 2 H, ArH), 3.12 – 3.00 (t, J = 7.3 Hz, 2 H, SCH_2), 1.67 (p, J = 7.3 Hz, 2 H, SCH$_2$CH_2), 1.53 – 1.17 (m, 8 H, SCH$_2$CH$_2$(CH_2)$_4$CH$_3$), 0.95 – 0.82 (t, J = 6.9 Hz, 3 H, CH_3).

^{13}C-NMR (101 MHz, CDCl$_3$) δ_C/ppm: 191.1 (q), 139.7 (q), 135.8 (q), 2 x 129.0 (+, +), 2 x 128.7 (+, +), 31.8 (–), 29.4 (–), 2 x 29.0 (–, –), 22.7 (–), 14.2 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2922 (m, sh), 2855 (w, sh), 1666 (s, sh), 1588 (m, sh), 1484 (w, sh), 1398 (w, sh), 1203 (s, sh), 1088 (s, sh), 913 (s, sh), 835 (s, sh), 719 (w, sh).
GC-MS (EI): t_R = 9.56 min, m/z = 280 (0.3, [$M^{+\bullet}$]), 139 (100, [$M^{+\bullet}$]-[$^\bullet S^nC_7H_{15}$]), 112 (17, [MH]-[$^{\bullet n}COSC_7H_{15}$]).
HR-MS (ESI): [$M^{+\bullet}$] calc. for $C_{14}H_{19}ClOSNa$ 270.0834, found 270.08397.

S-Heptyl 2-methylbenzothioate **5o**



According to the general procedure *S1*, **5o** was synthesized from 2-methylbenzoic acid (2.50 g, 10.0 mmol, 1.0 equiv.) with $^nC_7H_{15}SH$ (1.6 mL, 10.0 mmol, 1.0 equiv.). Purification of the crude product by column chromatography (Hexane/Et_2O: 99/1) provided **5o** as a colorless liquid (627.2 mg, 2.50 mmol, 25%).

$C_{15}H_{22}OS$ (250.4 g/mol), R_f: 0.40 (Hexane/Et_2O: 99/1).
^{1}H-NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.76 (dd, J = 8.1, 1.4 Hz, 1 H, Ar*H*), 7.42 – 7.33 (m, 1 H, Ar*H*), 7.29 – 7.20 (m, 1 H, Ar*H*), 3.08 – 3.00 (t, J = 7.3 Hz, 2 H, SCH_2), 2.48 (s, 3H, $ArCH_3$), 1.68 (p, J = 7.3 Hz, 2 H, SCH_2CH_2), 1.48 – 1.24 (m, 8 H, $SCH_2CH_2(CH_2)_4CH_3$), 0.89 (t, J = 6.9 Hz, 3 H, CH_3).
^{13}C-NMR (101 MHz, $CDCl_3$) δ_C/ppm: 194.8 (q), 138.0 (q), 136.7 (q), 2 x 131.6 (+, +), 128.5 (+), 125.8 (+), 31.9 (–), 29.8 (–), 29.7 (–), 29.1 (–), 29.0 (–), 22.7 (–), 20.65 (+), 14.2 (+).
FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2922 (m, sh), 2855 (w, sh), 1662 (s, sh), 1453 (w, sh), 1192 (s, sh), 905 (s, sh), 764 (m, sh), 723 (m, sh), 682 (w, sh).
GC-MS (EI): t_R = 8.95 min, m/z = 250 (0.6, [$M^{+\bullet}$]), 222 (12, [MH]-[$^\bullet C_2H_5$]), 137 (3, [MH]-[$^\bullet CH_3$]-[$^{\bullet n}C_7H_{15}$]), 119 (100, [$M^{+\bullet}$]-[$^\bullet S^nC_7H_{15}$]), 91 (33, [$M^{+\bullet}$]-[$^\bullet COS^nC_7H_{15}$]).
HR-MS (ESI): [$M^{+\bullet}$] calc. for $C_{15}H_{22}OSNa$ 273.1284, found 273.1285.

5.5.4. Tandem Reaction

General procedure **T1** for Tandem reaction

A flame-dried 30 mL schlenk tube was charged with thioester **5a-r** (1.0 mmol, 1.0 equiv.) which was dissolved in anhydrous THF (5 mL). The solution was stirred for 5 min at 0 °C. A vinylmagnesium bromide solution (**3**, 0.51 – 0.89 M in THF, 3.0 equiv.) was added *via* syringe within a period of 5 min and the reaction mixture was stirred for 1 h at 0 °C. The reaction was quenched by adding an aqueous, saturate solution of NH_4Cl (3 mL) and the reaction mixture was extracted with Et_2O (3 x 100 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography.

Kinetic measurements

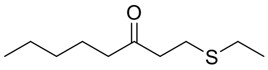
According to the general procedure **T1**, a kinetic study was performed by using **5a** as substrate. Therefore, *n*-pentadecane (100 µL) was added as an internal standard before the addition of the Grignard solution. Aliquots of the reaction mixture (100 µL) were taken at different reaction times. After quenching and extraction the conversions and the yields were determined by quantitative GC-FID (
Table 2).

Table 2: Conversions and Yields of the kinetic study for the tandem reaction of **5a** with vinylmagnesium bromide

Entry	Time [min]	Conv. [%]	Yield [%]
1	0	0	0
2	5	51	24
3	10	66	32
4	15	73	41
5	20	79	46
6	30	84	58
7	60	97	75
8	120	100	64

5.5.5. Tandem Reaction: Substrate Screening

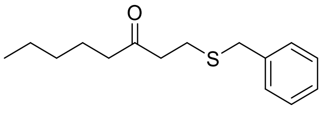
1-(Ethylthio)octan-3-one **6a**



According to the general procedure T1, **6a** was synthesized from **5a** (159 mg, 1.0 mmol, 1.0 equiv.). Purification of the crude product by column chromatography (Pentane/Et$_2$O: 99/1 and CyH/EtOAc (gradient CyH/EtOAc = 100/0 → 0/100)) provided **6a** as a colorless liquid (135 mg, 721 µmol, 73%).

$C_{10}H_{20}OS$ (188.33 g/mol), **R$_f$:** 0.02 (Pentane/Et$_2$O: 99/1).
^{1}H-NMR (300 MHz, CDCl$_3$) δ_H/ppm: 2.80 – 2.62 (m, 4 H, COC*H*$_2$C*H*$_2$S), 2.54 (q, *J* = 7.4 Hz, 2 H, SC*H*$_2$CH$_3$), 2.41 (t, J = 7.5 Hz, 2 H, COC*H*$_2$(CH$_2$)$_3$CH$_3$), 2.65 – 1.51 (m, 2 H, COCH$_2$C*H*$_2$(CH$_2$)$_2$CH$_3$), 1.37 – 1.19 (m, 4 H, CO(CH$_2$)$_2$(C*H*$_2$)$_2$CH$_3$), 1.25 (t, J = 7.4 Hz, 3 H, SCH$_2$C*H*$_3$), 0.88 (t, J = 6.9 Hz, 3 H, CO(CH$_2$)$_4$C*H*$_3$).
^{13}C-NMR (75 MHz, CDCl$_3$) δ_C/ppm: 209.5 (q), 43.1 (–), 42.7 (–), 31.4 (–), 26.3 (–), 25.4 (–), 23.4 (–), 22.5 (–), 14.7 (+), 13.9 (+).
FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2930 (s, sh), 2870 (m, sh), 1715 (s, sh), 1453 (m, sh), 1409 (m, sh), 1375 (m, br), 1264 (m, sh), 1077 (m, sh).
GC-MS (EI): t$_R$ = 6.89 min, m/z = 188 (47, [M$^{+\bullet}$]), 127 (29, [M$^{+\bullet}$]-[$^\bullet$SEt]), 99 (50, [M$^{+\bullet}$]-[$^\bullet$CH$_2$CH$_2$SEt]), 89 (100, [M$^{+\bullet}$]-[$^\bullet$CO(CH$_2$)$_4$CH$_3$]).
HR-MS (EI): [M$^{+\bullet}$] calc. for $C_{10}H_{20}OS$ 188.1229, found 188.1228.

1-(Benzylthio)octan-3-one **6d**



According to the general procedure T1, **6d** was synthesized from **5d** (200.1 mg, 900 µmol, 1.0 equiv.). Purification of the crude product by column chromatography (Hexane/Et$_2$O: 97.5/2.5 → Hexane/Et$_2$O: 9/1) provided **6d** as a colorless oil (123.0 mg, 491 µmol, 55%).

$C_{15}H_{22}OS$ (250.4 g/mol), **R_f:** 0.32 (PE/Et_2O: 9/1).

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.35 – 7.26 (m,4 H, Ar*H*), 7.28 – 7.19 (m, 1 H, Ar*H*), 3.72 (s, 2 H, $ArCH_2$), 2.71 – 2.55 (m, 4 H, $CO(CH_2)_2S$), 2.35 (t, J = 7.5 Hz, 2 H, $COCH_2$), 1.55 (p, J = 7.2 Hz, 2 H, $C(O)CH_2CH_2$), 1.35 – 1.19 (m, 4 H, $C(O)CH_2CH_2(CH_2)_2CH_3$), 0.88 (t, J = 7.1 Hz, 3 H, $C(O)(CH_2)_4CH_3$).

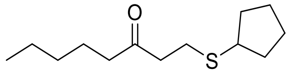
^{13}C-NMR (101 MHz, $CDCl_3$) δ_C/ppm: 209.4 (q), 138.5 (q), 2 x 129.0 (+, +), 2 x 128.7 (+, +), 127.2 (q), 43.2 (–), 42.6 (–), 37.0 (–), 31.5 (–), 25.5 (–), 23.6 (–), 22.6 (–), 14.1 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3060 (w, sh), 3027 (w, sh), 2952 (m, br), 2926 (m, br), 2859 (w, sh), 1710 (s, sh), 1491 (w, sh), 1453 (w, sh), 1409 (w, sh), 1368 (w, br), 1074 (m, sh), 768 (m, sh), 701 (s, br).

GC-MS (EI): t_R = 9.31 min, m/z = 250.1 (5, [$M^{+\bullet}$]), 123.1 (10, [$M^{+\bullet}$]-[$^\bullet C_2H_4CO^nC_5H_{11}$]), 99.1 (23, [$M^{+\bullet}$]-[$^\bullet C_4H_2SCH_2C_6H_5$]) 91.1 (100, [$M^{+\bullet}$]-[$^\bullet SC_2H_4CO^nC_5H_{11}$]), 70.1 (16, [$M^{+\bullet}$]-[$^\bullet COC_4H_2SCH_2C_6H_5$]).

HR-MS (EI): [$M^{+\bullet}$] calc. for $C_{15}H_{22}OS$ 250.1386, found 250.1376.

1-(Cyclopentylthio)octan-3-one **6e**



According to the general procedure T1, **6e** was synthesized from **5e** (180.3 mg, 900 µmol, 1.0 equiv.). Purification of the crude product by column chromatography (gradient: Hexane/Et_2O: 99/1 → Hexane/Et_2O: 95/5) provided **6e** as a colorless liquid (80.0 mg, 350 µmol, 39%).

$C_{13}H_{24}OS$ (228.2 g/mol), **R_f:** 0.23 (PE/Et_2O: 9/1).

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H/ppm: 3.09 (p, J = 7.0 Hz, 1 H, SC*H*), 2.91 – 2.64 (m, 4 H, $CO(CH_2)_2S$), 2.41 (t, J = 7.5 Hz, 2 H, $COCH_2$), 2.04 – 1.92 (m, 2 H, $SCHCH_2$), 1.73 (m, 2 H, CH_2), 1.64 – 1.43 (m, 6 H, CH_2), 1.28 (m, 4 H, CH_2), 0.89 (t, J = 7.0 Hz, 3 H, $C(O)(CH_2)_4CH_3$).

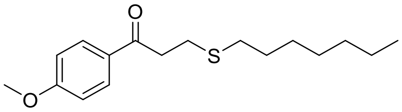
^{13}C-NMR (101 MHz, $CDCl_3$) δ_C/ppm: 209.4 (q), 44.3 (+), 43.2 (–), 43.0 (–), 33.9 (–), 31.5 (–), 25.8 (–), 25.0 (–), 23.6 (–), 22.6 (–), 14.1 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2952.1 (s, br), 2827 (m, sh), 1710 (s, sh), 1450 (w, sh), 1409 (w, sh), 1364 (w, br), 1241 (w, sh), 1126 (w, sh), 1074 (m, sh), 723 (w, sh).

GC-MS (EI): t_R = 8.17 min, m/z = 228.1 (9, $[M^{+\bullet}]$), 101.1 (26, $[M^{+\bullet}]$-$[^{\bullet}C_2H_4CO^nC_5H_{11}]$), 99.1 (19, $[M^{+\bullet}]$-$[^{\bullet}C_4H_2SCH_2C_5H_9]$), 70.1 (25, $[M^{+\bullet}]$-$[^{\bullet}SC_5H_9]$-$[^{\bullet n}C_4H_9]$), 67.1 (100, $[M^{+\bullet}]$-$[^{\bullet}SC_2H_4CO^nC_5H_{11}]-2[^{\bullet}H]$).

HR-MS (EI): $[M^{+\bullet}]$ calc. for $C_{13}H_{24}OS$ 228.1542, found 228.1556.

3-(Heptylthio)-1-(4-methoxyphenyl)propan-1-one **6k**



According to the general procedure T1, **6k** was synthesized from **5k** (239.8 mg, 900 µmol, 1.0 equiv.). Purification of the crude product by column chromatography (Hexane/Et_2O: 99/1 → Hexane/Et_2O: 9/1) provided a colorless oil containing **6k** (72.9 mg, 248 µmol, 28%) and 1-(4-methoxyphenyl)pent-4-en-1-one (16.0 mg, 84 µmol, 9%, based on NMR).

$C_{17}H_{26}O_2S$ (294.4 g/mol), **R_f:** 0.20 (PE/Et_2O: 9/1).

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.94 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 6.93 (d, J = 8.9 Hz, 2 H, Ar*H*), 3.87 (s, 3 H, OCH_3), 3.29 – 3.16 (t, J = 7.5 Hz, 2 H, $COCH_2$), 2.90 (t, J = 7.5 Hz, 2 H, $COCH_2CH_2$), 2.56 (t, J = 7.3 Hz, 2 H, $COCH_2CH_2SCH_2$), 1.60 (p, J = 7.2 Hz, 2 H, $COCH_2CH_2SCH_2CH_2$), 1.42 – 1.21 (m, 8 H, $SCH_2CH_2(CH_2)_4CH_3$), 0.87 (t, J = 7.0 Hz, 3 H, $SCH_2CH_2(CH_2)_4CH_3$).

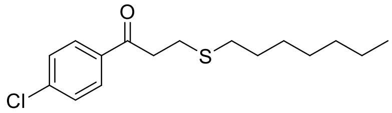
^{13}C-NMR (101 MHz, $CDCl_3$) δ_C/ppm: 197.2 (q), 163.7 (q), 2 x 130.4 (+, +), 129.9 (q), 2 x 113.9 (+, +), 55.6 (+), 38.9 (–), 32.7 (–), 31.9 (–), 29.8 (–), 29.0 (–), 29.0 (–), 26.7 (–), 22.8 (–), 14.2 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2922 (s, br), 2851 (m, sh), 1673 (s, sh), 1599 (s, sh), 1510 (m, sh), 1461 (w, sh), 1416 (w, sh), 1346 (w, sh), 1308 (w, sh), 1249 (s, sh), 1167 (s, sh), 1029 (m, sh), 973 (m, sh), 835 (m, sh).

GC-MS (EI): t_R = 11.31 min, m/z = 294 (3, $[M^{+\bullet}]$), 163 (54, $[M^{+\bullet}]$-$[^{\bullet}S^nC_7H_{15}]$), 148 (31, $[M^{+\bullet}]$-$[^{\bullet}S^nC_7H_{15}]$-$[^{\bullet}CH_3]$), 135 (100, $[M^{+\bullet}]$-$[^{\bullet}CH_2CH_2S^nC_7H_{15}]$), 121 (18, $[M^{+\bullet}]$-$[^{\bullet}CH_2CH_2S^nC_7H_{15}]$ -$[^{\bullet}CH_3]$), 98 (17, $[M^{+\bullet}]$-$[^{\bullet}CH_3OC_6H_4COCH_2CH_2S]$).

HR-MS (ESI): $[M^{+\bullet}]$ calc. for $C_{17}H_{26}O_2SNa$ 317.1546, found 317.1547.

3-(Heptylthio)-1-(4-(trifluoromethyl)phenyl)propan-1-one **6m**



According to the general procedure T1, **6m** was synthesized from **5m** (254.8 mg, 941 µmol, 1.0 equiv.). Purification of the crude product by column chromatography (Hexane/Et_2O: 99/1) and subsequent Kugelrohr distillation (190 °C) provided **6m** as a yellow crystals (75.7 mg, 186.7 µmol, 64%).

$C_{16}H_{23}O_2SCl$ (298.9 g/mol), **R_f:** 0.74 (CyH/EA: 8/2), **m.p.:** 43.2 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.90 (d, J = 8.6 Hz, 2 H, Ar*H*), 7.45 (d, J = 8.6 Hz, 2 H, Ar*H*), 3.24 (t, J = 7.4 Hz, 2 H, $COCH_2$), 2.90 (t, J = 7.4, 2 H, $COCH_2CH_2$), 2.56 (t, J = 7.4 Hz, 2 H, $COCH_2CH_2SCH_2$), 1.60 (p, J = 7.2 Hz, 2 H, $COCH_2CH_2SCH_2CH_2$), 1.41 – 1.26 (m, 8 H, $SCH_2CH_2(CH_2)_4CH_3$), 0.85 (t, J = 7.0 Hz, 3 H, $SCH_2CH_2(CH_2)_4CH_3$).

^{13}C-NMR (101 MHz, $CDCl_3$) δ_C/ppm: 197.4 (q), 139.9 (q), 135.1 (q), 129.6 (+), 129.1 (+), 38.9 (–), 32.7 (–), 31.9 (–), 29.8 (–), 29.1 (–), 29.0 (–), 26.4 (–), 22.8 (–), 14.2 (+).

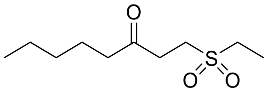
FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2952 (w, sh), 2922 (s, br), 2851 (m, sh), 1684 (s, sh), 1584 (m, sh), 1461 (w, sh), 1401 (w, sh), 1349 (m, sh), 1290 (w, sh), 1256 (w, sh), 1189 (m, sh), 1029 (m, sh), 980 (m, sh), 775 (s, sh).

GC-MS (EI): t_R = 10.79 min, m/z = 167 (70, $[M^{+\bullet}]^{+\bullet}]$-[$^\bullet S^nC_7H_{15}$]), 139 (100, $[M^{+\bullet}]$-[$^\bullet C_2H_4S^nC_7H_{15}$]), 111 (39, $[M^{+\bullet}]$-[$^\bullet COC_2H_4S^nC_7H_{15}$]), 70 (49, $[M^{+\bullet}]$-[$^\bullet ClC_6H_4COC_2H_4SCH_2$]-[$^\bullet CH_3$]), 57 (39, $[M^{+\bullet}]$-[$^\bullet ClC_6H_4COC_2H_4S^nC_3H_6$]).

HR-MS (ESI): $[M^{+\bullet}]$ calc. for $C_{16}H_{23}O_2SCl$ 298.1152, found 298.1125.

5.5.6. Application

1-(Ethylsulfonyl)octan-3-one **14**



Compound **6a** (115.0 mg, 610 µmol, 1 equiv.) was dissolved in DCM (3 mL) and cooled to 0 °C with an ice bath. *m*-CPBA (263.4 mg, 1.53 mmol, 2.5 eq) was added and the reaction was stirred over night until complete conversion (TLC control). The reaction was quenched with sat. Na_2CO_3 (6 mL) and $NaHCO_3$ (6 mL). The aqueous phase was extracted with DCM (3 x 4 mL). Purification of the crude product by column chromatography (CyH/EtOAc: 8/2 → CyH/EtOAc: 1/1) provided **11** as a colorless oil (95.0 mg, 431 µmol, 71%).

$C_{10}H_{20}O_3S$ (220.33 g/mol), **R$_f$:** 0.18 (CyH/EtOAc: 8/2), m.p.: 78.5 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H/ppm: 3.26 (t, J = 7.2 Hz, 2 H, $CO(CH_2)_2S(O_2)$), 3.06 – 2.95 (m, 4 H, $CO(CH_2)_2S(O_2)$, $S(O_2)CH_2CH_3$), 2.49 (t, J = 7.5 Hz, 2 H, $COCH_2$), 1.66 – 1.56 (m, 2 H, $COCH_2CH_2(CH_2)_2CH_3$), 1.42 (t, J = 7.5 Hz, 3 H, $S(O_2)CH_2CH_3$), 1.35 – 1.22 (m, 4 H, $CO(CH_2)_2(CH_2)_2CH_3$), 0.89 (t, J = 7.0 Hz, 3 H, $C(O)(CH_2)_4CH_3$).

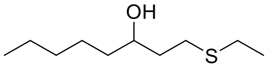
^{13}C-NMR (101 MHz, $CDCl_3$) δ_C/ppm: 207.0 (q), 48.4 (–), 46.1 (–), 43.0 (–), 34.2 (–), 31.4 (–), 23.6 (–), 22.6 (–), 14.1 (+), 6.84 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2933 (m, br), 2870 (w, br), 1710 (s, sh), 1461 (w, sh), 1416 (m, sh), 1290 (s, sh), 1272 (s, sh), 1126 (s, sh), 1085 (w, sh), 1047 (w, sh), 775 (m, sh), 731 (m, sh).

GC-MS (EI): t_R = 6.52 min, m/z = 220.2 (26, $[M^{+\bullet}]$), 205.1 (100, $[M^{+\bullet}]$-$[^\bullet CH_3]$), 177.1 (11, $[M^{+\bullet}]$-$[^\bullet C_3H_7]$), 121.0 (7, $[M^{+\bullet}]$-$[^\bullet CO^nC_5H_{11}]$), 57.1 (15, $[M^{+\bullet}]$-$[^\bullet CH_2COC_2H_4SO_2C_2H_5]$).

HR-MS (ESI): $[M^{+\bullet}]$ calc. for $C_{10}H_{20}O_3SNa$ 243.1025, found 243.1028.

1-(Ethylthiol)octan-3-ol **15**



Compound **6a** (115.0 mg, 610 µmol, 1 equiv.) was dissolved in MeOH (3 mL) and cooled to 0 °C with an ice bath. $NaBH_4$ (263.4 mg, 1.53 mmol, 2.5 eq) was added and the reaction was stirred for 30 min. The reaction was quenched with sat. Na_2CO_3 (2 mL). MeOH was removed and 6 M HCl was used to set a pH of 6. The aqueous phase was extracted with DCM (2 x 4 mL) and dried over $MgSO_4$. Evaporation of the solvent provided **12** as a colorless oil (126.3 mg, 663 µmol, 66%).

$C_{10}H_{22}OS$ (190.35 g/mol), **R_f:** 0.26 (CyH/EtOAc: 8/2).

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H/ppm: 3.74 (m, 1 H, *H*COH), 2.66 (t, J = 7.2 Hz, 2 H, SC*H*$_2$CH$_2$COH), 2.56 (q, J = 7.4 Hz, 2 H, SC*H*$_2$CH$_3$), 1.81 – 1.63 (m, 4 H, SCH$_2$C*H*$_2$COH, HC(OH)C*H*$_2$(CH$_2$)$_3$CH$_3$), 1.49 – 1.38 (m, 1 H, O*H*), 1.33 – 1.21 (m, 6 H, HC(OH)CH$_2$(C*H*$_2$)$_3$CH$_3$), 1.26 (t, J = 7.4 Hz, 3 H SCH$_2$C*H*$_3$), 0.89 (t, J = 6.8 Hz, 3 H, HC(OH)(CH$_2$)$_4$C*H*$_3$).

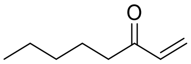
^{13}C-NMR (101 MHz, $CDCl_3$) δ_C/ppm: 207.0 (q), 48.4 (–), 46.1 (–), 43.0 (–), 34.2 (–), 31.4 (–), 23.6 (–), 22.6 (–), 14.1 (+), 6.84 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2933 (m, br), 2870 (w, br), 1710 (s, sh), 1461 (w, sh), 1416 (m, sh), 1290 (s, sh), 1272 (s, sh), 1126 (s, sh), 1085 (w, sh), 1047 (w, sh), 775 (m, sh), 731 (m, sh).

GC-MS (EI): t_R = 6.52 min, m/z = 220.2 (26, $[M^{+\bullet}]$), 205.1 (100, $[M^{+\bullet}]$-$[{}^\bullet CH_3]$), 177.1 (11, $[M^{+\bullet}]$-$[{}^\bullet C_3H_7]$), 121.0 (7, $[M^{+\bullet}]$-$[{}^\bullet CO^nC_5H_{11}]$), 57.1 (15, $[M^{+\bullet}]$-$[{}^\bullet CH_2COC_2H_4SO_2C_2H_5]$).

HR-MS (ESI): $[M^{+\bullet}]$ calc. for $C_{10}H_{20}O_3SNa$ 243.1025, found 243.1028.

<u>Oct-1-en-3-one **16**</u>



Following a literature procedure,[44] ketone **11** (100 mg, 454 µmol) was dissolved in dichloromethane (2 mL) and DBU (72.5 mg, 476 µmol) was added. The reaction mixture was stirred at room temperature for 2 h and analyzed by GC-FID, which confirmed 60% product and 40% starting material. Isolation led to lost of product and the procedure should be optimized.

C8H14O (126.20 g/mol)

5.6. Literature

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[2] V. Hirschbeck, *Dissertation*, University of Regensburg, Regensburg, **2018**.

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6. Summary

English

C-C bond formations play a crucial role in organic chemistry. In this thesis, acid catalysis and Grignard reactions were applied to transform benzylic alcohols and thioesters in valuable compounds *via* the generation of new carbon-carbon bonds.

In Chapter 2, a dehydrative homocoupling of benzylic alcohols *via* acid catalysis was described. Benzylic alcohols tend to oligomerize under acidic conditions. By applying triphenylphosphine as Lewis base, it was possible to directly synthesize substituted olefins with easy to handle and inexpensive reagents. This is due to the fact that the co-catalyst is interacting with the carbo-cationic intermediate inhibiting a second attack of an *in situ* generated styrene derivative. Additionally, a dehydrative hydroarylation was conducted without a co-catalyst, because of a faster nucleophilic addition of the electron-rich arenes.

The coupling of vanillin alcohol as benzylic alcohol with electron-rich arenes catalyzed by organic acids or by using acidic deep eutective solvents was shown in Chapter 3. The derived bisguaiacol structures were subsequently hydrogenated and demethoxylated with Raney-Ni as catalyst to symmetrical diols, which act as polymer building blocks. Polymerization was conducted with various esters and a carboxylic acid *via* transesterification with $Zn(OAc)_2$ and condensation. This route shows an alternative way to new thermoplastics from Lignin-derived starting materials under mild reaction conditions, which are in agreement with the principles of green chemistry.

Instead of acid catalysis, another possible way to activate C-O bonds of benzylic alcohols is the magnesiation with alkyl Grignard reagents. In Chapter 4, a naphthyl Grignard reagent was formed *in situ* with *n*-hexylmagnesium bromide by application of an iron catalyst and tricyclohexyl phosphine as ligand, and subsequently used as nucleophiles in the coupling with thioesters and CO_2. Interestingly, an *ortho*-selective nucleophilic attack was observed when using thioesters as electrophiles, which is most likely based on the formation of a six-membered transition state. Nevertheless, the product could not be obtained in over 43% yield.

Thioesters generally show an extraordinary reactivity as electrophiles in coupling reactions, due to the poor orbital overlap between the sulfur atom and the carbonyl group. A new application of thioesters for the generation of ketones is described in Chapter 5. In a transition metal-free tandem reaction with vinyl magnesium bromide, a β-sulfanyl ketone is generated by the *in-situ* formation of a Michael acceptor and subsequent attack of a free thiolate. The formation of a chelate complex hinders the attack of a second Grignard molecule to a tertiary alcohol. Oxidation of the product leads to β-sulfonyl ketones which are important structures for pharmaceuticals and pesticides.

Deutsch

C-C Bindungsknüpfungen spielen eine wichtige Rolle in der Organischen Chemie. In dieser Arbeit wurden Säurekatalyse oder Grignard Reaktionen verwendet, um benzylische Alkohole und Thioester in wertvolle Verbindungen mit neuen Kohlenstoff-Kohlenstoffbindungen umzuwandeln.

In Kapitel 2 wurde die dehydrative Kupplung von benzylischen Alkoholen beschrieben. Benzylische Alkohole tendieren dazu, unter sauren Bedingungen zu oligomierisieren. Wenn in der beschriebenen Reaktion allerdings Triphenylphosphin hinzugefügt wird, können substitutierte Olefine einfach, aus leicht handhabbaren und kostengünstigen Edukten direkt hergestellt werden. Das liegt daran, dass die Interaktion des Co-Katalysators mit dem kationischen Intermediat einen weiteren Angriff eines *in situ* erzeugten Styrolderivats verhindert. Zusätzlich dazu wurde eine dehydrative Hydroarylierung durchgeführt. Dabei konnte durch den schnelleren nukleophilen Angriff auf Co-Katalysatoren verzichtet werden.

In Kapitel 3 wurde gezeigt, dass Vanillin nach Umsatz zum benzylischen Alkohol mit elektronenreichen Aromaten gekoppelt werden kann, wenn organische Säuren als Katalysatoren oder saure stark eutektische Lösungsmittel verwendet werden. Die daraus resultierenden Bisguaiacolverbindungen wurden anschließend unter Nickelkatalyse hydriert und zu symmetrischen Diolen demethoxyliert. Diese wurden dann als Polymerbausteine mit verschiedenen Estern und einer Carbonsäure verwendet und mit $Zn(OAc)_2$ als Katalysator durch Umesterung und Kondensation zu Thermoplasten umgesetzt. Diese Vorgehensweise zeigt also einen alternativen Weg zu biobasierten Kunststoffen, die aus Lignin-basierten Edukten hergestellt werden können.

Neben Säure-Katalyse, gibt es auch noch andere Arten, C-O Bindungen von benzylischen Alkoholen zu aktivieren. Eine Möglichkeit wurde in Kapitel 4 vorgestellt. Ein Naphtyl Grignardreagenz wurde als Intermediat aus dem entsprechenden Alkohol durch Eisenkatalyse mit einem Alkyl Grignard-Reagenz hergestellt und anschließend wurden Thioester oder CO_2 als Elektrophile zugegeben. Interessanterweise wurde eine *ortho*-Selektivität beim nukleophilen

Angriff des Grignard-Reagenzes an Thioestern beobachtet. Diese ist höchstwahrscheinlich auf die Bildung eines sechsgliedrigen Übergangszustandes zurückzuführen. Leider konnte das entsprechende Produkt jedoch nur mit maximal 43% erzeugt werden.

Thioester besitzen wegen der geringen Orbitalüberlappung zwischen dem Schwefelatom und der Carbonylgruppe generell eine besondere Reaktivität als Elektrophil in Kupplungsreaktionen. In Kapitel 5 wurde eine neue, Übergangsmetall-freie Anwendung von Thioestern in Kupplungsreaktionen mit Vinylmagnesiumbromid beschrieben. β-Sulfanylketone konnten durch die *in situ* Bildung eines Michael Akzeptors und anschließendem Angriff des freien Thiolats synthetisiert werden. Ein chelatförmiger Übergangszustand verhindert dabei, dass ein zusätzlicher nukleophiler Angriff zu einem tertiären Alkohol stattfindet. Durch Oxidation des Produkts können β-Sulfonylketone gebildet werden, die in Medikamenten und Pestiziden zu finden sind.

7. Appendix

7.1. Abbreviations

Đ	M_w/M_n = molar dispersitiy
Ac	Acetate
Acac	Acetylacetonate
AD	Adipic acid
*t*Am	$CEtMe_2$
Ar	Aryl
Dba	Dibenzylideneacetone
BA	Brønsted acid
BINAP	(2,2'–Bis(diphenylphosphino)–1,1'–binaphthyl)
Bn	Benzyl
BTX	Benzene, toluene, xyleme
Bu	Butyl
Cat.	Catalyst
CA	Citric acid
ChCl	Choline chloride
COD	1,5-Cyclooctadien
COSY	Correlation spectroscopy
CPME	cyclopentyl methyl ether
Cy	Cyclohexyl
DBE	1,2-dibromoethane
DCC	Dicyclohexylcarbodiimid
DCE	1,2-dichloroethane
DCM	Dichloromethane
DEPT	Distorsionless enhancement by polarization transfer
DES	Deep eutectic solvents
DFDC	Dimethylfuran-2,5-dicarboxylate
DMAP	4-(Dimethylamino)-pyridine
DMB	1,3-Dimethoxybenzene
DMF	Dimethylformamide
DMS	dimethyl sulfone
DMSO	Dimethylsulfoxide
DP	Diphenyl carbonate
DPEPhos	Bis[(2-diphenylphosphino)phenyl] ether
DPP	diphenylphosphate
Dppe	1,2-bis(diphenylphosphino)ethane
Dppf	1,1’-bis(diphenylphosphino)ferrocene
DSC	Differential scanning calorimetry
DT	Dimethyl terephthalate

EA	Ethyl acetate
EI	Electronic ionization
Et	Ethyl
Equiv.	Equivalents
EWG	Electron withdrawing group
FC	Friedel-Crafts
FDCA	2,5-furan dicarboxylic acid
FID	Flame ionization detection
FTIR	Fourier transformation infrared spectroscopy
GC	Gas chromatography
GVL	γ-valerolactone
Hept	*n*-Heptane
Hex	*n*-Hexane
Me	Methyl
HBA	Hydrogen bon acceptor
HBD	Hydrogen bon donor
Hept	*n*-Heptane
Hex	Hexyl/ *n*-Hexane
5-HMF	5-Hydroxymethylfurfural
HMBC	Heteronuclear multiple bond correlation
HSQC	Heteronuclear single quantum coherence
ILS	Ionic liquids
LA	Lewis acid
LB	Lewis Base
LG	Leaving group
L/Lig.	Ligand
LADES	Lewis acid DES
M	Metal
MA	Malonic acid
MBC	*p,p′*-Methylene biscycloheanol
M_n	Number average molar mass
Mp	Melting point
MS	Mass spectrometry
Ms	Mesityl
M_w	Mass average molar mass/ molecular weight
NADES	Natural DES
NMP	N-methyl-2-pyrrolidone
NMR	Nuclear magnetic resonance
Nu	Nucleophile

OA	Oxalic acid
PBS	Polybutylene succinate
PE	Polyethylene
PEF	polyethylene 2,5-furandicarcoxylate
PEG	Polyethylene glycol
PET	Polyethylene terephthalate
Ph	Phenyl
PHA	Polyhydroxyalkanoates
PLA	Polylactic acid
PP&A	Polypropylene and polyamide
ppm	Parts per million
Pr	Propyl
PSA	Pressure sensitive adhesives
PVC	Polyvinylchloride
RCF	Reductive catalytic fractionation
R_f	Retention factor
rt	Room temperature
STD	Internal standard
$T_{5\%}d_{N2}$	Thermal decomposition temperature T5 (5%wt weight loss) under N_2 atmosphere
T_{cc}	Cold crystallization temperature
Tf	Triflate
TFA	Trifluoroacitic acid
TFP	Tri(2-furyl)phosphane
Tg	Glass-transition temperatures
TGA	Thermogravimetric analysis
THF	Tetrahydrofuran
TLC	Thin layer chromatography
T_m	Melting temperature
TM	Transition metal
$T_{max}d_{N2}$	Maximum thermal decomposition temperature
TMB	1,3,5-Trimethoxybenzene
TPA	terephthalic acid
T_R	Retention time
Ts	Tosylate
TsOH	*p*-toluenesulfonic acid
UV	Ultra violet
X	Halogen

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