Development of New Catalytic Systems for the Palladium-Catalyzed Carbonylation of Olefins

Dissertation

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Die Arbeit wurde angeleitet von: Prof. Dr. Ivana Fleischer,
Prof. Dr. Olga Garcia Mancheño

To Simon and my family

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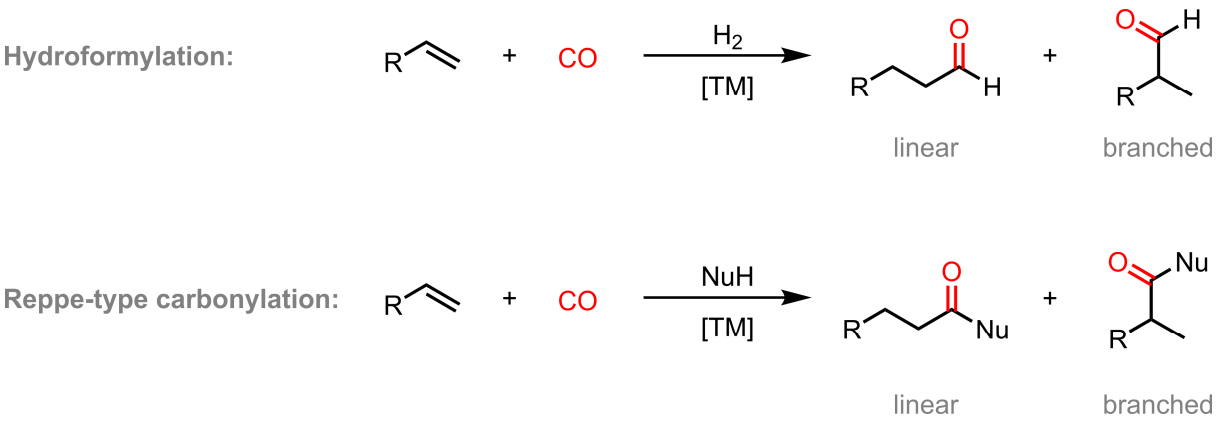
Chapter 1

Introduction

1.1 Carbonylation of Olefins

Carbonylation, the introduction of carbon monoxide (CO) into molecules, is of great importance for large scale industrial processes as well as in small laboratory syntheses. Many different substrates can be subjected to carbonylation, mainly alkynes, alkenes, organic halides, alcohols and ethers, more rarely also esters, aldehydes, amines and nitro compounds. Therefore, a wide range of products is accessible *via* this transformation in a highly atom economic fashion. The most effective carbonylation catalysts are based on Fe, Co, Ni, Ru, Rh, Pd, Os, Ir, Pt and Cu.[1] In the following, the most important carbonylative reactions of olefins - hydroformylation and Reppe-type carbonylation - will be introduced (Scheme 1.1). Both reaction types can take place in a linear or a branched fashion, whereas the regioselectivity (also referred to as *n*-/*iso*-selectivity) is influenced by the substrate, the choice of ligand, as well as ligand/metal ratio.



Scheme 1.1. The most important carbonylations of alkenes. TM = transition metal.

Hydroformylation

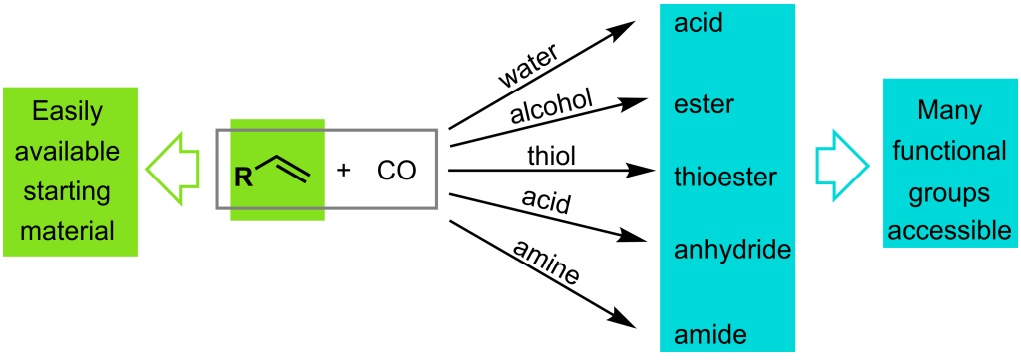
The first carbonylation reaction was discovered by Otto Roelen in 1938 during mechanistic investigations of the cobalt-catalyzed Fischer-Tropsch synthesis of hydrocarbons from carbon monoxide and hydrogen.[2] He observed the formation of propanal from ethylene and syngas (CO, H_2) in the presence of $HCo(CO)_4$. This reaction type was named oxo-synthesis, but it is nowadays known as hydroformylation. Hydroformylation attracted a considerable amount of attention, especially from industrial chemists. A significant milestone was achieved by Wilkinson *et al.*, who discovered highly active and selective rhodium catalysts.[3] Since then, numerous publications on highly active, chemo- and regioselective rhodium-based catalytic systems appeared in the literature.[4] Also alternative

transition metals, such as palladium, ruthenium and iridium were investigated.[5] Since aldehydes are highly demanded building blocks, hydroformylation is employed in numerous large scale industrial applications, catalyzed by Co- and Rh-complexes (more than 10 million tons of oxo-products per year).[6] The regioselective control of hydroformylation was also intensively investigated.[7] The linear product is desired for many bulk applications, whereas the branched aldehyde is of great interest in the synthesis of fine chemicals and pharmaceuticals.[8]

Since this thesis is mainly focused on Reppe-type carbonylation, this type of transformation will be discussed in more detail.

Reppe-type carbonylation

The second important type of carbonylation of olefins was discovered by Walter Reppe during the 1930s and 1950s.[9] In the first Reppe-type carbonylation acrylic acid was generated from acetylene, CO and water as a nucleophile using toxic $Ni(CO)_4$ as a catalyst. Later on, also alkenes were applied instead of alkynes, whereby higher temperatures and pressures were required. If another nucleophile, such as alcohol, thiol, acid or amine was applied, different carboxylic acid derivatives, such as esters, thioesters, anhydrides or amides were generated (Scheme 1.2). Additionally, a promotor acid is often required for these reactions. The Reppe-type carbonylation enables the formation of many different functional groups from easily available starting materials in a highly atom economic manner, which has been enveloped to industrial processes.[6a] Typical Reppe-type carbonylation catalysts of olefins are based on Fe, Ru, Co, Ni, Pd, Pt and Cu, whereas reactions with cobalt and palladium are more relevant due to their high activity, since these metals can already be used at lower temperatures.[1]



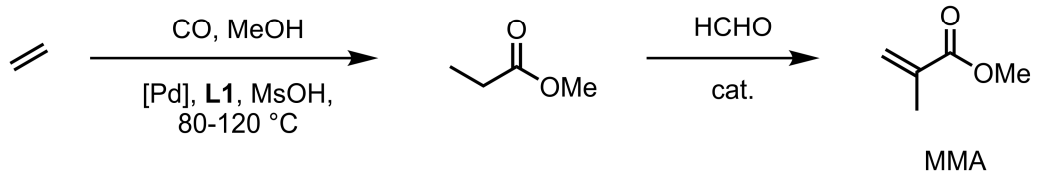
Scheme 1.2. Reppe-type carbonylation of olefins.

Reppe-type carbonylation of alkenes with CO and water, which is called hydrocarboxylation, provides carboxylic acids. A notable large scale industrial application at BASF is the synthesis of propionic acid from ethylene by using $Ni(CO)_4$ as catalyst, which is formed *in situ*.[6a]

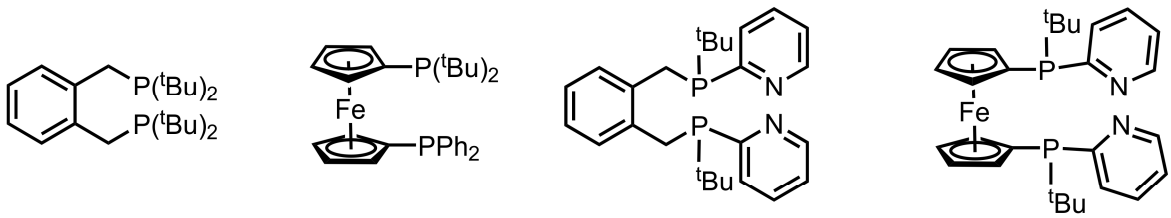
The hydroesterification of olefins with alcohols – also referred to as alkoxycarbonylation – is an important research field and well discussed in the literature.[10] Especially Pd/phosphine ligands are used in alkoxycarbonylation reactions, since they can be applied under milder reaction conditions.[11] The high affinity of CO to palladium can be explained by the fact that carbon monoxide is able to act as a σ-donor and π-acceptor. Since there is no simple carbonyl complex of palladium, an adequate combination of ligand, promotor acid and solvent is more difficult than for other metals.[1]

One important industrial application of alkoxycarbonylation is the synthesis of methyl methacrylate (MMA) by the Lucite ALPHA-process catalyzed by palladium and the current state-of-the art ligand dtbpx (**L1**, 1,2-bis(di-*tert*-butylphosphino-methyl)benzene, Scheme 1.3b), which is known for its unique activity and selectivity (Scheme 1.3a).[12]

a) Lucite ALPHA-process



b) Important ligands for the alkoxycarbonylation of olefins



L1, dtbpx **L2**, dppdtbpf **L3**, pytbpx **L4**

Scheme 1.3. Synthesis of methyl methacrylate (MMA) by the Lucite ALPHA-process and important ligands for the alkoxycarbonylation of olefins.

Beside other applications, **L1** is also of great importance for the alkoxycarbonylation of internal double bonds of long chain olefins, which was investigated by Mecking *et al.*.[13] In 2015, Bredenkamp *et al.* conducted a detailed ligand study for the methoxycarbonylation of

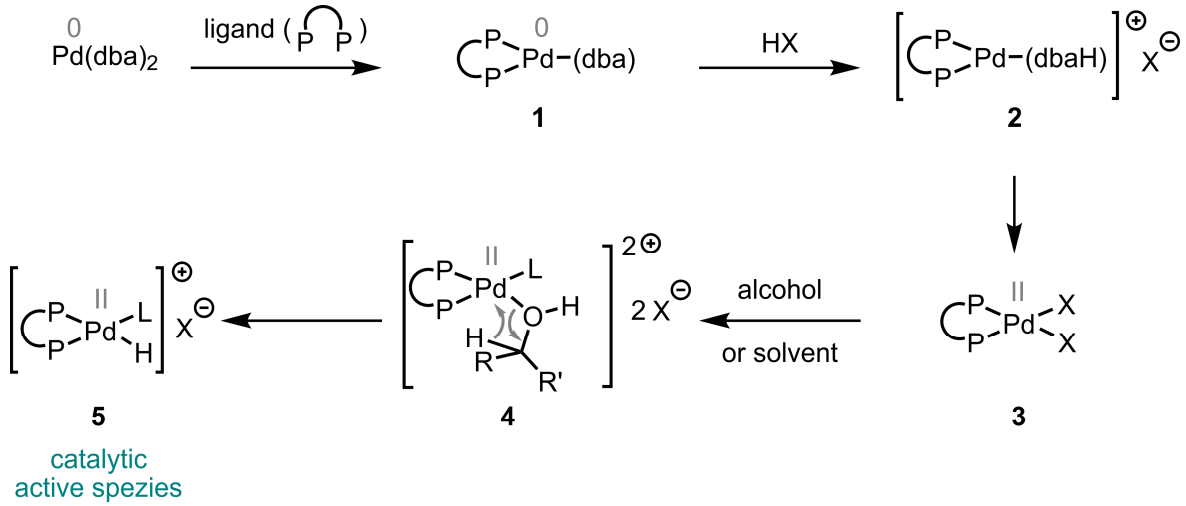
medium-chain alkenes.[14] The tested monodentate ligands were either inactive or low turnover frequencies (TOF) were observed, whereas **L1** furnished excellent activity and regioselectivity towards the linear ester in the methoxycarbonylation of 1-octene. The unique activity of **L1** can be explained by its properties to be a relatively flexible bidentate ligand with a moderate to large bite angle. In this study, the unsymmetrical ligand dppdtbpf (**L2**, 1-diphenylphosphino-1´-(di-tertbutylphosphino)ferrocene, Scheme 1.3b) was employed for the first time in an alkoxycarbonylation of olefins. The combination of two bulky electron-rich and -poor phosphine atoms enabled a considerable higher TOF than **L1**. Furthermore, the catalytic system with **L2** was stable up to 120 °C, which is an important property for the heavy chemical industry.

In 2016, Beller *et al.* introduced the novel ligand pytbpx (**L3**, 1,2-bis((tert-butyl(pyridin-2-yl)phosphanyl)methyl)benzene, Scheme 1.3b) for the alkoxycarbonylation of various alkenes, which is also more active than **L1**.[15] Notably, in comparison to previously known ligands, **L3** was able to carbonylate also tetra-substituted olefins, which are extremely difficult to transform (Keulemans´ rule),[16] in almost quantitative yields. Further on in 2017, Beller *et al.* developed a new class of ferrocenyl phosphine ligands.[17] In addition, a catalytic system of $PdCl_2$ and **L4** (1,1´-bis(tert-butyl(pyridin-2-yl)phosphino)ferrocene, Scheme 1.3b) enabled the transformation of ethylene in excellent yields and a high reaction rate, whereas no additional acid co-catalyst was necessary. Nevertheless, most of the reported catalytic systems still require high temperatures and CO-pressures.

The mechanism of the alkoxycarbonylation of olefins was initially investigated by Drent *et al.* in 1995.[18] In general, two different pathways are conceivable, in which either an alkoxide-(Pd–OR) or a hydride-palladium (Pd–H) complex is catalytically active.[18-19] Later on, Heaton *et al.* performed spectroscopic investigations, supporting the hydride mechanism theory, since all intermediates have been identified by multinuclear NMR spectroscopy and ^{13}C-labelling.[20] The palladium-hydride theory was also supported by Tooze, Cole-Hamilton and co-workers.[21] Accordingly, the catalytically active Pd(II)-hydride complex **5** is generated from a Pd-source in combination with a ligand and an acid, originally described by Heaton *et al.* (Scheme 1.4).[22] First of all, the ligand coordinates to the palladium precursor to form complex **1**, which is protonated with a Brønsted acid. In the next step, the Pd(II) species **3** is generated from the Brønsted acid anion binding to palladium, which is replaced by alcohol

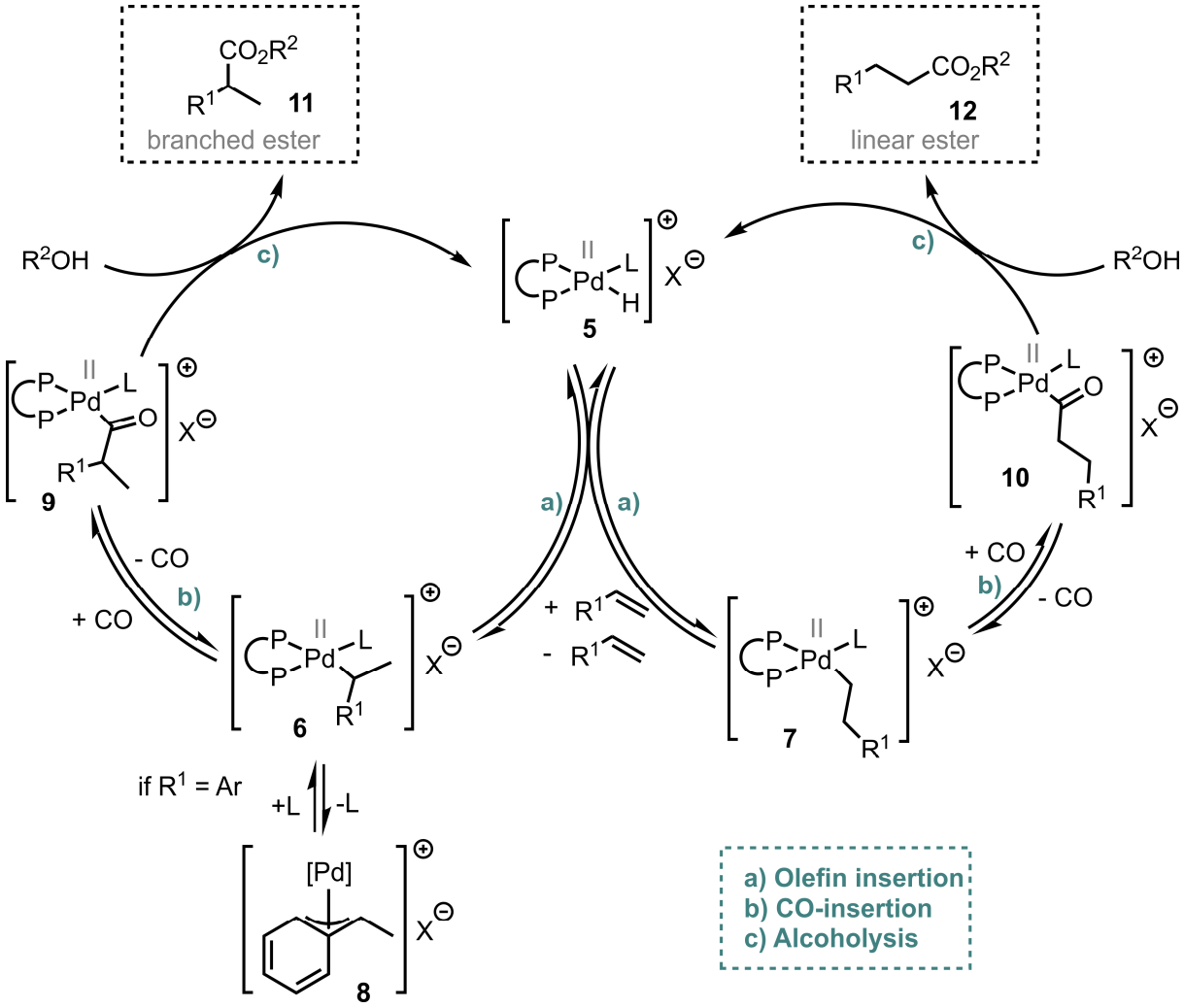
or solvent molecule afterwards. Subsequently, the hydride species **5** is formed by a β-hydride elimination of **4**.

Furthermore, there has to be an additional Pd-hydride formation pathway, since tertiary alcohols can also successfully be applied. Also the oxidative addition of an acid to Pd(0) is conceivable.[23]



Scheme 1.4. Formation of the catalytic active palladium-hydride species **5** described by Heaton *et al.*.[22]

The catalytic cycle starts with an olefin insertion in order to form the alkyl palladium species **6** or **7** (Scheme 1.5). The regioselectivity is already defined in this step, whereas in case of aromatic residues R^1 an additional equilibrium with the η^3-palladium species **8** is possible, favoring the branched products for these substrates. After the insertion of carbon monoxide, the Pd-acyl species **9** or **10** are formed. Finally, the catalytic cycle is closed by the rate determining alcoholysis, yielding either the branched or the linear ester (**11**, **12**) and regenerating the Pd(II)-hydride complex **5**. The alcoholysis is decelerated for higher alcohols. All the carbonylation catalysts are able to isomerize double bonds, which was investigated by Mecking *et al.*.[13c] Isomerizing alkoxycarbonylation is possible, because olefin- and CO-insertion are both reversible steps and the alcoholysis displays the highest energy barrier. Therefore isomerization of the double bond to the the Pd-acyl species with the lowest energy barrier, which is the linear Pd-acyl species, often takes place. Sterically demanding diphosphine ligands prefer the formation of the linear Pd-acyl species in addition.



Scheme 1.5. Commonly accepted alkoxycarbonylation mechanism.

1.2 Carbon Monoxide and CO Surrogates

Carbon monoxide (CO) is a stable, easily available, reactive and cost efficient C1 building block. Therefore, it is used to introduce carbonyl groups into molecules in many homogeneously catalyzed reactions. On the other side it is a toxic, flammable and potentially explosive gas. These properties require increased workplace safeguards, which is especially problematic for a standardly equipped laboratory.

In laboratory scale reactions, gaseous CO is often replaced by inorganic or organic CO-surrogates, molecules, which can release carbon monoxide under certain conditions and therefore represent a "CO-free" alternative. Many different CO-surrogates are known in the literature[24], for example formaldehyde (**13**),[24b, 25] alcohols (**14**),[26] CO_2 (**15**),[27] metal carbonyls (**16**),[28] formates (**17**),[10c, 10d, 29] formic acid (**18**),[30] formamides (**19**),[31] pivaloyl chloride (**20**),[32] *N*-formylsaccharin (**21**),[33] acid chlorides (COgen, **22**)[32, 34] and silacarboxylic acids (SilaCOgen, **23**)[35] (Figure 1.1). An ideal CO-surrogate should be also an atom economic alternative, since this is an important advantage of carbonylation chemistry. Therefore the amount of CO relative to the whole molecular weight is shown in brackets.

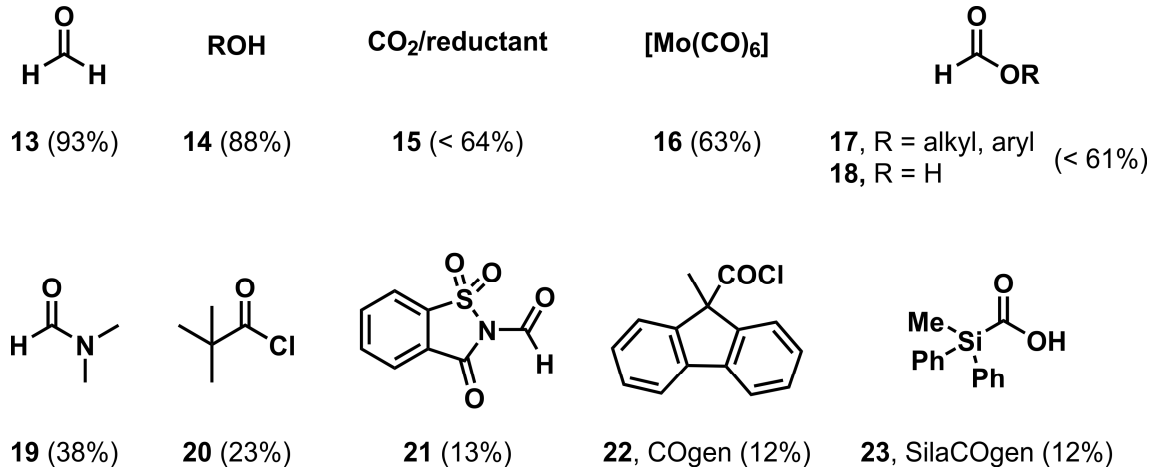
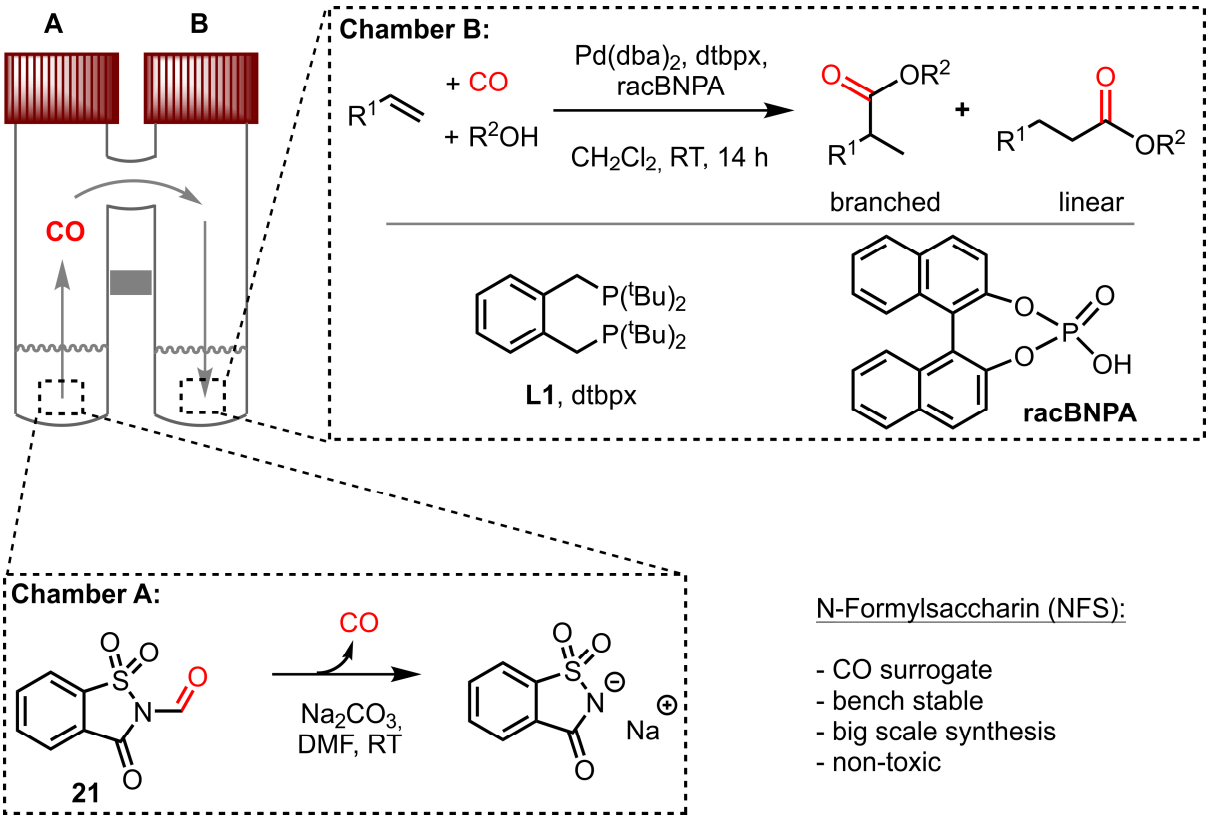


Figure 1.1. Typical CO surrogates with the amount of CO relative to the molecular weight in brackets.

The most promising CO-surrogate is the readily available greenhouse gas CO_2. Due to the thermodynamic and kinetic stability of CO_2, a highly active reductant is required to generate CO. In addition, also biomass, a renewable and easily accessible resource, is a very auspicious CO-surrogate.[26b, 36]

1.3 Preliminary Work on Alkoxycarbonylation of Styrene

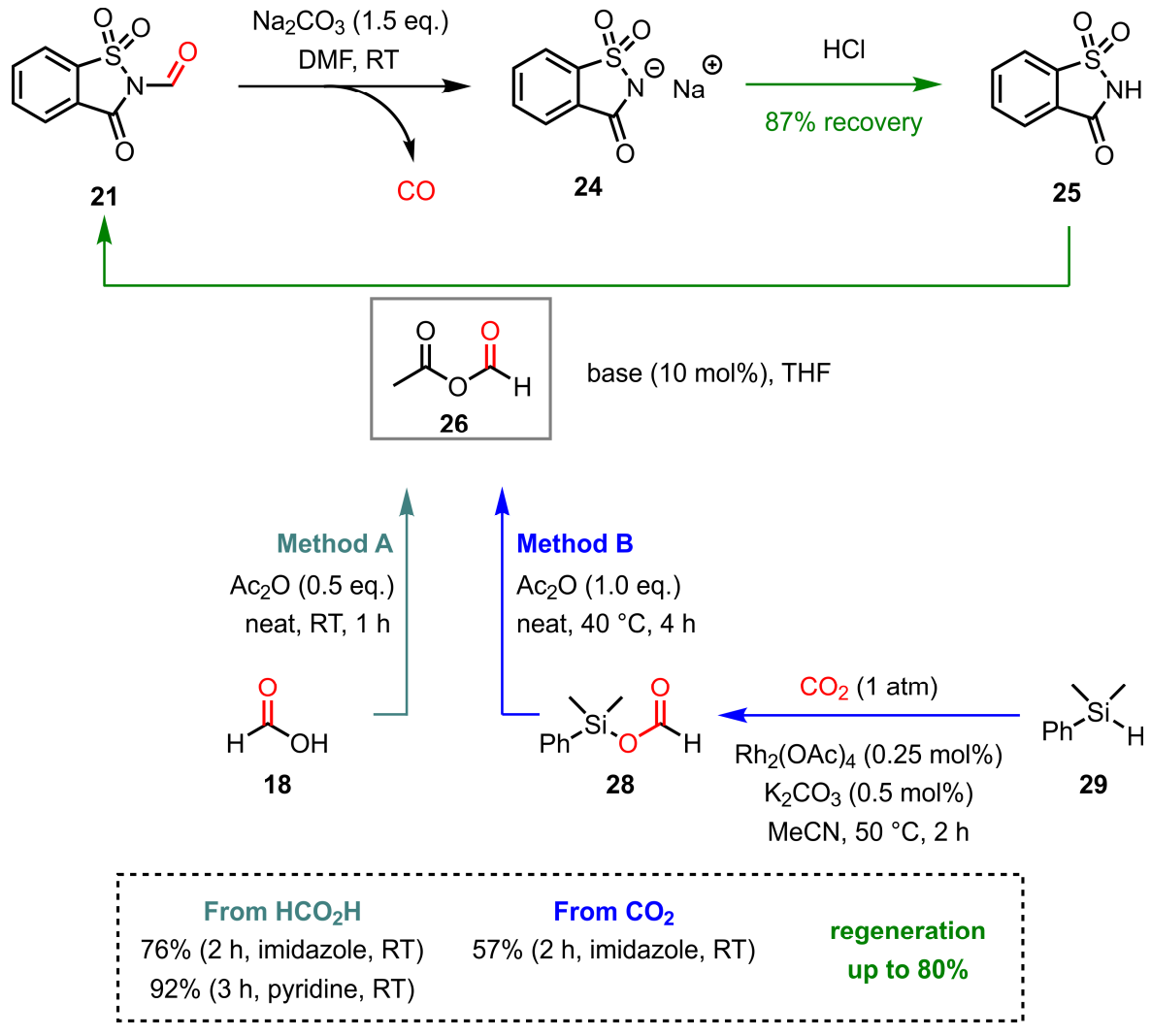
Recently, we described a highly active catalytic system for the alkoxycarbonylation of olefins under mild reaction conditions. Aromatic, aliphatic and functionalized alkenes were successfully carbonylated at room temperature (RT) in 14 h with 2.5 bar of CO (Scheme 1.6).[37] This was enabled by the development of a highly active catalytic system, based on $Pd(dba)_2$, dtbpx (**L1**) as a ligand and BNPA (1,1´-bi-2-naphthol phosphoric acid) as an acid. High regioselectivities towards the branched ester were observed for *meta*- and *para*-substituted styrene derivatives, whereas a complete breakdown in regioselectivity was obtained for *ortho*-substituted ones. Nevertheless, a great number of functional groups was tolerated by the catalytic system.



Scheme 1.6. Previously described alkoxycarbonylation of alkenes by using *N*-formylsaccharin as a CO surrogate in a two chamber pressure tube.[37]

For the reaction setup a two-chamber pressure tube, previously reported by Skrydstrup *et al.*[32], was used for decarbonylation in chamber **A** and simultaneous alkoxycarbonylation in chamber **B**. By the *ex-situ* generation of CO, the potential changes in reactivity and selectivity by additional reaction components were avoided. In order to overcome the

drawbacks of gaseous carbon monoxide, *N*-formylsaccharin (NFS, **21**) was applied as a CO-surrogate, originally described by Cossy *et al*.[38] and later on by Manabe and co-workers.[33] CO was liberated from NFS by treatment with Na_2CO_3 as a base in DMF. The type of base was important to guarantee a reproducible decarbonylation in the two-chamber pressure tube. NFS is a bench stable and non-toxic CO-surrogate, which can be synthesized on large scale from saccharin. On the other side, NFS contains only 13% carbon monoxide relative to its molecular weight, whereas many other CO-surrogates exhibit a considerably better atom economy. This drawback was overcome by the development of a suitable recovery and regeneration process (Scheme 1.7).



Scheme 1.7. Decarbonylation and regeneration of *N*-formylsaccharin.[37]

After decarbonylation of **21**, saccharin (**25**) can be precipitated in 87% yield after the addition of HCl to **24**. NFS was synthesized from **25** and the *in-situ* formed mixed anhydride

26 under basic conditions.[39] Two different reaction methods were described to synthesize **26**. In method **A** the synthesis of **26** from formic acid (**18**) and acetic anhydride is used for the larger laboratory scale synthesis of *N*-formylsaccharin (20 g scale). In comparison, method **B** featured a reductive activation of CO_2. A Rh-catalyzed CO_2 hydrosilylation was used to generate formate **28** under mild reaction conditions, which was quantitatively converted to the mixed anhydride **26**.[40] Therefore, an indirect use of CO_2 for the regioselective alkoxycarbonylation of alkenes was enabled.

Based on this catalytic system, other challenging Reppe-type carbonylations of olefins, like thiocarbonylation (Chapter 2) and cyclocarbonylation (Chapter 4) under mild reaction conditions were developed. Moreover, the attempted application of a cyclocarbonylation in the synthesis of a natural compound is reported (Chapter 4). Additionally, a tandem reaction of the synthesized thioester with vinyl magnesium bromide in order to generate β-sulfanyl ketones was established (Chapter 3).

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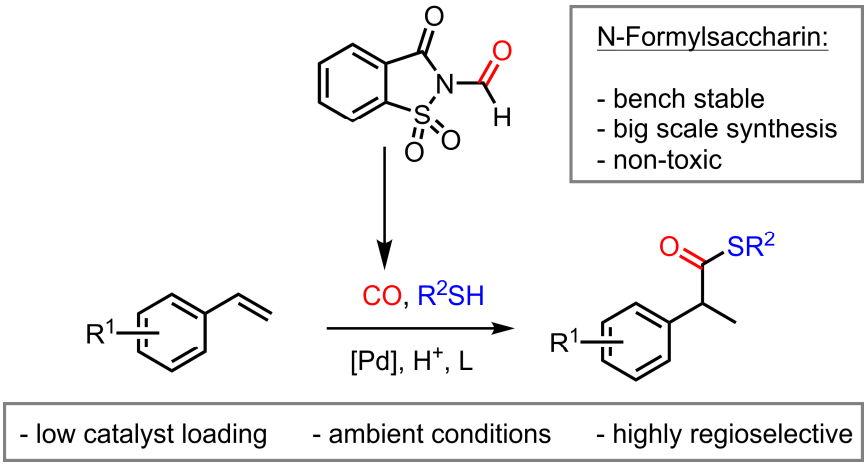
Chapter 2

Regioselective Thiocarbonylation of Vinyl Arenes



Abstract: A palladium-catalyzed thiocarbonylation of styrene derivatives is reported for the first time. The combination of thiols as nucleophiles and a bidentate ligand ensures a unique reaction outcome with high regioselectivity toward the more valuable branched isomer and new reactivity. The ambient reaction conditions (temperature, catalyst loading) and the use of a CO surrogate render this transformation a useful method for the synthesis of thioesters from available feedstock. Various functional groups on arene and thiol substituents are tolerated by the system. Notably, challenging *ortho*-substituted styrenes are converted with unprecedentedly high regioselectivity.

Author contribution:

VH: 80% of reproduced part

Initial optimizations; overcome reproducibility-problems; 50% of the ligand screening (Scheme 2.10); acid- and [Pd]-precursor screening (Table 2.1); 50% of the thiol screening (Table 2.2); influence of the amount of heptanethiol (Scheme 2.11); substrate screening (Table 2.3); thiocarbonylation of various olefins (Scheme 2.12); deuteration experiments (Scheme 2.13); comparison between alkoxy- and thiocarbonylation beside the substrates 1-hexene and 2-hexene (Figure 2.2).

PHG: 20% of reproduced part

50% of the ligand screening (Scheme 2.10); 50% of the thiol screening (Table 2.2); comparison between alkoxy- and thiocarbonylation for 1-hexene and 2-hexene (Figure 2.2); competition Experiments (Scheme 2.14).

VH wrote the manuscript with contributions from PHG.

IF: corresponding author

Author contribution:

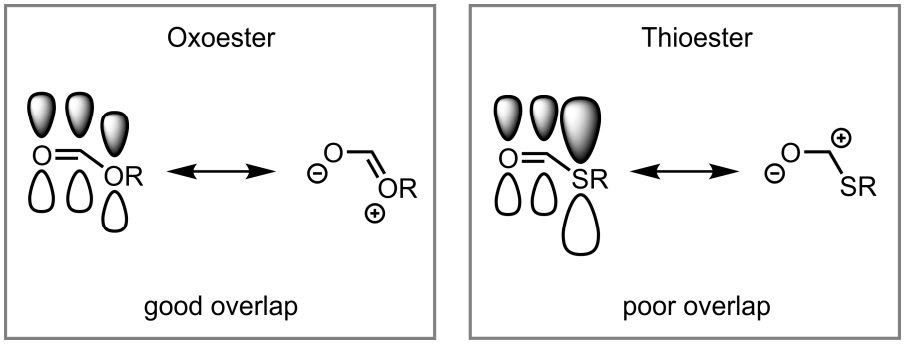
VH: 100% of reproduced part

IF: corresponding author.

2.1 Introduction - Thiocarbonylation

2.1.1 Reactivity and Biological Importance of Thioesters

Thioesters constitute a compound class of immense biological importance and they are also of considerable interest for synthetic organic chemists. Different hypotheses assume that thioesters played an important role in the origin of life on earth, since they are intermediates in several key processes of biochemistry.[3] Thioesters are activated esters and their reactivity is comparable to acid chlorides and anhydrides in nucleophilic substitution reactions. They are more active than alcohol-derived esters, because they are less stabilized by mesomeric effects, due to poorer orbital overlap between the sulfur atom and the carbonyl group (Scheme 2.1). In addition, thiolates are better leaving groups than alcoholates.



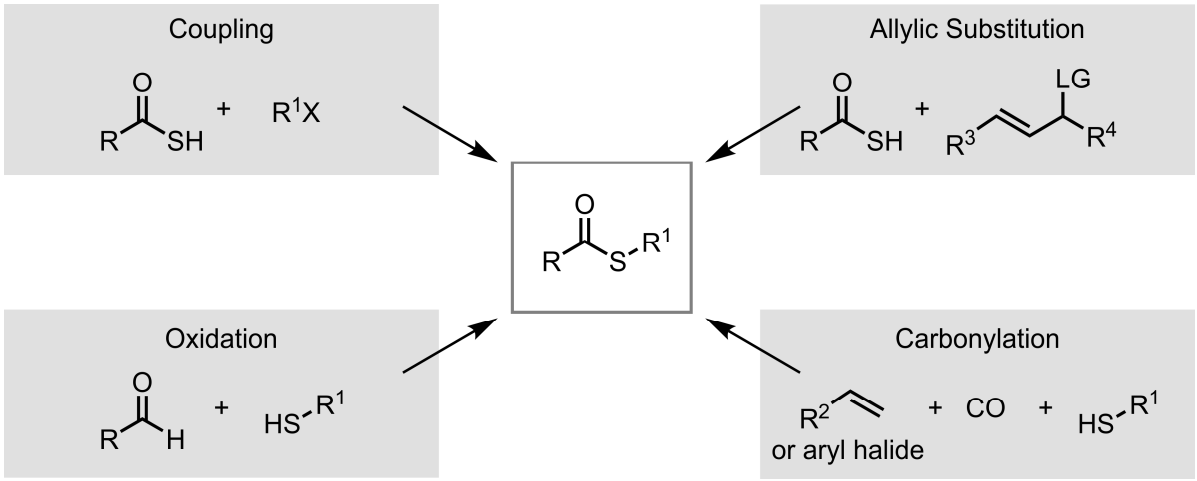
Scheme 2.1. Reactivity of thioesters in comparison to oxoesters.

Therefore, acyl substitution of thioesters is taking place more rapidly, which is the reason why they are often found as intermediates in biochemical processes, when an activated acyl functionality is needed, e.g. in transfer reactions assisted by coenzyme A.[4] Furthermore, thioesters are involved in polyketide biosynthesis.[4b] Additionally, their properties render thioesters expedient intermediates in numerous synthetic applications, such as the formation of esters,[5] amides,[6] and aldehydes[7] as well as the synthesis of ketones *via* transition-metal-catalyzed cross-coupling reactions(see Chapter 3.1).[7-8]

2.1.2 Synthesis of Thioesters

Many different methods are available to synthesize thioesters, but the most common one is acylation of thiols by using a carboxylic acid, acid anhydride, or chloride as the acyl source in

the presence of an activating reagent.[9] The main drawback of these reactions is the limited range of possible substrates. Therefore, many metal catalyzed syntheses of thioesters have been investigated (Scheme 2.2).

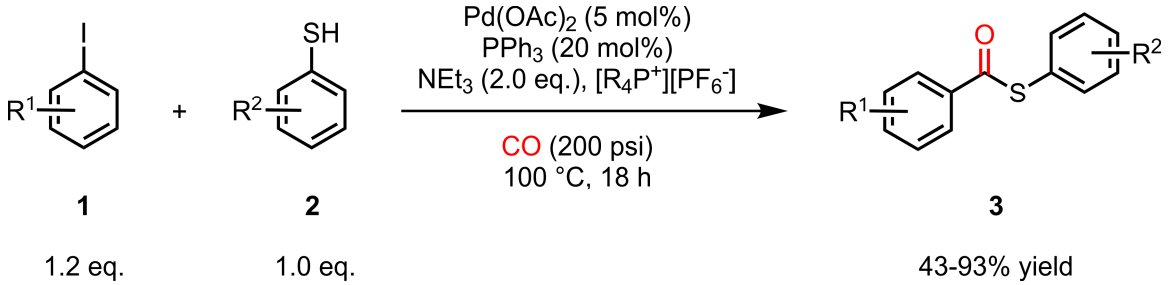


Scheme 2.2. Most important metal-catalyzed synthetic pathways for thioesters.

Thiocarboxylates can either be applied in the coupling with aryl halides,[10] or in allylic substitution reactions.[11] Additionally, thioesters can also be synthesized from aldehydes in an oxidative transformation, for example by using ^{t}Bu-hydroperoxide as an oxidant.[12] Moreover, carbonylation chemistry can also be used to generate thioesters, mainly from aryl halides or olefins. In following, this type of transformation will be discussed in more detail.

2.1.2.1 Synthesis of Thioesters by Carbonylation of Aryl Halides

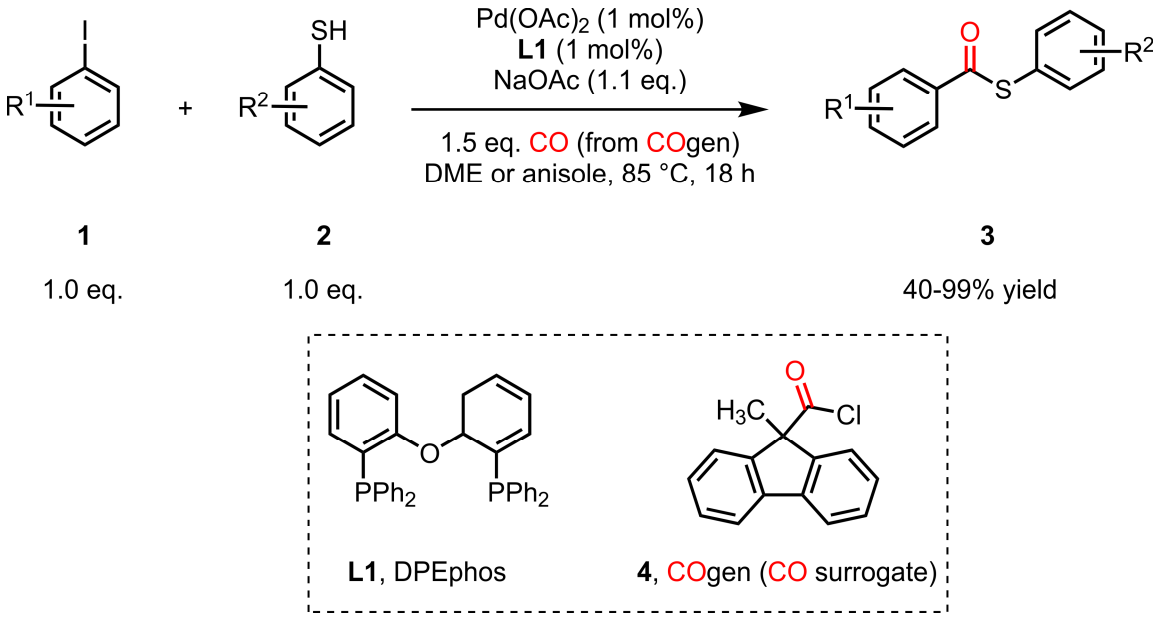
Aromatic thioesters **3** can be obtained by carbonylation of aryl halides **1** in the presence of thiols **2**. In the pioneering work of Alper the first Pd-catalyzed thiocarbonylation of aryl iodides **1** was published in 2008.[13] A catalytic system consisting of 5 mol% $Pd(OAc)_2$, 20 mol% PPh_3 as ligand in combination with 2.0 eq. of a base was used (Scheme 2.3).



Scheme 2.3. First thiocarbonylation of aryl iodides reported by Alper *et al*..[13]

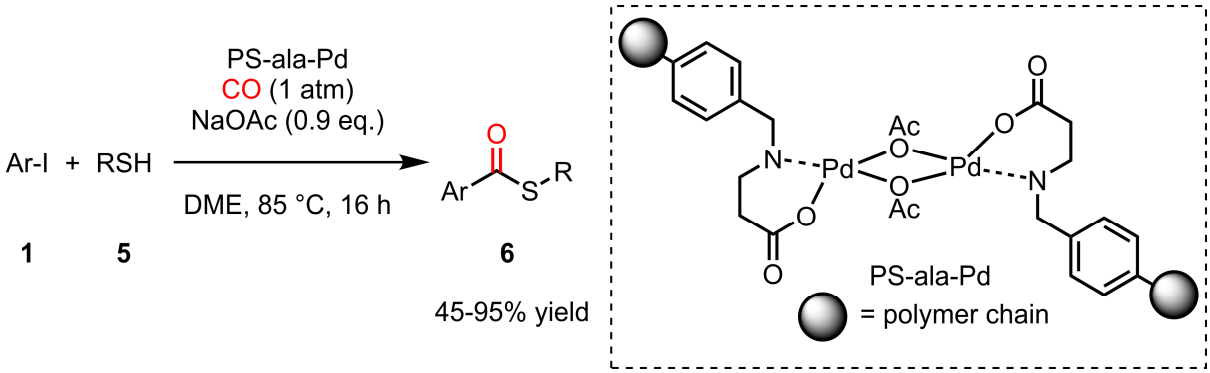
A phosphonium salt ionic liquid (PSIL) was chosen as a solvent, due to its excellent properties such a nonflammability, nonvolatility, chemical and thermal stability and most importantly the recyclability. The addition of hexane after the reaction enabled the formation of two phases with the palladium catalyst in the ionic liquid layer and the thioester in the organic phase. After recovery of the catalyst, another reaction cycle was possible without any loss of activity. The reaction featured a high functional group tolerance for both reaction partners, aryl iodides and thiols, whereas electron-withdrawing groups provided better yields than electron-donating substituents. Interestingly, also aliphatic thiols delivered good yields.

Similar to this work, Lei *et al*. reported a palladium-catalyzed thiocarbonylation of aryl iodides with sodium thiolates and a thiol/THF solvent mixture, which was able to afford also sterically hindered thioesters, such as ArCOS^{t}Bu.[14] Later on, in 2013 Skrydstrup *et al*. reported a Pd-catalyzed thiocarbonylation of aryl iodides **1** under milder reaction conditions, such as 1 mol% of $Pd(OAc)_2$, 1 mol% of ligand **L1** and especially by using only a stoichiometric amount of carbon monoxide, with NaOAc as a base and DME or anisol as a solvent.[6] CO was generated *ex situ* from 9-methylfluorene-9-carbonyl chloride (**4**, COgen) in a two-chamber pressure tube (Scheme 2.4). A thorough solvent and ligand screening led to prevention of the competing thioether formation and enabled a highly efficient method to transform electron-rich and electrondeficient aryl iodides.



Scheme 2.4. Thiocarbonylation of aryl iodides **1** using a CO surrogate reported by Skrydstrup *et al*..[6] DPEphos: bis[(2-diphenylphosphino)phenyl]ether.

Based on this work, the same group presented a modified catalyst system for carbonylation of aryl, vinyl and benzyl bromides.[15] The combination of 5 mol% $Pd(PhCN)_2Cl_2$ and 5 mol% of ligand Xantphos (= 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene) with NaOAc as a base in anisol at 120 °C for 18 h, proved to be the most efficient catalytic system, furnishing the desired products in up to 98% yield. An extensive substrate screening proved the applicability of the catalytic system. A phosphine free version for thiocarbonylation of aryl halides **1** was reported by Islam *et al*. in 2014 (Scheme 2.5).[16] They employed a polystyrene supported Pd(II) complex (PS-ala-Pd), which can easily be recovered by filtration after the reaction and can be reused up to six times without significant loss in activity.



Scheme 2.5. Ligand free thiocarbonylation of aryl halides **1** using a polymer supported catalyst.[16]

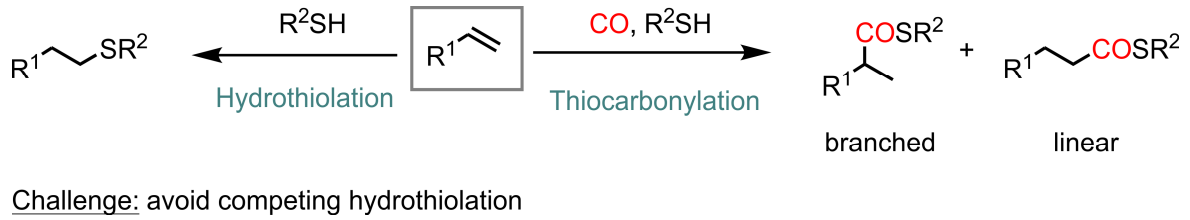
Most importantly, PS-ala-Pd is an air and moisture stable catalyst, which can be synthesized from inexpensive and commercial available starting materials (β-alanine, chloromethylated polystyrene, $Pd(OAc)_2$) in a two-step procedure. In 2016, Arndtsen *et al*. reported a method to introduce functionalized thiols, which are potentially incongruous for usual carbonylation conditions.[17] The solution is a two-step strategy generating an aminopyridinium salt from arylhalide, CO and DMAP (4-dimethylaminopyridine) in the presence of 5 mol% $Pd(P^tBu_3)_2$ *via* carbonylation, followed by a nucleophilic substitution with the corresponding thiol.

In addition to Pd-based chemistry, the first nickel-catalyzed synthesis of thioesters from aryl iodides was presented by Iranpoor, Firouzabadi and co-workers in 2015.[18] $NiCl_2$ was able to thiocarbonylate aryl iodides in the presence of a base, by using $Cr(CO)_6$ as a carbon monoxide source under air. Different functional groups and thiols were tolerated by the system providing good to excellent yields.

However, thiocarbonylation of aryl halides often proceeds under harsh reaction conditions or suffers from low atom economy. In comparison, the thiocarbonylation of alkenes is an interesting alternative.

2.1.2.2 Synthesis of Thioesters by Carbonylation of Alkenes/Alkynes

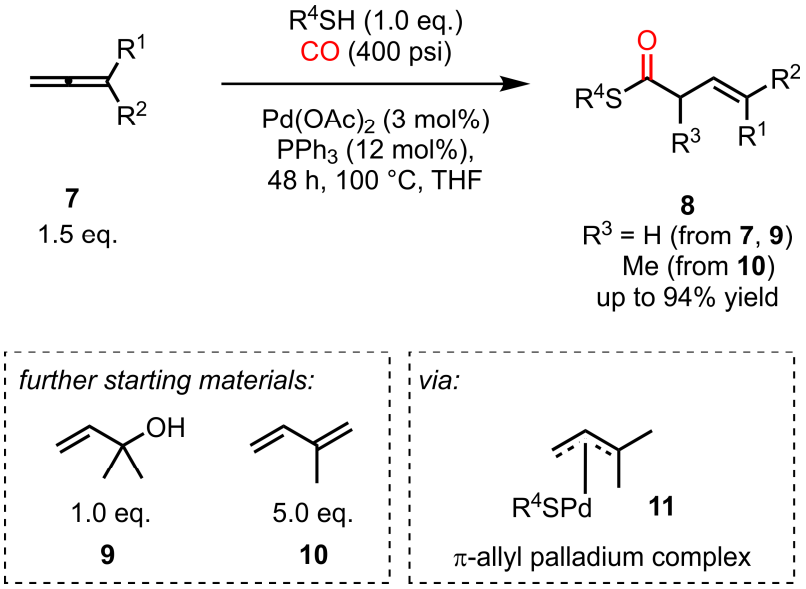
The direct carbonylation of olefins with thiols is based on the comprehensive research of Walter Reppe (*1892, †1969).[19] The so called Reppe-type thiocarbonylation – also referred to as hydrothioesterification – is a highly atom- and waste-economic method to synthesize complex thioesters in one step (Scheme 2.6).



Scheme 2.6. Reppe-type thiocarbonylation of olefins and competing hydrothiolation.

Although this is an attractive alternative to more common synthetic strategies, such as acylation of thiols, it is a poorly investigated research-field, since a number of obstacles need to be overcome. Working with free thiols is challenging, since they tend to oxidize and quickly generate the corresponding disulfides. Moreover, thiols are widely regarded as catalyst poisons for late transition metals, with their strong M–S bonding rationalized through a hard/soft acid/base (HSAB) soft–soft interaction.[20] Furthermore, the competing radical-mediated hydrothiolation of the olefin has to be avoided.[21]

Most investigations on thiocarbonylation were realized by Alper and co-workers. They reported on thiocarbonylations with thiophenols and carbon monoxide in order to generate β,γ-unsaturated thioesters **8** either from allenes **7**,[22] allylic alcohols **9**[23] or 1,3-conjugated dienes **10**[24] (Scheme 2.7). The best yields were obtained by using $Pd(OAc)_2$ in combination with the monodentate PPh_3 ligand. Pd(II) can be reduced to the catalytically active Pd(0) in the presence of the phosphine ligand and CO. The key intermediate for all three reactions is the π-allyl palladium complex **11**. In case of allylic alcohols **9** an acidic additive is required for protonation of the hydroxyl group, leading to elimination of water and generation of **11**. The reactions furnished excellent yields up to 94%. The high regioselectivity can be explained by the formation of the sterically less hindered π-allyl palladium complex **11**.



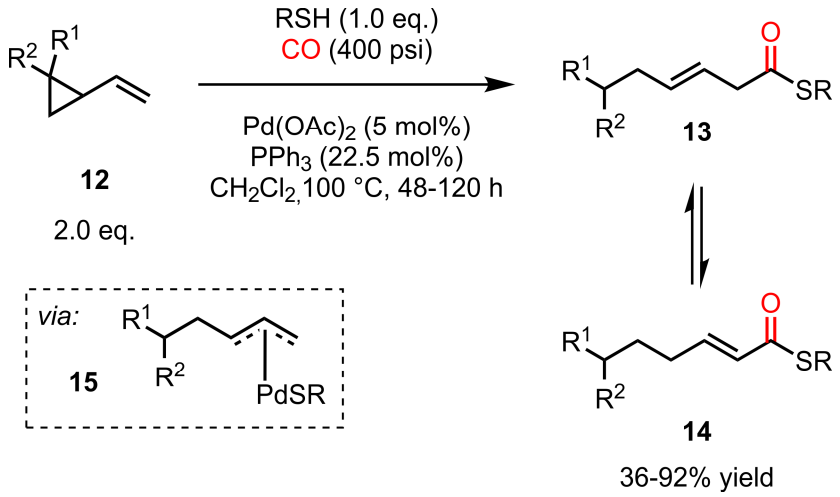
Scheme 2.7. Thiocarbonylation of allenes (**7**), allylic alcohols (**9**) and 1,3-conjugated dienes (**10**) reported by Alper *et al*..[22-24]

A direct utilization of the Pd(0)-source $Pd_2(dba)_3{\cdot}CHCl_3$ was also successful for all three synthetic strategies, albeit it led to slightly reduced yields. In 2001 Alper *et al*. reported the first enantioselective palladium catalyzed thiocarbonylation of prochiral 1,3-conjugated dienes.[25] They achieved good to excellent enantioselectivities up to 89% *ee* by using 5 mol% of $Pd(OAc)_2$ combined with 10 mol% of (*R*,*R*)-DIOP (= (*R*,*R*)-*O*-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane). The enantioselectivity-determining step was suggested to be the CO insertion to the π-allyl palladium complex **11**.

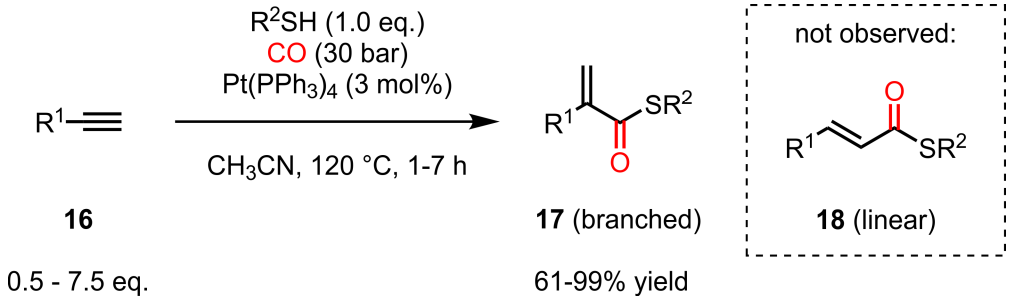
Later on, in 2009 Alper *et al.* investigated a ring opening thiocarbonylation of vinylcyclopropanes **12** catalyzed by 5 mol% $Pd(OAc)_2$, 22.5 mol% PPh_3 with 400 psi CO at 100 °C, forming β,γ- or α,β-unsaturated thioesters (**13**, **14**, Scheme 2.8).[26] The key intermediate is the π-allyl palladium complex **15**, which is converted to β,γ-unsaturated thioester **13**, and further on to its α,β-isomer **14**.[27]

Furthermore, a few publications are available on the thiocarbonylation of alkynes. In 1997, Ogawa *et al.* described the platinum catalyzed carbonylative addition of thiols to terminal alkynes **16**, generating α,β-unsaturated thioesters **17** (Scheme 2.9).[28] By using 3 mol% $Pt(PPh_3)_4$, 1-octyne was carbonylated with benzenethiol and CO (30 bar), providing regioselectively the branched product in 77% yield. Also aliphatic thiols were applied successfully. El Ali *et al*. presented a thiocarbonylation of terminal alkynes in 2001, which was catalyzed by 1 mol% $Pd(OAc)_2$ and 4 mol% of a bidentate ligand, dppb (= 1,4-

bis(diphenylphosphino)butane) or dppp (= 1,3-bis(diphenylphosphino)propane).[29] They were able to control the regioselectivity by a careful adjustment of the type of the ligand and the solvent, to obtain either the branched or the linear product.



Scheme 2.8. Palladium-catalyzed thiocarbonylation of vinylcyclopropanes **12**.[26]



Scheme 2.9. Carbonylation of alkynes providing α,β-unsaturated thioesters **17**.[28]

All of these reactions proceed with high catalyst loading (3–5 mol%), at elevated temperatures (100–110 °C) and pressures (27 bar) and cannot be applied to other types of double-bond containing compounds. Simple alkenes were used as substrates only in few examples in patents from Drent[30] and Foley.[31] Possibly, aggravated conditions of working with free thiols and the competing hydrothiolation reaction might have hindered progress in this area, although metal-catalyzed cross couplings with thiols are known.[32] Herein, the first chemoselective palladium-catalyzed thiocarbonylation of styrenes, which is carried out under mild reaction conditions (room temperature, low pressure, CO surrogate) and in a highly regioselective fashion is reported. Conscientious modulation of the catalyst system and reaction conditions led to a successful suppression of the side reaction.

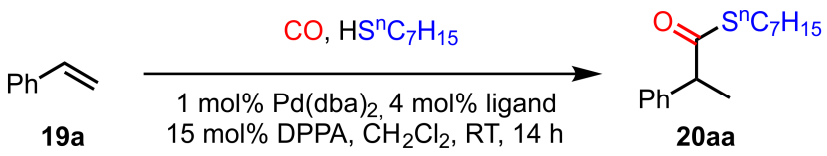
2.2 Results and Discussion

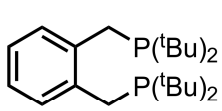
2.2.1 Initial Optimization Experiments

Recently, we have developed a method[33] for the alkoxycarbonylation of olefins[34] under mild conditions using a Pd(0)-precatalyst, a bidentate phosphine ligand and a recyclable CO surrogate (*N*-formylsaccharin[35]), which enables a convenient and safe reaction set up in two-chamber pressure tubes developed by Skrydstrup[36] (see Chapter 1.3). The originally envisioned direct transfer of the methodology to thiocarbonylation was not possible. Initially, we struggled with problems of reproducibility and low yields. Additionally, we observed the formation of linear thioethers from styrenes, which were found to stem from the oxygen-mediated thiol-ene (or hydrothiolation) reaction.[21] Fortunately, by thoroughly purifying all of the reaction components prior to use, we were able to prevent this side reaction.

2.2.1.1 Ligand Screening

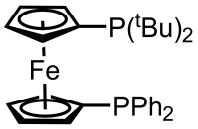
The initial screening of the ligands was performed using styrene (**19a**) and *n*-heptanethiol as model substrates and $Pd(dba)_2$ and diphenyl phosphoric acid (DPPA) as the catalyst system (Scheme 2.10). The screening was carried out in an autoclave under 2.5 bar CO atmosphere in order to ensure equal reaction conditions for all ligands. The known successful carbonylation ligand **L2** also showed a promising result in the thiocarbonylation, affording exclusively the branched thioester **20aa** in 79% yield (NMR). However, an improved yield was obtained using ligand **L3**, which was known from a detailed study by Holzapfel and Bredenkamp on ligand effects in the methoxycarbonylation of medium-chain alkenes, where the electronically differentiated **L3** was shown to outperform **L2**.[37] Those authors reasoned that such ligands might accelerate the final alcoholysis step in alkoxycarbonylation, which also emerges from several studies concerning ethene methoxycarbonylation by Pringle.[38] Another advantage of **L3** is its straightforward synthesis[39] and lower price per mole. To examine the effects of steric and electronic differentiation of **L3** on catalytic activity, we also tested the symmetrical ferrocene derivative **L4**, which showed a significantly reduced activity. We speculated that electronic differentiation might be the key to activate catalysts; however, the desmethylene analogue of **L2**, the known carbonylation ligand **L5**,[38a, 40] provided the product in low yield.





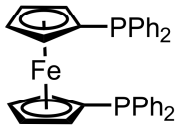
dtbpx, **L2**

Yield: 79%



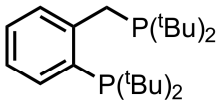
dppdtbpf, **L3**

88%



dppf, **L4**

20%

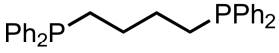


dtbpt[b], **L5**

Yield: 9%

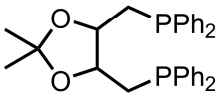
dppp, **L6**

0%



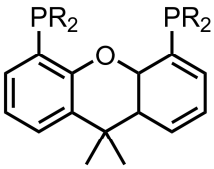
dppb, **L7**

2%



DIOP, **L8**

Yield: 10%

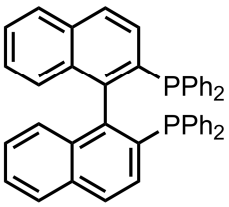


R = Ph, Xantphos, **L9**

34% +30%[c]

R = ^{t}Bu, ^{t}Bu-Xantphos, **L10**

0%



rac-BINAP, **L11**

10% + 6%[c]

Scheme 2.10. Ligand screening for the thiocarbonylation of styrene.[a]

[a] Reaction conditions: The reaction was carried out in the autoclave (2.5 bar of CO). Reaction vessel: styrene (115 µL, 1.0 mmol), Pd(dba)$_2$ (5.8 mg, 10 µmol, 1 mol%), ligand (40 µmol, 4 mol%), DPPA (38 mg, 150 µmol, 15 mol%), HeptSH (210 µL, 177 mg, 1.3 mmol), CH_2Cl_2 (790 µL), RT, 14 h. Yields were determined by quant. NMR spectroscopy using mesitylene as an internal standard. [b] 0.5 mmol. [c] Linear thioester, determined by quant. GC-FID using *n*-pentadecane as an internal standard. Ligand abbreviations: dtpbx, **L2** = 1,2-bis(di-*tert*-butylphosphinomethyl)benzene; dppdtbpf, **L3** = 1-diphenylphosphino-1'-(di-*tert*-butylphosphino)ferrocene; dppf, **L4** = 1,1'-bis(diphenylphosphino)ferrocene; dtbpt, **L5** = di-*tert*-butyl(2-(di-*tert*-butylphosphanyl)-benzyl)phosphane; dppp, **L6** = 1,3-bis(diphenylphosphino)propane; dppb, **L7** = 1,4-bis(diphenylphosphino)butane; *rac*-DIOP, **L8** = (±)-2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenyl-phosphino)butane; Xantphos, **L9** = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene; ^{t}Bu-Xantphos, **L10** = 4,5-bis(di-*tert*-butylphosphino)-9,9-dimethylxanthene; rac-BINAP, **L11** = (±)-2,2'-bis(diphenylphosphino)-1,1'-binaphthalene.

Additionally, also the comparatively electron-poor bidentate ligands **L6–L8** exhibited no or low activity. The typical carbonylation ligands **L9** and **L11** were active but not in a regioselective fashion. Interestingly, no product was obtained employing the sterically more

demanding ^{t}Bu-Xantphos (**L10**).[41] Probably, **L10** forms a *trans*-palladium complex, due to the steric repulsion of the ^{t}Bu groups.

Beside the electronic differentiation also the bite angle of the ligand plays an important role. Larger bite angles are able to accelerate the reductive elimination of the product and therefore diminish the occurrence of side reactions. On the other side, if the bite angle is too large the required *cis*-coordination to palladium cannot be adopted.[37] Therefore, the yields for the carbonylation of **19a** by using different ligands were also analyzed by taking the bite angles into account (Figure 2.1). Therefore, *cis*-ligand-Pd/Pt complexes from the literature (**L2**[42], **L4**[43], **L5**[42], **L6**[44], **L7**[45], **L8**[46], **L9**[47], **L11**[48]) were compared with the corresponding obtained yields. The bite angle of **L3** was measured from the crystal structure of (**L3**)$PdCl_2$ by P. H. Gehrtz. As expected, the yield can be increased by using ligands with larger bite angles, whereas an optimum of 102° (**L3**) was achieved.

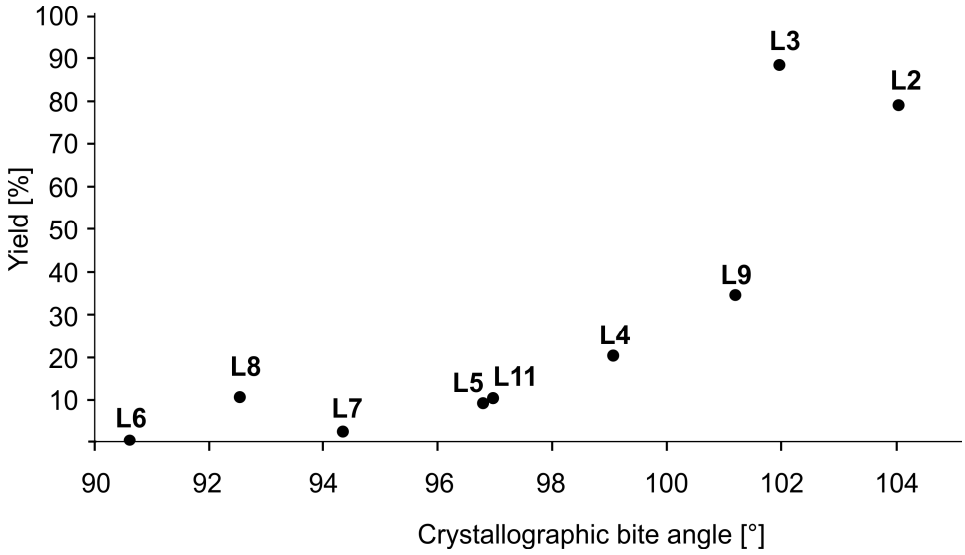


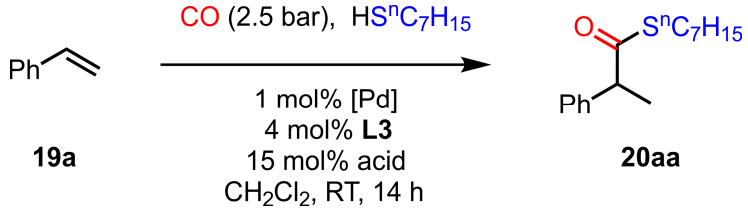
Figure 2.1. Relation between yield of **20aa** and crystallographic bite angles of cis-ligand-Pd/Pt complexes.

2.2.1.2 Catalyst and Acid Screening

Using the same model substrates and ligand **L3**, the influence of Pd source and acid co-catalyst was investigated (Table 2.1). First, several palladium precursors were tested. Among the Pd(II) sources, only $Pd(acac)_2$ (Table 2.1, entry 4) was able to catalyze the reaction, albeit in moderate yield. The best yield was achieved with $Pd(dba)_2$ as a catalyst precursor (Table 2.1, entry 5), affording **20aa** in 88% yield. In contrast to our previous studies on the alkoxycarbonylation, the acid screening showed no difference in activity between DPPA,

MsOH (methanesulfonic acid), BNPA (1,1´-bi-2-naphthol phosphoric acid) and *p*TsOH (*p*-toluenesulfonic acid) with yields around 90% (Table 2.1, entries 5–7, 9), whereas TFA (trifluoroacetic acid) and benzoic acid showed poor yields (Table 2.1, entries 8, 10). The moderately acidic DPPA was chosen as additive for substrate screening, in order to be able to employ substrates containing labile functional groups.

Table 2.1. Catalyst and acid screening for the thiocarbonylation of styrene.[a]



Entry	[Pd]	Acid	pK$_a$ (DMSO)	Conv.[b] [%]	Yield[b] (**20aa**) [%]
1	$PdCl_2$	DPPA	3.9	21	0
2	$Pd(OAc)_2$	DPPA	3.9	18	0
3	$Pd(PPh_3)_4$	DPPA	3.9	32	24
4	$Pd(acac)_2$	DPPA	3.9	74	53
5	$Pd(dba)_2$	DPPA	3.9	94	88
6	$Pd(dba)_2$	MsOH	1.6	100	91
7	$Pd(dba)_2$	BNPA	3.4	81	81
8	$Pd(dba)_2$	TFA	3.5	55	11
9	$Pd(dba)_2$	*p*TsOH	7.1	100	89
10	$Pd(dba)_2$	PhCOOH	11.1	23	4

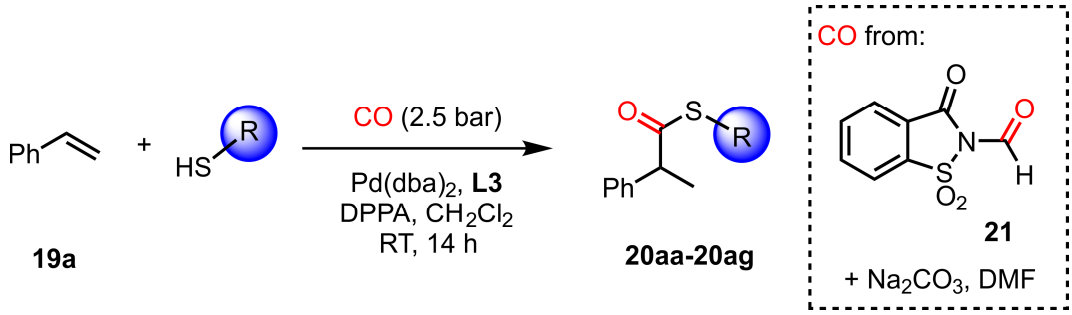
[a] Reaction conditions: The reaction was carried out in the autoclave (2.5 bar of CO). Reaction vessel: styrene (115 µL, 1.0 mmol), [Pd] (10 µmol, 1 mol%), **L3** (21 mg, 40 µmol, 4 mol%), acid (150 µmol, 15 mol%), HeptSH (210 µL, 177 mg, 1.3 mmol), CH_2Cl_2 (790 µL), RT, 14 h. [b] Determined by quant. NMR-spectroscopy using mesitylene as an internal standard.

2.2.2 Substrate Screening

The substrate scope was evaluated under the optimized conditions in glass pressure tubes by using *N*-formylsaccharin (**21**) as a CO surrogate, in order to liberate 2.5 bar CO by treatment with a base in DMF at room temperature (Table 2.2).[35] First, different thiols were tested using $Pd(dba)_2$, DPPA and **L3** as the catalyst system in the carbonylation of styrene. All

linear aliphatic thiols furnished high yields of the branched products **20aa–20ac** (>90%, Table 2.2, entries 1–3). Notably, we repeated the reaction of styrene and *n*-heptylthiol at 5 mmol scale and obtained the product **20aa** in quantitative yield and with excellent regioselectivity. The use of benzylthiol also resulted in product formation in a good yield of 82% (Table 2.2, entry 4). A good yield of product **20ae** was obtained when protected cysteine was employed as a substrate (Table 2.2, entry 5).

Table 2.2. Thiol screening of the carbonylation of styrene.[a]



Entry	Product	R	Yield[b] [%]
1	**20aa**	$^{n}C_7H_{15}$	95
2	**20ab**	^{n}Pr	92
3	**20ac**	Et	96
4	**20ad**	Bn	82
5	**20ae**	N-Boc-cysteine methylester	62
6	**20af**	Cy	28
7	**20ag**	Ph	33 + 26[c]

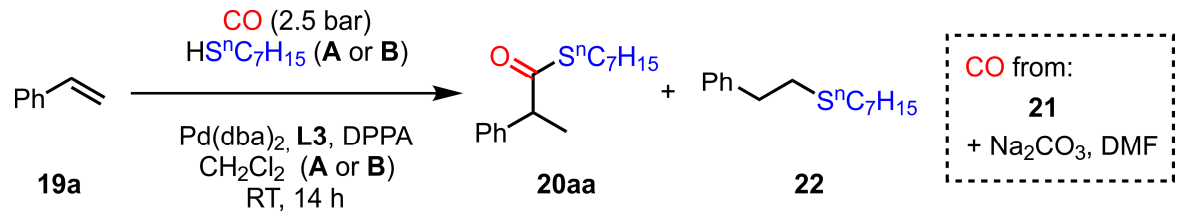
[a] Reaction conditions: The reaction was carried out in a 2-chamber system. Chamber A: CO generation (max. 2.5 bar): **21** (2.13 mmol, 450 mg), Na_2CO_3 (3.20 mmol, 339 mg) in DMF (1 mL); Chamber B: styrene (115 µL, 1.0 mmol), $Pd(dba)_2$ (5.8 mg, 10 µmol, 1 mol%), **L3** (21 mg, 40 µmol, 4 mol%), DPPA (38 mg, 150 µmol, 15 mol%), RSH (1.3 mmol), CH_2Cl_2 (790 µL), RT, 14 h. [b] Isolated yields. [c] Linear thioether.

As expected, a significantly reduced activity of the catalyst system was observed when a secondary thiol was used (Table 2.2, entry 6). Interestingly, thiophenol led to the formation of the desired thioester product **20ag**, but also the linear ether was observed (Table 2.2, entry 7). In general, arylthiols have a lower bond dissociation energy (S–H) than alkanethiols, resulting in more facile formation of thiyl radicals and the hydrothiolation side reaction. This side reaction could be initiated by molecule assisted electron transfer.[49] However, this result contradicts our previously described system for the alkoxycarbonylation of olefins,

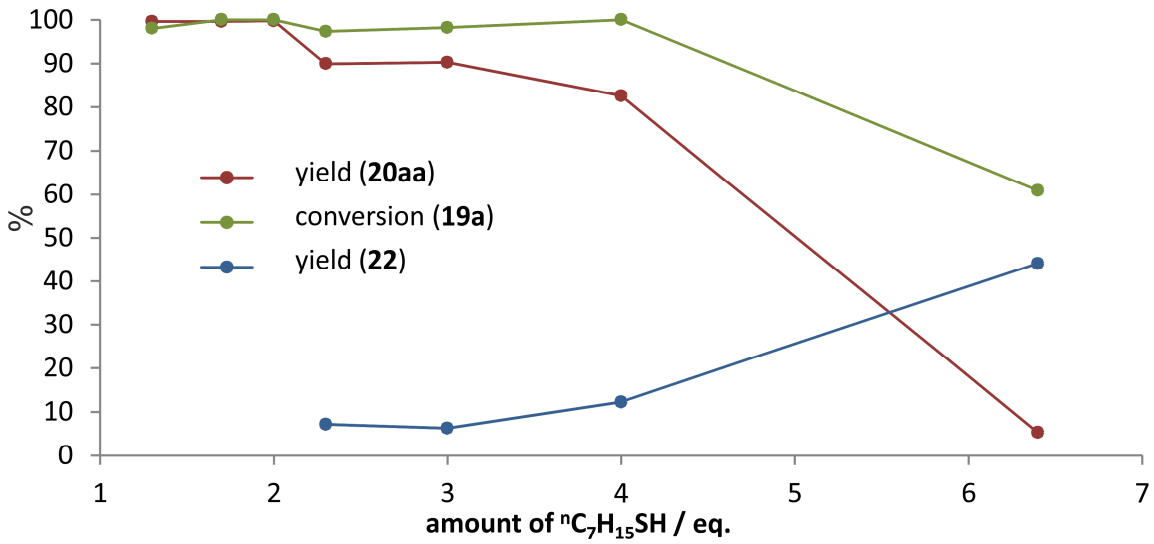
since in this case the ester was not formed when phenol was employed. We previously reasoned that a β-hydride elimination of a coordinated alcohol molecule is necessary to form the catalytically active palladium hydride species.[50] This disparity led us to the assumption that the catalyst activation mechanism of thiocarbonylation differs from the alkoxycarbonylation, or that more than one pathway for the activation exists.

Since the amount of thiol plays a central role in the suppression of the undesired hydrothiolation generating the linear thioether, different amounts of heptanethiol were applied in the carbonylation of **19a** under the optimized conditions (Scheme 2.11). In the first data set different amounts of heptanethiol were used by keeping the amount of liquid reaction components (thiol, solvent) and therefore the concentration of **19a** constant (Scheme 2.11A). By increasing the amount of thiol a substantial increase of the amount of the undesired thioether **22** was observed, whereas the yield of **20aa** dropped significantly. By performing the reaction under neat conditions (6.4 eq. heptanethiol) only 5% yield of the desired product was obtained. In the second data set different amounts of heptanethiol were used by keeping the amount of solvent constant (Scheme 2.11B). The impact of thiol amount under these conditions was less distinctive but the same tendency was observed. In conclusion, the concentration of the thiol is a key component of the reaction. If the concentration of the thiol is too high, a catalyst poisoning due to the strong palladium sulfur bond cannot be prevented and the undesired thioether formation predominates.

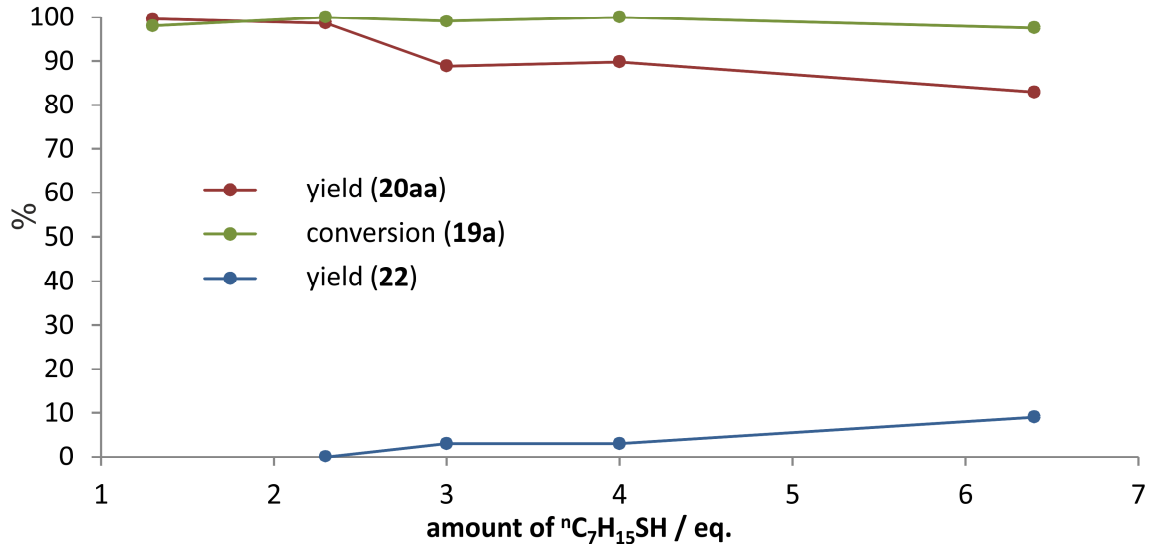
Furthermore, the reactivity of various alkenes was investigated, starting with the examination of styrene derivatives employing heptanethiol as the nucleophile (Table 2.3). In general, *ortho*-substituted styrenes (Table 2.3, entries 2−6) provided lower yields than the corresponding *meta*- and *para*-substituted derivatives (Table 2.3, entries 7−12), but most impressively with no breakdown in regioselectivity as was observed in the alkoxycarbonylation. Notably, thiocarbonylation of **19d** did not furnish the thioester, but rather the five-membered lactone **20da**, which was already observed in the alkoxycarbonylation reaction.[33] We were able to increase the yield with the new catalytic system for the desired lactone from 16% to 55%. Sterically more demanding groups, such as phenyl or ^{t}Bu groups (Table 2.3, entries 13, 14), were tolerated in the *para*-position, showing excellent yields.



A: *x* µL HS^{n}C$_7$H$_{15}$ (1.3 - 6.4 eq.), 1000 µL - *x* µL CH$_2$Cl$_2$ ⟶ constant concentration of **19a**



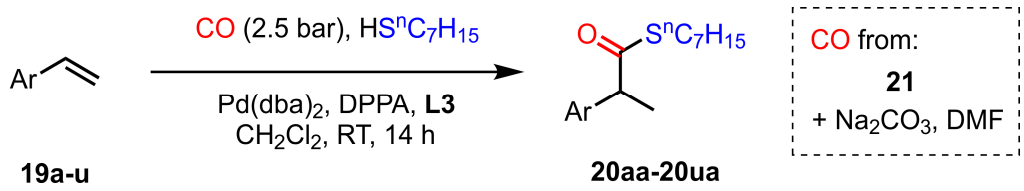
B: *x* µL HS^{n}C$_7$H$_{15}$ (1.3 - 6.4 eq.), 790 µL CH$_2$Cl$_2$ constant amount of CH$_2$Cl$_2$



Scheme 2.11. Influence of the amount of heptanethiol on the chemoselectivity in the carbonylation of styrene.[a]

[a] Reaction conditions: The reaction was carried out in a 2-chamber system. Chamber A: CO generation (max. 2.5 bar): **21** (2.13 mmol, 450 mg), Na$_2$CO$_3$ (3.20 mmol, 339 mg) in DMF (1 mL); Chamber B: styrene (115 µL, 1.0 mmol), Pd(dba)$_2$ (5.8 mg, 10 µmol), **L3** (21 mg, 40 µmol), DPPA (38 mg, 150 µmol), RT, 14 h. Yields of **20aa** and conversions of **19a** were determined by quant. NMR spectroscopy using mesitylene as an internal standard. Yields of **22** were determined by quant. GC-FID using *n*-pentadecane as an internal standard.

Table 2.3. Thiocarbonylation of substituted styrenes.[a]



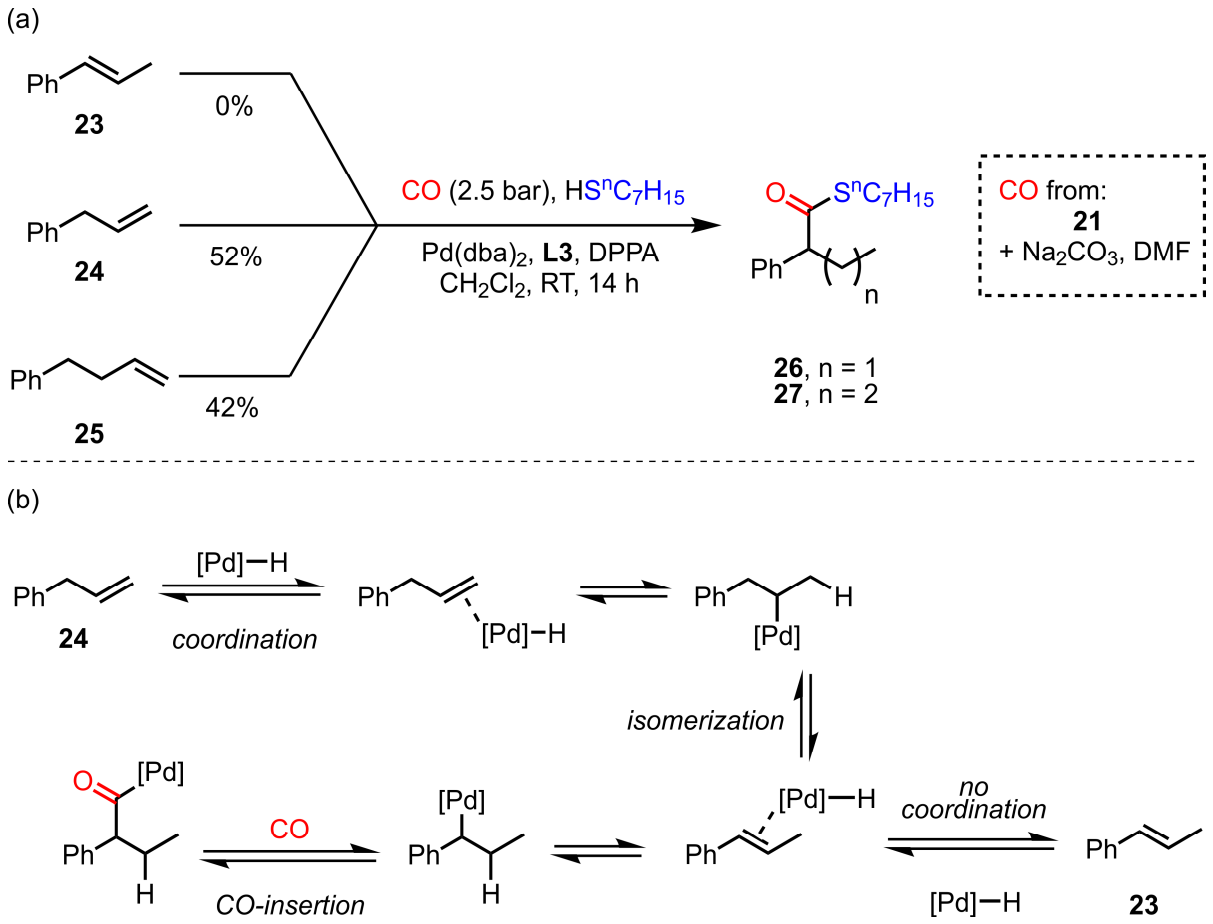
19a-u **20aa-20ua**

Entry	Starting material	Product	Ar	Yield[b] [%]
1	**19a**	**20aa**	C_6H_5	95
2	**19b**	**20ba**	2-Me-C_6H_4	89
3	**19c**	**20ca**	2-OMe-C_6H_4	97
4	**19d**	**20da**	2-OH-C_6H_4	55[c]
5	**19e**	**20ea**	2-OAc-C_6H_4	49
6	**19f**	**20fa**	2-CF_3-C_6H_4	0
7	**19g**	**20ga**	3-Me-C_6H_4	99
8	**19h**	**20ha**	3-OMe-C_6H_4	90
9	**19i**	**20ia**	4-Me-C_6H_4	99
10	**19j**	**20ja**	4-OMe-C_6H_4	99
11	**19k**	**20ka**	4-OAc-C_6H_4	93
12	**19l**	**20la**	4-CF_3-C_6H_4	50
13	**19m**	**20ma**	4-Ph-C_6H_4	86
14	**19n**	**20na**	4-^{t}Bu-C_6H_4	95
15	**19o**	**20oa**	4-OH-C_6H_4	49
16	**19p**	**20pa**	4-NH_2-C_6H_4	0
17	**19q**	**20qa**	4-NO_2-C_6H_4	0
18	**19r**	**20ra**	4-F-C_6H_4	91
19	**19s**	**20sa**	4-Cl-C_6H_4	81
20	**19t**	**20ta**	4-Br-C_6H_4	72
21	**19u**	**20ua**	6-OMe-naphth-2-yl	90

[a] Reaction conditions: The reaction was carried out in a 2-chamber system. Chamber A: CO generation (max. 2.5 bar): **21** (2.13 mmol, 450 mg), Na_2CO_3 (3.20 mmol, 339 mg) in DMF (1 mL); Chamber B: vinyl arenes (1.0 mmol), Pd(dba)$_2$ (5.8 mg, 10 µmol, 1 mol%), **L3** (21 mg, 40 µmol, 4 mol%), DPPA (38 mg, 150 µmol, 15 mol%), HeptSH (210 µL, 177 mg, 1.3 mmol), CH_2Cl_2 (790 µL), RT, 14 h. [b] Isolated yields. [c] The lactone was obtained.

An electronic effect on the reactivity was observed with the electron-withdrawing CF_3 group in the *para*-position, which decreased the yield to 50% (Table 2.3, entry 12), whereas no

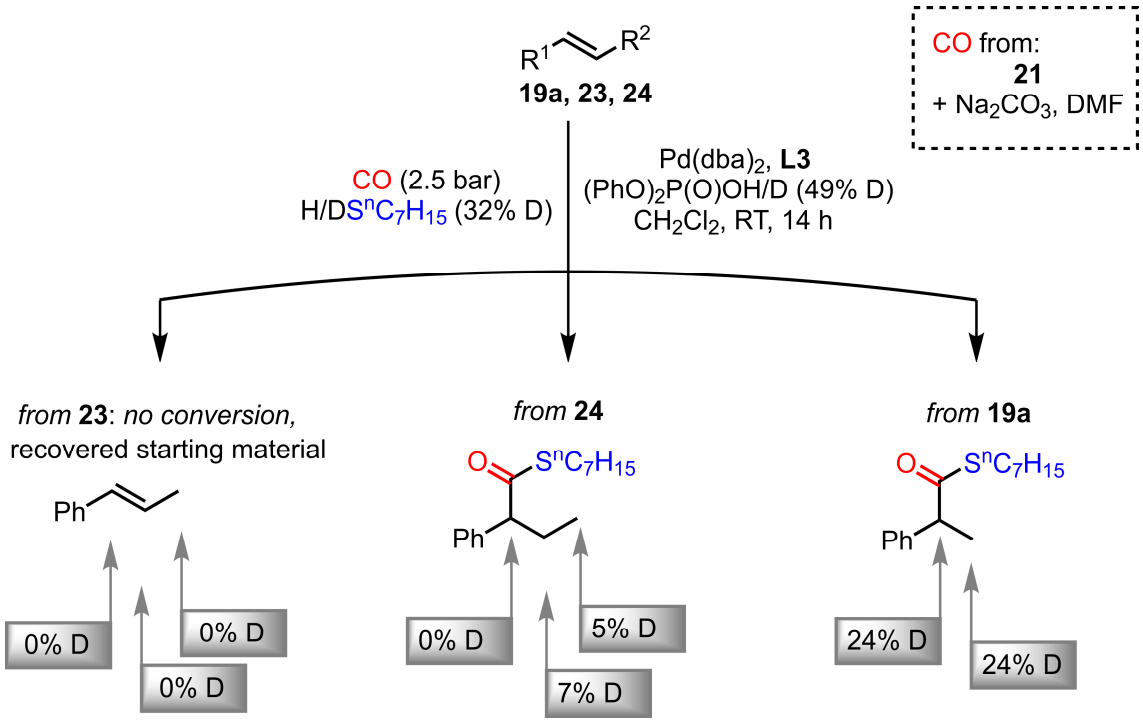
activity was observed with the CF_3 group in the *ortho*-position (Table 2.3, entry 6) and in the presence of a nitro group (Table 2.3, entry 17). Basic substituents, such as the amino group, were not tolerated by the catalytic system (Table 2.3, entry 16), since they neutralize the acidic promoter. This trend was also observed in the carbonylation of 2-vinylpyridine, where only the linear ether was generated. Moreover, an interesting trend for halides in the *para*-position was established (Table 2.3, entries 18–20). The yields decreased significantly from fluoro to chloro to bromo substitution, which might be explained by the fact that competitive oxidative addition to palladium becomes more likely along this row. The vinylnaphthalene **19u** delivered the corresponding branched ester **20ua**, which could be transformed to *rac*-Naproxen in an additional simple hydrolysis. Afterward, further alkenes were tested (Scheme 2.12a).



Scheme 2.12. Thiocarbonylation of various olefins and rationalization of the results.[a]

[a] Thiocarbonylations of **23-25**: Reaction conditions: The reaction was carried out in a 2-chamber system. Chamber A: CO generation (max. 2.5 bar): **21** (2.13 mmol, 450 mg), Na_2CO_3 (3.20 mmol, 339 mg) in DMF (1 mL); Chamber B: olefin (1.0 mmol), $Pd(dba)_2$ (5.8 mg, 10 µmol, 1 mol%), **L3** (21 mg, 40 µmol, 4 mol%), DPPA (38 mg, 150 µmol, 15 mol%), HeptSH (210 µL, 177 mg, 1.3 mmol), CH_2Cl_2 (790 µL), RT, 14 h. Isolated yields.

Surprisingly, the internal alkene **23** did not undergo any carbonylation reaction, whereas the terminal nonconjugated alkenes **24** and **25** generated exclusively the branched products **26** and **27** in moderate yields. A possible explanation might be that a direct carbonylation in the benzylic position of **23** is not possible due to steric hindrance, but a terminal insertion of substrates **24** and **25**, followed by an isomerization, is conceivable (Scheme 2.12b). A deuteration experiment using partially deuterated thiol and acid revealed that the insertion of the Pd catalyst is already the limiting factor for the carbonylation of **23**, as no deuterium was incorporated in the recovered starting material (Scheme 2.13). On the other hand, deuterium was found in β- and γ-positions of product **26**. In comparison, when using styrene, 24% deuterium was determined on both carbon atoms. A general limitation of the catalytic system seems to be substitution in the α- or β-position of styrene, since beside **23** also α-methyl styrene, *trans*- and *cis*-stilbene, cinnamyl alcohol and *trans*-β-vinylstyrene were not carbonylated.



Scheme 2.13. Deuteration experiments.[a]

[a] Reaction conditions: The reaction was carried out in a 2-chamber system. Chamber A: CO generation (max. 2.5 bar): **21** (2.13 mmol, 450 mg), Na_2CO_3 (3.20 mmol, 339 mg) in DMF (1 mL); Chamber B: olefin (1.0 mmol), $Pd(dba)_2$ (5.8 mg, 10 µmol, 1 mol%), **L3** (21 mg, 40 µmol, 4 mol%), DPPA-H/D (38 mg, 150 µmol, 15 mol%, 49% deuterated), HeptSH/D (210 µL, 177 mg, 1.3 mmol, 32% deuterated), CH_2Cl_2 (790 µL), RT, 14 h.

2.2.3 Comparison between Alkoxy- and Thiocarbonylation Conditions and Competition Experiments

In addition, a comparison between alkoxy- and thiocarbonylation was conducted, since several results suggested different behaviors of the two systems (Figure 2.2). Therefore, selected substrates were tested under either typical alkoxy (C.1.*x*) or thio conditions (C.2.*x*), and the nucleophile was varied (C.*x*.1 = HeptOH; C.*x*.2 = HeptSH), as well.

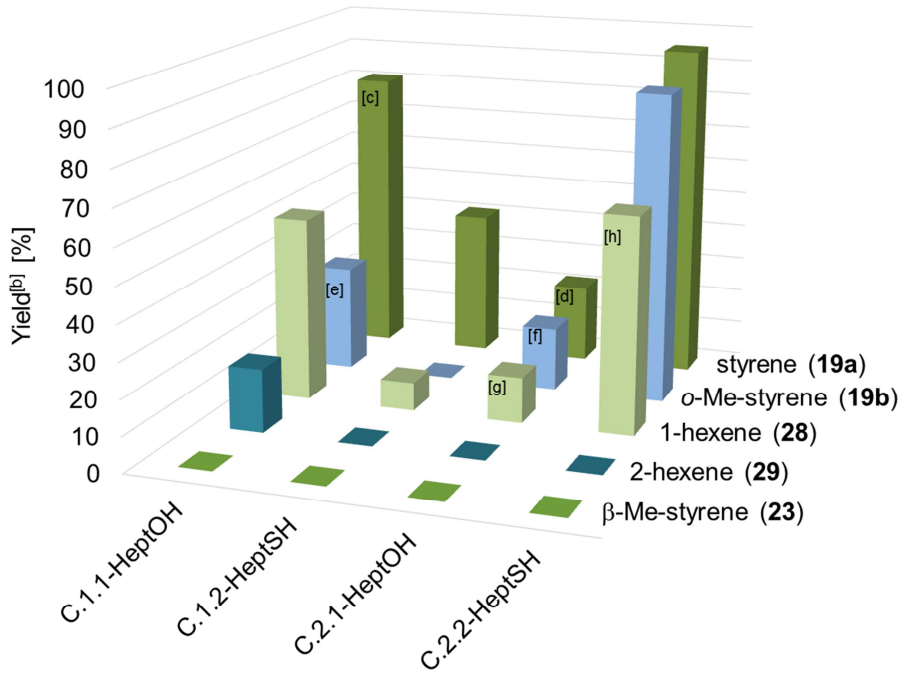
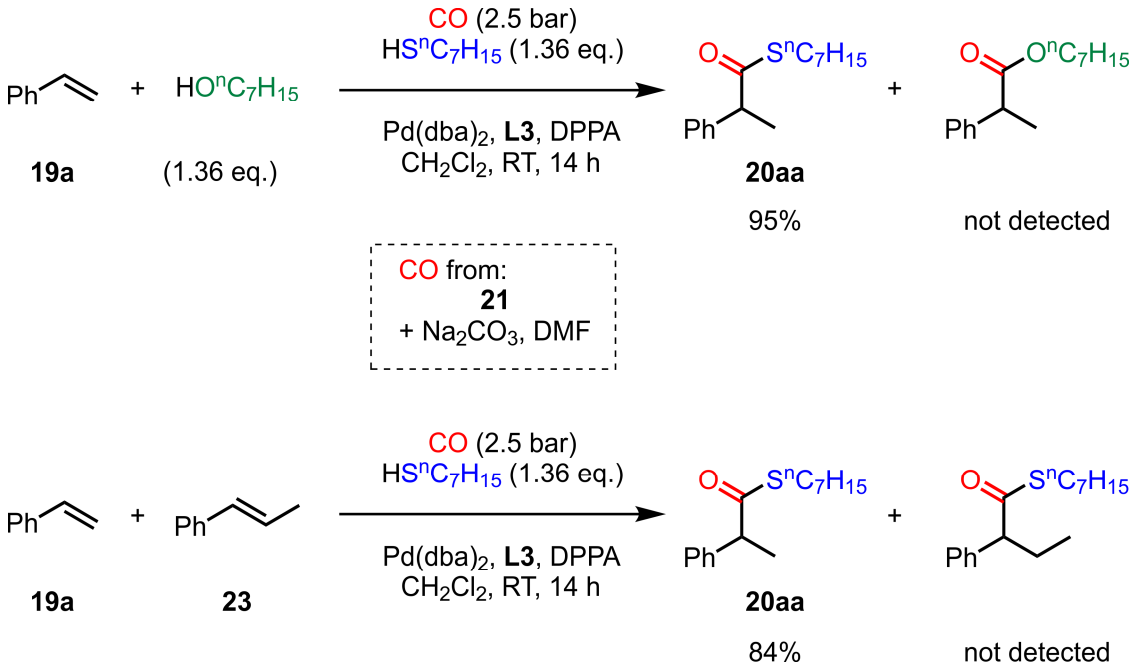


Figure 2.2. Comparison between alkoxy- and thiocarbonylation.[a]

[a] Reaction conditions: The reaction was carried out in a 2-chamber system. Chamber A: CO generation (max. 2.5 bar): **21** (2.13 mmol, 450 mg), Na_2CO_3 (3.20 mmol, 339 mg) in DMF (1 mL); Chamber B: C.1.1 and C.1.2 (alkoxy conditions), olefin (1.0 mmol), $Pd(dba)_2$ (5.8 mg, 10 µmol), **L2** (16 mg, 40 µmol), BNPA (52 mg, 150 µmol,), *x* µL HeptOH (280 µL, 232 mg, 2.0 mmol)/*x* µL HeptSH (315 µL, 265 mg, 2.0 mmol), 1000 − *x* µL CH_2Cl_2, RT, 14 h; C.2.1 and C.2.2 (thio conditions), olefin (1.0 mmol), $Pd(dba)_2$ (5.8 mg, 10 µmol, 1 mol%), **L3** (21 mg, 40 µmol, 4 mol%), DPPA (38 mg, 150 µmol, 15 mol%), *x* µL HeptSH (210 µL, 177 mg, 1.3 mmol)/*x* µL HeptOH (190 µL,156 mg, 1.3 mmol), 1000 − *x* µL CH_2Cl_2, RT, 14 h. [b] Isolated yields. [c] b/l = 94/6. [d] b/l = 94/6. [e] b/l = 25/75. [f] b/l = 69/31. [g] b_1/b_2/l = 17/44/39. [h] b_1/b_2/l = 22/43/35.

In summary, the best yields were observed under thio conditions using HeptSH as a nucleophile. One can conclude that the two different reaction conditions are closely related to the corresponding nucleophile. Whereas, for the carbonylation of **19a** under alkoxy conditions with HeptOH (C.1.1) as well as under thio conditions with HeptSH (C.2.2), high to excellent yields were generated, there was a significant breakdown in reactivity when using alkoxy conditions with HeptSH (C.1.2) or thio conditions with HeptOH (C.2.1). A similar

situation was observed when using the sterically demanding **19b** as a substrate. Nevertheless, in all different combinations of nucleophile and reaction conditions, no product formation was observed for **23**. Additionally, all reactions using HeptSH and a styrene derivative proceeded in a completely regioselective fashion, whereas also the linear product was observed for all reactions with HeptOH. In order to figure out if this concept can also be transferred to aliphatic olefins, 1-hexene (**28**) and 2-hexene (**29**) were investigated. Whereas **29** can only be carbonylated under alkoxy conditions (C.1.1), generating exclusively the linear product, **28** showed moderate yields for C.1.1 and C.2.2 and low yields for C.1.2 and C.2.1. In the carbonylation of **28** under thiocarbonylation conditions, an isomerization took place, followed by unselective carbonylation of each carbon atom. Under alkoxy conditions, only the terminal position was functionalized, which is a known regioselectivity for the ligand **L2**. Finally, two competition experiments were performed (Scheme 2.14).



Scheme 2.14. Competition Experiments[a]

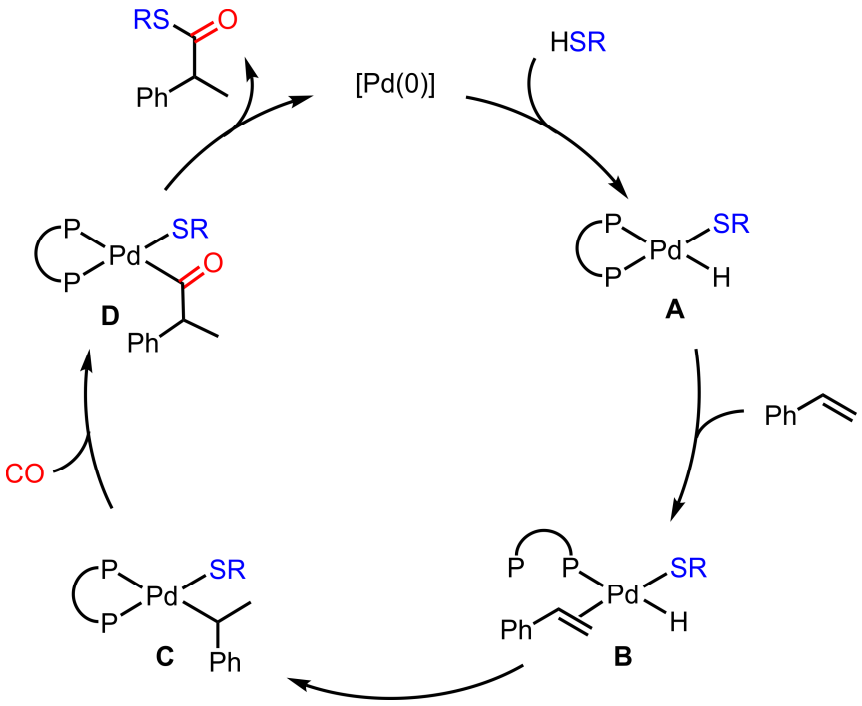
[a] Reaction conditions: The reaction was carried out in a 2-chamber system Chamber A: CO generation (max. 2.5 bar): **21** (2.13 mmol, 450 mg), Na_2CO_3 (3.20 mmol, 339 mg) in DMF (1 mL); Chamber B: styrene (115 µL, 1.0 mmol), $Pd(dba)_2$ (5.8 mg, 10 µmol, 1 mol%), **L3** (21 mg, 40 µmol, 4 mol%), DPPA (38 mg, 150 µmol, 15 mol%), HeptSH (210 µL, 177 mg, 1.3 mmol), HeptOH (190 µL, 156 mg, 1.3 mmol) or alkene **23** (130 µL, 1.0 mmol), CH_2Cl_2 (790 µL), RT, 14 h. Yields were determined by quant. NMR spectroscopy using mesitylene as an internal standard.

Interestingly, the carbonylation of styrene under thiocarbonylation conditions by adding both *O*- and *S*-nucleophiles generated exclusively thioester **20aa**, with no loss in activity

(95%). In a thiocarbonylation of a 1:1 mixture of styrene (**19a**) and the unreactive β-methylstyrene (**23**), only a slight decrease in the yield of the carbonylation product of styrene was observed. This shows that the catalyst is not inhibited by alkene **23**.

2.2.4 Mechanistic Proposal

The obtained results, especially the excellent regioselectivity and reactivity of sterically hindered ortho-substituted styrenes, suggest a different mechanism compared to the known alkoxycarbonylation reaction using ligand **L2**. The main difference might arise from the better coordinating ability of the thiol, which would influence the reactivity of the complex by its donor properties. Our postulated catalytic cycle is based on the accepted hydride mechanism for the carbonylation reaction, with the difference that the thiol acts as a ligand (Scheme 2.15). The catalytically active species **A** is formed from the Pd(0) precursor by oxidative addition of the thiol and a ligand exchange. Coordination of the alkene is enabled by a transitory decoordination of one phosphorus atom to give **B**. Insertion of the alkene into the Pd–H bond furnishes complex **C**, which undergoes a CO coordination and insertion. The resulting acyl complex **D** is converted to the product and hydride **A** in reductive elimination/oxidative addition steps. The Brønsted acid additive might play a role in the oxidative addition of the thiol and in the activation of the acyl species.



Scheme 2.15. Postulated Reaction Mechanism.

2.3 Conclusion

In summary, we developed the first chemoselective thiocarbonylation of vinyl arenes, which proceeds under mild reaction conditions and in a highly regioselective fashion. The devised catalytic system tolerates a wide variety of functional groups for the thiocarbonylation of substituted styrenes, generating exclusively the branched products, even for sterically demanding groups in the *ortho*-position. Interestingly, the system is also selective for terminal double bonds, whereas internal ones are not carbonylated. This property could be used in the transformation of compounds containing several double bonds. Comparative investigations of the thio- and the alkoxycarbonylations show that a different mechanism might be operating in the thiocarbonylation, which can result in new applications. A more detailed study is ongoing.

2.4 Experimental Part

2.4.1 General Information and Analytical Techniques

The ligand dppdtbpf (**L3**) was either commercially obtained from Sigma-Aldrich or synthesized according to Cullen *et al*.[39] The ligand dtbpt (**L5**) was synthesized from 2-bromobenzyl-di-*tert*-butylphosphine[38a] according to a procedure by Mecking.[40] *N*-formylsaccharin (**21**) was synthesized according to our procedure and stored under N_2.[33] Liquid alkene starting materials were purified immediately before use by Kugelrohr distillation. All other chemicals were purchased from ABCR, Acros, Sigma Aldrich, TCI or Merck and used without any further purification unless otherwise noted. Some olefins were synthesized *via* Wittig-reaction from the corresponding aldehyde. 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 (heat gun) and cooled under dry N_2 for three times. Furthermore, degassed and dry solvents were used where necessary; specifically dichloromethane, diethyl ether and tetrahydrofuran were obtained pre-dried from a Grubbs-type solvent purification system (MBraun, MB SPS-800). Pre-dried dichloromethane was refluxed over CaH_2, then distilled under nitrogen. Pre-dried diethyl ether and tetrahydrofuran were further dried with microwave-activated 3 Å molecular sieves (20% m/v, 3 days) and degassed when necessary by freeze-pump-thaw cycles (3×). Dry hexane was obtained by refluxing hexane (p.A. grade) over CaH_2, followed by distillation under N_2.

NMR and calibration data are available in the supporting information of the already published version.[1]

Chromatography

Column chromatography was carried out using Silica gel (60 Å) as a stationary phase, either using gravity flow or air overpressure flow conditions. Mobile phases are described in each experiment.

Thin layer chromatography (TLC) was performed with alumina plates coated with Merck silica gel 60 F254 (layer thickness: 0.2 mm) and analyzed under UV-light (254 nm) or stained with a potassium permanganate solution.

Autoclave

Autoclave reactions were performed in a high pressure vessel from Parr Instrument Company (model: 4774; volume: 0.16 L) with a metal inset for holding 6 septum-containing screw capped vials and controlled *via* a Parr reactor (model: 4838). Autoclave reactions with oven-dried screw-capped vials were set up under inert conditions.

Nuclear magnetic resonance spectroscopy (NMR)

NMR spectra were recorded using a Bruker Avance 400 (^{1}H: 400 MHz, ^{13}C: 101 MHz) or Bruker Avance 300 (^{1}H: 300 MHz, ^{13}C: 75 MHz). All measurements were performed at ambient temperature. Chemical shifts δ are reported in parts per million [ppm] relative to the solvent signals as internal standard, (^{1}H: $CDCl_3$: δ = 7.26 ppm, CD_3CN: δ = 1.94 ppm; ^{13}C: $CDCl_3$: δ = 77.1 ppm, CD_3CN: δ = 1.32, 118.26 ppm), coupling constants *J* are given in Hertz [Hz]. ^{1}H NMR splitting patterns are designated as follows: s = singlet; d = doublet; t = triplet; q = quartet; quin = quintet; sext = sextet; hept = heptet; m = multiplet. ABq = AB quartet. ^{13}C signals are analyzed as follows: (+) = primary/tertiary carbon, (−) = secondary carbon, (q) = quaternary carbon. The assignment resulted from COSY, DEPT-135°, HMBC or HSQC experiments.

The internal standard method was used for quantitative NMR in order to determine yields and conversions. For the calibration, samples with different amounts of substrate and standard (mesitylene) were measured with NMR and the obtained data were used to plot $A_{(substrate)}/A_{(standard)}$ against $m_{(substrate)}/m_{(standard)}$. The resulting slope, after linear regression, is the response factor R, which can be used to quantify unknown samples by using equation 1. y-Intercepts are unconsidered.

$$\frac{m\,(substrate)}{m\,(standard)} \cdot R = \frac{A\,(substrate)}{A\,(standard)} \quad (1)$$

Gas chromatography with flame ionization detector (GC-FID)

GC-FID was carried out on a HP6890 GC-System with injector 7683B and Agilent 7820A System by using dry hydrogen as a carrier gas. Program: 50-280M12: Heating from 50 °C to 280 °C within 12 min. The internal standard method was used for the quantitative GC-FID in order to determine yields and conversions. For the calibration, samples with different

amounts of substrate and standard (*n*-pentadecane) were measured with GC-FID and the obtained data were used to plot $A_{(substrate)}/A_{(standard)}$ against $m_{(substrate)}/m_{(standard)}$. The resulting slope, after linear regression, is equivalent to the response factor R, which can be used to quantify unknown samples by using equation 1. y-Intercepts are unconsidered.

Melting points (m.p.)

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

Infrared spectroscopy (IR)

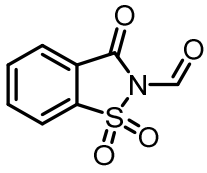
Infrared spectra were recorded on an Agilent Technologies Cary 630 FTIR spectrometer, equipped with an ATR-System. Absorption bands are given in wave numbers $\tilde{\nu}$ (cm^{-1}) and peak intensities are indicated as follows: s = strong, m = medium, w = weak and peak forms as: br = broad, sh = sharp.

Mass spectrometry (MS)

HR-MS and GC-MS were recorded on *Agilent* Q-TOF 6540 UHD, *Jeol* AccuTOF GCX, and *Finnigan* MAT SSQ 710 A, instruments at the Central Analytical Laboratory of the University of Regensburg.

2.4.2 Synthesis of *N*-Formylsaccharin (NFS)

3-Oxobenzo[d]isothiazole-2(3H)-carbaldehyde 1,1- dioxide (21)



Using a modified procedure by Goto[51], a dried 500 mL RBF was treated with formic acid (98 mL, 2.6 mol, 24.0 eq.) and acetic anhydride (113 mL, 1.2 mol, 12.0 eq.) and the solution was stirred for 1 h at RT to generate the formylating agent. A second dried 500 mL RBF was charged with saccharin (18.3 g, 100 mmol, 1.0 eq.), which was dissolved in THF (150 mL). Pyridine (2.0 mL, 25 mmol, 0.25 eq.) was added drop-wise, the resulting turbid solution was cooled down to 7 °C (CyH/CO_2 (solid) cooling bath) and the formylating agent was added by using a dropping funnel. The mixture was stirred for 1.5 h at 7 °C, the formed precipitate was

washed with MeOH p.A. and the filter cake was dried *in vacuo*. Product **21** was obtained as a white powder (16.9 g, 80.0 mmol, 80%). The obtained analytical data are in accordance to the literature.[52]

$C_8H_5NO_4S$ (211.19 g/mol), **R_f:** Decomposition on TLC, **m.p.:** 191 °C.

^{1}H-NMR (300 MHz, CD_3CN) δ_H/ppm: 9.16 (s, 1H, C<u>H</u>O), 8.21 – 8.16 (m, 1H, Ar<u>H</u>), 8.15 – 8.07 (m, 2H, Ar<u>H</u>), 8.05 – 7.99 (m, 1H, Ar<u>H</u>).

^{13}C-NMR (101 MHz, CD_3CN) δ_C/ppm: 157.7 (q), 157.4 (+), 137.9 (q), 137.3 (+), 135.3 (+), 126.0 (+), 124.6 (q), 121.2 (+).

2.4.3 General Procedure for Thiocarbonylation in the Autoclave

(Pd-precursor, Brønsted acid and ligand screening)

Reactions were carried out in autoclave vials (volume: 4 mL), sealed with a screw-cap septum, which were pricked with metal cannula for an ideal pressure equalization. After triple evacuation/inert gas backfilling of these autoclave vials, they were charged with 1 mol% [Pd]-source (10 µmol), 4 mol% ligand (40 µmol), 15 mol% acid (150 µmol), which were dissolved in 210 µL dist. HeptSH, 790 µL anhydrous dist. CH_2Cl_2. After the addition of styrene (115 µL, 1.0 mmol, 1 M solution) the vial was put into the autoclave and set under CO pressure (2.5 bar) for 14 h at RT. Afterwards, conversions and yields were determined with quantitative NMR. Therefore, mesitylene (100 µL) was used as an internal standard, which was added to the crude reaction mixture.

As a control method we additionally used quantitative GC-FID using *n*-pentadecane as the internal standard (100 µL). This method is however unreliable for the determination of the thioester yield (decomposition on the GC column), whereas conversions and yields of thioethers can be checked in this manner.

2.4.4 General Procedure *C1* for Carbonylation in a Two-chambered Pressure Vessel

A two-chambered pressure vessel (COware 20 mL, SyTracks A/S) equipped with stirring bars was charged with *N*-formylsaccharin (**21**) (450 mg, 2.13 mmol) and sodium carbonate (339 mg, 3.20 mmol) in chamber A; chamber B was charged with DPPA (15 mol%, 38 mg, 150 µmol) and sealed with a septum-containing screw cap assembly (COware type).

Chamber A was fitted with a vacuum adapter screwcap and the reaction vessel was evacuated for 10 min. Under N_2 atmosphere, $Pd(dba)_2$ (1 mol%, 5.8 mg, 10 µmol), dppdtbpf (**L3**) (4 mol%, 21 mg, 40 µmol) were added to chamber B, the vessel was then subjected to evacuation/N_2-backfilling (3×). Then, anhydrous dist. CH_2Cl_2, the thiol (1.34 eq.) and the olefin (100 mol%, 1 mmol) were added to chamber A, resulting in a dark-red solution which was stirred at 750 rpm.

Table 2.4. Exact amounts of thiol and CH_2Cl_2 for the thiocarbonylation reaction.

Entry	Thiol	V (thiol) [µL]	V (CH_2Cl_2) [µL]
1	$^{n}C_7H_{15}SH$	210	790
2	$^{n}PrSH$	125	875
3	EtSH	100	900
4	BnSH	160	840
5	N-Boc-cysteine methyl ester	280	720
6	CySH	165	835
7	PhSH	140	860

The vacuum adapter screw cap of chamber A was exchanged to a septum containing screw cap under positive N_2 pressure (using the septum inlet of chamber B). To start the decarbonylation, dry DMF (1 mL) was added to chamber A via septum addition. Pictures of the two-chambered pressure vessel setup are available in the supporting information of our previous work.[33] Both reaction chambers were stirred at 750 rpm for 14 h at RT. The reaction was stopped by opening the reaction vessel. The crude product was purified by column chromatography. The exact amounts of thiols and CH_2Cl_2 are shown in Table 2.4.

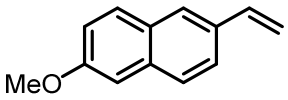
2.4.5 Preparation of Starting Materials

General procedure W1 to generate styrenes from aldehydes (Wittig-reaction)

A flame-dried RBF was charged with methyltriphenylphosphonium bromide (2.3 eq.) and potassium *tert*-butoxide (2.3 eq.), which were suspended in anhydrous THF. A solution of the salicylaldehyde (1.0 eq.) in anhydrous THF was added to the strongly orange suspension *via* syringe. The reaction mixture was heated up to 30 °C and stirred overnight. The reaction mixture was quenched with saturated aqueous ammonium chloride solution and extracted

with Et_2O (3 × 150 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (CyH/EtOAc: 95/5).

2-Methoxy-6-vinylnaphthalene (19u)



General procedure *W1* was used to generate **19u** from 6-methoxy-2-naphthaldehyde (1.00 g, 5.37 mmol, 1.0 eq.). **19u** was obtained as a white solid (930 mg, 5.05 mmol, 94%). The obtained analytical data are in accordance to the literature.[53]

$C_{13}H_{12}O$ (184.24 g/mol), **R_f:** 0.33 (CyH/EtOAc: 95/5), **m.p.:** 91 °C

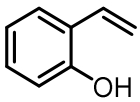
^{1}H-NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.75 – 7.66 (m, 3H, ArH), 7.64 – 7.58 (m, 1H, ArH), 7.18 – 7.10 (m, 2H, ArH), 6.86 (dd, *J* = 17.6, 10.8 Hz, 1H, ArCH), 5.83 (d, *J* = 17.6 Hz, 1H, ArCHCH$_2$), 5.28 (d, *J* = 10.8 Hz, 1H, ArCHCH$_2$), 3.92 (s, 3H, ArOCH$_3$).

^{13}C-NMR (101 MHz, $CDCl_3$) δ_C/ppm: 157.8 (q), 137.0 (+), 134.3 (q), 133.0 (q), 129.6 (+), 129.0 (q), 127.0 (+), 126.2 (+), 123.8 (+), 119.0 (+), 113.1 (–), 105.9 (+), 55.3 (+).

GC-MS (EI): t_R = 7.15 min, m/z = 184 (100, [$M^{+\bullet}$]), 169 (26, [$M^{+\bullet}$]-[$^\bullet CH_3$]), 141 (64, [$M^{+\bullet}$]-[$^\bullet COCH_3$]-[CH_2]).

HR-MS (EI): m/z = [$M^{+\bullet}$] calc. for $C_{13}H_{12}O$ 184.0883, found 184.0877.

2-Vinylphenol (19d)



General procedure *W1* was used to generate **19d** from salicylaldehyde (2.9 mL, 64.4 mmol, 1.0 eq.). **19d** was obtained as a bright yellow oil (2.97 g, 24.7 mmol, 88%). The obtained analytical data are in accordance to the literature.[54]

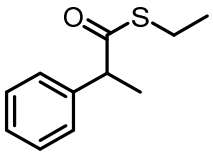
C_8H_8O (120.15 g/mol), **R_f:** 0.54 (CyH/EtOAc: 95/5), **m.p.**: Ambient temperature.

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.39 (dd, J = 7.7, 1.7 Hz, 1H, ArH), 7.19 – 7.11 (m, 1H, ArH), 7.01 – 6.88 (m, 2H, ArCH and ArH), 6.80 (dd, J = 8.0, 1.1 Hz, 1H, ArH), 5.75 (dd, J = 17.7, 1.4 Hz, 1H, ArCHCH$_{trans}$), 5.37 (dd, J = 11.2, 1.4 Hz, 1H, ArCHCH$_{cis}$), 5.03 (s, 1H, ArOH).

^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 152.8 (q), 131.5 (+), 128.9 (+), 127.4 (+), 124.8 (q), 121.0 (+), 115.9 (–).

2.4.6 Substrate Screening

S-Ethyl 2-phenylpropanethioate (20ac)



General procedure *C1* was used to carbonylate dist. styrene (115 µL, 1.00 mmol) with 1 mol% catalyst and EtSH (100 µL, 1.35 eq.) as the thiol component at RT. Purification by column chromatography (gradient CyH → CyH/EtOAc: 95/5) provided **20ac** as a bright yellow oil (186 mg, 957 µmol, 96%).

$C_{11}H_{14}OS$ (194.29 g/mol), **R_f:** 0.43 (CyH/EtOAc: 95/5), **m.p.:** Ambient temperature.

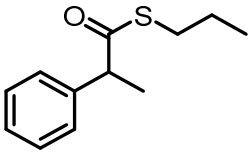
^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.38 – 7.27 (m, 5H, Ar<u>H</u>), 3.88 (q, *J* = 7.1 Hz, 1H, ArC<u>H</u>), 2.89 – 2.78 (m, 2H, SC<u>H$_2$</u>), 1.54 (d, *J* = 7.1 Hz, 3H, ArCHC<u>H$_3$</u>), 1.21 (t, *J* = 7.4 Hz, 3H, SCH_2C<u>H$_3$</u>).

^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 201.3 (q), 140.0 (q), 128.7 (+), 127.9 (+), 127.4 (+), 54.2 (+), 23.5 (–), 18.4 (+), 14.5 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3030 (w, sh), 2933 (m, sh), 2974 (m, sh), 2878 (w, sh), 1685 (s, sh), 1454 (m, sh), 1264 (m, sh), 947 (s, sh), 757 (s, sh).

HR-MS (APCI): m/z = [MH^+] calc. for $C_{11}H_{15}OS$ 195.0838, found 195.0841.

S-Propyl 2-phenylpropanethioate (20ab)



General procedure *C1* was used to carbonylate dist. styrene (115 µL, 1.00 mmol) with 1 mol% catalyst and ^{n}PrSH (125 µL, 1.35 eq.) as the thiol component at RT. Purification by column chromatography (gradient CyH → CyH/EtOAc: 95/5) provided **20ab** as a bright yellow oil (191 mg, 918 µmol, 92%).

$C_{12}H_{16}OS$ (208.32 g/mol), **R_f:** 0.50 (CyH/EtOAc: 95/5), **m.p.:** Ambient temperature.

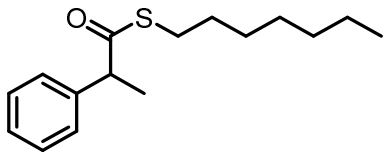
^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.38 – 7.26 (m, 5H, ArH), 3.89 (q, *J* = 7.1 Hz, 1H, ArCH), 2.90 – 2.74 (m, 2H, ArCHCOSCH_2), 1.49 – 1.59 (m, 2H, ArCHCOSCH_2CH_2), 1.54 (d, *J* = 7.1 Hz, 3H, ArCHCH_3), 0.92 (t, *J* = 7.3 Hz, 3H, ArCHCOSCH_2CH_2CH_3).

^{13}C-NMR (101 MHz, $CDCl_3$) δ_C/ppm: 201.3 (q), 140.1 (q), 128.7 (+), 128.5 (+), 128.4 (+), 127.9 (+), 127.4 (+), 54.3 (+), 31.0 (–), 22.9 (–), 18.5 (+), 13.3 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2967 (m, sh), 2933 (m, sh), 2874 (w, sh), 1685 (s, sh), 1454 (m, sh), 995 (m, sh), 947 (s, sh).

HR-MS (APCI): m/z = [MH^+] calc. for $C_{12}H_{17}OS$ 209.0995, found 209.0995.

S-Heptyl 2-phenylpropanethioate (20aa)



General procedure *C1* was used to carbonylate dist. styrene (115 µL, 1.00 mmol) with 1 mol% catalyst and dist. HeptSH (210 µL, stored under N_2, 1.34 eq.) as the thiol component at RT. Purification by column chromatography (gradient CyH → CyH/EtOAc: 95/5) provided **20aa** as a bright yellow oil (253 mg, 958 µmol, 95%).

$C_{16}H_{24}OS$ (264.43 g/mol), **R_f:** 0.50 (CyH/EtOAc: 95/5), **m.p.:** Ambient temperature.

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.37 – 7.27 (m, 5H, ArH), 3.88 (q, *J* = 7.1 Hz, 1H, ArCH), 2.91 – 2.73 (m, 2H, ArCHCOSCH_2), 1.53 (d, *J* = 7.1 Hz, 3H, ArCHCH_3), 1.52 – 1.45 (m, 2H, $SCH_2CH_2(CH_2)_4CH_3$), 1.37 – 1.16 (m, 8H, $SCH_2(CH_2)_4CH_3$), 0.86 (t, *J* = 6.8 Hz, 3H, $SCH_2(CH_2)_5CH_3$).

^{13}C-NMR (101 MHz, $CDCl_3$) δ_C/ppm: 201.3 (q), 140.1 (q), 128.7 (+), 127.9 (+), 127.4 (+), 54.3 (+), 31.7 (–), 29.4 (–), 29.1 (–), 28.8 (–), 28.8 (–), 22.6 (–), 18.5 (+), 14.1 (+).

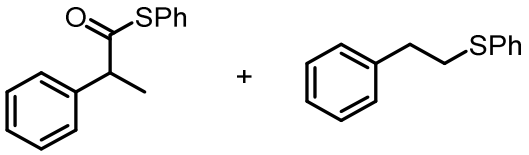
FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2930 (s, br), 2855 (m, sh), 1689 (s, sh), 1454 (m, sh), 995 (w, sh), 947 (s, sh), 701 (s, sh).

HR-MS (APCI): m/z = [MH^+] calc. for $C_{16}H_{25}OS$ 265.1621, found 265.1624.

Scale up: General procedure *C1* was used in a fivefold amount to carbonylate dist. styrene (575 µL, 5.00 mmol) with 1 mol% catalyst, and dist. HeptSH (1050 µL, stored under N_2, 1.34 eq.) as a thiol component at RT in a two-chambered pressure vessel (COware 100 mL,

SyTracks A/S). Purification by column chromatography (gradient CyH → CyH/EtOAc: 95/5) provided **20aa** as a bright yellow oil (1.32 g, 4.99 mmol, >99%).

S-Phenyl 2-phenylpropanethioate (20ag) and phenethyl(phenyl)sulfane (20ag')



General procedure *C1* was used to carbonylate dist. styrene (115 µL, 1.00 mmol) with 1 mol% catalyst and dist. PhSH (140 µL, stored under N_2, 1.37 eq.) as the thiol component at RT. Purification by column chromatography (gradient CyH → CyH/EtOAc: 95/5) provided an inseparable mixture of **20ag** and **20ag'** as a bright yellow oil (135 mg, ether/ester = 41/59 → **20ag**: 80 mg, 329 µmol, 33%, **20ag'**: 55 mg, 259 µmol, 26%).

$C_{15}H_{14}OS$ (242.34 g/mol) and $C_{14}H_{14}S$ (214.33 g/mol), **R_f:** 0.35, 0.20 (CyH/EtOAc: 95/5), **m.p.:** Ambient temperature.

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.42 – 7.27 (m, 14H, ArH), 7.24 – 7.15 (m, 3H, ArH), 4.01 (q, *J* = 7.1 Hz, 1H, ArCH), 3.24 – 3.12 (m, 2H, $ArCH_2$), 2.94 (dd, *J* = 9.3, 6.4 Hz, 2H, $ArCH_2CH_2$), 1.59 (d, *J* = 7.1 Hz, 3H, $ArCHCH_3$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 199.1 (q), 140.2 (q), 139.6 (q), 136.4 (q), 134.5 (+), 129.3 (+), 129.2 (+), 129.1 (+), 129.0 (+), 128.8 (+), 128. 6 (+), 128.1 (+), 127.9 (q), 127.6 (+), 126.5 (+), 126.0 (+), 54.1 (+), 35.7 (–), 35.1 (–), 18.7 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3027 (w, br), 2930 (w, br), 2974 (w, br), 1700 (s, sh), 1580 (m, sh), 1476 (s, sh), 1439 (s, sh), 932 (s, sh), 738 (s, sh), 690 (s, sh).

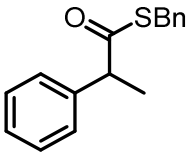
GC-MS (EI) **20ag**: 242 (2, $[M^{+\bullet}]$), 133 (10, $[M^{+\bullet}]$-$[PhS^{\bullet}]$), 105 (100, $[M^{+\bullet}]$-$[PhSCO^{\bullet}]$).

GC-MS (EI) **20ag'**: 214 (75, $[M^{+\bullet}]$), 123 (100, $[M^{+\bullet}]$-$[PhCH_2^{\bullet}]$), 105 (25, $[M^{+\bullet}]$-$[PhS^{\bullet}]$).

HR-MS (EI) **20ag**: m/z = $[M^{+\bullet}]$ calc. for $C_{15}H_{14}OS$ 242.0760, found 242.0767.

HR-MS (EI) **20ag'**: m/z = $[M^{+\bullet}]$ calc. for $C_{14}H_{14}S$ 214.0811, found 214.0814.

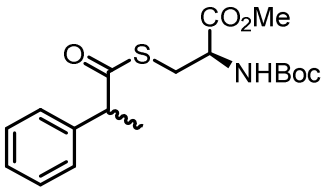
***S*-Benzyl 2-phenylpropanethioate (20ad)**



General procedure *C1* was used to carbonylate dist. styrene (115 µL, 1.00 mmol) with 1 mol% catalyst and dist. BnSH (160 µL, 1.34 mmol, 1.34 eq. stored under N_2) as the thiol component at RT. Purification by column chromatography (gradient CyH → CyH/EtOAc: 95/5) provided **20ad** as a colourless oil (210 mg, 820 µmol, 82%).

$C_{16}H_{16}OS$ (256.36 g/mol), **R_f:** 0.39 (CyH/EtOAc: 95/5), **m.p.:** Ambient temperature.
^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.41 – 7.16 (m, 10H, Ar<u>H</u>), 4.09 (ABq, $\Delta\delta_{AB}$ = 0.09, J_{AB} = 13 Hz, 2H, PhC<u>H$_2$</u>SR), 3.92 (q, *J* = 7.1 Hz, 1H, ArC<u>H</u>CH$_3$), 1.57 (d, *J* = 7.1 Hz, 3H, ArCHC<u>H$_3$</u>).
^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 200.6 (q), 139.7 (q), 137.4 (q), 128.9 (+), 128.7 (+), 128.6 (+), 128.0 (+), 127.6 (+), 127.3 (+), 54.1 (+), 33.5 (-), 18.5 (+).
FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3063 (w), 3030 (w), 2978 (w), 2933 (w), 1681 (s, sh), 1602 (m), 1494 (m, sh), 1453 (m, sh), 1099 (m, sh), 1069 (m, sh), 995 (m, sh), 939 (s, sh), 693 (s, sh).
HR-MS (APCI): m/z = [MH$^+$] calc. for $C_{16}H_{17}OS$ 257.0995, found 257.0995.

<u>Methyl *N*-(*tert*-butoxycarbonyl)-*S*-(2-phenylpropanoyl)-L-cysteinate (20ae)</u>



General procedure *C1* was used to carbonylate dist. styrene (115 µL, 1.00 mmol) with 1 mol% catalyst and *N*-Boc-L-cysteine methyl ester (205 µL, 1.00 mmol, 1.0 eq., stored under N_2) as the thiol component at RT. The crude reaction mixture was treated with Et_3N (160 µL, 1.15 mmol) and stirred for 15 min at RT in order to remove the unreacted thiol. Purification by column chromatography (CyH/EtOAc: 9/1) provided **20ae** as a colourless oil (227 mg, 620 µmol, 62%).

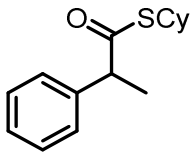
$C_{18}H_{25}NO_5S$ (367.46 g/mol), **R_f:** 0.16 (CyH/EtOAc: 9/1), **m.p.:** Ambient temperature.
^{1}H-NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.43 – 7.11 (m, 5H, Ar<u>H</u>), 5.23 (dd, *J* = 15.0, 8.1 Hz, 1H, N<u>H</u>), 4.47 (s br, 1H, RCOS-CH$_2$-C<u>H</u>(NHBoc)(CO$_2$Me)), 3.87 (q, *J* = 7.1 Hz, 1H, Ph-C<u>H</u>(CH$_3$)(COS-cysteine)), 3.62 (2x s, 3H, RCOS-CH$_2$-CH(NHBoc)(CO$_2$C<u>H$_3$</u>)),), 3.36 – 3.19 (m, 2H, RCOS-C<u>H$_2$</u>-CH(NHBoc)(CO$_2$Me)), 1.50 (dd, *J* = 7.1, 2.2 Hz, 3H, Ph-CH(C<u>H$_3$</u>)(COS-cysteine)), 1.41 – 1.39 (2x s, 9H, C(C<u>H$_3$</u>)$_3$).

^{13}C-NMR (101 MHz, $CDCl_3$) δ_C/ppm: 200.1 (q), 200.0 (q), 170.9 (q), 139.4 (q), 128.7 (+), 128.7 (+), 128.0 (+), 127.9 (+), 127.6 (q), 80.1 (q), 54.3 (+), 53.1 (+), 53.0 (+), 52.6 (+), 52.5 (+), 31.2 (-), 31.1 (-), 28.3 (+), 18.4 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3373 (w, br), 2978 (w, sh), 2937 (w, sh), 1748 (m, sh), 1700 (s, sh), 1692 (s, sh), 1494 (m, sh), 1453 (m, sh), 1394 (w, sh), 1364 (m, sh), 1244 (m, sh), 1215 (m, sh), 1159 (s, sh), 1054 (m, sh), 1010 (m, sh), 943 (s, sh), 864 (m), 775 (m), 730 (m), 700 (s, sh).

HR-MS (ESI): m/z = [MNa^+] calc. for $C_{18}H_{25}NNaO_5S$ 390.1346, found 390.1352.

S-Cyclohexyl 2-phenylpropanethioate (20af)



General procedure *C1* was used to carbonylate dist. styrene (115 µL, 1.00 mmol) with 1 mol% catalyst and freshly opened cyclohexanethiol (165 µL, stored under N_2) as the thiol component at RT. Purification by column chromatography (gradient CyH → CyH/EtOAc: 95/5) provided **20af** as a colourless oil (70 mg, 820 µmol, 28%).

$C_{15}H_{20}OS$ (248.38 g/mol), **R_f:** 0.47 (CyH/EtOAc: 95/5), **m.p.:** Ambient temperature.

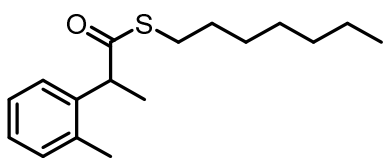
^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.42 – 7.09 (m, 5H, ArH), 3.86 (q, *J* = 7.1 Hz, 1H, ArCH(COSR)CH_3), 3.57 – 3.36 (m, 1H, cyclohexyl CH), 2.06 – 1.57 (m, 5H, cyclohexyl CH_2), 1.53 (d, *J* = 7.1 Hz, 3H, ArCH(COSR)CH_3), 1.48 – 1.08 (m, 5H, cyclohexyl CH_2).

^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 201.0 (q), 140.1 (q), 128.6 (+), 127.9 (+), 127.3 (+), 54.3 (+), 42.5 (+), 33.06 (-), 32.89 (-), 26.02 (-), 26.00 (-), 25.56 (-), 18.55 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3030 (w, br), 2929 (s, sh), 2855 (m, sh), 1700 (s, sh), 1681 (s, sh), 1494 (w, sh), 1449 (m, sh), 1263 (w, sh), 995 (m, sh), 943 (s, sh), 730 (m, sh), 697 (s, sh).

HR-MS (APCI): m/z = [MH^+] calc. for $C_{15}H_{21}OS$ 249.1308, found 249.1315.

S-Heptyl 2-(*o*-tolyl)propanethioate (20ba)



General procedure *C1* was used to carbonylate dist. *ortho*-methylstyrene (130 µL, 1.00 mmol) with 1 mol% catalyst and dist. HeptSH (210 µL, stored under N_2, 1.34 eq.) as the thiol component at RT. Purification by column chromatography (gradient CyH → CyH/EtOAc: 95/5) provided **20ba** as a bright yellow oil (248.6 mg, 893 µmol, 89%).

$C_{17}H_{26}OS$ (278.45 g/mol), **R_f:** 0.48 (CyH/EtOAc: 95/5), **m.p.:** Ambient temperature.

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.31 – 7.27 (m, 1H, ArH), 7.25 – 7.15 (m, 3H, ArH), 4.10 (q, *J* = 7.1 Hz, 1H, ArCH), 2.89 – 2.75 (m, 2H, SCH_2), 2.37 (s, 3H, $ArCH_3$), 1.51 (d, *J* = 7.1 Hz, 3H, $ArCHCH_3$), 1.56 – 1.47 (m, 2H, $SCH_2CH_2(CH_2)_4CH_3$), 1.34 – 1.17 (m, 8H, $SCH_2CH_2(CH_2)_4CH_3$), 0.86 (t, *J* = 6.8 Hz, 3H, $SCH_2(CH_2)_5CH_3$).

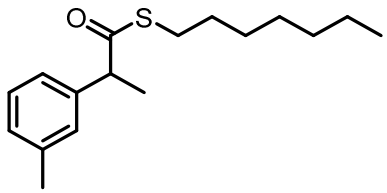
^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 201.8 (q), 138.3 (q), 136.2 (q), 130.5 (+), 127.3 (+), 127.2 (+), 126.4 (+), 50.1 (+), 31.7 (–), 29.5 (–), 29.1 (–), 28.78 (–), 28.77 (–), 22.6 (–), 19.9 (+), 18.1 (+), 14.1 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2926 (s, sh), 2855 (m, sh), 1681 (s, sh), 1491 (w, sh), 1457 (m, sh), 999 (m, sh), 939 (s, sh), 738 (s, br).

GC-MS (EI): t_R = 8.83 min, m/z = 119 (100, $[M^{+\bullet}]$-[$^\bullet$COSHept]), 91 (9, $[M^{+\bullet}]$-[$^\bullet$COSHept]-[CH_3]), 250 (0.4, $[M^{+\bullet}]$-[CO]).

HR-MS (EI): m/z = $[M^{+\bullet}]$ calc. for $C_{17}H_{26}OS$ 278.1699, found 278.1702.

S-Heptyl 2-(*m*-tolyl)propanethioate (20ga)



General procedure *C1* was used to carbonylate dist. *meta*-methylstyrene (130 µL, 990 µmol) with 1 mol% catalyst and dist. HeptSH (210 µL, stored under N_2, 1.34 eq.) as the thiol component at RT. Purification by column chromatography (gradient CyH → CyH/EtOAc: 95/5) provided **20ga** as a bright yellow oil (274 mg, 984 µmol, 99%).

$C_{17}H_{26}OS$ (278.45 g/mol), **R_f:** 0.53 (CyH/EtOAc: 95/5), **m.p.:** Ambient temperature.

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.25 – 7.18 (m, 1H, ArH), 7.14 – 7.04 (m, 3H, ArH), 3.84 (q, *J* = 7.1 Hz, 1H, ArCH), 2.92 – 2.73 (m, 2H, SCH_2), 2.35 (s, 3H, $ArCH_3$), 1.51 (d, *J* = 7.1 Hz, 3H,

ArCHC<u>H</u>$_3$), 1.57 – 1.47 (m, 2H, SCH$_2$C<u>H$_2$</u>(CH$_2$)$_4$CH$_3$), 1.36 – 1.15 (m, 8H, SCH$_2$CH$_2$(C<u>H$_2$</u>)$_4$CH$_3$)), 0.86 (t, *J* = 6.8 Hz, 3H, SCH$_2$(CH$_2$)$_5$C<u>H$_3$</u>).

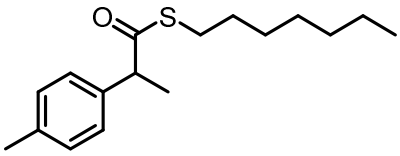
^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 201.4 (q), 140.0 (q), 138.3 (q), 128.6 (+), 128.5 (+), 128.2 (+), 124.9 (+), 54.2 (+), 31.7 (–), 29.4 (–), 29.1 (–), 28.80 (–), 28.77 (–), 22.6 (–), 21.5 (+), 18.5 (+), 14.1 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2926 (s, sh), 2855 (s, sh), 1684 (s, sh), 1607 (w, sh), 1454 (m, br), 947 (s, sh), 734 (m, br).

GC-MS (EI): t_R = 8.78 min, m/z = 119 (100, [M$^{+\bullet}$]-[$^{\bullet}$COSHept]), 91 (8, [M$^{+\bullet}$]-[$^{\bullet}$COSHept]-[CH$_3$]), 250 (4, [M$^{+\bullet}$]-[CO]), 180 (3, [M$^{+\bullet}$]-[$^{\bullet}$Hept]).

HR-MS (EI): m/z = [M$^{+\bullet}$] calc. for $C_{17}H_{26}OS$ 278.1699, found 278.1702.

<u>S-Heptyl 2-(*p*-tolyl)propanethioate (20ia)</u>



General procedure *C1* was used to carbonylate dist. *para*-methylstyrene (130 µL, 990 µmol) with 1 mol% catalyst and dist. HeptSH (210 µL, stored under N_2, 1.34 eq.) as the thiol component at RT. Purification by column chromatography (gradient CyH → CyH/EtOAc: 95/5) provided **20ia** as a bright yellow oil (275 mg, 988 µmol, 99%).

$C_{17}H_{26}OS$ (278.45 g/mol), **R_f:** 0.57 (CyH/EtOAc: 95/5), **m.p.:** Ambient temperature.

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.23 – 7.11 (m, 4H, Ar<u>H</u>), 3.84 (q, *J* = 7.1 Hz, 1H, ArC<u>H</u>), 2.90 – 2.72 (m, 2H, SC<u>H$_2$</u>), 2.33 (s, 3H, ArC<u>H$_3$</u>), 1.51 (d, *J* = 7.1 Hz, 3H, ArCHC<u>H$_3$</u>), 1.57 – 1.47 (m, 2H, SCH$_2$C<u>H$_2$</u>(CH$_2$)$_4$CH$_3$), 1.38 – 1.17 (m, 8H, SCH$_2$CH$_2$(C<u>H$_2$</u>)$_4$CH$_3$), 0.86 (t, *J* = 6.8 Hz, 3H, SCH$_2$(CH$_2$)$_5$C<u>H$_3$</u>).

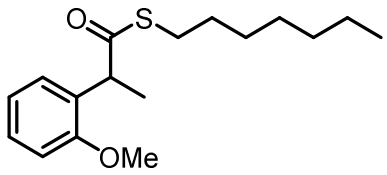
^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 201.6 (q), 137.10 (q), 137.07 (q), 129.4 (+), 127.8 (+), 53.9 (+), 31.7 (–), 29.4 (–), 29.1 (–), 28.8 (–), 28.8 (–), 22.6 (–), 21.1 (+), 18.5 (+), 14.1 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2926 (s, sh), 2855 (m, sh), 1681 (s, sh), 1513 (m, sh), 1454 (m, sh), 1003 (m, sh), 943 (s, sh), 753 (m, sh).

GC-MS (EI): t_R = 8.871 min, m/z = 119 (100, [M$^{+\bullet}$]-[$^{\bullet}$COSHept]), 91 (7, [M$^{+\bullet}$]-[$^{\bullet}$COSHept]-[CH$_3$]), 250 (2, [M$^{+\bullet}$]-[CO]).

HR-MS (EI): m/z = [M$^{+\bullet}$] calc. for $C_{17}H_{26}OS$ 278.1699, found 278.1699.

S-Heptyl 2-(2-methoxyphenyl)propanethioate (20ca)



General procedure *C1* was used to carbonylate dist. *ortho*-vinylanisole (135 µL, 1.01 mmol) with 1 mol% catalyst and dist. HeptSH (210 µL, stored under N_2, 1.34 eq.) as the thiol component at RT. Purification by column chromatography (gradient CyH → CyH/EtOAc: 95/5) provided **20ca** as a bright yellow oil (287 mg, 975 µmol, 97%).

$C_{17}H_{26}O_2S$ (294.45 g/mol), **R_f:** 0.40 (CyH/EtOAc: 95/5), **m.p.:** Ambient temperature.

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.32 – 7.20 (m, 2H, Ar<u>H</u>), 7.03 – 6.82 (m, 2H, Ar<u>H</u>), 4.26 (q, *J* = 7.1 Hz, 1H, ArC<u>H</u>), 3.83 (s, 3H, ArOC<u>H$_3$</u>), 2.81 (t, *J* = 7.3 Hz, 2H, SC<u>H$_2$</u>), 1.54 – 1.44 (m, 2H, $SCH_2C\underline{H_2}(CH_2)_4CH_3$), 1.48 (d, *J* = 7.1 Hz, 3H, ArCHC<u>H$_3$</u>), 1.34 – 1.18 (m, 8H, $SCH_2CH_2(C\underline{H_2})_4CH_3$), 0.86 (t, *J* = 6.8 Hz, 3H, $SCH_2(CH_2)_5C\underline{H_3}$).

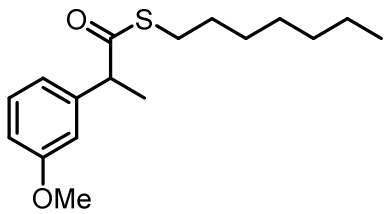
^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 202.2 (q), 157.0 (q), 128.6 (q), 128.5 (+), 128.4 (+), 120.7 (+), 110.7 (+), 55.5 (+), 47.3 (+), 31.7 (–), 29.6 (–), 28.9 (–), 28.81 (–), 28.80 (–), 22.6 (–), 17.3 (+), 14.1 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2926 (s, br), 2855 (m, sh), 1685 (s, sh), 1599 (w, sh), 1491 (s, sh), 1461 (s, br), 1245 (s, sh), 1122 (m, br), 1029 (s, sh), 943 (s, sh), 753 (s, sh).

GC-MS (CI): t_R = 9.207 min, m/z = 135 (100, $[MH^+]$-[$^\bullet$COSHept], 295 (75, $[MH^+]$), 163 (6, $[MH^+]$-[$^\bullet$SHept).

HR-MS (APCI): m/z = $[MH^+]$ calc. for $C_{17}H_{27}O_2S$ 295.1726, found 295.1737.

S-Heptyl 2-(3-methoxyphenyl)propanethioate (20ha)



General procedure *C1* was used to carbonylate dist. *meta*-vinylanisole (140 µL, 1.01 mmol) with 1 mol% catalyst and dist. HeptSH (210 µL, stored under N_2, 1.34 eq.) as the thiol component at RT. Purification by column chromatography (gradient CyH → CyH/EtOAc: 95/5) provided **20ha** as a bright yellow oil (287 mg, 906 µmol, 90%).

$C_{17}H_{26}O_2S$ (294.45 g/mol), **R_f:** 0.42 (CyH/EtOAc: 95/5), **m.p.:** Ambient temperature.

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.24 – 7.17 (m, 1H, ArH), 6.88 – 6.73 (m, 3H, ArH), 3.81 (q, *J* = 7.1 Hz, 1H, ArCH), 3.76 (s, 3H, $ArOCH_3$), 2.88 – 2.67 (m, 2H, SCH_2), 1.52 – 1.42 (m, 2H, $SCH_2CH_2(CH_2)_4CH_3$), 1.46 (d, *J* = 7.1 Hz, 3H, $ArCHCH_3$), 1.33 – 1.11 (m, 8H, $SCH_2CH_2(CH_2)_4CH_3$), 0.82 (t, *J* = 6.8 Hz, 3H, $SCH_2(CH_2)_5CH_3$).

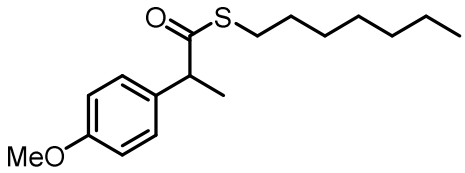
^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 201.2 (q), 159.7 (q), 141.6 (q), 129.6 (+), 120.3 (+), 113.6 (+), 112.7 (+), 55.2 (+), 54.3 (+), 31.7 (–), 29.4 (–), 29.1 (–), 28.80 (–), 28.77 (–), 22.6 (–), 18.4 (+), 14.1 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2926 (s, sh), 2855 (m, sh), 1681 (s, sh), 1599 (s, sh), 1454 (s, sh), 1260 (s, br), 1044 (s, sh), 950 (s, sh), 753 (s, sh), 697 (s, sh).

GC-MS (EI): t_R = 9.439 min, m/z = 135 (100, $[M^{+\bullet}]$-[$^\bullet$COSHept], 105 (9, $[M^{+\bullet}]$-[$^\bullet$COSHept]-[$^\bullet$OMe]), 296 (0.7, $[M^{+\bullet}]$).

HR-MS (EI): m/z = $[M^{+\bullet}]$ calc. for $C_{17}H_{26}O_2S$ 294.1648, found 294.1646.

S-Heptyl 2-(4-methoxyphenyl)propanethioate (20ja)



General procedure *C1* was used to carbonylate dist. *para*-vinylanisole (140 µL, 1.01 mmol) with 1 mol% catalyst and dist. HeptSH (210 µL, stored under N_2, 1.34 eq.) as the thiol component at RT. Purification by column chromatography (gradient CyH → CyH/EtOAc: 95/5) provided **20ja** as a bright yellow oil (295 mg, 1.00 µmol, 99%).

$C_{17}H_{26}O_2S$ (294.45 g/mol), **R_f:** 0.38 (CyH/EtOAc: 95/5), **m.p.:** Ambient temperature.

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.25 – 7.20 (m, 2H, ArH), 6.90 – 6.83 (m, 2H, ArH), 3.82 (q, *J* = 7.1 Hz, 1H, ArCH), 3.80 (s, 3H, $ArOCH_3$) 2.91 – 2.70 (m, 2H, SCH_2), 1.58 – 1.43 (m, 2H, $SCH_2CH_2(CH_2)_4CH_3$), 1.50 (d, *J* = 7.1 Hz, 3H, $ArCHCH_3$), 1.37 – 1.14 (m, 8H, $SCH_2CH_2(CH_2)_4CH_3$), 0.86 (t, *J* = 6.7 Hz, 3H, $SCH_2(CH_2)_5CH_3$).

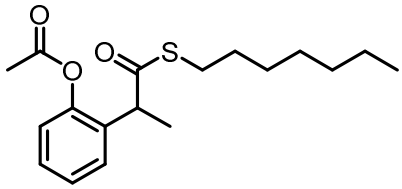
^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 201.8 (q), 158.9 (q), 132.1 (q), 129.0 (+), 114.0 (+), 55.3 (+), 53.4 (+), 31.7 (–), 29.4 (–), 29.1 (–), 28.8 (–), 28.8 (–), 22.6 (–), 18.5 (+), 14.1 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2926 (s, sh), 2855 (m, sh), 1677 (s, sh), 1610 (m, sh), 1513 (s, sh), 1461 (m, br), 1245 (s, sh), 1178 (s, sh), 943 (s, br), 831 (s, sh).

GC-MS (EI): t_R = 9.589 min, m/z = 135 (100, $[M^{+\bullet}]$-[$^{\bullet}$COSHept], 105 (6, $[M^{+\bullet}]$-[$^{\bullet}$COSHept]-[$^{\bullet}$OMe]), 295 (0.4, $[M^{+\bullet}]$).

HR-MS (EI): m/z = $[M^{+\bullet}]$ calc. for $C_{17}H_{26}O_2S$ 294.1648, found 294.1646.

2-(1-(Heptylthio)-1-oxopropan-2-yl)phenyl acetate (20ea)



General procedure *C1* was used to carbonylate dist. *ortho*-acetoxystyrene (162 mg, 1.00 mmol) with 1 mol% catalyst and dist. HeptSH (210 µL, stored under N_2, 1.34 eq.) as the thiol component at RT. Purification by column chromatography (gradient CyH → CyH/EtOAc: 95/5) provided **20ea** as a bright yellow oil (158 mg, 489 µmol, 49%).

$C_{18}H_{26}O_3S$ (322.46 g/mol), **R_f:** 0.29 (CyH/EtOAc: 95/5), **m.p.:** Ambient temperature.

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.39 (dd, *J* = 7.5, 1.8 Hz, 1H, ArH), 7.34 – 7.20 (m, 2H, ArH), 7.09 (dd, *J* = 7.9, 1.5 Hz, 1H, ArH), 4.02 (q, *J* = 7.1 Hz, 1H, ArCH), 2.96 – 2.72 (m, 2H, SCH_2), 2.34 (s, 3H, $ArOCOCH_3$), 1.61 – 1.45 (m, 2H, $SCH_2CH_2(CH_2)_4CH_3$), 1.50 (d, *J* = 7.1 Hz, $ArCHCH_3$), 1.26 (m, 8H, $SCH_2CH_2(CH_2)_4CH_3$), 0.87 (t, *J* = 7.0 Hz, 3H, $SCH_2(CH_2)_5CH_3$).

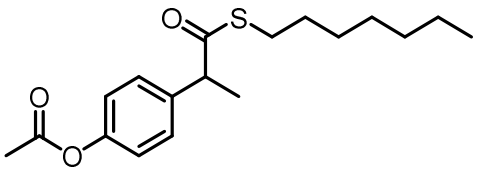
^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 200.7 (q), 169.2 (q), 148.5 (q), 131.9 (q), 128.7 (+), 128.4 (+), 126.4 (+), 122.7 (+), 47.9 (+), 31.7 (–), 29.4 (–), 29.1 (–), 28.8 (–), 22.6 (–), 21.0 (+), 17.5 (+), 14.1 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2930 (m, sh), 2855 (w, sh), 1767 (s, sh), 1685 (s, sh), 1491 (w, sh), 1454 (w, br), 1372 (m, sh), 1193 (s, sh), 947 (s, sh), 910 (s, sh), 746 (s, br).

GC-MS (CI): t_R = 9.549 min, m/z = 149 (100, $[MH^+]$-[$^{\bullet}$SHept]-[$^{\bullet}CH_3CO$]), 191 (18, $[MH^+]$-[$^{\bullet}$SHept]), 323 (7, $[MH^+]$), 263 (4, $[MH^+]$-[$^{\bullet}CH_3COO$]).

HR-MS (APCI): m/z = $[MH^+]$ calc. for $C_{18}H_{27}O_3S$ 323.1675, found 323.1682.

4-(1-(Heptylthio)-1-oxopropan-2-yl)phenyl acetate (20ka)



General procedure *C1* was used to carbonylate dist. *para*-acetoxystyrene (155 µL, 1.01 mmol) with 1 mol% catalyst and dist. HeptSH (210 µL, stored under N_2, 1.34 eq.) as the thiol component at RT. Purification by column chromatography (gradient CyH → CyH/EtOAc: 95/5) provided **20ka** as a bright yellow oil (304 mg, 942 µmol, 93%).

$C_{18}H_{26}O_3S$ (322.46 g/mol), **R_f:** 0.19 (CyH/EtOAc: 95/5), **m.p.:** Ambient temperature.

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.36 – 7.28 (m, 2H, Ar<u>H</u>), 7.08 – 7.00 (m, 2H, Ar<u>H</u>), 3.88 (q, *J* = 7.1 Hz, 1H, ArC<u>H</u>), 2.91 – 2.73 (m, 2H, SC<u>H$_2$</u>), 2.30 (s, 3H, ArOCOC<u>H$_3$</u>), 1.50 (d, *J* = 7.1 Hz, 3H, ArCHC<u>H$_3$</u>), 1.58 – 1.45 (m, 2H, $SCH_2C\underline{H_2}(CH_2)_4CH_3$), 1.37 – 1.15 (m, 8H, $SCH_2CH_2(C\underline{H_2})_4CH_3$), 0.86 (t, *J* = 6.7 Hz, 3H, $SCH_2(CH_2)_5C\underline{H_3}$).

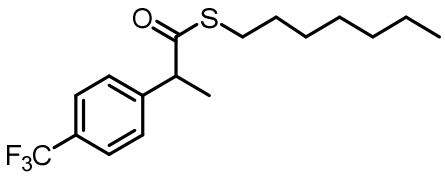
^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 201.1 (q), 269.5 (q), 149.9 (q), 137.5 (q), 128.9 (+), 121.7 (+), 53.6 (+), 31.7 (–), 29.4 (–), 29.1 (–), 28.8 (–), 28.8 (–), 22.6 (–), 21.2 (+), 18.6 (+), 14.1 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2930 (m, sh), 2855 (w, sh), 1763 (s, sh), 1681 (s, sh), 1506 (m, sh), 1368 (m, sh), 1193 (s, br), 947 (s, sh), 910 (s, sh).

GC-MS (EI): t_R = 10.16 min, m/z = 121 (100, $[M^{+\bullet}]$-[$^\bullet$COSHept]-[$^\bullet CH_2CO$]), 163 (21, $[M^{+\bullet}]$-[$^\bullet$COSHept]), 280 (2, $[M^{+\bullet}]$-[$^\bullet CH_2CO$]), 322 (1, $[M^{+\bullet}]$).

HR-MS (EI): m/z = $[M^{+\bullet}]$ calc. for $C_{18}H_{26}O_3S$ 322.1597, found 322.1591.

<u>S-Heptyl 2-(4-(trifluoromethyl)phenyl)propanethioate (20la)</u>



General procedure *C1* was used to carbonylate dist. *para*-trifluoromethyl-styrene (150 µL, 1.02 mmol) with 1 mol% catalyst and dist. HeptSH (210 µL, stored under N_2, 1.34 eq.) as the thiol component at RT. Purification by column chromatography (gradient CyH → CyH/EtOAc: 95/5) provided **20la** as a bright yellow oil (168 mg, 504 µmol, 50%).

$C_{17}H_{23}F_3OS$ (332.43 g/mol), **R_f:** 0.32 (CyH/EtOAc: 95/5), **m.p.:** Ambient temperature.

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.62 – 7.56 (m, 2H, Ar<u>H</u>), 7.46 – 7.41 (m, 2H, Ar<u>H</u>), 3.95 (q, *J* = 7.1 Hz, 1H, ArC<u>H</u>), 2.90 – 2.78 (m, 2H, SC<u>H$_2$</u>), 1.55 (d, *J* = 7.1 Hz, 3H, ArCHC<u>H$_3$</u>), 1.53 – 1.47 (m, 2H, $SCH_2C\underline{H_2}(CH_2)_4CH_3$), 1.33 – 1.19 (m, 8H, $SCH_2CH_2(C\underline{H_2})_4CH_3$), 0.86 (t, *J* = 6.9 Hz, 3H, $SCH_2(CH_2)_5C\underline{H_3}$).

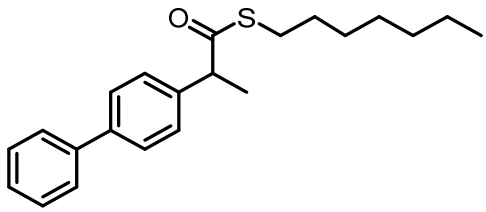
^{13}C-NMR (101 MHz, $CDCl_3$) δ_C/ppm: 200.4 (q), 143.95 (q), 129.7 (quartet, J = 32.5 Hz, q), 128.2 (+), 125.6 (quartet, J = 3.8 Hz, +), 124.1 (quartet, J = 272.0 Hz, q), 54.0 (+), 31.7 (–), 29.4 (–), 29.2 (–), 28.7 (–), 28.7 (–), 22.6 (–), 18.5 (+), 14.0 (+).

^{19}F-NMR (282 MHz, $CDCl_3$) δ_C/ppm: - 62.9 (CF_3).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2929 (w, br), 2858 (w, sh), 1684 (m, sh), 1323 (s, sh), 1162 (m, sh), 1118 (s, sh), 1169 (m, sh), 946 (m, sh), 842 (m, sh).

HR-MS (APCI): m/z = [MH^+] calc. for $C_{17}H_{24}F_3OS$ 333.1494, found 333.1499.

S-Heptyl 2-([1,1'-biphenyl]-4-yl)propanethioate (20ma)



General procedure *C1* was used to carbonylate dist. *para*-phenylstyrene (181 mg, 1.00 mmol) with 1 mol% catalyst and dist. HeptSH (210 µL, stored under N_2, 1.34 eq.) as the thiol component at RT. Purification by column chromatography (gradient CyH → CyH/EtOAc: 95/5) provided **20ma** as a bright yellow oil (293 mg, 860 µmol, 86%).

$C_{22}H_{28}OS$ (340.53 g/mol), **R_f:** 0.51 (CyH/EtOAc: 95/5), **m.p.:** Ambient temperature.

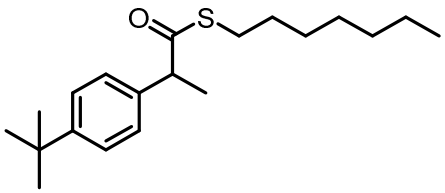
^{1}H-NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.61 – 7.54 (m, 4H, Ar<u>H</u>), 7.46 – 7.31 (m, 5H, Ar<u>H</u>), 3.93 (q, *J* = 7.1 Hz, 1H, ArC<u>H</u>), 2.92 – 2.77 (m, 2H, SC<u>H_2</u>), 1.57 (d, *J* = 7.1 Hz, 3H, ArCHC<u>H_3</u>), 1.55 – 1.48 (m, 2H, $SCH_2C\underline{H_2}(CH_2)_4CH_3$), 1.35 – 1.19 (m, 8H, $SCH_2CH_2(C\underline{H_2})_4CH_3$), 0.86 (t, *J* = 6.9 Hz, 3H, $SCH_2(CH_2)_5C\underline{H_3}$).

^{13}C-NMR (101 MHz, $CDCl_3$) δ_C/ppm: 201.3 (q), 140.8 (q), 140.3 (q), 139.1 (q), 128.8 (+), 128.3 (+), 127.4 (+), 127.3 (+), 127.1 (+), 54.0 (+), 31.7 (–), 29.4 (–), 29.2 (–), 28.8 (–), 28.8 (–), 22.6 (–), 18.5 (+), 14.1 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2926 (m, br), 2855 (w, sh), 1685 (s, sh), 1454 (m, sh), 980 (m, sh), 812 (w, sh), 738 (s, sh), 697 (s, sh).

HR-MS (APCI): m/z = [MH^+] calc. for $C_{22}H_{29}OS$ 341.1934, found 341.1941.

S-Heptyl 2-(4-(tert-butyl)phenyl)propanethioate (20na)



General procedure *C1* was used to carbonylate dist. *para*-*tert*-butylstyrene (185 µL, 1.01 mmol) with 1 mol% catalyst and dist. HeptSH (210 µL, stored under N_2, 1.34 eq.) as the thiol component at RT. Purification by column chromatography (gradient CyH → CyH/EtOAc: 95/5) provided **20na** as a bright yellow oil (307 mg, 957 µmol, 95%).

$C_{20}H_{32}OS$ (320.54 g/mol), **R_f:** 0.55 (CyH/EtOAc: 95/5), **m.p.:** Ambient temperature.

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.38 – 7.31 (m, 2H, ArH), 7.25 – 7.21 (m, 2H, ArH), 3.86 (q, *J* = 7.1 Hz, 1H, ArCH), 2.91 – 2.72 (m, 2H, SCH_2), 1.52 (d, *J* = 7.1 Hz, 3H, $ArCHCH_3$), 1.58 – 1.46 (m, 2H, $SCH_2CH_2(CH_2)_4CH_3$), 1.31 (s, 9H, $ArC(CH_3)_3$), 1.38 – 1.16 (m, 8H, $SCH_2CH_2(CH_2)_4CH_3$), 0.86 (t, *J* = 6.8 Hz, 3H, $SCH_2(CH_2)_5CH_3$).

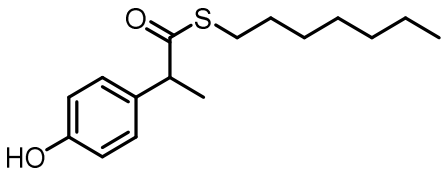
^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 201.6 (q), 150.2 (q), 136.9 (q), 127.5 (+), 125.6 (+), 53.8 (+), 31.7 (–), 31.4 (+), 29.4 (–), 29.1 (–), 28.81 (–), 28.78 (–), 22.6 (–), 18.5 (+), 14.1 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2960 (s, sh), 2930 (s, sh), 2855 (m, sh), 1685 (s, sh), 1461 (m, br), 1364 (m, sh), 999 (m, sh), 943 (s, sh), 835 (m, sh), 768 (m, sh).

GC-MS (EI): t_R = 9.79 min, m/z = 161 (100, $[M^{+\bullet}]$-[$^\bullet$COSHept], 146 (10, $[M^{+\bullet}]$-[$^\bullet$COSHept]-[$^\bullet CH_3$]), 320 (1, $[M^{+\bullet}]$).

HR-MS (EI): m/z = $[M^{+\bullet}]$ calc. for $C_{20}H_{32}OS$ 320.2168, found 320.2160.

S-Heptyl 2-(4-hydroxyphenyl)propanethioate (20oa)



A flame dried RBF was treated with 4-acetoxysyrene (155 µL, 1.01 mmol, 1.0 eq.) which was dissolved in dry THF (2 mL) and was chilled in an ice bath. Afterwards, a degassed solution of sodium hydroxide (102 mg, 2.53 mmol, 2.5 eq.) in water (0.5 mL) was added dropwise to the styrene solution and was stirred of 4 h. The reaction mixture was neutralized with HCl (2.5 mL, 1 M) and water (4 mL). The mixture was extracted with diethyl ether (2 × 5 mL). The

combined organic phases were washed with brine (2 × 50 mL), dried over $MgSO_4$, DCE (790 µL) was added *via* syringe and diethyl ether and THF were removed under reduced pressure.

General procedure *C1* was used to carbonylate 4-hydroxysyrene with 1 mol% catalyst and dist. HeptSH (210 µL, stored under N_2, 1.34 eq.) as the thiol component at RT by adding the DCE/4-hydroxysyrene solution directly to chamber B. No further CH_2Cl_2 was used.

Purification by column chromatography (gradient CyH → CyH/EtOAc: 95/5) provided **20oa** as a bright yellow liquid (137 mg, 488 µmol, 49%). Additionally, also the acetylated product **20ka** was isolated as a bright yellow oil (91 mg, 283 µmol, 28%).

$C_{16}H_{24}O_2S$ (280.43 g/mol), **R_f:** 0.47 (CyH/EtOAc: 80/20), **m.p.:** Ambient temperature.

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.17 – 7.09 (m, 2H, Ar<u>H</u>), 6.78 – 6.71 (m, 2H, Ar<u>H</u>), 4.85 (br, s, 1H, O<u>H</u>), 3.76 (q, *J* = 7.1 Hz, 1H, ArC<u>H</u>), 2.85 – 2.68 (m, 2H, SC<u>H$_2$</u>), 1.52 – 1.41 (m, 5H, ArCHC<u>H$_3$</u>, $SCH_2C\underline{H_2}(CH_2)_4CH_3$), 1.31 – 1.10 (m, 8H, $SCH_2CH_2(C\underline{H_2})_4CH_3$), 0.82 (t, *J* = 6.8 Hz, 3H, $SCH_2(CH_2)_5C\underline{H_3}$).

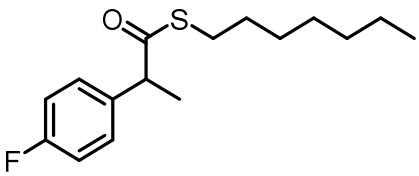
^{13}C-NMR (101 MHz, $CDCl_3$) δ_C/ppm: 201.9 (q), 154.9 (q), 132.3 (q), 129.2 (+), 115.5 (+), 53.4 (+), 31.7 (-), 29.4 (-), 29.1 (-), 28.80 (-), 28.76 (-), 22.6 (-), 18.5 (+), 14.1 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3399 (m, br), 2926 (s, br), 2855 (m, sh), 1655 (s, br), 1614 (m, sh), 1513 (s, sh), 1446 (m, sh), 1215 (s, br), 947 (s, sh), 835 (s, sh), 764 (m, sh).

GC-MS (CI): t_R = 9.749 min, m/z = 281 (100, [MH^+]), 121 (64, [MH^+]-[$^\bullet$COSHept]).

HR-MS (APCI): m/z = [MH^+] calc. for $C_{16}H_{25}O_2S$ 281.1570, found 281.1581.

<u>S-Heptyl 2-(4-fluorophenyl)propanethioate (20ra)</u>



General procedure *C1* was used to carbonylate dist. *para*-fluorostyrene (120 µL, 1.01 mmol) with 1 mol% catalyst and dist. HeptSH (210 µL, stored under N_2, 1.34 eq.) as the thiol component at RT. Purification by column chromatography (gradient CyH → CyH/EtOAc: 95/5) provided **20ra** as a bright yellow oil (257 mg, 910 µmol, 91%).

$C_{16}H_{23}FOS$ (282.42 g/mol), **R_f:** 0.48 (CyH/EtOAc: 95/5), **m.p.:** Ambient temperature.

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.32 – 7.22 (m, 2H, Ar<u>H</u>), 7.07 – 6.96 (m, 2H, Ar<u>H</u>), 3.86 (q, *J* = 7.1 Hz, 1H, ArCHC<u>H$_3$</u>), 2.90 – 2.74 (m, 2H, SC<u>H$_2$</u>), 1.51 (d, *J* = 7.1 Hz, 3H, ArCHC<u>H$_3$</u>), 1.57 – 1.45 (m, 2H, $SCH_2C\underline{H_2}(CH_2)_4CH_3$), 1.34 – 1.18 (m, 8H, $SCH_2CH_2(C\underline{H_2})_4CH_3$), 0.86 (t, *J* = 6.7 Hz, 3H, $SCH_2(CH_2)_5C\underline{H_3}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 201.2 (q), 162.1 (doublet, J = 245.8 Hz, q), 135.7 (doublet, J = 3.3 Hz, q), 129.4 (doublet, J = 8.0 Hz, +), 115.5 (doublet, J = 21.4 Hz, +), 53.4 (+), 31.7 (–), 29.4 (–), 29.1 (–), 28.8 (–), 22.6 (–), 18.6 (+), 14.1 (+).

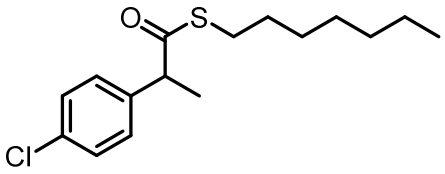
^{19}F-NMR (282 MHz, $CDCl_3$) δ_C/ppm: - 115.8 (CF).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2930 (s, br), 2855 (m, sh), 1681 (s, sh), 1603 (w, sh), 1510 (s, sh), 1457 (m, br), 1226 (s, sh), 1159 (m, sh), 999 (m, sh), 947 (s, sh), 835 (s, sh), 760 (s, sh).

GC-MS (EI): t_R = 8.347 min, m/z = 123 (100, $[M^{+\bullet}]$-[$^{\bullet}$COSHept], 184 (3, $[M^{+\bullet}]$-[$^{\bullet}$Hept]).

HR-MS (EI): m/z = $[M^{+\bullet}]$ calc. for $C_{16}H_{23}FOS$ 282.1448, found 282.1444.

<u>S-Heptyl 2-(4-chlorophenyl)propanethioate (20sa)</u>



General procedure *C1* was used to carbonylate dist. *para*-chlorostyrene (120 µL, 1.00 mmol) with 1 mol% catalyst and dist. HeptSH (210 µL, stored under N_2, 1.34 eq.) as the thiol component at RT. Purification by column chromatography (gradient CyH → CyH/EtOAc: 95/5) provided **20sa** as a bright yellow oil (242 mg, 811 µmol, 81%).

$C_{16}H_{23}ClOS$ (298.87 g/mol), **R_f:** 0.51 (CyH/EtOAc: 95/5), **m.p.:** Ambient temperature.

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.32 – 7.22 (m, 4H, Ar<u>H</u>), 3.85 (q, J = 7.1 Hz, 1H, ArC<u>H</u>), 2.82 (m, 2H, SC<u>H$_2$</u>), 1.50 (d, J = 7.1 Hz, 3H, ArCHC<u>H$_3$</u>), 1.55 – 1.47 (m, 2H, $SCH_2C\underline{H_2}(CH_2)_4CH_3$), 1.33 – 1.18 (m, 8H, $SCH_2CH_2(C\underline{H_2})_4CH_3$), 0.86 (t, J = 6.8 Hz, 3H, $SCH_2(CH_2)_5C\underline{H_3}$).

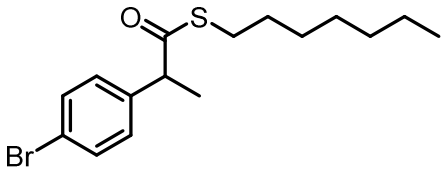
^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 200.9 (q), 138.5 (q), 133.3 (q), 129.2 (+), 128.8 (+), 53.6 (+), 31.7 (–), 29.4 (–), 29.2 (–), 28.8 (–), 22.6 (–), 18.5 (+), 14.1 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2926 (s, sh), 2855 (m, sh), 1685 (s, sh), 1491 (s, sh), 1457 (m, br), 1092 (s, sh), 943 (s, br), 821 (s, sh), 757 (s, sh).

GC-MS (EI): t_R = 9.329 min, m/z = 139 (100, $[M^{+\bullet}]$-[$^{\bullet}$COSHept], 103 (24, $[M^{+\bullet}]$-[$^{\bullet}$COSHept]-[HCl]).

HR-MS (EI): m/z = [$M^{+\bullet}$] calc. for $C_{16}H_{23}ClOS$ 298.1153, found 298.1155.

S-Heptyl 2-(4-bromophenyl)propanethioate (20ta)



General procedure *C1* was used to carbonylate dist. *para*-bromostyrene (130 µL, 1.00 mmol) with 1 mol% catalyst and dist. HeptSH (210 µL, stored under N_2, 1.34 eq.) as the thiol component at RT. Purification by column chromatography (gradient CyH → CyH/EtOAc: 95/5) provided **20ta** as the bright yellow oil (248 mg, 722 µmol, 72%).

$C_{16}H_{23}BrOS$ (342.32 g/mol), **R_f:** 0.46 (CyH/EtOAc: 95/5), **m.p.:** Ambient temperature.

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.49 – 7.42 (m, 2H, Ar<u>H</u>), 7.22 – 7.15 (m, 2H, Ar<u>H</u>), 3.84 (q, *J* = 7.1 Hz, 1H, ArCHC<u>H</u>$_3$), 2.81 (m, 2H, SC<u>H</u>$_2$), 1.50 (d, *J* = 7.1 Hz, 3H, ArCHC<u>H</u>$_3$), 1.55 – 1.46 (m, 2H, $SCH_2C\underline{H}_2(CH_2)_4CH_3$), 1.34 – 1.18 (m, 8H, $SCH_2CH_2(C\underline{H}_2)_4CH_3$), 0.86 (t, *J* = 6.8 Hz, 3H, $SCH_2(CH_2)_5C\underline{H}_3$).

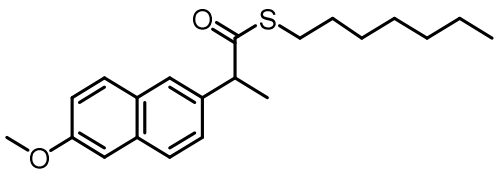
^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 200.8 (q), 139.0 (q), 131.8 (+), 129.6 (+), 121.4 (q), 53.7 (+), 31.7 (–), 29.4 (–), 29.2 (–), 28.8 (–), 22.6 (–), 18.4 (+), 14.1 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2926 (s, br), 2855 (m, sh), 1685 (s, sh), 1487 (s, sh), 1457 (m, sh), 1074 (s, sh), 1010 (s, br), 947 (s, sh), 828 (s, sh), 753 (s, sh).

GC-MS (CI): t_R = 9.683 min, m/z = 343 (97, [MH^+]), 183 (26, [MH^+]-[$^\bullet$COSHept).

HR-MS (CI): m/z = [MH^+] calc. for $C_{16}H_{24}BrOS$ 343.0726, found 343.0727.

S-Heptyl 2-(6-methoxynaphthalen-2-yl)propanethioate (20ua)



General procedure *C1* was used to carbonylate 2-methoxy-6-vinylnaphthalene (184 mg, 1.00 mmol) with 1 mol% catalyst and dist. HeptSH (210 µL, stored under N_2, 1.34 eq.) as the thiol component at RT. Purification by column chromatography (gradient CyH → CyH/EtOAc: 95/5) provided **20ua** as a as a white solid (317 mg, 919 µmol, 92%).

$C_{21}H_{28}O_2S$ (344.51 g/mol), **R_f:** 0.32 (CyH/EtOAc: 95/5), **m.p.:** Ambient temperature.

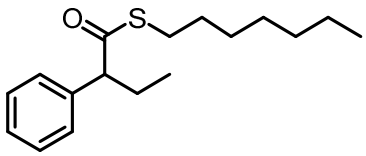
^{1}H-NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.74 – 7.66 (m, 3H, ArH), 7.40 (dd, *J* = 8.5, 1.8 Hz, 1H, ArH), 7.17 – 7.10 (m, 2H, ArH), 4.01 (q, *J* = 7.1 Hz, 1H, ArCH), 3.92 (s, 3H, $ArOCH_3$), 2.90 – 2.75 (m, 2H, SCH_2), 1.60 (d, *J* = 7.1 Hz, 3H, $ArCHCH_3$), 1.57 – 1.47 (m, 2H, $SCH_2CH_2(CH_2)_4CH_3$), 1.35 – 1.15 (m, 8H, $SCH_2CH_2(CH_2)_4CH_3$), 0.85 (t, *J* = 6.9 Hz, 3H, $SCH_2(CH_2)_5CH_3$).

^{13}C-NMR (101 MHz, $CDCl_3$) δ_C/ppm: 201.5 (q), 157.8 (q), 135.2 (q), 133.9 (q), 129.4 (+), 129.0 (q), 127.2 (+), 126.6 (+), 126.5 (+), 119.0 (+), 105.7 (+), 55.3 (+), 54.3 (+), 31.7 (–), 29.4 (–), 29.2 (–), 28.80 (–), 28.77 (–), 22.6 (–), 18.5 (+), 14.1 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2926 (m, br), 2855 (w, sh), 1681 (s, sh), 1607 (m, sh), 1461 (m, sh), 1390 (m, sh), 1267 (s, sh), 1033 (m, sh), 947 (s, sh), 850 (m, sh).

HR-MS (APCI): m/z = [MH^+] calc. for $C_{21}H_{29}O_2S$ 345.1883, found 345.1891.

S-Heptyl 2-phenylbutanethioate (26)



General procedure *C1* was used to carbonylate dist. allylbenzene (120 µL, 997 mmol) with 1 mol% catalyst and dist. HeptSH (210 µL, stored under N_2, 1.34 eq.) as the thiol component at RT. Purification by column chromatography (gradient CyH → CyH/EtOAc: 95/5) provided **26** as a bright yellow oil (144 mg, 517 µmol, 52%).

$C_{17}H_{26}OS$ (278.45 g/mol), **R_f:** 0.47 (CyH/EtOAc: 95/5), **m.p.:** Ambient temperature.

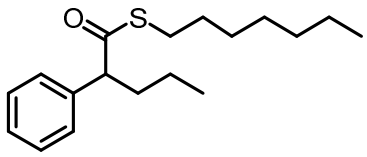
^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.37 – 7.27 (m, 5H, ArH), 3.63 (t, *J* = 7.6 Hz, 1H, ArCH), 2.93 – 2.72 (m, 2H, SCH_2), 2.21 – 2.10 (m, 1H, $ArCHCH_2$), 1.89 – 1.76 (m, 1H, $ArCHCH_2$), 1.56 – 1.48 (m, 2H, $SCH_2CH_2(CH_2)_4CH_3$), 1.32 – 1.21 (m, 8H, $SCH_2CH_2(CH_2)_4CH_3$), 0.94 – 0.81 (m, 6H, $SCH_2(CH_2)_5CH_3$ / $ArCHCH_2CH_3$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 200.7 (q), 138.7 (q), 128.6 (+), 128.5 (+), 128.2 (+), 127.4 (+), 126.1 (+), 62.3 (+), 31.7 (–), 29.5 (–), 29.1 (–), 28.8 (–), 26.6 (–), 22.6 (–), 14.1 (+), 12.1 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2926 (m, br), 2855 (w, sh), 1685 (s, sh), 1454 (m, sh), 980 (m, br), 812 (w, sh), 738 (s, sh), 697 (s, sh).

HR-MS (APCI): m/z = [MH^+] calc. for $C_{17}H_{27}OS$ 279.1777, found 279.1779.

S-Heptyl 2-phenylpentanethioate (27)



General procedure *C1* was used to carbonylate dist. 4-phenyl-1-butene (150 µL, 998 mmol) with 1 mol% catalyst and dist. HeptSH (210 µL, stored under N_2, 1.34 eq.) as the thiol component at RT. Purification by column chromatography (gradient CyH → CyH/EtOAc: 95/5) provided **27** as a bright yellow oil (122 mg, 417 µmol, 42%).

$C_{18}H_{28}OS$ (292.48 g/mol), **R_f:** 0.61 (CyH/EtOAc: 95/5), **m.p.:** Ambient temperature.

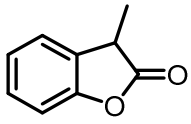
^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.39 – 7.27 (m, 5H, ArH), 3.73 (t, *J* = 7.6 Hz, 1H, ArCH), 2.96 – 2.71 (m, 2H, SCH_2), 2.69 – 2.51 (m, 1H, $ArCHCH_2$), 2.20 – 2.00 (m, 1H, $ArCHCH_2$), 1.90 – 1.44 (m, 4H, $ArCHCH_2CH_2$ / SCH_2CH_2), 1.41 – 1.14 (m, 8H, $SCH_2CH_2(CH_2)_4CH_3$), 0.96 – 0.79 (m, 6H, $SCH_2(CH_2)_5CH_3$ / $ArCHCH_2CH_2CH_3$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 200.8 (q), 138.8 (q), 128.6 (+), 128.4 (+), 128.3 (+), 128.2 (+), 127.3 (+), 60.3 (+), 35.5 (–), 31.7 (–), 29.4 (–), 29.1 (–), 28.8 (–), 28.8 (–), 22.6 (–), 20.7 (–), 14.1 (+), 13.9 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2926 (s, br), 2855 (m, br), 1685 (s, sh), 1454 (m, br), 1021 (w, br), 962 (m, sh), 891 (w, sh), 749 (m, br), 697 (s, sh).

HR-MS (APCI): m/z = [MH^+] calc. for $C_{18}H_{29}OS$ 293.1934, found 293.1935.

3-Methylbenzofuran-2(3H)-one (20da)



General procedure *C1* was used to carbonylate dist. *ortho*-vinylphenol (121 mg, 1.00 mmol) with 1 mol% catalyst and dist. HeptSH (210 µL, stored under N_2, 1.34 eq.) as the thiol component at RT. Purification by column chromatography (gradient CyH → CyH/EtOAc: 95/5) provided **20da** as a bright yellow oil (82.3 mg, 556 µmol, 56%).[55]

$C_9H_8O_2$ (148.16 g/mol), **R_f:** 0.18 (CyH/EtOAc: 95/5), **m.p.:** Ambient temperature.

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.35 – 7.23 (m, 2H, ArH), 7.19 – 7.06 (m, 2H, ArH), 3.74 (q, J = 7.6 Hz, 1H, ArCH), 1.58 (d, J = 7.6 Hz, 3H, $ArCHCH_3$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 178.0 (q), 153.5 (q), 128.8 (q), 128.8 (+) 124.2 (+), 123.9 (+), 110.8 (+), 38.4 (+), 15.9 (+).

2.4.7 Comparison of Thiocarbonylation and Alkoxycarbonylation

General procedure *C1* was used for the comparison reactions. Different substrates, acids, ligands and nucleophiles were employed to run the reaction either under thiocarbonylation- or under alkoxycarbonylation conditions. All entries for the comparison of thiocarbonylation and alkoxycarbonylation are shown in Table 2.5.

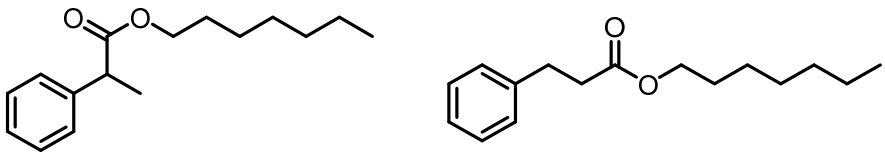
Table 2.5. Yields and regioselectivity for the comparison of thiocarbonylation and alkoxycarbonylation.

Entry	Substrate	Cond.	Acid	Ligand	Nucleophile	Yield[b] [%]	b/l
1	**19a**	thio	DPPA	dppdtbpf	HeptOH	22	94/6
2	**19a**	alkoxy	BNPA	dtbpx	HeptOH	81	94/6
3	**19a**	alkoxy	BNPA	dtbpx	HeptSH	41	100/0
4	**19a**	thio	DPPA	dppdtbpf	HeptSH	95	100/0
5	**19b**	thio	DPPA	dppdtbpf	HeptOH	18	69/31
6	**19b**	alkoxy	BNPA	dtbpx	HeptOH	30	25/75
7	**19b**	alkoxy	BNPA	dtbpx	HeptSH	0	-
8	**19b**	thio	DPPA	dppdtbpf	HeptSH	89	100/0
9	**23**	thio	DPPA	dppdtbpf	HeptOH	0	-
10	**23**	alkoxy	BNPA	dtbpx	HeptOH	0	-
11	**23**	alkoxy	BNPA	dtbpx	HeptSH	0	-
12	**23**	thio	DPPA	dppdtbpf	HeptSH	0	-
13	**28**	thio	DPPA	dppdtbpf	HeptOH	13	17/44/39[c]
14	**28**	alkoxy	BNPA	dtbpx	HeptOH	52	0/0/100[c]
15	**28**	alkoxy	BNPA	dtbpx	HeptSH	8	0/0/100[c]
16	**28**	thio	DPPA	dppdtbpf	HeptSH	61	21/44/35[c]
17	**29**	thio	DPPA	dppdtbpf	HeptOH	0	-
18	**29**	alkoxy	BNPA	dtbpx	HeptOH	18	0/0/100[c]
19	**29**	alkoxy	BNPA	dtbpx	HeptSH	0	-

Entry	Substrate	Cond.	Acid	Ligand	Nucleophile	Yield[b] [%]	b/l
20	**29**	thio	DPPA	dppdtbpf	HeptSH	0	-

[a] Reaction conditions: The reaction was carried out in a 2-chamber system. Chamber A: CO generation (2.5 bar): NFS (2.13 mmol, 450 mg), Na_2CO_3 (3.20 mmol, 339 mg) in DMF (1 mL); Chamber B: substrate (1.0 mmol), $Pd(dba)_2$ (5.8 mg, 10 µmol, 1 mol%), dppdtbpf (21 mg, 40 µmol, 4 mol%)/dtbpx (16 mg, 40 µmol, 4 mol%), DPPA (38 mg, 150 µmol, 15 mol%)/BNPA (52 mg, 150 µmol, 15 mol%), x µL HeptSH (210 µL, 1.34 eq. under thio-conditions; 315 µL, 2.00 eq. under alkoxy-conditions)/ x µL HeptOH (190 µL, 1.34 eq. under thio-conditions; 280 µL, 2.00 eq. under alkoxy-conditions), (1000 – x) µL CH_2Cl_2, RT, 14 h; [b] isolated yields. [c] b_1/b_2/l ratio determined by NMR and GC-MS. b_1 refers to the C^3-branched isomer, b_2 to the C^2-branched isomer.

Heptyl 2-phenylpropanoate (30-b) and heptyl 3-phenylpropanoate (30-l)



Purification by column chromatography (gradient CyH → CyH/EtOAc: 95/5) provided the regioisomeric compounds as a bright yellow oil.

$C_{16}H_{24}O_2$ (248.37 g/mol), **R_f:** 0.42 (CyH/EtOAc: 95/5), **m.p.:** Ambient temperature.

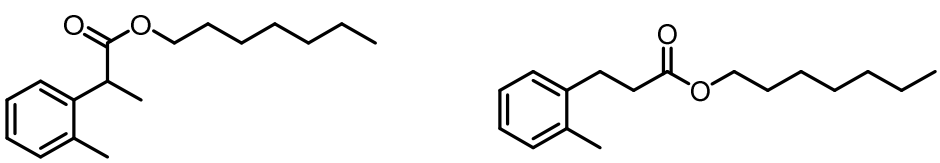
^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.36 – 7.20 (m, 5H, Ar<u>H</u>), 4.05 (t, *J* = 6.7 Hz, 2H, SC<u>H</u>$_2$), 3.71 (q, *J* = 7.2 Hz, 1H, ArC<u>H</u>), 1.65 – 1.52 (m, 2H, $SCH_2C\underline{H}_2(CH_2)_4CH_3$), 1.50 (d, *J* = 7.2 Hz, 3H, $ArCHC\underline{H}_3$), 1.35 – 1.16 (m, 8H, $SCH_2(C\underline{H}_2)_4CH_3$), 0.87 (t, *J* = 6.8 Hz, 3H, $SCH_2(CH_2)_5C\underline{H}_3$). Additional signals from linear regioisomer: 2.95 (t, *J* = 7.8 Hz, 2H, $ArC\underline{H}_2CH_2$), 2.63 (t, *J* = 7.8 Hz, 2H, $ArCH_2C\underline{H}_2$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 174.7 (q), 140.7 (q), 128.6 (+), 127.5 (+), 127.1 (+), 64.9 (–) 45.6 (+), 31.7 (–), 28.8 (–), 28.5 (–), 25.7 (–), 22.6 (–), 18.5 (+), 14.1 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2930 (m, br), 2859 (m, br), 1733 (s, sh), 1454 (m, sh), 1200 (s, sh), 1163 (s, br), 1066 (m, br), 697 (s, sh).

HR-MS (APCI): m/z = [MH^+] calc. for $C_{16}H_{25}O_2$ 249.1849, found 249.1855.

Heptyl 2-(o-tolyl)propanoate (31-b) and heptyl 3-(o-tolyl)propanoate (31-l)



Purification by column chromatography (gradient CyH → CyH/EtOAc: 95/5) provided the regioisomeric compounds as a bright yellow oil.

$C_{17}H_{26}O_2$ (262.39 g/mol), **R_f:** 0.42 (CyH/EtOAc: 95/5), **m.p.:** Ambient temperature.

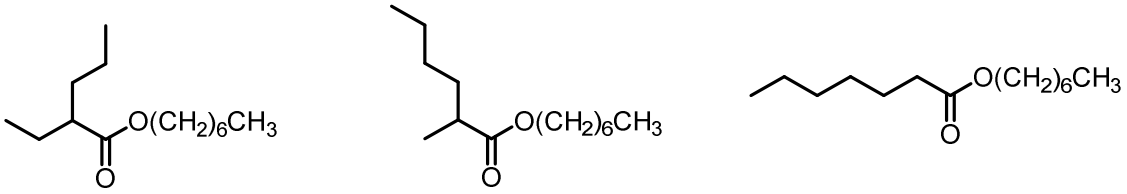
^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.23 – 7.09 (m, 5H, Ar<u>H</u>), 4.11 – 4.01 (m, 2H, SC<u>H</u>$_2$), 3.94 (q, *J* = 7.1 Hz, 1H, ArC<u>H</u>), 2.37 (s, 3H, ArC<u>H</u>$_3$), 1.69 – 1.51 (m, 2H, $SCH_2C\underline{H}_2(CH_2)_4CH_3$), 1.47 (d, *J* = 7.1 Hz, 3H, $ArCHC\underline{H}_3$), 1.37 – 1.15 (m, 8H, $SCH_2(\underline{CH}_2)_4CH_3$)), 0.86 (t, *J* = 6.7 Hz, 3H, $SCH_2(CH_2)_5C\underline{H}_3$). Additional signals from linear regioisomer: 2.94 (t, 2H, $ArC\underline{H}_2CH_2$), 2.58 (t, 2H, $ArCH_2C\underline{H}_2$), 2.33 (s, 3H, ArC<u>H</u>$_3$),

^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 175.0 (q), 173.2 (q), 139.3 (q), 138.7 (q), 136.0 (q), 135.7 (q), 130.4 (+), 130.3 (+), 128.5 (+), 126.9 (+), 126.5 (+), 126.4 (+), 126.4 (+), 126.1 (+), 64.8 (–), 64.7 (–), 41.4 (+), 34.7 (–), 31.7 (–), 31.7 (–), 28.9 (–), 28.8 (–), 28.6 (–), 28.5 (–), 28.4 (–), 25.9 (–), 25.7 (–), 22.6 (–), 22.6 (–), 19.7 (+), 19.3 (+), 17.8 (+), 14.1 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2930 (m, br), 2859 (m, br), 1733 (s, sh), 1491 (w, sh), 1461 (m, sh), 1193 (s, br), 910 (m, sh), 731 (s, sh).

HR-MS (APCI): m/z = [MH^+] calc. for $C_{17}H_{27}O_2$ 263.2006, found 263.2005.

<u>Isomeric mixture of heptyl 2-ethylpentanoate (32-b$_1$), heptyl 2-methylhexanoate (32-b$_2$) and heptyl heptanoate (32-l) (from 1-hexene)</u>



The regioisomeric composition was detected after the reaction by GC-MS. Purification by column chromatography (CyH/EtOAc: 95/5) provided the regioisomers as a yellow oil. The regioisomeric composition was cross-checked by integral comparison of characteristic ^{1}H-NMR signals (linear isomer CH_2 signal: 2.28 as a triplet, C^2-branched CH signal: 2.40 ppm as a quartet, C^3-branched CH signal could not be detected due to signal overlap, however three ^{13}C carbonyl peaks were detected in the ratios comparable to the GC-MS analysis[§]), after isolation and found to be 13:38:49. NMR resonances of the isolated regioisomeric mixture could not be assigned with 2D experiments due to signal overlap.

$C_{16}H_{24}O_2$ (228.38 g/mol), **R_f:** 0.38 (all isomers, CyH/EtOAc: 95/5, only visible with $KMnO_4$ stain), **m.p.:** Ambient temperature.

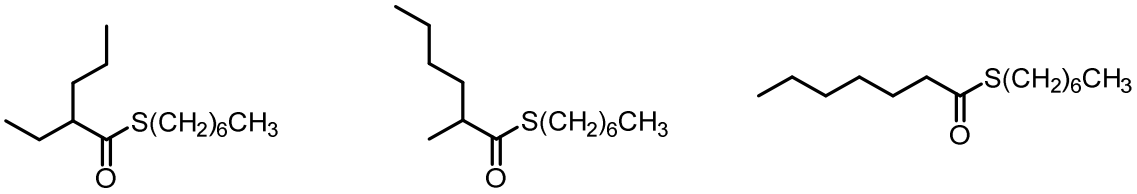
GC-MS (EI)**:** $t_{R,lin}$ = 7.78 min, m/z = 200.2 (1, $[M^{+\bullet}]$-[CO]), 186.2 (1, $[M^{+\bullet}]$-[CO]-$[Me^{\bullet}]$), 131.1 (100), 113.1 (35, $[M^{+\bullet}]$-$[C_7H_{15}O^{\bullet}]$).

$t_{R,b2}$ = 7.87 min, m/z = 171.1 (1, $[M^{+\bullet}]$-$[C_5H_{11}^{\bullet}]$), 131.1 (100), 113.1 (65, $[M^{+\bullet}]$-$[C_7H_{15}O^{\bullet}]$).

$t_{R,lin}$ = 8.25 min, m/z = 171.1 (1, $[M^{+\bullet}]$-$[C_5H_{11}^{\bullet}]$), 131.1 (100), 113.1 (65, $[M^{+\bullet}]$-$[C_7H_{15}O^{\bullet}]$).

[§] We are aware that the integration of ^{13}C signals does not lend well to determination of isomeric composition due to differences in relaxation times; this analysis should be seen as a approximate cross-check only.

Isomeric mixture of S-heptyl 2-ethylpentanethioate (33-b_1), S-heptyl 2-methylhexanethioate (33-b_2) and S-heptyl heptanethioate (33-l) (from 1-hexene)



The regioisomeric composition was detected after the reaction by GC-MS. Purification by column chromatography (gradient CyH → CyH/EtOAc: 95/5) provided the regioisomers as a yellow oil. The regioisomeric composition was cross-checked by integral comparison of characteristic ^1H-NMR signals (linear isomer CH_2 signal: 2.46 as a triplet, C^2-branched CH signal: 2.54 ppm as a quartet, C^3-branched CH signal: 2.42 – 2.37 ppm as a multiplet), after isolation and found to be 20:35:45. NMR resonances of the isolated regioisomeric mixture could not be assigned with 2D experiments due to signal overlap.

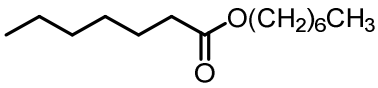
$C_{16}H_{24}O_2$ (244.44 g/mol), **R_f:** 0.13 (all isomers, CyH), **m.p.:** Ambient temperature.

GC-MS (EI)**:** $t_{R,b1}$ = 8.65 min, m/z = 244.2 (1, $[M^{+\bullet}]$), 159 (1, $[M^{+\bullet}]$-$[C_6H_{13}^{\bullet}]$ 145.1 (5, $[M^{+\bullet}]$-$[C_7H_{15}^{\bullet}]$), 113.1 (30, $[M^{+\bullet}]$-$[C_7H_{15}S^{\bullet}]$).

$t_{R,b2}$ = 8.75 min, m/z = 244.2 (1, $[M^{+\bullet}]$), 159 (1, $[M^{+\bullet}]$-$[C_6H_{13}^{\bullet}]$ 145.1 (5, $[M^{+\bullet}]$-$[C_7H_{15}^{\bullet}]$), 113.1 (30, $[M^{+\bullet}]$-$[C_7H_{15}S^{\bullet}]$).

$t_{R,lin}$ = 9.12 min, m/z = 244.2 (1, $[M^{+\bullet}]$), 159 (1, $[M^{+\bullet}]$-$[C_6H_{13}^{\bullet}]$ 145.1 (10, $[M^{+\bullet}]$-$[C_7H_{15}^{\bullet}]$), 113.1 (100, $[M^{+\bullet}]$-$[C_7H_{15}S^{\bullet}]$).

Heptyl heptanoate (32-l) (from 1-hexene and 2-hexene)



The regioisomeric composition was detected by GC-MS after the reaction. Purification by column chromatography (CyH/EtOAc: 95/5) provided the regioisomer as a colourless oil. The regioisomeric composition was cross-checked by integration of characteristic ^{1}H-NMR signals after isolation. The obtained analytical data are in accordance to the literature.

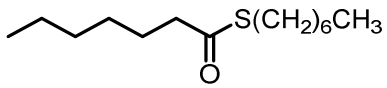
$C_{14}H_{28}O_2$ (228.38 g/mol), **R_f:** 0.38 (CyH/EtOAc: 95/5, only visible with $KMnO_4$ stain), **m.p.:** Ambient temperature.

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 4.04 (t, *J* = 6.7 Hz, 2H), 2.28 (t, *J* = 7.5 Hz, 2H), 1.60 (p, *J* = 7.2 Hz, 4H), 1.36 – 1.21 (m, 14H), 0.87 (t, *J* = 6.8 Hz, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 174.0 (q), 64.4 (–), 34.4 (–), 31.7 (–), 31.5 (–), 28.9 (–), 28.8 (–), 28.7 (–), 25.9 (–), 25.0 (–), 22.6 (–), 22.5 (–), 14.1 (+), 14.0 (+).

GC-MS (EI)**:** $t_{R,lin}$ = 8.25 min, m/z = 171.1 (1, $[M^{+\bullet}]$-$[C_5H_{11}^{\bullet}]$), 131.1 (100), 113.1 (65, $[M^{+\bullet}]$-$[C_7H_{15}O^{\bullet}]$).

S-Heptyl heptanethioate (33-l) (from 1-hexene)



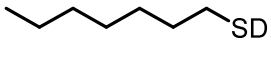
The regioisomeric composition was detected after the reaction by GC-MS. Purification by column chromatography (gradient CyH → CyH/EtOAc: 95/5) provided the regioisomer as a yellow oil. The regioisomeric composition and purity was cross-checked by GC-MS after isolation by comparison to the data obtained from Table 2.5, entry 16.

$C_{14}H_{28}OS$ (244.44 g/mol), **R_f:** 0.13 (all isomers, CyH), **m.p.:** Ambient temperature.

GC-MS (EI)**:** $t_{R,lin}$ = 9.12 min, m/z = 244.2 (1, $[M^{+\bullet}]$), 159 (1, $[M^{+\bullet}]$-$[C_6H_{13}^{\bullet}]$ 145.1 (10, $[M^{+\bullet}]$-$[C_7H_{15}^{\bullet}]$), 113.1 (100, $[M^{+\bullet}]$-$[C_7H_{15}S^{\bullet}]$).

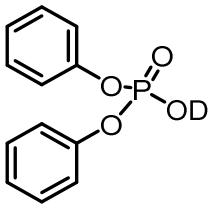
2.4.8 Deuteration Experiments

Generation of deuterated heptanethiol:



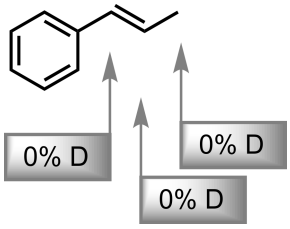
A flame dried reaction flask was treated with dist. heptanthiol (1.5 mL, 9.6 mmol, 1.0 eq.), which was dissolved in MeOD (1.6 mL, 39 mmol, 4.0 eq.) and stirred for 48 h at RT. The solvent was removed under reduced pressure and the product was used without further purification. HeptSD was obtained as a colorless liquid (1.1 g, 8.3 mmol, 86% yield, 49% deuterated).

Generation of deuterated diphenylphosphate (DPPA-d1):



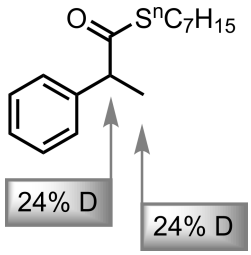
A flame dried reaction flask was treated with diphenylphosphate (375 mg, 1.5 mmol, 1 eq.), which was dissolved in MeOD (1.0 mL, 25 mmol, 16 eq.) and CH_2Cl_2 (2 mL) and stirred for 24 h at RT (repeat procedure ones more). The solvent was removed under reduced pressure and the product was used without further purification. DPPA-d1 was obtained as a white solid (375 mg, 1.5 mmol, > 99% yield, 32% deuterated).

Deuteration experiment with β-methyl-styrene (23)



General procedure *C1* was used to carbonylate dist. β-methyl-styrene (**23**) (130 µL, 1.00 mmol) with 1 mol% catalyst and dist. HeptSD (210 µL, stored under N_2, 1.34 eq., 32% D) as the thiol component and DPPA-d1 (49% D) as an acid at RT for the deuteration experiments. Purification by column chromatography (gradient CyH → CyH/EtOAc: 95/5) provided starting material **23** as a colorless liquid (0% deuterated).

Deuteration experiment with styrene (19a)



General procedure *C1* was used to carbonylate dist. styrene (**19a**) (115 µL, 1.00 mmol) with 1 mol% catalyst and dist. HeptSD (210 µL, stored under N_2, 1.34 eq., 32% D) as the thiol component and DPPA-d1 (49% D) as an acid at RT for the deuteration experiments. Purification by column chromatography (gradient CyH → CyH/EtOAc: 95/5) provided partially deuterated **20aa** as a colorless liquid.

Specifying the amount of deuterium:

^{1}H-NMR: Integral CH (3.88 ppm) of not-deuterated reaction: 1.00

^{1}H-NMR: Integral CH (3.88 ppm) of deuterated reaction: 0.76

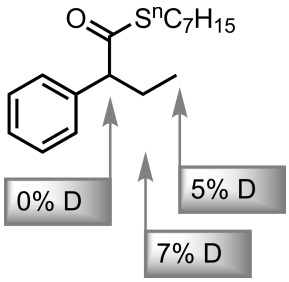
→ 24% D at CH

^{2}H-NMR: Integral CH (3.88 ppm) of deuterated reaction: 1.00

^{2}H-NMR: Integral CH_3 (1.53 ppm) of deuterated reaction: 3.03

→ 24% D at CH_3

Deuteration experiment with allylbenzene (24)



General procedure *C1* was used to carbonylate dist. allylbenzene (**24**) (120 µL, 997 mmol) with 1 mol% catalyst and dist. HeptSD (210 µL, stored under N_2, 1.34 eq., 32% D) as the thiol component and DPPA-d1 (49% D) as an acid at RT for the deuteration experiments. Purification by column chromatography (gradient CyH → CyH/EtOAc: 95/5) provided partially deuterated **26** as a colorless liquid.

Specifying the amount of deuterium:

^{1}H-NMR: Integral CH (3.63 ppm) of not-deuterated reaction: 1.00

^{1}H-NMR: Integral CH (3.63 ppm) of deuterated reaction: 1.00

→ 0% D at CH

^{1}H-NMR: Integral CH_2 (2.93 – 2.72 / 2.21 – 2.10 ppm) of not-deuterated reaction: 2.04

^{1}H-NMR: Integral CH_2 (2.93 – 2.72 / 2.21 – 2.10 ppm) of deuterated reaction: 1.90

→ 7% D at CH_2

^{2}H-NMR: Integral CH_2 (2.93 – 2.72 / 2.21 – 2.10 ppm) of deuterated reaction: 1.00

^{2}H-NMR: Integral CH_3 (0.94 – 0.81 ppm) of deuterated reaction: 1.07

→ 5% D at CH_3

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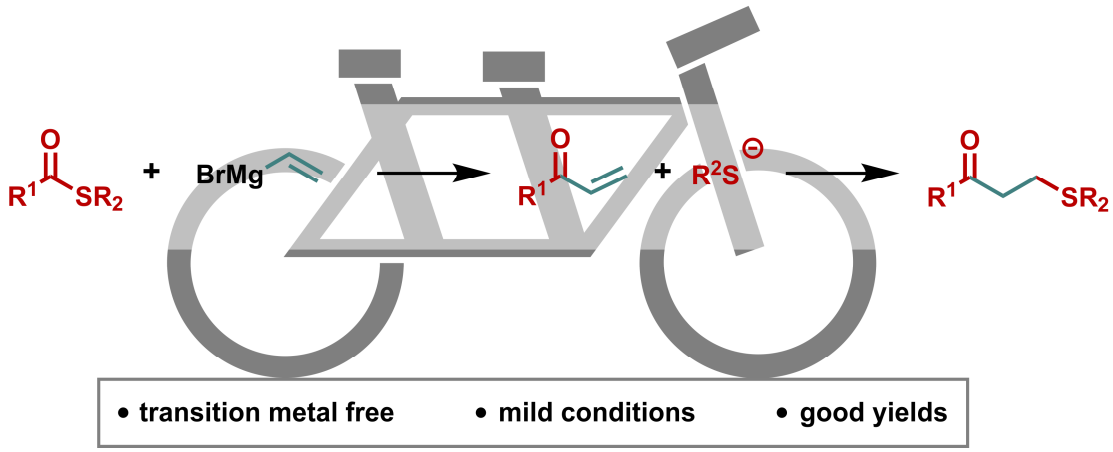
Chapter 3

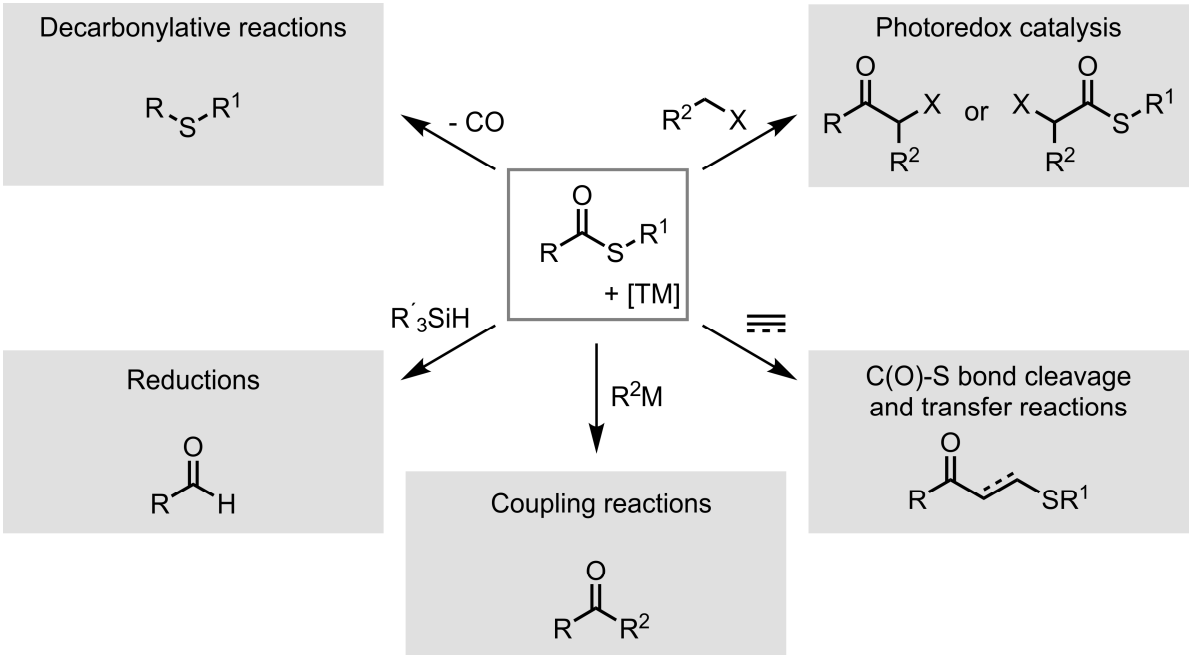
Tandem Acyl Substitution/Michael Addition of Thioesters with Vinylmagnesium Bromide



Abstract: Herein, a tandem reaction of thioesters with vinylmagnesium bromide is reported. The initial acyl substitution provides the 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 reaction conditions enabled the transformation of many different substrates in moderate to good yields.

3.1 Introduction – Application of Thioesters

Since thioesters are more reactive than alcohol-derived esters (see. Chapter 2.1.1) they are of great importance in many different synthetic applications. Not only the reactivity of thioesters in nucleophilic substitution reactions differs from oxoesters, also enolization of thioesters is faster, due to better stabilization of the α-anion. One suitable example showing the different reactivity of thioesters and oxoesters is the Claisen ester condensation. The Claisen ester condensation of thioesters requires considerably milder reaction conditions and gives better yields, because each of the three reaction steps (enolate anion formation/nucleophilic attack on thiol ester/departure of leaving group) is faster for thioester than for ordinary esters.[1] The application of thioesters varies from dynamic enzymatic resolution, which takes advantage of the α-proton acidity of thioesters,[2] to the synthesis of polypeptides *via* native chemical ligation.[3] Additionally, also many metal catalyzed applications of thioesters are known in the literature (Scheme 3.1). One example is the decarbonylation of thioesters in order to synthesize thioethers.[4] The CO extrusion can also be coupled to a carbothiolation of terminal alkynes, generating vinyl sulfides.[5]

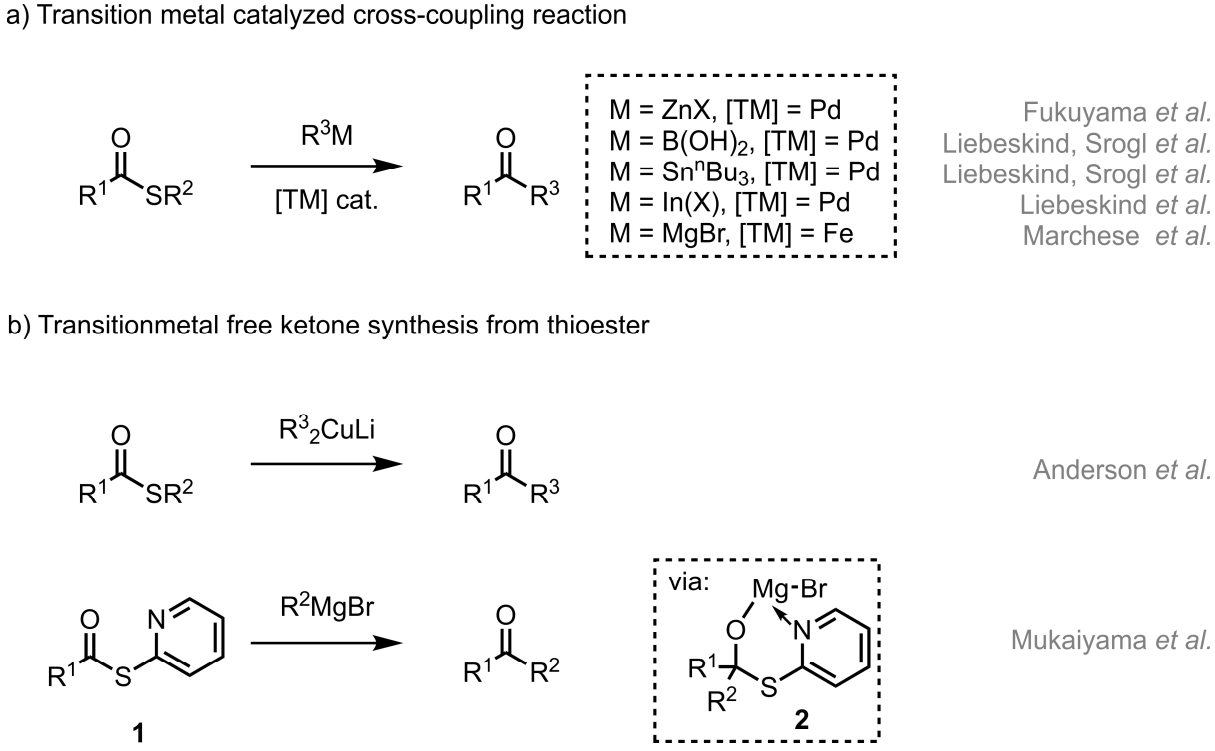


Scheme 3.1. Most important metal-catalyzed synthetic applications of thioesters.

The combination of transition metal- and photoredox catalysis can also be used for the conversion of thioesters. In this case, either the C–C(O) or the weaker C(O)–S bond of the thioester can be activated and combined with a functionalization of a sp^3 C–H bond in α-

position to a hetero atom of the coupling partner.[6] Another TM-catalyzed application of thioesters is the synthesis of aldehydes in a chemoselective reduction, which was developed by Fukuyama *et al.*.[7]

A highly important application of thioesters is the synthesis of ketones *via* coupling reactions. The synthesis of ketones from carboxylic acid derivatives by a nucleophilic substitution of organometallic reagents was intensively investigated.[8] The main problem of this reaction is the control of chemoselectivity. The second attack of a C-nucleophile to the desired ketone, generating a tertiary alcohol has to be avoided (overaddition). Thioesters are less affected by this problem than ordinary esters, since they are more reactive than the resulting ketones, but the overaddition still may be a problem. Therefore, transition metal (TM) catalyzed cross coupling reaction can be used as an alternative. An oxidative addition of the TM into the C(O)–S bond, followed by transmetalation with an organometallic compound and reductive elimination enable the chemoselective formation of ketones (Scheme 3.2a).



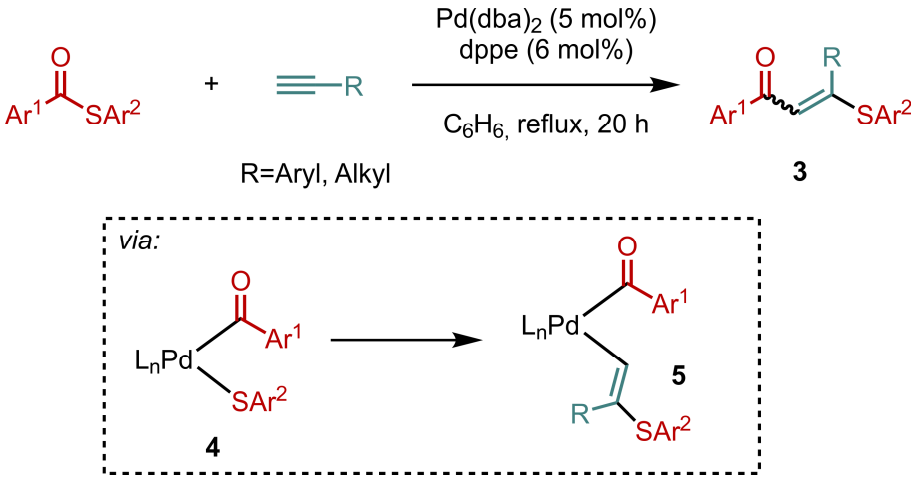
Scheme 3.2. Transition metal and transition metal free synthesis of ketones from thioesters.

Especially, Fukuyama, Liebeskind and Strogl reported a number of publications with different organometallic compounds (based on Zn, B, Sn, In) in combination with a palladium

catalyst.[9] Moreover, the reaction of thioester and Grignard reagent was presented by Marchese *et al.*.[10] The transformation was catalyzed by 4 mol% $Fe(acac)_3$ and conducted under mild reaction conditions (0 °C, 5-10 min) in THF. In the course of this protocol, also aromatic and aliphatic Grignard reagents were suitable.

Since the employment of some transition metals is expensive, TM-free versions are always of considerable interest (Scheme 3.2b). Anderson *et al.* reported the generation of ketones from S-alkyl and S-aryl thioesters with organocopper(I) complexes (e.g. $(^nBu)_2CuLi$) in good yields.[11] By the application of 1.0 eq. ^{n}BuMgBr they observed the tertiary alcohol and the starting material in equal amounts, whereas thioester with 1.5 eq. ^{n}BuMgBr·CuI generated the desired ketone in >80% yield. A successful conversion of S(2-pyridyl) thioates (**1**) with Grignard reagent without the formation of a tertiary alcohol was shown by Mukaiyama *et al.*.[12] They argued that these substrates are able to form a six-membered complex **2**, with nitrogen being coordinated to the magnesium ion. This complex reacts very slowly with a second Grignard molecule in comparison to the starting material and therefore enables a complete suppression of the side-product. Thus, 2-pyridyl thioesters can be considered as alternatives to Weinreb amides.[8b]

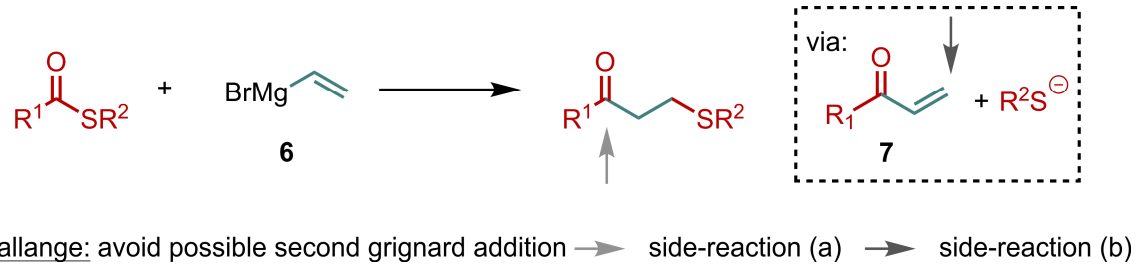
Furthermore, also TM-catalyzed C(O)–S bond cleavage/transfer reactions are known in the literature, whereas the acyl and thiol moieties are transferred to the reaction partner (Scheme 3.1).[13] In 2009, Kuniyasu, Kambe *et al.* reported a TM-catalyzed acetylthiolation of alkynes (Scheme 3.3).[13a]



Scheme 3.3. Palladium-catalyzed thioacylation of alkynes reported by Kuniyasu, Kambe *et al.*.[13a]

They suggested a mechanism starting with an oxidative addition of Pd(0) into the C(O)–S bond to generate complex **4**. This is followed by an alkyne insertion into the Pd–S bond in order to form complex **5** while product **3** is released after a reductive elimination.

Herein, we report a TM-free variation of this transformation based on tandem reaction of thioester with vinylmagnesium bromide (**6**), which takes place under mild reaction conditions (0 °C, 1 h) (Scheme 3.4). An initial nucleophilic substitution of the thioester with **6** generates the Michael acceptor **7**, followed by a nucleophilic addition of the free thiolate. We proposed the formation of a complex, similar to **2**, which enables a chemoselective formation of ketones, whereas the formation of the tertiary alcohol is suppressed. This reactivity was also inadvertently observed by Chen *et al.* in the synthesis of (+)-Biotin.[14]



Scheme 3.4. Tandem reaction of thioester with vinylmagnesium bromide (**6**).

3.2 Results and Discussion

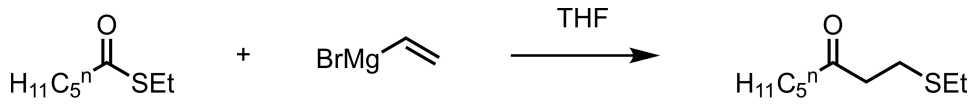
3.2.1 Initial Optimization Experiments

The initial optimization was performed using thioester **8a** and Grignard reagent **6** in THF. At the beginning of this project we struggled with reproducibility problems. We come to the conclusion that crystallization of vinylmagnesium bromide (**6**) 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 exact same conditions for each reaction. Therefore, batch of 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 **6** 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 optimizations different temperatures, reaction times, equivalents of Grignard and additives were tested, by using **8a** as a test substrate (Table 3.1). At –78 °C no reaction was observed, because vinylmagnesium bromide crystallizes instantly at this temperature and therefore it is not available any more as a reaction component. On the other hand, side-reactions become more likely by performing the reaction at room temperature, generating the product in only 51% yield (Table 3.1, Entry 4). The best result was observed at 0 °C (Table 3.1, Entry 3), forming **9a** in 75% yield with almost full conversion. Since a smaller amount of Grignard reagent might prevent a second attack of vinylmagnesium bromide either to product **9a** or to the intermediate **7**, 1.2 eq. and 2.0 eq. of **6** were applied. However, the yields dropped significantly (Table 3.1, Entries 5, 6). The combination of a low concentration of the substrate (0.12 mol/L) and a large amount of the Grignard could aggravate side-reaction (b) (Scheme 3.4), which might be avoided by the addition of external EtSH (Table 3.1, Entry 7). Interestingly, lower amounts of the product were formed under this condition. Despite the small concentration of free thiol, the high selectivity for the nucleophilic addition of EtSH instead of **6** to the Michael-acceptor **7** is remarkable. Therefore, we suggest the formation of chelate **10**, in which the thiol is not leaving the coordination sphere, and is able to attack the Michael-acceptor rapidly (Scheme 3.5). Lowering the amount of solvent and thereby increasing the substrate concentration leads to a decreased amount of the product.

This could be explained by the partial crystallization of **6**, which was observed during the reaction. LiCl might accelerate the nucleophilic attack to **8a** or **7** (Table 3.1, Entry 9) or modulate the reactivity of **6**,[15] but no effect was observed. Increasing the reaction time leads 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 doubtlessly assigned.

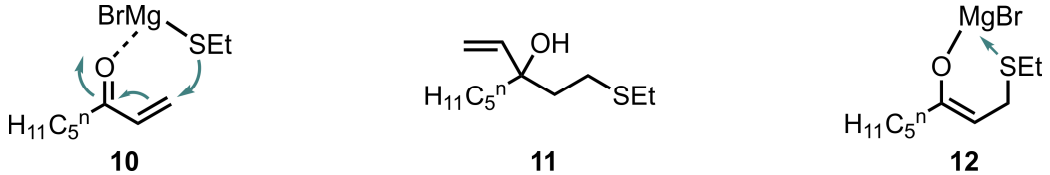
Table 3.1. Initial optimizations.[a]



8a 1.0 eq. **6** 1.2-3.0 eq. **9a**

Entry	Temp [°C]	Time [h]	**6** [eq.]	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[b]	92	66
8	0	1	3	THF[c]	99	65
9	0	1	3	LiCl[d]	96	74
10	0	2	3	-	100	64
11	0	4	3	-	99	65

[a] Reaction conditions: **8a** (163 mg, 1.02 mmol, 1.0 eq.), **6** (0.89 M in THF), THF (5 mL), yields and conversions were determined by quant. GC-FID using *n*-pentadecane as an internal standard. [b] 1.0 eq. EtSH, [c] **8a** (163 mg, 1.02 mmol, 1.0 eq.), **6** (0.89 M in THF), THF (1 mL) [d] 0.2 eq. LiCl.



10 **11** **12**

Scheme 3.5. Possible side-product and intermediates.

Since the reaction time plays an important role, the reaction progress was measured, in order to find the optimum between product formation and degradation (Figure 3.1). Indeed, it takes one hour in order to obtain the best yield and almost full conversion, afterwards the decomposition predominates. Interestingly, by treatment of isolated **9a** with vinylmagnesium bromide (3.0 eq.) in THF at 0 °C for 1 h, **11** was generated in 83% (100% conversion). In the kinetic study only 11% of the product reacted with the remaining Grignard reagent. Therefore it may be assumed that chelate **12** is formed in the reaction mixture, which stabilizes the product and decelerates the attack of a second vinylmagnesium bromide molecule. In conclusion, the best result was observed using 3.0 eq. of **6** at 0°C for 1 h. **9a** was generated in a yield of 75%, which is satisfying for a two-step tandem reaction.

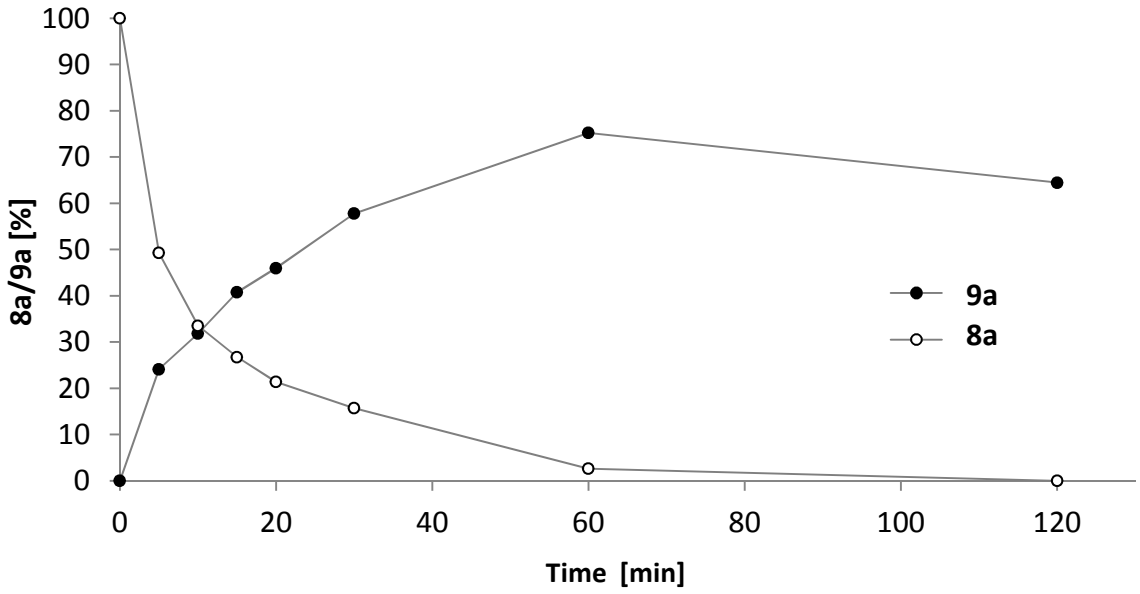
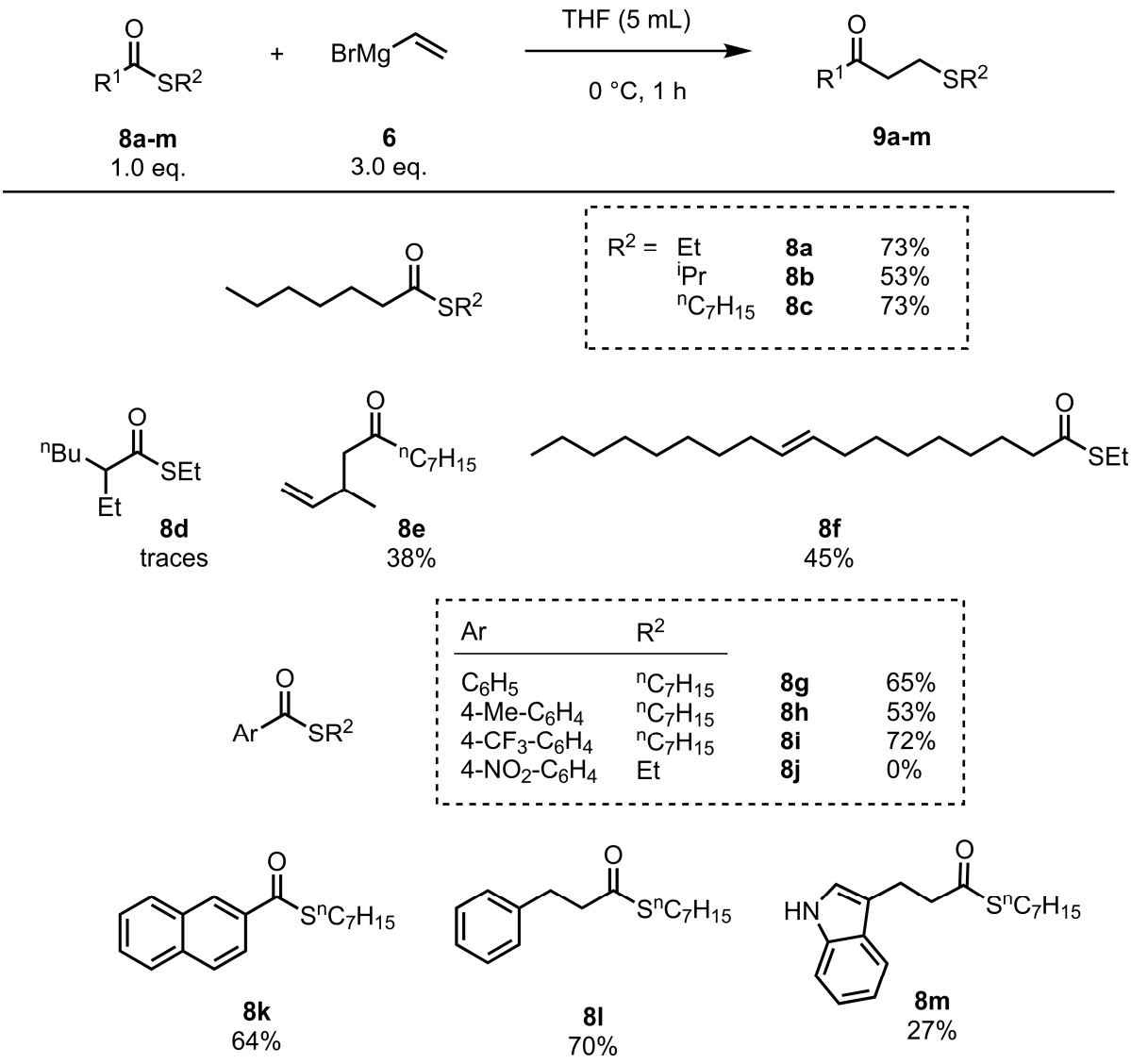


Figure 3.1. Reaction profile for the conversion of **8a** with vinylmagnesium bromide (**6**).[a]

[a] Reaction conditions: **8a** (160 mg, 998 µmol, 1.0 eq.), **6** (0.52 – 0.89 M in THF, 3.0 eq.), THF (5 mL), 0 °C, 1 h. Yields were determined by quant. GC-FID using *n*-pentadecane as an internal standard.

3.2.2 Substrate Screening

With the optimized conditions in hand, a substrate screening was performed (Scheme 3.6). Interestingly, the same yield was observed by using **8c** instead of the ethylthioester **8a**. The sterically more demanding ^{i}Pr-thioester **8b** was less reactive, generating only 53% yield. Disappointingly, only traces of the product were observed for the α-substituted **8d**, whereas β-substituted **8e** generated **9e** in 38% yield. The long chain thioester **8f** was also less active, forming **9f** in 45% yield.



Scheme 3.6. Substrate screening.[a]

[a] Reaction conditions: **8a-m** (1.0 mmol, 1.0 eq.), **6** (0.52 – 0.89 M in THF, 3.0 eq.), THF (5 mL), 0 °C, 1 h. Isolated yields.

Furthermore, different aryl-substituted benzothioates (**8g – 8j**) were tested. The unsubstituted **8g** showed a yield of 65%, whereas the electron donating **8h** was less reactive. Increasing the electron density at the carbonyl center reduces the electrophilicity and therefore diminishes the nucleophilic attack of **6**. As expected the electron deficient CF_3 group in *para*-position increased the yield to 72% (**8i**). The nitro-group was not tolerated, which is not surprising, since reactions of nitroarenes with Grignard reagents are known in the literature.[16] Moreover, **8k** showed a similar reactivity as **8g**, with a yield of 64%. Whereas, **8l** is more compatible to **8a**. Unfortunately, an amine functionality seems to be a limitation of this reaction, since **8m** was transformed only in a yield of 27%.

3.3 Conclusion

In conclusion, a transition metal free two-step tandem reaction of thioesters with vinylmagnesium bromide was investigated. The formation of a chelate complex might have hindered 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.

3.4 Experimental Part

3.4.1 General Information and Analytical Techniques

Chemicals were purchased from ABCR, Acros, Sigma Aldrich, TCI or Merck and used without any further purification unless otherwise noted. Vinylmagnesium bromide (**6**) 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.[17] 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 a stationary phase, either using gravity flow or air overpressure flow conditions. Mobile phases are described in each experiment.

Thin layer chromatography (TLC) was performed with alumina plates coated with Merck silica gel 60 F254 (layer thickness: 0.2 mm) and analyzed under UV-light (254 nm) or stained with a potassium permanganate solution.

Nuclear magnetic resonance spectroscopy (NMR)

NMR spectra were recorded using a Bruker Avance 400 (^{1}H: 400 MHz, ^{13}C: 101 MHz) or Bruker Avance 300 (^{1}H: 300 MHz, ^{13}C: 75 MHz). All measurements were performed at ambient temperature. Chemical shifts δ are reported in parts per million [ppm] relative to the solvent signals as internal standard, (^{1}H: $CDCl_3$: δ = 7.26 ppm; ^{13}C: $CDCl_3$: δ = 77.1 ppm), coupling constants *J* are given in Hertz [Hz]. ^{1}H NMR splitting patterns are designated as follows: s = singlet; d = doublet; t = triplet; q = quartet; quin = quintet; sext = sextet; hept = heptet; m = multiplet. ^{13}C signals are analyzed as follows: (+) = primary/tertiary carbon, (−) = secondary carbon, (q) = quaternary carbon. The assignment resulted from COSY, DEPT-135°, HMBC or HSQC experiments.

Gas chromatography with flame ionization detector (GC-FID)

GC-FID was carried out on SHIMADZU GC-2010 Plus with SHIMADZU AOC-20i Auto-injector, carrier gas: dry hydrogen. Program 50-280M3:

Rate [°C·min^{-1}]	Temperature [°C]	Hold Temperature [min]
-	50	0.5
50	130	0
3	170	0
50	280	3

The internal standard method was used for the quantitative GC-FID in order to determine yields and conversions. For the calibration, samples with different amounts of substrate and standard (*n*-pentadecane) were measured with GC-FID and the obtained data were used to plot $A_{(substrate)}/A_{(standard)}$ against $m_{(substrate)}/m_{(standard)}$. The resulting slope, after linear regression, is equivalent to the response factor R, which can be used to quantify unknown samples by using equation 1. y-Intercepts are unconsidered.

$$\frac{m\,(substrate)}{m\,(standard)} \cdot R = \frac{A\,(substrate)}{A\,(standard)} \quad (1)$$

Melting points (m.p.)

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

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.

Mass spectrometry (MS)

HR-MS and GC-MS were recorded on *Agilent* Q-TOF 6540 UHD, *Jeol* AccuTOF GCX, and *Finnigan* MAT SSQ 710 A, instruments at the Central Analytical Laboratory of the University of Regensburg.

3.4.2 General Procedure *T1* for Tandem Reaction

A flame-dried 30 mL schlenk tube was charged with thioester **8a-m** (1.00 mmol, 1.0 eq.) which was dissolved in anhydrous THF (5 mL). The solution was stirred for 5 min at 0 °C. A vinylmagnesium bromide solution (**6**, 0.52 – 0.89 M in THF, 3.0 eq) 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, saturated solution of NH_4Cl (3 mL) and the reaction mixture was extracted with Et_2O (3 × 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.

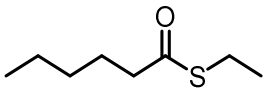
3.4.3 Preparation of Starting Materials

General procedure S1 for the synthesis of thioesters

The thioesters were synthesized *via* Steglich-esterification.[18] A flame-dried 25 mL RBF was charged with carboxylic acid (1.0 eq.), which was dissolved in anhydrous CH_2Cl_2 (10 mL, DMF for less soluble acids). DMAP (0.1 eq.) and thiol (1.0 eq.) were added and the reaction mixture was cooled down to 0 °C. After the addition of DCC (1.0 eq.) 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 $NaHCO_3$ and brine, 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).

Substrates **8d**, **8e**, **8f**, **8j** and **8m** were synthesized by Paul H. Gehrtz.[19]

S-Ethyl hexanethioate (8a)



According to the general procedure *S1*, **8a** was synthesized from hexanoic acid (1.00 mL, 7.93 mmol, 1.0 eq.) with EtSH (685 µL, 9.51 mmol, 1.2 eq.). Purification of the crude product by column chromatography (gradient: CyH → CyH/EtOAc: 95/5) provided **8a** as a colorless liquid (926 mg, 5.78 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, 2H, $SC\underline{H_2}$), 2.53 (t, *J* = 7.4 Hz, 2H, $COC\underline{H_2}(CH_2)_3CH_3$), 1.72 – 1.61 (m, 2H, $COCH_2C\underline{H_2}(CH_2)_2CH_3$), 1.36 – 1.27 (m, 4H, $CO(CH_2)_2(C\underline{H_2})_2CH_3$), 1.24 (t, *J* = 7.4 Hz, 3H, $SCH_2C\underline{H_3}$), 0.89 (t, *J* = 6.9 Hz, 3H, $CO(CH_2)_4C\underline{H_3}$).

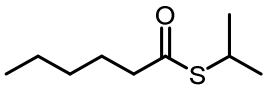
^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 199.9 (q), 44.1 (–), 31.1 (–), 25.4 (–), 23.2 (–), 22.3 (–), 14.8 (+), 13.9 (+).

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-Isopropyl hexanethioate (8b)



According to the general procedure *S1*, **8b** was synthesized from hexanoic acid (2.0 mL, 15.9 mmol, 1.0 eq.) with ^{i}PrSH (1.8 mL, 19.0 mmol, 1.2 eq.). Purification of the crude product by column chromatography (gradient: CyH → CyH/EtOAc: 95/5) provided **8b** as a colorless liquid (1.89 g, 10.8 mmol, 68%).

$C_9H_{18}OS$ (174.30 g/mol), **R_f:** 0.67 (CyH/EtOAc: 95/5).

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 3.63 (hept, *J* = 6.9 Hz, 1H, $SC\underline{H}$), 2.49 (t, *J* = 7.4 Hz, 2H, $COC\underline{H_2}(CH_2)_3CH_3$), 1.71 – 1.59 (m, 2H, $COCH_2C\underline{H_2}(CH_2)_2CH_3$), 1.36 – 1.24 (m, 4H, $COCH_2CH_2(C\underline{H_2})_2CH_3$), 1.29 (d, *J* = 6.9 Hz, 6H, $CH(C\underline{H_3})_2$), 0.96 – 0.83 (m, 3H, $CO(CH_2)_4C\underline{H_3}$).

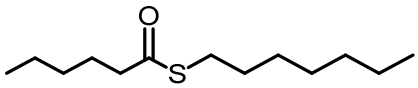
^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 200.0 (q), 44.1 (–), 34.5 (+), 31.1 (–), 25.4 (–), 2 × 23.0 (+, +), 22.3 (–), 13.9 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2960 (m, sh), 2930 (m, sh), 2866 (w, sh), 1685 (s, sh), 1457 (w, sh), 1122 (w, br), 1014 (m, br), 962 (m, sh), 738 (w, br).

GC-MS (EI): t_R = 5.10 min, m/z = 131 (24, $[M^{+\bullet}]$-[$^\bullet{}^i$Pr]), 99 (100, $[M^{+\bullet}]$-[$^\bullet$S^{i}Pr]).

HR-MS (EI): $[M^{+\bullet}]$ calc. for $C_9H_{18}OS$ 174.1073, found 174.1078.

S-Heptyl hexanethioate (8c)



According to the general procedure *S1*, **8c** was synthesized from hexanoic acid (2.0 mL, 15.9 mmol, 1.0 eq.) with $^{n}C_7H_{15}SH$ (2.9 mL, 19.0 mmol, 1.2 eq.). Purification of the crude product by column chromatography (gradient: CyH → CyH/EtOAc: 95/5) provided **8c** as a colorless liquid (2.65 g, 11.5 mmol, 73%).

$C_{13}H_{26}OS$ (230.41 g/mol), **R_f:** 0.64 (CyH/EtOAc: 95/5).

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 2.86 (t, 2H, SC$\underline{H}_2$), 2.53 (t, 2H, COC$\underline{H}_2$), 1.73 – 1.60 (m, 2H, C$\underline{H}_2$), 1.60 – 1.49 (m, 2H, C$\underline{H}_2$), 1.39 – 1.20 (m, 12H, 6 × C$\underline{H}_2$), 0.88 (td, *J* = 6.9, 4.7 Hz, 6H, 2 × C$\underline{H}_3$).

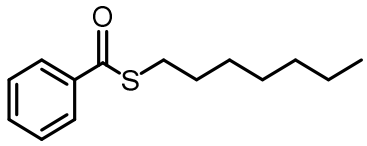
^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 200.0 (q), 44.1 (–), 31.7 (–), 31.1 (–), 29.6 (–), 2 × 28.8 (–, –), 28.8 (–), 25.4 (–), 22.6 (–), 22.34 (–), 14.1 (+), 13.9 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2926 (s, br), 2855 (m, sh), 1692 (s, sh), 1461 (w, sh), 1122 (w, sh), 1014 (m, br), 962 (m, sh), 731 (w, br).

GC-MS (EI): t_R = 8.13 min, m/z = 131 (10, $[M^{+\bullet}]$-$[^{\bullet}{}^{n}SC_7H_{15}]$), 99 (100, $[M^{+\bullet}]$-$[^{\bullet}S^{n}C_7H_{15}]$).

HR-MS (EI): $[M^{+\bullet}]$ calc. for $C_{13}H_{26}OS$ 230.1699, found 230.1703.

S-Heptyl benzothioate (8g)



According to the general procedure *S1*, **8g** was synthesized from benzoic acid (1.00 g, 8.19 mmol, 1.0 eq.) with $^{n}C_7H_{15}SH$ (1.3 mL, 8.19 mmol, 1.0 eq.). Purification of the crude product by column chromatography (gradient: CyH → CyH/EtOAc: 95/5) provided **8g** as a colorless liquid (1.59 g, 6.74 mmol, 82%).

$C_{14}H_{20}OS$ (236.37 g/mol), **R_f:** 0.45 (CyH/EtOAc: 95/5).

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 8.02 – 7.93 (m, 2H, Ar$\underline{H}$), 7.61 – 7.52 (m, 1H, Ar$\underline{H}$), 7.49 – 7.39 (m, 2H, Ar$\underline{H}$), 3.07 (t, *J* = 7.3 Hz, 2H, SC$\underline{H}_2$), 1.75 –1.60 (m, 2H, $SCH_2C\underline{H}_2$), 1.49 – 1.24 (m, 8H, $S(CH_2)_2(C\underline{H}_2)_4CH_3$), 0.89 (t, *J* = 6.9 Hz, 3H, C$\underline{H}_3$).

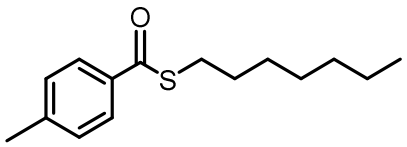
^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 192.2 (q), 137.3 (q), 133.2 (+), 2 × 128.6 (+, +), 2 × 127.2 (+, +), 31.7 (–), 29.6 (–), 29.1 (–), 28.93 (–), 28.86 (–), 22.6 (–), 14.1 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2926 (m, sh), 2855 (w, sh), 1662 (s, sh), 1204 (s, sh), 1174 (m, sh), 910 (s, sh), 772 (m, sh), 686 (s, sh).

GC-MS (EI): t_R = 8.52 min, m/z = 236 (1, $[M^{+\bullet}]$), 105 (100, $[M^{+\bullet}]$-$[^{\bullet}S^{n}C_7H_{15}]$).

HR-MS (EI): $[M^{+\bullet}]$ calc. for $C_{14}H_{20}OS$ 236.1229, found 236.1232.

S-Heptyl 4-methylbenzothioate (8h)



According to the general procedure *S1*, **8h** was synthesized from 4-methylbenzoic acid (1.00 g, 7.34 mmol, 1.0 eq.) with $^{n}C_7H_{15}SH$ (1.2 mL, 7.34 mmol, 1.0 eq.). Purification of the crude product by column chromatography (gradient: CyH → CyH/EtOAc: 95/5) provided **8h** as a colorless liquid (1.34 g, 5.34 mmol, 73%).

$C_{15}H_{22}OS$ (250.40 g/mol), R_f: 0.59 (CyH/EtOAc: 95/5).

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.87 (d, 2H, *J* = 8.1 Hz, Ar<u>H</u>), 7.24 (d, *J* = 8.1 Hz, 2H, Ar<u>H</u>), 3.05 (t, *J* = 7.3 Hz, 2H, $SC\underline{H_2}$), 2.40 (s, 3H, $ArC\underline{H_3}$), 1.67 (dt, *J* = 15.2, 7.3 Hz, 2H, $SCH_2C\underline{H_2}$), 1.49 – 1.38 (m, 2H, $S(CH_2)_2C\underline{H_2}$), 1.36 – 1.22 (m, 6H, $S(CH_2)_3(C\underline{H_2})_3$), 0.89 (t, *J* = 6.9 Hz, 3H, $S(CH_2)_6C\underline{H_3}$).

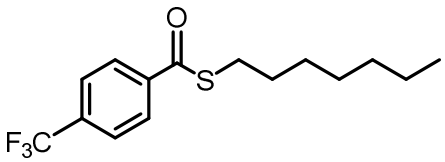
^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 191.8 (q), 144.0 (q), 134.8 (q), 2 × 129.2 (+, +), 2 × 127.3 (+, +), 31.7 (–), 29.6 (–), 29.0 (–), 28.9 (–), 28.9 (–), 22.6 (–), 21.7 (+), 14.1 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2926 (m, sh), 2855 (w, sh), 1659 (s, sh), 1607 (m, sh), 1208 (s, sh), 1174 (s, sh), 910 (s, sh), 820 (s, sh).

GC-MS (EI): t_R = 9.15 min, m/z = 250 (1, $[M^{+\bullet}]$), 119 (100, $[M^{+\bullet}]$-$[^{\bullet}S^{n}C_7H_{15}]$), 91 (14, $[M^{+\bullet}]$-$[^{\bullet}COS^{n}C_7H_{15}]$).

HR-MS (EI): $[M^{+\bullet}]$ calc. for $C_{15}H_{22}OS$ 250.1386, found 250.1388.

S-Heptyl 4-(trifluoromethyl)benzothioate (8i)



According to the general procedure *S1*, **8i** was synthesized from 4-(trifluoromethyl)benzoic acid (1.00 g, 5.26 mmol, 1.0 eq.) with $^{n}C_7H_{15}SH$ (825 µL, 5.26 mmol, 1.0 eq.). Purification of the crude product by column chromatography (gradient: CyH → CyH/EtOAc: 95/5) provided **8i** as a colorless liquid (1.18 g, 3.88 mmol, 74%).

$C_{15}H_{19}F_3OS$ (304.37 g/mol), R_f: 0.56 (CyH/EtOAc: 95/5).

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 8.06 (d, *J* = 8.1 Hz, 2H, ArH), 7.71 (d, *J* = 8.1 Hz, 2H, ArH), 3.10 (t, *J* = 7.3 Hz, 2H, SCH_2), 1.69 (dt, *J* = 15.2, 7.3 Hz, 2H, SCH_2CH_2), 1.49 – 1.38 (m, 2H, $S(CH_2)_2CH_2$), 1.37 – 1.23 (m, 6H, $S(CH_2)_3(CH_2)_3$), 0.89 (t, *J* = 6.9 Hz, 3H, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 191.3 (q), 140.0 (q), 134.5 (quartet, *J* = 32.7 Hz, q), 2 × 127.5 (+, +), 2 × 125.7 (quartet, *J* = 3.8 Hz, +, +), 123.6 (quartet, *J* = 272.7 Hz, q), 31.7 (–), 29.4 (–), 29.4 (–), 28.9 (–), 28.8 (–), 22.6 (–), 14.1 (+).

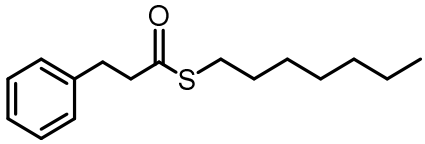
^{19}F-NMR (282 MHz, $CDCl_3$) δ_F/ppm: -63.6 (CF_3).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2930 (m, sh), 2855 (w, sh), 1662 (s, sh), 1409 (m, sh), 1320 (s, sh), 1208 (s, sh), 1170 (s, sh), 1129 (s, sh), 1066 (s, sh), 917 (s, sh), 850 (s, sh).

GC-MS (EI): t_R = 8.12 min, m/z = 304 (0.4, $[M^{+\bullet}]$), 173 (100, $[M^{+\bullet}]$-$[^{\bullet}S^{n}C_7H_{15}]$), 145 (20, $[M^{+\bullet}]$-$[^{\bullet}COS^{n}C_7H_{15}]$).

HR-MS (EI): $[M^{+\bullet}]$ calc. for $C_{15}H_{19}F_3OS$ 304.1103, found 304.1098.

S-Heptyl 3-phenylpropanethioate (8l)



According to the general procedure *S1*, **8l** was synthesized from 3-phenylpropanoic acid (1.00 g, 6.66 mmol, 1.0 eq.) with $^{n}C_7H_{15}SH$ (1.0 mL, 6.66 mmol, 1.0 eq.). Purification of the crude product by column chromatography (gradient: CyH → CyH/EtOAc: 95/5) provided **8l** as a colorless liquid (1.50 g, 5.67 mmol, 85%).

$C_{16}H_{24}OS$ (264.43 g/mol), **R_f:** 0.63 (CyH/EtOAc: 95/5).

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.34 – 7.26 (m, 2H, ArH), 7.25 – 7.14 (m, 3H, ArH), 3.02 – 2.92 (m, 2H, $ArCH_2$), 2.92 – 2.81 (m, 4H, $ArCH_2CH_2$; SCH_2CH_2), 1.63 – 1.48 (m, 2H, SCH_2CH_2), 1.40 – 1.19 (m, 8H, $S(CH_2)_2(CH_2)_4CH_3$), 0.88 (t, *J* = 6.8 Hz, 3H, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 198.8 (q), 140.2 (q), 2 × 128.5 (+, +), 2 × 128.3 (+, +), 126.3 (+), 45.6 (–), 31.7 (–), 31.5 (–), 29.5 (–), 28.9 (–), 28.8 (–), 28.8 (–), 22.6 (–), 14.1 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2926 (s, sh), 2855 (m, sh), 1685 (s, sh), 1454 (m, sh), 1044 (s, sh), 969 (s, sh), 742 (s, sh), 697 (s, sh).

GC-MS (EI): t_R = 9.23 min, m/z = 264 (3, $[M^{+\bullet}]$), 133 (29, $[M^{+\bullet}]$-$[^{\bullet}S^nC_7H_{15}]$), 105 (100, $[M^{+\bullet}]$-$[^{\bullet}COS^nC_7H_{15}]$).

HR-MS (EI): $[M^{+\bullet}]$ calc. for $C_{16}H_{24}OS$ 264.1542, found 264.1536.

3.4.4 Kinetic Measurement and Substrate Screening

Kinetic measurement

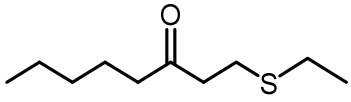
According to the general procedure *T1*, a kinetic study was performed by using **8a** as substrate. Therefore, *n*-pentadecane (100 µL) was added as an internal standard before the addition of the Grignard solution. Aliquots of the reaction mixture (100 µL) were taken at different reaction times. After quenching and extraction the conversions and the yields were determined by quantitative GC-FID (Table 3.2).

Table 3.2. Conversions and yields of the kinetic study for the tandem reaction of **8a** with vinylmagnesium bromide (**6**)

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

Substrate screening

1-(Ethylthio)octan-3-one (9a)



According to the general procedure *T1*, **9a** was synthesized from **8a** (159 mg, 1.00 mmol, 1.0 eq.). Purification of the crude product by column chromatography ((Pentane/Et_2O: 99/1 and CyH/EtOAc (gradient CyH/EtOAc = 100/0 → 0/100) provided **9a** as a colorless liquid (135 mg, 721 µmol, 73%).

$C_{10}H_{20}OS$ (188.33 g/mol), **R_f:** 0.02 (Pentane/Et_2O: 99/1).

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 2.80 – 2.62 (m, 4H, $COCH_2CH_2S$), 2.54 (q, *J* = 7.4 Hz, 2H, SCH_2CH_3), 2.41 (t, *J* = 7.5 Hz, 2H, $COCH_2(CH_2)_3CH_3$), 2.65 – 1.51 (m, 2H, $COCH_2CH_2(CH_2)_2CH_3$), 1.37 – 1.19 (m, 4H, $CO(CH_2)_2(CH_2)_2CH_3$), 1.25 (t, *J* = 7.4 Hz, 3H, SCH_2CH_3), 0.88 (t, *J* = 6.9 Hz, 3H, $CO(CH_2)_4CH_3$).

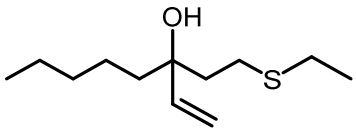
^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 209.5 (q), 43.1 (–), 42.7 (–), 31.4 (–), 26.3 (–), 25.4 (–), 23.4 (–), 22.5 (–), 14.7 (+), 13.9 (+).

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, $[M^{+\bullet}]$-[$^\bullet CH_2CH_2SEt$]), 89 (100, $[M^{+\bullet}]$-[$^\bullet CO(CH_2)_4CH_3$]).

HR-MS (EI): $[M^{+\bullet}]$ calc. for $C_{10}H_{20}OS$ 188.1229, found 188.1228.

3-(2-(Ethylthio)ethyl)oct-1-en-3-ol (11)



A flame-dried flask was charged with **9a** (94.4 mg, 501 µmol, 1.0 eq.), which was dissolved in anhydrous THF and stirred for 5 min at 0 °C. A vinylmagnesium bromide solution (0.61 M in THF, 2.5 mL, 3.0 eq) was added *via* syringe within a period of 5 min and the reaction mixture was stirred for 1 h at 0 °C (no starting material at GC-FID). 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 × 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 (gradient: Pentane/Et_2O = 99/1 → 0/100) provided **11** as an orange oil (90 mg, 416 µmol, 83%).

$C_{12}H_{24}OS$ (216.38 g/mol), **R_f:** 0.50 (Pentane/Et_2O: 90/10).

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 5.80 (dd, *J* = 17.3, 10.8 Hz, 1H, CH_2=C<u>H</u>), 5.31 – 5.11 (m, 2H, C<u>H_2</u>=CH), 2.62 – 2.48 (m, 4H, C(OH)CH_2C<u>H_2</u>SC<u>H_2</u>), 2.07 (s, 1H, OH), 1.93 – 1.67 (m, 2H, CH_2C(OH)C<u>H_2</u>CH_2SCH_2), 1.57 – 1.40 (m, 2H, C<u>H_2</u>C(OH)CH_2CH_2S), 1.38 – 1.15 (m, 9H, COHCH_2(C<u>H_2</u>)$_3$$CH_3$ and SCH_2C<u>H_3</u>), 0.87 (t, *J* = 7.1 Hz, 3H, COH$(CH_2)_4$C<u>H_3</u>).

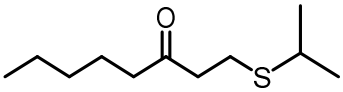
^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 143.1 (+), 113.2 (–), 75.8 (q), 41.5 (–), 39.5 (–), 32.2 (–), 26.1 (–), 25.8 (–), 23.0 (–), 22.6 (–), 14.7 (+), 14.1 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3452 (m, br), 2930 (s, br), 2859 (m, sh), 1454 (m, br), 1379 (m, sh), 1267 (m, sh), 995 (s, sh), 917 (s, sh).

GC-MS (EI): t_R = 6.67 min, m/z = 198 (3, $[M^{+\bullet}]$-$[H_2O]$), 187 (35, $[M^{+\bullet}]$-$[^{\bullet}C_2H_5]$), 75 (100, $[^{\bullet}CH_2SEt]$).

HR-MS (EI): $[M^{+\bullet}]$ calc. for $C_{12}H_{24}OS$ 216.1542, found 216.1545.

<u>1-(Isopropylthio)octan-3-one (9b)</u>



According to the general procedure *T1*, **9b** was synthesized from **8b** (175 mg, 1.01 mmol, 1.0 eq.). Purification of the crude product by column chromatography (Pentane/Et_2O: 99/1 and CyH/EtOAc (gradient CyH/EtOAc = 100/0 → 0/100) in order to remove ^{i}PrSH) provided **9b** as a colorless liquid (108 mg, 534 µmol, 53%).

$C_{11}H_{22}OS$ (202.36 g/mol), **R_f:** 0.14 (Pentane/Et_2O: 99/1).

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 2.92 (hept, *J* = 6.7 Hz, 1H, SC<u>H</u>), 2.81 – 2.70 (m, 2H, COC<u>H_2</u>CH_2S), 2.72 – 2.63 (m, 2H, $COCH_2$C<u>H_2</u>S), 2.41 (t, *J* = 7.5 Hz, 2H, COC<u>H_2</u>$(CH_2)_3CH_3$), 1.65 – 1.52 (m, 2H, $COCH_2$C<u>H_2</u>$(CH_2)_2CH_3$), 1.37 – 1.19 (m, 4H, $CO(CH_2)_2$(C<u>H_2</u>)<u>$_2$</u>CH_3), 1.26 (d, *J* = 6.7 Hz, 6H, 2 × CHC<u>H_3</u>), 0.88 (t, *J* = 6.9 Hz, 3H, $CO(CH_2)_4$C<u>H_3</u>).

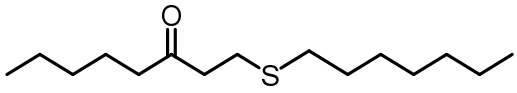
^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 209.5 (q), 43.1 (–), 42.8 (–), 35.3 (+), 31.4 (–), 24.3 (–), 23.5 (–), 2 × 23.4 (+, +), 22.5 (–), 13.9 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2960 (s, sh), 2866 (m, sh), 1715 (s, sh), 1461 (m, sh), 1364 (m, br), 1245 (m, sh), 1074 (m, sh).

GC-MS (EI): t_R = 7.16 min, m/z = 202 (61, $[M^{+\bullet}]$), 127 (29, $[M^{+\bullet}]$-$[^{\bullet}S^{i}Pr]$), 75 (100, $[^{\bullet}S^{i}Pr]$), 99 (82, $[M^{+\bullet}]$-$[^{\bullet}CH_2CH_2S^{i}Pr]$).

HR-MS (EI): $[M^{+\bullet}]$ calc. for $C_{11}H_{22}OS$ 202.1386, found 202.1383.

1-(Heptylthio)octan-3-one (9c)



According to the general procedure *T1*, **9c** was synthesized from **8c** (230 mg, 997 µmol, 1.0 eq.). Purification of the crude product by column chromatography (Pentane/Et_2O: 99/1 and CyH/EtOAc (gradient CyH/EtOAc = 100/0 → 0/100) in order to remove $H_{15}C_7SH$) provided **9c** as a colorless oil (188 mg, 729 µmol, 73%).

$C_{15}H_{30}OS$ (258.46 g/mol), **R_f:** 0.14 (Pentane/Et_2O: 99/1).

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 2.81 – 2.62 (m, 4H, $COC\underline{H_2}C\underline{H_2}S$), 2.52 (t, *J* = 7.4 Hz, 2H, $COCH_2CH_2SC\underline{H_2}$), 2.41 (t, *J* = 7.3 Hz, 2H, $C\underline{H_2}COCH_2CH_2S$), 1.67 – 1.49 (m, 4H, $C\underline{H_2}CH_2COCH_2CH_2SCH_2C\underline{H_2}$), 1.43 – 1.14 (m, 12H, 6 × $C\underline{H_2}$), 0.96 – 0.81 (m, 6H, 2 × $C\underline{H_3}$).

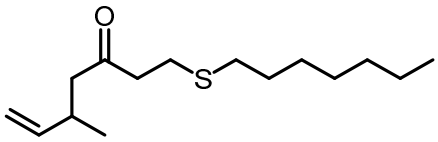
^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 209.6 (q), 43.1 (–), 42.8 (–), 32.5 (–), 31.7 (–), 31.4 (–), 29.6 (–), 28.9 (–), 28.9 (–), 25.9 (–), 23.5 (–), 22.6 (–), 22.5 (–), 14.1 (+), 13.9 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2926 (s, br), 2855 (m, sh), 1715 (s, sh), 1461 (m, sh), 1375 (m, br), 1074 (m, sh), 723 (m, sh).

GC-MS (EI): t_R = 9.70 min, m/z = 258 (29, [$M^{+\bullet}$]), 127 (57, [$M^{+\bullet}$]-[$^{\bullet}S^nC_7H_{15}$]), 99 (48, [$M^{+\bullet}$]-[$^{\bullet}CH_2CH_2S^nC_7H_{15}$]).

HR-MS (EI): [$M^{+\bullet}$] calc. for $C_{15}H_{30}OS$ 258.2012, found 258.2010.

1-(Heptylthio)-5-methylhept-6-en-3-one (9e)



According to the general procedure *T1*, **9e** was synthesized from **8e** (228 mg, 999 µmol, 1.0 eq.). Purification of the crude product by column chromatography (gradient: Pentane/Et_2O: 99/1 → 90/10) provided **9e** as a colorless oil (97 mg, 378 µmol, 38%).

$C_{15}H_{28}OS$ (256.45 g/mol), **R_f:** 0.02 (Pentane/Et_2O: 99/1); 0.38 (Pentane/Et_2O: 90/10).

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 5.85 – 5.64 (m, 1H, $COCH_2CHC\underline{H}=CH_2$), 5.05 – 4.88 (m, 2H, $COCH_2CHCH=C\underline{H_2}$), 2.81 – 2.61 (m, 5H, $C\underline{H_2}C\underline{H_2}COCH_2C\underline{H}CH=CH_2$), 2.57 – 2.42 (m, 3H, $C\underline{H_2}COCH_2CH_2SC\underline{H_2}$), 2.42 – 2.27 (m, 1H, $COC\underline{H_2}CH$), 1.63 – 1.51 (m, 2H, $COCH_2CH_2SCH_2C\underline{H_2}$),

1.41 – 1.22 (m, 8H, $S(CH_2)_2(C\underline{H_2})_4CH_3$), 1.02 (d, *J* = 6.8 Hz, 3H, $COCH_2CHC\underline{H_3}$), 0.88 (t, *J* = 6.7 Hz, 3H, $S(CH_2)_6C\underline{H_3}$).

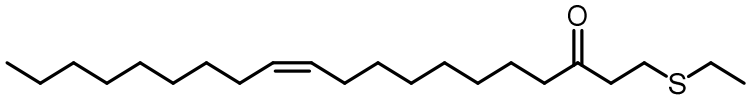
^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 208.3 (q), 142.7 (+), 113.3 (–), 49.7 (–), 43.5 (–), 33.4 (+), 32.5 (–), 31.7 (–), 29.6 (–), 28.91 (–), 28.86 (–), 25.7 (–), 22.6 (–), 19.8 (+), 14.1 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2926 (s, br), 2855 (m, sh), 1715 (s, sh), 1461 (m, sh), 1409 (m, sh), 1361 (m, br), 995 (m, sh), 913 (s, sh).

GC-MS (EI): t_R = 8.33 min, m/z = 256 (13, $[M^{+\bullet}]$), 187 (20, $[M^{+\bullet}]$-$[^{\bullet}C_5H_9]$), 159 (69, $[^{\bullet}CH_2CH_2S^nC_7H_{15}]$), 145 (100, $[^{\bullet}CH_2S^nC_7H_{15}]$).

HR-MS (EI): $[M^{+\bullet}]$ calc. for $C_{15}H_{28}OS$ 256.1855, found 256.1848.

(Z)-1-(Ethylthio)icos-11-en-3-one (9f)



According to the general procedure *T1*, **9f** was synthesized from **8f** (329 mg, 1.01 mmol, 1.0 eq.). Purification of the crude product by column chromatography (gradient: Pentane/Et_2O: 99/1 → 90/10) provided **9f** as a colorless oil (161 mg, 453 µmol, 45%). The product contains small amount of unknown impurities.

$C_{22}H_{42}OS$ (354.64 g/mol), **R_f:** 0.42 (Pentane/Et_2O: 90/10).

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 5.41 – 5.31 (m, 2H, $C\underline{H}=C\underline{H}$), 2.82 – 2.62 (m, 4H, $COC\underline{H_2}C\underline{H_2}S$), 2.54 (q, *J* = 7.4 Hz, 2H, $SC\underline{H_2}CH_3$), 2.41 (t, *J* = 7.4 Hz, 2H, $C\underline{H_2}COCH_2CH_2S$), 2.07 – 1.91 (m, 4H, $C\underline{H_2}CH=CHC\underline{H_2}$), 1.63 – 1.51 (m, 2H, $C\underline{H_2}CH_2COCH_2CH_2S$), 1.38 – 1.21 (m, 23H, $SCH_2C\underline{H_3}$; 10 × $C\underline{H_2}$), 0.87 (t, *J* = 7.0 Hz, 3H, $C\underline{H_3}$).

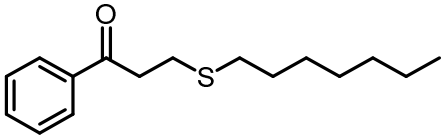
^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 209.5 (q), 130.0 (+), 129.8 (+), 43.1 (–), 42.7 (–), 31.9 (–), 29.8 (–), 29.7 (–), 29.5 (–), 2 × 29.34 (–, –), 29.32 (–), 29.2 (–), 29.1 (–), 27.23 (–), 27.18 (–), 26.3 (–), 25.4 (–), 23.8 (–), 22.7 (–), 14.7 (+), 14.2 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2922 (s, sh), 2855 (s, sh), 1715 (s, sh), 1461 (m, br), 1372 (m, br), 969 (m, br), 723 (m, br).

GC-MS (EI): t_R = 9.96 min, m/z = 293 (21, $[M^{+\bullet}]$-$[^{\bullet}SEt]$), 265 (9, $[M^{+\bullet}]$-$[^{\bullet}CH_2CH_2SEt]$).

HR-MS (EI): $[M^{+\bullet}]$ calc. for $C_{22}H_{42}OS$ 354.2951, found 354.2948.

3-(Heptylthio)-1-phenylpropan-1-one (9g)



According to the general procedure *T1*, **9g** was synthesized from **8g** (236 mg, 998 µmol, 1.0 eq.). Purification of the crude product by column chromatography (Pentane/Et_2O: 99/1) provided **9g** as a bright yellow oil (171 mg, 647 µmol, 65%).

$C_{16}H_{24}OS$ (264.43 g/mol), **R_f:** 0.02 (Pentane/Et_2O: 99/1).

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 8.02 – 7.92 (m, 2H, ArH), 7.62 – 7.52 (m, 1H, ArH), 7.52 – 7.42 (m, 2H, ArH), 3.28 (t, *J* = 7.2, 2H, $COCH_2$), 2.91 (t, *J* = 7.2, 2H, $COCH_2CH_2$), 2.54 (t, *J* = 7.3, 2H, $COCH_2CH_2SCH_2$), 1.67 – 1.52 (m, 2H, $COCH_2CH_2SCH_2CH_2$), 1.47 – 1.15 (m, 8H, $S(CH_2)_2(CH_2)_4CH_3$), 0.88 (t, *J* = 7.0 Hz, 3H, CH_3).

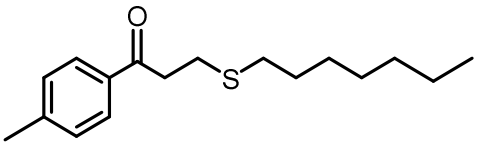
^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 198.5 (q), 136.6 (q), 133.3 (+), 2 × 128.7 (+, +), 2 × 128.1 (+, +), 39.1 (–), 32.6 (–), 31.8 (–), 29.7 (–), 28.9 (–), 28.9 (–), 26.3 (–), 22.6 (–), 14.1 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2926 (s, br), 2855 (m, sh), 1685 (s, sh), 1446 (m, sh), 1349 (m, sh), 1230 (m, br), 1193 (m, br), 969 (m, sh), 738 (s, sh), 690 (s, sh).

GC-MS (EI): t_R = 9.83 min, m/z = 264 (13, $[M^{+\bullet}]$), 133 (65, $[M^{+\bullet}]$-$[^{\bullet}S^nC_7H_{15}]$), 105 (100, $[M^{+\bullet}]$-$[^{\bullet}COCH_2CH_2S^nC_7H_{15}]$).

HR-MS (EI): $[M^{+\bullet}]$ calc. for $C_{16}H_{24}OS$ 264.1542, found 264.1535.

3-(Heptylthio)-1-(p-tolyl)propan-1-one (9h)



According to the general procedure *T1*, **9h** was synthesized from **8h** (251 mg, 1.00 µmol, 1.0 eq.). Purification of the crude product by column chromatography (Pentane/Et_2O: 99/1) provided **9h** as a colorless oil (149 mg, 536 µmol, 53%).

$C_{17}H_{26}OS$ (278.45 g/mol), R_f: 0.02 (Pentane/Et_2O: 99/1).

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.86 (d, *J* = 8.2 Hz, 2H, ArH), 7.26 (d, *J* = 8.2 Hz, 2H, ArH), 3.24 (t, *J* = 7.5 Hz, 2H, $COCH_2$), 2.91 (t, *J* = 7.5 Hz, 2H, $COCH_2CH_2$), 2.56 (t, *J* = 7.4 Hz, 2H,

$COCH_2CH_2SC\underline{H_2}$), 2.41 (s, 3H, $ArC\underline{H_3}$), 1.66 – 1.52 (m, 2H, $COCH_2CH_2SCH_2C\underline{H_2}$), 1.43 – 1.21 (m, 8H, $S(CH_2)_2(C\underline{H_2})_4CH_3$), 0.88 (t, *J* = 7.0 Hz, 3H, $S(CH_2)_6C\underline{H_3}$).

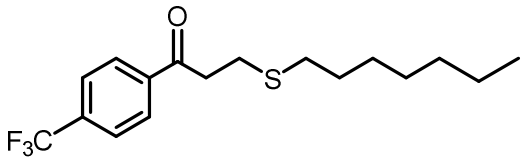
^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 198.2 (q), 144.1 (q), 134.2 (q), 129.4 (+, +), 2 × 128.2 (+, +), 39.0 (–), 32.6 (–), 31.8 (–), 29.7 (–), 28.9 (–), 28.9 (–), 26.4 (–), 22.6 (–), 21.7 (+), 14.1 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2926 (s, br), 2855 (m, sh), 1681 (s, sh), 1607 (s, sh), 1346 (m, sh), 1178 (s, sh), 969 (m, sh), 813 (s, sh).

GC-MS (EI): t_R = 8.81 min, m/z = 278 (2, $[M^{+\bullet}]$), 147 (25, $[M^{+\bullet}]$-$[^{\bullet}S^nC_7H_{15}]$), 119 (100, $[M^{+\bullet}]$-$[^{\bullet}CH_2CH_2S^nC_7H_{15}]$), 91 (46, $[M^{+\bullet}]$-$[^{\bullet}COCH_2CH_2S^nC_7H_{15}]$).

HR-MS (EI): $[M^{+\bullet}]$ calc. for $C_{17}H_{26}OS$ 278.1699, found 278.1697.

3-(Heptylthio)-1-(4-(trifluoromethyl)phenyl)propan-1-one (9i)



According to the general procedure *T1*, **9i** was synthesized from **8i** (305 mg, 1.00 µmol, 1.0 eq.). Purification of the crude product by column chromatography (Pentane/Et_2O: 99/1) provided **9i** as a colorless solid (240 mg, 721 µmol, 72%).

$C_{17}H_{23}F_3OS$ (332.43 g/mol), R_f: 0.11 (Pentane/Et_2O: 99/1), **m.p.:** 42 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 8.06 (d, *J* = 8.1 Hz, 2H, $Ar\underline{H}$), 7.73 (d, *J* = 8.1 Hz, 2H, $Ar\underline{H}$), 3.30 (t, *J* = 7.3 Hz, 2H, $COC\underline{H_2}$), 2.92 (t, *J* = 7.3 Hz, 2H, $COCH_2C\underline{H_2}$), 2.56 (t, *J* = 7.3 Hz, 2H, $COCH_2CH_2SC\underline{H_2}$), 1.67 – 1.52 (m, 2H, $COCH_2CH_2SCH_2C\underline{H_2}$), 1.43 – 1.20 (m, 8H, $S(CH_2)_2(C\underline{H_2})_4CH_3$), 0.88 (t, *J* = 7.1 Hz, 3H, $C\underline{H_3}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 197.5 (q), 139.2 (q), 134.6 (quartet, *J* = 32.7 Hz, q), 2 × 128.4 (+, +), 2 × 125.8 (quartet, *J* = 3.7 Hz, +, +), 123.6 (quartet, *J* = 272.8 Hz, q), 39.4 (–), 32.7 (–), 31.7 (–), 29.6 (–), 28.9 (–), 28.9 (–), 26.1 (–), 22.6 (–), 14.1 (+).

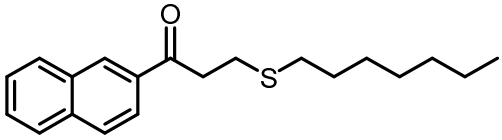
^{19}F-NMR (282 MHz, CDCl3) δ_F/ppm: -63.6 (CF_3).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2930 (m, br), 2855 (m, sh), 1692 (s, sh), 1409 (m, sh), 1323 (s, sh), 1170 (s, sh), 1133 (s, sh), 1066 (s, sh).

GC-MS (EI): t_R = 8.05 min, m/z = 332 (3, $[M^{+\bullet}]$), 201 (22, $[M^{+\bullet}]$-$[^{\bullet}S^nC_7H_{15}]$), 173 (100, $[M^{+\bullet}]$-$[^{\bullet}CH_2CH_2S^nC_7H_{15}]$), 145 (72, $[M^{+\bullet}]$-$[^{\bullet}COCH_2CH_2S^nC_7H_{15}]$).

HR-MS (EI): $[M^{+\bullet}]$ calc. for $C_{17}H_{23}F_3OS$ 332.1416, found 332.1418.

3-(Heptylthio)-1-(naphthalen-2-yl)propan-1-one (9k)



According to the general procedure *T1*, **9k** was synthesized from **8k** (288 mg, 1.01 mmol, 1.0 eq.). Purification of the crude product by column chromatography (Pentane/Et_2O: 99/1) provided **9k** as a bright yellow solid (202 mg, 641 µmol, 64%).

$C_{20}H_{26}OS$ (314.49 g/mol), **R_f:** 0.02 (Pentane/Et_2O: 99/1), **m.p.:** 35 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 8.48 (s, 1H, ArH), 8.09 – 7.83 (m, 4H, ArH), 7.67 – 7.50 (m, 2H, ArH), 3.42 (t, 2H, *J* = 7.5 Hz, $COCH_2$), 2.98 (t, *J* = 7.5 Hz, 2H, $COCH_2CH_2$), 2.60 (t, *J* = 7.3 Hz, 2H, $COCH_2CH_2SCH_2$), 1.71 – 1.53 (m, 2H, $COCH_2CH_2SCH_2CH_2$), 1.45 – 1.19 (m, 8H, $S(CH_2)_2(CH_2)_4CH_3$), 0.88 (t, *J* = 6.9 Hz, 3H, CH_3).

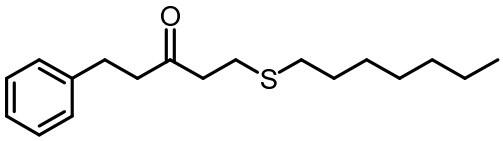
^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 198.5 (q), 135.7 (q), 134.0 (q), 132.5 (q), 129.8 (+), 129.6 (+), 128.58 (+), 128.57 (+), 127.8 (+), 126.9 (+), 123.8 (+), 39.2 (–), 32.6 (–), 31.8 (–), 29.7 (–), 28.9 (–), 28.9 (–), 26.5 (–), 22.6 (–), 14.1 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2926 (m, br), 2855 (s, br), 1677 (s, sh), 1215 (s, sh), 1126 (m, sh), 746 (s, br), 667 (m, sh).

GC-MS (EI): t_R = 10.40 min, m/z = 314 (10, $[M^{+\bullet}]$), 183 (79, $[M^{+\bullet}]$-$[^\bullet S^nC_7H_{15}]$), 155 (100, $[M^{+\bullet}]$-$[^\bullet CH_2CH_2S^nC_7H_{15}]$), 127 (71, $[M^{+\bullet}]$-$[^\bullet COCH_2CH_2S^nC_7H_{15}]$).

HR-MS (EI): $[M^{+\bullet}]$ calc. for $C_{20}H_{26}OS$ 314.1699, found 314.1692.

1-(Heptylthio)-5-phenylpentan-3-one (9l)



According to the general procedure *T1*, **9l** was synthesized from **8l** (263 mg, 996 µmol, 1.0 eq.). Purification of the crude product by column chromatography (Pentane/Et_2O: 99/1) provided **9l** as a colorless oil (205 mg, 701 µmol, 70%).

$C_{18}H_{28}OS$ (292.48 g/mol), **R_f:** 0.02 (Pentane/Et_2O: 99/1).

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.34 – 7.24 (m, 2H, ArH), 7.24 – 7.15 (m, 3H, ArH), 2.96 – 2.85 (m, 2H, $COCH_2CH_2S$), 2.81 – 2.62 (m, 6H, $ArCH_2CH_2COCH_2$), 2.49 (t, *J* = 7.4 Hz, 2H,

$COCH_2CH_2SC\underline{H_2}$), 1.62 – 1.49 (m, 2H, $COCH_2CH_2SCH_2C\underline{H_2}$), 1.43 – 1.19 (m, 8H, $S(CH_2)_2(C\underline{H_2})_4CH_3$), 0.88 (t, *J* = 6.7 Hz, 3H, $C\underline{H_3}$).

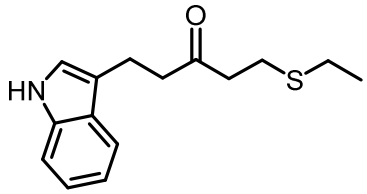
^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 208.3 (q), 140.9 (q), 2 × 128.5 (+, +), 2 × 128.3 (+, +), 126.18 (+), 44.6 (–), 43.1 (–), 32.5 (–), 31.8 (–), 29.7 (–), 29.6 (–), 28.9 (–), 28.9 (–), 25.8 (–), 22.6 (–), 14.1 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2926 (s, br), 2855 (m, sh), 1715 (s, sh), 1454 (m, sh), 1364 (m, br), 1088 (m, br), 749 (s, br), 701 (s, sh).

GC-MS (EI): t_R = 10.58 min, m/z = 292 (60, $[M^{+\bullet}]$), 159 (100, $[M^{+\bullet}]$-$[^{\bullet}COCH_2CH_2Ph]$), 105 (62, $[M^{+\bullet}]$-$[^{\bullet}COCH_2CH_2S^nC_7H_{15}]$).

HR-MS (EI): $[M^{+\bullet}]$ calc. for $C_{18}H_{28}OS$ 292.1855, found 292.1850.

1-(Ethylthio)-5-(1H-indol-3-yl)pentan-3-one (9m)



According to the general procedure *T1*, **9m** was synthesized from **8m** (236 mg, 1.01 mmol, 1.0 eq.). Purification of the crude product by column chromatography (CyH/EtOAc: 80/20) provided **9m** as a colorless solid (71.2 mg, 272 µmol, 27%).

$C_{15}H_{19}NOS$ (261.38 g/mol), **R_f:** 0.15 (CyH/EtOAc: 80/20), **m.p.:** 63 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.96 (s, 1H, N$\underline{H}$), 7.59 (dd, *J* = 7.8, 0.6 Hz, 1H, Ar$\underline{H}$), 7.40 – 7.33 (m, 1H, Ar$\underline{H}$), 7.24 – 7.09 (m, 2H, Ar$\underline{H}$), 7.02 – 6.96 (m, 1H, Ar$\underline{H}$), 3.07 (t, *J* = 7.4 Hz, 2H, $COC\underline{H_2}CH_2S$), 2.86 (t, *J* = 7.4 Hz, 2H, $COCH_2C\underline{H_2}S$), 2.79 – 2.63 (m, 4H, $ArC\underline{H_2}C\underline{H_2}CO$), 2.51 (q, *J* = 7.4 Hz, 2H, $SC\underline{H_2}CH_3$), 1.24 (t, *J* = 7.4 Hz, 3H, $SCH_2C\underline{H_3}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 209.0 (q), 136.3 (q), 127.1 (q), 122.1 (+), 121.5 (+), 119.4 (+), 118.7 (+), 115.1 (q), 111.2 (+), 43.5 (–), 43.0 (–), 26.2 (–), 25.3 (–), 19.3 (–), 14.7 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3403 (m, br), 2967 (m, br), 2922 (m, br), 1703 (s, sh), 1457 (m, sh), 1342 (m, br), 1092 (s, sh), 742 (s, sh).

GC-MS (EI): t_R = 9.52 min, m/z = 261 (46, $[M^{+\bullet}]$), 144 (40, $[M^{+\bullet}]$-$[^{\bullet}COCH_2CH_2SEt]$), 130 (100, $[M^{+\bullet}]$-$[^{\bullet}CH_2COCH_2CH_2SEt]$).

HR-MS (EI): $[M^{+\bullet}]$ calc. for $C_{15}H_{19}NOS$ 261.1182, found 261.1181.

3.5 References

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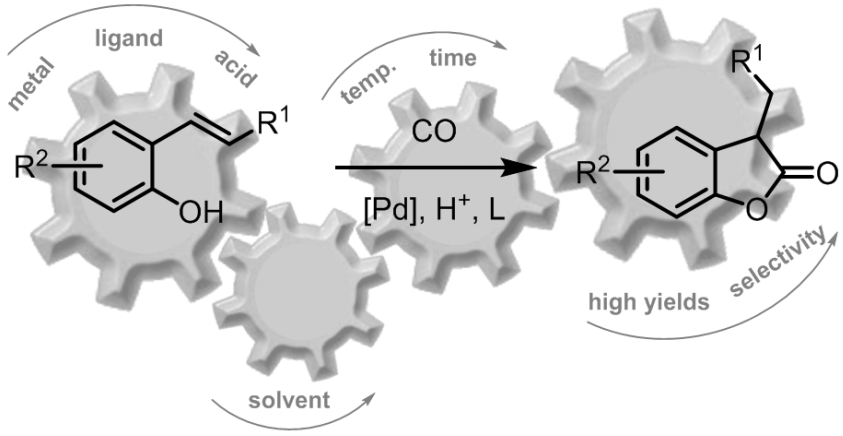
Chapter 4

Synthesis of Benzofuranones *via* Palladium-Catalyzed Intramolecular Alkoxycarbonylation of Alkenylphenols



Abstract: Herein, a new catalytic system to synthesize benzofuranones is reported. A palladium-catalyzed intramolecular alkoxycarbonylation is employed to generate 3-substituted-benzofuran-2(3H)-ones from alkenylphenols under mild reaction conditions, linked to an *ex situ* formation of CO from *N*-formylsaccharin. The carefully chosen catalytic system enables an efficient reaction with a novel functional group tolerance, despite the high polymerization tendency of the starting material.

Author contribution:

VH: 100% of reproduced part

IF: corresponding author.

Author contribution:

VH: 100% of reproduced part

IF: corresponding author.

Preparatory work for the synthesis of (±)-Agropyrenone was already performed:

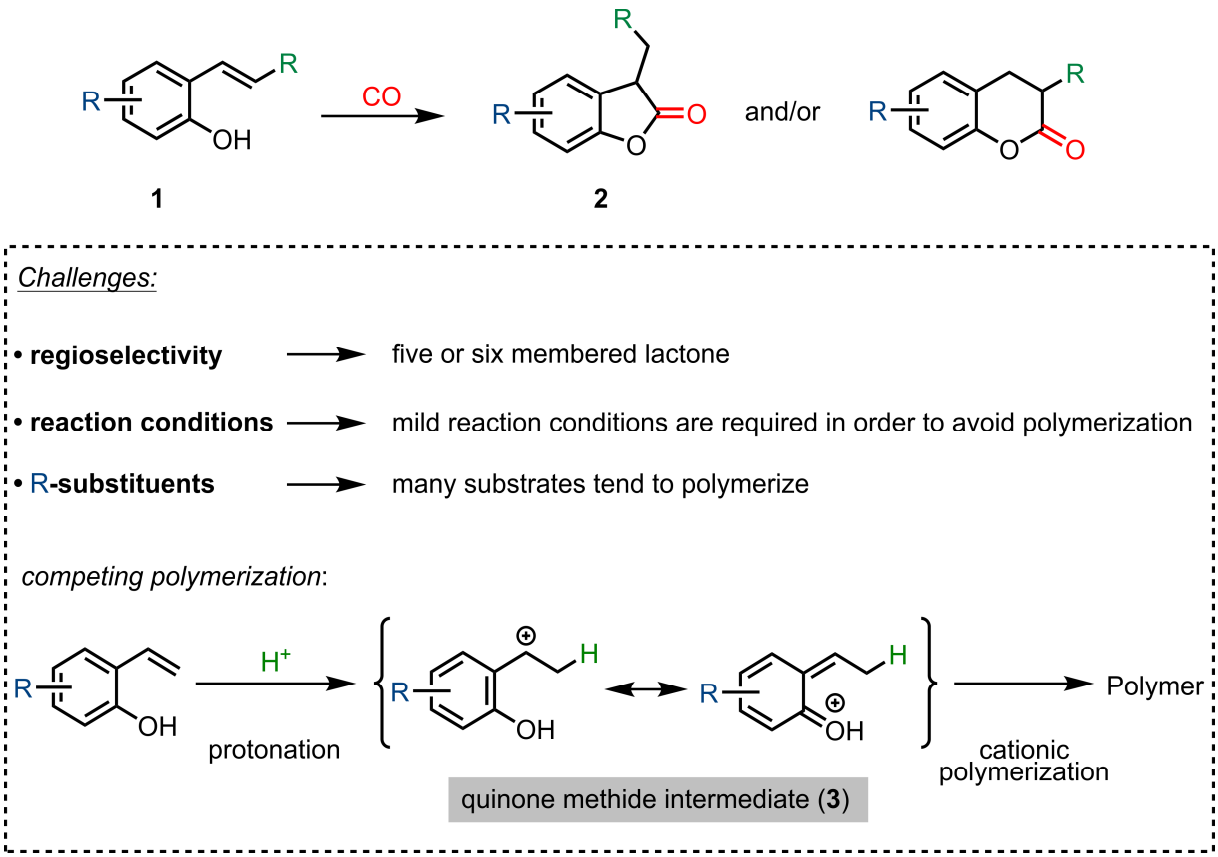
V. Hirschbeck, *Master Thesis, University of Regensburg* **2015**.

P. H. Gehrtz, *Master Thesis, University of Regensburg* **2015**.

4.1 Introduction - Intramolecular Alkoxycarbonylation

4.1.1 Application and Synthesis of Benzofuran-2(3H)-ones

Benzofuran-2(3H)-ones, which can often be found in natural products, constitute interesting structural motives of unique pharmaceutical importance.[3] Moreover, substituted derivatives play an important role in polymer chemistry, in which they are used as antioxidants in order to inhibit oxidative degradation of polymers. Due to the weak benzylic C–H bond, benzofuranyl radicals can easily be formed, which are able to trap oxygen and therefore prevent autoxidation.[4] Many different strategies to synthesize benzofuran-2(3H)-ones are known in the literature.[5] A convenient and atom-economic way to generate benzo-fused 5-, 6- or 7-membered lactones is the intramolecular Reppe-type carbonylation of alkenyl- or allylphenols (Scheme 4.1).[6]



Scheme 4.1. Regioselectivity of cyclocarbonylation and polymerization tendency.

The control of regioselectivity is one of the main challenges of this transformation. Several approaches to the synthesis of 6-membered lactones were reported.[7] A general method for the synthesis of benzofuran-2(3H)-ones (**2**) from alkenylphenols (**1**) proved more difficult.

Alper employed a catalyst system based on a Pd^0 precursor and bidentate ligand dppb (1,4-bis(diphenylphosphino)butane) in an ionic liquid to obtain a series of 5-membered lactones with no or moderate regioselectivity.[8] Better results were achieved by Manabe *et al.*, who developed a cyclization of 2-vinyl aryl formates using $Ru_3(CO)_{12}$ under harsh reaction conditions (135 °C, 15 mol% of [Ru]).[9] In 2014, Shi and co-workers reported a hydroesterification of alkenylphenols with phenyl formate as CO surrogate generating benzofuran-2(3H)-ones.[10] They described a catalytic system consisting of $Pd(OAc)_2$ (5 mol%) and PPh_3 (20 mol%), which showed a good functional group tolerance for α-, β- or nonsubstituted alkenylphenols. However, only one example with substituent on aryl ring was shown, probably because of the high polymerization tendency of some substrates and the employed high temperature (90 °C) in combination with an acid. Protonation of the substrate leads to the protonated quinone methide intermediate **3**, which undergoes cationic polymerization (Scheme 4.1).

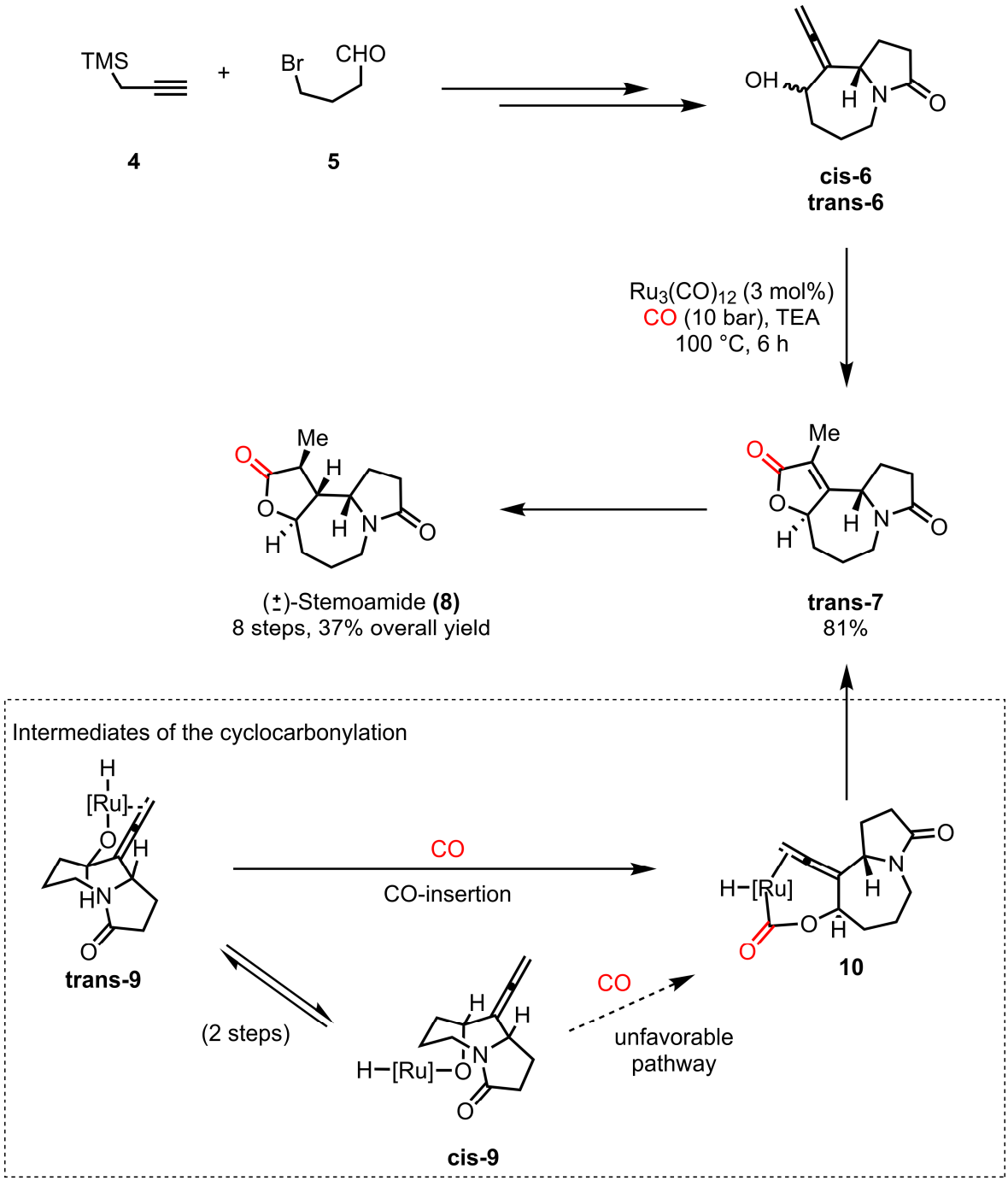
Herein we report the first cyclocarbonylation of 2-vinylphenols proceeding at room temperature, which allows for the expansion of the substrate scope to vinylphenols with substituted aryl ring. In order to avoid working with gaseous carbon monoxide, *N*-formylsaccharin (NFS, **20**) — originally described by Manabe and co-workers[11] — was used as a CO surrogate in combination with a two-chamber pressure tube developed by Skrydstrup.[12]

4.1.2 Application of Cyclocarbonylation in the Synthesis of a Natural Compound

4.1.2.1 Reppe-type Cyclocarbonylation of Natural Compounds in Literature

Cyclocarbonylation based on Reppe chemistry is also of interest in the synthesis of natural compounds. Hong and co-workers developed a bioinspired strategy to synthesize (±)-Stemoamide (**8**) in eight steps, including a cyclocarbonylation reaction.[13] Stemoamide, which was isolated from *Stemona tuberosa* Lour, is a member of the stemona class of alkaloids.[14] These compounds often contain a perhydroazaazulene ring and an α-methyl-γ-butyrolacton functionality. They are used in traditional Chinese medicine in order to treat respiratory disorders such as asthma, tuberculosis, bronchitis and pertussis. Some of these compounds also exhibit insecticidal activity.[15] The synthesis started with aldehyde **5** and propargyl trimethylsilane (**4**) to generate **6** as a mixture of two diastereoisomers in six steps (Scheme 4.2). The subsequent Reppe-type carbonylation required forcing reaction

conditions (3 mol% of $Ru_3(CO)_{12}$, 10 bar CO, 100 °C). Hong and co-workers proposed that the cyclocarbonylation proceeds through a metallacycle intermediate.

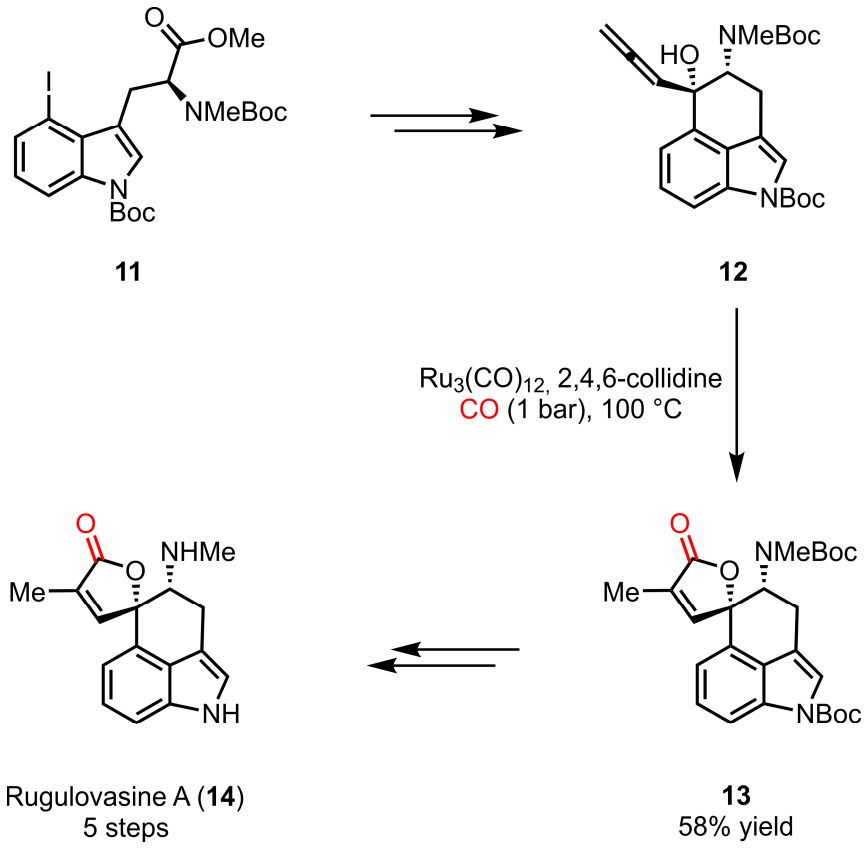


Scheme 4.2. The total synthesis of (±)-Stemoamide (**8**) including a Ru-catalyzed cyclocarbonylation to generate lactone **7**.[13]

Interestingly, only *trans*-**7** was formed when a mixture of the two diastereomers *cis*- and *trans*-**6** was subjected to carbonylation. Therefore, the proposed mechanism suggests an equilibrium between *cis*- and *trans*-**9**, wherein *trans*-**9** is the favored conformation for the

Ru-catalyzed CO-insertion, generating only *trans*-**7** in a yield of 81%. The hydrogenation of *trans*-**7** led to the formation of **8** in an overall yield of 37% (8 steps).

An analogous application of the carbonylation was reported by Jia and co-workers in the synthesis of Rugulovasine A (**14**, Scheme 4.3).[16]



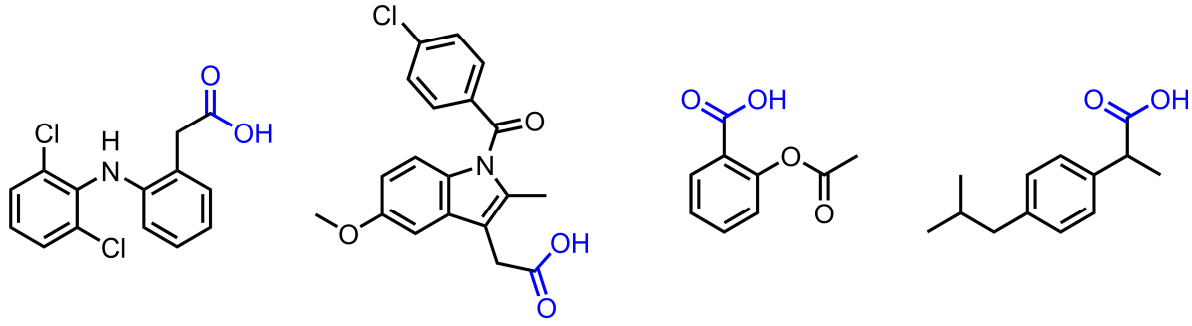
Scheme 4.3. The total synthesis of Rugulovasine A (**14**) *via* Ru-catalyzed cyclocarbonylation to generate the spirocyclic lactone **13**.[16]

This indole alkaloid is a member of the ergot family and can be isolated either from *Penicillium rugulosum* or from *Penicillium islandicum* in a racemic form.[16] Starting from **11**, the allenyl alcohol **12** was generated in two steps. The spirocyclic butyrolactone subunit **13** was constructed by a Ru-catalyzed cyclocarbonylation of **12**. The reaction took place in the presence of $Ru_3(CO)_{12}$ in 2,4,6-collidine at 100 °C with only 1 bar of CO. Butyrolactone **13** was obtained in a yield of 58% within two hours. Rugulovasine A (**14**) was generated after deprotection of the two Boc groups in two single steps. The overall yield for the synthesis of **14** was not calculated, since only the yield based on recovered starting material was indicated for each reaction.

4.1.2.2 Biological Importance of Agropyrenone

In order to confirm the practicability of the reported catalytic system, the lactonization should be applied in the synthesis of the natural compound (±)-Agropyrenone (**17**) (Scheme 4.4c). Until now, Reppe-type cyclocarbonylation of alkenes has not been applied in the synthesis of natural compounds. Agropyrenone is an exemplarily selected natural compound, since it constitutes one of the ambitious synthetic problems for direct lactonization *via* Reppe-type carbonylation.

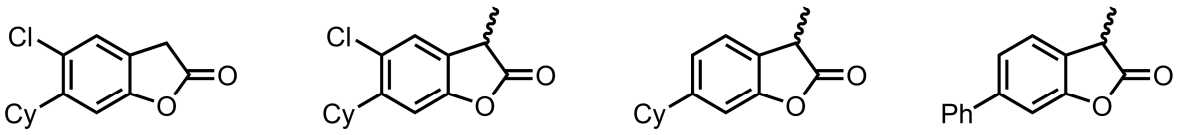
a) Examples of NSAIDs, with biologically active acid group



Diclofenac **Indomethacin** **Aspirin** **Ibuprofen**

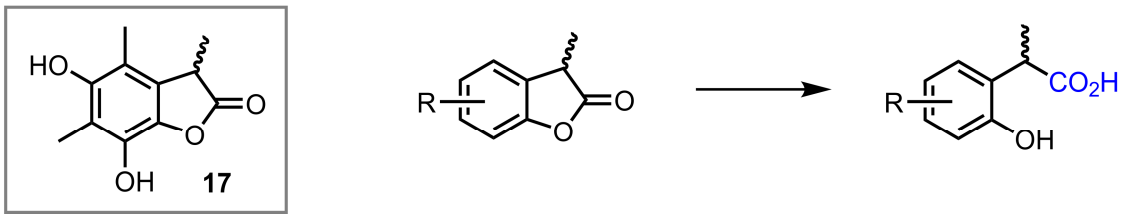
b) *In vitro* study of Sandoz *et al.* to prove anti-inflammatory properties of benzofuranones

IC_{50} (inhibitor concentration) of prostaglandin	**Diclofenac**	**Indomethacin**
	500 nM	200 nM



15, 50 nM **16**, 70 nM 400 nM 500 nM

c) Agropyrenone (**17**) and benzofuran-2(3H)-ones as NSAIDs



Scheme 4.4. Common drugs containing a free acid group and anti-inflammatory properties of benzofuranones.

Four electron donating substituents promote polymerization, which require a mild catalytic system. In case of successful synthesis other less challenging natural compounds should be accessed more easily. Agropyrenone was extracted from the liquid culture of the fungus *Ascochyta agropyrina var. nana* and has already been tested for phytotoxicity, antimicrobial activity and zootoxicity, where it was completely inactive.[17] Nevertheless, Agropyrenone might be used as a nonsteroidal anti-inflammatory drug (NSAID), by inhibiting the activity of cyclooxygenases (COX-1 and/or COX-2).[18] Cyclooxygenases are enzymes, which are involved in the synthesis of the inflammatory mediator prostaglandin and therefore are responsible for the incurrence of inflammations. A lot of common NSAIDs contain a free acid moiety, which is able to react with cyclooxygenases and therefore cause inhibition (Scheme 4.4a). Moreover, the ability of benzofuranones to inhibit prostaglandin was observed in an *in vitro* study by Sandoz *et al.* (Scheme 4.4b).[19] The anti-inflammatory properties acquired from this study were compared to Diclofenac and Indomethacin. It became obvious that the combination of an alkyl or aryl group in 6-position and an additional substituent in 5-position lead to significantly more effective inhibitors of prostaglandin synthesis than Diclofenac and Indomethacin. The most effective anti-inflammatory 3-methylbenzofuran-2(3H)-one was 5-chloro-6-cyclohexyl-3-methylbenzofuran-2(3H)-one (**16**) with an IC_{50}(prostaglandin) of 70 nM. This was only surpassed by 2,3-dihydrobenzofuranones, such as **15**. However, it was not fully investigated if the lactone itself or the free acid, which can be generated by an ester cleavage reaction, is the biologically active form (Scheme 4.4c). Thus, a potential anti-inflammatory activity should be assessed in biological studies in case of a successful synthesis.

4.2 Results and Discussion

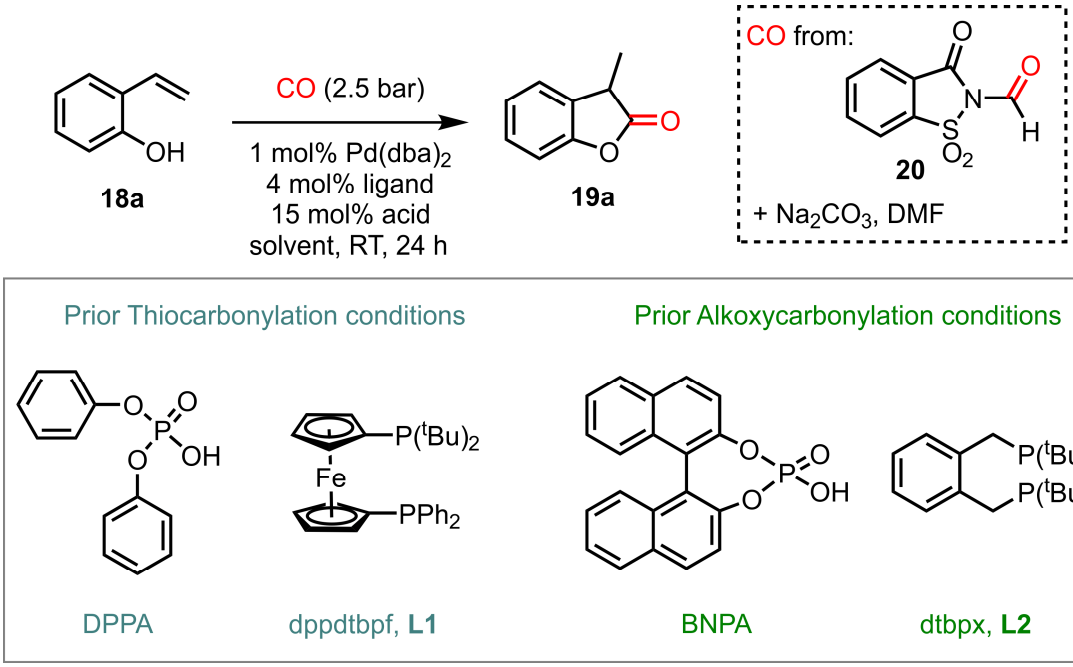
4.2.1 Initial Optimization Experiments

4.2.1.1 Catalyst and Additive Screening

Based on our earlier reports on the alkoxy- and the thiocarbonylation of alkenes at ambient temperature, a modified Pd(0)-based catalytic system for lactonization was identified.[20] We found that the combination of $Pd(dba)_2$, ligand **L1** (dppdtbpf; 1-diphenylphosphino-1'-(di-*tert*-butylphosphino)-ferrocene)[21] and diphenylphosphoric acid (DPPA) that was previously used in the thiocarbonylation led to 81% of **19a** (Table 4.1, entry 1). Whereas, the original alkoxycarbonylation conditions (**L2**, (dtbpx; bis(di-*tert*-butylphosphinomethyl)-benzene)[22] /BNPA (1,1'-bi-2-naphthol phosphoric acid)) generated only 73% yield (Table 4.1, entry 2). A transpose of the respective ligand/acid pair led to decreased activity (Table 4.1, entries 3, 4), which is in accordance to the previous described thiocarbonylation (see Chapter 2).[20b] A slightly increased yield was observed by using TFA (Table 4.1, entry 5), but because of its volatility and in order to circumvent possible reproducibility issues in the two-chamber pressure tube, we decided to use DPPA in further studies. The acid is essential for the generation of the catalytically active Pd-hydride, as confirmed by the corresponding control experiment without any acid (Table 4.1, entry 6).[22c, 23]

Also, few additives were tested. In the thiocarbonylation project we suggested that the used thiol forms the Pd-H *via* oxidative addition, therefore the same amount of $^{n}C_7H_{15}SH$ was added. In addition, it also may form the reactive thioester first and this would undergo fast trans-esterification.[24] However, this led to a reduction of catalytic activity in case of intramolecular alkoxycarbonylation resulting in 70% yield (Table 4.1, entry 7). Then, we examined if there may be a positive influence by the addition of methanol (Table 4.1, entries 8, 9). Beside the intramolecular reaction, also an intermolecular carbonylation (generation of the branched methyl ester) followed by trans-esterification to generate **19a** is conceivable. Unfortunately, no positive influence was observed by the addition of MeOH. By increasing the amount of MeOH more of the undesired branched methylester was observed. LiCl was tested as Lewis acid additives since it might accelerate the final rate-determining alcoholysis by coordination to the carbonyl group (Table 4.1, entry 10).[25] However, a white precipitate and no lactone were observed. The corresponding intermolecular transformation of styrene with phenol under this reaction conditions was not successful, which might be reasoned with steric effects.

Table 4.1. Initial optimizations for the lactonization of **18a**.[a]



Entry	Ligand	Acid	Solvent	Additive	Yield[b] [%]
1	**L1**	DPPA	CH_2Cl_2	-	81
2	**L2**	BNPA	CH_2Cl_2	-	73
3	**L2**	DPPA	CH_2Cl_2	-	75
4	**L1**	BNPA	CH_2Cl_2	-	69
5	**L1**	TFA	CH_2Cl_2	-	83
6	**L1**	-	CH_2Cl_2	-	0
7	**L1**	DPPA	CH_2Cl_2[c]	$^nC_7H_{15}SH$[c]	70
8	**L1**	DPPA	CH_2Cl_2[d]	MeOH[d]	27[e]
9	**L1**	DPPA	MeOH	-	9[f]
10	**L1**	DPPA	CH_2Cl_2	LiCl[g]	0

[a] Reaction conditions: The reaction was carried out in a 2-chamber system. Chamber A: CO generation (2.5 bar): **20** (2.13 mmol, 450 mg), Na_2CO_3 (3.20 mmol, 339 mg) in DMF (1 mL); Chamber B: **18a** (115 µL, 1.0 mmol), $Pd(dba)_2$ (5.8 mg, 10 µmol, 1 mol%), ligand (40 µmol, 4 mol%), acid (150 µmol, 15 mol%), solvent (1 mL), RT, 24 h. [b] Determined by quant. NMR spectroscopy using $OHCNPh_2$ as an internal standard. [c] CH_2Cl_2 (790 µL), $^nC_7H_{15}SH$ (210 µL, 177 mg, 1.3 mmol). [d] CH_2Cl_2 (790 µL), MeOH (210 µL, 166 mg, 5.2 mmol). [e] Further 47% of branched methyl ester (determined by GC-FID). [f] Further 62% of branched methyl ester (determined by NMR spectroscopy). [g] LiCl (200 µmol, 8.5 mg, 0.2 eq.).

4.2.1.2 Solvent Screening

Furthermore, a solvent screening was performed considering Kamlet–Taft parameters (Figure 4.1).[26]

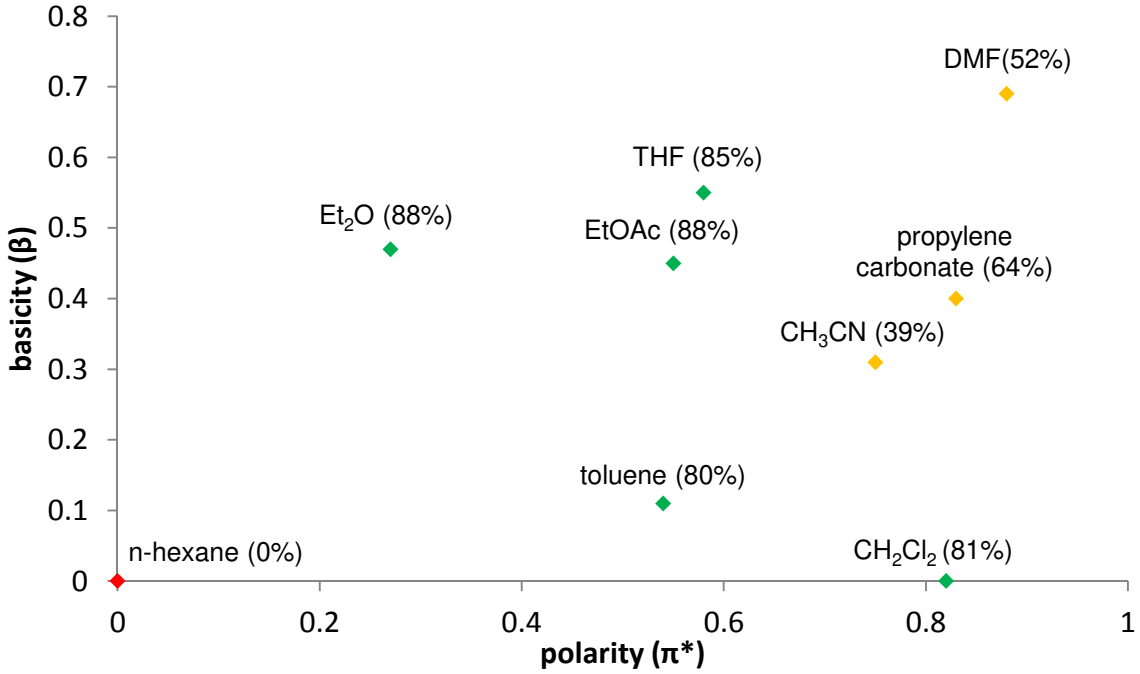


Figure 4.1. Solvent screening considering Kamlet–Taft parameters.[26]

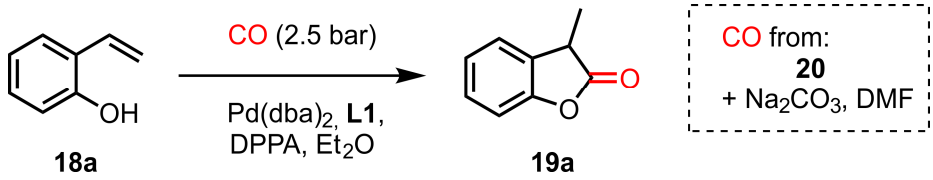
The choice of the solvent depends on its properties and other factors, such as waste management. On one side the solvent must be polar in order to dissolve the acid and other reaction components, on the other side the solvent should not be too basic, because otherwise it can coordinate to the catalyst. Other important factors influencing the search of a suitable solvent, for example the viscosity plays an important role if one reaction partner is a gas, such as CO in carbonylations.[27] Various solvents were tested and the yield could be increased to 88% by using Et_2O or EtOAc, instead of CH_2Cl_2 (81%). As expected no yield was observed by using hexane, because of its poor ability to solubilize reaction components. The lower yield in propylene carbonate can be traced back to the high viscosity and acetonitrile can coordinate to the catalyst and therefore deactivate it (acetonitrile is a better ligand because of π-backbonding). We decided to use Et_2O for further studies, since it can be easily removed after the reaction also in case of more volatile products.

4.2.2 Final Optimizations

For the final optimizations, the temperature was increased to 30 °C, which led to higher yield of 95% (Table 4.2). Almost the same result was observed by performing the reaction for 48 h at room temperature. Since most of the envisaged substrates show a high polymerization

tendency, which is significantly influenced by the temperature, 48 h and RT were chosen as the optimized reaction conditions.

Table 4.2. Final optimizations for the lactonization of **18a**.[a]



18a **19a**

Entry	Time [h]	Temp [°C]	Yield[b] [%]
1	24	RT	88
2	24	30	95
3	48	RT	94

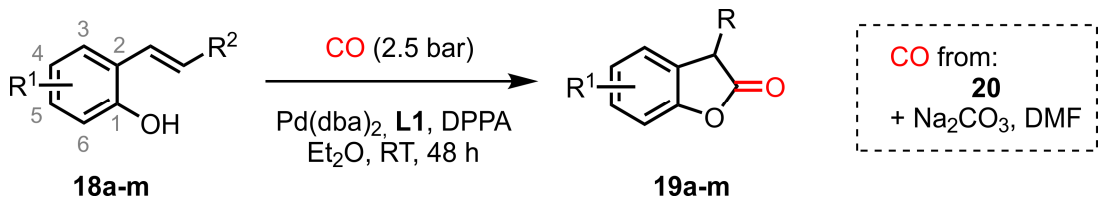
[a] Reaction conditions: The reaction was carried out in a 2-chamber system. Chamber A: CO generation (2.5 bar): **20** (2.13 mmol, 450 mg), Na_2CO_3 (3.20 mmol, 339 mg) in DMF (1 mL); Chamber B: **18a** (115 µL, 1.0 mmol), $Pd(dba)_2$ (5.8 mg, 10 µmol, 1 mol%), **L1** (21 mg, 40 µmol, 4 mol%), DPPA (38 mg, 150 µmol, 15 mol%), Et_2O (1 mL). [b] Determined by quantitative NMR spectroscopy using $OHCNPh_2$ as an internal standard. No 6-membered lactone was detected.

4.2.3 Substrate Screening

Subsequently, the substrate scope for the lactonization of 2-vinylphenol derivatives was evaluated (Table 4.3). Therefore, 1 mol% of $Pd(dba)_2$, 4 mol% of **L1**, 15 mol% of DPPA in Et_2O for 48 h at RT were applied in order to carbonylate aryl-, α- or β- substituted substrates by using 2.5 bar of *ex situ* generated CO. Methyl substituents in 3' and 5' positions are well-tolerated, whereas there was breakdown in activity for double 3',6'-substitution (Table 4.3, entries 2–4). The steric influence of the methyl groups next to both reaction sites seems to be too strong. Another challenge is the carbonylation of vinylphenols containing electron donating methoxy groups, due to polymerization issues. Under the mild reaction conditions, we were able to convert 4'-and 6'-MeO-substituted substrates in excellent yields (88, 90%, Table 4.3, entries 5, 7). However, a polymerization was observed for 5-methoxy-2-vinylphenol (**18f**) under the reaction conditions (Table 4.3, entry 6), and also already during its synthesis. To our delight, ^{t}Bu and COOMe groups were tolerated in 4' position, providing good yields of 85% and 77% respectively (Table 4.3, entries 8, 9). Then, we examined the influence of substituents on the double bond. For α-substituted substrates such as **18j**, the formation of five-membered lactone was not observed, whereas the six-membered lactone

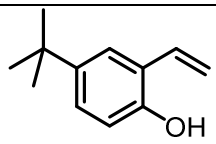
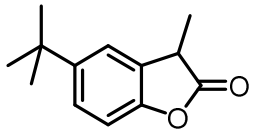
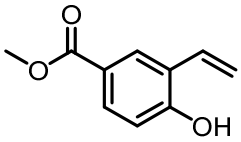
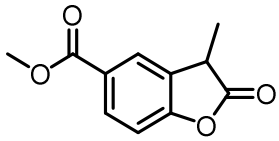
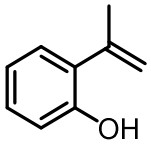
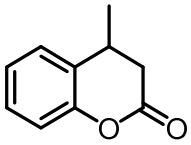
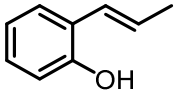
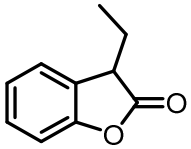
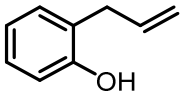
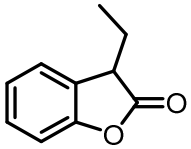
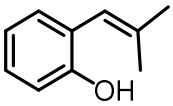
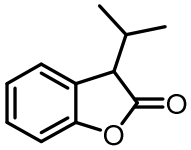
19j was generated albeit in low yield of 22% (Table 4.3, entry 10). By applying the β-substituted alkene **18k**, **19k** was observed in excellent yield of 88%, whereas **18l** led to the same product in 78% yield *via* initial isomerization (Table 4.3, entries 11, 12). As expected, carbonylation of sterically demanding **18m** generated **19m** in low yield of 11% (Table 4.3, entry 13). Double substitution in β-position seems to be a limitation of the catalytic system.

Table 4.3. Carbonylation of different aryl-, α- or β- substituted 2-vinylphenols.[a]



18a-m **19a-m**

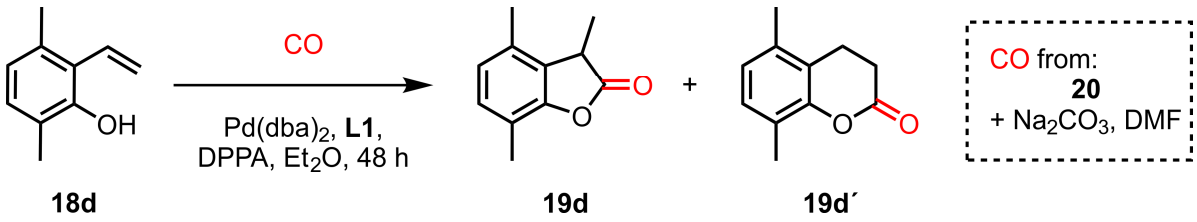
Entry	Substrate	Product	Yield[b] [%]
1	**18a**	**19a**	95
2	**18b**	**19b**	87
3	**18c**	**19c**	83
4	**18d**	**19d**	11[c]
5	**18e**	**19e**	88
6	**18f**	**19f**	0[d]
7	**18g**	**19g**	90

Entry	Substrate	Product	Yield[b] [%]
8	**18h** 	**19h** 	85
9	**18i** 	**19i** 	78
10	**18j** 	**19j** 	22
11[e]	**18k** 	**19k** 	88
12	**18l** 	**19k** 	77
13	**18m** 	**19m** 	11

[a] Reaction conditions: The reaction was carried out in a 2-chamber system. Chamber A: CO generation (2.5 bar): **20** (2.13 mmol, 450 mg), Na_2CO_3 (3.20 mmol, 339 mg) in DMF (1 mL); Chamber B: **18a–18m** (1.0 mmol), $Pd(dba)_2$ (5.8 mg, 10 µmol, 1 mol%), **L1** (21 mg, 40 µmol, 4 mol%), DPPA (38 mg, 150 µmol, 15 mol%), Et_2O (1 mL), RT, 48 h. [b] Isolated yields. [c] 31% conversion, six-membered lactone was observed but not quantified [d] Complete polymerization. [e] E/Z (77:23) mixture.

Subsequently, we turned our attention back to the challenging substrate **18d** and an additional optimization was performed (Table 4.4). It became apparent that simple optimizations, such as increasing pressure, temperature and catalyst amount enable carbonylation also for sterically demanding substrates.

Table 4.4. Optimization of the carbonylation of 3,6-dimethyl-2-vinylphenol (**18d**).[a]



18d **19d** **19d´**

Entry	p(CO) [bar]	Temp [°C]	Ratio[Pd]/lig/H^+ [mol%]	Conv.[b] [%]	Yield[c] **19d** [%]	Yield[c] **19d´** [%]
1	2.5	RT	2/8/15	65	44	23
2	5	RT	1/4/15	58	30	23
3	2.5	35	1/4/15	88	51	34
4	2.5	35	2/8/15	97	62	36

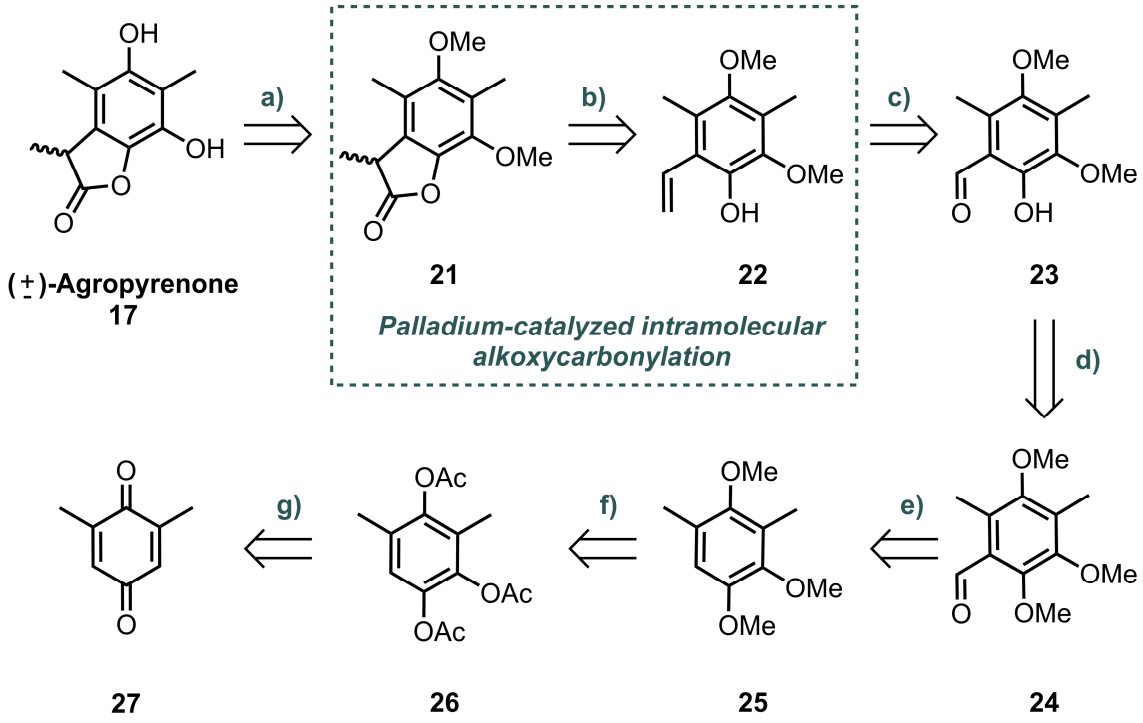
[a] Reaction conditions: The reaction was carried out in a 2-chamber system. Chamber A: CO generation: 2.5 bar → **20** (2.13 mmol, 450 mg), Na_2CO_3 (3.20 mmol, 339 mg) in DMF (1 mL); 5 bar → **20** (4.26 mmol, 900 mg), Na_2CO_3 (6.40 mmol, 678 mg) in DMF (2 mL); Chamber B: **18d** (165 µL, 1.0 mmol), $Pd(dba)_2$ (5.8 mg, 10 µmol, 1 mol%; 11.6 mg, 20 µmol, 2 mol%), **L1** (21 mg, 40 µmol, 4 mol%; 42 mg, 80 µmol, 8 mol%), DPPA (38 mg, 150 µmol, 15 mol%), Et_2O (1 mL), RT/35 °C, 48 h. [b] determined by quantitative but not calibrated NMR using $OHCNPh_2$ as an internal standard [c] determined by quantitative NMR using $OHCNPh_2$ as an internal standard.

The amount of acid was always maintained in order to prevent polymerization. Almost full conversion was observed by carrying out the reaction at 35 °C with doubled amount of palladium and ligand, generating 62% of the desired five-membered lactone **19d** and 36% of **19d'**.

4.2.4 Attempted Application in the Synthesis of Agropyrenone

4.2.4.1 Synthetic Strategy for the Synthesis of Agropyrenone

In order to proof the applicability of the previously described catalytic cyclocarbonylation of alkenylphenols, the natural compound (±)-Agropyrenone (**17**), which contains a benzofuran-2(3H)-one moiety, should be synthesized. The retrosynthetic strategy is shown in Scheme 4.5. The final step of the synthesis is a deprotection of the methoxy groups from **21**. This is followed by the key step of the synthetic strategy, the regioselective palladium catalyzed intramolecular alkoxycarbonylation of **22**, with the optimized conditions of the sterically hindered substrate **18d** (Table 4.4, entry 4). Afterwards a Nysted-methylenation is used in order to form **22** from **23**. A selective deprotection of **24** is required for the generation of **23**. Further on, the formyl group should be introduced *via* Rieche-formylation of **25,** which is synthesized from the acetylated **26** by exchanging the protection group. **26** is formed in a Thiele-Winter acetoxylation from the commercially available 2,6-dimethylbenzoquinone (**27**).

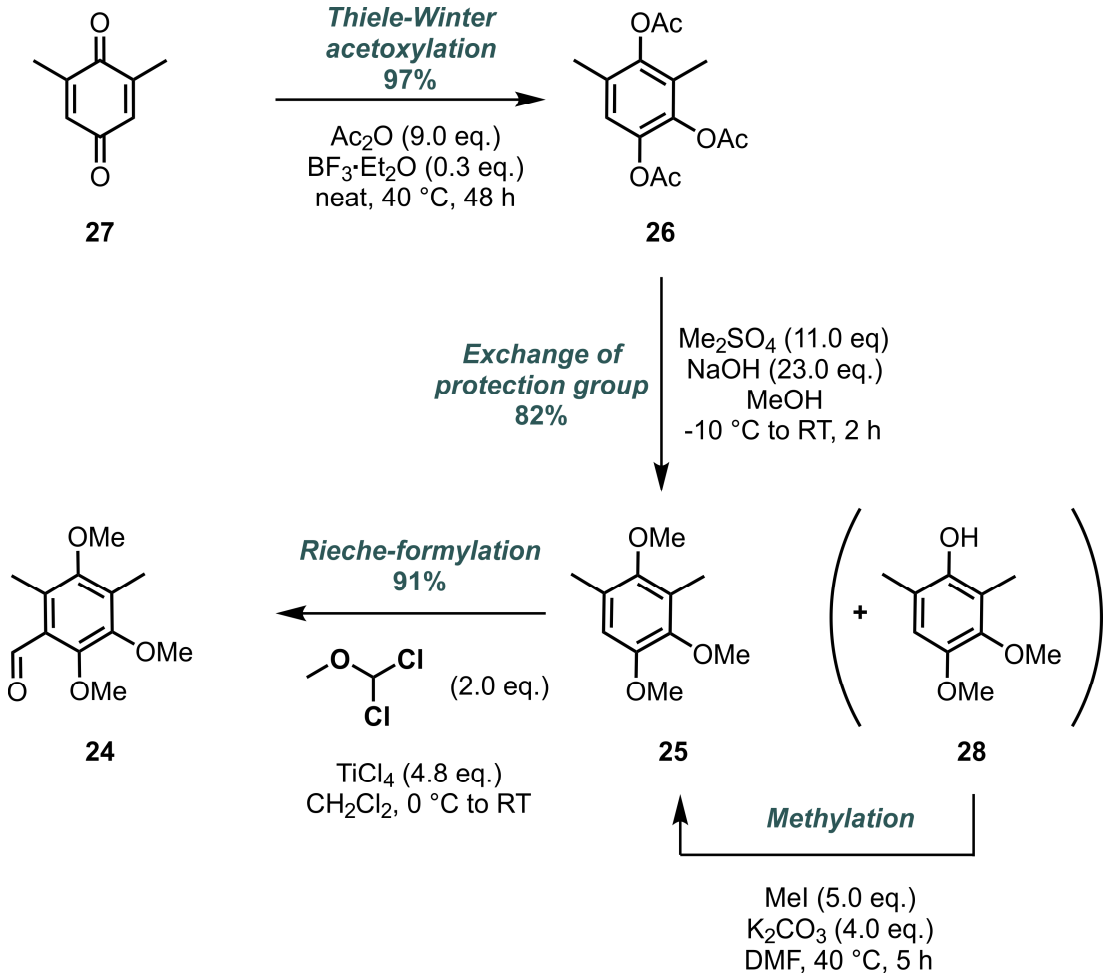


Scheme 4.5. Retrosynthesis of (±) Agropyrenone (**17**) from commercially available 2,6-dimethylbenzoquinone (**27**).

4.2.4.2 Synthesis of Agropyrenone

The first step of the synthesis, the Thiele-Winter acetoxylation of 2,6-dimethylbenzoquinone (**27**) by using acetic anhydride and $BF_3 \cdot Et_2O$ as a Lewis acid catalyst is already known from the literature.[28] The acetylated **26** was generated in almost quantitative yield of 97% by carrying out the reaction for 48 h at 40 °C under neat conditions (Scheme 4.6). The exchange of the protecting group is necessary in order to enable the following Rieche-formylation. Paul H. Gehrtz found out that the direct Rieche-formylation of **26** was not possible, since the acetoxy groups were deactivating the aromatic system.[29] The exchange of the protecting group was accomplished with dimethyl sulfate as a methylating agent and an aqueous solution of NaOH.[28c, 30] Since the desired product **25** was accompanied by the partly demethylated compound **28**, an extra methylation step by using methyl iodide under basic conditions was required. The overall yield for the exchange of the protecting group was 82%. Rieche-formylation, which proceeds under mild reaction conditions and can be applied for sterically demanding aromatic systems, was chosen to form **24** from **25**.[30-31] Therefore, dichloro(methoxy)methane and an excess of $TiCl_4$ were used to generate **24** in excellent

yield of 91%. In order to enable the subsequent cyclocarbonylation, a selective deprotection by using LiCl as a Lewis acid was carried out first (Table 4.5). At this point, a complete deprotection would certainly not have been possible, due to polymerization issues of the following vinylphenol.

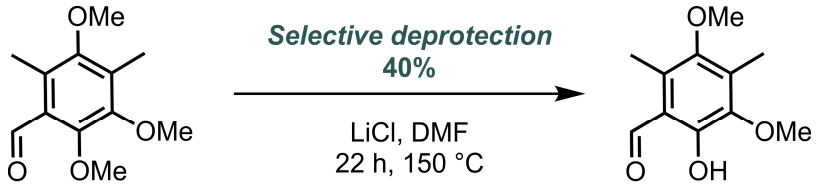


Scheme 4.6. Thiele-Winter acetoxylation, exchange of protection group and Rieche-formylation to synthesize **24** from **27**.

The amount of LiCl plays an important role in the successful generation of **23**. Between 1.2 eq. and 1.8 eq. of LiCl 27% yield of **23** was observed, whereas higher amounts led to slightly decreased yields (Table 4.5, entries 1-4). Furthermore, the yield is significantly influenced by the scope of reaction (Table 4.5, entries 5, 6). By using 9.47 mmol of **24**, the desired mono deprotected product was observed in 40% isolated yield. Additionally also $AlCl_3$ was used as a Lewis acid, but disappointingly also the double deprotected product was formed.[32] The next step is the methylenation of **23** to generate the tetra-substituted

2-vinylphenol **22**. Previous work has shown that the steric demand of **23** is incompatible with usual Wittig reaction, generating **22** to a maximum of 19%.[32]

Table 4.5. Selective deprotection of **24** using LiCl.



24 **23**

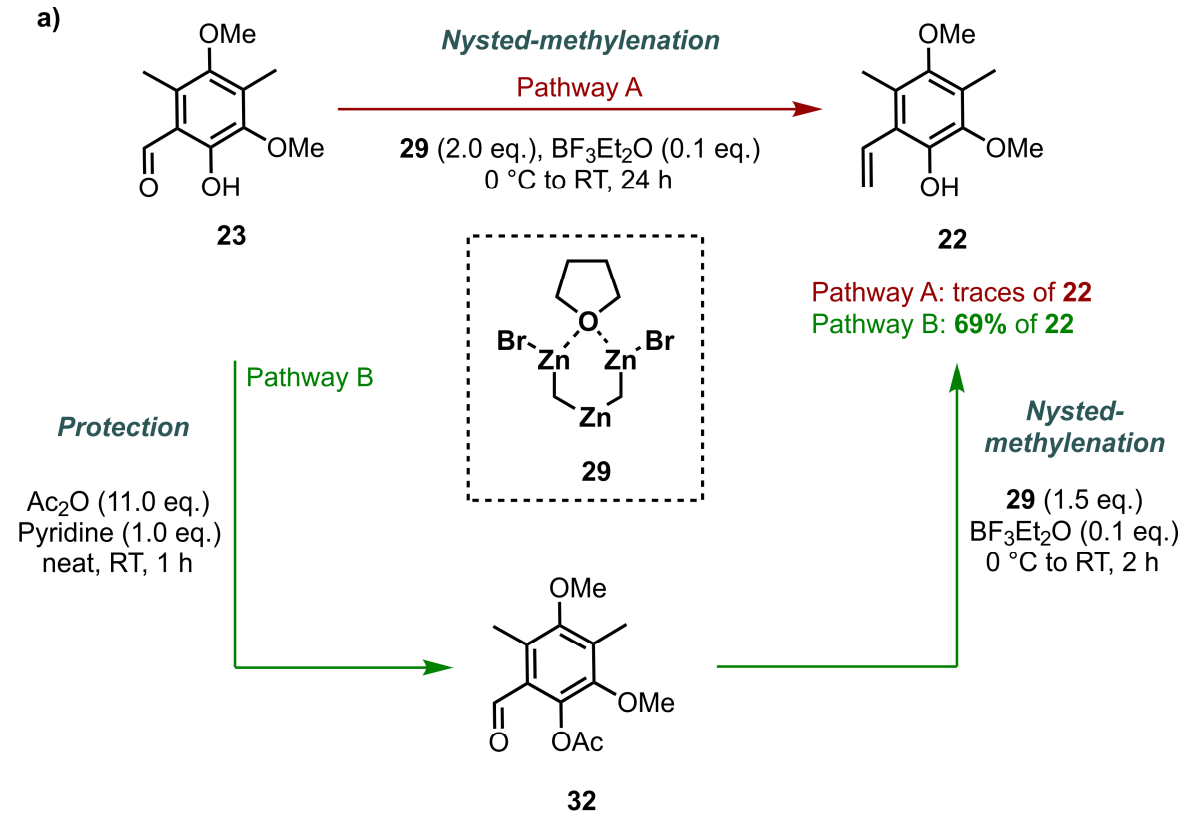
Entry	**24** [mmol]	LiCl [eq.]	Yield[a] [%]
1	0.89	3.0	20
2	0.89	2.0	24
3	0.89	1.8	27
4	0.89	1.2	27
5	3.68	1.8	40
6	9.57	1.8	40[b]

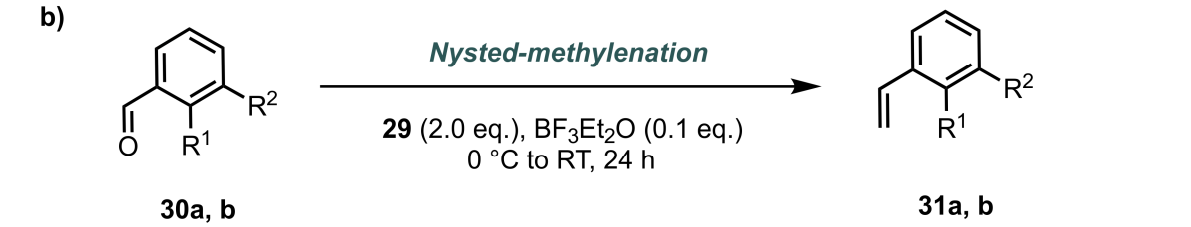
[a] Yields were determined by quant. NMR analysis using $OHCNPh_2$ as an internal standard without calibration.
[b] Isolated yield.

Therefore, another methylenation strategy has to be pursued, whereas many different synthetic approaches beside Wittig reaction are known in the literature.[33] Nysted-methylenation was chosen, since it can be effectively applied for sterically hindered substrates.[34] In the direct Nysted-methylenation of **23**, only traces of **22** were observed (Scheme 4.7a). Additional investigations revealed that free hydroxyl groups hinder successful methylenation with Nysted reagent **29** (Scheme 4.7b). No yield was observed for the application of the test substrate **30a**, whereas 32% yield of **31b** was formed by using the protected substrate **30b**. Therefore, a further protection step was required in the reaction pathway. **32** was generated from **23** with acetic anhydride and pyridine and directly applied in the following Nysted-methylenation. This reaction pathway enabled the formation of **22** in a good yield of 69% over both steps. Fortunately, the acetoxy group was already cleaved under the applied conditions, whereby no additional deprotection step was required.

Finally, the palladium catalyzed intramolecular alkoxycarbonylation of **22** was performed, with the optimized conditions of **18d** (Table 4.4, entry 4; Scheme 4.8). Disappointingly, only 14% of the desired five membered lactone **21** was obtained, which was quantified by NMR

spectroscopy using $CHONPh_2$ as an internal standard (not calibrated), because it was not possible to remove all impurities of the product fraction with the common separation methods. Additionally, also 9% of the undesired six membered lactone **33** was observed. The steric demand of **22** seems to be a limitation of the catalytic system, which led to low yield and a complete breakdown of regioselectivity.

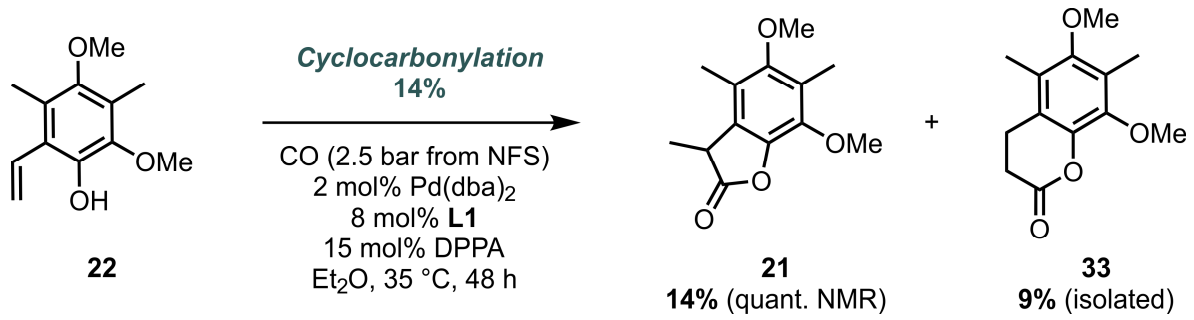




Entry	R^1	R^2	Conv.[a] [%]	Yield[a] [%]
1, **30a**	OH	OH	22	-
2, **30b**	OMe	OMe	68	32

[a] Yields were determined by quant. NMR using $OHCNPh_2$ as an internal standard without calibration.

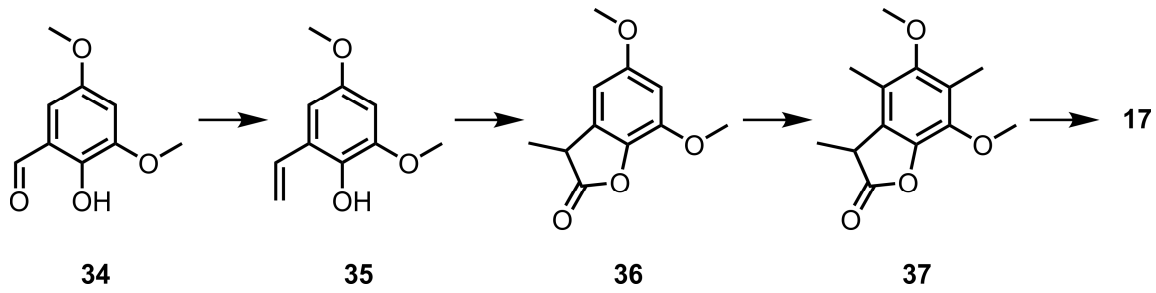
Scheme 4.7. Nysted-methylenation of **23**.



Scheme 4.8. Palladium-catalyzed cylocarbonylation of **22**.

In conclusion, the application of the cyclocarbonylation in the synthesis of the natural compound (±)-Agropyrenone did not produce a satisfactory result and therefore no further investigations were carried out. Consequently, the last deprotection step of the plant synthesis was not accomplished.

In the future, an alternative synthetic route could be applied (Scheme 4.9). The key problem of this synthetic strategy will be the first methylenation step to generate **35** from **34**, due to polymerization issues of **35**. A cyclocarbonylation of **35** should be possible, since substrates **18e** and **18g** produced high yields. After a following methylation and deprotection, **17** could be obtained.



Scheme 4.9. Alternative synthetic route for the synthesis of (±)-Agropyrenone (**17**).

4.3 Conclusion

In conclusion, we investigated a highly active catalytic system for the lactonization of alkenylphenols, which proceeds at room temperature and therefore allows to employ various substrates with polymerization tendency. This enabled a new substrate scope of vinylphenols with substituents on the aryl ring. In addition, single substitution at both positions of the double bond was tolerated. The avoidance of gaseous carbon monoxide and heating render this transformation an environmentally friendly way of generating lactones, with a good functional group tolerance also for sterically demanding and electron-donating substituents. Furthermore, the application of this transformation was tested in the synthesis of the natural compound (±)-Agropyrenone. Disappointingly, the key lactonization step of the synthetic strategy provided only 14% of the desired five membered lactone.

4.4 Experimental Part

4.4.1 General Information and Analytical Techniques

The ligand dppdtbpf (**L1**) was purchased from Sigma-Aldrich. *N*-formylsaccharin (NFS) was synthesized according to our already reported procedure, which is also described in Chapter 2.4.2, and stored under N_2.[20] All chemicals were purchased from ABCR, Acros, Sigma Aldrich, TCI or Merck and used without any further purification unless otherwise noted. Olefins were synthesized *via* Wittig-reaction from the corresponding aldehyde. All reactions were carried out under an atmosphere of dry nitrogen. All reactions with oxygen- or moisture-sensitive reagents were carried out in flame-dried glassware. Furthermore, degassed and anhydrous solvents were used where necessary; specifically dichloromethane, diethyl ether and tetrahydrofuran were obtained pre-dried from a Grubbs-type solvent purification system (MBraun, MB SPS-800). Pre-dried dichloromethane was refluxed over CaH_2, then distilled under nitrogen. Pre-dried diethyl ether and tetrahydrofuran were refluxed over Na and further dried with activated 3 Å molecular sieves. Anhydrous hexane was obtained by refluxing hexane (p.A. grade) over CaH_2, followed by distillation under N_2.
NMR and calibration data are available in the supporting information of the already published version.[1]

Chromatography

Column chromatography was carried out using Silica gel (60 Å) as a stationary phase, either using gravity flow or air overpressure flow conditions. Mobile phases are described in each experiment.
Thin layer chromatography (TLC) was performed with alumina plates coated with Merck silica gel 60 F254 (layer thickness: 0.2 mm) and analyzed under UV-light (254 nm) or stained with a potassium permanganate solution.

Nuclear magnetic resonance spectroscopy (NMR)

NMR spectra were recorded using a Bruker Avance 400 (^{1}H: 400 MHz, ^{13}C: 101 MHz) or Bruker Avance 300 (^{1}H: 300 MHz, ^{13}C: 75 MHz). All measurements were performed at ambient temperature. Chemical shifts δ are reported in parts per million [ppm] relative to the solvent signals as internal standard, (^{1}H: $CDCl_3$: δ = 7.26 ppm; toluene-d_8: δ = 2.08, 6.97, 7.01, 7.09 ppm; ^{13}C: $CDCl_3$: δ = 77.1 ppm; toluene-d_8: δ = 137.5, 128.9, 128.0, 125.1,

20.4 ppm), coupling constants *J* are given in Hertz [Hz]. ^{1}H NMR splitting patterns are designated as follows: s = singlet; d = doublet; t = triplet; q = quartet; quin = quintet; sext = sextet; hept = heptet; m = multiplet. ^{13}C signals are analyzed as follows: (+) = primary/tertiary carbon, (–) = secondary carbon, (q) = quaternary carbon. The assignment resulted from COSY, DEPT-135°, HMBC or HSQC experiments.

The internal standard method was used for quantitative NMR in order to determine yields and conversions. For the calibration, samples with different amounts of substrate and standard (*N*,*N*-diphenylformamide) were measured with NMR and the obtained data were used to plot $A_{(substrate)}/A_{(standard)}$ against $m_{(substrate)}/m_{(standard)}$. The resulting slope, after linear regression, is the response factor R, which can be used to quantify unknown samples by using equation 1. y-Intercepts are unconsidered.

$$\frac{m\,(substrate)}{m\,(standard)} \cdot R = \frac{A\,(substrate)}{A\,(standard)} \qquad (1)$$

Melting points (m.p.)

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

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.

Mass spectrometry (MS)

HR-MS and GC-MS were recorded on *Agilent* Q-TOF 6540 UHD, *Jeol* AccuTOF GCX, and *Finnigan* MAT SSQ 710 A, instruments at the Central Analytical Laboratory of the University of Regensburg.

4.4.2 General Procedure *L1* for Lactonization in a Two-chambered Pressure Vessel

A two-chambered pressure vessel (COware 20 mL, SyTracks A/S) equipped with stirring bars was charged with *N*-formylsaccharin (NFS) (450 mg, 2.13 mmol) and sodium carbonate (339 mg, 3.20 mmol) in chamber A; chamber B was charged with diphenylphosphoric acid (15 mol%, 38 mg, 150 µmol) and sealed with a septum-containing screw cap assembly (COware type). Chamber A was fitted with a vacuum adapter screwcap and the reaction vessel was evacuated for 10 min. Under N_2 atmosphere, $Pd(dba)_2$ (1 mol%, 5.8 mg, 10 µmol) and **L1** (4 mol%, 21 mg, 40 µmol) were added to chamber B, the vessel was then subjected to evacuation/N_2-backfilling (3×).

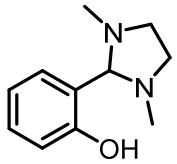
Then, anhydrous dist. Et_2O and the olefin (100 mol%, 1.00 mmol) were added to chamber B, resulting in a dark-red solution which was stirred at 500 rpm. The vacuum adapter screw cap of chamber A was exchanged to a septum containing screw cap under positive N_2 pressure (using the septum inlet of chamber B). To start the decarbonylation, anhydrous DMF (1 mL) was added to chamber A *via* septum addition. Pictures of the two-chambered pressure vessel setup are available in the supporting information of our previous work.[20a] Both reaction chambers were stirred at 500 rpm for 48 h at RT. The reaction was stopped by opening the reaction vessel. The crude product was purified by column chromatography.

The amount of olefin was adjusted to the correct purity, which was analyzed by NMR-spectroscopy.

4.4.3 Preparation of Starting Materials

4.4.3.1 Synthesis of 6-Methylsalicylaldehyde

2-(1,3-Dimethylimidazolidin-2-yl)phenol (38)



A flame-dried RBF was charged with salicylaldehyde (**39a**) (1.00 mL, 9.38 mmol, 1.0 eq.), with was dissolved in anhydrous EtOH (4 mL). After the addition of N,N´-dimethylethylenediamine (2.00 mL, 18.8 mmol, 2.0 eq.) the reaction mixture was stirred for 22 h at RT. $MgSO_4$ (ca. 2 g) was added and the suspension was stirred for 30 min. The reaction mixture was filtered and the solvent was removed under reduced pressure. The crude product was purified by

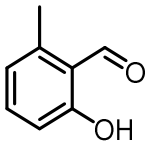
Kugelrohr distillation (20 mbar. 200 °C). **38** was obtained as a luminous yellow/green liquid (1.69 g, 8.78 mmol, 94%). The obtained analytical data are in accordance to the literature.[35]

$C_{11}H_{16}N_2O$ (192.26 g/mol); **m.p.:** Ambient temperature.

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 11.52 (s, 1H, O<u>H</u>), 7.22 (m, 1H, Ar<u>H</u>), 6.97 (dd, *J* = 7.4, 1.7 Hz, 1H, Ar<u>H</u>), 6.90 – 6.74 (m, 2H, Ar<u>H</u>), 3.51 – 3.31 (m, 3H, 2 × NC<u>H</u>$_2$, NC<u>H</u>), 2.66 – 2.50 (m, 2H, 2 × NC<u>H</u>$_2$), 2.28 (s, 6H, 2 × NC<u>H</u>$_3$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 158.5 (q), 130.6 (+), 129.9 (+), 120.5 (q), 118.3 (+), 116.9 (+), 91.9 (+), 52.3 (–), 39.1 (+).

<u>6-Methylsalicylaldehyde (39b)</u>



A flame-dried RBF was charged with imidazoline **38** (2.40 g, 12.5 mmol, 1.0 eq.), which was dissolved in anhydrous Et_2O (150 mL). After the addition of TMEDA (7.5 mL, 50.0 mmol, 4.0 eq.), *n*BuLi (2.5 M in *n*-hexane, 20 mL, 50.0 mmol, 4.0 eq.) was added dropwise within a period of 25 min. The reaction mixture was stirred at RT for 6 h and MeI (6.6 mL, 106 mmol, 8.5 eq.) was added *via* syringe over 15 min. HCl (2 M, 100 mL) was added to hydrolyze the aminal, the resulted mixture was stirred for 20 min and extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were washed with aq. sat. solution of NH_4Cl and brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by Kugelrohr distillation (20 mbar, 200 °C) led to the product **39b** as a yellow oil (1.256 g, 9.23 mmol, 74%). The obtained analytical data are in accordance to the literature.[36]

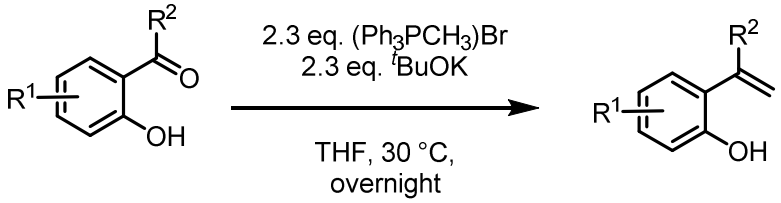
$C_8H_8O_2$ (136.15 g/mol), **m.p.:** Ambient temperature.

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 11.27 (s, 1H, ArO<u>H</u>), 9.88 (s, 1H, ArC<u>H</u>O), 7.44 – 7.35 (m, 2H, Ar<u>H</u>), 6.93 (t, *J* = 7.5 Hz, 1H, Ar<u>H</u>), 2.27 (s, 3H, ArC<u>H</u>$_3$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 196.8 (+), 160.0 (q), 137.9(+), 131.4 (+), 126.9 (q), 120.0 (q), 119.4 (+), 15.1 (+).

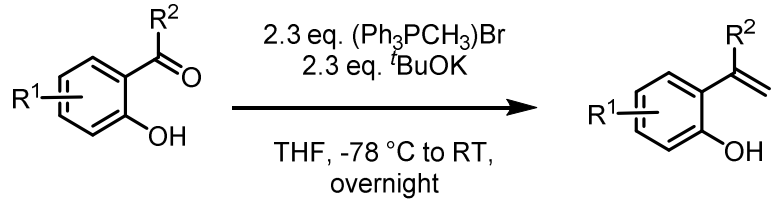
4.4.3.2 Wittig Reactions

General procedure W1 to generate styrenes from aldehydes (Wittig-reaction)



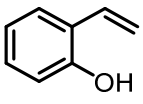
A flame-dried RBF was charged with methyltriphenylphosphonium bromide (2.3 eq.) and potassium *tert*-butoxide (2.3 eq.), which were suspended in anhydrous THF. A solution of the salicylaldehyde (1 eq.) in anhydrous THF was added to the strongly orange suspension *via* syringe. The reaction mixture was heated up to 30 °C and stirred overnight. The reaction mixture was quenched with saturated aqueous ammonium chloride solution and extracted with Et_2O (3 × 150 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography.

General procedure W2 to generate styrenes from aldehydes (Wittig-reaction)



A flame-dried RBF was charged with methyltriphenylphosphonium bromide (2.3 eq.) and potassium *tert*-butoxide (2.3 eq.), which were suspended in anhydrous THF and stirred for 2 h at RT. The resulting orange reaction mixture was cooled down to -78 °C and a solution of the salicylaldehyde (1 eq.) in anhydrous THF was added *via* syringe. The reaction mixture was allowed to warm up to RT and stirred overnight. The reaction mixture was quenched with saturated aqueous ammonium chloride solution and extracted with Et_2O (3 × 150 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography.

2-Vinylphenol (18a)



According to the general procedure *W1*, **18a** was synthesized from salicylaldehyde (3.44 g, 28.2 mmol, 1.0 eq.). Purification of the crude product by column chromatography (pentane/Et_2O: 80/20) and by Kugelrohr distillation (20 mbar, 180 °C) provided **18a** as a colorless oil, which solidified in the fridge (2.97 g, 24.7 mmol, 88%). The obtained analytical data are in accordance to the literature.[37]

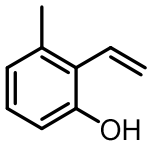
C_8H_8O (120.15 g/mol); **R_f:** 0.45 (pentane/Et_2O: 80/20); **m.p.:** Ambient temperature.

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.39 (dd, *J* = 7.7, 1.5 Hz, 1H, ArH), 7.19 – 7.11 (m, 1H, ArH), 7.01 – 6.88 (m, 2H, ArCH and ArH), 6.80 (dd, *J* = 8.1, 0.9 Hz, 1H, ArH), 5.75 (dd, *J* = 17.7, 1.3 Hz, 1H, ArCHCH$_{trans}$), 5.37 (dd, *J* = 11.2, 1.3 Hz, 1H, ArCHCH$_{cis}$), 5.03 (s, 1H, ArOH).

^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 152.8 (q), 131.5 (+), 128.9 (+), 127.4 (+), 124.8 (q), 121.0 (+), 115.91 (–), 115.86 (+).

GC-MS (EI): t_R = 4.31 min, m/z = 91 (100, $[M^{+\bullet}]$-$[CH_2]$-$[^{\bullet}OH]$), 120 (76, $[M^{+\bullet}]$).

3-Methyl-2-vinylphenol (18b)



According to the general procedure *W1*, **18b** was synthesized from 6-methylsalicylaldehyde (**39b**) (412 mg, 3.03 mmol, 1.0 eq.). Purification of the crude product by column chromatography (pentane/Et_2O: 80/20) provided **18b** as a bright yellow oil, which solidified in the fridge (248 mg, 1.85 mmol, 61%). The obtained analytical data are in accordance to the literature.[38]

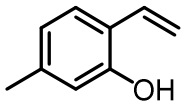
$C_9H_{10}O$ (134.18 g/mol); **R_f:** 0.24 (pentane/Et_2O: 80/20); **m.p.:** Ambient temperature.

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.26 – 7.20 (m, 1H, ArH), 7.05 (dd, *J* = 7.4, 0.7 Hz, 1H, ArH), 7.01 – 6.78 (m, 2H, ArH and ArCH), 5.72 (dd, *J* = 17.8, 1.4 Hz, 1H, ArCHCH$_{trans}$), 5.37 (dd, *J* = 11.2, 1.4 Hz, 1H, ArCHCH$_{cis}$), 2.26 (s, 3H, ArCH$_3$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 151.2 (q), 131.9 (+), 130.3 (+), 125.2 (+), 124.4 (q), 123.7 (q), 120.4 (+), 116.2 (–), 15.9 (+).

GC-MS (EI): t_R = 4.64 min, m/z = 134 (100, $[M^{+\bullet}]$), 91 (82, $[M^{+\bullet}]$-$[CH_2]$-$[^{\bullet}OH]$-$[^{\bullet}CH_3]$), 119 (21, $[M^{+\bullet}]$-$[^{\bullet}CH_3]$), 103 (13, $[M^{+\bullet}]$-$[^{\bullet}OH]$-$[^{\bullet}C_2H_3]$).

5-Methyl-2-vinylphenol (18c)



According to the general procedure *W1*, **18c** was synthesized from 4-methylsalicylaldehyde (1.00 g, 7.34 mmol, 1.0 eq.). Purification of the crude product by column chromatography (pentane/Et_2O: 80/20) provided **18c** as a colorless oil, which solidified in the fridge (793 mg, 5.91 mmol, 81%). The obtained analytical data are in accordance to the literature.[39]

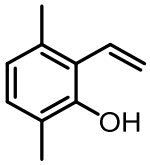
$C_9H_{10}O$ (134.18 g/mol); **R_f:** 0.44 (pentane/Et_2O: 80/20); **m.p.:** 52 - 54 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.29 – 7.26 (m, 1H, ArH), 6.90 (dd, *J* = 17.7, 11.2 Hz, 1H, ArH), 6.76 – 6.71 (m, 1H, ArCH), 6.62 (s, 1H, ArH), 5.70 (dd, *J* = 17.7, 1.4 Hz, 1H, ArCHCH_{trans}), 5.34 – 5.28 (m, 1H, ArCHCH_{cis}), 4.93 (s, 1H, OH), 2.30 (s, 3H, $ArCH_3$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 152.6 (q), 139.2 (q), 131.4 (+), 127.20 (+), 121.9 (q), 121.8 (+), 116. 5 (+), 114.9 (–), 21.2 (+).

GC-MS (EI): t_R = 5.03 min, m/z = 134 (100, $[M^{+\bullet}]$), 91 (78, $[M^{+\bullet}]$-$[CH_2]$-$[^{\bullet}OH]$-$[^{\bullet}CH_3]$), 119 (20, $[M^{+\bullet}]$-$[^{\bullet}CH_3]$), 103 (11, $[M^{+\bullet}]$-$[^{\bullet}OH]$-$[^{\bullet}C_2H_3]$).

3,6-Dimethyl-2-vinylphenol (18d)



According to the general procedure *W1*, **18d** was synthesized from 3,6-dimethylsalicylaldehyde (500 mg, 3.33 mmol, 1.0 eq.). Purification of the crude product by column chromatography (pentane/Et_2O: 80/20) provided **18d** as a bright yellow oil (372 mg, 2.51 mmol, 75%).

$C_{10}H_{12}O$ (148.21 g/mol), **R_f:** 0.53 (pentane/Et_2O: 80/20); **m.p.:** Ambient temperature.

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.00 – 6.90 (m, 1H, ArH), 6.78 – 6.61 (m, 2H, ArH, ArCH), 5.75 – 5.65 (m, 2H, ArCHCH_{trans}, OH), 5.56 (dd, *J* = 18.2, 1.8 Hz, 1H, ArCHCH_{cis}), 2.24 (s, 3H, $ArCH_3$), 2.22 (s, 3H, $ArCH_3$).

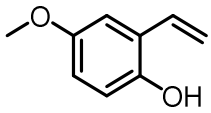
^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 150.7 (q), 134.4 (q), 133.0 (+), 129.6 (+), 123.4 (q), 121.6 (q), 121.2 (+), 120.4 (–), 20.0 (+), 16.1 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3019 (w, br), 2922 (w, br), 2863 (w, br), 1625 (w, sh), 1461 (m, br), 1424 (m, br), 1260 (m, sh), 1211 (s, sh), 1044 (m, sh), 936 (m, sh), 805 (m, sh), 753 (s, sh).

GC-MS (EI): t_R = 5.05 min, m/z = 148 (100, $[M^{+\bullet}]$), 105 (64, $[M^{+\bullet}]$-$[^{\bullet}CH_3]$-$[^{\bullet}CO]$), 133 (61, $[M^{+\bullet}]$-$[^{\bullet}CH_3]$), 119 (13, $[M^{+\bullet}]$-$[^{\bullet}CH_3]$-$[^{\bullet}C_2H_3]$).

HR-MS (EI): m/z = $[M^{+\bullet}]$ calc. for $C_{10}H_{12}O$ 148.0883, found 148.0881.

4-Methoxy-2-vinylphenol (18e)



According to the general procedure *W1*, **18e** was synthesized from 2-hydroxy-5-methoxybenzaldehyde (600 µL, 4.81 mmol, 1.0 eq.). Purification of the crude product by column chromatography (pentane/Et_2O: 80/20) provided **18e** as a yellow oil (602 mg, 4.01 mmol, 83%). The obtained analytical data are in accordance to the literature.[38]

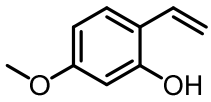
$C_9H_{10}O_2$ (150.18 g/mol); **R_f:** 0.26 (pentane/Et_2O: 80/20); **m.p.:** Ambient temperature.

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 6.99 – 6.85 (m, 2H, ArH), 6.76 – 6.68 (m, 2H, ArH, ArCH), 5.73 (dd, *J* = 17.7, 1.3 Hz, 1H, ArCHCH_{trans}), 5.36 (dd, *J* = 11.2, 1.3 Hz, 1H, ArCHCH_{cis}), 4.76 (s, 1H, OH), 3.78 (s, 3H, ArOCH_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 153.8 (q), 147.0 (q), 131.4 (+), 125.5 (q), 116.8 (+), 115.9 (–), 114.7 (+), 111.9 (+), 55.8 (+).

GC-MS (EI): t_R = 5.99 min, m/z = 150 (100, $[M^{+\bullet}]$), 135 (89, $[M^{+\bullet}]$-$[CH_3^{\bullet}]$.

5-Methoxy-2-vinylphenol (18f)



According to the general procedure *W2*, **18f** was synthesized from 4-methoxy-salicylaldehyde (500 mg, 3.29 mmol, 1.0 eq.). Purification of the crude product by column chromatography (pentane/Et_2O: 80/20) provided **18f** as a bright yellow oil, which solidified in the fridge (390 mg, 2.60 mmol, 79%). The obtained analytical data are in accordance to the literature.[38, 40] The product decomposes quickly in $CDCl_3$.

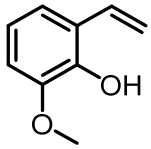
$C_9H_{10}O_2$ (150.18 g/mol); **R_f:** 0.16 (pentane/Et_2O: 80/20); **m.p.:** Ambient temperature.

^{1}H-NMR (300 MHz, toluene-d_8) δ_H/ppm: 7.18 (d, *J* = 8.6 Hz, 1H, ArH), 6.96 – 6.84 (m, 1H, ArCH), 6.31 (dd, *J* = 8.6, 2.5 Hz, 1H, ArH), 5.82 (d, *J* = 2.5 Hz, 1H, ArH), 5.56 (dd, *J* = 17.7, 1.6 Hz, 1H, ArCHCH$_{trans}$), 5.09 (dd, *J* = 11.2, 1.6 Hz, 1H, ArCHCH$_{cis}$), 4.24 (s, 1H, OH), 3.28 (s, 3H, ArOCH$_3$).

GC-MS (EI): t_R = 6.02 min, m/z = 150 (100, [$M^{+\bullet}$]), 135 (13, [$M^{+\bullet}$]-[$CH_3^\bullet$]).

Analytical data not fully investigated, due to quick polymerization.

6-Methoxy-2-vinylphenol (18g)



According to the general procedure *W1*, **18g** was synthesized from 3-methoxysalicylaldehyde (999 mg, 6.57 mmol, 1.0 eq.). Purification of the crude product by column chromatography (pentane/Et_2O: 90/10) provided **18g** as a colorless oil (844 mg, 5.62 mmol, 86%). The obtained analytical data are in accordance to the literature.[38]

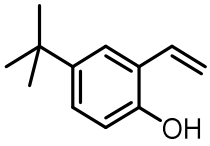
$C_9H_{10}O_2$ (150.18 g/mol); **R_f:** 0.19 (pentane/Et_2O: 90/10); **m.p.:** Ambient temperature.

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.13 – 6.94 (m, 2H, ArH), 6.88 – 6.72 (m, 2H, ArH and ArCH), 5.89 (s, 1H, OH), 5.81 (dd, *J* = 17.8, 1.5 Hz, 1H, ArCHCH$_{trans}$), 5.35 – 5.25 (dd, *J* = 11.2, 1.5 Hz, 1H, ArCHCH$_{cis}$), 3.90 (s, 3H, ArOCH$_3$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 146.7 (q), 143.2 (q), 131.1 (+), 123.9 (q), 119.4 (+), 118.8 (+), 114.8 (–), 109.6 (+), 56.1 (+).

GC-MS (EI): t_R = 5.57 min, m/z = 150 (100, [$M^{+\bullet}$]), 107 (79, [$M^{+\bullet}$]-[$^\bullet$OMe]-[$^\bullet C_2H_3$]), 77 (51, [$M^{+\bullet}$]-[$^\bullet$OMe]-[$^\bullet$OH]-[$^\bullet C_2H_3$]), 135 (32, [$M^{+\bullet}$]-[$^\bullet$Me]).

4-(*Tert*-butyl)-2-vinylphenol (18h)



According to the general procedure *W1*, **18h** was synthesized from 5-(*tert*-butyl)-2-hydroxybenzaldehyde (600 µL, 3.50 mmol, 1.0 eq.). Purification of the crude product by column chromatography (pentane/Et_2O: 80/20) provided **18h** as an orange oil (540 mg, 3.07 mmol, 88%). The obtained analytical data are in accordance to the literature.[37]

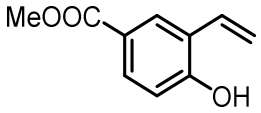
$C_{12}H_{16}O$ (176.26 g/mol); **R_f:** 0.29 (pentane/Et_2O: 80/20); **m.p.:** Ambient temperature.

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.38 (d, *J* = 2.5 Hz, 1H, ArH), 7.18 (dd, *J* = 8.4, 2.5 Hz, 1H, ArH), 6.93 (dd, *J* = 17.7, 11.2 Hz, 1H, ArCH), 6.74 (d, *J* = 8.4 Hz, 1H, ArH), 5.74 (dd, *J* = 17.7, 1.4 Hz, 1H, ArCHCH_{trans}), 5.36 (dd, *J* = 11.2, 1.4 Hz, 1H, ArCHCH_{cis}), 4.89 (s, 1H, OH), 1.31 (s, 9H, C(CH_3)$_3$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 151.6 (q), 143.6 (q), 132.2 (+), 126.0 (+), 124.2 (+), 123.9 (q), 115.7 (–), 115.5 (+), 34.1 (q), 3 × 31.5 (+, +, +).

GC-MS (EI): t_R = 6.35 min, m/z = 176 (25, [$M^{+\bullet}$]), 161 (100, [$M^{+\bullet}$]-[$CH_3^\bullet$]).

Methyl 4-hydroxy-3-vinylbenzoate (18i)



According to the general procedure *W1*, **18i** was synthesized from methyl 3-formyl-4-hydroxybenzoate (500 mg, 2.78 mmol, 1.0 eq.). Purification of the crude product by column chromatography (pentane/Et_2O: 80/20) provided **18i** as a colorless solid (389 mg, 2.18 mmol, 79%). The obtained analytical data are in accordance to the literature.[37]

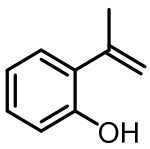
$C_{10}H_{10}O_3$ (178.19 g/mol); **R_f:** 0.10 (pentane/Et_2O: 80/20); **m.p.:** 106 -108 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 8.11 (d, *J* = 2.2 Hz, 1H, ArH), 7.84 (dd, *J* = 8.5, 2.2 Hz, 1H, ArH), 6.93 (dd, *J* = 17.7, 11.2 Hz, 1H, ArCH), 6.85 (d, *J* = 8.5 Hz, 1H, ArH), 5.93 (s, 1H, OH), 5.83 (dd, *J* = 17.7, 1.2 Hz, 1H, ArCHCH_{trans}), 5.42 (dd, *J* = 11.2, 1.2 Hz, 1H, ArCHCH_{cis}), 3.90 (s, 3H, ArCOOCH_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 167.1 (q), 157.0 (q), 130.6 (+), 130.6 (+), 129.4 (+), 124.8 (q), 122.7 (q), 117.0 (–), 115.7 (+), 52.1 (+).

GC-MS (EI): t_R = 7.33 min, m/z = 178 (44, [$M^{+\bullet}$]), 147 (100, [$M^{+\bullet}$]-[$OCH_3^\bullet$]).

2-(Prop-1-en-2-yl)phenol (18j)



According to the general procedure *W1*, **18j** was synthesized from 1-(2-hydroxyphenyl)ethan-1-one (1.00 mL, 8.32 mmol, 1.0 eq.). Purification of the crude product

by column chromatography (pentane/Et_2O: 80/20) provided **18j** as a bright yellow oil (951 mg, 7.08 mmol, 85%). The obtained analytical data are in accordance to the literature.[37]

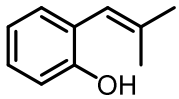
$C_9H_{10}O$ (134.18 g/mol); **R_f:** 0.40 (pentane/Et_2O: 80/20); **m.p.:** Ambient temperature.

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.22 – 7.10 (m, 2H, ArH), 6.98 – 6.85 (m, 2H, ArH), 5.74 (s, 1H, OH), 5.44 – 5.39 (m, 1H, ArCCH_2), 5.18 – 5.13 (m, 1H, ArCCH_2), 2.14 – 2.10 (m, 3H, ArCCH_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 151.8 (q), 142.1 (q), 128.8 (q), 128.6 (+), 127.8 (+), 120.2 (+), 115.8 (–), 115.5 (+), 24.3 (+).

GC-MS (EI): t_R = 4.08 min, m/z = 91 (100, $[M^{+\bullet}]$-$[^{\bullet}CH_3]$-[$^{\bullet}$CO]), 134 (93, $[M^{+\bullet}]$), 119 (54, $[M^{+\bullet}]$-$[^{\bullet}CH_3]$).

2-(2-Methylprop-1-en-1-yl)phenol (18m)



According to the general procedure *W1*, **18m** was synthesized from salicylaldehyde (500 mL, 4.79 mmol, 1 eq.) by using isopropyltriphenylphosphonium iodide (4.76 g, 11.0 mmol, 2.3 eq.) and potassium *tert*-butoxide (1.24 g, 11.0 mmol, 2.3 eq.) in order to generate the ylide. Purification of the crude product by column chromatography (pentane/Et_2O: 80/20) provided **18m** as a bright yellow oil (614 mg, 4.14 mmol, 87%). The obtained analytical data are in accordance to the literature.[41]

$C_{10}H_{12}O$ (148.21 g/mol), **R_f:** 0.17 (pentane/Et_2O: 80/20); **m.p.:** Ambient temperature.

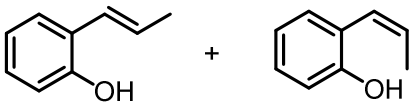
^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.21 – 7.11 (m, 1H, ArH), 7.11 – 7.01 (m, 1H, ArH), 6.96 – 6.84 (m, 2H, ArH), 6.13 (s, 1H, ArCH), 5.07 (s, 1H, OH), 1.97 –1.91 (m, 3H, ArCHCCH_3), 1.71 – 1.67 (m, 3H, ArCHCCH_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 152.8 (q), 140.6 (q), 129.9 (+), 128.2 (+), 124.7 (q), 120.2 (+), 118.7 (+), 114.8 (+), 25.9 (+), 19.5 (+).

GC-MS (EI): t_R = 4.90 min, m/z = 148 (91, $[M^{+\bullet}]$), 133 (100, $[M^{+\bullet}]$-$[CH_3^{\bullet}]$).

4.4.3.3 Synthesis of β-Methyl-vinylphenol

(E)-2-(Prop-1-en-1-yl)phenol and (Z)-2-(Prop-1-en-1-yl)phenol (18k)



E-isomer Z-isomer

A flame-dried RBF was charged with potassium *tert*-butoxide (2.08 g, 18.4 mmol, 4.0 eq.), which was dissolved in anhydrous THF. Allylphenol (600 µL, 4.60 mmol, 1.0 eq.) was added *via* syringe and the solution was stirred at ambient temperature overnight. The reaction mixture was quenched with saturated aqueous ammonium chloride solution and extracted with Et_2O (3×). The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by Kugelrohr distillation (20 mbar, 180 °C). **18k** was obtained as a bright yellow oil (597 mg, 4.45 mmol, 97% (E/Z = 77/23)). The obtained analytical data are in accordance to the literature.[42]

$C_9H_{10}O$ (134.18 g/mol); **m.p.:** Ambient temperature.

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm:

E-isomer: 7.31 (dd, *J* = 7.6, 1.7 Hz, 1H, ArH), 7.15 – 7.06 (m, 1H, ArH), 6.97 – 6.85 (m, 1H, ArH), 6.79 (dd, *J* = 8.0, 1.2 Hz, 1H, ArH), 6.65 – 6.54 (m, 1H, ArCH), 6.21 (dq, *J* = 15.9, 6.6 Hz, 1H, ArCHCH), 5.18 – 4.90 (m, 1H, OH), 1.92 (dd, *J* = 6.6, 1.7 Hz, 3H, CH_3).

Z-isomer: 7.23 – 7.15 (m, 1H, ArH), 7.15 – 7.06 (m, 1H, ArH), 6.97 – 6.85 (m, 2H, ArH), 6.46 – 6.35 (m, 1H, ArCH), 6.03 (dq, *J* = 11.2, 6.9 Hz, 1H, ArCHCH), 5.18 – 4.90 (m, 1H, OH), 1.73 (dd, *J* = 6.9, 1.8 Hz, 3H, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm:

E-isomer: 152.3 (q), 128.4 (+), 128.0 (+), 127.4 (+), 125.3 (+), 125.1 (q), 120.9 (+), 115.6 (+), 19.0 (+).

Z-isomer: 152.3 (q), 131.3 (+), 129.7 (+), 128.6 (+), 125.1 (q), 124.0 (+), 120.3 (+), 115.1 (+), 14.6 (+).

GC-MS (EI):

E-isomer: t_R = 5.14 min, m/z = 134 (100, $[M^{+\bullet}]$), 119 (37, $[M^{+\bullet}]$-$[CH_3^{\bullet}]$);

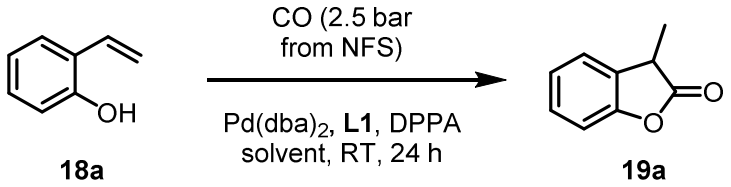
Z-isomer: t_R = 4.33 min, m/z = 134 (100, $[M^{+\bullet}]$), 119 (37, $[M^{+\bullet}]$-$[CH_3^{\bullet}]$).

4.4.4 Solvent and Substrate Screening

Solvent Screening

General procedure *L1* was applied using 2-vinylphenol (**18a**) as a test substrate and the reaction was carried out at RT for 24 h. The Kamlet-Taft parameters as well as the yields of the corresponding solvents are summarized in Table 4.6.

Table 4.6. Solvent screening for the lactonization of 2-vinylphenol (**18a**).[a]



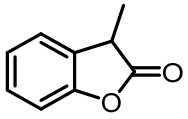
18a **19a**

Entry	Solvent	Kamlet-Taft[26]			Yield[b] [%]
		Polarity/ polarizability (π*)	Basicity (β)	Proticity (α)	
1	*n*-hexane	0	0	0	0
2	toluene	0.54	0.11	0	80
3	Et_2O	0.27	0.47	0	88
4	CH_2Cl_2	0.82	0	0.30	81
5	THF	0.58	0.55	0	85
6	CH_3CN	0.75	0.31	0.19	39
7	Propylene carbonate	0.83	0.40	0	64
8	DMF	0.88	0.69	0	52
9	EtOAc	0.55	0.45	0	88

[a] reaction conditions: The reaction was carried out in a 2-chamber system. Chamber A: CO generation (max. 2.5 bar): **20** (2.13 mmol, 450 mg), Na_2CO_3 (3.20 mmol, 339 mg) in DMF (1 mL); Chamber B: **18a** (115 µL, 1.0 mmol), $Pd(dba)_2$ (5.8 mg, 10 µmol), **L1** (21 mg, 40 µmol), DPPA (38 mg, 150 µmol), solvent, RT, 24 h. [b] determined by quantitative NMR using $OHCNPh_2$ as an internal standard.

Substrate Screening

3-Methylbenzofuran-2(3H)-one (19a)



According to the general procedure *L1*, **19a** was synthesized from **18a** (115 µL, 1.00 mmol). Purification of the crude product by column chromatography (CyH/EtOAc: 95/5) provided **19a** as a bright yellow oil (140.6 mg, 959 µmol, 95%). The obtained analytical data are in accordance to the literature.[5a]

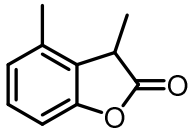
$C_9H_8O_2$ (148.16 g/mol), **R_f:** 0.18 (CyH/EtOAc: 95/5); **m.p.:** Ambient temperature.

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.35 – 7.23 (m, 2H, ArH), 7.19 – 7.06 (m, 2H, ArH), 3.74 (q, *J* = 7.6 Hz, 1H, ArCH), 1.58 (d, *J* = 7.6 Hz, 3H, ArCHCH_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 178.0 (q), 153.5 (q), 128.8 (q), 128.8 (+) 124.2 (+), 123.9 (+), 110.8 (+), 38.4 (+), 15.9 (+).

GC-MS (EI): t_R = 5.06 min, m/z = 148 (95, [$M^{+\bullet}$]), 120 (100, [$M^{+\bullet}$]-[CO]).

3,4-Dimethylbenzofuran-2(3H)-one (19b)



According to the general procedure *L1*, **19b** was synthesized from **18b** (156 mg, 87% purity, 1.01 mmol). Purification of the crude product by column chromatography (CyH/EtOAc: 95/5) provided **19b** as a bright yellow oil (143 mg, 876 µmol, 87%).

$C_{10}H_{10}O_2$ (162.19 g/mol), **R_f:** 0.33 (CyH/EtOAc: 95/5); **m.p.:** Ambient temperature.

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.19 – 6.99 (m, 3H, ArH), 3.73 (q, *J* = 7.6 Hz, ArCH), 2.32 (s, 3H, ArCH_3), 1.57 (d, *J* = 7.6 Hz, 3H, ArCHCH_3).

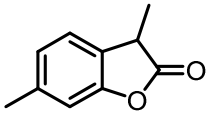
^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 178.2 (q), 152.0 (q), 130.2 (+), 128.3 (q), 124.0 (+), 121.1 (+), 121.0 (q), 38.8 (+), 16.0 (+), 15.1 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2982 (w, sh), 2937 (w, sh), 1797 (s, sh), 1454 (m, br), 1223 (m, br), 1118 (s, sh), 1010 (s, sh), 880 (s, sh), 743 (s, sh).

GC-MS (EI): t_R = 5.71 min, m/z = 162 (75, [$M^{+\bullet}$]), 134 (100, [$M^{+\bullet}$]-[CO]).

HR-MS (EI): m/z = [$M^{+\bullet}$] calc. for $C_{10}H_{10}O_2$ 162.0675, found 162.0678.

3,6-Dimethylbenzofuran-2(3H)-one (19c)



According to the general procedure *L1*, **19c** was synthesized from **18c** (161 mg, 84% purity, 1.01 mmol). Purification of the crude product by column chromatography (CyH/EtOAc: 95/5) provided **19c** as a colorless oil (135 mg, 832 µmol, 83%). The obtained analytical data are in accordance to the literature.[5e]

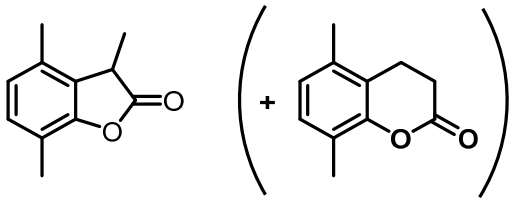
$C_{10}H_{10}O_2$ (162.19 g/mol), **R_f:** 0.29 (CyH/EtOAc: 95/5); **m.p.:** Ambient temperature.

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.16 – 7.09 (m, 1H, ArH), 7.01 – 6.89 (m, 2H, ArH), 3.69 (q, *J* = 7.6 Hz, 1H, ArCH), 2.38 (s, 3H, ArCH_3), 1.55 (d, *J* = 7.6 Hz, 3H, ArCHCH_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 178.4 (q), 153.6 (q), 139.2 (q), 125.7 (q), 124.8 (+), 123.5 (+), 111.4 (+), 38.3 (+), 21.7 (+), 16.1 (+).

GC-MS (EI): t_R = 5.82 min, m/z = 162 (87, [$M^{+\bullet}$]), 134 (100, [$M^{+\bullet}$]-[CO]).

3,4,7-Trimethylbenzofuran-2(3H)-one (19d) (and 5,8-dimethylchroman-2-one (19d´))



According to the general procedure *L1*, **19d/19d´** were synthesized from **18d** (161 mg, 92% purity, 1.0 mmol). Purification of the crude product by column chromatography (CyH/EtOAc: 95/5) provided **19d** as a colorless oil (18.6 mg, 106 µmol, 11%). **19d´** was observed as a side product but was not quantified. See Table 4.4 for optimization of the carbonylation of **18d**.

Data of **19d**:

$C_{11}H_{12}O_2$ (176.22 g/mol), **R_f:** 0.29 (CyH/EtOAc: 95/5); **m.p.:** Ambient temperature.

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.01 (d, *J* = 7.8 Hz, 1H, ArH), 6.84 (d, *J* = 7.8 Hz, 1H, ArH), 3.71 (q, *J* = 7.6 Hz, 1H, ArCH), 2.30 (s, 3H, ArCH_3), 2.28 (s, 3H, ArCH_3), 1.60 (d, *J* = 7.6 Hz, 3H, ArCHCH_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 178.5 (q), 151.9 (q), 131.9 (q), 130.0 (+), 126.5 (q), 125.4 (+), 118.2 (q), 38.7 (+), 18.1 (+), 15.5 (+), 14.8 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2930 (w, br), 1797 (s, sh), 1453 (m, sh), 1252 (w, br), 1133 (s, sh), 988 (s, sh), 805 (s, sh), 749 (s, sh).

GC-MS (EI): t_R = 5.95 min, m/z = 176 (82, $[M^{+\bullet}]$), 148 (100, $[M^{+\bullet}]$-[CO]), 133 (61, $[M^{+\bullet}]$-[CO]-$[CH_3^{\bullet}]$).

HR-MS (EI): m/z = $[M^{+\bullet}]$ calc. for $C_{11}H_{12}O_2$ 176.0832, found 176.0831.

Data of **19d´:**

$C_{11}H_{12}O_2$ (176.22 g/mol), **R_f:** 0.17 (CyH/EtOAc: 95/5); **m.p.:** Ambient temperature.

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.00 (d, *J* = 7.5 Hz, 1H, ArH), 6.87 (d, *J* = 7.5 Hz, 1H, ArH), 2.96 – 2.87 (m, 2H, $ArCH_2$), 2.82 – 2.71 (m, 2H, $ArCH_2CH_2$), 2.27 (s, 6H, 2 × $ArCH_3$).

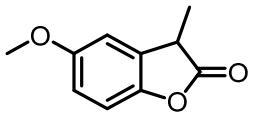
^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 168.9 (q), 150.4 (q), 133.4 (q), 129.2 (+), 125.4 (+), 123.8 (q), 121.0 (q), 28.9 (–), 20.9 (–), 19.0 (+), 15.6 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2922 (w, br), 1759 (s, sh), 1495 (m, sh), 1481 (m, br), 1271 (m, sh), 1245 (s, sh), 1170 (s, sh), 1141 (s, br), 1055 (m, br), 805 (s, sh), 701 (m, sh).

GC-MS (EI): t_R = 6.82 min, m/z = 176 (100, $[M^{+\bullet}]$), 148 (50, $[M^{+\bullet}]$-[CO]), 134 (83, $[M^{+\bullet}]$-$[CH_2CO]$).

HR-MS (EI): m/z = $[M^{+\bullet}]$ calc. for $C_{11}H_{12}O_2$ 176.0832, found 176.0831.

5-Methoxy-3-methylbenzofuran-2(3H)-one (19e)



According to the general procedure *L1*, **19e** was synthesized from **18e** (155 mg, 96% purity, 988 µmol). Purification of the crude product by column chromatography (CyH/EtOAc: 95/5) provided **19e** as a white solid (154 mg, 866 µmol, 88%).

$C_{10}H_{10}O_3$ (178.19 g/mol), **R_f:** 0.14 (CyH/EtOAc: 95/5); **m.p.:** 66 – 68 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.07 – 6.96 (m, 1H, ArH), 6.86 – 6.75 (m, 2H, ArH), 3.80 (s, 3H, $ArOCH_3$), 3.71 (q, *J* = 7.6 Hz, 1H, ArCH), 1.57 (d, *J* = 7.6 Hz, 3H, $ArCHCH_3$).

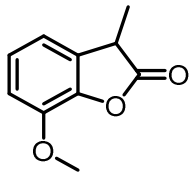
^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 178.3 (q), 156.6 (q), 147.3 (q), 129.8 (q), 113.5 (+), 111.1 (+), 110.1 (+), 55.9 (+), 39.1 (+), 15.9 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2997 (m, br), 2945 (m, br), 2840 (m, sh), 1789 (s, sh), 1610 (m, sh), 1484 (s, br), 1223 (s, sh), 1156 (s, sh), 1126 (s, sh), 1021 (s, sh), 992 (s, sh), 872 (s, sh).

GC-MS (EI): t_R = 6.77 min, m/z = 178 (61, [$M^{+\bullet}$]), 150 (100, [$M^{+\bullet}$]-[CO]), 135 (94, [$M^{+\bullet}$]-[CO]-[$CH_3^{\bullet}$]).

HR-MS (EI): m/z = [$M^{+\bullet}$] calc. for $C_{10}H_{10}O_3$ 178.0625, found 178.0620.

7-Methoxy-3-methylbenzofuran-2(3H)-one (19g)



According to the general procedure *L1*, **19g** was synthesized from **18g** (160 mg, 95% purity, 1.01 mmol). Purification of the crude product by column chromatography (CyH/EtOAc: 95/5) provided **19g** as a bright yellow oil (163 mg, 915 µmol, 90%).

$C_{10}H_{10}O_3$ (178.19 g/mol), **R_f:** 0.28 (CyH/EtOAc: 95/5); **m.p.:** Ambient temperature.

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.09 – 7.01 (m, 1H, ArH), 6.88 – 6.77 (m, 2H, ArH), 3.88 (s, 3H, ArOCH_3), 3.69 (q, *J* = 7.7 Hz, 1H, ArCH), 1.52 (d, *J* = 7.7 Hz, 3H, ArCHCH_3).

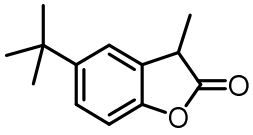
^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 177.5 (q), 144.0 (q), 141.8 (q), 130.0 (q), 124.8 (+), 115.7 (+), 112.7 (+), 56.4 (+), 38.7 (+), 16.0 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2981 (w, sh), 2941 (w, sh), 1804 (w, sh), 1629 (m, sh), 1498 (m, sh), 1461 (m, sh), 1275 (m, sh), 1126 (s, sh), 999 (s, sh), 880 (m, sh), 753 (m, sh).

GC-MS (EI): t_R = 6.68 min, m/z = 178 (81, [$M^{+\bullet}$]), 150 (100, [$M^{+\bullet}$]-[CO]).

HR-MS (EI): m/z = [$M^{+\bullet}$] calc. for $C_{10}H_{10}O_3$ 178.0625, found 178.0629.

5-(Tert-butyl)-3-methylbenzofuran-2(3H)-one (19h)



According to the general procedure *L1*, **19h** was synthesized from **18h** (173 mg, 96% purity, 944 µmol). Purification of the crude product by column chromatography (CyH/EtOAc: 95/5) provided **19h** as a colorless solid (165 mg, 805 µmol, 85%).

$C_{13}H_{16}O_2$ (204.27 g/mol), **R_f:** 0.29 (CyH/EtOAc: 95/5); **m.p.:** 70 – 72 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.36 – 7.26 (m, 2H, ArH), 7.02 (d, *J* = 8.5 Hz, 1H, ArH), 3.72 (q, *J* = 7.6 Hz, 1H, ArCH), 1.58 (d, *J* = 7.6 Hz, 3H, ArCHCH$_3$), 1.33 (s, 9H, ArC(CH$_3$)$_3$).

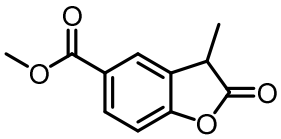
^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 178.5 (q), 151.3 (q), 147.5 (q), 128.3 (q), 125.6 (+), 120.8 (+), 110.0 (+), 38.7 (+), 34.7 (q), 3 × 31.6 (+, +, +), 16.0 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2963 (m, br), 2874 (w, sh), 1804 (s, sh), 1487 (s, sh), 1234 (m, sh), 1148 (m, sh), 1103 (s, sh), 1033 (s, sh), 995 (m, sh), 869 (m, sh), 753 (s, sh).

GC-MS (EI): t_R = 7.16 min, m/z = 204 (29, $[M^{+\bullet}]$), 189 (92, $[M^{+\bullet}]$-$[CH_3^{\bullet}]$), 161 (100, $[M^{+\bullet}]$-$[CH_3^{\bullet}]$-[CO]).

HR-MS (EI): m/z = $[M^{+\bullet}]$ calc. for $C_{13}H_{16}O_2$ 204.1145, found 204.1140.

Methyl 3-methyl-2-oxo-2,3-dihydrobenzofuran-5-carboxylate (19i)



According to the general procedure *L1*, **19i** was synthesized from **18i** (183 mg, 97% purity, 998 µmol). Purification of the crude product by column chromatography (CyH/EtOAc: 95/5) provided **19i** as a white solid (160 mg, 774 µmol, 78%).

$C_{11}H_{10}O_4$ (206.20 g/mol), **R_f:** 0.10 (CyH/EtOAc: 95/5); **m.p.:** 92 - 94 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 8.08 – 8.01 (m, 1H, ArH), 8.00 – 7.94 (m, 1H, ArH), 7.16 (d, *J* = 8.4 Hz, 1H, ArH), 3.93 (s, 3H, ArCOOCH$_3$), 3.77 (q, *J* = 7.6 Hz, 1H, ArCH), 1.61 (d, *J* = 7.6 Hz, 3H, ArCHCH$_3$).

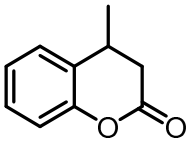
^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 177.2 (q), 166.3 (q), 156.9 (q), 131.3 (+), 129.0 (q), 126.4 (q), 125.6 (+), 110.6 (+), 52.3 (+), 38.1 (+), 15.8 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2956 (w, sh), 1812 (s, sh), 1715 (s, sh), 1625 (m, sh), 1439 (m, sh), 1297 (s, sh), 1260 (s, sh), 1200 (s, sh), 1096 (s, sh), 1025 (s, sh), 992 (m, br), 861 (m, sh), 768 (s, sh).

GC-MS (EI): t_R = 7.71 min, m/z = 206 (40, $[M^{+\bullet}]$), 178 (34, $[M^{+\bullet}]$-[CO]), 147 (100, $[M^{+\bullet}]$-[CO]-$[CH_3O^{\bullet}]$).

HR-MS (EI): m/z = $[M^{+\bullet}]$ calc. for $C_{11}H_{10}O_4$ 206.0574, found 206.0570.

4-Methylchroman-2-one (19j)



According to the general procedure *L1*, **19j** was synthesized from **18j** (141 mg, 95% purity, 995 µmol). Purification of the crude product by column chromatography (CyH/EtOAc: 95/5) provided **19j** as a bright yellow oil (39 mg, 237 µmol, 92% purity, 22%). The obtained analytical data are in accordance to the literature.[10]

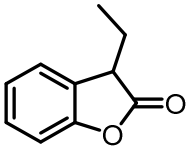
$C_{10}H_{10}O_2$ (162.19 g/mol), **R_f:** 0.29 (CyH/EtOAc: 95/5); **m.p.:** Ambient temperature.

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.30 – 7.19 (m, 2H, ArH), 7.19 – 7.03 (m, 2H, ArH), 3.29 – 3.07 (m, 1H, ArCH), 2.85 (dd, *J* = 15.8, 5.5 Hz, 1H, ArCHCH_2), 2.59 (dd, *J* = 15.8, 7.2 Hz, 1H, ArCHCH_2), 1.35 (d, *J* = 7.0 Hz, 3H, ArCHCH_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 168.4 (q), 151.3 (q), 128.3 (+), 127.9 (q), 126.5 (+), 124.6 (+), 117.0 (+), 36.8 (–), 29.5 (+), 19.9 (+).

GC-MS (EI): t_R = 6.19 min, m/z = 162 (100, $[M^{+\bullet}]$), 147 (77, $[M^{+\bullet}]$-$[CH_3^{\bullet}]$).

3-Ethylbenzofuran-2(3H)-one (19k)



According to the general procedure *L1*, **19k** was synthesized either from 2-allylphenol (**18l**) (130 µL, 996 µmol) or from **18k** (132 mg, 985µmol). Purification of the crude product by column chromatography (CyH/EtOAc: 95/5) provided **19k** as a bright yellow oil (125 mg, 771 µmol, 77% or 141 mg, 869 µmol, 88%). The obtained analytical data are in accordance to the literature.[10]

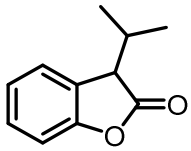
$C_{10}H_{10}O_2$ (162.19 g/mol), **R_f:** 0.37 (CyH/EtOAc: 95/5); **m.p.:** Ambient temperature.

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.36 – 7.24 (m, 2H, ArH), 7.20 – 7.06 (m, 2H, ArH), 3.71 (t, *J* = 5.9, 1H, ArCH), 2.06 (qd, *J* = 7.4, 5.9 Hz, 2H, ArCHCH_2), 0.97 (t, *J* = 7.4 Hz, 3H, ArCHCH_2CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 177.2 (q), 153.9 (q), 128.8 (+), 127.2 (q), 124.2 (+), 124.1 (+), 110.7 (+), 44.6 (+), 24.3 (–), 10.2 (+).

GC-MS (EI): t_R = 5.66 min, m/z = 162 (100, $[M^{+\bullet}]$), 134 (67, $[M^{+\bullet}]$-[CO]), 119 (67, $[M^{+\bullet}]$-[CO]-$[CH_3^{\bullet}]$).

3-Isopropylbenzofuran-2(3H)-one (19m)



According to the general procedure *L1*, **19m** was synthesized from **18m** (157 mg, 97% purity, 1.03 mmol). Purification of the crude product by column chromatography (Pentan/Et_2O: 95/5) provided **19m** as a colorless oil (19.8 mg, 112 µmol, 11%). The obtained analytical data are in accordance to the literature.[10]

$C_{11}H_{12}O_2$ (176.22 g/mol), $\mathbf{R_f}$: 0.34 (Pentan/Et_2O: 95/5); **m.p.**: Ambient temperature.

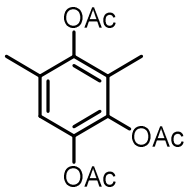
^{1}H-NMR (300 MHz, CDCl3) δ_H/ppm: 7.35 – 7.26 (m, 2H, ArH), 7.18 – 7.06 (m, 2H, ArH), 3.64 (d, *J* = 3.7 Hz, 1H, ArCH), 2.59 – 2.39 (m, 1H, ArCHCH), 1.09 (d, *J* = 6.9 Hz, 3H, ArCHCHCH_3), 0.98 (d, *J* = 6.9 Hz, 3H, ArCHCHCH_3).

^{13}C-NMR (75 MHz, CDCl3) δ_C/ppm: 176.5 (q), 154.1 (q), 128.8 (+), 126.2 (q), 124.6 (+), 123.9 (+), 110.6 (+), 49.7 (+), 31.4 (+), 19.4 (+), 18.5 (+).

GC-MS (EI): t_R = 5.02 min, m/z = 176 (26, $[M^{+\bullet}]$), 134 (100, $[M^{+\bullet}]$-$[C_3H_6]$).

4.4.5 Synthesis of Agropyrenone

3,5-Dimethylbenzene-1,2,4-triyl triacetate (26)



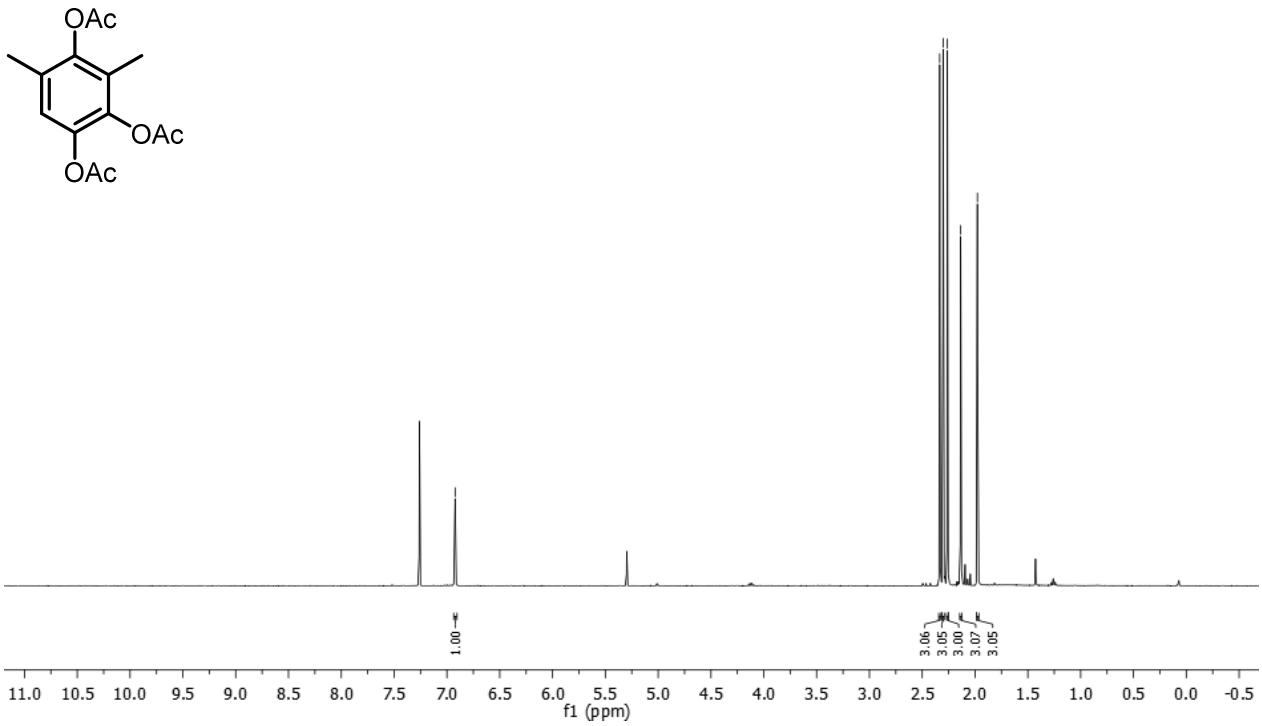
A dried 50 mL RBF was charged with 2,6-dimethylbenzoquinone (**27**) (2.00 g, 15.0 mmol, 1.0 eq.), which was dissolved in acetic anhydride (12.5 mL, 132 mmol, 9.0 eq.) and boron trifluoride diethyl etherate (560 µL, 4.40 mmol, 0.3 eq.) was added *via* syringe. The reaction mixture was heated up to 40 °C and stirred for 48 h. The reaction was quenched by pouring the reaction mixture into dest. H_2O (100 mL) and the brown solution was extracted with EtOAc (3×100 mL). The combined organic layers were washed with H_2O (50 mL), $NaHCO_3$ ($3 \times$ 50 mL) and brine (50 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (CyH/EtOAc: 70/30 to 50/50). **26** was obtained as a bright yellow solid (3.98 g, 14.2 mmol, 97%). The obtained analytical data are in accordance to the literature.[28c]

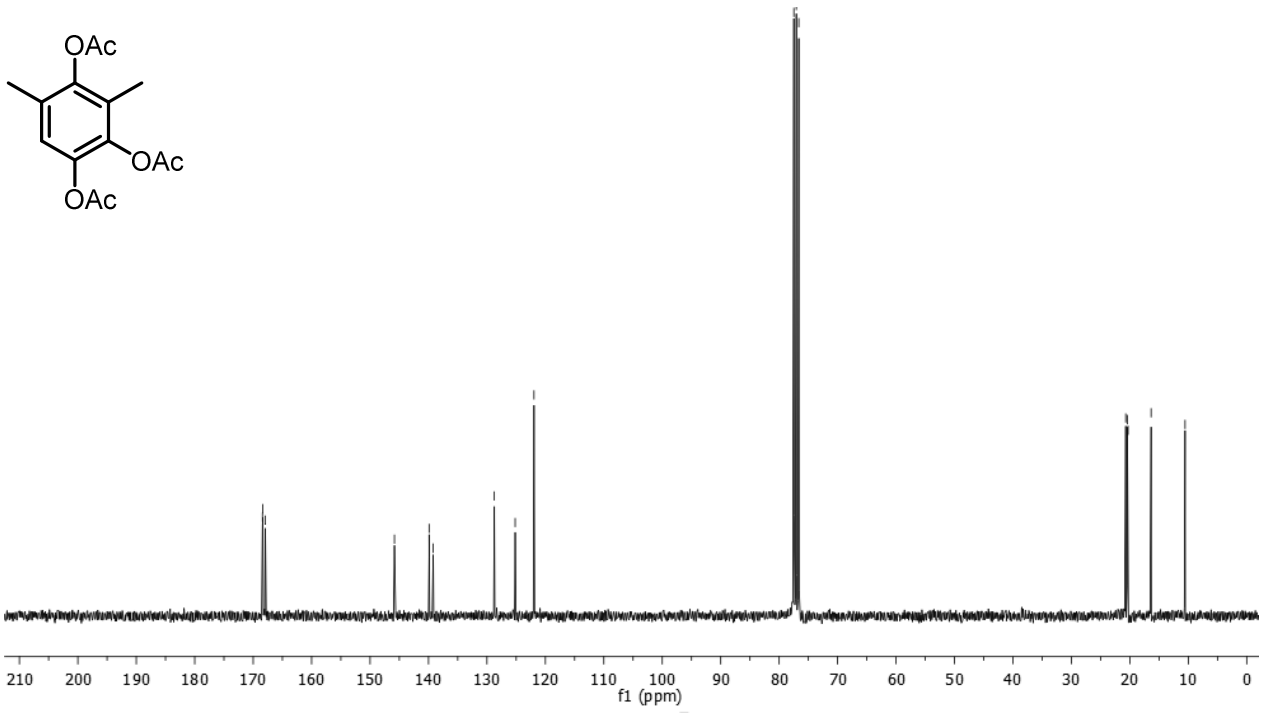
$C_{14}H_{16}O_6$ (280.28 g/mol), **R_f:** 0.30 (CyH/EtOAc: 70/30), **m.p.:** 101 °C (lit: 103-104 °C).[28c]

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H/ppm: 6.92 (s, 1H, ArH), 2.33 (s, 3H, OCOCH_3), 2.30 (s, 3H, OCOCH_3), 2.26 (s, 3H, OCOCH_3), 2.14 (s, 3H, ArCH_3), 1.98 (s, 3H, ArCH_3).

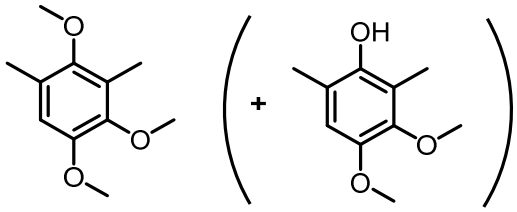
^{13}C-NMR (101 MHz, $CDCl_3$) δ_C/ppm: 168.33 (q), 168.27 (q), 167.8 (q), 145.8 (q), 139.9 (q), 139.2 (q), 128.7 (q), 125.2 (q), 121.9 (+), 20.7 (+), 20.4 (+), 20.3 (+), 16.3 (+), 10.5 (+).

GC-MS (EI): t_R = 8.14 min, m/z = 154 (100, $[M^{+\bullet}]$-$[CH_2CO]$-$[CH_2CO]$-$[CH_2CO]$), 196 (27, $[M^{+\bullet}]$-$[CH_2CO]$-$[CH_2CO]$), 238 (10, $[M^{+\bullet}]$-$[CH_2CO]$), 280 (2, $[M^{+\bullet}]$).


OAc
OAc
OAc
1.00
3.06
3.05
3.00
3.07
3.05
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
f1 (ppm)


OAc
OAc
OAc
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

1,2,4-Trimethoxy-3,5-dimethylbenzene (25) and (3,4-dimethoxy-2,6-dimethylphenol (28))



A flame-dried 500 mL RBF was charged with 3,5-dimethylbenzene-1,2,4-triyl triacetate (**26**) (4.77 g, 17.0 mmol, 1.0 eq.), which was dissolved in MeOH p.a. (50 mL). Dimethyl sulfate (18.0 mL, 190 mmol, 11.0 eq.) was added by syringe and the pale brown solution was stirred for 15 min at RT. The solution was cooled to -10 °C (ice water/NaCl cooling bath) and an aqueous solution of NaOH (17 M, 15.7 g in 23 mL) was added *via* syringe carefully within a period of 45 min (highly exothermic reaction!). The reaction mixture was stirred for 1 h at RT, quenched with dist. H_2O and extracted with EtOAc (3×100 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by Kugelrohr distillation (20 mbar, 180 °C) and the NMR showed a mixture of product **25** and the C4-demethylated analogue **28** in a ratio of 45/55.

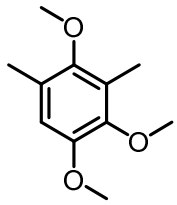
The distillate was directly methylated, without additional separation step. Therefore, a flame-dried 100 mL RBF was charged the distillate (2.782 g = **25** (1.31 g, 6.66 mmol, 0.81 eq.) + **28** (1.48 g, 8.14 mmol, 1.0 eq.)), which was dissolved in anhydrous DMF (8 mL). After the addition of K_2CO_3 (4.5 g, 32.6 mmol, 4.0 eq.), methyl iodide (2.5 mL, 40.7 mmol, 5.0 eq.) was added by syringe within a period of 2 min. The reaction mixture was heated up to 40 °C and stirred for 14 h. The reaction was quenched by adding an aqueous saturate solution of NH_4Cl (100 mL) and the reaction mixture was extracted with EtOAc (3×100 mL). The combined organic layers were washed with brine (150 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The product **25** was obtained as a dark red oil and was used without further purification (2.74 g, 14.0 mmol, 82%). The obtained analytical data are in accordance to the literature.[28c]

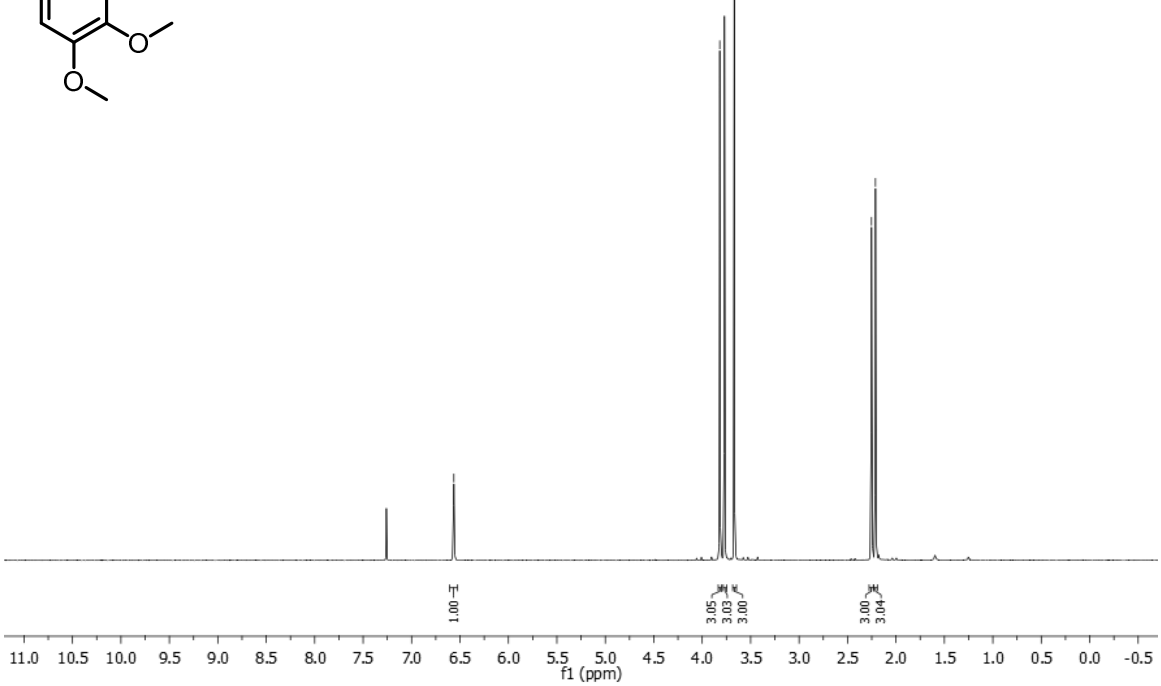
$C_{11}H_{16}O_3$ (196.25 g/mol), **R_f:** 0.20 (CyH/EtOAc: 95/5), **m.p.:** Ambient temperature.

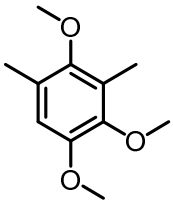
^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 6.56 (s, 1H, Ar<u>H</u>), 3.81 (s, 3H, OC<u>H$_3$</u>), 3.77 (s, 3H, OC<u>H$_3$</u>), 3.67 (s, 3H, OC<u>H$_3$</u>), 2.25 (s, 3H, ArC<u>H$_3$</u>), 2.21 (s, 3H, ArC<u>H$_3$</u>).

^{13}C-NMR (101 MHz, $CDCl_3$) δ_C/ppm: 150.6 (q), 149.0 (q), 145.8 (q), 125.8 (q), 125.3 (q), 111.5 (+), 60.3 (+), 60.1 (+), 55.9 (+), 16.1 (+), 9.5 (+).

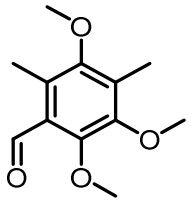
GC-MS (EI): t_R = 5.81 min, m/z = 196 (100, $[M^{+\bullet}]$), 181 (96, $[M^{+\bullet}]$-$[CH_3^{\bullet}]$).







2,3,5-Trimethoxy-4,6-dimethylbenzaldehyde (24)



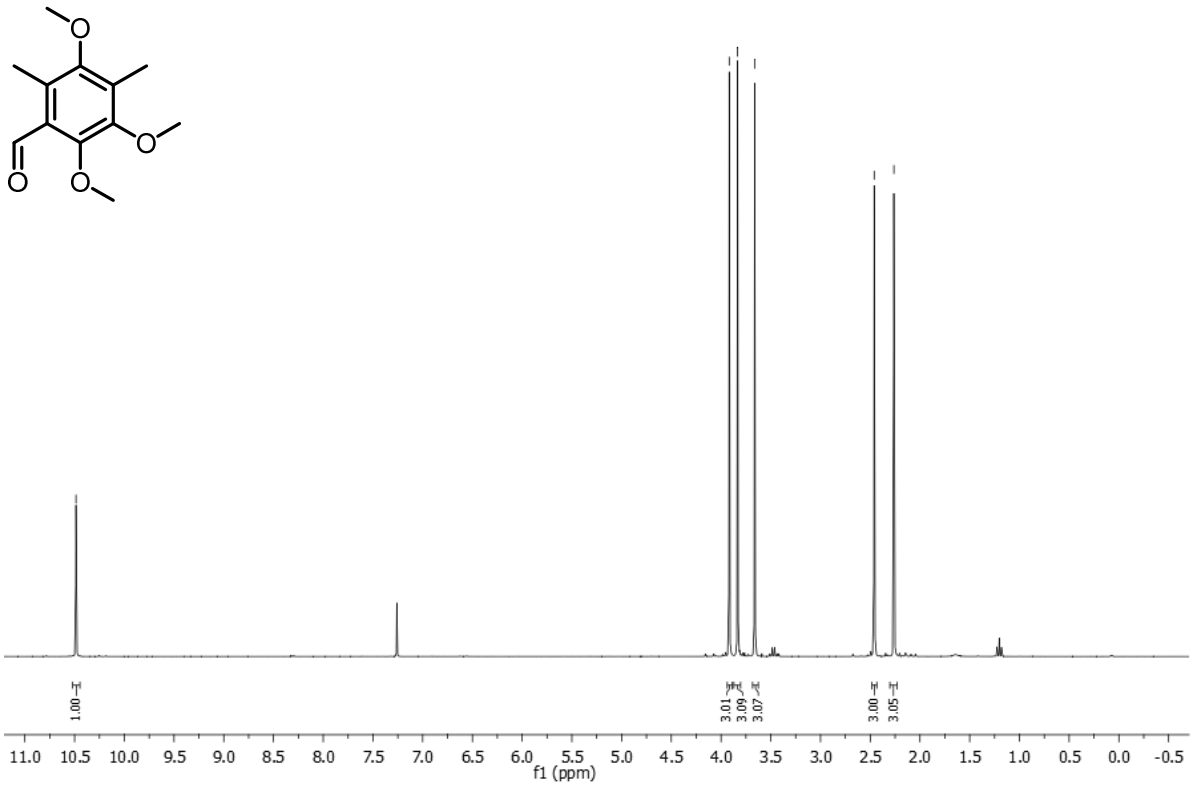
A dried 25 mL RBF was treated with 1,2,4-trimethoxy-3,5-dimethylbenzene (**25**) (2.74 g, 14.0 mmol, 1.0 eq.) and dissolved in anhydrous CH_2Cl_2 (5 mL). The solution was cooled to 0 °C (ice water/NaCl cooling bath) and $TiCl_4$ (7.35 mL, 67.0 mmol, 4.8 eq.) was added *via* syringe. After the addition of dichloromethyl methyl ether (2.50 mL, 16.5 mmol, 2.0 eq.) the cooling bath was removed and the deep red reaction mixture was stirred for 6 h at RT. The reaction was quenched by pouring the reaction mixture on ice. The mixture was extracted with Et_2O (3 × 30 mL), the combined organic layers were washed with dist. H_2O (1 × 50 mL), $NaHCO_3$ (3 × 50 mL) and brine (50 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. **24** was purified by Kugelrohr distillation (20 mbar, 200 °C) and was obtained as a yellow solid (2.85 g, 12.7 mmol, 91%). The obtained analytical data are in accordance to the literature.[30]

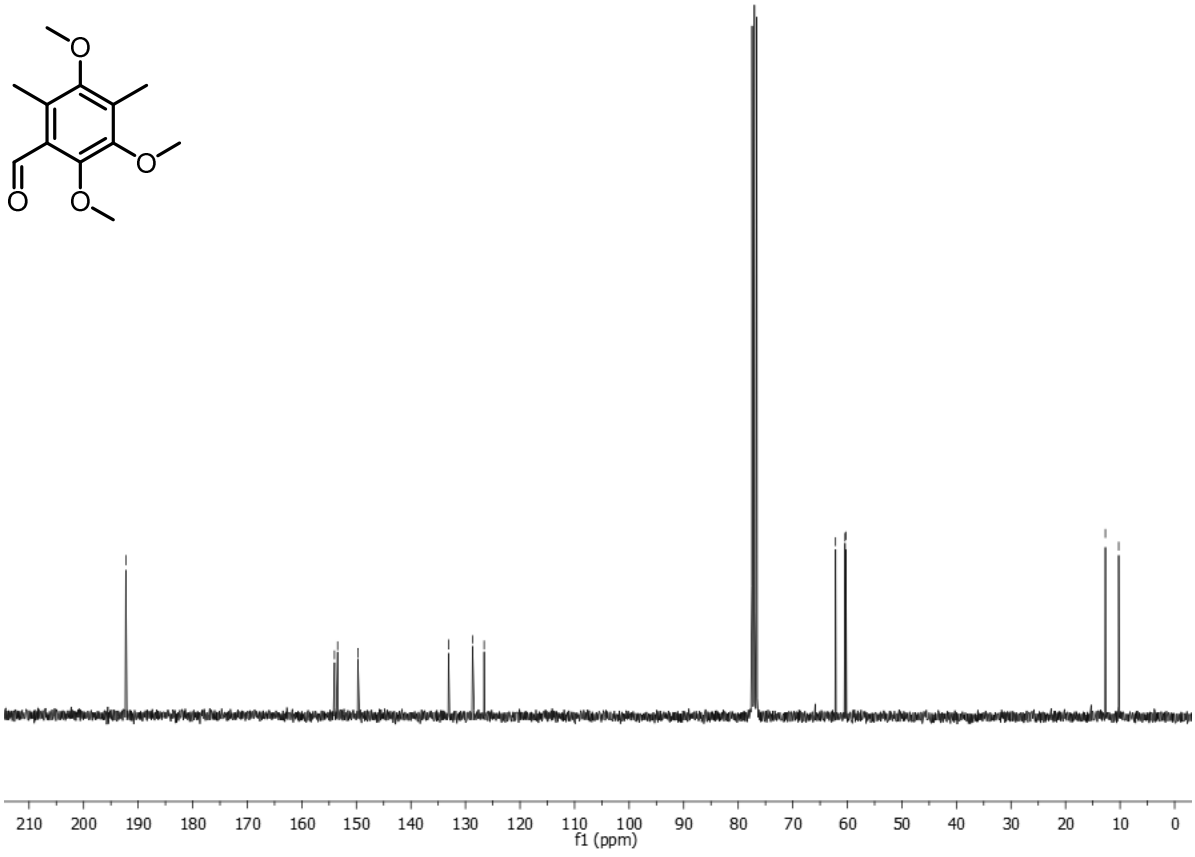
$C_{12}H_{16}O_4$ (224.26 g/mol), **R_f:** 0.15 (CyH/EtOAc: 95/5), **m.p.:** Ambient temperature.

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 10.49 (s, 1H, ArCO<u>H</u>), 3.92 (s, 3H, OC<u>H</u>$_3$), 3.84 (s, 3H, OC<u>H</u>$_3$), 3.67 (s, 3H, OC<u>H</u>$_3$), 2.46 (s, 3H, ArC<u>H</u>$_3$), 2.27 (s, 3H, ArC<u>H</u>$_3$).

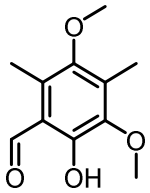
^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 192.3 (+), 154.0 (q), 153.4 (q), 149.7 (q), 133.1 (q), 128.7 (q), 126.6 (q), 62.2 (+), 60.4 (+), 60.3 (+), 12.7 (+), 10.3 (+).

GC-MS (EI): t_R = 7.14 min, m/z = 224 (100, [$M^{+\bullet}$]), 209 (74, [$M^{+\bullet}$]-[$CH_3^\bullet$]), 194 (30, [$M^{+\bullet}$]-[$CH_3^\bullet$]-[$CH_3^\bullet$]).


1.00
3.01
3.09
3.07
3.00
3.05
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
f1 (ppm)


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-Hydroxy-3,5-dimethoxy-4,6-dimethylbenzaldehyde (23)



A dried 50 mL RBF was charged with 2,3,5-trimethoxy-4,6-dimethylbenzaldehyde (**24**) (2.15 g, 9.57 mmol, 1.0 eq.) and anhydrous DMF (10 mL). After the addition of anhydrous LiCl (730 mg, 17.2 mmol, 1.8 eq.) the solution was refluxed at 150 °C for 22 h. The reaction was quenched by addition of 10% aqueous NaOH (40 mL), washed with Et_2O (2 × 50 mL), then acidified with 10% aqueous HCl (50 mL) and extracted with Et_2O (3 × 100 mL). The combined organic phases were washed with brine (2 × 150 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by Kugelrohr distillation (20 mbar, 200 °C). **23** was obtained as a yellow solid (343 mg, 4.50 mmol, 86% purity, 40% yield).

$C_{11}H_{14}O_4$ (210.23 g/mol), **R_f:** 0.24 (CyH/EtOAc: 95/5), **m.p.:** 40 °C

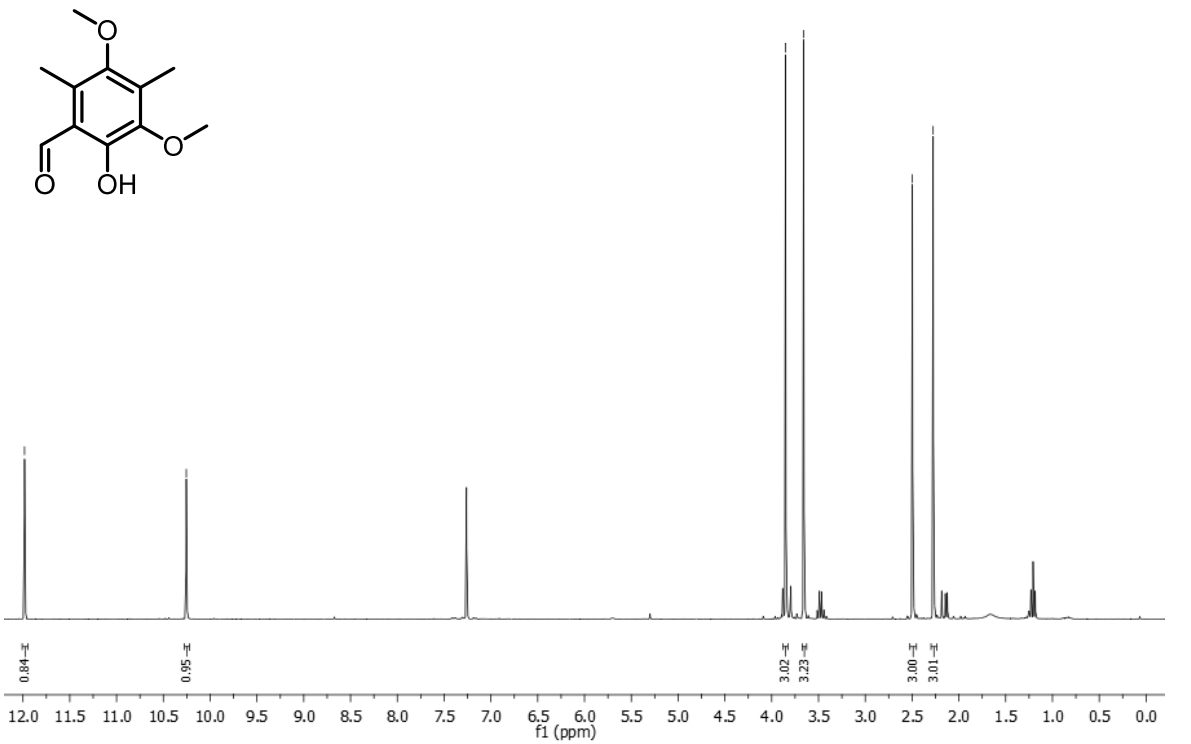
^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 11.96 (s, 1H, ArO<u>H</u>), 10.25 (s, 1H, ArC<u>H</u>O), 3.85 (s, 3H, ArOC<u>H_3</u>), 3.66 (s, 3H, ArOC<u>H_3</u>), 2.50 (s, 3H, ArC<u>H_3</u>), 2.27 (s, 3H, ArC<u>H_3</u>).

^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 195.2 (+), 153.4 (q), 149.0 (q), 144.8 (q), 136.0 (q), 128.2 (q), 117.1 (q), 60.7 (+), 60.2 (+), 10.6 (+), 10.2 (+).

FT-IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2941 (m, br), 1741 (m, sh), 1644 (s, sh), 1454 (m, sh), 1405 (s, sh), 1368 (m, sh), 1297 (s, sh).

GC-MS (EI): t_R = 7.23 min, m/z = 210 (100, $[M^{+\bullet}]$), 195 (68, $[M^{+\bullet}]$-$[CH_3^\bullet]$), 180 (14, $[M^{+\bullet}]$-$[CH_3^\bullet]$-$[CH_3^\bullet]$), 167 (34, $[M^{+\bullet}]$-$[CH_3^\bullet]$-[CO]).

HR-MS (APCI): m/z = $[MH^+]$ calc. for $C_{11}H_{14}O_4$ 211.0965, found 211.0969.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O
O
OH
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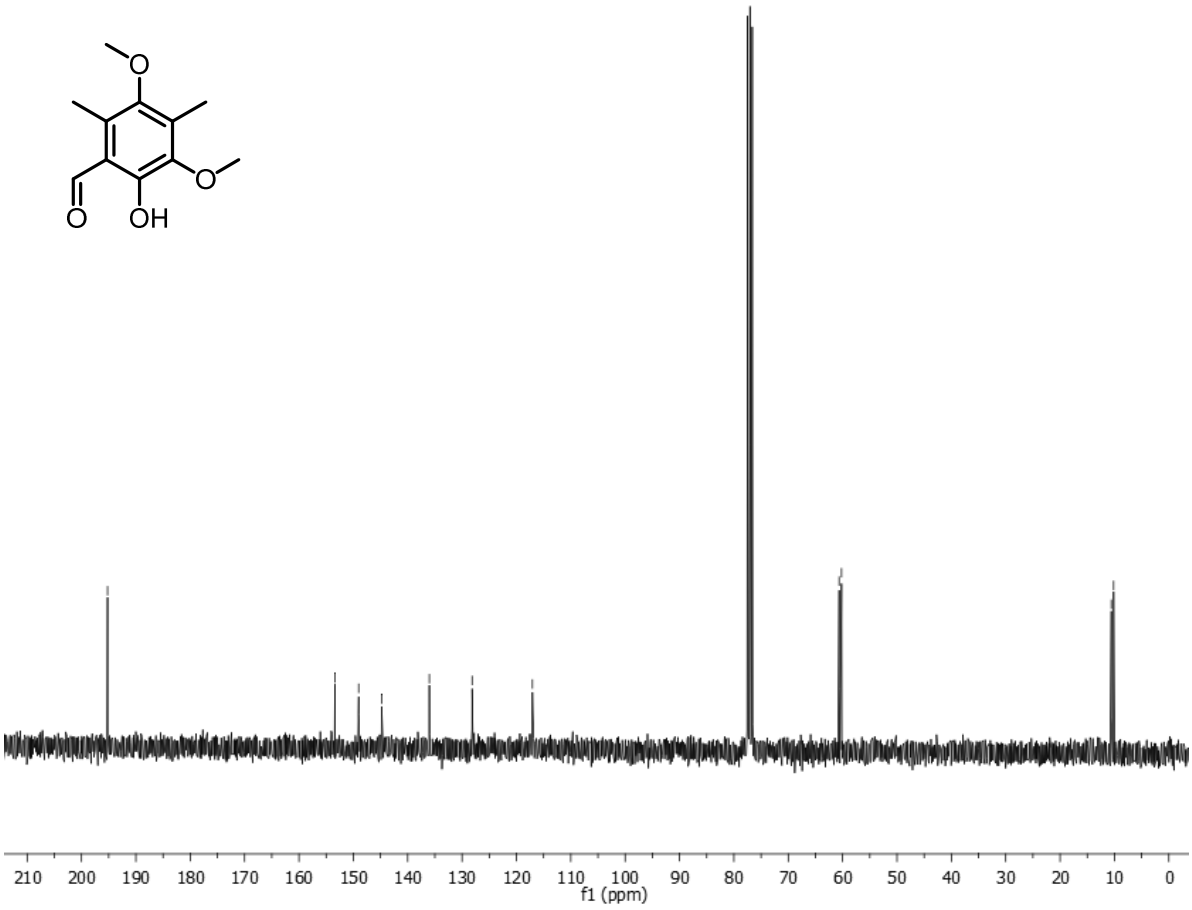
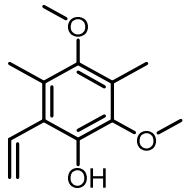
0.95
3.02
3.23
3.00
3.01
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


O
O
O
OH
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

2,4-Dimethoxy-3,5-dimethyl-6-vinylphenol (22)



A flame-dried 10 mL Schlenk tube was charged with acetic anhydride (0.5 mL) and pyridine (40 µL, 496 µmol, 1.0 eq.). 2-Hydroxy-3,5-dimethoxy-4,6-dimethylbenzaldehyde (**23**, 100 mg, 476 µmol, 1.0 eq.) was added *via* syringe and the mixture was stirred for 1 h at RT in order to generate the C1-acetylated product (**32**). The remaining acetic anhydride and pyridine were removed under reduced pressure. **32** was dissolved in anhydrous THF (2 mL) and *tert*-butyl-catechol (3 mg, 18 µmol, 0.04 eq.) was added as an polymerization inhibitor. A flame-dried 25 mL RBF was charged with Nysted reagent (**29**, 1.4 mL, 714 µmol, 20 weight% in THF, 1.5 eq.), which was dissolved in anhydrous THF. The mixture was cooled to 0 °C, the **32**-solution was added and the resulting mixture was stirred for 2 h at RT. The reaction was quenched by the addition of water and extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (Pentane/Et_2O: 80/20). **22** was obtained as a bright yellow oil (68 mg, 327 µmol, 69%).

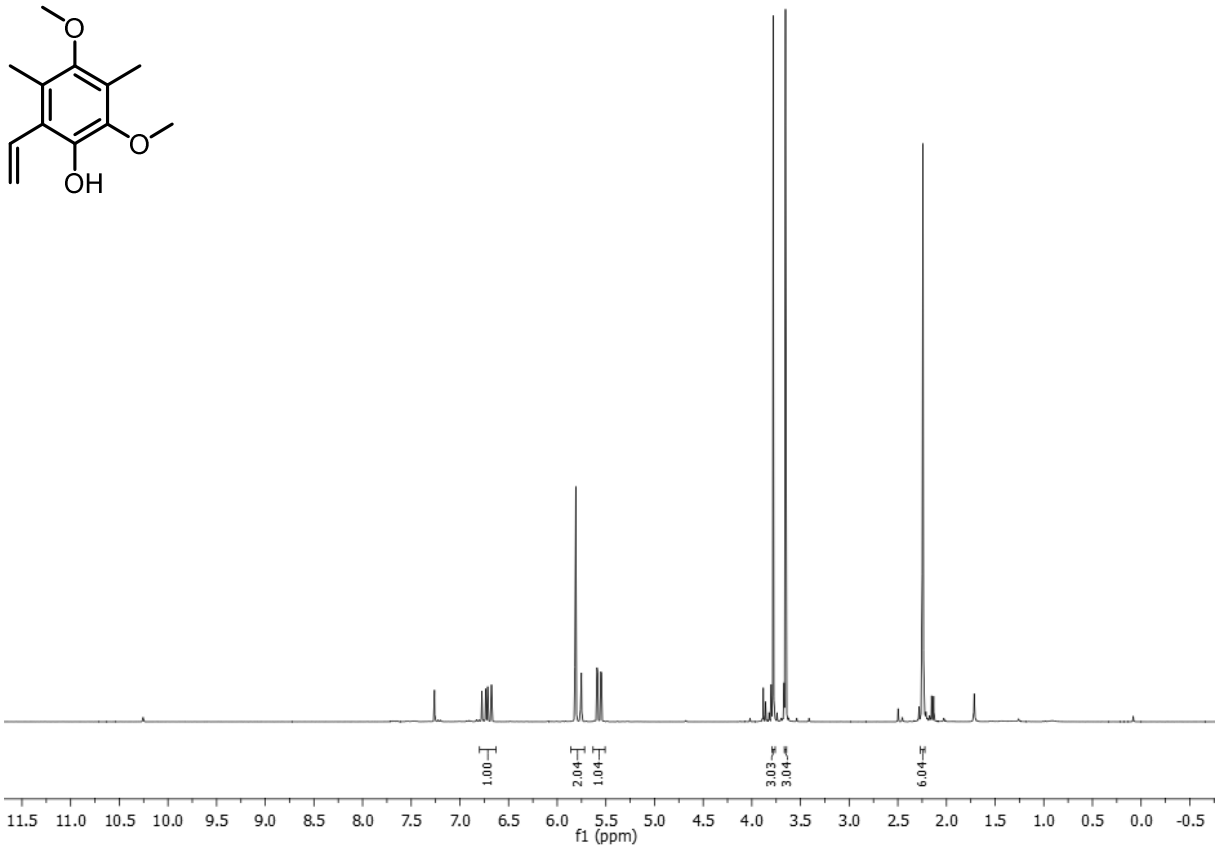
$C_{12}H_{16}O_3$ (208.26 g/mol), **R_f:** 0.15 (CyH/EtOAc: 95/5), **m.p.:** Ambient temperature.

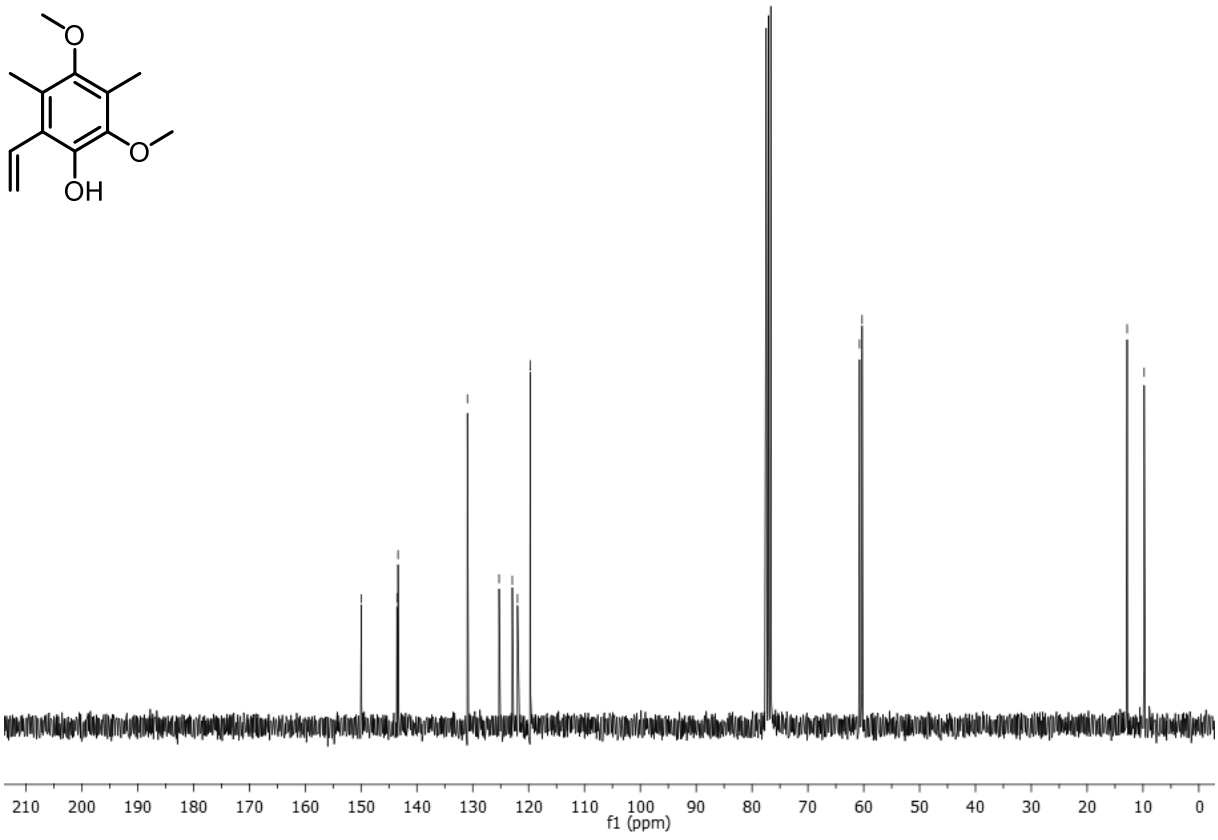
^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 6.72 (dd, *J* = 11.8, 18.0 Hz, 1H, ArC<u>H</u>), 5.78 (dd, *J* = 2.1, 18.0 Hz, 1H, ArCHC<u>H</u>$_{2,trans}$), 5.56 (dd, *J* = 2.1, 11.8 Hz, 1H, ArCHC<u>H</u>$_{2,cis}$), 3.78 (s, 3H, ArOC<u>H</u>$_3$), 3.66 (s, 3H, ArOC<u>H</u>$_3$), 2.244 (s, 3H, ArC<u>H</u>$_3$), 2.238 (s, 3H, ArC<u>H</u>$_3$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ_C/ppm: 149.9 (q), 143.6 (q), 143.4 (q), 131.0 (+), 125.3 (q), 122.9 (q), 122.0 (q), 119.7 (–), 60.8 (+), 60.3 (+), 12.8 (+), 9.8 (+).

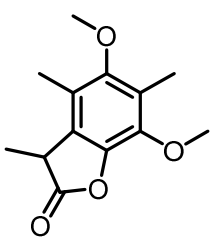
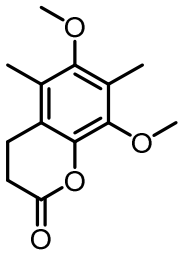
GC-MS (EI)**:** t_R = 7.00 min, m/z = 208 (100, [$M^{+\bullet}$]), 193 (35, $M^{+\bullet}$]-[$CH_3^{\bullet}$]).

HR-MS (EI): m/z = [$M^{\bullet+}$] calc. for $C_{12}H_{16}O_3$ 208.1094, found 208.1098.


O
O
OH
1.00
2.04
1.04
3.03
3.04
6.04
11.5 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
f1 (ppm)


O
O
OH
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

5,7-Dimethoxy-3,4,6-trimethylbenzofuran-2(3H)-one (21) and 6,8-dimethoxy-5,7-dimethylchroman-2-one (33)

Modified general procedure *L1*, was used to synthesized **21** and **33** from 2,4-dimethoxy-3,5-dimethyl-6-vinylphenol (**22**) (75 mg, 358 µmol).

$Pd(dba)_2$	dppdtbpf	DPPA	Et_2O	Temp.
4.1 mg, 7.15 µmol, 2 mol%	14.7 mg, 28.6 µmol, 8 mol%	13.4 mg, 53.7 µmol, 15 mol%	500 µL	35 °C

Purification of the crude product by column chromatography (CyH/EtOAc: 97.5/2.5) provided **21** as a brown oil consisting unknown side product (GC-MS: m/z = 212) and **33** as a yellow oil (7.5 mg, 31.2 µmol, 9%).

Since unknown impurities were visible in NMR/GC-MS, the yield of **21** (11 mg, 48.3 µmol, 14%) was analyzed by quantitative (not calibrated) NMR spectroscopy using $CHONPh_2$ as an internal standard. The assignment resulted from DEPT-135°, HMBC and HSQC experiments.

Analytical data of **21**:

$C_{13}H_{16}O_4$ (236.27 g/mol), **R_f:** 0.17 (CyH/EtOAc: 95/5), **m.p.:** Ambient temperature.

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H/ppm: 3.88 (s, 3H, OC$\underline{H_3}$), 3.61 (s, 3H, OC$\underline{H_3}$), 3.63 – 3.59 (m, 1H, ArC$\underline{H}$), 2.14 (s, 3H, ArC$\underline{H_3}$), 2.13 (s, 3H, ArC$\underline{H_3}$), 1.52 (d, *J* = 7.6 Hz, 3H, ArCHC$\underline{H_3}$).

^{13}C-NMR (101 MHz, $CDCl_3$) 178.1 (q), 153.7 (q), 140.6 (q), 140.1 (q), 126.2 (q), 123.9 (q), 121.6 (q), 60.5 (+), 60.3 (+), 38.5 (+), 15.9 (+), 12.2 (+), 9.6 (+).

HR-MS (APCI): m/z = [MH^+] calc. for $C_{13}H_{17}O_4$ 237.1121, found 237.1121.

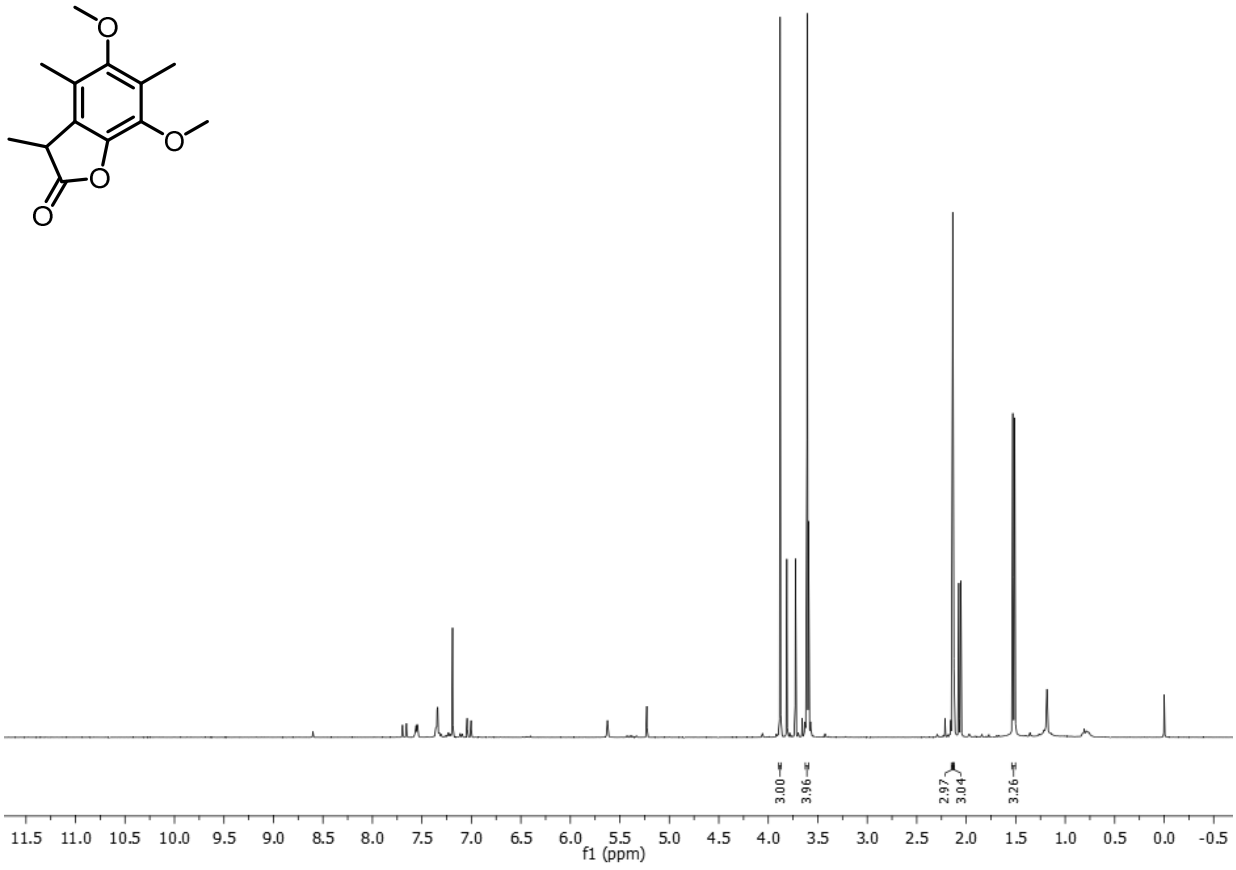
Analytical data of **33**:

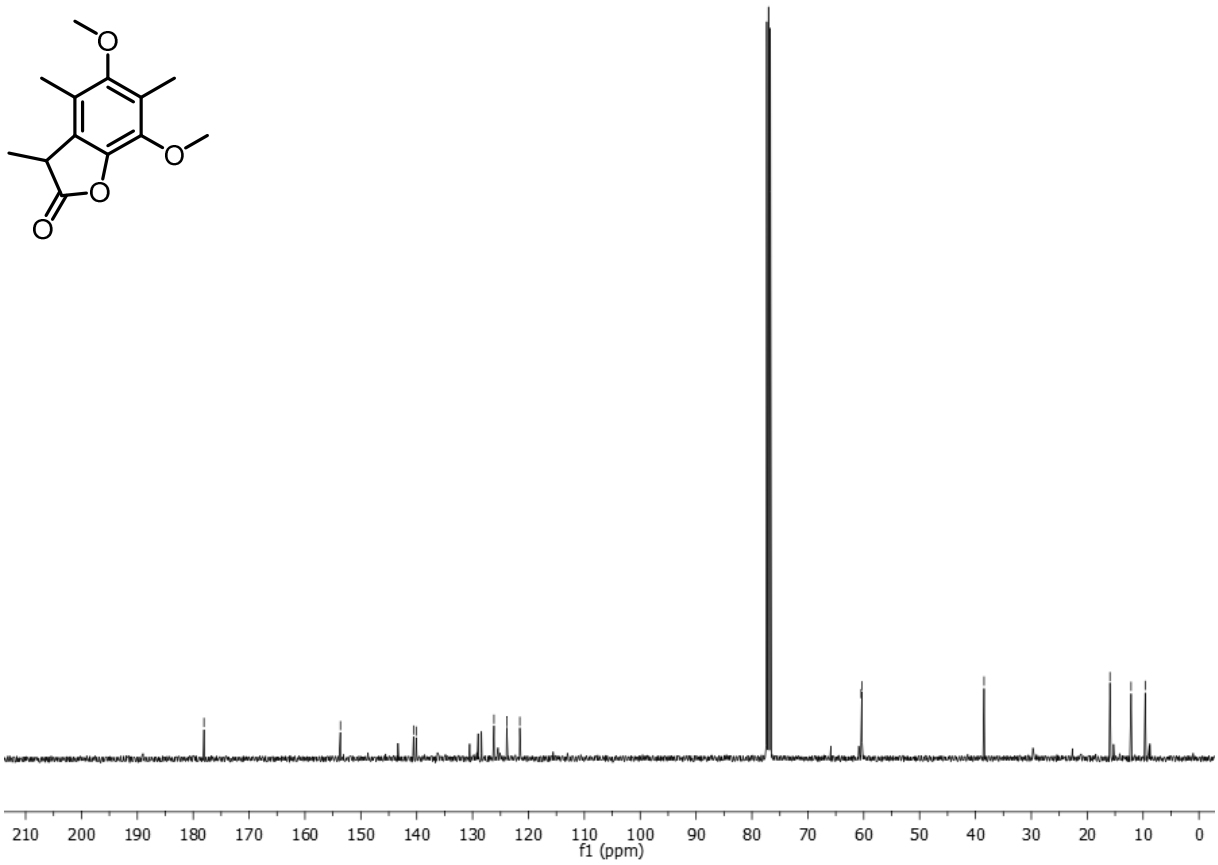
$C_{13}H_{16}O_4$ (236.27 g/mol), **R_f:** 0.15 (CyH/ EtOAc 95:5), **m.p.:** Ambient temperature.

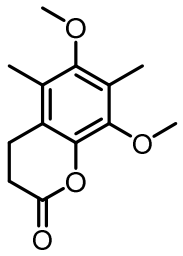
^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 3.84 (s, 3H, ArOC$\underline{H_3}$), 3.67 (s, 3H, ArOC$\underline{H_3}$), 2.95 – 2.88 (m, 2H, ArC$\underline{H_2}$), 2.79 – 2.71 (m, 2H, $ArCH_2C\underline{H_2}$), 2.21 (s, 3H, ArC$\underline{H_3}$), 2.18 (s, 3H, ArC$\underline{H_3}$).

^{13}C-NMR (101 MHz, $CDCl_3$) δ_C/ppm: 168.1 (q), 153.3 (q), 144.5 (q), 141.9 (q), 124.2 (q), 123.4 (q), 120.3 (q), 61.1 (+), 60.3 (+), 28.9 (–), 21.4 (–), 11.9 (+), 9.5 (+).

HR-MS (APCI): m/z = [MH^+] calc. for $C_{13}H_{17}O_4$ 237.1121, found 237.1124.


3.00
3.96
2.97
3.04
3.26
11.5 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
f1 (ppm)


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



3.00
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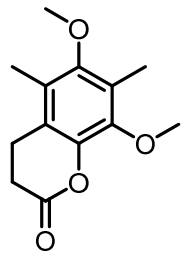
f1 (ppm)



210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

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Chapter 5

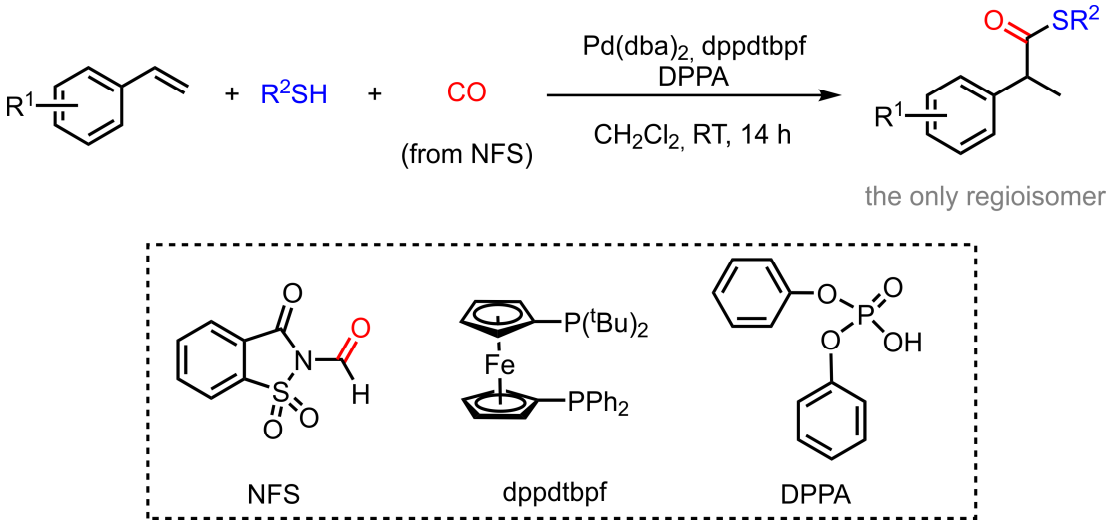
Summary

Carbonylation reactions, the introduction of carbon monoxide (CO) into molecules, represent one of the most important processes in industry, which are also widely spread in academic research. The reaction of olefins, carbon monoxide and nucleophiles in order to generate different carboxylic acid derivatives, is based on the pioneering work of Walter Reppe.

In 2015 we developed an effective palladium-catalyzed alkoxycarbonylation of olefins. A carefully chosen catalytic system enabled the synthesis of esters under mild reaction conditions with a good functional group tolerance. Carbon monoxide is the most versatile C1 building block, but since there are also considerable disadvantages of working with gaseous CO, *N*-formylsaccharin was used as a CO-surrogate. The reaction was conducted in a two-chamber pressure tube, since the separation of CO-generation and carbonylation reaction prevented unwanted side reactions.

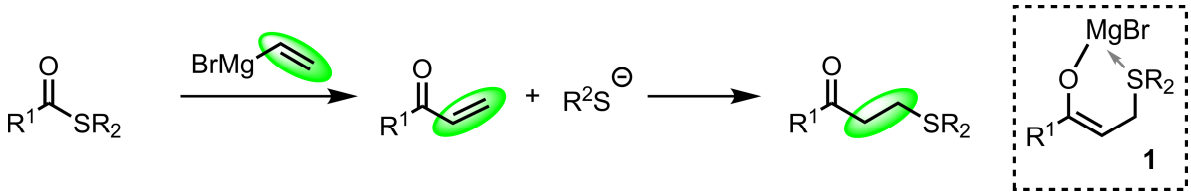
General information about carbonylation, carbon monoxide, CO-surrogates and our previously published work is summarized in **Chapter 1**. Based on the preparatory work this thesis focuses on the development of new catalytic systems for the palladium-catalyzed carbonylation of olefins.

Whereas there are a lot of examples for alkoxy- and aminocarbonylation in the literature, the synthesis of thioesters *via* the so called thiocarbonylation is more rare, even though it is a highly atom- and waste- economic method. Working with free thiols is difficult, which might have hindered progress in this research field. Thiols can easily be oxidized to the corresponding disulfides and are known to act as a catalyst poisons especially for late transition metals. Moreover, the competing hydrothiolation, a typical reaction of thiols with olefins to generate thioethers, has to be suppressed. In the reported literature, high catalyst loadings (3 – 5 mol%), temperatures (100 – 110 °C) and pressures (27 bar) were required and only activated double bonds were applied. In **Chapter 2** the first chemoselective thiocarbonylation of styrenes is reported, which proceeds under mild reaction conditions (1 mol% [Pd], room temperature, 2.5 bar CO) and moreover in a highly regioselective fashion (Scheme 5.1). The reaction of styrene derivatives with heptanethiol and carbon monoxide, catalyzed by $Pd(dba)_2$, dppdtbpf and DPPA enabled the formation of thioesters in excellent yields up to 99%. Many different functional groups were tolerated by the system. Even sterically demanding groups in *ortho*-position exclusively generated the branched products.



Scheme 5.1. Regioselective thiocarbonylation of vinyl arenes.

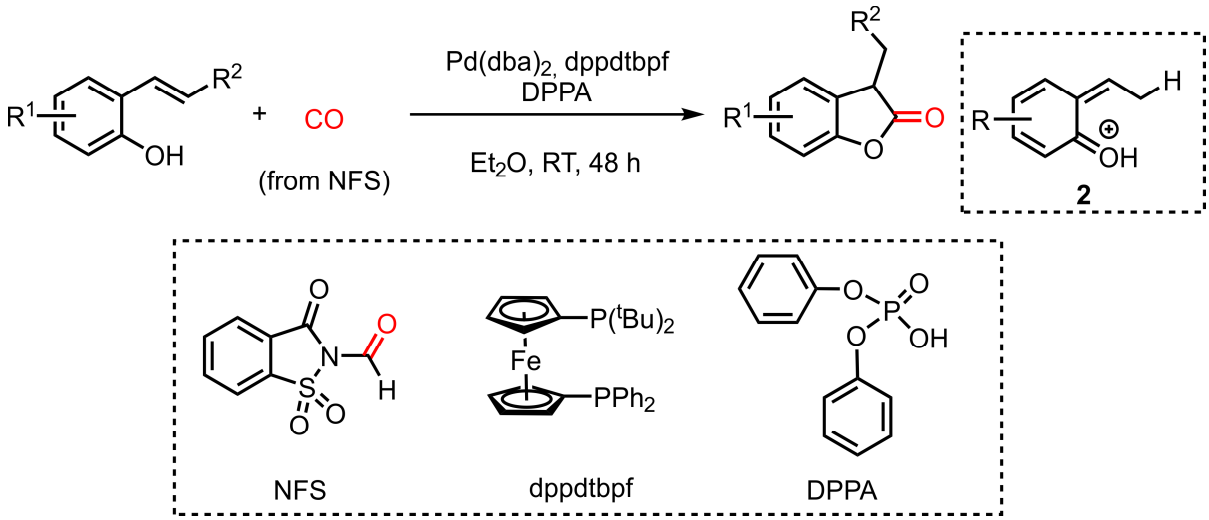
Thioesters are attractive starting materials for various transformations. A new application of thioesters is described in **Chapter 3**. A transition metal free tandem reaction of thioesters with vinyl magnesium bromide in order to generate β-sulfanyl ketones was described (Scheme 5.2). The main problem of the reaction of thioesters with Grignard reagent is the competing overaddition to the corresponding tertiary alcohol. The formation of a chelate complex **1** might have hindered the attack of a second Grignard molecule and enabled the formation of various products in moderate to good yields.



Scheme 5.2. Tandem acyl substitution/Michael addition of thioesters with vinylmagnesium bromide.

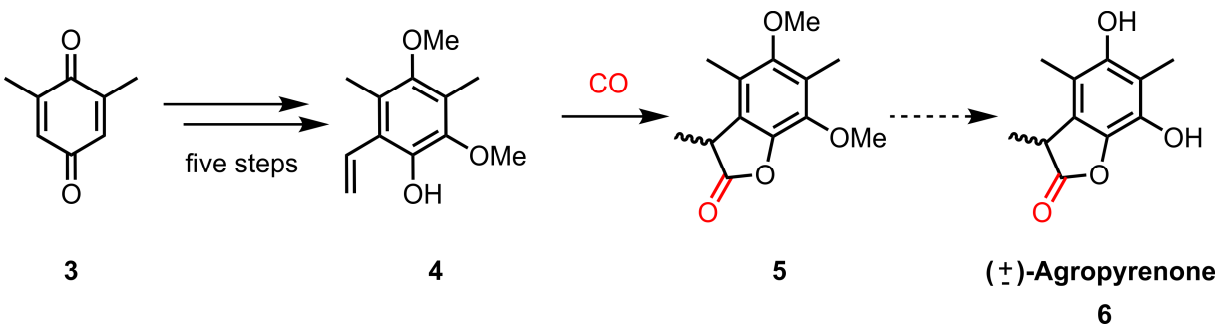
In **Chapter 4**, an intramolecular alkoxycarbonylation of 2-vinylphenols in order to synthesize benzofuranones was investigated (Scheme 5.3). Herein, the control of regioselectivity is highly important, since five- and six-membered lactones can be obtained. Nevertheless, the main challenge of this reaction is to avoid the competing polymerization. Therefore, a considerably mild catalytic system is necessary. 2-Vinylphenols can get protonated by the required promotor acid to form the quinone methide intermediate **2**, which easily polymerizes. In order to enhance the substrate scope of the literature, a catalytic system for

the intramolecular alkoxycarbonylation of 2-vinylphenols, which proceeds at room temperature, was developed. The avoidance of heating enabled a good functional group tolerance also for sterically demanding and electron-donating substituents.



Scheme 5.3. Synthesis of benzofuranones *via* palladium-catalyzed intramolecular alkoxycarbonylation of alkenylphenols.

In order to proof the applicability of the previously described catalytic cyclocarbonylation the synthesis of natural compound (±)-Agropyrenone (**6**), which contains a benzofuran-2(3H)-one moiety, was attempted (Scheme 5.4). The synthesis of the tetra-substituted 2-vinylphenol **4** was successfully conducted in five steps from the commercially available 2,6-dimethylbenzoquinone (**3**) in good to excellent yields. However, the key cyclocarbonylation step generated only 14% of the desired five-membered lactone **5**. Therefore, the synthesis of (±)-Agropyrenone was not accomplished.



Scheme 5.4. Synthetic strategy for the synthesis of (±)-Agropyrenone (**6**).

Chapter 6

Appendix

6.1 List of Abbreviations

Ac	acetyl
acac	acetylacetonate
APCI	atmospheric pressure chemical ionization (MS)
aq.	aqueous
Ar	aryl
ATR	attenuated total reflection (IR)
BINAP	2,2′-bis(diphenyl-phosphino)-1,1′-binaphthalene
Bn	benzyl
BNPA	1,1´-bi-2-naphthol phosphoric acid
Boc	*tert*-butyloxycarbonyl
br	broad (IR)
Bu	butyl
CI	chemical ionization
CO	carbon monoxide
COgen	9-methylfluorene-9-carbonyl chloride
Conv.	conversion
COSY	correlation spectroscopy (NMR)
COX	cyclooxygenase
Cy	cyclohexyl
d	doublet (NMR)
δ	chemical shift
dba	dibenzylideneacetone
DCC	*N,N*′-dicyclohexyl-carbodiimide
DCE	dichloroethene
DEPT	distortionless enhancement by polarization transfer
DIOP	*O*-isopropylidene-2,3-di-hydroxy-1,4-bis(diphenyl phosphino)butane
DMAP	4-(dimethylamino)pyridine
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DPEphos	bis[(2-diphenylphosphino)-phenyl]ether
DPPA	diphenylphosphoric acid
dppb	1,4-bis(diphenylphosphino) butane
dppdtbpf	1-diphenylphosphino-1´-(di-tertbutylphosphino) ferrocene
dppe	1,2-Bis(diphenylphosphino) ethane
dppf	1,1′-bis(diphenylphosphino)-ferrocene
dppp	1,3-bis(diphenylphosphino) propane
dtbpt	di-*tert*-butyl(2-(di-*tert*-butyl-phosphanyl)-benzyl) phosphane

dtbpx	1,2-bis(di-*tert*-butyl-phosphinomethyl)benzene
EI	electron impact ionization (MS)
eq.	equivalent
ESI	electrospray ionization (MS)
Et	ethyl
FID	flame ionization detector (GC)
FT	fourier-transformation (IR)
GC	gas chromatography
h	hour(s)
Hept	heptyl
hept	heptet (NMR)
HMBC	heteronuclear multiple bond correlation (NMR)
HR	high resolution (MS)
HSAB	hard and soft acids and bases
HSQC	heteronuclear single quantum coherence (NMR)
Hz	hertz (NMR)
i	*iso*
IC_{50}	half maximal inhibitory concentration
IR	infrared spectroscopy
J	coupling constant
LR	low resolution (MS)
M	mol per liter
M	metal
m	multiplet (NMR); medium (IR)
Me	methyl
min.	minute(s)
MMA	methyl methacrylate
m.p.	melting point
MS	mass spectrometry
MsOH	methansulfonic acid
m/z	mass to charge ratio (MS)
NFS	*N*-formylsaccharin
NMR	nuclear magnetic resonance
NSAID	nonsteroidal anti-inflammatory drug
Nu	nucleophile
Ph	phenyl
pK_a	logarithmic acidity constant
ppm	parts per million
Pr	propyl
psi	pound-force per square inch
PSIL	phosphonium salt ionic liquid
***p*TsOH**	*para*-toluenesulfonic acid
q	quartet (^{1}H-NMR); quaternary carbon (^{13}C-NMR)
quin	quintet (NMR)
rac	racemic
RBF	round-bottom flask
R_f	retention value
RT	room temperature
s	singlet (NMR); strong (IR)
sat.	saturated
sext	sextet (NMR)
sh	sharp (IR)

t	triplet (NMR)	**TMEDA**	tetramethylethylenediamine
t	*tert*	**TOF**	time-of-flight (MS)
TEA	triethylamine	**TOF**	turnover frequency
Temp.	temperature	**UV**	ultra violet
TFA	trifluoroacetic acid	$\tilde{\nu}$	wave number (IR)
THF	tetrahydrofuran	**w**	weak (IR)
TLC	thin layer chromatography	**Xantphos**	4,5-bis(diphenylphosphino)-
TM	transition metal		9,9-dimethylxanthene

6.2 Acknowledgements

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Danke

6.3 Curriculum Vitae

Vera Hirschbeck

Personal Data

Birthday:	15.04.1991
Birthplace:	Munich, Germany
Nationality	German

Education

Since 10/15:	Doctoral Thesis at the University of Regensburg, Institute of Organic Chemistry in the working group of Prof. Dr. Ivana Fleischer (University of Tübingen). "*Development of New Catalytic Systems for the Palladium-Catalyzed Carbonylation of Olefins*"
10/13 – 09/15:	M.Sc. Chemistry at the University of Regensburg Master thesis in the working group of Prof. Dr. Ivana Fleischer, Institute of Organic Chemistry, University of Regensburg. "*Alkoxycarbonylation of olefins and its attempted application in the synthesis of a natural compound"*
10/10 – 07/13:	B.Sc. Chemistry at the University of Regensburg Bachelor thesis in the working group of Prof. Dr. Oliver Reiser, Institute of Organic Chemistry, University of Regensburg. "*Recycling von Pd-Nanopartikeln mit Hilfe von magnetischen ionischen Flüssigkeiten"*
09/01 – 06/10:	Abitur (A-level) at the Humboldt-Gymnasium Vaterstetten

Fellowships

04/16 – 03/18:	Ph.D. fellowship from the Fonds of the German Industry
Since 04/18:	Ph.D fellowship from the University of Regensburg (Bayerisches Programm zur Realisierung der Chancengleichheit für Frauen in Forschung und Lehre)
06/16 and 03/17:	Conference travel fellowship from the GDCh

Congress contributions and other presentations

2018:	"*Entwicklung neuer Katalysatorsysteme zur Carbonylierung von Olefinen*" (oral presentation), Regional meeting of the Fonds of the German Industry, Regensburg, Germany.
2017:	*"Regioselective thiocarbonylation of vinyl arenes"* (poster), 8th Münster Symposium on cooperative effects in chemistry, Münster, Germany.
2017:	*"Regioselective thiocarbonylation of vinyl arenes"* (poster), 50. Jahrestreffen Deutscher Katalytiker, Weimar, Germany.
2016:	*"Regioselective alkoxycarbonylation of alkenes with CO surrogates"* (poster), 17th Tetrahedron Symposium, Sitges, Spain.

6.4 List of Publications

6) V. Hirschbeck, M. Böldl, P. H. Gehrtz, I. Fleischer,* *manuscript in preparation*. *„Tandem Acyl Substitution/Michael Addition of Thioesters with Vinylmagnesium Bromide"*

5) V. Hirschbeck, I. Fleischer,* *Chem. Eur. J.*, **2018**, *24*, 2854-2857. ("Hot Paper", highlighted in *ChemistryViews*), *"Synthesis of Benzofuranones via Palladium-Catalyzed Intramolecular Alkoxycarbonylation of Alkenylphenols"*

4) V. Hirschbeck, P. H. Gehrtz, I. Fleischer,* *Chem. Eur. J.* **2018**, *24*, 7092-7107, *"Metal Catalyzed Synthesis and Use of Thioesters: Recent Developments"*

3) V. Hirschbeck, P. H. Gehrtz, I. Fleischer,* *J. Am. Chem. Soc.* **2016**, *138,* 16794-16799. (highlighted in Synfacts **2017**, *13*, 275)*, "Regioselective Thiocarbonylation of Vinyl Arenes"*

2) P. H. Gehrtz, V. Hirschbeck, Benjamin Ciszek, I. Fleischer,* *Synthesis* **2016**, *48*, 1573-1596, *"Carbonylations of Alkenes in the Total Synthesis of Natural Compounds"*

1) P. H. Gehrtz, V. Hirschbeck, I. Fleischer,* Chem. Commun. **2015**, 51, 12574-12577, *"A Recyclable CO Surrogate in Regioselective Alkoxycarbonylation of Alkenes: Indirect Use of Carbon Dioxide"*

6.5 Eidesstattliche Erklärung

(1) Ich erkläre hiermit an Eides statt, dass ich die vorliegende Arbeit ohne unzulässige Hilfe Dritter und ohne Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe; die aus anderen Quellen direkt oder indirekt übernommenen Daten und Konzepte sind unter Angabe des Literaturzitats gekennzeichnet.

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(4) Die Arbeit wurde bisher weder im In- noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde vorgelegt.

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Vera Hirschbeck