“Iron- and Cobalt-Catalyzed Hydrogenation and Cross-Coupling Reactions”

Dissertation

zur Erlangung des Doktorgrades der Naturwissenschaften

Dr. rer. nat.

an der Fakultät für Chemie und Pharmazie

der Universität Regensburg

vorgelegt von

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Regensburg 2015

Der experimentelle Teil dieser Arbeit wurde in der Zeit zwischen Oktober 2012 und Oktober 2015 am Institut für Organische Chemie der Universität Regensburg unter Anleitung von Prof. Dr. Axel Jacobi von Wangelin angefertigt.

Die Arbeit wurde angeleitet von:		Prof. Dr. Axel Jacobi von Wangelin
Promotionsgesuch eingereicht am:		16.10.2015
Disputationsvortrag am:		20.11.2015
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Table of Contents

1 Introduction 1

1.1 Transition metal catalyzed processes 1

1.2 Distinction between Homogeneous and Heterogeneous Catalysis 3

1.2.1. Kinetic studies and reaction progress analyses 5

1.2.2 Poisoning experiments 9

1.2.3 Summary 26

1.3 References 27

2 Highly Practical Iron-Catalyzed C-O Cleavage Reactions 33

2.1 Introduction 34

2.2 Initial Optimization Experiments 34

2.3 Iron-Catalyzed Deallylation of Functionalized Aryl Ethers 35

2.4 Cleavage of Other Aryl Ethers and Iron/NHC-Catalyzed Deallyl-ation 38

2.5 Proposed Mechanism 40

2.6 Conclusion 42

2.7 Experimental Section 43

2.7.1 Preparation of O-allyl phenyl ethers 44

2.7.2 Synthesis of *O*-allyl alkylethers 54

2.7.3 Synthesis of *O*/*N*-Allyloxycarbonyl compounds 56

2.7.4 Other Starting Materials 58

2.7.5 Iron-Catalyzed Ether Cleavage Reactions 68

2.8 References 71

3 Iron-Catalyzed Cross-Coupling of Alkenyl Acetates 75

3.1 Introduction 76

3.2 Selected Optimization Experiments 77

3.3 Comparison of *O*-Based Leaving Groups and Substrate Scope 79

3.4 Mechanistic Investigation 82

3.5 Cross-Coupling of 2-Pyrones 84

3.6 Arylation of Alkenyl Acetates 84

3.7 Summary 85

3.8 Experimental Section 86

3.8.1 Preparation of Starting Materials 87

3.8.2 Iron catalyzed cross-coupling reactions of alkenyl acetates with alkylmagnesium halides 116

3.8.3 Ring-Opening/Cross-Coupling Reactions 150

3.8.4 Iron catalyzed cross-coupling reactions of alkenyl acetates with aryllmagnesium halides 151

3.9 References 158

4 Heteroatom-Free Arene-Cobalt and Arene-Iron Catalysts for Hydrogenations 163

4.1 Introduction 164

4.2 Hydrogenation of alkenes, alkynes and arenes 165

4.3 Hydrogenation of ketones and imines with cobaltate 1 168

4.4 Mechanistic studies 169

4.5 Summary 172

4.6 Experimental Section 173

4.6.1 Preparation of Starting Materials 176

4.6.2 Hydrogenation Reactions 187

4.6.3 Further mechanistic studies 199

4.7 References 201

5 Reductive Cross-Coupling Reactions between Two Electrophiles 205

5.1 Introduction 206

5.2 Cobalt Catalysis 209

5.2.1 Zinc-Mediated Reaction 210

5.2.2 Manganese Mediated Reactions 213

5.2.3 Magnesium-Mediated Reactions 218

5.3 Palladium Catalysis 219

5.3.1. Zinc-Mediated Reactions 219

5.3.2 Non-metallic Reductant 222

5.4 Nickel Catalysis 223

5.4.1 Zinc-Mediated Reactions 223

5.4.2 Manganese-mediated reactions 231

5.5 Iron catalysed reactions 235

5.5.1 Magnesium mediated reactions 236

5.6 Summary and Outlook 237

5.7 References 239

6 Summary 242

7 List of Abbreviations 245

8 Acknowledgements 248

9 Curriculum Vitae 251

10 Eidesstattliche Versicherung 254

1 Introduction[I,II]

1.1 Transition metal catalyzed processes

Transition metal-catalysts represent a powerful tool due to their valuable potential to lower activation barriers of chemical transformations by various modes. Their potential to act as catalysts for sustainable and selective reactions has been widely used over the past century. Nowadays, 80 to 90% of all industrial processes are performed with the use of catalysts.[1] The importance of metal-catalyzed transformations is also illustrated by bestowal of three Nobel Prizes to work in this field over the past 10 years.[2]

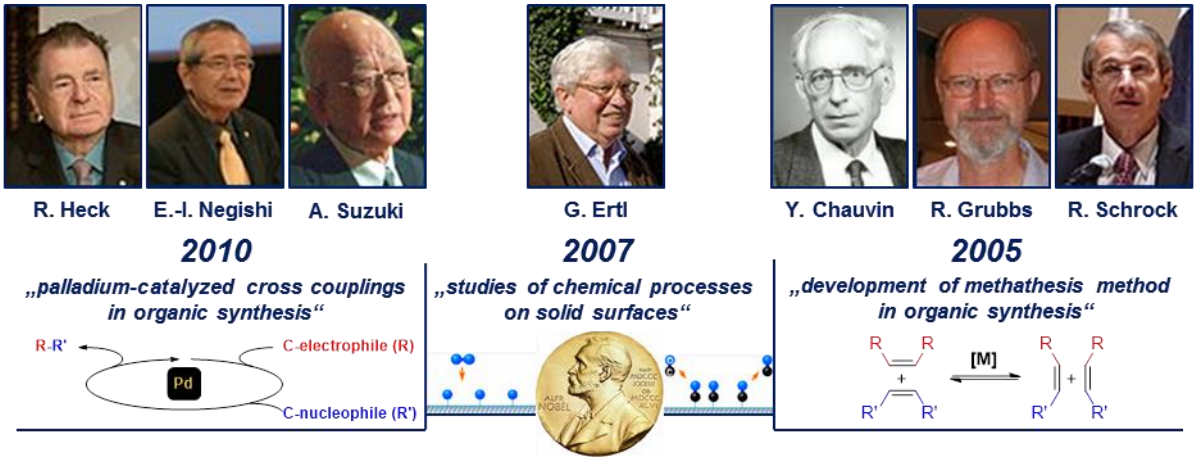


Figure 1.1: Nobel Prizes for pioneering work in the field of metal-catalysis.[2]

Transition metal-catalyzed reactions where C-H (hydrogenations) or C-C/N-bonds (cross-couplings) are formed, constitute one of the most important operations for the synthesis of pharmaceuticals, fine and bulk chemicals.[3] Some precious metals became so commonly used in these reactions that some of them are inextricably linked to these processes (cross-couplings: Pd, Ni, Cu; hydrogenations: Pd, Ni, Rh).[4]

Despite the fact, that there are numerous advantages in using precious metals for these transformations, there is a large interest to develop processes where noble metals can be substituted by abundant, cheap and environmentally friendly metals.[5] Interesting alternatives are especially 3d-block metals, except for nickel-catalysts due to their relative high toxicity.[6] In recent years, iron- and cobalt-based catalysts have

been demonstrated to exhibit high potential as catalysts for cross-coupling and hydrogenation reactions; nickel.[7,8]

First row transition metals have in general a weak crystal field splitting (Δ), so high spin states of corresponding complexes are tendentious.[9] Such high-spin complexes, which can be viewed as metallo-radicals, can undergo single electron transfer reactions (SET) and decompose. Therefore, studies in the 1970s predicted non-selective radical chemistry for the high-spin first row transition metal complexes. The high-spin character of many 3d-metal complexes also limit the application of magnetic resonance (NMR) spectroscopy to study their reaction mechanisms.[10]

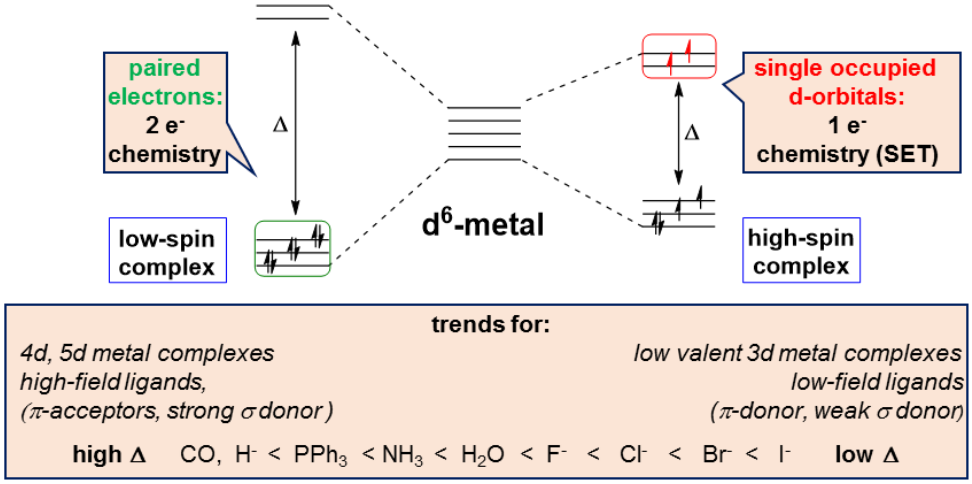


Figure 1.2: General trends of low- and high-spin complexes.

Nevertheless numerous examples in the recent literature demonstrated that 3d metal catalysts can be used in selective 2 electron transformations.[4,7] Generally, there are two possible ways how two-electron chemistry can be enabled for 3d metal complexes. One possibility is the formation of low-spin 3d metal complexes, e.g. with strong π acceptor ligands. But these complexes are rare and they often have strong binding ligands and an 18e$^-$-configuration, so their application in catalysis is limited.[8] A second possibility is the use of high-spin complexes with redox-active ligands. These ligands can undergo reversible electron transfer reactions and act as electron reservoirs. When the radical pathway is inhibited by reversible metal-ligand-interactions, the metal can undergo the 2-electron process.[11] There is also a compromise between high-spin and low-spin complexes, as 3d metals often have multiple spin states with similar energies. This can allow the presence of simultaneously existing spin states with varying activities, which is unwanted for

selective reactions. Yet, this characteristic can also be advantageous. Change of geometry during a reaction can trigger a flip/switch of spin states, despite the presence of low-field ligands. Thus, low-spin complexes and two-electron processes can become accessible under certain reaction conditions, even if high-spin complexes are the predominant species. This phenomenon has been called “spin acceleration”. Such spin-switches through metal-ligand orbital interactions constitute a key rationale for two-electron processes with redox-active ligands.[10]

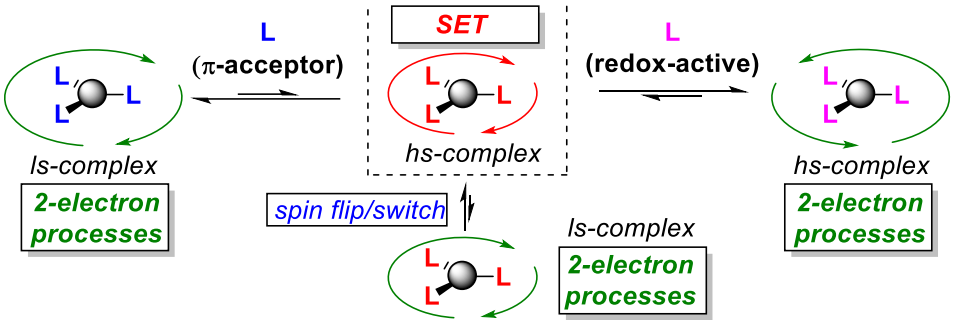


Figure 1.2: Pathways by which two-electron processes are accessible from high-spin complexes.

Although large progress in the field of catalysis with earth abundant metals has been made, several limitations (e.g. low stability, low lifetime, low selectivity and low productivity[12]) still prevent large-scale applications. To overcome these limitations, further improvements and adjustments of these catalytic systems are necessary and therefore a detailed mechanistic understanding is essential.[13] Except for a few examples in the literature, detailed mechanistic studies are widely available. A first step in the classification of catalyst composition, structure and appearance is the distinction between homogeneous or heterogeneous catalyst species. While for precious metals there are several well-established methods and techniques to distinguish between their physical aggregation mode,[13–15] most of these methods are poorly developed for 3d-metals.

1.2 Distinction between Homogeneous and Heterogeneous Catalysis

It should be emphasized that the classical Ostwald definition of the terms “homogeneous” and "heterogeneous”, where the catalyst is either in the same phase with the substrate or not, is not most relevant the answering of such questions

Ostwald`s definition is imprecise for contemporary standards as even nanoparticles (NPs)[16] and colloids can be soluble (e.g. dispersible)[17] in substrate solutions, despite their behavior as heterogeneous catalyst. Schwartz therefore introduced a new definition based upon the mechanistic operation of the catalyst.[13]

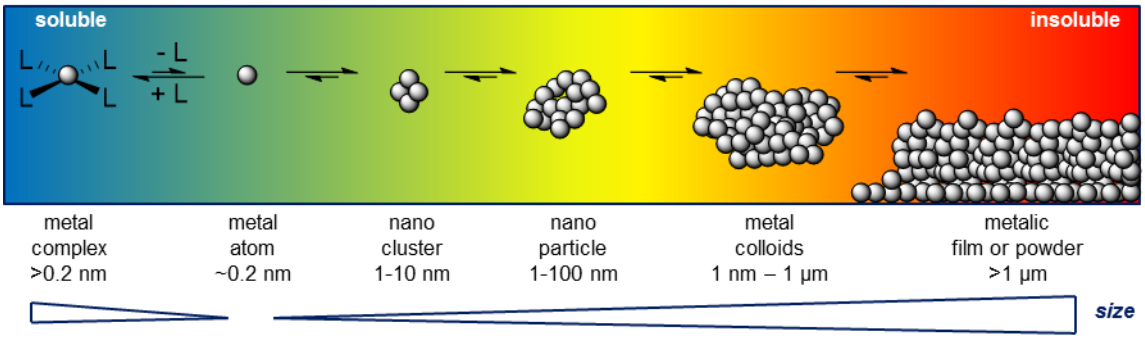


Figure 1.4: Correlation between size and solubility of different metal conditions.

According to Schwartz's definition, a homogeneous catalyst has a single active site, whereas heterogeneous catalysts have a multiple active sites. It should be mentioned, that authors in general do not clearly differentiate between Ostwald`s and Schwartz's definition. To avoid this definition conflict, Crabtree suggested the use of the "topicity" terminology (homotopic vs. heterotopic).[13]

Although we have multiple techniques in hand to characterize well-defined metal complexes, nanoparticles, and colloids, the identification of the true active catalyst in a reaction is still challenging. There is not a single conclusive test that can unambiguous distinguish between a homotopic or heterotopic catalysts, so that mostly several different and independent methods have to be applied.[18] Tests can be classified into *operando* and *post* operando (e.g. microscopy) techniques, while more significant results are achieved by *operando* methods under reaction conditions (*in situ*).

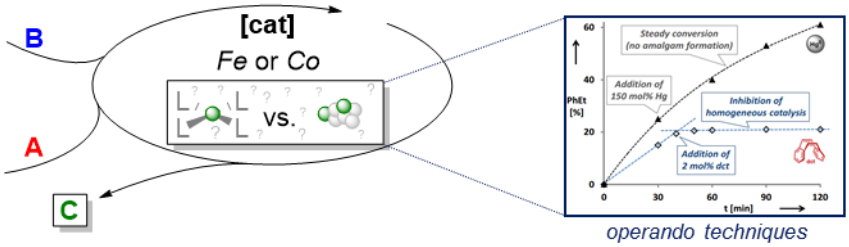


Figure 1.5: How to distinguish between homotopic and heterotopic catalysts.

In the following we wish to discuss some of the most reliable and powerful *operando* techniques that have been applied to modern iron- and cobalt- catalyzed reactions. A special focus is placed on catalyst development at the fine borderline of homotopic and heterotopic reaction mechanisms.

1.2.1. Kinetic studies and reaction progress analyses

Kinetic studies and reaction progress analyses are probably one of the most powerful *in operando* techniques to determine the active catalyst system. They have been widely applied for various metal complexes and catalytic reactions.[18] In general, well reproducible kinetics indicate to homotopic catalysts.[19] The activity and formation of NPs in catalytic reactions is strongly dependent on the conditions (e.g. temperature, solvent, concentration, etc.), and subject to significant change indeed by smooth changes. Therefore reactions with NPs are not easy reproducible.[18] But reproducible kinetics must not be associated with homotopic catalysis, and have also been observed with nanoparticles.[20]

Next, the shape of the reaction curve is an important feature. Some representative reaction progress analyses are shown in the following scheme.

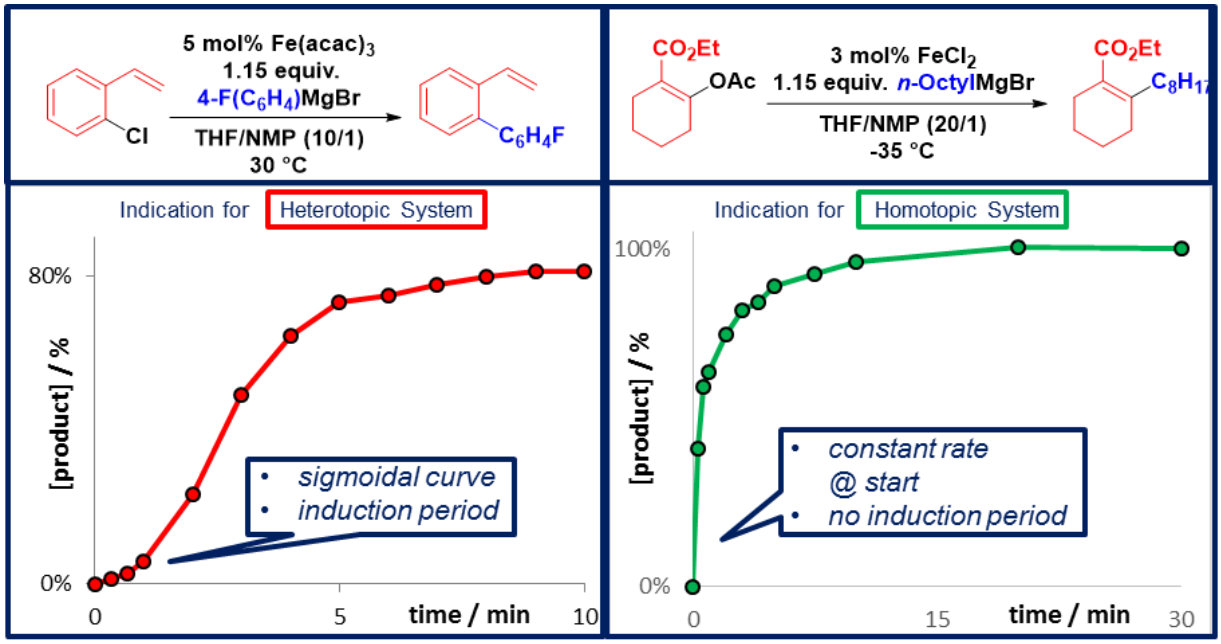
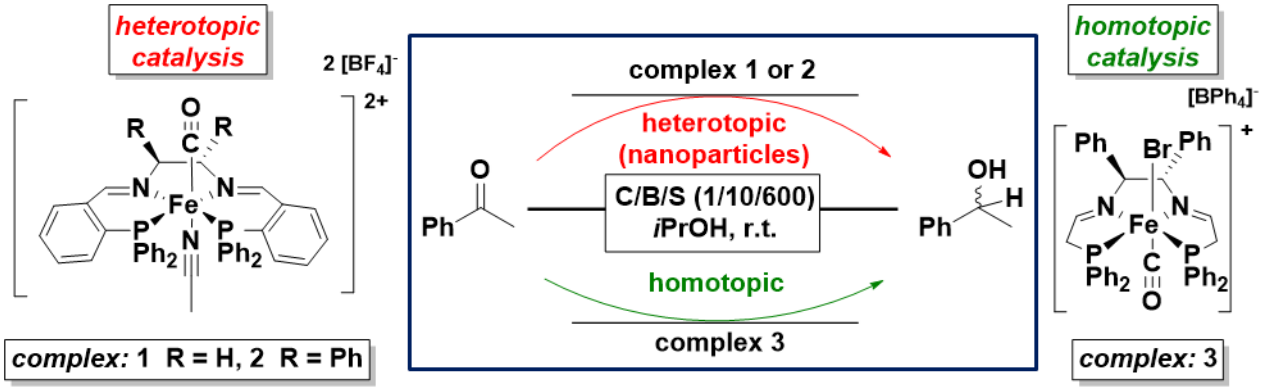


Figure 1.5: Left side: Cross-coupling of 2-chlorostyrenes (hetero-topic);[21] right side: Cross-coupling of alkenyl acetates (homotopic).[22,23]

Mostly, the transition-metal salt or complex is added to a reaction mixture is not the active catalytic species itself, but rather a precursor or pre-catalyst that forms the active catalyst under the reaction conditions.[18] Therefore a careful analysis of the initial reaction is interesting. In figure 1.5 left, the curve can be divided into three phases (initiation, catalysis and completion), whereas the initiation phase is missing in figure 1.5 right. Due to nucleation and growth phase, prolonged induction periods are common for heterotopic catalysts, whereas the activation/generation of an active homotopic catalyst is normally a fast process.[19] This points to a heterotopic catalyst for the reaction of figure 1.5 left and a homotopic species for figure 1.5 right. Further mechanistic experiments (e.g. poisoning experiments) have supported these.[21–23] However, interpretations of kinetic assumptions can also be misleading. The Morris group reported highly active iron(II) PNNP pre-catalysts that could be used in either asymmetric transfer hydrogenations (ATH), direct hydrogenations of ketones[19,24,25,26] and the dehydrogenation of ammonia-boranes.[27] It was later shown that totally different mechanisms are involved, though similar Fe(II) PNNP-complexes (see scheme 1.1) for asymmetric transfer hydrogenation have been used. When complexes **1** or **2** were used as pre-catalysts, a heterotopic pathway catalyzed by nanoparticles (NP) was operative,[24,26] whereas a homotopic pathway could be observed for complex **3** (see scheme 1.1).[18,19]



Scheme 1.1: Iron(II) PNNP complexes in ATHs by Morris *et al;* C/B/S is the molar ratio of complex, base (KO*t*Bu) and substrate.

First mechanistic studies in 2009 for the heterotopic catalyst system indicated a homotopic catalyst.

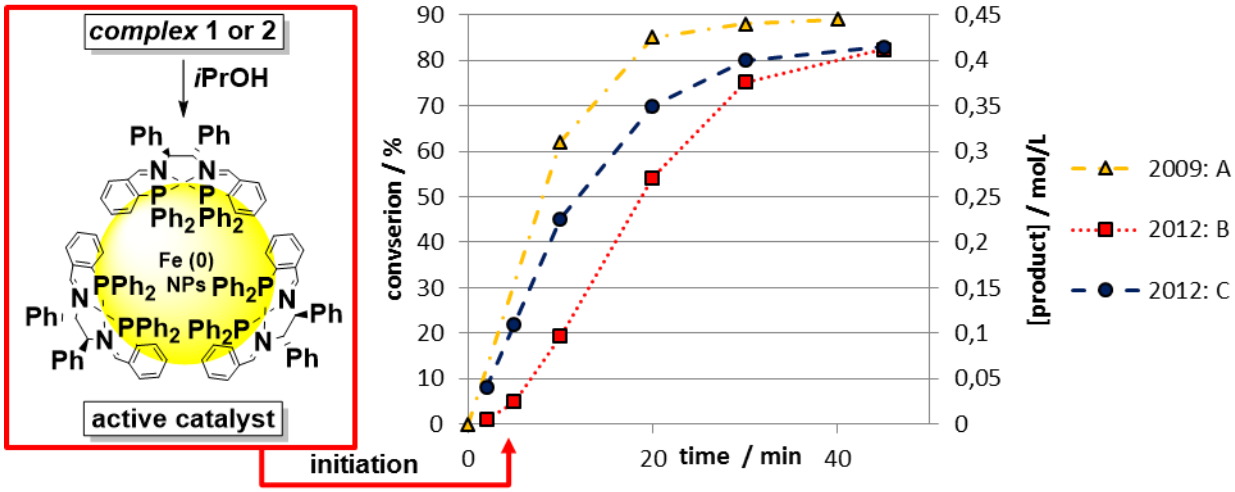


Figure 1.6: ATH of acetophenone using complex 1. A is referred to the conversion of starting material (left y-axis); B and C is related to the formation of product (right y-axis). Conditions: A, B: substrate in *i*PrOH added to solid 1 and base; C: preformation of catalyst in solvent with base (10 min) prior the addition to substrate.[24,26]

The reaction commence with a constant rate until the plateau has been reached. So, no initiation phase has been described in this case (see figure 1.4: 2009: **A**).[26] However, further investigations in 2012 revealed that there indeed is an initiation phase (see figure 1.6: 2012: **B**). In contrast to their previous work in 2009, the product formation in the beginning of the reaction (0-10 min) was precisely monitored to obtain a more detailed kinetic profile. It is not apparent whether there is any initiation process at curve **A**, because the first sample was taken after 10 minutes, when the conversion already exceeded 60%. Furthermore, in 2012 the kinetic curves to the product formation were investigated and not the substrate consumption. This is important due to the fact that substrates can be involved and also consumed during the catalyst formation process.[19,28] When complex **1** was pretreated with a strong base and *iso*-propanol for 10 minutes, which presumably formed the active catalyst, similar results compared to their work in 2009 could be achieved (see figure 1.6: 2012: **C**).[24,26]

Kinetic studies on the homotopic pathway of complex **3** manifested an untypical initiation phase (see figure 1.7: **A**).

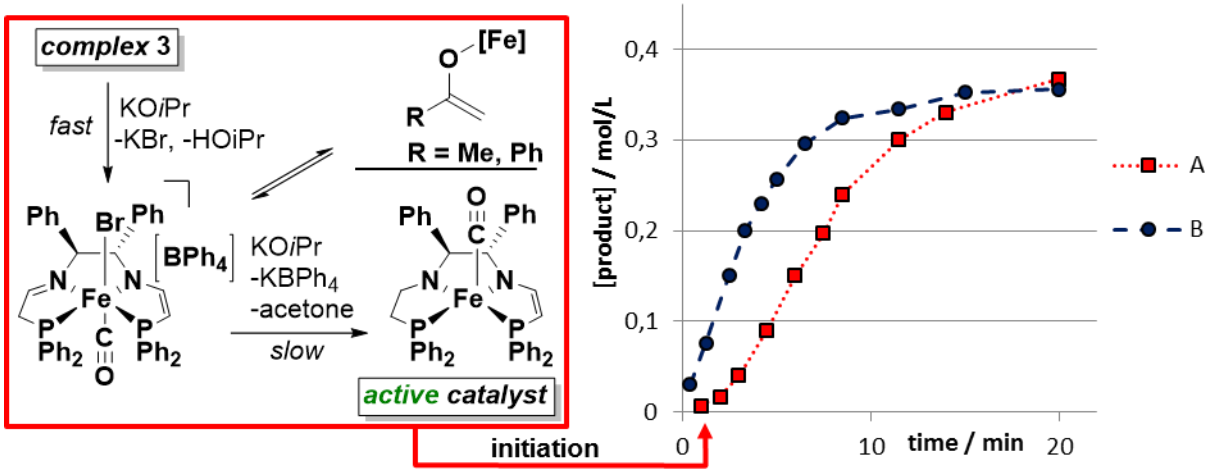


Figure 1.7: ATH of acetophenone using complex 3. Conditions: A : substrate in *i*PrOH added to solid 1 and base; B: preformation of catalyst in *i*PrOH (12 min) prior to addition of substrate.[19]

Such an initiation phase for homotopic catalysts is untypical but has been reported for molecular catalysts.[29,30] When complex **3** was pretreated with *iso*-propanol and potassium *tert*-butoxide for 10 minutes, no induction period was observed, indicating that the active catalyst is formed slowly in the presence of the solvent and the base. Because of the high reactivity of the catalyst in its active state, isolation and identification is often not possible. In this case, a big step for the identification of the active catalyst was the formation and isolation of another complex, after treatment of the reaction with hydrochloric acid (see figure 1.8).

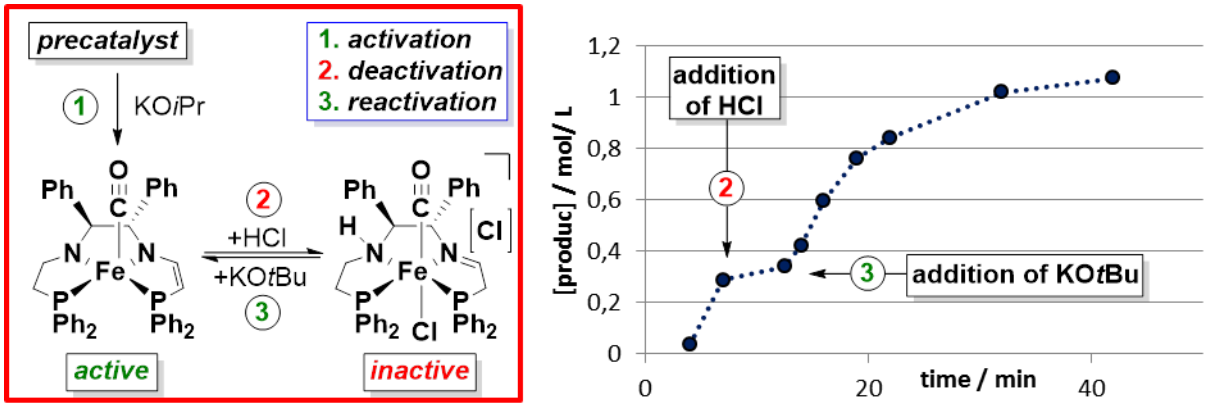


Figure 1.8: Quenching/reactivation experiments for iron-catalyzed ATH of acetophenone 3.[18,19]

After pre-treatment of the pre-catalysts with *iso*-propanol and base (to form the active catalyst by ligand exchange and ligand hydrogenation), a standard catalytic ATH was studied. At approx. 15% conversion, an excess of hydrochloric acid was added, to inhibit the reaction. After addition of base, catalytic activity was re-established.

The same experiment was performed with the heterotopic catalyst system. But in contrast to the prior results, addition of base could not re-established, the catalytic activity.

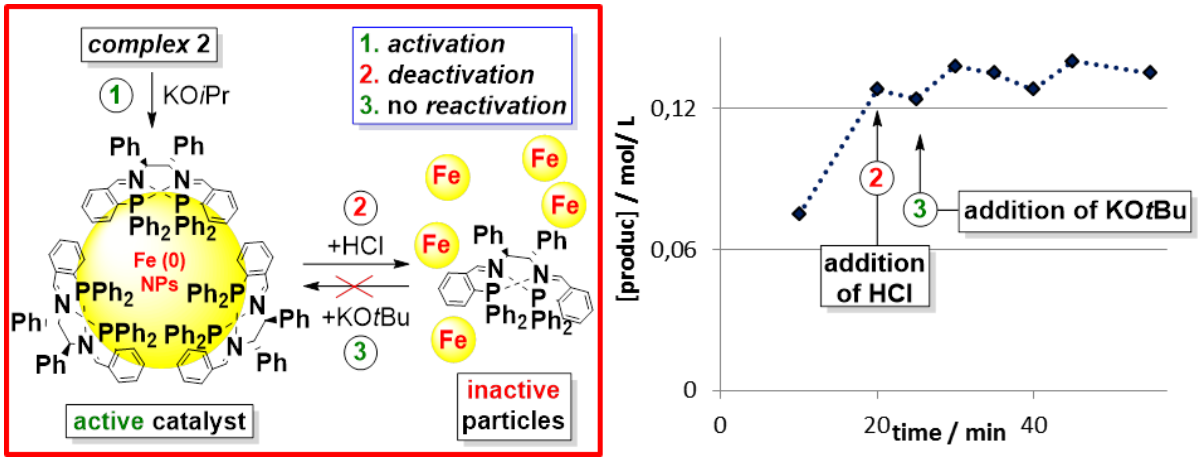


Figure 1.9: Quenching/reactivation experiments for iron-catalyzed ATH of acetophenone with 2.[18,24]

A rapid deactivation/reactivation phenomenon is more indicative of homotopic catalysts. In this case, treatment of the active homotopic catalyst with hydrochloric acid afforded a chloro-carbonyl complex.[18,24] This complex was isolated and used as a pre-catalyst with a superior activity.[18]

Such quenching/reactivation experiments by acids will not be suitable to more sensitive and basic systems. Metal can form inactive metal oxides and coordinate nucleophilic/basic ligands, or the reagents can react irreversibly in an acid/base reaction.

1.2.2 Poisoning experiments

Processes that inhibit catalysis are normally unwanted, and the replacement of catalysts lost by catalyst deactivation costs industry billions of dollars. Catalyst poisoning is one possible pathway how a catalyst deactivation can occur. Deactivation describes a strong chemisorption of substrates, additives, cocatalysts or impurities on the active site of a catalyst.[31] This leads to lowering or even total inhibition of selectivity and activity of a catalytic system. Such unwanted poisonings can naturally occur by substrates, additives or impurities.[32] In contrast, poisoning by additives or pretreatment of catalyst has also been useful utilized. For example lead poisoned palladium catalysts (Lindlar catalyst) are a selective catalyst for the semi-

hydrogenation of alkynes.[33,34] But the selective inhibition of catalysts by poisons has been also successful utilized in the so called poisoning experiments. Poisoning studies are a very important *in operando* technique and a powerful tool to distinguish between heterotopic and homotopic catalysts. Such studies are normally performed in combination with reaction kinetics.[13]

In a typical experimental setup, the catalyst poison has to be added, after the active catalyst has been formed. Otherwise it can influence the catalyst formation. To ensure that the active catalyst has been formed, poisons are typically added to a running reaction at approx. 50% conversion. The comparison of a standard reaction process with a process where poisons are involved can provide important information about, how the active catalyst looks like.[13] Generally, one can divide poisoning experiments in quantitative and qualitative ones.

1.2.2.1 Quantitative poisons

Quantitative poisons act as strongly metal binding ligands, and react as well with homotopic, as with heterotopic catalysts.[35] The most common used quantitative poisons are phosphines, thiophenes and CS_2.[36] Important information about the nature of the active catalyst can be obtained by partial poisoning experiments.[34]

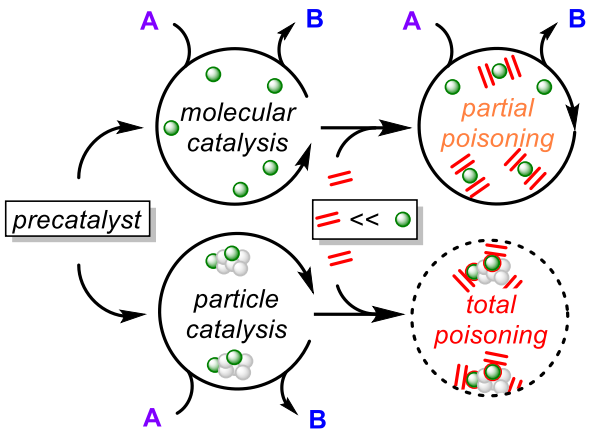


Figure 1.10: Stoichiometry of partial poisoning of molecular and particle catalysts.[34]

As most heterotopic catalysts are composed of compact particles, they have only a fraction of active metal atoms on the surface, and much less than 1 equivalent of poison should be needed for catalyst inhibition. Whereas molecular catalysts should need at least one or more equivalents to poison them.[29,31]

When the group of Szymczak conducted poisoning experiments for their iron-catalyzed olefin hydroboration, much more than one equivalent of PMe_3 for an effective catalyst deactivation was needed.

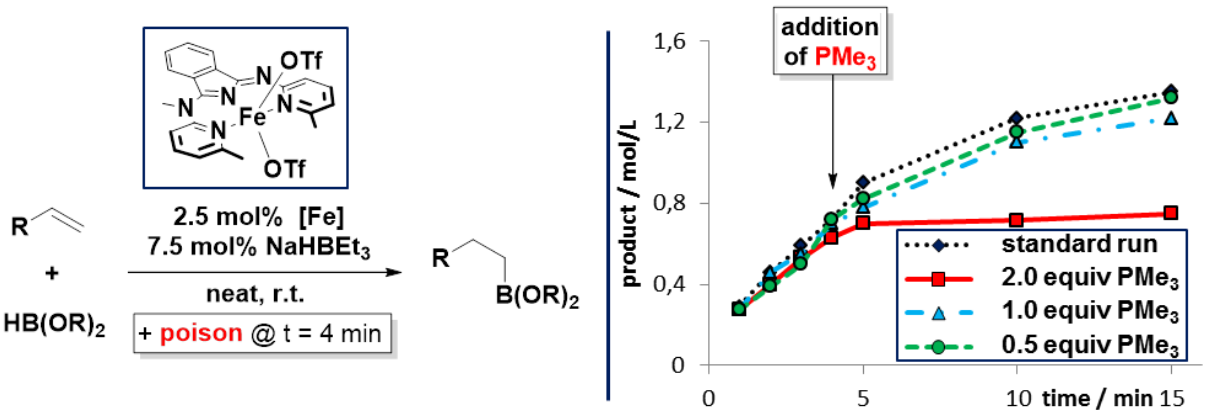


Figure 1.11: Poisoning experiments in the iron-catalyzed hydroboration of olefin with PMe_3.[20]

The application of less than two equivalents showed almost no effect on the reaction rate (see figure 1.11).[20]

Depending on the nature of the heterotopic catalyst, also an unusual amount of poison can be necessary to show any effect on activity and selectivity, as shown in the next example.

Gao *et al.* used relatively high amounts of triphenylphosphine as poison to inhibit their iron catalyzed asymmetric hydrogenation (AH) of ketones that is supposed to be heterotopic (see figure 1.12).[37]

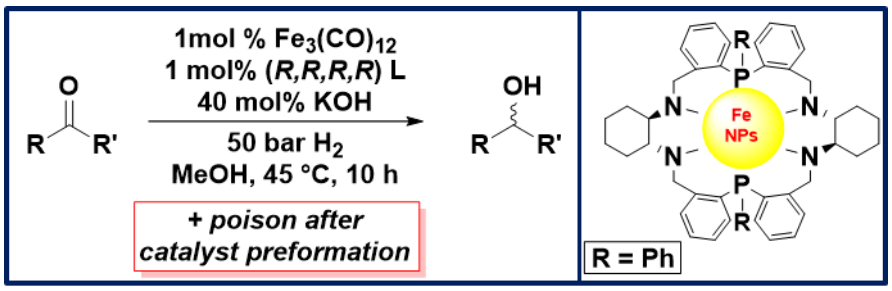


Figure 1.12: Iron-catalyzed assymetric hydrogenation of ketones according to Gao *et al.*.[37]

Under standard conditions they obtained usually very high conversions, and an enantiomeric excess (*ee*) of more than 99%, respectively 98%. The addition of 0.1 equivalent of PMe_3 had almost no effect. Only the addition of 0.3 equivalents and more resulted in a sharp loss of catalytic activity and selectivity.[37]

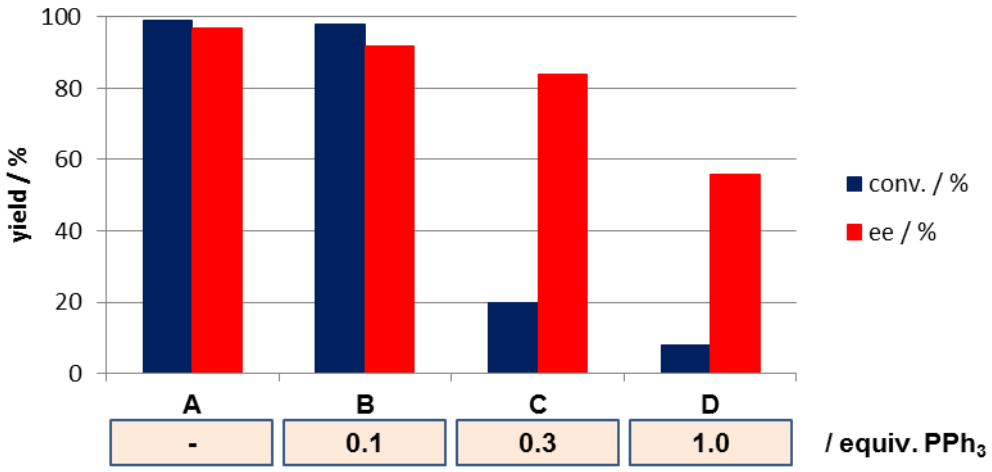


Figure 1.13: Effect of catalyst poisoning on the AH of acetophenone according to Gao *et al*.[37]

The authors missed to monitor their poisoning experiments. Maybe apparent difference between results **A** and can be observed here. The use of at least 0.3 equivalents suggests that approximately 30% of the iron is involved in catalysis. That could either mean that about 30% of the used iron is active on the surface of the NP or that just 30% of a potential homotopic catalyst is active.[24] However, the authors used different kinds of poisons to underline the heterotopicity of the catalyst, therefore it is hard to make any conclusions therefore it is hard to make any conclusions.

As there are many different poisoning reagents, the right choice of the poison is also important. When Morris *et al.* performed several poisoning experiments with their iron NP-catalyzed ATH, they could see a variety of effects depending on the used poisoning reagent:

The employed amine, phosphine, phosphite and thiol based additives were added in corresponding solvents (isopropanol, pentane, toluene or benzene) after 8 or 11 minutes after reaction start (see figure 1.14). Prior control experiments with the addition of pure solvents had no influence on the catalytic activity.[24,18] The amine additives 1,4-diazabicyclo[2.2.2]octane (DABCO) and ethylene diamine showed absolutely no effect. One can assume that nitrogen-based ligands are not suitable catalytic poison for the used catalytic system. The addition of 0.15 equivalents of 1-pentanethiol completely stopped the reaction. More interesting were the effects of phosphorous additives. When 0.2 equivalents tricyclohexylphosphine (not drawn in

figure 1.15) or triphenylphoshpine were added, an increase of reactivity without loss of selectivity could be observed.

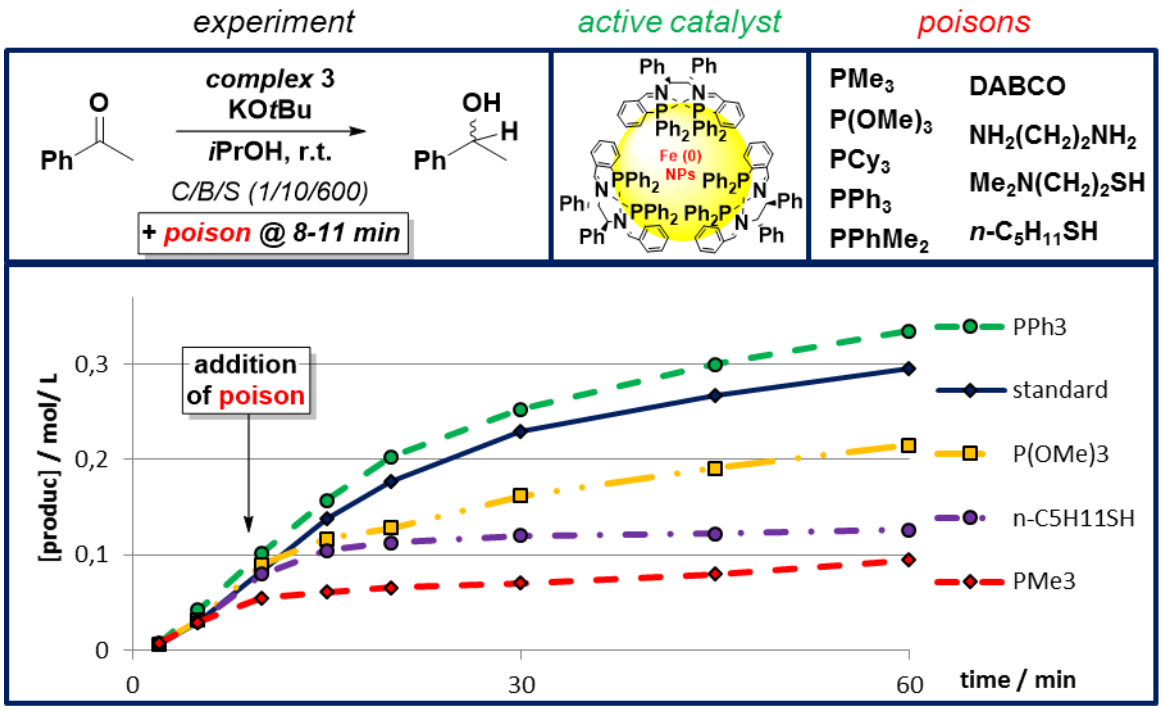


Figure 1.14: Poisoning experiments of the iron NP-catalyzed ATH of acetophenone.[24]

The authors suggest, that phosphines with bulky substituents can stabilize NPs better against agglomeration, and therefore prevent them better against deactivation. One could oppose that the added phosphines are acting as more suitable ligands than the PNNP ligands, and the increased reactivity is due to a different catalyst species that is formed with the additives. But the unchanged stereoselectivity argues against this theory.

On the contrary, addition of 0.1 equivalents trimethylphosphine or dimethyl-phenylphosphine almost entirely stopped the reaction. One possible explanation is the fact that the phosphines with smaller ligands can more easily penetrate the outer-sphere of the NP shell, blocking the active site of the catalyst more efficiently Addition of electronically different trimethylphosphite (0.2 equiv.) only lead to slower rates of the catalysis.[24,18] The catalyst slowdown can be explained by a reversible adsorption of phosphite to the active site of the catalyst.

Depending on the catalyst, even trimethylphosphine can be an inefficient poison, due to side reactions with substrates[38] or by being non-selective for the used catalytic

system.[39,19] These selectivity problems may can be solved by use of other types of poisons. For example, 1,10-phenanthroline[37] and *tert*-BuCN[39] showed in two specific cases better poisoning potential compared to trimethylphosphine. 1,10-Phenanthroline is so far the only catalytic poison for hydrogenation reactions under harsh conditions (≥ 100 °C, ≥ 50 bar H_2 pressure).[40] Reaction conditions at which poisoning experiments are conducted are important as well. Most of the reported poisoning experiments are performed at temperatures below 50 °C. At higher temperatures the used ligands/poisons can dissociate from the metal, and the original catalyst activity can be restored.[41]

Normally the poisoning reagent is directly added to the reaction mixture under reaction conditions. In some cases device- or condition-based circumstances could prevent a direct addition. For this reason the reaction can be interrupted, e.g. by lowering the temperature or by removal of reagents. In the meantime, the addition of poison can be carried out. Afterwards, the reaction conditions are restored and the effect of poisoning can be monitored. Important is, that the way how the catalysis is interrupted, does not irreversibly affect the system.

When Beller *et al.* performed poisoning experiments with their iron-catalyzed dehydrogenation of methanol (see figure 1.16), they had obviously similar concerns about the addition of their poisons:

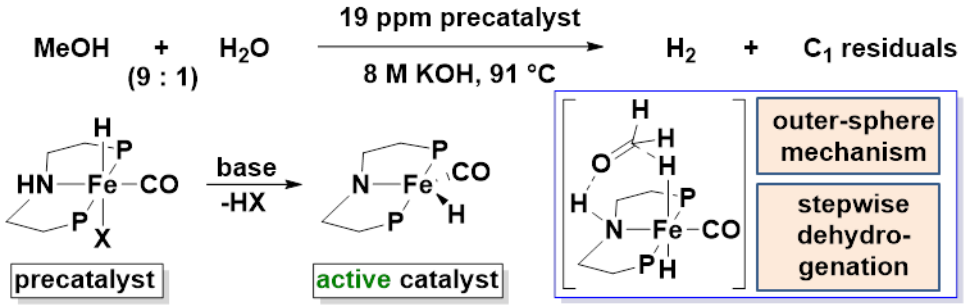


Figure 1.15: Dehydrogenation of methanol using an iron PNP-catalyst; diisopropyl substituents of phosphorus are removed for clarity reasons; X = BH_4^-, or Br^- .[42,43]

Before the addition of poison, they dramatically slowed down the reaction progress by lowering the temperature. This is probably due to the low boiling point (~40 °C) of the used PMe_3,[44] because it would not be appropriate to add it at the reaction temperature (91 °C).[42]

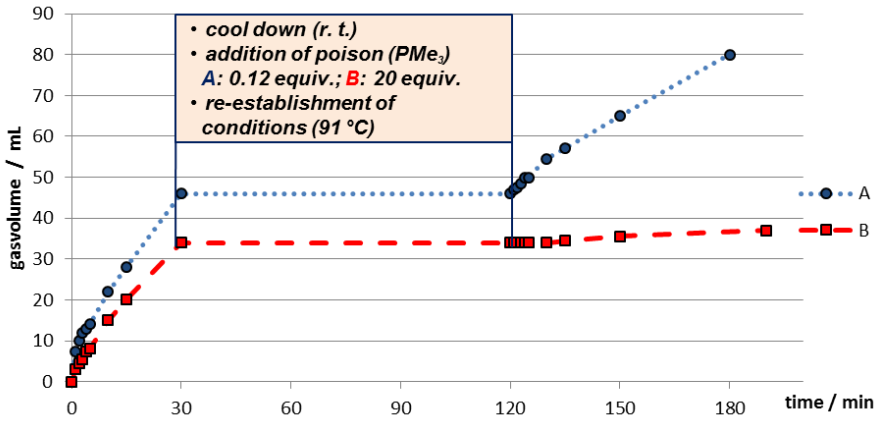


Figure 1.16: Sequential interuption, poisoning and reestablishment of reaction conditions.[42]

As shown, the substoichiometric addition of 0.12 equivalents of PMe_3 had almost no influence on the dehydrogenation when the temperature was restored, whereas the addition of 20 equivalents almost totally killed catalytic activity, despite the high reaction temperature.[42]

1.2.2.2 Qualitative poisons

Qualitative poisons can selectively interact with either homotopic or heterotopic catalysts. In contrast to quantitative poisons not the amount of additive is relevant for the differentiation, but it's the structure of the catalytic poison itself.

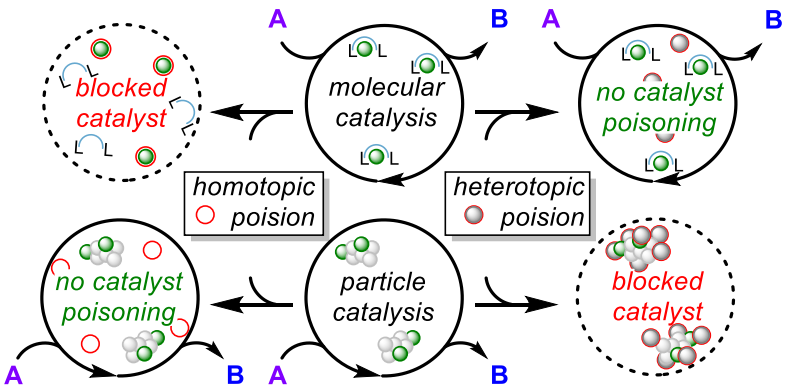


Figure 1.17: Effect of selective poisoning reagents on molecular and particle catalysts.

These selective poisoning tests conducted in parallel with a reaction, where the catalytic poison was not added, and differences are analyzed. Especially interesting are complementary test with one additive special for hetero- and one for homotopic catalysts. Valuable results should indicate opposing results; inhibition with poison

and no effect for the other one. These selective poisons have been especially used for 4d- and 5d-metal catalysts. However, as in the past decade there has been an increased interest in 3d-matal catalysis, they have been utilized also for iron and cobalt based-catalysts.

Selective heterotopic catalyst poisoning

For 3d-metals, especially the mercury test is a prominent example for the selective heterotopic poisoning experiment. The basic concept is that mercury can interact with other metals, either by adsorption or by formation of amalgams.[36] Homotopic metals, typically surrounded by shielding ligands, have no direct contact to the mercury, therefore interaction with mercury are supposed to be prohibited.

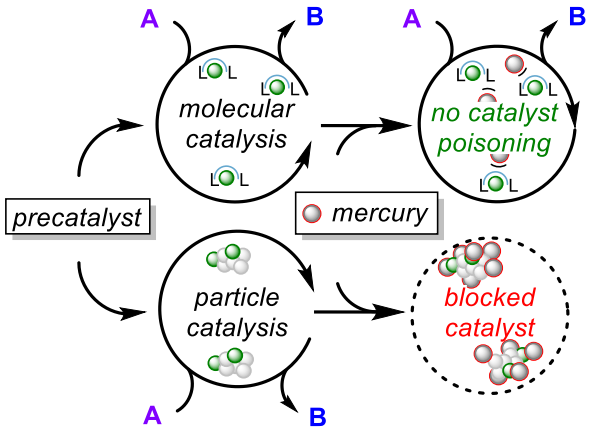


Figure 1.18: Effect of mercury poisoning on molecular and particle catalysts.

Although mercury poisoning has been widely used for iron and cobalt catalysts, validity of theses of these experiments is a subject of dispute.[45] And indeed, just from the physical properties, its application for cobalt and iron catalysts seems to be inappropriate. First of all iron and cobalt have a very low solubility in mercury; for Fe and Co $> 10^{-5}$ wt%. So incorporation by mercury is hindered just by solubility.[46] Nevertheless, also platinum metals like ruthenium, rhodium and iridium, were the mercury test is proposed to be selective, have a low solubility.[47] To compensate this disadvantage, a large excess of mercury should be used. So even for metals that are easily amalgamated like palladium, platinum or nickel, an excess of at least 500 equivalents of mercury should be added, and even more for metals that are not that easy amalgamated, like iron and cobalt. Also, under reductive conditions, solubility can be dramatically increased, at least for a short period of time.[46] The second and

probably more substantial disadvantage is the fact that iron and cobalt forms metastable alloys.[48,49] So under certain reaction conditions, formed alloys may be not stable and might decompose. In such cases the original catalytic activity can be restored. That is especially important for non-monitored poisoning experiments, because after recovery of catalytic activity the reaction may be able to proceed without consequences at the end of the reaction. In this case an effect could be seen directly after addition of mercury and after the formation of an alloy. Therefore kinetic monitoring should be a part of poisoning experiments. So, the crucial parameters for mercury poisoning are especially the lifetime, the reversibility of amalgam formation/adsorption and the concentrations of added mercury. The mentioned disadvantages are probably the reason why there are in literature quite a lot false negative results reported for heterotopic iron and cobalt catalyzed reactions.[50] Despite this fact, there are also some examples where iron and cobalt catalysts could be effectively inhibited by mercury.[37,51–53]

An interesting mercury poisoning experiment has been shown by Kou *et al.* in the hydroformylation reaction of 1-hexene catalyzed by Co NPs.[52]

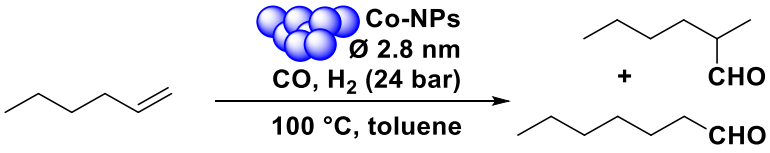


Figure 1.19: Effect of mercury poisoning on Co NPs and a homotopic rhodium catalyst.[52]

They injected mercury after 30 minutes to a highly pressurized reaction vessel by an external syngas pulse, and compared their results to a hydroformylation reaction catalyzed by the Wilkinson catalyst (Rh), that is supposed to be homotopic. The reaction was monitored by measurement of internal pressure respective to the conversion of used syngas.[52]

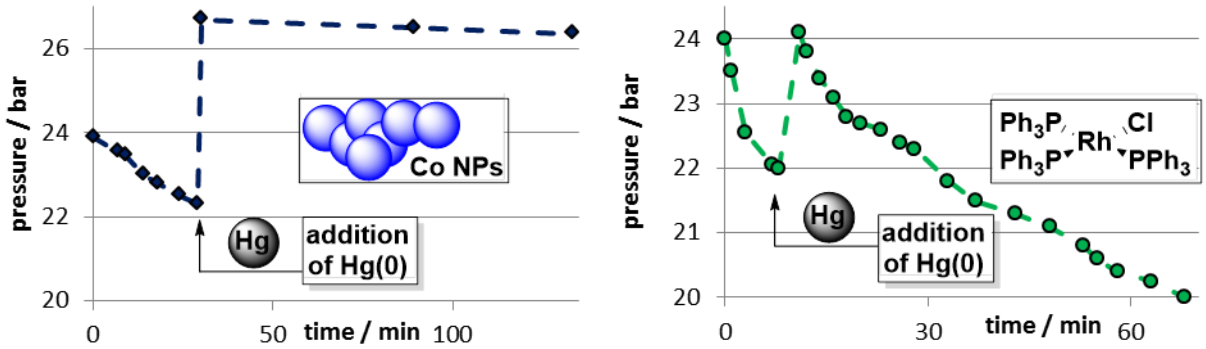


Figure 1.20: Effect of mercury poisoning on Co NPs and a homotopic rhodium catalyst.[52]

The Co–catalyzed system is completely inactive after addition of mercury, indicating the heterotopicity of the used system. In contrast the well-known homotopic hydroformylation by the Wilkinson catalyst is unaffected by the mercury.[52]

In some reported cases, the mercury additive reacted with molecular complexes and caused side reactions or even improved yields.[14,54] But also total inactivation of homotopic catalysts by mercury has been observed. [13,55] Possible deactivation pathways are shown in figure 1.21.

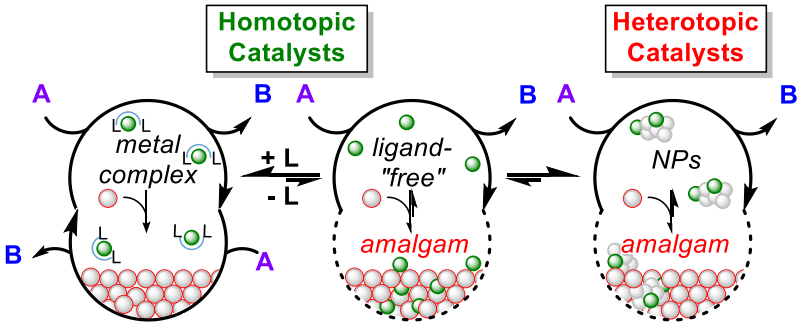


Figure 1.21: Possible catalyst deactivation pathways by interaction with mercury.[48]

Ligands are in general subjected to an association and dissociation equilibrium. As shown, homotopic catalysts can be amalgamated when no or less shielding ligands are present. So poisoning by mercury over time can occur for homotopic catalysts. Another possibility is the amalgamation of NP-precatalysts that can leach the so called *homeopathic* catalysts.[13,56]

In principal, mercury poisoning experiments are in combination with complementary tests a powerful tool, especially for late transition metals. The reported misleading results and their reasons should also be considered when applying this test. Relatively nonselective poisoning results with 3d-metal catalysts give reasonable doubts for the general validity of this test; iron and cobalt catalysts can but definitely do not necessary have to be inhibited.[57,58]

Selective homotopic catalyst poisoning

Homotopic catalyst poisons should selectively interact with molecular complexes. Usually polymer or silica bound poisoning reagents like phosphines,[59] thiols[60] and pyridines[13,61] have been utilized. Due to the sterically hindered environment during

the poisoning step, they should very effectively bind molecular catalysts. A penetration into particle shells or a poisoning of active frustrated sites in heterotopic catalysts should not be possible.

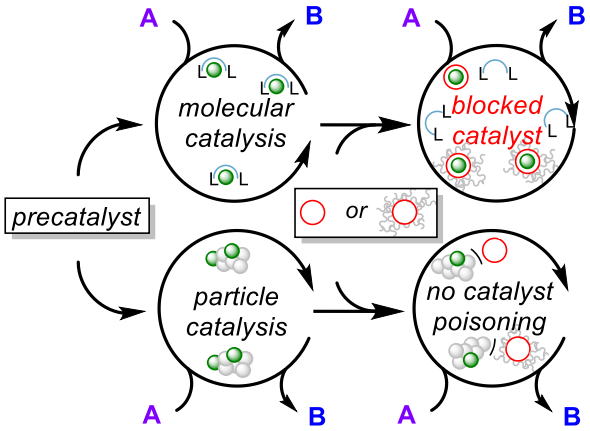
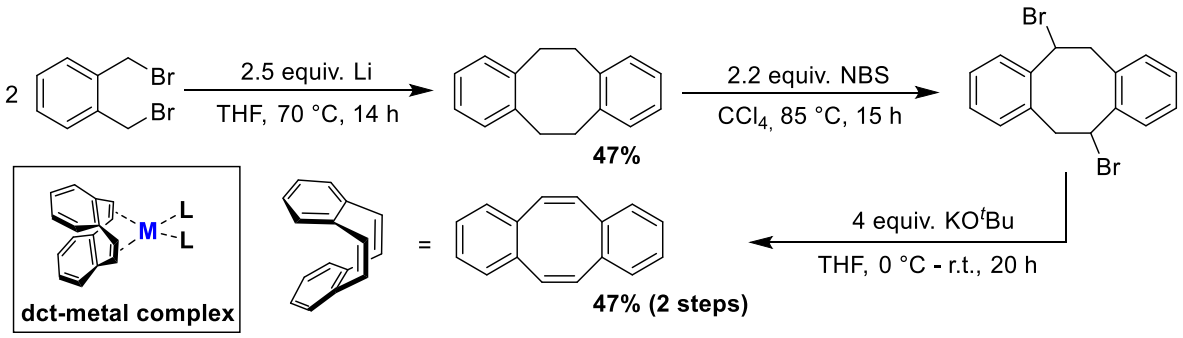


Figure 1.22: Effect of selective molecular poisons on molecular or particle catalysts.

But even if these poisoning reagents selectively react with homotopic reagents, the resultant complexes still can exhibit catalytic activity.[59,62] It is not abnormal because the used poisoning ligands are also often used as the stabilizing ligands for homotopic catalysis. The reversible binding mode (ligands dissociation / association) of such poisoning reagents, and therefore resistant catalytic activity, has been mentioned above. For example, at higher temperatures, the used poisons can dissociate from the metal and the original catalyst activity can be restored.[41] Alternatively, matrix bound poisons can also leach under certain reaction conditions. In this way liberated poisons can affect with both catalysts, heterotopic and homotopic.[60]

Ideal poison reagent does not have the above mentioned disadvantages. An interesting poisoning test with dibenzo[a,e]cyclooctatetraene (dct) has been reported by Crabtree *et al*. Dibenzo[a,e]cyclooctatetraene (dct) is an antiaromatic molecule with a rigid boat conformation, 1,5-cyclooctadiene (cod) has.[63] Because of the rigid and bulky conformation, dct should show by far less effects on heterotopic catalysts.[64,63] In difference to cod, it binds more strongly to metals, because of its strong d-π^*-acceptor ability that is in the range of phosphites.[65]



Scheme 1.2: Synthesis of dct and examplary dct-mtal complex.

Some remarkable benchmark data respective to the stability are reported: Dibenzo[*a,e*]cyclooctatetraene-complexes are prone to be stable against hydrogenations even under harsh conditions as has been shown with Rh- or Ir-dct complexes. Also no replacements of dct by $P(OEt)_3$ have been observed treating an Ir-dct-complex in refluxing ethanol for 12 hours.[66]

In literature there are not so many characterized metal complexes with dct. Examples have been shown with platinum metals,[66,67] but also molybdenum[68,66], chromium[69,68] cobalt[70] and copper[71] complexes are known. In case of chromium there is also an example in which the metal is coordinated to the annulated benzene and dibenzene moiety.[68,69] Because of its strong binding characteristics to molecular metals and its resistance against harsh reaction conditions it has been proposed as a selective molecular poisoning reagent. In literature there are some cases for platinum group complexes where dct has been used to underline the homotopicity of a given complex.[72,73]

An interesting example was given by Fisher *et al.* dct was used as a poisoning reagent for defined Pt(0) complexes in hydrosillylation reactions.

The effect of dct on an active molecular catalyst was compared to the Karstedt catalyst (see figure 1.10), that is known to react as heterotopic catalyst in these reactions.[72]

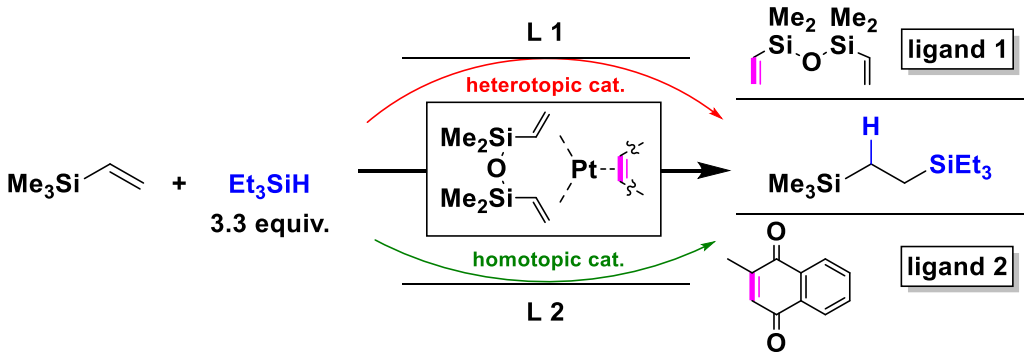


Figure 1.23: Hydrosylations with olefin platinum(0) complexes according to Fisher *et al.*; reaction conditions: 0.2 mol% of [Pt], solvent: n-hexane, 30 °C.[72]

As shown, dct has no noteworthy effect on the hydrosillylation reaction with the Karstedt catalyst (see figure 1.24). On the contrary the addition of 5 equivalents of dct could totally inhibit the catalysis at 60% product formation. Two important aspects for the molecular poisoning should be noted. First, even the addition of 2 equivalents of dct did not stop the reaction. The initial rate slowed down, but nevertheless the reaction came to completion eventually. Second, it took about 60 minutes to inhibit the reaction. It should be mentioned that dct was added to the catalyst solution 60 minutes prior reaction start. In a different reaction also 2 hours were needed until dct completely inhibited a rhodium catalyzed reaction.[63]

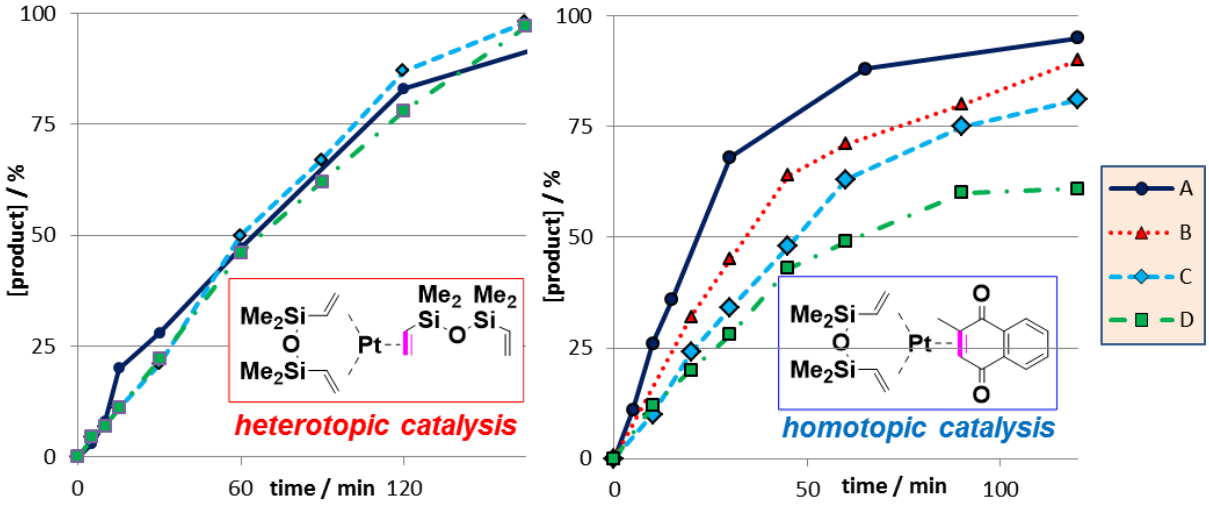


Figure 1.24: Dct-poisoning experiments according to Fisher *et al.*; reaction conditions as mentioned in figure 1.10; dct was added to the precatalyst 60 min prior the addition of triethylsilane; Curves: A = without dct; B = 1 equiv. dct; C 2 equiv. dct; D = 5 equiv. dct.[72]

Such long reaction times with metals can be unfavorable, because reactions of interest can go to completion before the poisoning occurs. Under these circumstances a false negative result can be indicated.

Only few examples by Wolf, Jacobi von Wangelin and coworkers are reported in which dct has been used as poisoning reagent for iron and cobalt catalyzed reactions.[23,70,74–76]

The dct and the complementary mercury test were used in a key experiment when Jacobi von Wangelin and Wolf *et al.* determined the homotopicity of bis(anthacene)-cobaltate in hydrogenation reactions of olefins (see figure 1.25).[74]

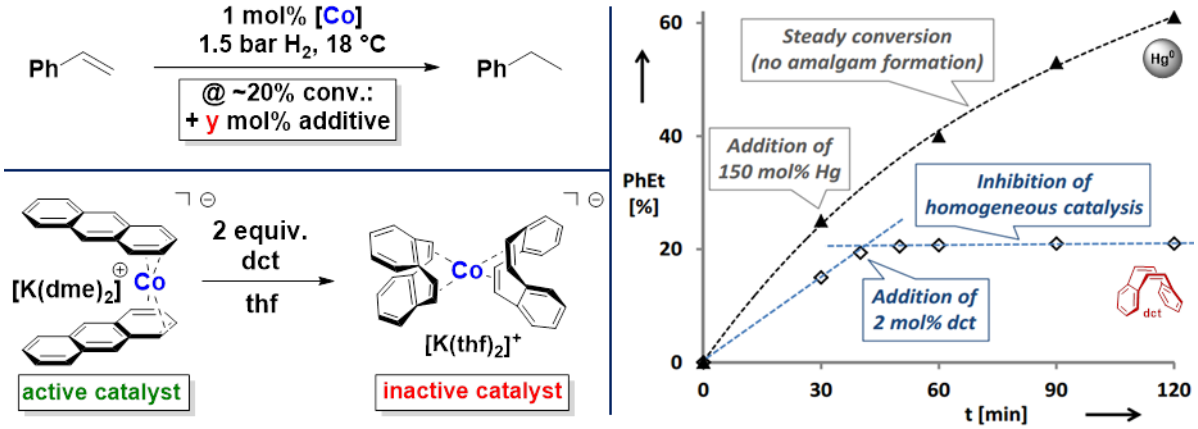


Figure 1.25: Complementary poisoning tests with dct and mercury in cobalt-catalyzed hydrogenation reactions according to Wolf and Jacobi von Wangelin *et al.*[74]

The negative mercury test and the total inhibition of catalysis after addition of 2 equiv. of dct argue strongly for a homotopic catalyst. It turned out, that after addition of dct, a bis(dct)cobaltate complex was formed. The formed complex did not show catalytic activity after isolation.[70] However in a quite similar reaction dct did not inhibit the reaction (see scheme 1.13).

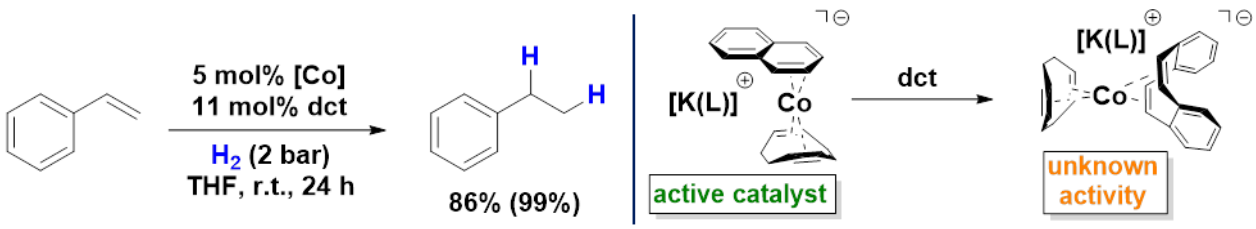


Figure 1.26: Dct-poisoning of cod-napthalene cobaltate according to Wolf and Jacobi von Wangelin *et al*; L = [18-crown-6]; yields in parenthesis are without poisoning reagent.[70]

When adding 2 equivalents of dct directly to a solution of the used catalyst a heteroleptic cod-dct cobaltate complex is formed overnight. A homoleptic bis(dct) cobaltate complex, comparable to figure 1.6 was only found in trace amounts. Maybe longer reaction times would lead to the already described inactive bis(dct) complex. The activity of the formed naphthalene-dct complex is still unknown, but some examples in literature revealed the potential of heteroleptic dct-metal complexes as catalysts.[77] So the formations of heteroleptic dct-complexes may pose a problem in poisoning experiments. Since there are still labile ligands respectively to dct coordinated to the metal, an active coordination sites can be provided by dissociation processes.

Another interesting example, in which dct has been used, was the iron-catalyzed hydrogenation of olefins with $FeCl_3$ as precatalyst.[76]

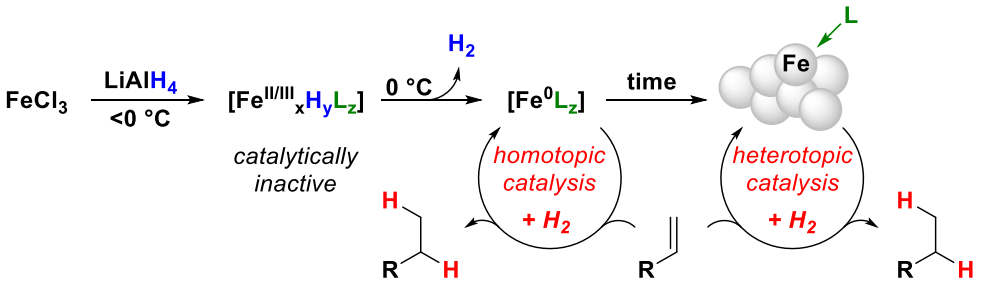


Figure 1.27: Proposed formation and catalysis of low-valent iron species according to Wolf and Jacobi von Wangelin *et al.*[74]

The authors suggest that in the beginning of the reaction a homotopic mechanism is predominant. After some time, the naked molecular catalysts experience ageing and particle agglomeration, so heterotopic catalysts are formed. The heterotopic catalysts are less active than their homotopic precursors. The proposed mechanism was inter alia supported by kinetics and poisoning studies. As shown in figure 1.28, the hydrogenation of α-methylstyrene was used as a model reaction for the poisoning experiments.

Although there is a constant reaction progress without initial phase (section I) at the beginning of the reaction, a missing initial period can not be used as a indication for a homotopic catalyst, because the catalyst was preformed 10 minutes before reaction start. After 30 minutes dct and mercury respectively, were added. In case of mercury no change in activity was observed; the reaction went to completion. When dct was added. The reaction slowed down dramatically after addition (section II) and was totally inhibited at around 60 % reaction progress (section III).

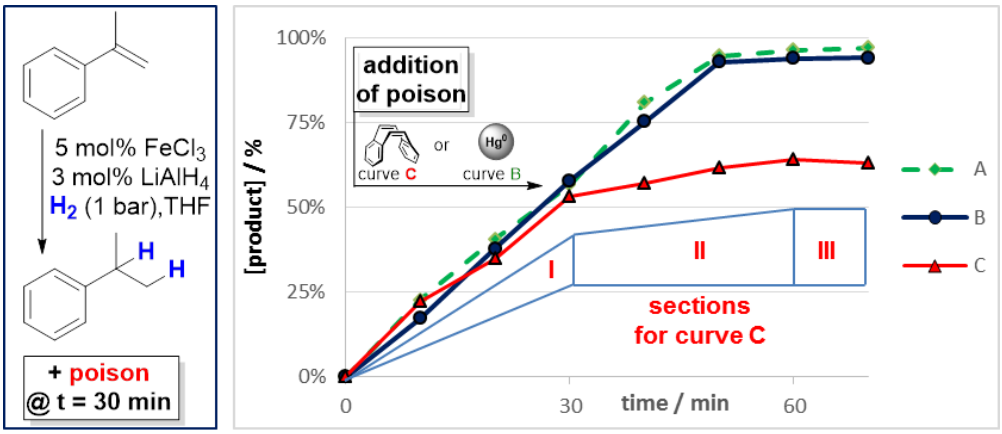


Figure 1.28: Reaction progress and poisoning experiments with the iron-catalyzed hydrogenation of olefins according to Wangelin *et al.*; A = reaction without poisoning, B = addition of 300 mol% of Hg after 30 min; C = addition of 30 mol% dct after 30 min.

A reaction slow down and catalysis quenching after dct addition are characteristic for homotopic catalysts.[72] In a different reaction with a low valent iron catalyst dct addition caused an instant reaction shut down.[23] So the still existent low activity in section II can becaused by somealready formed less active heterotopic particles. A schematic reaction progress of the dct poisoning experiment is shown in figure 1.29.

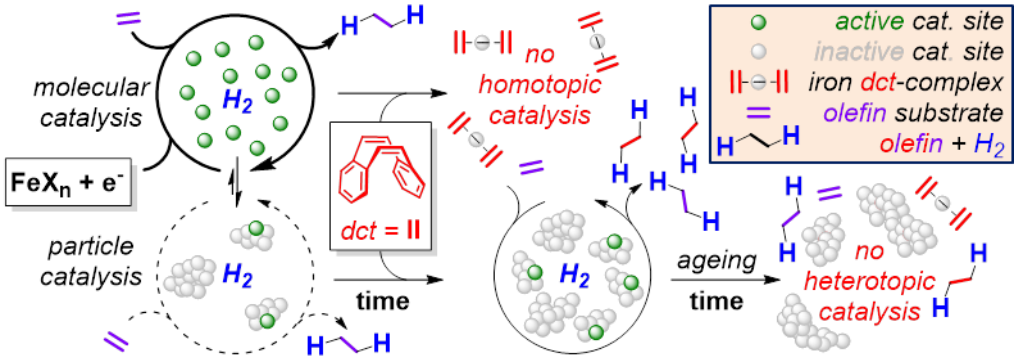


Figure 1.29: Proposed reaction progress with dct-poisoning experiment according to Wangelin *et al.* ; A = reaction without poisoning, B = addition of 300 mol% of Hg after 30 min; C = addition of 30 mol% dct after 30 min.

As proposed, after reduction of the iron precursor, there is a predominant homotopic iron catalyst, responsible for the initial rapid reaction progress. Under the non-stabilizing reaction conditions, agglomeration and particle formation proceeds and less-active heterotopic particles are formed. After addition of dct, the homotopic catalyst is inhibited, and only the less active heterotopic catalyst remains. After several minutes the catalyst ages and becomes inactive.

As indicated in scheme 1.29 there was a very interesting abnormal observation; dct was hydrogenated at even mild conditions (r.t., 1 bar of H_2). The hydrogenation by a molecular catalyst should be unlikely. To our best knowledge, it is the first time that the hydrogenation of dct has been reported at all.[78] The hydrogenation of dct was also observed by our group, using an *in situ* generated Co catalyst, presumably by Co NPs.[35,79]

Further mechanistic studies revealed a more detailed mechanistic insight. A further poisoning experiment with dct indicated that dct has no effect at all on the catalytic activity at least for 10 minutes after addition (figure 1.30 curve C). In this experiment all hydrogenated sites have been determined, so sites of substrate and dct reagent. If only the substrate is considered, an immediate slow down is recognizable (figure 1.30 curve B). In addition, when the reaction was filtered after 20 min through a 100 nm pore filter, the reaction stopped immediately. These new results may suggest a single heterotopic catalytic pathway (see figure 1.30).

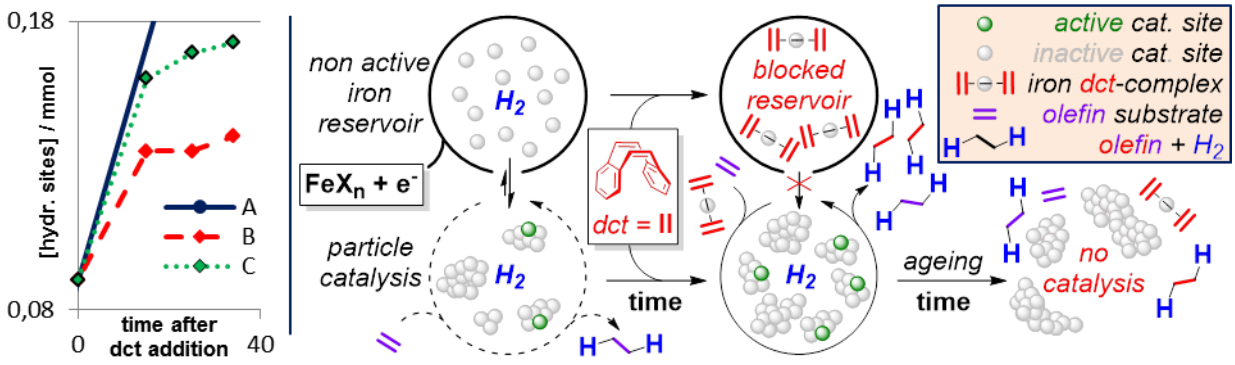


Figure 1.30: Dct-poisoning experiment according to Wangelin *et al.*; reaction A = reaction without poisoning, reaction (B, C) = addition of 10 mol% of dct. after 20 min; B = amount of hydrogenated substrate; C = amount of hydrogenated substrate and dct.

So after reduction of the iron salt a molecular iron reservoir for NPs is formed. Out of this reservoir, active iron NPs are formed. Filtration experiments and DLS measurments suggest, that the active particles have a size above 250 nm. After addition of dct, all molecular iron species from the *reservoir* are blocked by dct, so the formation of new active particles is prohibited. A different precatalyst deactivation of NPs by mercury has been suggested by Crabtree.[13] As shown, the catalyst is unaffected by the dct and since there are no new active particles formed from the reservoir, the catalyst deactivates slowly by ageing. As discussed above, the

negative result of the mercury poisoning experiment has not to be significant for heterotopic iron or cobalt catalysts.

Drawbacks of the dct poisoning are a tedious synthesis,[80] sometimes long reaction times with catalysts[63] and maybe an unexpected formation of the catalytically active dct complex.[70] Also, since there are no further evaluations for the application of dct in iron or cobalt catalyzed processes, the general vadility of this test remains unclear, and has to be varified in combination with other established techniques.

1.2.3 Summary

The application of sustainable, abundant and non-toxic catalytic processes becomes more and more important. Especially 3d-metals like iron and cobalt based catalysts constitute to be an interesting alternative to well-established noble metal catalysts. But several limitations (e.g. lifetime, selectivity, etc.) still prevent their industrial application. Mechanistic understanding is the key for further catalyst adjustments. In this review, two of the most important techniques, how to distinguish between homotopic and heterotopic catalysts, have been highlighted for iron and cobalt catalysts. The mentioned methods, kinetics and poisoning experiments, are powerful tools, but nevertheless results from these tests can be misleading. Since there is not a single test that can proof homo- or heterotopicity of catalytic system, various tests should always be performed to validate the result.[81] There are several other techniques for mechanistic studies. Most important and significant are *in operando* techniques, because with these methods the operating active catalyst can be observed. A lot of these tests have also been used for iron and cobalt catalyzed processes. Frequently described and of special interest are especially filtration or hot filtration tests,[39,53,82] 3-phase tests,[18,24] spectroscopic or spectrometric methods,[58,70,74,83] Detailed review articles about mechanistic tests in general are reported by Crabtree and Finke.[13–15] There are also interesting articles in which a specific reaction mechanism was investigated by several methods.[18,19,24,40,84]

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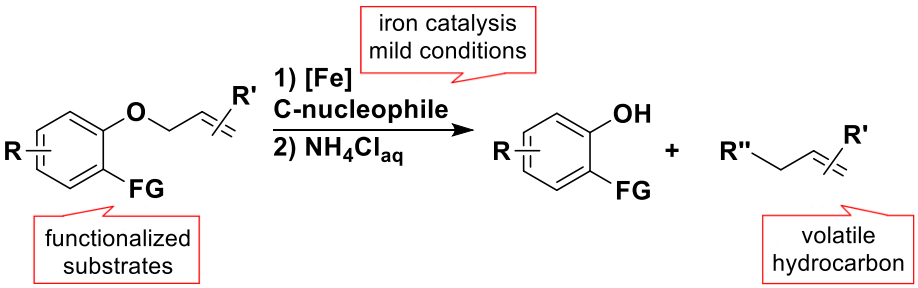
2 Highly Practical Iron-Catalyzed C-O Cleavage Reactions



Abstract: Facile iron-catalyzed cleavage of various allyl, cinnamyl and benzyl C–O linkages has been effected in the presence of ethylmagnesium chloride. The protocol is operationally simple (xylene–THF, r.t., 1 h), requires low catalyst loading (1 mol% $FeCl_2$) and tolerates halides, esters, amines, ethers and olefins. The allyl moiety is converted to volatile hydrocarbons which renders laborious product separation unnecessary.[I,II,III]

[I] Reproduced with permission from: D. Gärtner, H. Konnerth, A. Jacobi von Wangelin, *Catal. Sci. Technol.* **2013**, *3*, 2541-2545. Copyright 2013 The Royal Society of Chemistry; schemes, figures and text may differ from published version.

[II] Initial Investigations of *"Iron-catalyzed cleavage of allyl and phenyl ethers"* were performed by H. Konnerth. See: H. Konnerth, *Bachelor Thesis*, University of Cologne **2011**.

[III] Contents of table 2.1 entries 1-9 and 11-12, table 2.2, table 2.3 entries 1-3 and 5-7, table 2.4 entries 1-3, table 2.5, scheme 2.1 reaction of 1-allyloxyoctane, scheme 2.3, scheme 2.4 and all corresponding starting materials were performed and synthesized by D. Gärtner. See: D. Gärtner, *Master Thesis*, University of Regensburg, **2012**.

2.1 Introduction

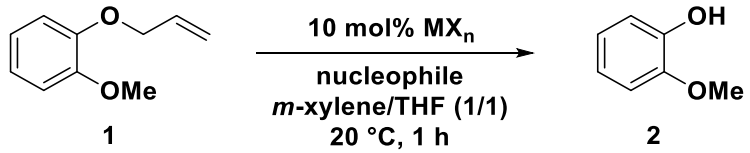
The masking of alcohol functions as allyl ethers constitutes a common protective group strategy in organic synthesis.[1] The allylation of alcohols is usually effected by base-promoted substitution of allyl halides.[2] On the other hand, many protocols have been reported for the deallylation of ethers under acidic, basic, reductive, or oxidative conditions or with the aid of transition metal catalysts.[3] Palladium catalysts are most widely used for deallylation of ethers.[4] While the functional group tolerance of such reactions is usually high, low chemoselectivity is observed when other olefin moieties are present. This is largely due to the high competence of palladium complexes for catalytic olefin isomerization. We have developed efficient iron-catalyzed cross-coupling and reduction protocols which exceed the scope of conventional palladium catalysis in many instances.[5] Now we have expanded our studies to also include selective C–O bond activation.[6] In the past few years, nucleophilic ether cleavage reactions have been reported with the aid of palladium and nickel catalysts.[7] The activity of iron catalysts for selective C–O bond activation was already demonstrated in the context of nucleophilic allylic substitutions.[8] Such protocols exploit the allyl moiety for complex molecule synthesis, while our program targets the formal leaving group, the allylic oxy-substituent. Here, we report iron-catalyzed deallylations that selectively cleave functionalized ethers under mild conditions and release volatile hydrocarbons as by-products after aqueous work-up (Scheme 2.1).

2.2 Initial Optimization Experiments

Table 2.1 summarizes initial optimization with the model substrate 1-allyloxy-2-methoxybenzene (**1**), a constitutional isomer of the natural product eugenol. $FeCl_2$, $NiCl_2$, $CoCl_2$, and CuCl as pre-catalysts displayed equal activities when using ethylmagnesium chloride (EtMgCl) as a nucleophilic scavenger of the allyl group. We continued our study with by far the cheapest and least toxic pre-catalyst, $FeCl_2$, which also exhibited the highest activity among other iron salts ($FeCl_3$, $Fe(acac)_3$). The choice of solvent proved to be essential, with a mixture of *m*-xylene and THF (1 : 1 v/v) providing best yields of guaiacol (**2**). Alternative nucleophiles (i.e. $LiAlH_4$, $NaBH_4$, 1,1,3,3-tetramethyldisiloxane (TMDSO)), triethylsilane, and pressurized hydrogen fared much poorer.[9] The catalyst loading (1 mol% $FeCl_2$) and

nucleophile/substrate ratio (1.05/1) could be reduced to render this protocol a highly practical and cheap alternative to conventional palladium- or nickel-catalyzed methods (entry 6).[3,7]

Table 2.1: Initial optimization experiments with model substrate 1.



1 2

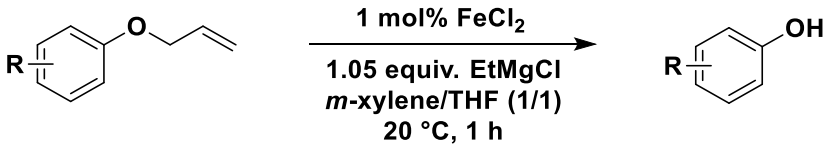
Entry	MX_n	Nucleophile (equiv.)	Change of conditions	2[a] [%]
1	$MnCl_2$	EtMgCl (1.3)	–	51 (57)
2	$CoCl_2$		–	96 (98)
3	$NiCl_2$		–	90 (99)
4	CuCl		–	90 (100)
5	$FeCl_2$		–	96 (99)
6	**$FeCl_2$**	**EtMgCl (1.05)**	**1 mol% $FeCl_2$**	**97 (100)**
7	–	EtMgCl (1.3)	12 h	3 (3)
8	$FeCl_2$	$LiAlH_4$ (1.5)	12 h	24 (31)
9	$FeCl_2$	$NaBH_4$ (1.5)	12 h	1 (15)
10	$FeCl_2$	Et_3SiH (3.0)	16 h, 60 °C	0 (4)
11	$FeCl_2$	TMDSO (1.5)	12 h	1 (12)
12	$FeCl_2$	H_2 (8 bar)	DME, 80 °C, 12 h	1 (3)

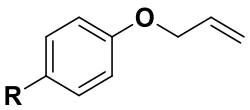
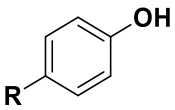
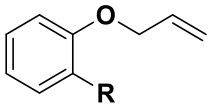
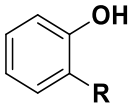
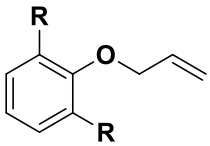
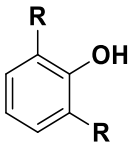
[a] GC yields after aqueous work-up; conversion [%] of **1** in parentheses; TMDSO = 1,1,3,3-tetramethyldisiloxan; DME = 1,2-dimethoxyethane;

2.3 Iron-Catalyzed Deallylation of Functionalized Aryl Ethers

It is important to note that competitive reduction, demethylation, carbometalation and Claisen rearrangement were not observed, which attests to the high chemoselectivity of the catalyst and reaction conditions.[10] We then applied the optimized set of conditions to other allyloxyarenes (Table 2.2).

Table 2.2: Iron-catalyzed deallylation of aryl ethers.



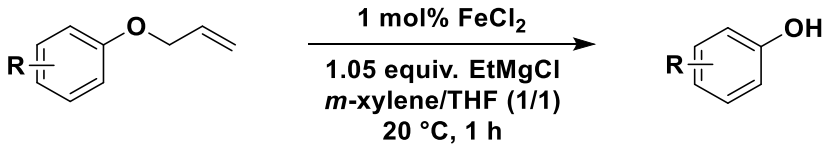
Entry	Allyl aryl ether	Phenol		Yield[a] [%]
1			R = Me	97 (99)
2			F	100 (100)
3			R = Cl	96 (99)[b]
4			Br	47 (49)[b]
5			OMe	97 (100)
6			R = OMe	89 (99)
7			Ph	88 (89)

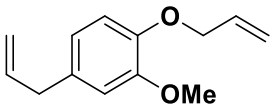
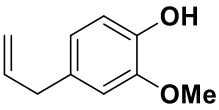
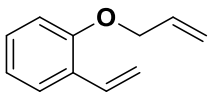
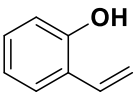
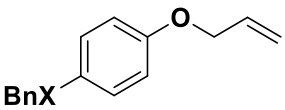
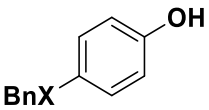
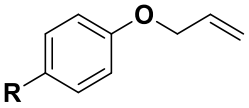
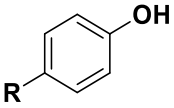
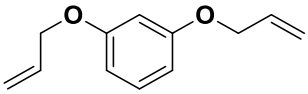
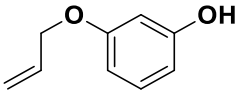
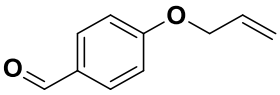
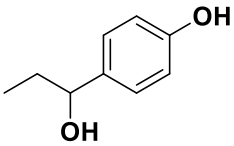
[a] GC yield after aqueous work-up; conversion [%] of allyl ethers in parentheses; [b] no cross-coupling product formed.

Clean and chemoselective deallylation was observed with phenyl ethers bearing halo substituents, and no cross-coupling products were formed. The sterically hindered *ortho*-bromo derivative showed slow conversion but still with very high selectivity. Interestingly, the catalyst tolerates steric bulk around the aryloxy groups as reactions with di-*ortho*-substituted substrates gave excellent yields (entries 6 and 7).

Chemoselective deallylations were also studied with substrates bearing sensitive functional groups that are prone to nucleophilic addition (e.g. carbonyls and carboxylates) or isomerization (e.g. alkenes) and commonly employed in organic synthesis. As illustrated in Table 2.3, the presence of alkenes, benzylethers and methylethers, methylthioethers, and benzyl-amines was largely tolerated under the nucleophilic reaction conditions.

Table 2.3: Chemoselective deallylation of functionalized aryl ethers.



Entry	Allyl aryl ether	Phenol		Yield[a] [%]
1				86 (98)[b]
2				75 (75)
3			X = O	100 (100)
4			NH	88 (96)[c]
5			R = SMe	79 (95)[d]
6			CO_2Me	69 (73)[e]
7				97 (99)[f]
8				76 (98)[g]

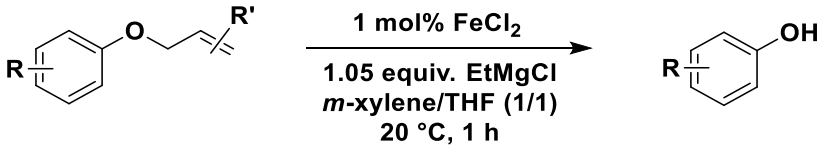
[a] GC yield after aqueous work-up; conversion [%] of allyl ether in parentheses; [b] slow addition of EtMgCl (10 min); ca. 5% *O*-(1-propenyl)eugenol; [c] 2.05 equiv. EtMgCl, isolated yield; [d] ca. 5% Me-S bond cleavage; [e] slow addition (20 min) of *tert*-BuMgCl instead of EtMgCl; [f] 2% resorcin formed; [g] NMR yield; 5 mol% $FeCl_2$, 2.1 equiv. EtMgCl; formation of ca. 5% 1-(4-allyloxyphenyl)propanol.

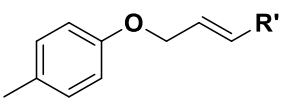
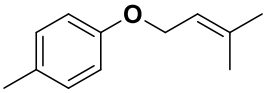
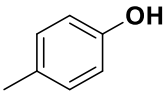
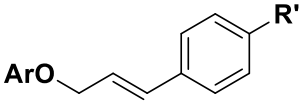
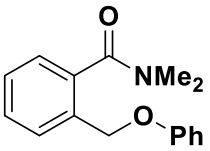
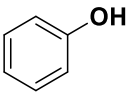
Only minimal isomerization was observed with *O*-allyl eugenol (entry 1),[11] whereas no reduction of terminal alkenes was observed (entries 1 and 2). Substrates with ester groups were subject to competitive carboxylate substitution. When resorting to bulky *tert*-butylmagnesium chloride (*tert*-BuMgCl) as a nucleophile, methyl 4-(allyloxy)-benzoate underwent selective deallylation (entry 6). Mono-deallylation of bis-(allyloxy)arenes can be easily controlled by the stoichiometry of the nucleophile (entry 7). As expected, 4-allyloxybenzaldehyde effected quantitative carbonyl addition, while tandem ethylation–deallylation was observed when employing 2 equiv. of EtMgCl (entry 8).

2.4 Cleavage of Other Aryl Ethers and Iron/NHC-Catalyzed Deallylation

Substituted allyl groups proved to be much more resistant to allylic C–O cleavage under the standard conditions (Table 2.4). Interestingly, this decrease in reactivity is not only a consequence of the steric hindrance about the allyl moiety, but is strongly controlled by electronic effects.

Table 2.4: Cleavage of aryl ethers.

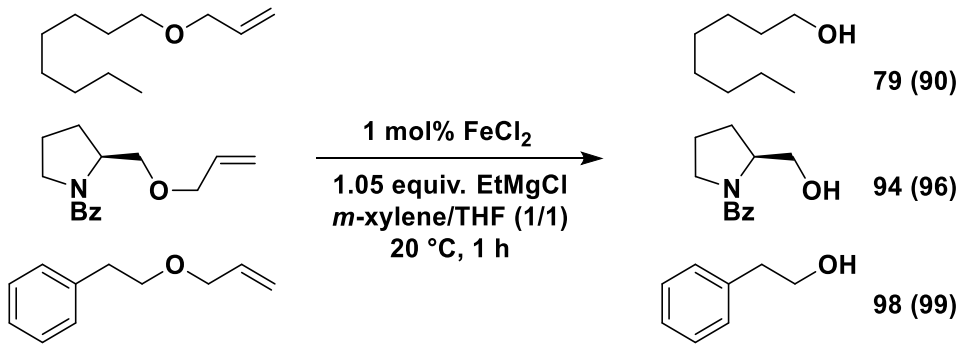


Entry	Aryl ether		Phenol	Yield[a] [%]
1		R' = Me		13 (18)
2		CO_2Me		59 (80)[b]
3				1 (3)
4		R' = Cl		99[c]
5		H		44 (45)
6	(Ar = *para*-tolyl)	OMe		36 (40)
7				92 (95)[d]

[a] after aqueous work-up; conversion [%] of allyl ether in parentheses; [b] slow addition of EtMgCl (10 min); [c] no cross-coupling observed; [d] yield based on conversion and recovered starting material.

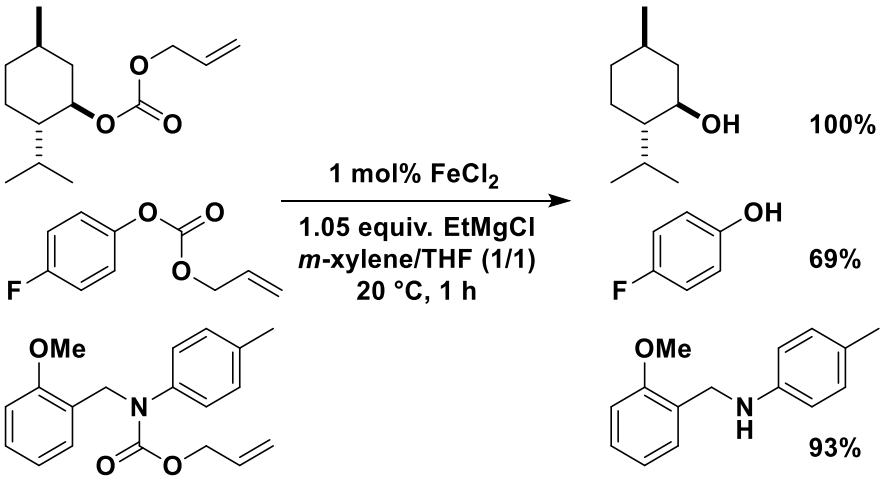
The substitution of a methyl group with an electron-withdrawing ester re-established the reactivity in terminally substituted allyloxytoluenes (entries 1 and 2). The deactivation by electron-donating substituents at the allylic terminus became evident in reactions with *para*-substituted cinnamyl ethers (entries 4–6). The chloro derivative cleanly afforded *para*-cresol within 1 h under standard conditions; the phenyl and *para*-anisyl analogues gave merely ca. 40–45% conversion (65% after 6 h). Benzylethers are generally inert under standard conditions (entry 3, Table 2.3).

Intramolecular activation by a benzamide moiety led to clean ether cleavage (entry 7, Table 2.4). The extension of the optimized protocol to alkylether and *O*-allylcarbonate derivatives also proved to be successful. 1-Allyloxyoctane, *O*-allyl-*N*-benzylprolinol, and (2-allyloxyethyl)benzene gave high yields, respectively (Scheme 2.1).



Scheme 2.1: Deallylation of aliphatic ethers. Yield (conversion) in [%].

The allyloxycarbonyl group (Alloc) is a common protective group of alcohols.[1] Selective decarboxylative cleavage of *O*-allyl carbonates and carbamates was effected under standard conditions (Scheme 2.2).[12]

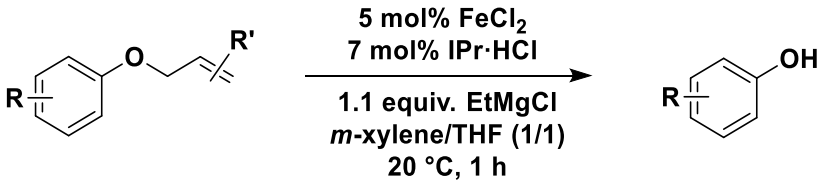


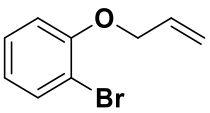
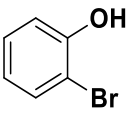
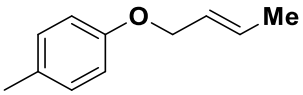
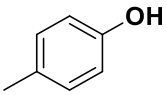
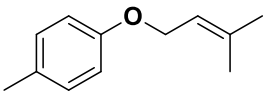
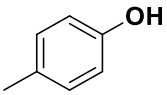
Scheme 2.2: Iron-catalyzed cleavage of carbonic acid derivatives.

Low to moderate conversions were observed with sterically encumbered allylether derivatives. While elevated temperatures and longer reaction times gave slightly increased yields (but at the cost of lower selectivities), we considered the employment of electron-donating ligands. Previously, *N*-heterocyclic carbenes (NHCs) were shown to enhance the catalytic activity of iron complexes under basic/reducing conditions.[13] Consistently, the addition of 1,3-bis(2,6-diisopropyl-phenyl)imidazolium chloride (IPr·HCl) showed a dramatic increase in catalyst activity

in reactions with *O*-allyl *ortho*-bromophenol, *para*-tolyl crotylether, and *para*-tolyl prenylether, respectively, under otherwise identical conditions (Table 2.5).[14]

Table 2.5: Cleavage of aryl ethers.



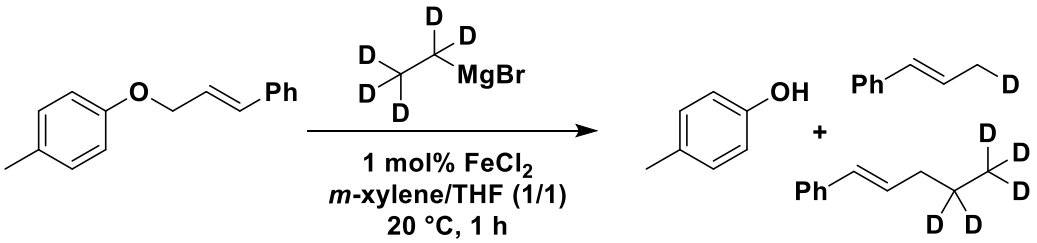
Procedure[a]	Allyl ether	Phenol	Yield [%]
A			47 (49)
B			94 (99)
A			13 (18)
B			83 (87)[b]
A			0 (0)
B			23 (27)

[a] Procedure **A** as in Tables 2.2 and 2.3; procedure **B** as given in the header of Table 2.5; [b] *E/Z* ratio (allyl ether): 5/1 (before), 10/1 (after reaction).

2.5 Proposed Mechanism

We postulate a reaction mechanism which involves the intermediacy of allyliron complexes generated by rapid substitution of the allyl ether by the nucleophilic catalyst species. Several groups have carefully investigated η^3-allyl-iron complexes in the context of related allylic substitution reactions.[15] Our group has recently developed iron-catalyzed coupling[5a-c] and isomerization[11c] reactions which possibly involve intermediate allyl-iron complexes generated under similar conditions as used in this work. The absence of any potentially oxidizing reagent (e.g. organic halides, aerobic atmosphere) favours the participation of reduced iron species, possibly in oxidation states ≤1.[16] This is in accord with earlier work by de Vries *et al.* and us on the reduction of iron salts with EtMgCl to give iron(0) species.[5e,17] While such complexes rapidly age to give larger clusters, the excess amounts of olefins, alcoholates, and ethers present in the reactions are likely to stabilize low-valent iron complexes.[18] Further mechanistic insight was derived from deuteration experiments.

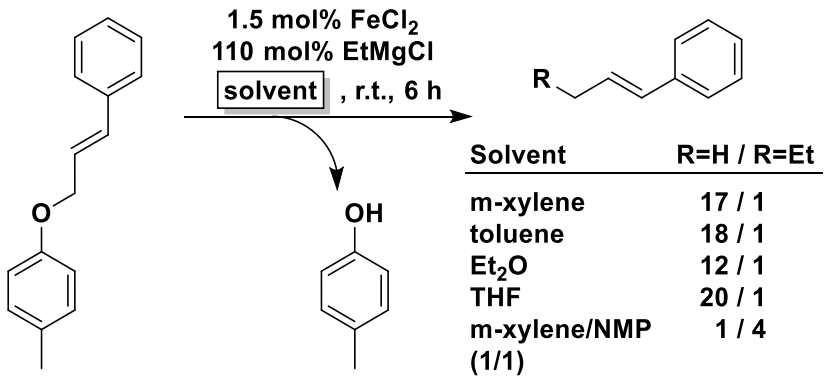
Aqueous work-up of a cinnamyl ether cleavage reaction with D_2O exhibited no deuterium incorporation into the emerging 1-phenyl-1-pentene, but quantitative formation of deutero-cresol (>98% by ^1H, ^2H-NMR). Consistent with a nucleophilic allylic substitution mechanism, employment of d_5-ethylmagnesium bromide afforded 1-phenyl-1-pentene (and 1-phenyl-1-propene) with nearly complete transfer of deuterium atoms (Scheme 2.3).



Scheme 2.3: Iron-catalyzed deuterium transfer from d_5-EtMgBr.

The nucleophilic substitution of the phenolate by a formal ethyl-iron species competes with the rapid iron-centered β-hydride elimination[19] and hence a resultant hydride transfer.

As already observed in the context of iron-catalyzed cross-coupling reactions, the addition of *N*-methyl-2-pyrrolidinone (NMP) disfavours the latter pathway giving rise to the preferential formation of 1-phenyl-1-pentene as a by-product (Scheme 2.4).[20] The standard conditions (*m*-xylene/THF) strongly favour the formation of phenylpropene (20/1) and ethylene.



Scheme 2.4: Solvent-dependent nucleophile delivery: hydride *vs.* ethyl transfer

2.6 Conclusion

We have shown that the simple pre-catalyst $FeCl_2$ effects rapid and selective deallylation of various ethers and carbonates. The reaction conditions tolerate the presence of halide, olefin, ester, methylthio, allylamine, and benzylether groups. Enhanced conversion was observed in the presence of nucleophilic neighboring groups or upon employment of *N*-heterocyclic carbene ligands. The general protocol allows the selective ether cleavage and generates volatile by-products (propene, pentene, CO_2, etc.), which obviates the need for laborious product separation. The ease of operation, mild conditions, and exclusive employment of commercial reagents make this procedure a valuable tool for organic synthesis.

2.7 Experimental Section

Chemicals und Solvents. If not indicated, commercial reagents were used without purification. For catalytic reactions, exclusively dried solvents were used. Tetrahydrofuran (THF) was distilled over sodium / benzophenone before use. Iron(II)-chloride (98%) and iron(III) chloride (99.9%, anhydrous) were weighed in a glove box from *MBraun* (Argon 99.996 %). All reactions were carried out using standard *Schlenk* techniques under nitrogen (99.5%) in rubber septa-capped vials. Solvents for chromatography were distilled under reduced pressure prior to use.

Analytical thin-layer chromatography. TLC was performed using aluminium plates with silica gel and fluorescent indicator (*Merck*, $60F_{254}$). Thin layer chromatography plates were visualized by exposure to UV light and/or by immersion in an aqueous staining solution of $KMnO_4$.

Column chromatography. Flash column chromatography with silica gel 60 Å (220-240 mesh) from *Acros*. Pure petroleum ether or mixtures of petroleum ether and ethyl acetate were used as eluents.

Gas chromatography with mass-selective detector. *Agilent* 6890N Network GC-System, mass detector 5975 MS. Column: BPX5 (30 m x 0.25 mm x 0.25, from *SGE*, carrier gas: H_2. Standard heating procedure: 50 °C (2 min), 25 °C/min -> 300 °C (5 min).

Gas chromatography with FID. *Agilent* 7820A GC-Systems. Column: HP 5 19091J 413 (30 m x 0.32 mm x 0.25 µm) from *Agilent*, carrier gas: N_2. GC-FID was used for catalyst screening (Calibration with internal standard *n*-pentadecane and analytically pure samples).

NMR. ^{1}H and ^{13}C nuclear magnetic resonance spectra were recorded with a *Bruker* Avance 300 (300 MHz ^{1}H; 75 MHz ^{13}C) and *Bruker* Avance 400 (400 MHz ^{1}H, 101 MHz ^{13}C) spectrometers Chemicals shifts are reported in ppm (δ) relative to internal tetramethylsilane (TMS). Coupling constants (*J*) are reported in Hertz (Hz). Following abbreviations are used for spin multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, dt = doublet of triplet,

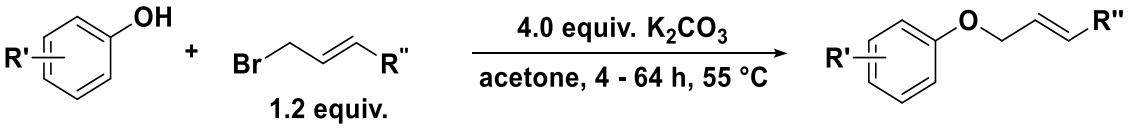
dq = doublet of quartet, ddt = doublet of doublet of triplet. For yield determinations, hexamethyl-disiloxane was used as internal standard.

IR spectroscopy. Infrared spectra were recorded on a *Varian* Scimitar 1000 FT-IR equipped with a ATR unit. Wavenumbers are indicated in cm^{-1}. Intensive absorption bands are indicated with „s“ (strong), medium intensive bands with „m“ (medium) und weak intensive bands with „w“ (weak).

High resolution mass spectrometry (HRMS). The spectra were recorded by the Central Analysis Lab at the Department of Chemistry at the University of Regensburg with a MAT SSQ 710 A from *Finnigan*.

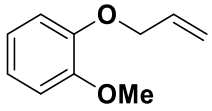
Superscripts behind compound names are literature references.

2.7.1 Preparation of O-allyl phenyl ethers



Representative procedure for the *O*-allylation of guaiacol: To a solution of guaiacol (40 mmol, 5.95 g) in acetone (40 mL), anhydrous K_2CO_3 (160 mmol, 22.1 g) and allyl bromide (48 mmol, 4.15 mL) were added. The reaction mixture was heated to reflux for 12 hours, cooled to room temperature, filtered and washed with acetone (2 x 10 mL). The filtrate was concentrated under reduced pressure to obtain a residue which was purified by column chromatography (hexanes/ethyl acetate 3/1).[21]

_O_-Allyl-2-methoxy phenyl ether[22]



$C_{10}H_{12}O_2$, 164.20 g/mol

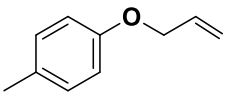
^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 6.98-6.84 (m, 4H), 6.10 (ddt, *J* = 17.2 Hz, 10.7 Hz, 5.4 Hz, 1H), 5.41 (d, *J* = 17.3 Hz, 1H), 5.28 (d, *J* = 10.5 Hz, 1H), 4.61 (d, *J* = 5.4 Hz, 2H), 3.87 (s, 3H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ [ppm] = 149.6, 148.1, 133.5, 121.3, 120.8, 117.9, 113.7, 111.8, 69.3, 51.8.

LR MS (EI, 70 eV, m/z): 164 $[M]^+$.

***O*-Allyl-4-tolyl ether[23]**

The substance was purified by column chromatography (hexanes/ethyl acetate 10/1).



$C_{10}H_{12}O$, 148.21 g/mol

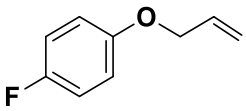
^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.04-6.82 (m, 4H), 6.02 (ddt, *J* = 17.1, 10.5, 5.3 Hz, 1H), 5.42 (dd, *J* = 17.3, 1.5 Hz, 1H), 5.30 (d, *J* = 10.5, 1.4 Hz, 1H), 4.50 (dt, *J* = 5.3, 1.5 Hz, 2H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ [ppm] = 156.5, 133.6, 130.1, 129.9, 117.5, 114.7, 68.9, 20.5.

LR MS (EI, 70 eV, m/z): 148 $[M]^+$.

***O*-Allyl-4-fluorophenyl ether[24]**

The substance was purified by column chromatography (hexanes/ethyl acetate 3/1).



C_9H_9FO, 152.17 g/mol

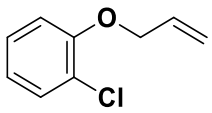
^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.11 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 6.09 (ddt, *J* = 17.2, 10.5, 5.3 Hz, 1H), 5.44 (d, *J* = 17.3 Hz, 1H), 5.28 (d, *J* = 10.5 Hz, 1H), 4.54 (d, *J* = 5.3 Hz, 2H), 3.87 (s, 3H).

$^{13}C\{^{1}H\}$-NMR (101 MHz, $CDCl_3$): δ [ppm] = 157.4, 154.7, 133.2, 117.7, 115.9, 115.7, 69.4.

LR MS (EI, 70 eV, m/z): 152 $[M]^+$.

***O*-Allyl 2-chlorophenyl ether[25]**

The substance was purified by column chromatography (hexanes/ethyl acetate 10/1).



C_9H_9ClO, 168.62 g/mol

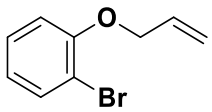
^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.37 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.20 (ddd, *J* = 8.3, 7.5, 1.6 Hz, 1H), 6.91 (m, 2H), 6.08 (ddt, *J* = 17.2, 10.4, 5.1 Hz, 1H), 5.47 (d, *J* = 17.3 Hz, 1H), 5.32 (d, *J* = 10.6 Hz, 1H), 4.62 (dt, *J* = 5.1, 1.6 Hz, 2H).

$^{13}C\{^{1}H\}$-NMR (101 MHz, $CDCl_3$): δ [ppm] = 154.1, 132.7, 130.4, 127.6, 123.1, 121.5, 117.9, 113.8, 69.7.

LR MS (EI, 70 eV, m/z): 168 $[M]^+$.

***O*-Allyl 2-bromophenyl ether[26]**

The substance was purified by column chromatography (hexanes/ethyl acetate 10/1).



C_9H_9BrO, 213.07 g/mol

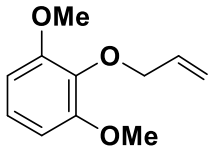
^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.55 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.27-7.21 (m, 1H), 6.90 (dd, *J* = 8.3, 1.3 Hz, 1H), 6.84 (ddd, *J* = 8.4, 7.7, 1.4 Hz, 1H), 6.07 (ddt, *J* = 17.2, 10.4, 5.0 Hz, 1H), 5.49 (d, *J* = 17.3 Hz, 1H), 5.31 (d, *J* = 10.6 Hz, 1H), 4.62 (dt, *J* = 5.0, 1.6 Hz, 2H).

$^{13}C\{^{1}H\}$-NMR (101 MHz, $CDCl_3$): δ [ppm] = 155.0, 133.4, 132.6, 128.4, 122.0, 117.8, 113.6, 112.3, 69.7.

LR MS (EI, 70 eV, m/z): 212 $[M]^+$.

_O_-Allyl 2,6-dimethoxyphenyl ether[27]

The substance was purified by column chromatography (hexanes/ethyl acetate 10/1).



$C_{11}H_{14}O_3$, 194.23 g/mol

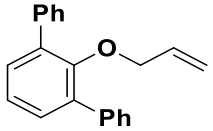
^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 6.95 (t, *J* = 8.4 Hz, 1H), 6.54 (d, *J* = 8.4 Hz, 2H), 6.10 (ddt, *J* = 16.4 Hz, 10.3, 6.1 Hz, 1H), 5.29 (d, *J* = 17.2 Hz, 1H), 5.15 (d, *J* = 10.3 Hz, 1H), 4.50 (dt, *J* = 6.1 Hz, 2H), 3.80 (s, 6H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ [ppm] = 153.7, 136.8, 134.6, 123.7, 117.6, 105.3, 74.1, 56.1.

LR MS (EI, 70 eV, m/z): 194 $[M]^+$.

_O_-Allyl 2,6-diphenylphenyl ether

The substance was purified by column chromatography (hexanes/ethyl acetate 10/1).



$C_{21}H_{18}O$, 286.37 g/mol

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.74 (d, *J* = 7.2 Hz, 4H), 7.57-7.29 (m, 9H), 5.53 (m, 1H), 5.02-4.85 (m, 2H), 3.90-3.79 (m, 2H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ [ppm] = 153.8, 138.9, 136.3, 133.8, 130.4, 129.7, 128.2, 127.3, 124.5, 117.3, 73.9.

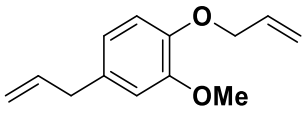
LR MS (EI, 70 eV, m/z): 286 $[M]^+$.

HR MS (CI, m/z): found 287.1438 $[M+H]^+$ (calculated 287.143)

IR in [cm^{-1}]: 3058 (w), 3027 (w), 2863 (w), 1599 (w), 1497 (w), 1461 (m), 1413 (s), 1215 (s), 749 (s), 699 (s).

_O_-Allyl eugenol

The substance was purified by column chromatography (hexanes/ethyl acetate 20/1).



$C_{13}H_{16}O_2$, 204.27 g/mol

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 6.95 (t, *J* = 8.4 Hz, 1H), 6.54 (d, *J* = 8.4 Hz, 2H), 6.10 (ddt, *J* = 16.4, 10.3, 6.1 Hz, 1H), 5.29 (d, *J* = 17.2 Hz, 1H), 5.15 (d, *J* = 10.3 Hz, 1H), 4.50 (dt, *J* = 6.1 Hz, 2H), 3.80 (s, 6H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ [ppm] = 149.5, 146.4, 137.7, 133.6, 133.1, 120.4, 117.8, 115.7, 113.7, 112.3, 70.0, 55.9, 39.9.

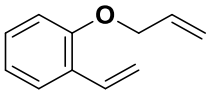
LR MS (EI, 70 eV, m/z): 204 $[M]^+$.

HR MS (CI, m/z): found 205.1224 $[M+H]^+$ (calculated 205.1223)

IR in [cm^{-1}]: 3079 (w), 2935 (w), 2836 (w), 1590 (w), 1510 (s), 1464 (m), 1420 (m), 1259 (s), 1229 (s)

2-Allyloxy styrene[28]

The substance was purified by column chromatography (hexanes/ethyl acetate 10/1).



$C_{11}H_{12}O$, 160.22 g/mol

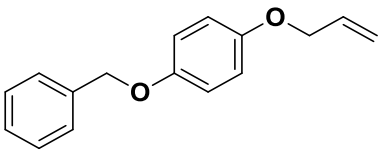
^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.50 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.22 (m, 1H), 7.11 (dd, *J* = 17.8, 11.2 Hz, 1H), 6.95 (t, *J* = 7.5 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 6.09 (ddt, *J* = 17.2, 10.4, 5.1 Hz, 1H), 5.76 (dd, *J* = 17.8, 1.4 Hz,1H), 5.44 (dd, *J* = 17.3, 1.6 Hz, 1H), 5.34-5.20 (m, 2H), 4.58 (d, *J* = 5.1 Hz, 2H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ [ppm] = 155.8, 133.4, 131.7, 128.8, 127.1, 126.5, 120.9, 117.3, 114.4, 112.4, 69.2.

LR MS (EI, 70 eV, m/z): 160 $[M]^+$.

_O_-Allyl 4-benzyloxyphenyl ether[29]

The substance was purified by column chromatography (hexanes/ethyl acetate 10/1).



$C_{16}H_{16}O_2$, 240.30 g/mol

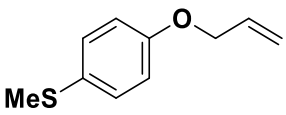
^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.45-7.28 (m, 5H), 6.93-6.82 (m, 4H), 6.05 (ddt, *J* = 17.2, 10.6, 5.3 Hz, 1H), 5.40 (d, *J* = 17.3 Hz, 1H), 5.27 (d, *J* = 10.5 Hz, 1H), 5.02 (s, 2H) 4.49 (dt, *J* = 5.3, 1.5 Hz, 2H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ [ppm] = 153.1, 153.0, 137.3, 133.6, 128.6, 127.9, 127.5, 117.5, 115.8, 115.7, 70.7, 69.5.

LR MS (EI, 70 eV, m/z): 240 $[M]^+$.

_O_-Allyl 4-methylthiophenyl ether[25]

The substance was purified by column chromatography (hexanes/ethyl acetate 10/1).



$C_{10}H_{12}OS$, 180.27 g/mol

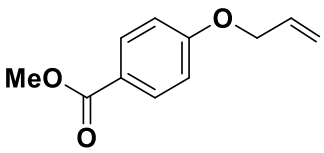
^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.27 (d, *J* = 8.9 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.06 (ddt, *J* = 17.2, 10.5, 5.3 Hz, 1H), 5.43 (d, *J* = 17.2 Hz, 1H), 5.30 (d, *J* = 10.5 Hz, 1H), 4.51 (d, *J* = 5.1 Hz, 2H), 2.45 (s, 3H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ [ppm] = 157.2, 133.3, 130.3, 130.0, 129.1, 117.7, 115.5, 68.9, 17.9.

LR MS (EI, 70 eV, m/z): 180 $[M]^+$.

Methyl 4-allyloxy benzoate[30]

The substance was purified by column chromatography (hexanes/ethyl acetate 10/1).



$C_{11}H_{12}O_3$, 192.21 g/mol

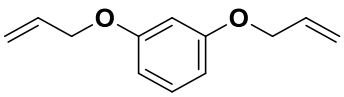
^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 8.04-7.90 (m, 2H), 6.97-6.85 (m, 2H), 6.11-5.96 (m, 1H), 5.41 (dd, *J* = 17.3, 1.4 Hz, 1H), 5.34-5.23 (m, 1H), 4.63-4.49 (m, 2H), 3.87 (s, 3H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δC [ppm] = 166.8, 162.3, 132.6, 132.6, 122.7, 118.6, 114.3, 68.8, 51.7.

LR MS (EI, 70 eV, m/z): 192 $[M]^+$.

1,3-Bis(allyloxy)benzene[31]

The substance was purified by column chromatography (hexanes/ethyl acetate 10/1).



$C_{12}H_{14}O_2$, 190.24 g/mol

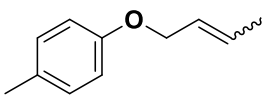
^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.24-7.15 (m, 1H), 6.60-6.42 (m, 3H), 6.08 (ddt, *J* = 17.2, 10.6, 5.3 Hz, 2H), 5.44 (d, *J* = 17.3 Hz, 2H), 5.31 (d, *J* = 10.5 Hz, 2H), 4.54 (d, *J* = 5.3 Hz, 4H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ [ppm] = 159.9, 133.3, 129.9, 117.7, 107.2, 107.2, 102.2, 68.8.

LR MS (EI, 70 eV, m/z): 190 $[M]^+$.

(*E*/*Z*)-But-2'-enyl-4-tolyl ether

The substance was purified by column chromatography (hexanes/ethyl acetate 10/1).



$C_{11}H_{14}O$, 162.23 g/mol, *E*/*Z* ratio**:** 5/1

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.19-7.10 (m, 2H), 6.93-6.84 (m, 2H), 5.99-5.72 (m, 2H), 4.66-4.59 (m, 2H, (*Z*)), 4.51-4.45 (m, 2H, (*E*)), 2.34 (s, 3H), 1.82 (m, 3H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ [ppm] = 156.7, 130.3, 129.9, 129.8, 128.4, 126.4, 126.0, 114.6, 68.8, 63.8, 20.5, 17.9, 13.4.

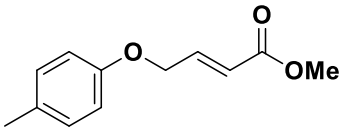
LR MS (EI, 70 eV, m/z): 162 $[M]^+$.

HR MS (CI, m/z): found 163.1119 $[M+H]^+$ (*E*), 163.1117 $M+H]^+$ (*Z*) (calculated 163.1117).

IR in [cm^{-1}]: 3040 (w), 2900 (w), 2880 (w), 1620 (m), 1520 (s), 1450 (m), 1360 (m), 1240 (s), 1160 (m), 1000 (s).

Methyl (*E*)-4-(4′-tolyloxy) 2-butenoate [32]

The substance was purified by column chromatography (hexanes/ethyl acetate 100/1).



$C_{12}H_{14}O_3$, 206.24 g/mol

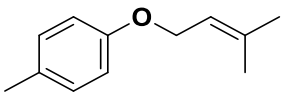
^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.05-6.97 (m, 3H), 6.77-6.71 (m, 2H), 6.16 (dt, *J* = 15.8, 2.0 Hz, 1H), 4.51 (dd, *J* = 4.0 Hz, 2H), 3.68 (s, 3H), 2.23 (s, 3H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ [ppm] = 166.5, 156.0, 143.3, 130.4, 130.0, 114.4, 66.3, 51.4, 20.3.

LR MS (EI, 70 eV, m/z): 206 $[M]^+$.

Prenyl-4-tolyl ether

The substance was purified by column chromatography (hexanes/ethyl acetate 100/1).



$C_{12}H_{16}O$, 176.26 g/mol

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.14 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 5.57 (t, *J* = 6.7 Hz, 1H), 4.54 (d,

J = 6.7 Hz, 2H), 2.35 (s, 3H), 1.86 (s, 3H), 1.80 (s, 3H).

$^{13}C\{^{1}H\}$-NMR (101 MHz, $CDCl_3$): δ [ppm] = 156.9, 137.9, 129.9, 129.8, 120.1, 114.6, 64.8, 25.9, 20.5, 18.2.

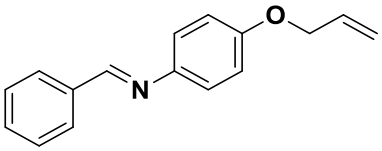
LR MS (EI, 70 eV, m/z): 176 $[M]^+$.

HR MS (CI, m/z): found 177.1274 $[M+H]^+$ (calculated 177.1274)

IR in [cm^{-1}]: 3000 (w), 2950 (w), 2850 (w), 1620 (m), 1520 (s), 1440 (m), 1400 (m), 1240 (s), 1160 (m), 1000 (s).

(*E*)-4-(Allyloxy)-*N*-benzylidene aniline

The substance was purified by column chromatography (hexanes/ethyl acetate 3/2).



$C_{16}H_{15}O$, 237.30 g/mol

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 8.48 (s, 1H), 7.94-7.84 (m, 2H), 7.51-7.43 (m, 3H), 7.29-7.18 (m, 2H), 7.00-6.91 (m, 2H), 6.08 (ddt, *J* = 17.2, 10.6, 5.3 Hz, 1H), 5.44 (m, 1H), 5.31 (m, 1H), 4.56 (dt, *J* = 5.3, 1.5 Hz, 2 H).

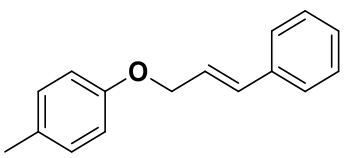
$^{13}C\{^{1}H\}$-NMR (101 MHz, $CDCl_3$): δ [ppm] = 158.5, 157.3, 145.1, 136.5, 133.3, 131.1, 128.8, 128.6, 122.2, 117.7, 115.3, 69.1.

LR MS (EI, 70 eV, m/z): 237 $[M]^+$.

HR MS (CI, m/z): found 237.1151[M+] (calculated 237.1154).

(*E*)-Cinnamyl-4-tolyl ether[33]

The substance was purified by recrystallization from methanol.



$C_{16}H_{16}O$, 224.30 g/mol

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.44-7.39 (m, 2H), 7.36–7.30 (m, 2H), 7.29-7.23 (m, 1H), 7.13-7.07 (m, 2H), 6.90–6.85 (m,

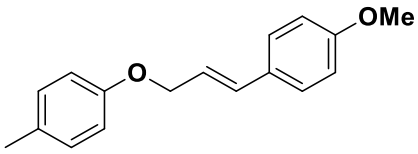
2H), 6.73 (d, *J* = 16.0 Hz, 1H), 6.43 (dt, *J* = 16.0, 5.8 Hz, 1H), 4.68 (dd, *J* = 5.8, 1.5 Hz, 2H).

$^{13}C\{^{1}H\}$-NMR (101 MHz, $CDCl_3$): δ [ppm] = 156.6, 136.5, 132.9, 130.2, 130.0 2, 128.6, 127.9, 126.6, 124.8, 114.7 2, 68.8, 20.5.

LR MS (EI, 70 eV, m/z): 224 $[M]^+$.

(*E*)-4-Methoxycinnamyl-4'-tolyl ether[34]

The substance was purified by recrystallization from methanol.



$C_{16}H_{16}O_2$, 240.30 g/mol

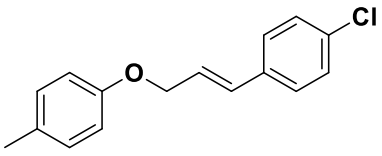
^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.39-7.32 (m, 2H), 7.09 (d, *J* = 8.1 Hz, 2H), 6.91-6.82 (m, 4H), 6.67 (d, *J* = 16.0 Hz, 1H), 6.29 (dt, *J* = 15.9, 6.0 Hz, 1H), 4.65 (dd, *J* = 6.0, 1.4 Hz, 2H), 3.81 (s, 3H), 2.29 (s, 3H).

$^{13}C\{^{1}H\}$-NMR (101 MHz, $CDCl_3$): δ [ppm] = 159.4, 156.6, 132.7, 130.1, 129.9, 129.3, 127.8, 122.4, 114.7, 114.0, 69.0, 55.3, 20.5.

LR MS (EI, 70 eV, m/z): 254 $[M]^+$.

(*E*)-4-Chlorocinnamyl-4'-tolyl ether[35]

The substance was purified by recrystallization from methanol.



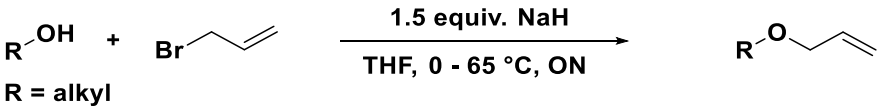
$C_{15}H_{13}ClO$, 244.72 g/mol

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.35-7.27 (m, 4H), 7.09 (d, *J* = 8.2 Hz, 2H), 6.88-6.83 (m, 2H), 6.68 (d, *J* = 16.0 Hz, 1H), 6.39 (dt, *J* = 16.0, 5.7 Hz, 1H), 4.66 (dd, *J* = 5.7, 1.5 Hz, 2H), 2.29 (s, 3H).

$^{13}C\{^{1}H\}$-NMR (101 MHz, $CDCl_3$): δ [ppm] = 156.5, 133.5, 131.5, 130.3, 123.0, 128.8, 127.8, 125.5, 114.7, 68.5, 20.5.

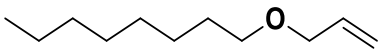
LR MS (EI, 70 eV, m/z): 258 $[M]^+$.

2.7.2 Synthesis of *O*-allyl alkylethers



Representative procedure for the *O*-allylation of 1-octanol: The reaction was carried out under an inert atmosphere (N_2). To a suspension of NaH, a 60% dispersion in mineral oil (0.60 g, 15 mmol) in dry THF (20 mL), was added at 0 °C 1-octanol (1.5 mL, 10 mmol). The reaction mixture was stirred at room temperature for 30 minutes. The allyl bromide (1.3 mL, 15 mmol) was added slowly and the reaction was heated to reflux overnight. The reaction mixture was allowed to cool to room temperature. Excess NaH was quenched with 1.5 M aqueous NH_4Cl-solution (5 mL). The organic layer was separated and the aqueous phase was extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL) and dried over Na_2SO_4. The product was purified via column chromatography (hexanes/ ethyl acetate 10/1).[36]

Allyl *n*-octyl ether[37]



$C_{11}H_{22}O$, 170.30 g/mol

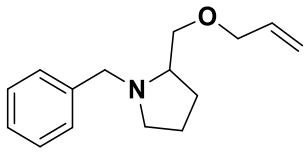
^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 5.90 (ddt, *J* = 17.1, 10.6, 5.6 Hz, 1H), 5.25 (d, *J* = 17.2 Hz, 1H), 5.14 (d, *J* = 10.4 Hz, 1H), 3.95 (dt, *J* = 5.6, 1.4 Hz, 2H), 3.41 (t, *J* = 6.7 Hz, 2H), 1.63-1.51 (m, 2H), 1.43-1.16 (m, 10H), 0.87 (t, *J* = 6.9 Hz, 3H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ [ppm] = 135.1, 116.5, 71.8, 70.5, 31.8, 29.8, 29.5, 29.3, 26.2, 22.7, 14.1.

LR MS (EI, 70 eV, m/z): 170 $[M]^+$.

2-(Allyloxy)-1-benzylpyrrolidine

The substance was purified by column chromatography (hexanes/ethyl acetate 2/1 + 0.1% NEt_3).



$C_{15}H_{21}NO$, 231.34 g/mol

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.40-7.16 (m, 5H), 5.95 (ddt, *J* = 17.2, 10.4, 5.6 Hz, 1H), 5.35-5.27 (m, 1H), 5.21 (m, 1H), 4.16 (d, *J* = 13.0 Hz, 1H), 4.03 (dt, *J* = 5.5, 1.4 Hz, 2H), 3.65 (dd, *J* = 9.4, 5.3 Hz, 1H), 3.46-3.38 (m, 2H), 3.00-2.93 (m, 1H), 2.79 (ddd, *J* = 11.1, 8.4, 5.8 Hz, 1H), 2.29-2-19 (m, 1H), 2.04-1.91 (m, 1H), 1.83-1.63 (m, 3H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ [ppm] = 139.8, 135.0, 129.0, 128.1, 126.8, 116.8, 74.2, 72.3, 128.6, 63.0, 59.7, 54.6, 28.7, 22.9.

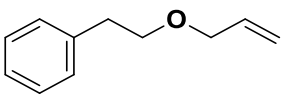
LR MS (EI, 70 eV, m/z): 231 $[M]^+$.

HR MS (ESI, 170 V, m/z): found 232.1693 $[M+H]^+$ (calculated 232.1696)

IR in [cm^{-1}]: 2953 (w), 2915 (w), 2850 (w), 2788 (w), 1495 (w), 1453 (w), 1098 (s), 989 (m).

2-Phenylethyl allyl ether[38]

The substance was purified by column chromatography (hexanes/ethyl acetate 2/1).



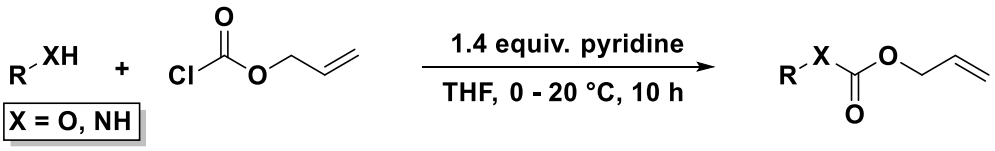
$C_{11}H_{14}O$, 162.23 g/mol

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.38-7.15 (m, 5H), 5.91 (ddt, *J* = 17.2, 10.5, 5.6 Hz, 1H), 5.26 (m, 1H), 5.17 (m, 1H), 4.00 (dt, *J* = 5.6, 1.4 Hz, 1H), 3.65 (t, *J* = 7.3 Hz, 1H), 2.91 (t, *J* = 7.3 Hz, 1H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ [ppm] = 139.0, 134.9, 128.9, 128.4, 126.2, 116.9, 71.9, 71.3, 36.4.

LR MS (EI, 70 eV, m/z): 162 $[M]^+$.

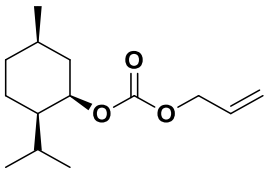
2.7.3 Synthesis of *O*/*N*-Allyloxycarbonyl compounds



Representative procedure for the synthesis of (-)-menthyl *O*-allylcarbonate:

To a solution of (-)-menthol (20.0 mmol, 3.13 g) in freshly dried/distilled THF (20 mL) was added pyridine (28.0 mmol, 2.26 mL). The reaction mixture was cooled to 0 °C and allyl chloroformiate (24.0 mmol, 2.56 mL) was added slowly. The suspension was stirred at room temperature for 10 hours. After addition of water (5 mL) the mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were successively washed with 1 N HCl (2 x 10 mL), saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL). After drying over Na_2SO_4 and removal of the solvent under reduced pressure, the crude product was purified by column chromatography (hexanes/ethyl acetate 10/1).[12]

(-)-Menthyl *O*-allyl carbonate[12]



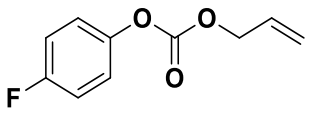
$C_{14}H_{24}O_3$, 240.34 g/mol

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 5.94 (ddt, *J* = 17.2, 10.4, 5.7 Hz, 1H), 5.35 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.26 (dq, *J* = 10.4, 1.3 Hz, 1H), 4.61 (ddd, *J* = 5.8, 2.6, 1.2 Hz, 2H), 4.57–4.46 (m, 1H), 2.12–2.03 (m, 2H), 1.97 (tt, *J* = 9.6, 3.5 Hz, 1H), 1.68 (qd, *J* = 5.8, 3.1 Hz, 2H), 1.54–1.35 (m, 2H), 1.12 – 0.97 (m, 2H), 0.90 (dd, *J* = 6.8, 5.5 Hz, 6H), 0.79 (d, *J* = 7.0 Hz, 3H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ [ppm] = 154.7, 131.8, 118.6, 78.5, 68.2, 47.0, 0.7, 34.1, 31.4, 26.0, 23.3, 22.0, 20.7, 16.2.

_O_-Allyl (4-fluorophenyl) carbonate

The substance was purified by column chromatography (hexanes/ethyl acetate 10/3).



$C_{10}H_9FO_3$, 196.18 g/mol

^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm] = 7.22–6.99 (m, 4H), 6.10–5.89 (m, 1H), 5.43 (dq, *J* = 17.2, 1.4 Hz, 1H), 5.34 (dq, *J* = 10.4, 1.2 Hz, 1H), 4.77–4.68 (m, 2H).

^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ [ppm] = 194.6, 162.0, 147.0, 131.0, 122.6, 119.7, 116.2, 69.3.

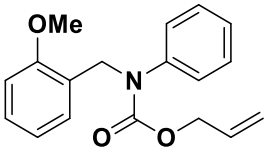
LR MS (EI, 70 eV, m/z): 196 $[M]^+$.

HR MS (CI, m/z): found 196.0538 $[M+H]^+$ (calculated 196.0536).

IR in [cm^{-1}]: 3084 (w), 2949 (w), 1758 (s), 1650 (m), 1504 (s), 1454 (m), 1365 (m), 1236 (s), 1190 (s), 1149 (m), 1091 (m).

_O_-Allyl 2-methoxybenzyl (4'-tolyl) carbamate

The substance was purified by column chromatography (hexanes/ethyl acetate 2/1).



$C_{19}H_{21}NO_3$, 311.38 g/mol

^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm] = 7.14–6.98 (m, 4H), 6.95–6.84 (m, 2H), 6.79-6.69 (m, 2H), 5.92–5.72 (m, 1H), 5.19–5.01 (m, 2H), 4.71 (s, 2H), 3.73 (s, 3H), 2.27 (s, 3H).

^{13}C{^{1}H}-NMR (300 MHz, $CDCl_3$): δ [ppm] = 158.8, 155.7, 132.8, 130.1, 129.5, 127.1, 113.7, 66.2, 55.2, 53.9, 21.1.

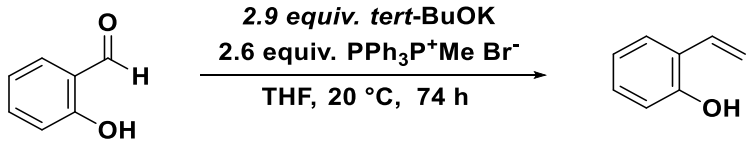
LR MS (EI, 70 eV, m/z): 311 $[M]^+$.

HR MS (CI, m/z): found 311.1519 $[M+H]^+$ (calculated 311.1521).

IR in [cm^{-1}]: 2934 (w), 2836 (w), 1698 (s), 1647 (w), 1613 (m), 1512 (s), 1441 (m), 1393 (m), 1244 (s), 1175 (m), 1032 (s).

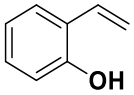
2.7.4 Other Starting Materials

Preparation of 2-hydroxy styrene



The reaction was carried out under an inert atmosphere (N_2). Triphenylphosphonium bromide (52.9 mmol, 19.3 g) was dissolved in THF (86 mL) and *tert*-BuOK (57.2 mmol, 6.24 g) was added slowly. The reaction mixture was stirred at room temperature for 1 hour. Then, 2-hydroxybenzaldehyde (20.1 mmol, 2.1 mL) was added slowly and the mixture was stirred at room temperature for 73 hours. CH_2Cl_2 (200 mL) was added and the solution was washed with water (25 mL) and brine (25 mL). The organic layer was dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (hexanes/ethylacetate 10/1).[39]

2-Hydroxy styrene[40]



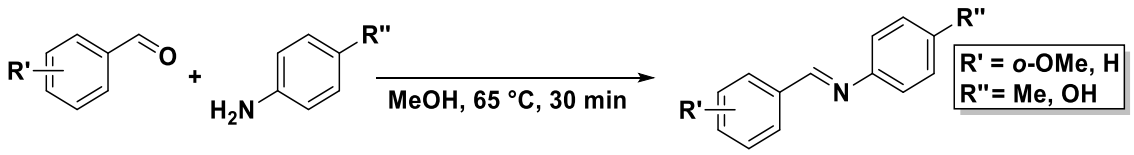
C_8H_8O, 120.15 g/mol

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.44 (d, *J* = 7.7 Hz, 1H), 7.19-7.12 (m, 1H), 7.07-6.90 (m, 2H), 6.81 (dd, *J* = 8.1, 1.0 Hz, 1H), 5.84 (s, 1H), 5.78 (dd, *J* = 17.7, 1.4 Hz, 1H), 5.36 (dd, *J* = 11.2, 1.4 Hz, 1H).

^{13}C{^{1}H}-NMR(101 MHz, $CDCl_3$): δ [ppm] = 151.9, 130.4, 127.8, 126.1, 123.9, 119.8, 114.8, 114.4.

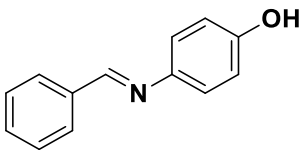
LR MS (EI, 70 eV, m/z): 120 $[M]^+$.

Synthesis of (*E*)-*N*-benzylideneanilines[41]



Representative procedure for the synthesis of (*E*)-4-benzylidene aminophenol: To a solution of 4-hydroxyaniline (4.41 g, 40 mmol) in anhydrous methanol (100 mL) was added benzaldehyde (4.1 mL, 40 mmol). The reaction mixture was heated to reflux for 30 minutes. After removal of solvent the crude product was recrystallized in toluene.

(*E*)-4-Benzylidene aminophenol[41]

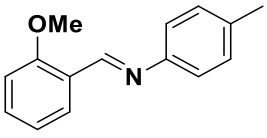


$C_{13}H_{11}NO$, 197.24 g/mol

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 8.48 (s, 1H), 7.93-7.85 (m, 2H), 7.48-7.44 (m, 3H), 7.22-7.16 (m, 2H), 6.89-6.84 (m, 2H), 4.91 (s, 1H).

LR MS (EI, 70 eV, m/z): 197 $[M]^+$.

(*E*)-*N*-(2-methoxybenzylidene)-4-toluidine



$C_{15}H_{15}NO$, 225.29 g/mol

^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm] = 8.40 (s, 1H), 7.86 (d, *J* = 8.6 Hz, 2H), 7.17 (q, *J* = 8.3 Hz, 4H), 7.01–6.96 (m, 2H), 3.89 (s, 3H), 2.37 (s, 3H).

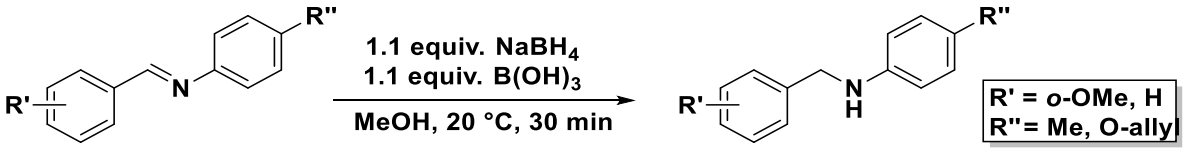
^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ [ppm] = 159.0, 130.6, 129.8, 120.8, 114.2, 55.5, 21.0.

LR MS (EI, 70 eV, m/z): 225 $[M]^+$.

HR MS (CI, m/z): found 225.1155 $[M+H]^+$ (calculated 225.1154).

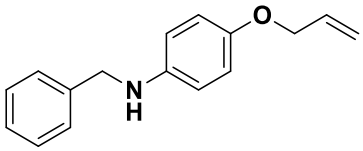
IR in [cm^{-1}]: 3078 (w), 3006 (w), 2877 (w), 2842 (w), 1602 (m), 1595 (s), 1568 (s), 1505 (s), 1461 (m), 1305 (m), 1246 (s), 1165 (s), 1105 (s), 1023 (s).

Synthesis of 4-(allyloxy)-*N*-benzylaniline[42]



Representative procedure for the synthesis of 4-(allyloxy)-*N*-benzylaniline: To a solution of (*E*)-4-(allyloxy)-*N*-benzylidene aniline (7 mmol, 1.7 g) and boric acid (7.7 mmol, 0.29 g) in methanol (9 mL) was slowly added sodium borohydride (7.7 mmol, 0.47 g). The reaction mixture was stirred at room temperature for 30 minutes. Excess sodium borohydride was quenched with water (10 mL). The mixture was filtered and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (hexanes / ethyl acetate 3/2).

4-(Allyloxy)-*N*-benzylaniline



$C_{16}H_{17}NO$, 239.32 g/mol

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.48-7.28 (m, 5H), 6.84-6.74 (m, 2H), 6.66-6.57 (m, 2H), 6.05 (ddt, *J* = 17.2, 10.6, 5.3 Hz, 1H), 5.52-5.39 (m, 1H), 5.36-5.25 (m, 1H), 4.71 (s, 1H), 4.46 (dt, *J* = 5.3, 1.5 Hz, 2 H), 4.29 (s, 2 H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ [ppm] = 151.3, 142.4, 139.5, 133.9, 129.1, 128.6, 128.2, 127.6, 127.2, 117.3, 114.2, 69.7, 49.4.

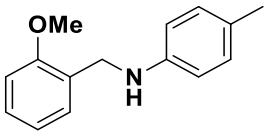
LR MS (EI, 70 eV, m/z): 239 $[M]^+$.

HR MS (CI, m/z): found 239.1311 [M+] (calculated 239.1310)

IR in [cm^{-1}]: 3394 (w), 3080 (w), 3029 (w), 2911 (w), 2865 (w), 1508 (s), 1465 (m), 1365 (m), 1294 (m), 1230 (s), 1120 (m), 1023 (s).

***N*-(2-Methoxybenzyl)-4'-methylaniline**

Differing to the protocol, the crude product was purified by recrystallization in methanol.



$C_{15}H_{17}NO$, 227.13 g/mol

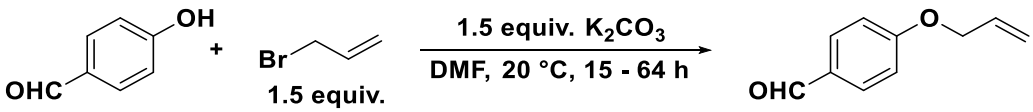
^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm] = 7.24 (d, J = 8.7 Hz, 2H), 6.94 (d, *J* = 8.0 Hz, 2H), 6.86–6.79 (m, 2H), 6.55 (dd, *J* = 8.4, 1.9 Hz, 2H), 4.19 (s, 2H), 3.75 (s, 3H), 2.19 (s, 3H).

LR MS (EI, 70 eV, m/z): 227 $[M]^+$.

HR MS (CI, m/z): found 227.1312 $[M+H]^+$ (calculated 227.1310).

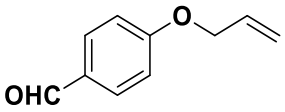
IR in [cm^{-1}]: 3009 (w), 2841 (w), 1604 (m), 1569 (m), 1508 (s), 1462 (m), 1422 (m), 1298 (m), 1246 (s), 1165 (s)m 1106 (s).

Allylation of 4-hydroxybenzaldehyde[43]



4-Hydroxybenzaldehyde (20 mmol, 2.44 g) and allyl bromide (30 mmol, 5.04 mL) were dissolved in DMF (25 mL). After addition of K_2CO_3 (30 mmol, 4.15 g), the reaction mixture was stirred at room temperature for 64 hours and then hydrolyzed with water (100 mL). The aqueous phase was separated and extracted with *n*-pentane (3 x 50 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 and filtered. The crude product was concentrated under reduced pressure and purified via column chromatography (hexanes/ethyl acetate 3/1).

4-Allyloxybenzaldehyde[44]



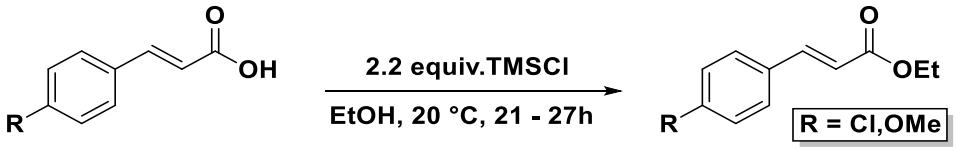
$C_{10}H_{10}O_2$, 162.19 g/mol

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 9.80 (s, 1H), 7.75 (d, *J* = 8.6 Hz, 2H), 6.93 (d, *J* = 8.7 Hz, 2H), 5.97 (ddt, *J* = 17.4, 10.5, 5.2 Hz, 1H), 5.36 (d, *J* = 17.3 Hz, 1H), 5.25 (d, *J* = 10.6 Hz, 1H), 4.54 (d, *J* = 5.2 Hz, 2H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ [ppm] = 189.6, 162.5, 131.3, 130.9, 129.0, 117.2, 113.9, 67.9.

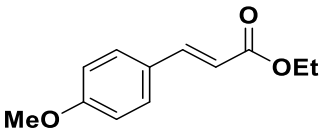
LR MS (EI, 70 eV, m/z): 162 $[M]^+$.

Synthesis of ethyl cinnamates[45]



Representative procedure for the esterification of 4-methoxycinnamic acid: To a solution of 4-methoxycinnamic acid (4.74 g, 26.6 mmol) in ethanol (130 mL) was added TMSCl (7.5 mL, 59 mmol). The solution was stirred for 21 hours at room temperature. The product was concentrated under vacuum. A purification process was not necessary.

Ethyl 4-methoxycinnamate[46]



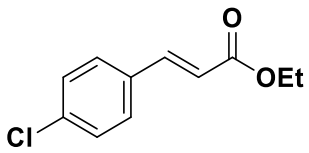
$C_{12}H_{14}O_3$, 206.24 g/mol

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.64 (d, *J* = 16.0 Hz, 1H), 7.50-7.44 (m, 2H), 6.94-6.87 (m, 2H), 6.31 (d, *J* = 16.0 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.83 (s, *J* = 4.1 Hz, 3H), 1.33 (t, *J* = 7.1 Hz, 3H).

$^{13}C\{^{1}H\}$-NMR (101 MHz, $CDCl_3$): δ [ppm] = 167.4, 161.3, 144.3, 129.7 2, 127.2, 115.8, 114.3, 60.4, 55.38, 14.4

LR MS (EI, 70 eV, m/z): 206 $[M]^+$.

Ethyl 4-chlorocinnamate[46]



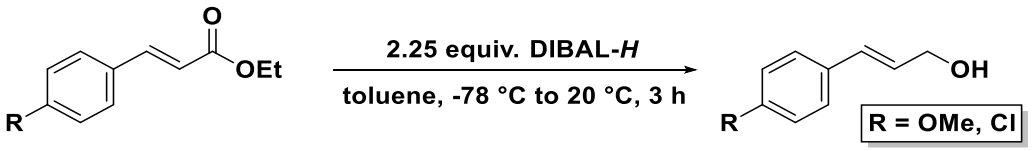
$C_{11}H_{11}IO_2$, 210.66 g/mol

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.63 (d, *J* = 16.0 Hz, 1H), 7.47-7.43 (m, 2H), 7.38-7.33 (m, 2H), 6.41 (d, *J* = 16.0 Hz, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H).

$^{13}C\{^{1}H\}$-NMR (101 MHz, $CDCl_3$): δ [ppm] = 166.8, 143.1, 136.14, 133.0, 129.2, 118.9, 60.6, 14.3

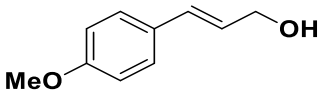
LR MS (EI, 70 eV, m/z): 210 $[M]^+$.

Synthesis of cinnamyl alcohols[44]



Representative procedure for the reduction of ethyl 4-methoxycinnamate: To a suspension of ethyl 4-methoxycinnamate (2.85 g, 13.8 mmol) in toluene (40 mL) was added a solution of 1.2 M DIBAL-*H* in toluene (25.9 mL, 31.1 mmol) over a period of 45 minutes at -78 °C. The reaction mixture was then stirred for 2.5 hours at room temperature. The reaction was carefully hydrolyzed with aqueous 1.5 M NH_4Cl-solution. The suspension was filtered and extracted diethyl ether (3 x 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (hexanes / ethyl acetate 1/1).

4-Methoxycinnamyl alcohol[47]



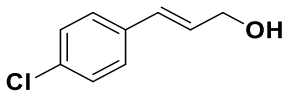
$C_{11}H_{12}O_2$, 164.20 g/mol

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.35-7.30 (m, 2H), 6.89-6.84 (m, 2H), 6.56 (d, *J* = 15.9 Hz, 1H), 6.24 (dt, *J* = 15.8, 6.0 Hz, 1H), 4.30 (d, *J* = 5.6 Hz, 2H), 3.81 (s, 3H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ [ppm] = 159.4, 131.0, 129.4, 127.7, 126.3, 114.0, 64.0, 55.3.

LR MS (EI, 70 eV, m/z): 164 $[M]^+$.

4-Chlorocinnamyl alcohol[45,47]



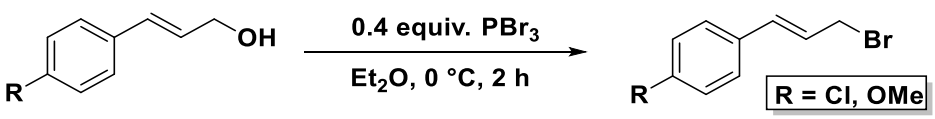
C_9H_9ClO, 168.62 g/mol

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.37-7.17 (m, 4H), 6.53 (dt, *J* = 15.9, 1.4 Hz, 1H), 6.29 (dt, *J* = 15.9, 5.5 Hz, 1H), 4.28 (dd, *J* = 5.6, 1.5 Hz, 2H) 1.50 (s, 1H)

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ [ppm] = 135.2, 133.3, 129.8, 129.2, 128.8, 127.3, 63.6.

LR MS (EI, 70 eV, m/z): 168 $[M]^+$.

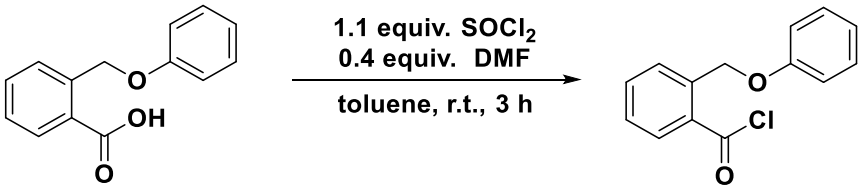
Bromination of cinnamyl alcohols[48]



Representative procedure for the bromination of 4-methoxycinnamyl alcohol: The reaction was carried out under an inert atmosphere (N_2). To a solution of 4-methoxy-cinnamyl alcohol (1.68 g, 10 mmol) in dry diethyl ether (40 mL) was added PBr_3 (260 µL, 2.8 mmol) at 0 °C. The solution was then stirred for 2 hours at room temperature, hydrolyzed with an saturated aqueous $NaHCO_3$ solution (50 mL) and

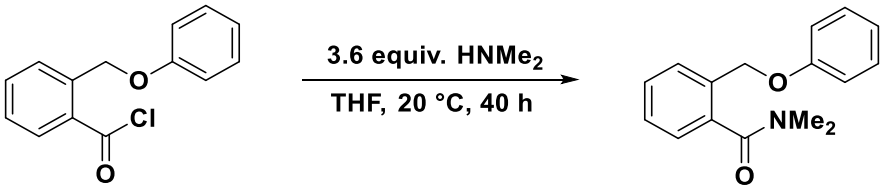
diluted with brine (25 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude products were directly used in the next step without further purification.

Synthesis of 2-(phenoxymethyl)benzoyl chlorideyu[49]



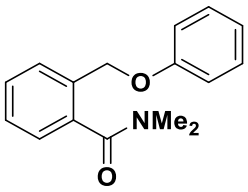
The reaction was carried out under an inert atmosphere (N_2). To a suspension of 2-(phenoxymethyl)benzoic acid (0.98 g, 4.3 mmol) in 2.3 mL toluene was added thionyl chloride (0.35 mL, 4.8 mmol) and DMF (0.15 mL, 1.9 mmol). The reaction mixture was stirred at room temperature for 3 hours. The crude product was concentrated under reduced pressure and directly used in the next step without purification.

Synthesis of *N*,*N*-dimethyl-2-(phenoxymethyl) benzamide[50]



The reaction was carried out under an inert atmosphere (N_2). To the crude 2-(phenoxymethyl)benzoylchloride was added a 2.0 M solution of dimethyl amine (7.7 mL, 15.4 mmol) in THF, The reaction mixture was stirred at room temperature for 40 hours. The reaction was hydrolyzed with a saturated aqueous $NHCO_3$-solution (8 mL). The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 7 mL). The combined organic layers were washed with water (7 mL) and dried over Na_2SO_4, filtered and concentrated under reduced pressure. A purification process was not necessary.

_N_,_N_-dimethyl-2-(phenoxymethyl) benzamide



$C_{16}H_{17}NO_2$, 255.32 g/mol

^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm] = 7.61-7.48 (m, 1H), 7.44-7.33 (m, 2H), 7.32-7.22 (m, 3H), 7.02-6.86 (m, 3H), 5.08 (s, 2H), 3.07 (s, 3H), 2.85 (s, 3H).

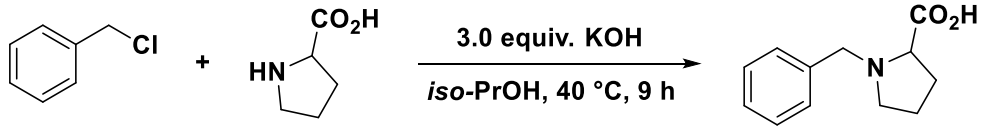
^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ [ppm] = 170.8, 158.6, 136.2, 133.9, 129.5, 129.2, 129.1, 128.1, 126.2, 121.1, 114.7, 67.7, 39.1, 34.7.

LR MS (EI, 70 eV, m/z): 255 $[M]^+$.

HR MS (CI, m/z): found 255.1256 [M+] (calculated 255.1259).

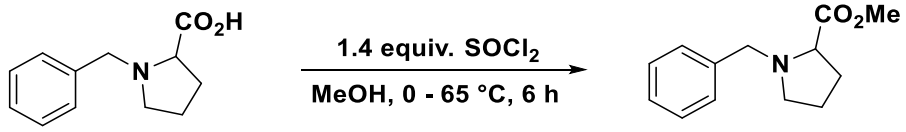
IR in [cm^{-1}]: 3063 (w), 3031 (w), 2885 (w), 1630 (s), 1492 (m), 1456 (m), 1237 (m), 750 (m), 690 (m).

Synthesis of 1-(phenylmethyl)-_L_-proline[51]



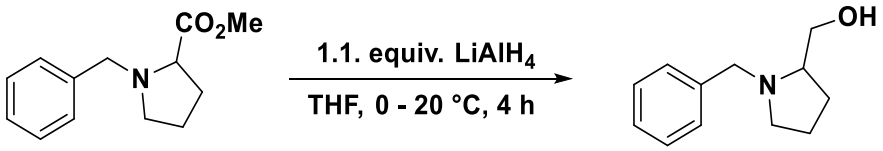
L-Proline (2.3 g, 20 mmol) and potassium hydroxide (3.4 g, 60 mmol) were dissolved in *iso*-propanol and the reaction was heated to 40 °C. Then, benzyl chloride was added over 1 hour with a syringe pump. The reaction mixture was stirred at 40 °C for 8 hours. After cooling to room temperature, the reaction mixture was acidified with conc. HCl (6 mL) until a pH value of 4-5 was reached. The mixture was diluted with chloroform and stirred over night at room temperature. The colorless precipitate was removed through filtration and the solvent removed under reduced pressure. The resulting yellow solid was directly used in the next step without purification.

Synthesis of methyl 1-benzylpyrrolidine-2-carboxylate[51]



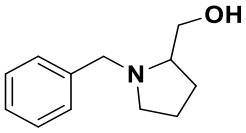
Thionyl chloride (2.0 mL, 27 mmol) was added slowly to methanol (30 mL) at 0 °C. Then 1-(phenylmethyl)-*L*-proline (4.5 g, 20 mmol) was added at 0 °C. The reaction was heated to reflux for 6 hours. The reaction was allowed to cool to room temperature overnight and the solvent was removed under reduced pressure. The crude product, a brown oil, was directly used in the next step.

Synthesis of 1-(benzyl)-2-pyrrolidine methanol[51]



The synthesis was carried out under dry and inert conditions. To a suspension of $LiAlH_4$ (0.84 g, 22 mmol) in abs. THF (20 mL) was added at 0 °C a solution of methyl 1-benzylpyrrolidine-2-carboxylate (5.4 g, 20 mmol) in abs. THF (10 mL) over 1 hour via syringe pump. The reaction was allowed to warm to room temperature and was stirred for 3 hours. The reaction mixture was hydrolyzed at 0 °C with 1 M NaOH (1.5 mL). The grey participate was filtered and washed with diethyl ether four times. The filtrate was dried over Na_2SO_4.The product was purified via column chromatography (*n*-pentane/ethyl acetate 99/1). The obtained product was an orange oil.

1-(Benzyl)-2-pyrrolidine methanol[51]



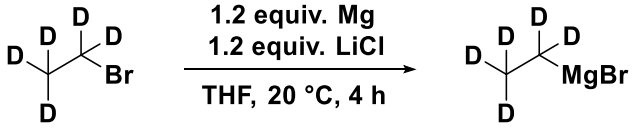
$C_{13}H_{17}NO_2$, 219.282 g/mol

^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm] = 7.41-7.13 (m, 5H), 3.97 (d, *J* = 13.0 Hz, 1H), 3.65 (dt, *J* = 10.7, 3.4 Hz, 1H), 3.43 (dd, *J* = 10.8, 2.0 Hz, 1H), 3.36 (d, *J* = 13.0 Hz, 1H), 3.05-2.92 (m, 1H), 2.74 (ddd, *J* = 9.1, 5.8, 2.7 Hz, 1H), 2.28 (tt, *J* = 16.4, 8.0 Hz, 1H), 2.02-1.77 (m, 2H), 1.77-1.60 (m, 2H).

$^{13}C\{^{1}H\}$-NMR (75 MHz, $CDCl_3$): δ [ppm] = 139.4, 128.7, 128.4, 127.1, 64.3, 61.8, 58.6, 54.5, 27.8, 23.5.

LR MS (EI, 70 eV, m/z): 190 $[M]^+$.

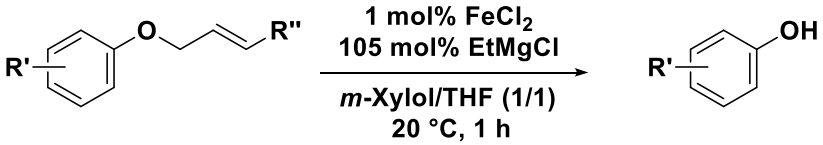
Synthesis of d_5-ethylmagnesium bromide (d_5-EtMgBr) in THF[52]



A modified protocol of Knochel *et al.* was followed. The reaction was carried out under an inert atmosphere (N_2). To magnesium turnings (117 mg, 4.8 mmol) and anhydrous LiCl (203 mg, 4.8 mmol) was added a solution of d_5-bromoethane from *Deutero* (456 mg, 4.0 mmol) in abs. THF (2 mL). After addition, the reaction mixture was stirred at room temperature for 4 hours. The resulting dark brown solution was directly used in the ether cleavage reaction.

2.7.5 Iron-Catalyzed Ether Cleavage Reactions

Standard procedure:

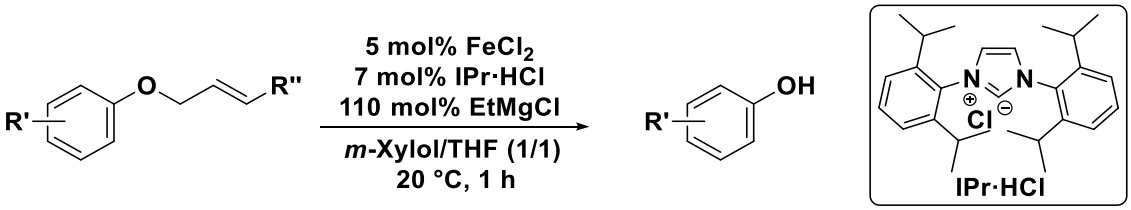


Representative protocol with 1 mol% $FeCl_2$ and 105 mol% EtMgCl: The reaction was carried out under dry and inert conditions. First, a $FeCl_2$-stock solution was prepared. $FeCl_2$ (5.7 mg, 45 µmol) was dissolved in abs. THF (6 mL) and stirred at room temperature for 2 hours.

To a solution of 2-(allyloxy) anisole (74 mg, 0.45 mmol) in *m*-xylene (0.6 mL) was added the $FeCl_2$-stock solution (0.6 mL). The reaction mixture was degassed twice by the freeze-pump-thaw method. Then, a 2.0 M solution of ethyl magnesium chloride in THF (240 µL, 0.48 mmol) was added over 20 seconds. The reaction was stirred at room temperature for 1 hour and hydrolyzed with 1.5 M aqueous NH_4Cl solution (1 mL). After addition of *n*-pentadecane (50 µL, 0.18 mmol, internal GC

reference), the product was extracted with diethyl ether (2 x 1 mL). The combined organic layers were dried over Na_2SO_4 and directly analysed by quantitative GC-FID. Preparative reactions were performed on 5-fold scales and the crude products purified by SiO_2 column chromatography.

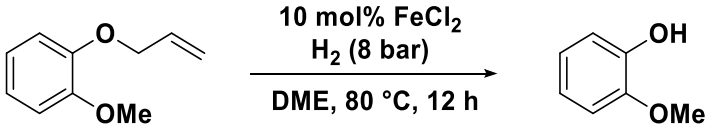
Iron/NHC-catalyzed deallylation:



First, a $FeCl_2$-stock solution was prepared. $FeCl_2$ (5.7 mg, 45 µmol) was dissolved in abs. THF (6 mL) and stirred at room temperature for 2 hours.

A glass vial was charged with 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (IPr·HCl) (134 mg, 0.32 mmol) and purged with nitrogen. 6 mL of the $FeCl_2$ stock solution was added, and the resulting solution stirred at room temperature for 1 hour. The next operations followed the standard procedure above.

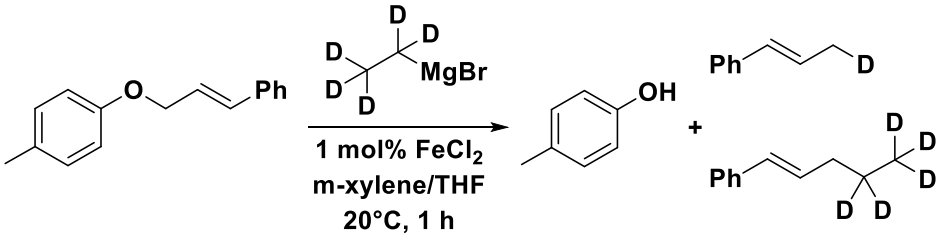
Reactions in high-pressure reactors:



First, a $FeCl_2$-stock solution was prepared in 1,2-dimethoxyethane (DME): $FeCl_2$ (5.7 mg, 45 µmol) was dissolved in abs. DME (6 mL) and stirred at room temperature for 2 hour.

To a solution of 2-(allyloxy) anisole (0.074 g, 0.45 mmol) in *m*-xylene (0.6 mL) was added the $FeCl_2$-stock solution (0.6 mL). The reaction mixture was degassed twice by the freeze-pump-thaw method. The reaction vessels were transferred into a Parr high-pressure stainless steel reactor, and the reactor purged with H_2. Pressure and temperature were set.

Iron catalyzed deuterium transfer from d_5-EtMgBr



A freshly prepared d_5-EtMgBr in THF was used. Otherwise, see standard procedure.

2.8 References

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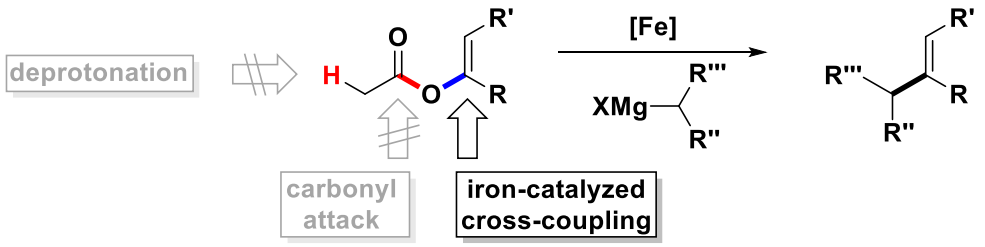
3 Iron-Catalyzed Cross-Coupling of Alkenyl Acetates



Abstract: Stable C-O linkages are generally unreactive in cross-coupling reactions which mostly employ more electrophilic halides or activated esters (triflates, tosylates). Acetates are cheap and easily accessible electrophiles but have not been used in cross-couplings because the strong C-O bond and high propensity to engage in unwanted acetylation and deprotonation. Reported herein is a selective iron-catalyzed cross-coupling of diverse alkenyl acetates, which operates under mild reaction conditions (0 °C, 1 h) with a ligand-free catalyst (1–3 mol%).[I-IV]

[I] Reproduced with permission from: D. Gärtner, A. L. Stein, S. Grupe, J. Arp, A. Jacobi von Wangelin, *Angew. Chem. Int. Ed.* **2015**, *54*, 10545-10549. Copyright 2015 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim; schemes, figures and text may differ from published version.

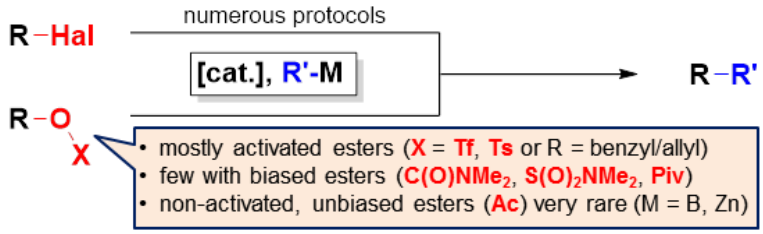
[II] Initial Investigations were performed by J. Arp. See: J. Arp, *Master Thesis*, University of Cologne, **2011**.

[III] Contents of table 3.1 entries 1-7 and 9, table 3.2 entries 1-9 and 11, table 3.3 entries 1-6 and 16 were performed by A. L. Stein.; contents of table 3.4 were performed by S. Grupe; contents of scheme 3.3 were performed by S. Sandl under supervision of D. Gärtner.

[IV] Own workshare is about 60%.

3.1 Introduction

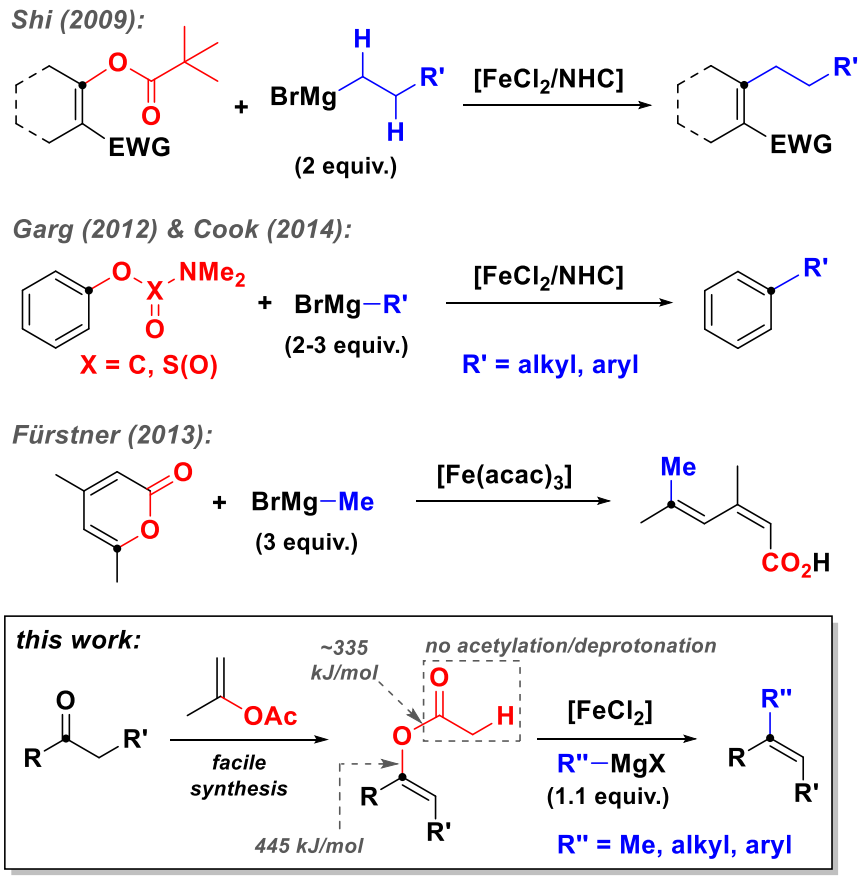
The recent developments of selective iron-catalyzed cross-coupling reactions rival their conventional palladium- and nickel-catalyzed counterparts in terms of reactivity and scope while displaying higher sustainability and operational simplicity.[1] However, the use of non-activated halide-free electrophiles remains a true challenge for all cross-coupling methods (Scheme 3.1).[2]



Scheme 3.1: Elecrophiles in metal-catalyzed cross-coupling reactions. Tf = trifluoromethanesulfonyl, Ts = 4-toluenesulfonyl.

Oxygen-based electrophiles are especially attractive starting materials because of their ubiquitous occurrence in biomass-derived chemicals and facile preparation from alcohols or carbonyl compounds. However, the general stability of C-O bonds has limited the scope of most cross-coupling methods to activated esters (triflate, tosylate or in benzyl/allyl position). There are very few nickel- or rhodium-catalyzed protocols which employ non-activated ester derivatives at elevated temperatures.[3]

Iron-catalyzed cross-coupling was reported with alkenyl pivalates and aryl carbamates/sulfamates (Scheme 3.2) where the undesired carbonyl/sulfonyl attack is suppressed by steric shielding (*tert*-butyl) or electronic deactivation (OR, NR_2).[4] To the best of our knowledge, there are no reports of iron-catalyzed cross-coupling reactions of simple unbiased esters. Among them, organic acetates are an especially attractive class of cheap, halide-free C-O electrophiles bearing a small, non-hazardous leaving group, and is easily accessible by various acetylation protocols.[5] However, the considerable electrophilicity and acidity (pK_a 24), and low bond dissociation energy of the acetyl-O bond appear to prohibit, on thermodynamic grounds, the use of acetates in coupling reactions with highly basic/nucleophilic organometallic reagents.



Scheme 3.2: Iron-catalyzed cross-coupling of non-activated C-O electrophiles. EWG = electron-withdrawing group; NHC = *N*-heterocyclic carbene.

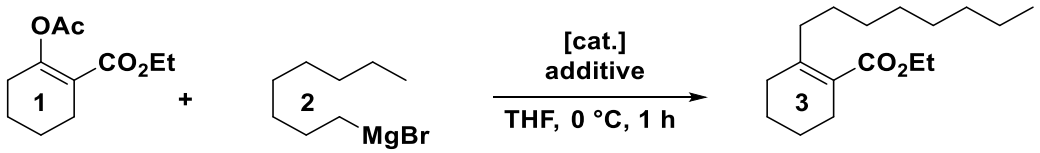
Consistently, all known cross-coupling protocols involve mild organoboron/zinc species.[3] Thus, iron-catalyzed cross-couplings between organic acetates and Grignard reagents require an especially active catalyst which operates under kinetic control where the competing deprotonation and acetylation pathways are suppressed.

3.2 Selected Optimization Experiments

We envisioned capitalizing on the combination of a) a ligand-free, low-valent iron catalyst which favors rapid oxidative addition of the non-activated electrophile, b) Grignard reagents as good nucleophiles which exhibit rapid transmetalation, and c) low temperatures/short reaction times to achieve selective cross-coupling of alkenyl acetates. Similar reaction conditions have been reported for the mechanistically different ring-opening of 2-pyrones (Scheme 3.2).[6] To provide reaction conditions

which would strictly favor kinetic control, we set out to study ligand-free iron catalysts (prepared *in situ* by reduction of ferrous salts with strongly nucleophilic alkyl Grignard reagents) in cross-coupling reactions at 0 °C. We initially tested the feasibility of chemoselective cross-coupling of *n*-octylmagnesium bromide with the alkenyl acetate **1**, bearing a vicinal ester group, to give the tetrasubstituted olefin **3** (Table 3.1).[7]

Table 3.1: Selected optimization experiments.[a]



Entry	Catalyst (mol%)	Additive (equiv.)	Yield [%][b]
1	$FeCl_2$ (10)	–	31[c]
2	$FeCl_2$ (10)	LiCl (1)	62
3	$FeCl_2$ (10)	SIMes·HCl	57
4	$FeCl_2$ (10)	IPr·HCl (0.2)	62
5	$FeCl_2$ (10)	TMEDA (0.2)	82
6	$FeCl_2$ (10)	BDMAEE (0.2)	91
7	$FeCl_2$ (10)	NMP (2)	98
8	-	NMP (2)	2
9	-	–	0 (0)[d,e]
10	$FeCl_2$ (3)	NMP (2)	99[d] (97)[f]

[a] reaction condition: 0.25 mmol **1**, 0.5 mmol **2** in 1 mL THF, 1 h, 0 °C; [b] quantitative GC versus internal *n*-$C_{15}H_{32}$; [c] 25 °C; [d] Addition of 1.25 equiv. **2** over 5 min; [e] 6 h, 60 °C, **1** was recovered; [f] 1.1 equiv. **2**, -30 °C; BDMAEE = bis(2-(*N*,*N*-dimethylamino)ethyl)ether, NMP = *N*-methyl-2-pyrrolidinone, SIMes = 1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene, THF = tetrahydrofuran, TMEDA = *N,N,N',N'*-tetramethyletylenediamine.

To our delight, iron precatalysts showed far superior activity to $PdCl_2$, $NiCl_2$, and CuI (< 8% yield). Donor ligands (chloride, amine, phosphine, *N*-heterocyclic carbene) enhanced the selectivity (entries 2–7). As expected from thermodynamic control, catalyst-free reaction conditions effected rapid acetyl deprotonation (determined by D_2O quench) and only minimal conversion of **1** (< 10%, entry 9). The optimized reaction conditions involved reaction of **1** with a slight excess of **2** (1.1–1.25 equiv.

slow addition) in the presence of 3 mol% $FeCl_2$ in THF/NMP (20:1) at 0 °C for 1 hour (entry 10).

3.3 Comparison of *O*-Based Leaving Groups and Substrate Scope

The reactivity of the starting materials with different *O*-based leaving groups followed the order OTf > OAc > OPiv > $OC(O)NMe_2$ (Figure 3.1).

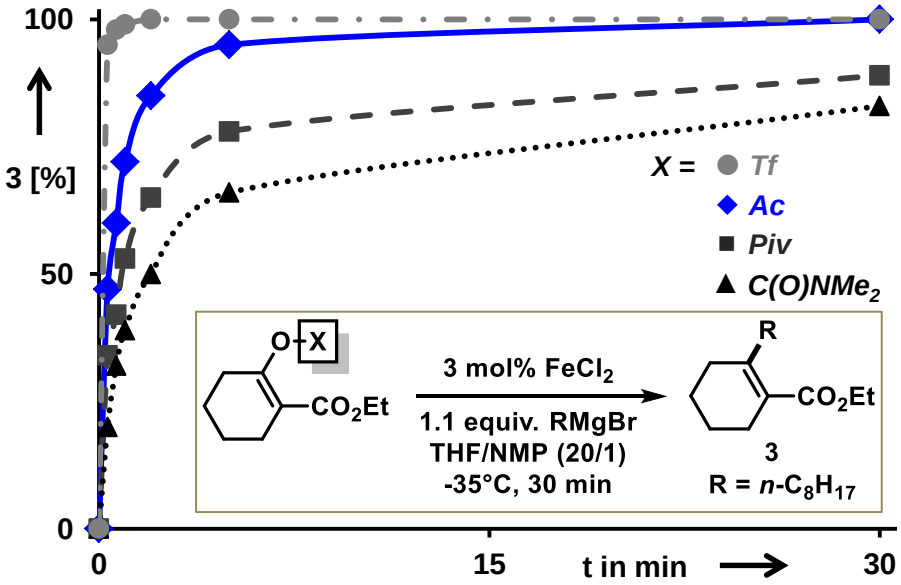
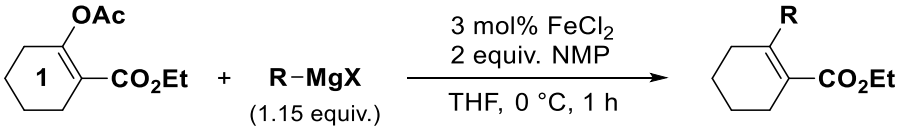
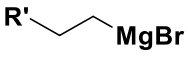
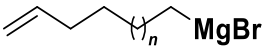
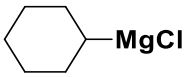
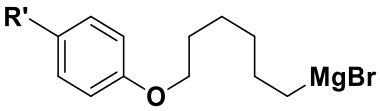
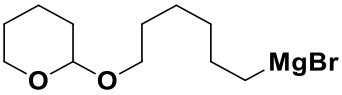


Figure 3.1: Comparison of *O*-based leaving groups (X = Tf, Ac, Piv, $C(O)NMe_2$). Piv = pivaloyl.

The substrate scope of this protocol was further explored by variation of the Grignard reagents (Table 3.2).[7] Primary and secondary alkylMgX were effective, and *t*BuMgCl gave low conversion and some deacetylation.[8] The reaction conditions also allowed clean methyl transfer from MeMgCl (entry 4). Vinyl and phenyl magnesium bromides gave very low conversion of **1**. Halides (F, Cl), amines, alcoholates, aryl methyl ethers, aryl sulfides, esters, ketones, and nitriles were tolerated, with the latter two proceeding at lower temperature (< -10 °C).

Table 3.2: Cross-coupling of 1 with organomagnesium halides.[a]

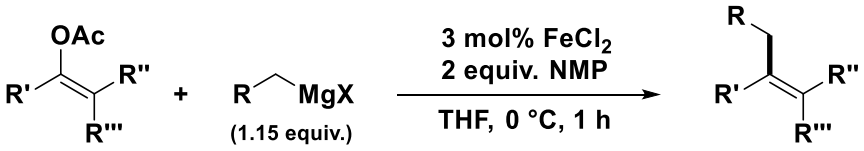


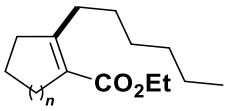
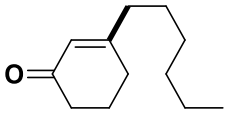
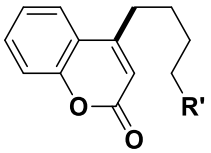
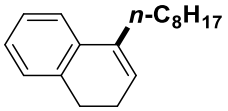
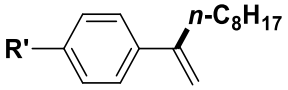
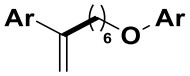
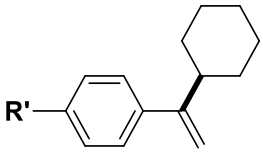
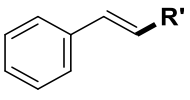
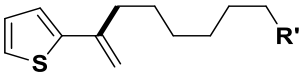
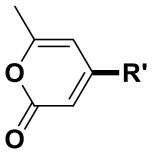
Entry	Grignard reagent		Yield [%][b]
1		R' = H	86[c]
2		R' = *n*-$C_{10}H_{21}$	94[c]
3		R' = Ph	87[c]
4	MeMgBr		85[c]
5		*n* = 1	79[c]
6		*n* = 2	83[c]
7			74
8		R' = Cl	89[c]
9		R' = F	68[c]
10		R' = OMe	76
11		R' = SMe	75
12			71
13	$TMSCH_2MgCl$		–[c]
14	H_2C=CHMgBr		< 5[c]
15	PhMgBr		16

[a] reaction conditions: 0.5 mmol **1**, 0.58 mmol (1.15 equiv.) Grignard reagent, 2 mol% $FeCl_2$, 1 mmol NMP in 1.9 mL THF, 0 °C, 1 h; [b] Yield of isolated product; [c] 0.76 mmol (1.5 equiv.) Grignard reagent; TMS = trimethylsilyl.

A wide chemical space was explored by use of various alkenyl acetates, vinylogous carbonates and anhydrides, 1-styryl acetates, and 2-pyrones (Table 3.3). Thermodynamic migration to the higher substituted olefin products was not observed (entries 8–15, 18, 19).[9]

Table 3.3: Cross-coupling of alkenyl acetates with alkylmagnesium halides.[a]



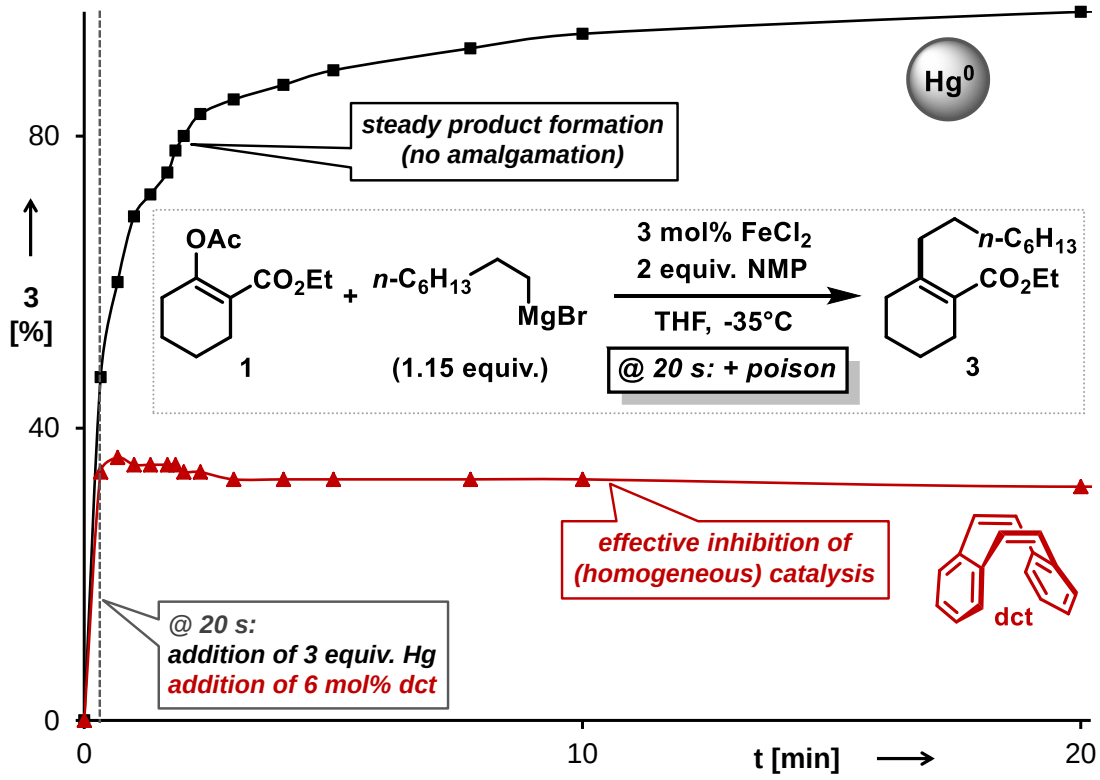
Entry	Product		Yield [%][b]
1		*n* = 1	83[c]
2		*n* = 2	99
3			68[d]
4		R' = Et	86[c]
5		R' = Cl	76[c]
6		R' = OMe	81[c]
7[e]			84
8		R' = H	66[d]
9		R' = Cl	65
10		R' = OMe	91
11		Ar = 4-anisyl	76
12		R' = OMe	92[e]
13		R' = F	69[e]
14		R' = CO_2Me	48[e]
15		R' = CN	28[e]
16		R' = *n*-C_6H_{13}	66[c,f]
17		R' = *c*-C_6H_{11}	69[e,f]
18		R' = Et	82
19		R' = OC_6H_4-4-OMe	75
20		R' = Me	78[d]
21		R' = *n*-C_8H_{17}	49

[a] reaction conditions (see Table 3.2); [b] yield of isolated product; [c] 1.5 equiv. Grignard reagent; [d] 1.05 equiv. *n*-hexylMgBr; [e] *c*-hexylMgCl; [f] *E/Z* (starting material) 3.2/1; *E/Z* (product) 5/1.

3.4 Mechanistic Investigation

Homogeneous and heterogeneous catalysis mechanisms can be distinguished by kinetic experiments.[10] Quantitative analyses of the model reaction between **1** and **2** documented an extremely rapid onset of catalyst activity even between -35 and 0 °C without induction periods or sigmoidal curves, which could indicate nanocluster nucleations *en route* to particle formation.[10,11] The reaction is complete (> 97% yield) after 3 minutes at 0 °C (20 min at -35 °C) with turnover frequencies (TOF) of 3000 h^{-1}.

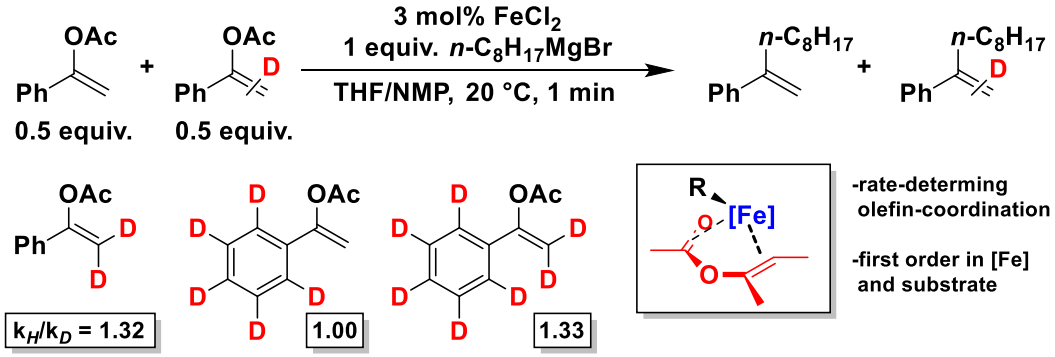
Kinetic poisoning studies were also in agreement with a homogeneous catalysis. The addition of mercury (100 equiv. per Fe, at 45% conversion) resulted in no alteration of catalyst activity (Scheme 3.3).[12] A similar experiment with the π-acceptor ligand dibenzo[*a*,*e*]cyclooctatetraene (dct; 2 equiv. per Fe, at 35% conversion)[10,13] resulted in immediate and complete inhibition.[7]



Scheme 3.3: Poisoning studies with Hg (100 equiv./Fe) and dct (2 equiv./Fe).

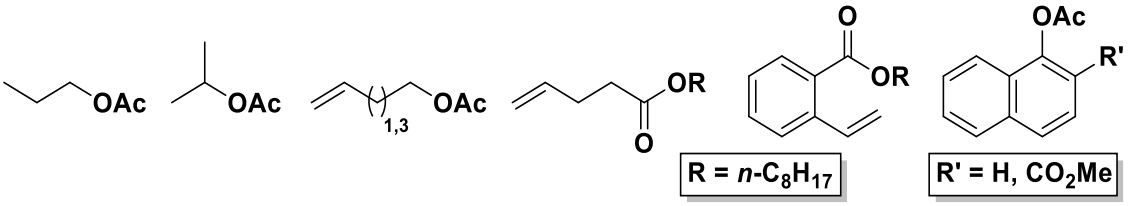
We thus postulate the operation of a homogeneous mechanism by soluble low-valent iron catalysts. In the absence of strong ligands, such iron species were reported to

coordinate π-hydrocarbons.[14] In recent studies, we discovered an assisting role of olefin substituents in cross-couplings at strong C-X bonds within the electrophile.[15] The significant secondary kinetic isotope effects (secondary KIE)[14] observed with *D*-labelled alkenyl acetates are consistent with a rate-determining olefin coordination, whereas catalyst–arene interactions are negligible (Scheme 3.4.1).



Scheme 3.4.1: The assisting role of conjugated olefin substituents: Experiments with *D*-labelled alkenyl acetates.

Accordingly, saturated and aromatic acetates and substrates with distal olefin units did not undergo cross-coupling (< 10%), possibly because of the lack of competent coordination sites (Scheme 3.4.2).[15,16]



Scheme 3.4.2: The assisting role of conjugated olefin substituents: unreactive substrates.

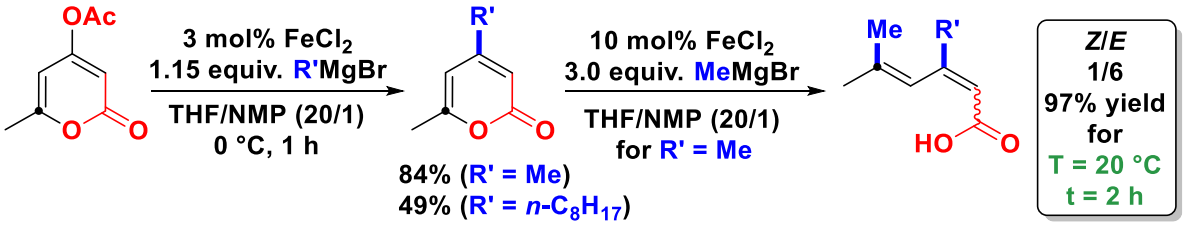
Alkylations of allyl acetates were reported earlier.[17a] The reaction order **1**→**3**, with respect to [$FeCl_2$], is about 1 at low concentrations (< 10 mM, < 5 mol%), and about 0.9 with respect to [**1**] under standard conditions.[7,18]

Therefore, we postulate a mechanism involving rate-determining olefin coordination to the catalyst.[19] The formation of iron(I) catalysts under similar reaction conditions was recently shown by various studies.[20]

3.5 Cross-Coupling of 2-Pyrones

The coordination of pentadienoates to iron catalysts under similar reaction conditions was proposed, by Sun and Fürstner, to operate in the ring-opening methylation of 2-pyrones to (2*Z*)-hexadienoates.[6]

Accordingly, we performed sequential cross-couplings with 4-acetoxy-6-methyl-2-pyrone.



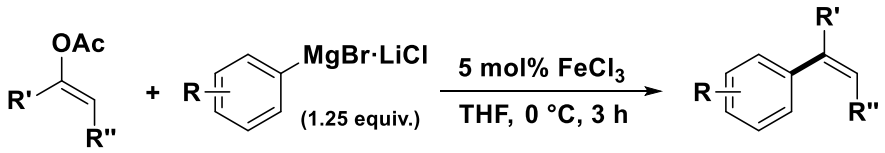
Scheme 3.5: Cross-coupling of 2-pyrones according to Fürstner and Sun.[6]

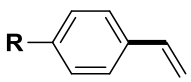
Clean acetate substitution occurred with subsequent methylative ring-opening with a vinylogous acetate acting as formal leaving group to give the (2*E*,4*E*)-hexadienoate at room temperature in excellent yield (Scheme 3.5).

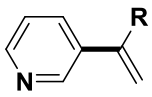
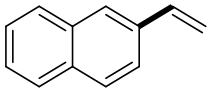
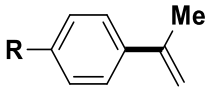
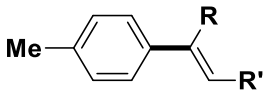
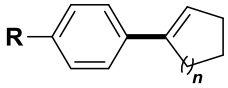
3.6 Arylation of Alkenyl Acetates

Arylations of alkenyl acetates were very sensitive to steric bulk (Table 3.2, entry 15,).[7] Good conversions were only obtained with vinyl acetate and monosubstituted alkenyl acetates (Table 3.4).[21]

Table 3.4: Cross-coupling of alkenyl acetates with arylmagnesium bromides.[a]



Entry	Product	R	Yield [%]
1		R = H	97
2		R = Me	99
3		R = OMe	83
4		R = F	53
5		R = Cl	60
6		R = CN	50

Entry	Product	R	Yield [%][b]
7		R = H	95
8		R = Me	96
9			96
10		R = Me	100
11		R = OMe	81
12		R = F	83
13		R = Ph, R' = H	75
14		R = H, R' = *n*-C_8H_{17}	69
15		R = H, *n* = 1	40
16		R = OMe, *n* = 2	15

[a] reaction conditions: Mg (1.5 equiv.), LiCl (1.5 equiv.), THF (2 mL), 0 °C, ArBr (1.25 equiv.), 0→20 °C over 2 h, then addition of $FeCl_3$ (5 mol%) in THF (0.5 mL) at 0 °C, alkenyl acetate (1 mmol), 3 h; [b] yield of isolated product.

The addition of LiCl and NMP afforded similar results.[22] The formation of arylmagnesium halides was effected by LiCl-assisted magnesium insertion to give ArMgBr·LiCl reagents which were directly employed in the subsequent cross-coupling.

3.7 Summary

In summary, we have developed a practical iron-catalyzed cross-coupling of alkenyl acetates with Grignard reagents which effectively suppresses the thermodynamically favored acylation and deprotonation as well as post-synthesis olefin migration. Kinetic studies support a homogeneous mechanism. The observed secondary KIEs suggest rate-determining coordination of the conjugated alkenyl acetate. This protocol constitutes a significant extension of the scope of metal-catalyzed cross-coupling methods which, thus far, mostly employed organohalides or activated esters as electrophiles.

3.8 Experimental Section

Chemicals and Solvents. Commercial reagents were used without purification if not indicated otherwise. For catalytic reactions, dried solvents were used exclusively. Liquid substrates were distilled prior to use. THF was dried over sodium/benzophenone and distilled. All Fe-catalyzed reactions were performed under an atmosphere of dry argon using standard Schlenk and glovebox techniques.

Analytical thin-layer chromatography. TLC was performed using aluminium plates with silica gel and fluorescent indicator (*Merck*, $60F_{254}$). Thin layer chromatography plates were visualized by exposure to UV light and/or by immersion in an aqueous staining solution of $KMnO_4$.

Column chromatography. Flash column chromatography with silica gel 60 Å (220-240 mesh) from *Acros*. Pentane, hexanes or mixtures thereof with ethyl acetate were used as eluents.

Gas chromatography with mass-selective detector. *Agilent* 6890N Network GC-System, mass detector 5975 MS. Column: BPX5 (30 m x 0.25 mm x 0.25, from *SGE*, carrier gas: H_2.
Standard heating procedure: 50 °C (2 min), 25 °C/min (10 min) -> 300 °C (5 min).

Gas chromatography with FID. *Agilent* 7820A GC-Systems. Column: HP 5 19091J 413 (30 m x 0.32 mm x 0.25 µm) from *Agilent*, carrier gas: N_2. GC-FID was used for catalyst screening (Calibration with internal standard *n*-pentadecane and analytically pure samples).
Standard heating procedure: 50 °C (0 min), 5 °C/min (21 min) -> 300 °C (5 min).

NMR. ^{1}H and ^{13}C nuclear magnetic resonance spectra were recorded on a *Bruker* Avance 300 (300 MHz ^{1}H; 75 MHz ^{13}C) and *Bruker* Avance 400 (400 MHz ^{1}H, 101 MHz ^{13}C) spectrometers. Chemical shifts are reported in ppm (δ) relative to internal tetramethylsilane (TMS). Coupling constants (*J*) are reported in Hertz (Hz). Following abbreviations are used for spin multiplicities:

s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, ddt = doublet of doublet of triplets. For yield determinations, *n*-pentadecane was used as internal standard.

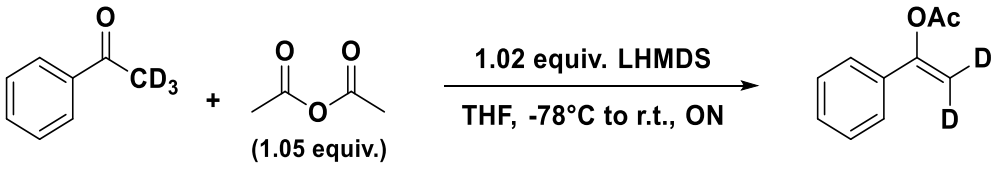
IR spectroscopy. Infrared spectra were recorded on a *Varian* Scimitar 1000 FT-IR equipped with a ATR unit. Wavenumbers are indicated in cm^{-1}. Intensive absorption bands are indicated with „s“ (strong), medium bands with „m“ (medium), and weak bands with „w“ (weak).

High resolution mass spectrometry (HRMS). The spectra were recorded by the Central Analytics Lab at the Department of Chemistry, University of Regensburg, on a MAT SSQ 710 A from *Finnigan*.

Superscripts behind compound names are literature references.

3.8.1 Preparation of Starting Materials

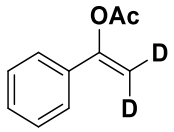
General preparation of alkenyl acetates with lithium bis(trimethylsilyl)amide (LHMDS):



Representative procedure for the acetylation of acetophenone-d_3: In an argon-filled glovebox lithium LHMDS (2.06 g, 12.3 mmol) was placed to a round bottom flask and suspended in dry THF (20 mL). The flask was sealed with a rubber septum and removed from the glovebox. The reaction mixture was cooled to -78 °C and acetophenone-d_3 (1.48 g, 12 mmol) in THF (10 mL) was added slowly over a period of 30 min. After addition the mixture was stirred for 30 min at this temperature. A solution of acetic anhydride (1.19 mL, 12.6 mmol) in THF (15 mL) was added dropwise for 15 minutes at -78 °C. The mixture was stirred for 1.5 hours at -78 °C and then allowed to reach room temperature overnight. The resulting mixture was poured into a 1 M aqueous solution of hydrochloric acid and extracted with diethyl ether (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and

evaporated under reduced pressure. The residue was purified by column chromatography (hexanes/CH_2Cl_2 3/2).[23]

1-Phenyl-vinyl-*d*$_2$ acetate[23]



$C_{10}H_8D_2O_2$, 164.20 g/mol

Yield: 1.14 g, 6.97 mmol, 58% (isolated).

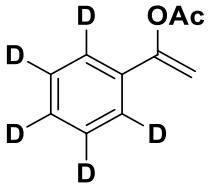
^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 7.54-7.42 (m, 2H), 7.42-7.27 (m, 3H), 2.29 (s, 3H).

$^{13}C\{^1H\}$-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 169.1, 129.0, 128.5, 131.4, 124.9, 21.0.

LR MS (EI, 70 eV, m/z): 164 $[M]^+$.

1-Phenyl-*d*$_5$-vinyl acetate

A 3.41 mmol scale reaction procedure was used.



$C_{10}H_5D_5O_2$, 167.22 g/mol

Yield: 0.32 g, 1.89 mmol, 55% (isolated).

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 5.49 (d, *J* = 2.2 Hz, 1H), 5.03 (d, *J* = 2.2 Hz, 1H), 2.29 (s, 3H).

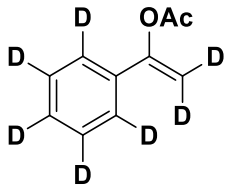
$^{13}C\{^1H\}$-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 102.2, 21.0.

LR MS (EI, 70 eV, *m/z*): 167 $[M]^+$.

HR MS (CI, *m/z*): found 168.1069 $[M+H]^+$ (calculated: 168.1067).

1-Phenyl-d_5-vinyl-d_2 acetate

A 4.00 mmol scale reaction procedure was used.



$C_{10}H_3D_7O_2$, 169.23 g/mol

Yield: 2.84 g, 1.68 mmol, 42% (isolated).

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 2.25 (s, 3H).

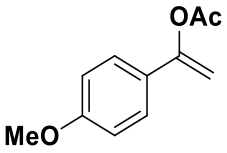
$^{13}C\{^1H\}$-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 169.1, 21.0.

LR MS (EI, 70 eV, *m/z*): 169 $[M]^+$.

HR MS (CI, *m/z*): found 170.1198 $[M+H]^+$ (calculated: 170.1193).

1-(4'-Methoxyphenyl)vinyl acetate[24]

The crude product was purified by column chromatography twice. First a solvent mixture of hexanes and dichloromethane (3/2) was used. For the second purification a solvent mixture of hexanes/diethyl ether (2/1) was used.



$C_{11}H_{12}O_3$, 192.21 g/mol

Yield: 1.25 g, 6.49 mmol, 54% (isolated).

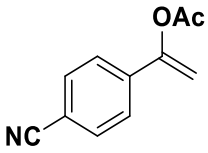
^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 7.40 (d, *J* = 9.0 Hz, 2H), 6.87 (d, *J* = 9.0 Hz, 2H), 5.36 (d, *J* = 2.2 Hz, 1H), 4.92 (d, *J* = 2.2 Hz, 1H), 3.81 (s, 3H), 2.27 (s, 3H).

$^{13}C\{^1H\}$-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 162.2, 160.2, 152.7, 126.8, 126.3, 113.9, 110.3, 55.3, 21.0.

LR MS (EI, 70 eV, *m/z*): 192 $[M]^+$.

1-(4'-Cyanophenyl)vinyl acetate

The crude product was purified by column chromatography twice. First a solvent mixture of hexanes and diethylether (3/1) was used. For the second purification a solvent mixture of hexanes/diethyl ether (2/1) was used.



$C_{11}H_9NO_2$, 187.20 g/mol

Yield: 0.98 g, 4.45 mmol, 30% (isolated).

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H [ppm] = 7.69-7.62 (m, 2H), 7.57-7.52 (m, 2H), 5.60 (d, *J* = 2.6 Hz, 1H), 5.21 (d, *J* = 2.6 Hz, 1H), 2.29 (s, 3H).

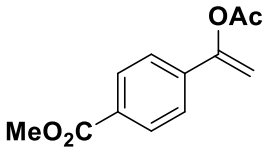
$^{13}C\{^1H\}$-NMR (101 MHz, $CDCl_3$): δ_C [ppm] = 168.8, 151.3, 138.7, 132.4, 125.5, 118.5, 112.5, 105.4, 20.9.

LR MS (EI, 70 eV, *m/z*): 187 $[M]^+$.

HR MS (CI, *m/z*): found 187.0621 (calculated: 187.0628).

Methyl 4-(1-acetoxyvinyl)benzoate[25]

A 15.0 mmol scale reaction procedure was used. The crude product was purified by column chromatography (hexanes/dichloromethane 4/1).



$C_{12}H_{12}O_4$, 220.22 g/mol

Yield: 0.98 g, 5.23 mmol, 44% (isolated).

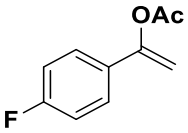
^{1}H-NMR (400 MHz, $CDCl_3$): δ_H [ppm] = 8.04-7.97 (m, 2H), 7.55-7.48 (m, 2H), 5.59 (d, *J* = 2.4 Hz, 1H), 5.15 (d, *J* = 2.4 Hz, 1H), 3.92 (s, 3H), 2.29 (s, 3H).

$^{13}C\{^1H\}$-NMR (101 MHz, $CDCl_3$): δ_C [ppm] = 169.0, 166.5, 152.0, 138.5, 130.4, 129.9, 124.8, 104.4, 52.2, 21.0.

LR MS (EI, 70 eV, m/z): 220 $[M]^+$.

1-(4'-Fluorophenyl)vinyl acetate[25]

A 20.0 mmol scale reaction procedure was used. The crude product was purified by column chromatography (hexanes/ethyl acetate 5/1).



$C_{10}H_9FO_2$, 180.18 g/mol

Yield: 2.08 g, 11.6 mmol, 58% (isolated).

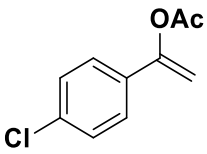
^{1}H-NMR (400 MHz, $CDCl_3$): δ_H [ppm] = 7.50-7.38 (m, 2H), 7.08-6.99 (m, 2H), 5.41 (d, *J* = 2.2 Hz, 1H), 5.01 (d, *J* = 2.2 Hz, 1H), 2.27 (s, 3H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ_C [ppm] = 169.0, 163.1 (d, *J* = 248.8 Hz), 152.0, 130.7 (d, *J* = 3.4 Hz), 126.8 (d, *J* = 8.3 Hz), 115.6 (d, *J* = 21.9 Hz), 101.9, 20.9.

LR MS (EI, 70 eV, m/z): 180 $[M]^+$.

1-(4'-Chlorophenyl)vinyl acetate

A 20.0 mmol scale reaction procedure was used. The crude product was purified by column chromatography (hexanes/ethyl acetate 5/1).



$C_{10}H_9ClO_2$, 196.63 g/mol

Yield: 2.30 g, 11.7 mmol, 58% (isolated).

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H [ppm] = 7.41-7.36 (m, 2H), 7.34-7.29 (m, 2H), 5.46 (d, *J* = 2.4 Hz, 1H), 5.05 (d, *J* = 2.4 Hz, 1H), 2.28 (s, 3H).

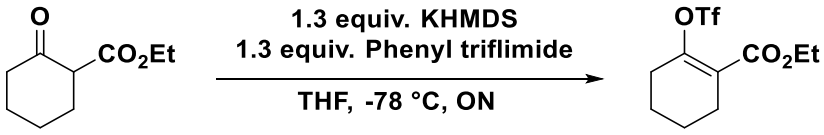
^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ_C [ppm] = 168.9, 151.9, 134.9, 132.9, 128.8, 126.2, 102.7, 21.1.

LR MS (EI, 70 eV, m/z): 196 $[M]^+$.

HR MS (CI, *m/z*): found 197.0366 $[M+H]^+$ (calculated: 197.0364)

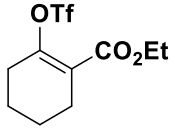
FT-IR 3100(w), 1760(s), 1686(m), 1642(m), 1592(w), 1491(m), 1370(m), 1261(w), 1281(w), 1197(s), 1095(s), 1011(s), 960(m), 848(m).

Synthesis of ethyl 2-trifluoromethanesulfonyloxy-cyclohex-1-enecarboxylate:



The reaction was carried out under dry and inert (N_2) conditions. A solution of ethyl 2-oxocyclohexanecarboxylate (1.34 g, 7.9 mmol) in abs. THF (10 mL) was added to a cooled solution (-78 °C) of potassium bis(trimethylsilyl)amide (KHMDS) (21 ml, 0.5 M in THF, 10.5 mmol), followed by a solution of *N*-phenyl-bis(trifluoromethanesulfon-imide) (3.72 g, 10.4 mmol) in THF (10 mL). The mixture was allowed to reach ambient temperature and was stirred for 70 hours. Water was added (20 mL), the organic phase was separated and the aqueous phase was extracted with diethyl ether (3 x 20 mL). The combined organic phases were dried over Na_2SO_4. The pure product was obtained after column chromatography (hexanes/ethyl acetate 98/2).[26]

Ethyl 2-trifluoromethanesulfonyloxy-cyclohex-1-ene-1-carboxylate[26]



$C_{10}H_{13}F_3O_5S$, 302.26 g/mol

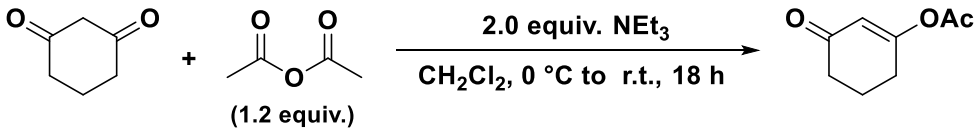
Yield: 2.01 g, 6.64 mmol, 84% (isolated).

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 4.27 (q, *J* = 7.1 Hz, 3H), 2.54-2.29 (m, 4H), 1.18-1.59 (m, 4H), 1.32 (t, *J* = 7.1 Hz, 2H).

$^{13}C\{^1H\}$-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 164.8, 151.3, 135.0, 123.3, 61.6, 28.5, 26.2, 22.3, 21.0, 14.0.

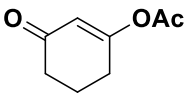
LR MS (EI, 70 eV, m/z): 303 [M^+].

General preparation of alkenyl acetates with triethylamine and acetic anhydride



Representative procedure for the preparation of 3-oxocyclohex-1-enyl acetate: A modified procedure as reported was used: To a solution of 1,3-cyclohexadione (4.49 g, 40.0 mmol) and triethylamine (5.91 mL, 80.0 mmol) in dichloromethane (60 mL) was added at 0 °C acetic anhydride (4.54 mL, 48.0 mmol). The reaction mixture was stirred at room temperature for 18 hours. Afterwards the organic phase was washed with water (10 mL) and a saturated aqueous solution of ammonia chloride (10 mL). The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (*n*-pentane/ethyl acetate, 100% *n*-pentane -> 1/1).[4a]

3-Oxocyclohex-1-enyl acetate[27]



$C_8H_{10}O_3$, 154.17 g/mol

Yield: 2.75 g, 17.8 mmol, 45% (isolated).

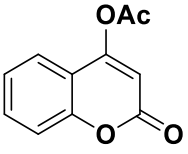
^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 5.83 (s, 1H), 2.49-2.45 (m, 2H), 2.36-2.32 (m, 2H), 2.15 (s, 3H), 2.04-1.95 (m, 2H).

$^{13}C\{^1H\}$-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 199.5, 169.7, 167.4, 117.6, 36.7, 28.3, 21.3, 21.2.

LR MS (EI, 70 eV, m/z): 154 $[M]^+$.

2-Oxo-2*H*-chromen-4-yl acetate[28]

A 10.0 mmol scale reaction procedure was used. The crude product was purified by column chromatography (dichloromethane).



$C_{11}H_8O_4$, 204.18 g/mol

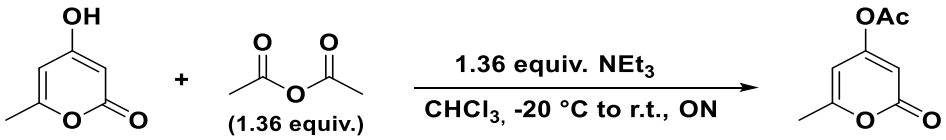
Yield: 1.42 g, 6.95 mmol, 70% (isolated).

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 7.65-.7.55 (m, 2H), 7.38-7.26 (m, 2H), 6.51 (s, 1H), 2.45 (s, 3H).

$^{13}C\{^1H\}$-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 166.6, 161.5, 158.3, 153.7, 132.8, 124.3, 122.7, 117.1, 115.4, 105.2, 21.3.

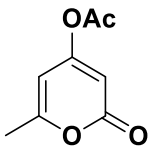
LR MS (EI, 70 eV, m/z): 204 $[M]^+$.

Preparation of 4-acetoxy-6 methyl-2-pyrone



A modified procedure as reported was used: To a solution of acetic anhydride (3.06 g, 30 mmol) in chloroform (10 mL) was slowly added at -20 °C a solution of 4-hydroxy-6 methyl-2-pyrone (2.77 g, 22 mmol) and triethylamine (3.04 g, 30 mmol) in chloroform (30 mL). Once the addition was complete, the cooling bath was removed and stirring continued overnight at ambient temperature. The mixture was washed afterwards with an 1 N aqueous solution of hydrochloric acid (20 mL). The aqueous layer was extracted with chloroform (3 x 20 mL) and the combined organic phases were dried over Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography (hexanes/ethyl acetate 7/3).[6]

4-Acetoxy-6 methyl-2-pyrone[29]



$C_8H_8O_4$, 168.15 g/mol

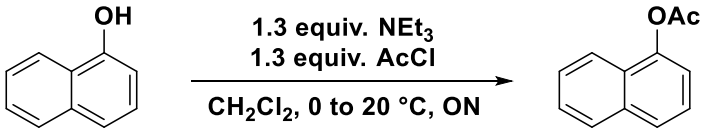
Yield: 3.59 g, 21.4 mmol, 97% (isolated).

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H [ppm] = 6.05-6.01 (m, 1H), 5.97-5.92 (m, 1H), 2.28 (s, 3H), 2.26-2.25 (m, 3H).

$^{13}C\{^1H\}$-NMR (101 MHz, $CDCl_3$): δ_C [ppm] = 166.9, 163.7, 163.3, 163.0, 101.3, 101.1, 21.3, 20.1.

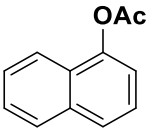
LR MS (EI, 70 eV, m/z): 168 $[M]^+$.

General preparation of alkenyl acetates with triethyl amine and acetic chloride



Representative procedure for the acetylation of 1-naphthol: To a stirred solution of 1-naphthol (1.44 g, 10 mmol) and triethylamine (1.80 mL, 13 mmol) in abs. CH_2Cl_2 (15 mL) was added acetyl chloride (930 µL, 13 mmol) at 0 °C. The reaction mixture was taken slowly to r.t. and stirred overnight. To the crude reaction mixture was added CH_2Cl_2 (5 mL) and a sat. $NaHCO_3$-solution (5 mL). The organic phase was removed and washed with water (2 x 5 mL). After drying over Na_2SO_4, filtration and evaporation of the solvent the product was purified by flash column chromatography (100% hexanes -> hexanes/ethyl acetate 20/1).[30]

Naphthalen-1-yl acetate[31]



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

Yield: 1.25 g, 6.72 mmol, 67% (isolated).

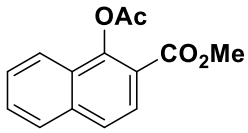
^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 7.88 (ddd, *J* = 6.0, 3.6, 1.4 Hz, 2H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.58-7.35 (m, 3H), 7.28-7.23 (m, 1H), 2.48 (m, 3H).

^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 169.5, 146.6, 134.7, 128.1, 126.5, 126.1, 125.4, 121.1, 118.1, 21.1.

LR MS (EI, 70 eV, m/z): 168 $[M]^+$.

Methyl 1-acetoxy-2-naphthoate

A 5.0 mmol scale reaction procedure was used. The product was purified by flash column chromatography (100% hexanes -> hexanes/ethyl acetate 5/1).



$C_{14}H_{12}O_4$, 244.25 g/mol

Yield: 0.95 g, 3.87 mmol, 77% (isolated).

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 8.07-7.92 (m, 2H), 7.89-7.78 (m, 1H), 7.72 (d, *J* = 8.7 Hz, 1H), 7.65-7.45 (m, 2H), 3.89 (s, 3H), 2.49 (s, 3H).

^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 169.5, 136.5, 128.7, 127.9, 127.5, 127.2, 126.2, 125.7, 122.8, 118.7, 52.3, 21.1.

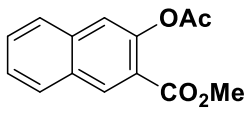
LR MS (EI, 70 eV, m/z): 244 $[M]^+$.

HR MS (CI, *m/z*): found 245.0814 $[M+H]^+$ (calculated: 245.0808)

FT-IR 3063(w), 3004(w), 2955(w), 1751(s), 1710(s), 1632(m), 1599(m), 1505(w), 1468(m), 1278(s), 1244(s), 1203(s), 995(s).

Methyl 3-acetoxy-2-naphthoate

The product was purified by flash column chromatography (hexanes -> hexanes/ethyl acetate 5/1).



$C_{14}H_{12}O_4$, 244.25 g/mol

Yield: 2.44 g, 9.99 mmol, 100% (isolated).

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 8.61 (s, 1H), 8.00-7.89 (m, 1H), 7.86-7.78 (m, 1H), 7.59-7.44 (m, 3H), 3.94 (s, 3H), 2.41 (s, 3H).

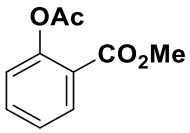
^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 169.3, 134.6, 132.8, 128.0, 127.9, 126.2, 125.5, 120.7, 120.0, 51.3, 20.1.

LR MS (EI, 70 eV, m/z): 244 $[M]^+$.

HR MS (CI, *m/z*): found 245.0812 $[M+H]^+$ (calculated: 245.0808)

FT-IR 2952(w), 1628(m), 1722(m), 1714(s), 1461(w), 1427(m), 1384(m), 1334(w), 1285(s), 1200(s), 1133(m), 1069(s), 957(m).

Methyl acetylsalicylate[32]



$C_{10}H_{10}O_2$, 194.19 g/mol

Yield: 1.48 g, 7.62 mmol, 76% (isolated).

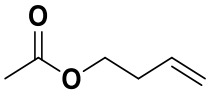
^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 8.02 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.57 (ddd, *J* = 8.1, 7.4, 1.8 Hz, 1H), 7.40-7-20 (m, 1H), 7.11 (dd, *J* = 8.1, 1.2 Hz, 1H), 3.88 (s, 3H), 2.36 (s, 3H).

^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 169.8, 164.9, 150.7, 133.9, 131.8, 126.0, 123.8, 123.1, 52.2, 21.0.

LR MS (EI, 70 eV, m/z): 194.7 $[M]^+$.

But-3-en-1-yl acetate[33]

A 100 mmol scale reaction procedure was used. After evaporation of the solvent no further purification was necessary.



$C_6H_{10}O_2$, 114.14 g/mol

Yield: 5.62 g, 49.2 mmol, 49% (isolated).

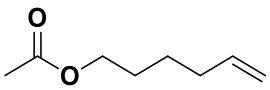
^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 5.83-5.61 (m, 1H), 5.14-4.94 (m, 2H), 4.07 (t, *J* = 6.8 Hz, 2H), 2.41-2.23 (m, 2H), 2.20 (s, 3H).

^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 171.1, 134.0, 117.2, 63.5, 33.0, 21.0.

LR MS (EI, 70 eV, m/z): 114 $[M]^+$.

Hex-5-en-1-yl acetate[33]

A 47.4 mmol scale reaction procedure was used. The product was purified by Kugelrohr destillation (120 °C, 30 mbar).



$C_8H_{14}O_2$, 142.20 g/mol

Yield: 5.01 g, 35.3 mmol, 74% (isolated).

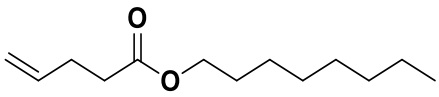
^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 5.80 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.06-4.92 (m, 2H), 4.06 (t, *J* = 6.6 Hz, 2H), 2.13-2.02 (m, 5H), 1.70-1.57 (m, 2H), 1.51-1.38 (m, 2H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ_C [ppm] = 171.3, 138.4, 114.8, 64.4, 33.3, 28.0, 25.2, 21.0.

LR MS (EI, 70 eV, m/z): 142 $[M]^+$.

Octyl 4-pentenoate[34]

4-Pentenoic acid chloride was synthesized according to literature.[17a] A 7.69 mmol scale reaction procedure was used. The product was purified by flash column chromatography (100% hexanes -> hexanes/ethyl acetate 99/1).



$C_{13}H_{24}O_2$, 212.33 g/mol

Yield: 398 mg, 1.87 mmol, 24% (isolated).

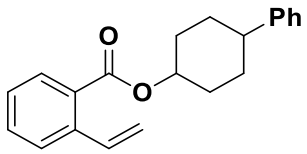
^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 5.92-5.73 (m, 1H), 5.17-4.93 (m, 2H), 4.06 (t, *J* = 6.7 Hz, 2H), 2.47-2.31 (m, 4H), 1.17-1.15 (m, 12H), 0.87 (t, *J* = 6.8 Hz, 3H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ_C [ppm] = 173.2, 136.8, 115.4, 64.6, 33.6, 31.8, 29.2, 29.2, 28.9, 28.6, 25.9, 22.7, 14.1.

LR MS (EI, 70 eV, m/z): 212 $[M]^+$.

4-Phenylcyclohexyl 2-vinylbenzoate

2-Vinylbenzoic acid chloride was synthesized according to literature.[17b] A 1.10 mmol scale reaction procedure was used. The product was purified by flash column chromatography (100% hexanes -> hexanes/ethyl acetate 99/1).



$C_{21}H_{22}O_2$, 306.41 g/mol

Yield: 239 mg, 0.78 mmol, 71% (isolated).

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 7.88 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.59 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.53-7.39 (m, 2H), 5.37-7.17 (m, 6H), 5.66 (dd, *J* = 17.4, 1.3 Hz, 1H), 5.36 (dd, *J* = 11.0, 1.3 Hz, 1H), 5.14-4.86 (m, 1H), 2.68-2.49 (m, 1H), 2.35-1.92 (m, 4H), 1.79-1.57 (m, 4H).

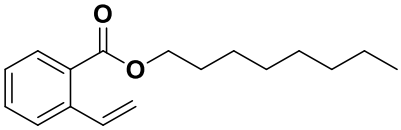
^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 167.1, 146.2, 139.3, 135.9, 131.9, 130.2, 129.4, 128.5, 127.4, 127.2, 126.8, 126.2, 116.3, 73.8, 43.4, 32,3, 32.1.

LR MS (EI, 70 eV, m/z): 306 $[M]^+$.

FT-IR 3060(w), 2930(m), 2859(m), 1767(m), 1707(s), 149a(m), 1450(m), 1260(m), 1133(m), 1066(m), 752(s), 701(s).

Octyl 2-vinylbenzoate

2-Vinylbenzoic acid chloride was synthesized according to literature.[17a] A 3.84 mmol scale reaction procedure was used. The product was purified by flash column chromatography (100% hexanes -> hexanes/ethyl acetate 98/1).



$C_{17}H_{24}O_2$, 260.38 g/mol

Yield: 777 mg, 2.98 mmol, 78% (isolated).

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 7.88 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.58 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.53-7.39 (m, 2H), 5.37-7.28 (m, 1H), 5.66 (dd, *J* = 17.5, 1.3 Hz, 1H), 5.35 (dd, *J* = 11.0, 1.3 Hz, 1H), 4.30 (t, *J* = 6.7 Hz, 2H), 1.85-1.67 (m, 2H), 1.51-1.19 (m, 10H), 0.93-0.85 (m, 3H).

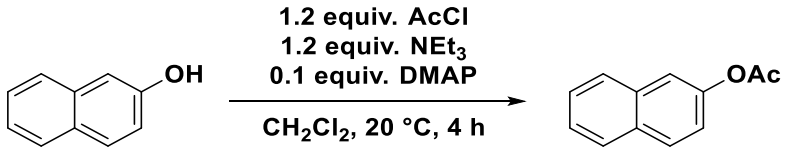
^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ_C [ppm] = 139.5, 136.0, 132.0, 130.2, 127.4, 127.2, 116.3, 65.3, 31.8, 29.3, 29.2, 28.7, 26.1, 22.7, 14.1.

LR MS (EI, 70 eV, m/z): 260 $[M]^+$.

HR MS (CI, *m/z*): found 261.1855 $[M+H]^+$ (calculated: 261.1849)

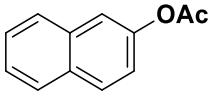
FT-IR 3068(w), 2926(m), 2855(m), 1714(s), 1465(m), 1282(m), 1249(s), 1129(s), 1074(s), 913(m), 768(s).

***Preparation of naphthalen-2-yl acetate*[3a]**



The reaction was carried out under dry and inert (N_2) condition. To solution of 2-naphthol (5.77 g, 40 mmol) in CH_2Cl_2 (150 mL) was added triethylamine (6.65 mL, 48 mmol) and 4-dimethylaminopyridine (DMAP) (0.49 g, 4 mmol). Acetic acid (5.91 mL, 48 mmol) was added over a period of 5 minutes. After 4 hours the reaction was hydrolyzed with a 0.5 M solution of $NaHCO_3$ (75 mL). The mixture was extracted with diethyl ether (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (hexanes/ethyl acetate 5/1).

Naphthalen-2-yl acetat[35]



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

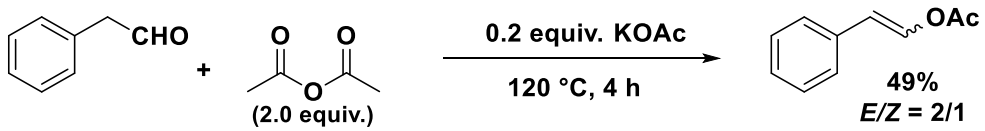
Yield: 6.74 g, 36. 2 mmol, 90% (isolated).

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H [ppm] = 7.89-7.77 (m, 3H), 7.53-7.43 (m, 3H), 7.24 (dd, *J* = 8.9, 2.3 Hz, 1H), 2.36 (s, 3H).

$^{13}C\{^1H\}$-NMR (101 MHz, $CDCl_3$): δ_C [ppm] = 169.7, 148.4, 133.8, 131.5, 129.4, 127.8, 127.7, 126.6, 125.7, 121.2, 118.6, 21.2.

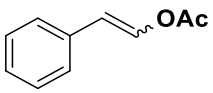
LR MS (EI, 70 eV, m/z): 186 $[M]^+$.

Preparation of styryl acetate



A mixture of phenylacetaldehyde (2.40 g, 20.0 mmol), acetic anhydride (3.77 mL, 40.0 mmol) and KOAc (392 mg, 4.0 mmol) was stirred at 10 °C for 4 hours. The reaction mixture was allowed to reach room temperature and then diluted with ethyl acetate (50 mL). The solution was washed with a saturated aqueous solution of Na_2CO_3 (2 x 30 mL) and the solvent was afterwards removed under reduced pressure. The crude product was purified by column chromatography (hexanes /dichloromethane (1/1).[4a]

Styryl acetate[7,36]



$C_{10}H_{10}O_2$, 162.19 g/mol

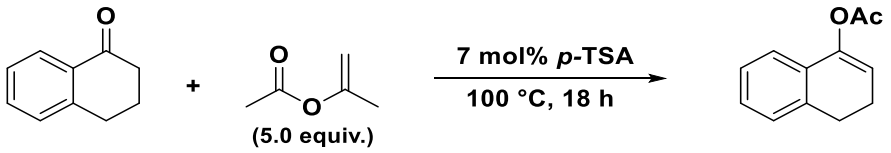
Yield: 0.83 g, 5.12 mmol, 26% (*E*/*Z* = 2/1) (isolated).

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 7.85 (d, *J* = 12.8 Hz, 1H, (*E*)), 7.58 (d, *J* = 7.2 Hz, 2H, (*Z*)), 7.38-7.12 (m, 9H), 6.40 (d, *J* = 12.8, 0.96 Hz, 1H, (*E*)), 5.71 (d, *J* = 7.2, 0.43 Hz, 1H, (*Z*)), 2.28 (s, 3H), 2.91 (s, 3H).

$^{13}C\{^1H\}$-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 168.1, 136.2, 134.1, 133.9, 129.1, 128.7, 128.4, 127.4, 127.3, 126.2, 115.3, 111.9, 20.8.

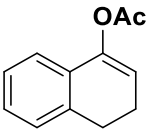
LR MS (EI, 70 eV, m/z): 162 $[M^+]$.

General preparation of alkenyl acetates with 4-toluenesulfonic acid monohydrate (p-TSA·H_2O)



<u>*Representative procedure for the acetylation of α-tetralone:*</u> To a solution of α-tetralone (2.92 g, 20 mmol) in *iso*-propenyl acetate (10.9 mL, 100 mmol) was added *p*-TSA·H_2O (274 mg, 1.44 mmol). The resulting mixture was heated under reflux conditions (100 °C) for 18 hours. The mixture was allowed to cool to room temperature and the remaining *iso*-propenyl acetate was removed under reduced pressure. The brown oily residue was diluted with diethyl ether (50 mL) and the organic phase was washed with water (3 x 15 mL). Afterwards the organic phase was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (hexanes/ dichloromethane 3/2).[24]

3,4-Dihydro-1-naphthyl acetate[37]



$C_{12}H_{12}O_2$, 188.23 g/mol

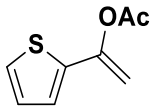
Yield: 3.44 g, 18.3 mmol, 91% (isolated).

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 7.20-7.08 (m, 4H), 5.72 (t, *J* = 4.7 Hz, 1H), 2.88 (t, *J* = 8.1 Hz, 2H), 2.49-2.42 (m, 2H), 2.31 (s, 3H).

^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 169.3, 145.6, 136.4, 130.4, 127.9, 127.6, 126.4, 120.7, 115.5, 27.5, 22.0, 20.9.

LR MS (EI, 70 eV, m/z): 164 $[M]^+$.

1-(Thiophen-2-yl)vinyl acetate[24]



$C_8H_8O_2S$, 168.21 g/mol

Yield: 1.83 g, 10.9 mmol, 54% (isolated).

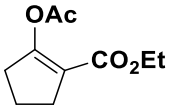
^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 7.24 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.10 (dd, *J* = 3.7, 1.2 Hz, 1H), 6.98 (dd, *J* = 5.0, 3.7 Hz, 1H), 5.39 (d, *J* = 2.5 Hz, 1H), 4.94 (d, *J* = 2.5 Hz, 1H) 2.28 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 168.9, 147.7, 138.2, 127.5, 125.9, 124.7, 101.3, 21.0.

LR MS (EI, 70 eV, m/z): 168 $[M]^+$.

Ethyl 2-acetoxycyclopent-1-ene-1-carboxylate

A 10.0 mmol scale reaction procedure was used.



$C_{10}H_{14}O_4$, 198.22 g/mol

Yield: 1.43 g, 7.21 mmol, 72% (isolated).

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 4.15 (q, *J* = 7.1 Hz, 2H), 2.65-2.58 (m, 4H), 2.22 (s, 3H), 1.94 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 3H).

^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 167.7, 163.7, 159.5, 118.5, 60.1, 33.5, 29.4, 20.9, 19.1, 14.3.

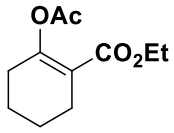
LR MS (EI, 70 eV, m/z): 198 $[M^+]$.

HR MS (CI, *m/z*): found 199.0960 $[M+H]^+$ (calculated: 199.0965)

FT-IR 2979(w), 1765(m), 1708(s), 1657(m), 1435(w), 1370(m), 1349(m), 1300(m), 1267(m), 1167(s), 1128(s), 1004(s), 873(m), 770(w).

Ethyl 2-acetyloxycyclohex-1-ene-1-carboxylate

A 10.0 mmol scale reaction procedure was used. For the purification by column chromatography a solvent mixture of hexanes/diethyl ether of 2/1 was used.



$C_{11}H_{16}O_4$, 212.24 g/mol

Yield: 1.90 g, 8.93 mmol, 89% (isolated).

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H [ppm] = 4.15 (q, *J* = 7.1 Hz, 2H), 2.39 (ddd, *J* = 8.4, 6.0, 2.4 Hz, 2H), 2.27-2.20 (m, 2H), 2.18 (s, 3H), 1.77-1.61 (m, 4H), 1.27 (t, *J* = 7.1 Hz, 3H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ_C [ppm] = 168.6, 165.7, 155.5, 117.8, 60.3, 29.2, 25.4, 22.0, 21.7, 21.0, 14.2.

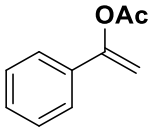
LR MS (EI, 70 eV, m/z): 212 $[M]^+$.

HR MS (CI, *m/z*): found 213.1118 $[M+H]^+$ (calculated: 213.1121).

FT-IR 2939(w), 2865(w), 2761(s), 1706(s), 1659(m), 1368(m), 1285(m), 1239(s), 1211(s), 1178(s), 1120(s), 1074(s), 1052(s), 1025(m), 922(w).

1-Phenylvinyl acetate[24]

A 20.0 mmol scale reaction procedure was used. For the purification by column chromatography a solvent mixture of hexanes/dichloromethane of 3/2 was used.



$C_{10}H_{10}O_2$, 162.19 g/mol

Yield: 1.87 g, 11.5 mmol, 58% (isolated).

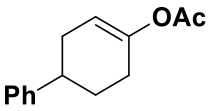
^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 7.51-7.44 (m, 2H), 7.40-7.29 (m, 3H), 5.48 (d, *J* = 2.2 Hz, 1H), 5.03 (d, *J* = 2.2 Hz, 1H), 2.28 (s, 3H).

^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 169.1, 153.0, 134.3, 129.0, 128.5, 124.9, 102.2, 21.0.

LR MS (EI, 70 eV, m/z): 162 $[M]^+$.

4-Phenyl-1-cyclohexen-1-yl acetate[38]

A 15.0 mmol scale reaction procedure was used. The product was purified by flash column chromatography hexanes -> hexanes/dichloromethane 4/1.



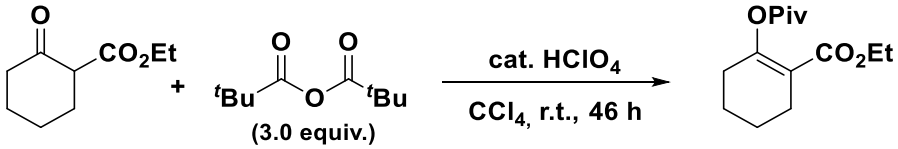
$C_{14}H_{18}O_2$, 216.28 g/mol

Yield: 2.89 g, 13.4 mmol, 89% (isolated)

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 7.42-7.07 (m, 5H), 5.51-5.40 (m, 1H), 2.95-2.76 (m, 1H), 2.55-2.09 (m, 8H), 2.07-1.77 (m, 2H).

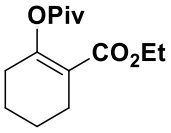
LR MS (EI, 70 eV, m/z): 216 $[M]^+$.

Preparation of Ethyl 2-pivaloxycyclohex-1-enyl-1-carboxylate



To a solution of ethyl 2-oxocyclohexane carboxylate (1.70 g, 10.0 mmol) and pivalic anhydride (5.59 g, 30 mmol) in carbon tetrachloride (10 mL) was added perchloric acid (approx. 70 µL). The resulting mixture was stirred at room temperature for 46 hours. The mixture was diluted with dichloromethane (5 mL) and the solution was washed with bidest. water (5 mL) and a saturated aqueous solution of $NaHCO_3$. The organic phase was dried over Na_2SO_4 and the solvent was removed afterwards under reduced pressure. The crude product was purified by column chromatography (hexanes/ethyl acetate 100/1) as eluent.[4a]

Ethyl 2-pivaloxycyclohex-1-enyl-1-carboxylate[4a]



$C_{14}H_{22}O_4$, 254.33 g/mol

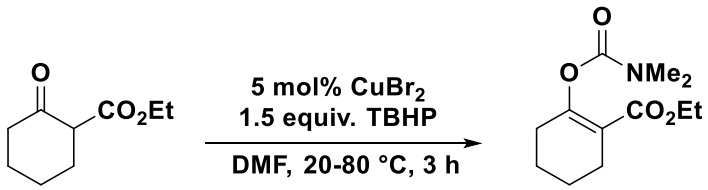
Yield: 1.63 g, 6.41 mmol, 64% (isolated)

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 4.16 (*J* = 7.1 Hz, 2H), 2.44-2.36 (m, 2H), 2.24-2.16 (m, 2H), 1.75-1.60 (m, 4H), 1.29-1.22 (m, 12H).

^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 165.9, 158.0, 154.8, 118.1, 60.3, 38.9, 28.7, 27.0, 25.4, 22.0, 21.8, 14.3.

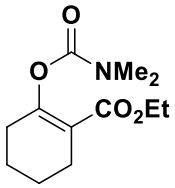
LR MS (EI, 70 eV, m/z): 254 $[M]^+$.

Preparation of Ethy 2-((dimethylcarbamoyl)oxy)cyclohex-1-ene-1-carboxylate



To a mixture of ethyl 2-oxocyclohexane carboxylate (1.70 g, 10.0 mmol) and $CuBr_2$ (112 g, 0.5 mmol) in dimethylformamide (DMF) (20 mL) was added slowly an aqueous solution of *tert*-butylhydroperoxide (TBHP) (70%, 2.08 mL, 15.0 mmol). After addition the reaction mixture was heated to 80 °C and stirred at this temperature for 3 hours. The reaction mixture was allowed to cool to room temperature and ethyl acetate (15 mL) was added. The organic phase was separated and the aqueous phase was extracted once with ethyl acetate (10 mL). To the aqueous phase was added a sat. sodium thiosulfate solution (10 mL) and then extracted again with ethyl acetate (10 mL). The combined organic layers were dried over Na_2SO_4. After filtration and evaporation of the solvent the crude product was purified flash column chromatography (hexanes/ ethyl acetate 98/2 -> 90/10).[39]

Ethyl 2-((dimethylcarbamoyl)oxy)cyclohex-1-ene-1-carboxylate[39]



$C_{12}H_{19}NO_4$, 241.29 g/mol

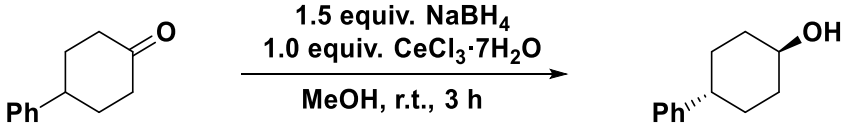
Yield: 648 mg, 2.69 mmol, 27% (isolated).

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 4.15 (q, *J* = 7.1 Hz, 2H), 2.97 (s, 6H), 2.45-2.21 (m, 4H), 1.80-1.57 (m, 4H), 1.24 (t, *J* = 7.1 Hz, 3H).

^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 166.2, 156.0, 153.9, 117.7, 60.2, 36.5, 29.7, 25.3, 22.1, 21.8, 14.1.

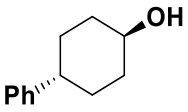
LR MS (EI, 70 eV, m/z): 241 $[M]^+$.

Synthesis of trans-4-phenylcyclohexanol



To a solution of 4-phenylcyclohexanone (2.10 g, 12.1 mmol) and cerium(III) chloride heptahydrate (4.50 g, 12.1 mmol) in methanol (25 mL) was added slowly sodium borohydride (685 mg, 18.5 mmol). The reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was carefully hydrolyzed with water (30 mL) and diethyl ether (30 mL) was added. The organic layer was separated and the aqueous phase was extracted with diethyl ether (2 x 30 mL). The combined organic layers were dried over Na_2SO_4. After filtration and evaporation of the solvent the pure product was obtained after flash column chromatography (hexanes/ ethyl acetate 3/1 -> 1/1).[40]

***trans*-4-Phenyl cyclohexan-1-ol[41]**

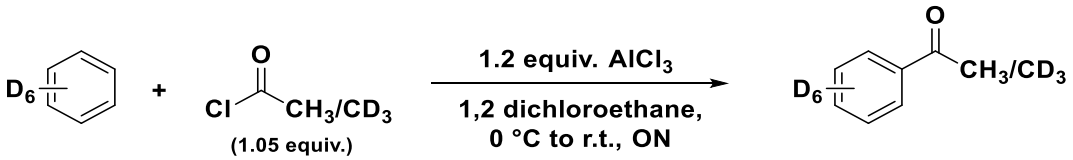


$C_{12}H_{16}O$, 176.26 g/mol

Yield: 705 mg, 3.40 mmol, 33% (isolated).

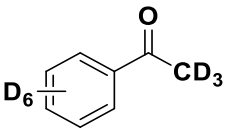
^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 7.37-7.11 (m, 5H), 3.70 (tt, *J* = 10.6, 4.3 Hz, 1H), 2.50 (tt, *J* = 11.9, 3.5 Hz, 1H), 2.16-2.04 (m, 2H), 2.00-1.88 (m, 2H), 1.67-1.34 (m, 4H).

Synthesis of deuterated acetophenones



Representative procedure: Under an atmosphere of N_2, aluminium trichloride (1.60 g, 12 mmol) was suspended in 1,2-dichloroethane (4 mL). The suspension was cooled to 0 °C and acetylchloride-d_3 was added over a period of 10 minutes. Then benzene-d_6 (0.89 mL, 10 mmol) was added dropwise for 10 minutes. After addition the mixture was stirred for 1 hour at room temperature. The mixture was allowed to stand overnight. Then ice-cold water (4 mL) was added and the resulting precipitate was solved by adding conc. hydrochloric acid (aprox. 100 µL). The organic phase was separated and the aqueous phase was extracted with 1,2-dichloroethane (2 x 4 mL). The combined organic layers were washed with water (4 mL), an aqueous solution of sodium hydroxide (4 mL, 2% w/w) and again with water (4 mL). The organic phase was dried over K_2CO_3, filtered and the solvent was removed under reduced pressure. The crude product was purified by Kugelrohr distillation (100-140 °C, 30 mbar).[42]

Acetophenone-d_8



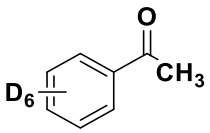
C_8D_8O, 128.20 g/mol

Yield: 0.91 g, 7.07 mmol, 71% (isolated).

LR MS (EI, 70 eV, m/z): 128 [M^+].

Acetophenone-2‘,3‘,4‘,5‘,6‘-d_5 [43]

A 25.0 mmol scale reaction procedure was used. Instead of acetylchloride-d_3, acetylchloride (1.87 mL, 26.3 mmol) was used as acylating reagent. Also in a different way as reported 1,2-dichloromethane was used as solvent instead of 1,2-dichloroethane probably causing the low yield.



$C_8H_3D_5O$, 125.18 g/mol

Yield: 0.64 g, 5.11 mmol, 20% (isolated).

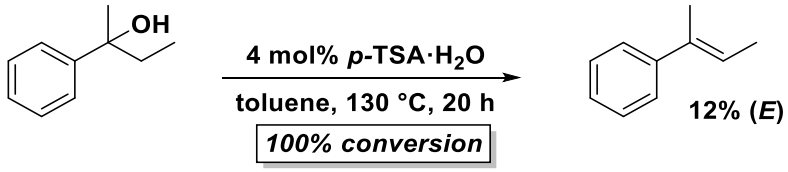
^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 2.61 (s, 3H).

$^{13}C\{^1H\}$-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 26.6.

LR MS (EI, 70 eV, m/z): 125 $[M]^+$.

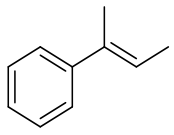
Synthesis of butenyl benzene

Method A:



A modified procedure as reported was used. 2-Phenyl-2-butanol (0.72 g, 5.00 mmol) was solved in toluene (5 mL) and *p*-TSA·H_2O (38.0 mg, 0.20 mmol) was added. The reaction mixture was heated to 130 °C and stirred overnight. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (100% hexanes).[16b,44] (*E*)-2-Butenyl benzene was obtained in 12% yield. In addition 264 mg of a dimer mixture was isolated (*m*/*z* = 264). Further products seem to be polymerization products.

(*E*) 2-Butenyl benzene[45]



$C_{10}H_{12}$, 132.21 g/mol

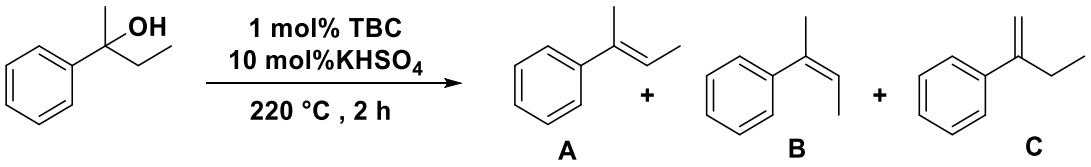
Yield: 79 mg, 0.6 mmol, 12% (isolated).

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H [ppm] = 7.44-7.37 (m, 2H), 7.36-7.29 (m, 2H), 7.28-7.20 (m, 1H), 5.90 (qq, *J* = 6.8, 1.3 Hz, 1H), 2.09-2.04 (m, 3H), 1.83 (dd, *J* = 6.9, 1.1 Hz, 3H).

$^{13}C\{^{1}H\}$-NMR (101 MHz, $CDCl_3$): δ_C [ppm] = 144.1, 135.6, 128.2, 126.4, 125.6, 122.5, 15.5, 14.4.

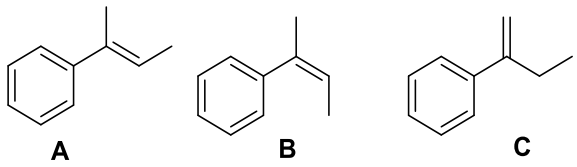
LR MS (EI, 70 eV, m/z): 132 $[M]^+$.

Method B:



A modified procedure as reported was used: A flask was charged with $KHSO_4$ (272 mg, 2mmol) and 4-*tert*-butylcatechol (TBC) (166 mg, 1.00 mol) was added. At 200 °C 2-phenyl-2-butanol (3.00 g, 20 mmol) was added and the resulting products were distilled (220 °C, 2 h). Afterwards the water was separated and the organic phase was diluted with diethyl ether (10 mL) and dried over Na_2SO_4. The solvent was evaporated and a reaction mixture of A, B and C was obtained as colorless oil.[46]

2-Butenyl benzenes[45,47]



$C_{10}H_{12}$, 132.21 g/mol

Yield: 1.87 mg, 14.0 mmol, 71% (A/B/C = 4/2/1) (isolated).

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H [ppm] = 7.48-7.17 (m, 5H (A, B, C)), 5.88 (q, *J* = 6.9 Hz, 1H (A)), 5.58 (q, *J* = 6.9 Hz, 1H (B)), 5.29 (s, 1H (C)), 5.08 (m, 1H (C)), 2.53 (q, *J* = 7.1 Hz, 2H (C)), 2.04 (s, 3H (A,B)), 1.81 (d, *J* = 6.9 Hz, 3H (A)), 1.61 (d, *J* = 6.9 Hz, 3H (B)), 1.12 (td, *J* = 7.4, 0.6 Hz, 3H (C)).

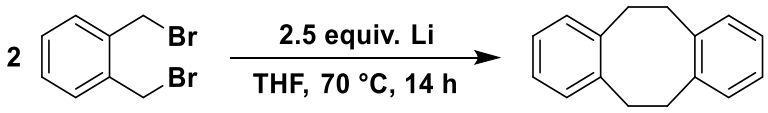
$^{13}C\{^{1}H\}$-NMR (101 MHz, $CDCl_3$): δ_C [ppm] = 144.1, 136.8, 135.5, 128.3, 128.2, 128.1, 128.0, 127.3, 126.4, 126.4, 126.0, 125.6, 122.5, 121.6, 111.0, 28.1, 25.4, 15.5, 14.9, 14.4, 13.0.

LR MS (EI, 70 eV, m/z): 132 $[M]^+$.

Synthesis of dibenzo[a,e] cyclooctene (dct)

All reactions were carried out under dry and inert (Ar) conditions.

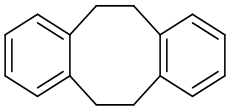
Synthesis of 5,6,11,12-tetrahydrodibenzo[a,e]cyclooctene



Caution: Once *α*,*α*'-dibromo-*ortho*-xylene is dissolved it becomes lachrymatory!

To a suspension of lithium (791 mg, 114 mmol) in THF (20 mL) was added via a syringe pump a solution of *α*,*α*-dibromo-*ortho*-xylene (12.0 g, 45.5 mmol) in dry THF (20 mL) over a period of 2 hours. After complete addition the reaction mixture was heated under reflux conditions (80 °C) for 14 hours. The residual lithium was filtered through a fritted glass funnel. The funnel was subsequently rinsed with THF (10 mL). The solvent was removed under reduced pressure and dichloromethane (100 mL) was added. After stirring for 2 minutes, insoluble material was removed by filtration with a fritted glass funnel filled with silica gel. The residue was washed with dichloromethane (100 mL) and the resulting yellow solution was dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (100% *n*-pentane).[13b]

5,6,11,12-Tetrahydrodibenzo[a,e]cyclooctene[13b]



$C_{16}H_{16}$, 208.30 g/mol

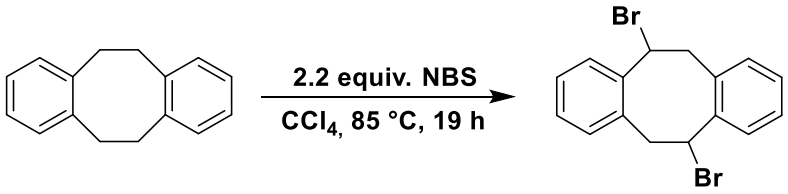
Yield: 2.23 g, 10.7 mmol, 47% (isolated).

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H [ppm] = 7.05-6.96 (m, 8H), 3.07 (s, 8H).

$^{13}C\{^1H\}$-NMR (101 MHz, $CDCl_3$): δ_C [ppm] = 140.6, 129.7, 126.1, 35.2.

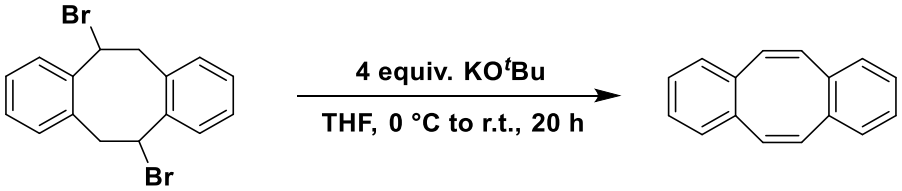
LR MS (EI, 70 eV, m/z): 208 $[M]^+$.

Synthesis of 5,11-dibromo-5,6,11,12-tetrahydrodibenzo[*a*,*e*]-cyclooctene



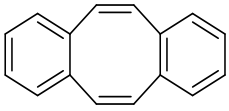
To a solution of 5,6,11,12-tetrahydrodibenzo[*a*,*e*] cyclooctene (2.08 g, 10.0 mmol) in dry carbon tetrachloride (35 mL) was added *N*-bromosuccinimide (3.92 g, 22.0 mmol) and the resulting reaction mixture was heated under reflux conditions (80 °C) for 19 hours. The hot suspension was filtered through a fritted glass funnel and the residue was washed with carbon tetrachloride (10 mL). The solvent of the filtrate was evaporated under reduced pressure. A pale yellow solid was obtained that was directly used in the next step.[13b]

Synthesis of dibenzo[*a*,*e*]-cyclooctene (dct)



A modified protocol than reported was used. To an ice cooled suspension of potassium-*tert*-butoxide (4.26 g, 38.0 mmol) in dry THF (10 mL) was added a solution of 5,11-dibromo-5,6,11,12-tetrahydrodibenzo[*a*,*e*]-cyclooctene (3.45 g, 9.42 mmol) in dry THF over a period of 5 minutes. After addition the ice bath was removed and the reaction mixture was stirred for 20 hours at room temperature. Water (1.5 mL) was added and the mixture was poured onto a pad of silica gel that has already been wetted with diethyl ether. The pad was rinsed with diethyl ether (8 mL) and the collected organic phase was dried over Na_2SO_4. The solvent was removed under reduced pressure[13b] and the crude product was purified by column chromatography (100% *n*-pentane) and following recrystallization from ethanol.

Dibenzo[a,e]-cyclooctene (dct)[13b]



$C_{16}H_{12}$, 204.27 g/mol

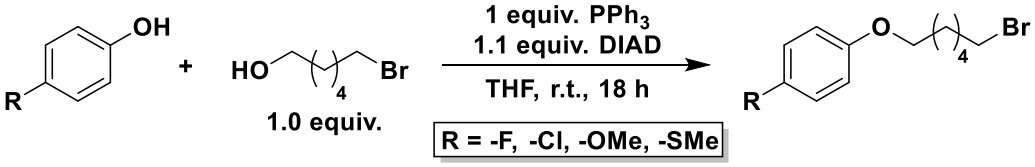
Yield: 912 mg, 4.46 mmol, 47% (isolated).

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 7.19-7.01 (m, 8H), 6.76 (s, 4H).

$^{13}C\{^{1}H\}$-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 137.1, 133.3, 129.1, 126.8.

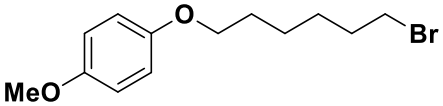
LR MS (EI, 70 eV, m/z): 204 [M^+].

Synthesis of alkyl bromides



Representative procedure for the synthesis of 1-(6'-bromohexyloxy)-4-methoxy-benzene: A modified reaction procedure than reported was used. The reaction was carried out under dry and inert reaction conditions. To a solution of triphenylphosphine (2.62 g, 10.0 mmol), 4-methoxyphenol (1.24 g, 10.0 mmol) and 6-bromohexan-1-ol (13.1 mL, 10.0 mmol,) in dry THF (10 mL) was added at 0 °C diisopropyl azodicarboxylate (DIAD) (23 mL, 11 mmol), 94% purity) dropwise. After addition the reaction mixture was stirred overnight. The mixture was concentrated in vacuo and purified by column (hexanes/ethyl acetate 10/1).[16b]

1-(6'-Bromohexyloxy)-4-methoxybenzene[48]



$C_{13}H_{19}BrO_2$, 287.20 g/mol

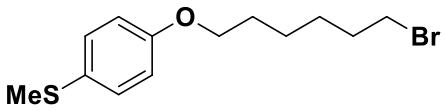
Yield: 2.61 g, 9.09 mmol, 91% (isolated).

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H [ppm] = 6.83 (s, 4H), 3.91 (t, *J* = 6.4 Hz, 2H), 3.77 (s, *3*H), 3.42 (m, 2H), 1.95-1.72 (m, 4H), 1.53-1.45 (m, 4H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ_C [ppm] = 153.8, 153.5, 115.5, 114.7, 68.4, 55.8, 33.8, 32.7, 29.2, 28.0, 25.3.

LR MS (EI, 70 eV, m/z): 287 [M^+].

1-(6'-Bromohexyloxy)-4-methylthiobenzene[16b]



$C_{13}H_{19}BrOS$, 303.26 g/mol

Yield: 2.11 g, 6.96 mmol, 70% (isolated).

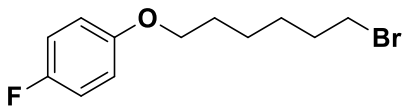
^{1}H-NMR (400 MHz, $CDCl_3$): δ_H [ppm] = 7.29-7.23 (m, 2H), 6.86-6.81 (m, 2H) 3.94 (t, *J* = 6.4 Hz, 2H), 3.42 (t, *J* = 6.8 Hz, 2H) 2.44 (s, *3*H), 1.94-1.74 (m, 4H), 1.54-1.45 (m, 4H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ_C [ppm] = 157.7, 130.2, 128.6, 115.2, 67.9, 33.8, 32.7, 29.1, 27.9, 25.3, 18.1.

LR MS (EI, 70 eV, m/z): 303 [$M]^+$.

1-(6'-Bromohexyloxy)-4-fluorobenzene[16b]

A 2.93 mmol scale reaction procedure was used.



$C_{12}H_{16}BrFO$, 274.04 g/mol

Yield: 745 mg, 2.72 mmol, 93% (isolated).

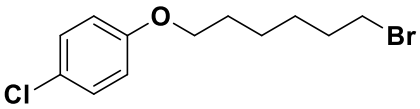
^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 7.02-6.77 (m, 4H), 3.91 (t, *J* = 6.4 Hz, 2H), 3.43 (t, *J* = 6.8 Hz, 2H), 1.95-1.73 (m, 4H), 1.55-1.43 (m, 4H).

^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 157.3 (d, *J* = 237.8 Hz), 155.3 (d, *J* = 2.1 Hz), 115.9 (d, *J* = 23.0 Hz), 115.2 (d, *J* = 7.9 Hz), 68.2, 33.9, 32.8, 29.2, 28.1, 25.4.

LR MS (EI, 70 eV, m/z): 274 [M^+].

1-(6'-Bromohexyloxy)-4-chlorobenzene

A 5.73 mmol scale reaction procedure was used.



$C_{12}H_{16}BrClO$, 291.61 g/mol

Yield: 1.05 g, 3.60 mmol, 63% (isolated).

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 7.30-7.16 (m, 2H), 6.86-6.76 (m, 2H), 3.92 (t, *J* = 6.4 Hz, 2H), 3.47-3.38 (m, 2H), 1.97-1.72 (m, 4H), 1.55-1.40 (m, 4H).

^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 157.7, 129.3, 125.4, 115.7, 68.2, 33.8, 32.7, 29.0, 27.9, 25.3.

LR MS (EI, 70 eV, m/z): 292 [M^+].

HR MS (Cl, *m/z*): found 290.0068 [M] (calculated: 290.0068).

3.8.2 Iron catalyzed cross-coupling reactions of alkenyl acetates with alkylmagnesium halides

3.8.2.1 General procedure for the cross coupling of alkenyl acetate with Grignard reagents via Fe catalysis

Method A:

Representative procedure for the cross-coupling of 2-acetoxycyclohex-1-ene-carboxylate with *n*-hexylmagnesium bromide: The reaction was carried out under dry and inert conditions. To an oven dried Schlenk tube was added $FeCl_2$ (2 mol%), THF (1 mL), ethyl 2-acetoxycyclohex-1-enecarboxylate (53 mg, 0.25 mmol), and *N*-methyl-2-pyrrolidone (NMP) (0.48 mL, 0.5 mmol). The mixture was cooled to 0 °C in an ice-water bath and 375 µL of *n*-hexylmagnesium bromide (1.0 M in THF) was added during 5-10 seconds. After stirring at that temperature for an hour, the reaction was hydrolyzed by addition of saturated aqueous NH_4Cl solution and extracted with ethyl acetate (2 x 1 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. After removal of the solvent, the residue was applied to column chromatography eluting with ethyl acetate and *n*-pentane.

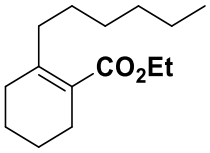
Method B:

Representative procedure for the cross-coupling of 1-Phenylvinyl acetate with *n*-octylmagnesium bromide: The reaction was carried out under dry and inert conditions. First a $FeCl_2$-NMP-stock solution was prepared in a glovebox. Therefore an oven dried flask was charged with $FeCl_2$ (19.0 mg, 0.15 mmol) and NMP (0.96 mL, 10.0 mmol). THF (19 mL) was added and the mixture was stirred until the iron salt was completely solved.

An oven dried reaction tube was introduced in a glovebox and charged with 1-phenylvinyl acetate (81.1 mg, 0.50 mmol) and 2.0 mL of a freshly prepared $FeCl_2$-NMP-stock solution. The reaction tube was sealed with a rubber septum and removed from the glovebox. The reaction mixture was cooled with an ice bath to 0 °C and 530 µL of a *n*-octylmagnesium bromide solution in THF (0.53 mmol, 1.0 M) were added via syringe pump over a period of 10 minutes. After stirring at that temperature for an hour, the reaction was hydrolyzed with a saturated aqueous NH_4Cl solution

(1 mL), and extracted with ethyl acetate (3 x 1.5 mL). The combined organic layers were dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was subjected to quantitative GC-FID (internal reference: *n*-pentadecane), NMR (internal reference: *n*-pentadecane) or silica gel flash column chromatography with *n*-pentane as eluent.

Ethyl 2-hexylcyclohex-1-ene carboxylate[4a]



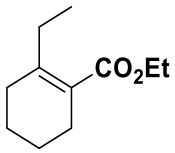
$C_{15}H_{26}O_2$, 238.37 g/mol

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 4.13 (q, *J* = 7.1 Hz, 2H), 2.26-2.21 (m, 4H), 2.06-2.05 (m, 2H), 1.54-1.51 (m, 4H), 1.39-1.34 (m, 2H), 1.28-1.21 (m, 9H), 0.82 (t, *J* = 7.1 Hz, 3H).

^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 169.4, 149.9, 124.4, 59.9, 35.5, 31.8, 31.1, 29.6, 28.7, 26.5, 22.6, 22.4, 14.3, 14.1.

LR MS (EI, 70 eV, m/z): 238 $[M]^+$.

Ethyl 2-ethylcyclohex-1-ene carboxylate[4a]



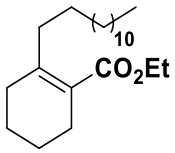
$C_{11}H_{18}O_2$, 182.26 g/mol

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 4.12 (q, *J* = 7.4 Hz, 2H), 2.28-2.18 (m, 4H), 2.09-2.04 (m, 2H), 1.58-1.50 (m, 4H), 1.26-1.20 (m, 3H), 0.99 (t, *J* = 7.6 Hz, 3H).

^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 169.3, 150.2, 124.1, 59.9, 30.5, 29.1, 28.5, 26.5, 22.4, 14.3, 13.1.

LR MS (EI, 70 eV, m/z): 182 $[M]^+$.

Ethyl 2-dodecylcyclohex-1-ene carboxylate[4a]



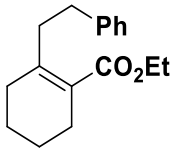
$C_{21}H_{38}O_2$, 322.53 g/mol

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 4.12 (q, *J* = 7.1 Hz, 2H), 2.26-2.21 (m, 4H), 2.06-2.05 (m, 2H), 1.55-1.51 (m, 4H), 1.39-1.34 (m, 2H), 1.27-1.20 (m, 21H), 0.82 (t, *J* = 7.1 Hz, 3H).

^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 169.4, 148.9, 124.4, 59.8, 35.5, 31.9, 29.9, 29.7, 29.68, 29.66, 29.64, 29.59, 29.4, 28.7, 26.5, 22.7, 22.4, 14.3, 14.1

LR MS (EI, 70 eV, m/z): 322 $[M]^+$.

Ethyl 2-phenethylcyclohex-1-ene carboxylate[4a]



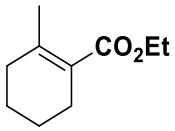
$C_{17}H_{22}O_2$, 258.36 g/mol

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 7.31-7.19 (m, 5H), 4.19 (q, *J* = 7.4 Hz, 2H), 2.80-2.74 (m, 2H), 2.66-2.63 (m, 2H) 2.31-2.30 (m, 2H), 2.14-2.13 (m, 2H), 1.63-1.59 (m, 4H), 1.30 (t, *J* = 7.4 Hz, 3H).

^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 168.9, 148.4, 142.3, 128.4, 128.3, 125.8, 125.2, 59.9, 37.7, 35.1, 31.6, 26.5, 22.3, 14.3.

LR MS (EI, 70 eV, m/z): 258 $[M]^+$.

Ethyl 2-methylcyclohex-1-ene carboxylate



$C_{10}H_{16}O_2$, 168.24 g/mol

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 4.12 (q, *J* = 7.4 Hz, 2H), 2.22-2.18 (m, 2H), 2.05-2.04 (m, 2H), 1.92 (s, 3H), 1.56-1.52 (m, 4H), 1.24 (t, *J* = 7.4 Hz, 3H).

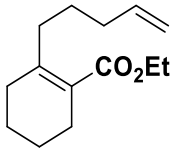
^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 169.3, 145.5, 124.4, 59.9, 33.6, 26.3, 22.32, 22.31, 21.9, 14.3.

LR MS (EI, 70 eV, m/z): 168 $[M]^+$.

HR MS (EI, 70 eV *m/z*): found 168.1149$[M]^+$ (calculated: 168.1150)

FT-IR 2932(m), 2860(w), 1710(s), 1641(m), 1446(m), 1368(m), 1227(s), 1077(s), 1054(s), 1021(m), 858(w).

Ethyl 2-(pent-4'-en-1'-yl)cyclohex-1-ene carboxylate



$C_{14}H_{22}O_2$, 222.33 g/mol

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 5.86-5.77 (m, 1H), 5.03-4.91 (m, 2H), 4.13 (q, *J* = 7.4 Hz, 2H), 2.34-2.26 (m, 4H), 2.11-2.03 (m, 4H), 1.61-1.50 (m, 6H), 1.28 (t, *J* = 7.4 Hz, 3H).

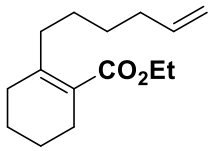
^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 169.2, 148.5, 138.7, 124.8, 114.5, 59.9, 35.0, 33.9, 31.1, 27.9, 26.5, 22.4, 22.3, 14.3.

LR MS (m/z): 222 $[M]^+$.

HR MS (EI, 70 eV,, *m/z*): found 223.1693$[M+H]^+$ (calculated: 223.1693).

FT-IR 2930(m), 2860(w), 1709(s), 1640(m), 1448(m), 1369(m), 1225(s), 1178(m), 1093(m), 1049(m), 991(w).

Ethyl 2-(hex-5-en-1-yl)cyclohex-1-ene carboxylate



$C_{15}H_{24}O_2$, 236.36 g/mol

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 5.87-5.73 (m, 1H), 5.02-4.90 (m, 2H), 4.16 (q, *J* = 7.4 Hz, 2H), 2.33-2.23 (m, 4H), 2.13-2.02 (m, 4H), 1.60-1.56 (m, 4H), 1.47-1.37 (m, 4H), 1.28 (t, *J* = 7.4 Hz, 3H).

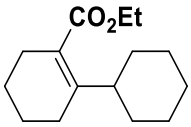
^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 169.3, 148.7, 139.0, 124.6, 114.3, 59.9, 35.3, 33.7, 31.2, 29.1, 28.2, 26.5, 22.4, 22.3, 14.3.

LR MS (EI, 70 eV, m/z): 236 $[M]^+$.

HR MS (CI, *m/z*): found 237.1852$[M+H]^+$ (calculated: 237.1849).

FT-IR 2930(m), 2859(w), 1710(s), 1639(m), 1448(m), 1369(m), 1225(s), 1076(m), 1044(m), 993(w), 909(m).

Ethyl [1, 1'-bi(cyclohex)]-1-ene-2-carboxylate



$C_{15}H_{24}O_2$, 236.36 g/mol

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 4.18 (q, *J* = 7.4 Hz, 2H), 2.82-2.74 (m, 1H), 2.26-2.24 (m, 2H), 2.06-2.04 (m, 2H), 1.59-1.55 (m, 9H), 1.32-1.25 (m, 8H).

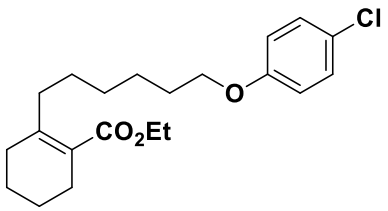
^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 170.3, 150.0, 124.9, 59.9, 42.7, 30.9, 26.8, 26.5, 26.2, 25.2, 22.3, 22.2, 14.3.

LR MS (EI, 70 eV, m/z): 236 $[M]^+$.

HR MS (EI, 70 eV, *m/z*): found 236.1777$[M]^+$ (calculated: 237.1776)

FT-IR 2924(s), 2852(m), 1708 (s), 1621(w), 1449(m), 1369(w), 1278(m), 1221(s), 1194(s), 1097(s), 1048(s).

Ethyl 2-(6'-(4'-chlorophenoxy)hexyl)cyclohex-1-ene carboxylate



$C_{21}H_{29}ClO_3$, 364.91 g/mol

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 7.16 (d, *J* = 9.0 Hz, 2H), 6.76 (d, *J* = 9.0 Hz, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.86 (t, *J* = 6.5 Hz, 2H), 2.29-2.22 (m, 4H), 2.09-2.06 (m, 2H), 1.76-1.67 (m, 2H), 1.60-1.52 (m, 4H), 1.44-1.29 (m, 6H), 1.23 (t, *J* = 7.1 Hz, 3H).

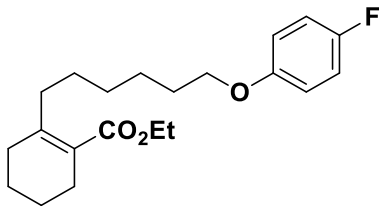
^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 148.9, 130.2, 128.4, 124.5, 115.2, 68.1, 59.9, 35.4, 31.2, 29.6, 29.2, 28.6, 26.5, 25.9, 24.4, 22.3, 18.1, 14.4.

LR MS (EI, 70 eV, m/z): 238 $[M\text{-}C_6H_4ClO]^+$.

HR MS (ESI, 120 V, *m/z*): found 364.1782$[M]^+$ (calculated: 364.1800)

FT-IR 2933(m), 2857(w), 1707(s), 1632(w), 1596(w), 1492(s), 1473(m), 1369(m), 1278(m), 1226(s), 1169(m) 1090(m), 1045(m), 823(m).

Ethyl 2-(6'-(4'-fluorophenoxy)hexyl)cyclohex-1-ene carboxylate



$C_{21}H_{29}FO_3$, 348.46 g/mol

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 6.98-6.92 (m, 2H), 6.83-6.79 (m, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.89 (t, *J* = 6.5 Hz, 2H), 2.34-2.26 (m, 4H), 2.13-2.10 (m, 2H), 1.80-1.68 (m, 2H), 1.61-1.57 (m, 4H), 1.48-1.36 (m, 6H), 1.28 (t, *J* = 7.1 Hz, 3H).

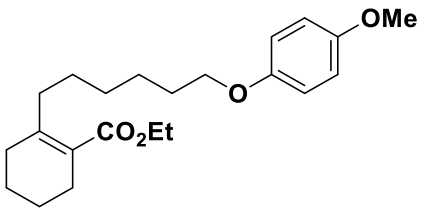
$^{13}C\{^{1}H\}$-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 169.3, 157.1 (d, *J* = 237.7 Hz), 155.2 (d, *J* = 2.0 Hz), 148.9, 125.5, 115.7 (d, *J* = 23 Hz), 115.4 (d, *J* = 7.9 Hz), 68.5, 59.9, 35.4, 31.2, 29.6, 29.2, 28.6, 26.5, 25.9, 22.4, 22.3, 14.3.

LR MS (EI, 70 eV, m/z): 238 $[M\text{-}C_6H_4FO]^+$.

HR MS (ESI, 120 V, *m/z*): found 348.2082$[M]^+$ (calculated: 348.2095)

FT-IR 2932(m), 2859(w), 1707(s), 1631(w), 1506(s), 1475(w), 1371(w), 1278(m), 1221(s), 1088(m), 1044(m) 914(w), 827(s), 758(m).

Ethyl 2-(6'-(4'-(methoxy)phenoxyhexyl)cyclohex-1-ene carboxylate



$C_{22}H_{32}O_4$, 360.49 g/mol

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H [ppm] = 6.82 (s, 4H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.90 (t, *J* = 6.6 Hz, 2H), 3.77 (s, 3H), 2.38-2.23 (m, 4H), 2.18-2.05 (m, 2H), 1.80-1.70 (m, 2H), 1.63-1.56 (m, 4H), 1.52-1.33 (m, 6H), 1.28 (t, *J* = 7.1 Hz, 3H).

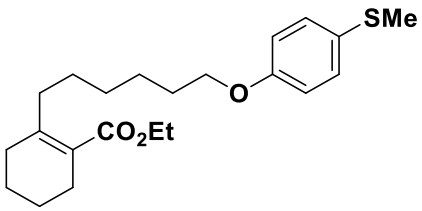
$^{13}C\{^{1}H\}$-NMR (101 MHz, $CDCl_3$): δ_C [ppm] = 169.3, 153.7, 153.3, 148.8, 124.6, 115.4, 114.6, 68.6, 59.9, 55.8, 35.2, 31.2, 29.7, 29.4, 28.6, 26.6, 26.0, 22.38, 22.36, 14.3.

LR MS (EI, 70 eV, m/z): 238 $[M\text{-}C_6H_4ClOMe]^+$.

HR MS (ESI, 120 V, *m/z*): found 361.2376$[M+H]^+$ (calculated: 361.2373)

FT-IR 3045(w), 2929(w), 2859(w), 1707(s), 1633(s), 1505(s), 1464(m), 1390(w), 1222(s), 1084(w), 1039(m), 823(m).

Ethyl 2-(6'-(4'-(methylthiophenoxy)hexyl)cyclohex-1-ene carboxylate



$C_{22}H_{32}O_3S$, 376.56 g/mol

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 7.25 (d, *J* = 8.8 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.91 (t, *J* = 6.5 Hz, 2H), 2.43 (s, 3H), 2.34-2.26 (m, 4H), 2.11-2.10 (m, 2H), 1.81-1.70 (m, 2H), 1.60-1.56 (m, 4H), 1.48-1.35 (m, 6H), 1.28 (t, *J* = 7.1 Hz, 3H).

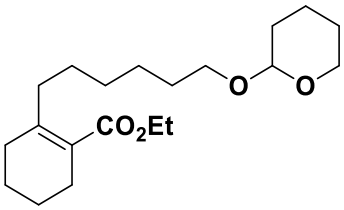
^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 169.3, 157.8, 148.9, 130.2, 128.4, 124.5, 115.2, 68.1, 59.9, 35.4, 31.2, 29.6, 29.2, 28.6, 26.5, 25.9, 24.4, 22.3, 18.1, 14.4.

LR MS (EI, 70 eV, m/z): 238 $[M\text{-}C_6H_4ClSCH_3]^+$.

HR MS (ESI, 120 V, *m/z*): found 377.2133$[M+H]^+$ (calculated: 377.2145).

FT-IR 2931(m), 2858(w), 1707(s), 1632(w), 1595(w), 1493(s), 1439(w), 1278(m), 1226(s), 1176(m), 1087(m), 1044(m), 968(w), 915(w).

Ethyl 2-(2'-(oxanoxyhexyl)cyclohex-1-ene-carboxylate[4a]

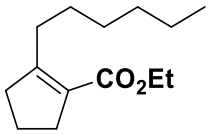


$C_{20}H_{34}O_4$, 338.49 g/mol

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 4.57 (t, *J* = 3.4 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.86 (ddd, *J* = 11.0, 7.3, 3.4 Hz, 1H), 3.72 (dt, *J* = 9.5, 6.9 Hz, 1H), 3.54–3.44 (m, 1H), 3.37 (dt, *J* = 9.5, 6.6 Hz, 1H), 2.37–2.20 (m, 4H), 2.10 (d, *J* = 2.3 Hz, 2H), 1.95–1.18 (m, 21H).

LR MS (EI, 70 eV, m/z): 238 $[M]^+$.

Ethyl 2-hexylcyclopent-1-ene carboxylate



$C_{14}H_{24}O_2$, 224.34 g/mol

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 4.17 (q, *J* = 7.1 Hz, 2H), 2.62-2.53 (m, 4H), 2.50-2.45 (m, 2H), 1.84-1.74 (m, 2H), 1.45-1.36 (m, 2H), 1.30-1.25 (m, 7H), 0.89-0.85 (m, 3H).

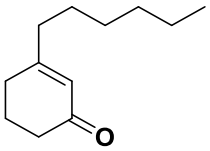
^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 166.4, 160.0, 127.0, 59.6, 38.2, 33.7, 31.7, 30.1, 29.4, 28.0, 22.6, 21.5, 14.4, 14.1.

LR MS (EI, 70 eV, m/z): 224 $[M]^+$.

HR MS (EI, 120 eV, *m/z*): found 224.1775 $[M]^+$. (calculated: 224.1775).

FT-IR 2926(m), 2858(m), 1708(s), 1639(w), 1465(w), 1372(m), 1298(m), 1255(m), 1214(m), 1096(m), 1039(m) 862(w), 771(m), 665(m).

3-Hexylcyclohex-2-enone[4a]



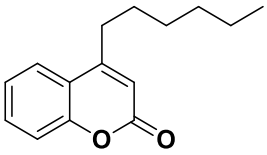
$C_{12}H_{20}O$, 180.29 g/mol

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 5.85 (s, 1H), 2.36-2.32 (m, 2H), 2.27 (t, *J* = 5.9 Hz, 2H), 2.19 (t, *J* = 7.6 Hz, 2H), 2.01-1.92 (m, 2H), 1.50-1.43 (m, 2H), 1.31-1.24 (m, 6H), 0.89-0.85 (m, 3H).

^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 200.1, 166.9, 125.6, 38.1, 37.4, 31.6, 29.7, 28.9, 26.9, 22.8, 22.5, 14.1.

LR MS (EI, 70 eV, m/z): 180 $[M]^+$.

4-Hexyl-2*H*-chromen-2-one[4a]



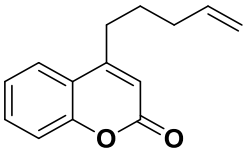
$C_{15}H_{18}O_2$, 230.31 g/mol

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 7.65-7.62 (m, 1H), 7.55-7.49 (m, 1H), 7.35-7.26 (m, 2H), 6.28 (s, 1H), 2.79-2.73 (m, 2H), 1.74-1.64 (m, 2H), 1.46-1.24 (m, 6H), 0.92-0.87 (m, 3H).

^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 161.1, 156.4, 153.8, 131.6, 124.3, 124.2, 119.4, 117.3, 113.9, 31.8, 31.6, 29.2, 28.1, 22.6, 14.1.

LR MS (EI, 70 eV, m/z): 230 $[M]^+$.

4-(Pent-4'-en-1'-yl)-2*H*-chromen-2-one



$C_{14}H_{14}O_2$, 214.26 g/mol

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 7.62 (dd, *J* = 7.9, 1.5 Hz 1H), 7.52 (ddd, *J* = 8.6, 7.3, 1.5 Hz, 1H), 7.35-7.26 (m, 2H), 6.28 (s, 1H), 5.90-5.76 (m, 1H), 5.12-5.02 (m, 2H), 2.80-2.75 (m, 2H), 2.24-2.17 (m, 2H), 1.86-1.76 (m, 2H).

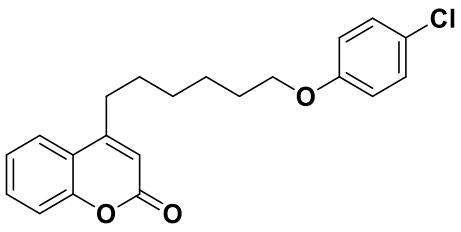
^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 161.0, 156.0, 153.8, 137.4, 131.7, 124.3, 124.2, 119.3, 117.4, 115.9, 114.1, 33.2, 30.9, 27.2.

LR MS (EI, 70 eV, m/z): 214 $[M]^+$.

HR MS (ESI, 120 V, *m/z*): found 214.0986 $[M]^+$ (calculated: 214.0988).

FT-IR 3078(w), 2933(w), 1720(s), 1604(m), 1566(m), 1449(m), 1384(m), 1320(w), 1253(w), 1181(m), 1130(w), 1038(w), 993(w), 930(s).

4-(6'-(4''-Chlorophenoxy)hexyl)-2*H*-chromen-2-one



$C_{21}H_{21}ClO_3$, 356.85 g/mol

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 7.63 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.53 (ddd, *J* = 8.6, 7.3, 1.5 Hz, 1H), 7.35-7.26 (m, 2H), 7.21 (d, *J* = 9.0 Hz, 2H), 6.80 (d, *J* = 9.0 Hz, 2H), 6.28 (s, 1H), 3.92 (t, *J* = 6.3 Hz, 2H), 2.80-2.75 (m, 2H), 1.81-1.71 (m, 4H), 1.53-1.50 (m, 4H).

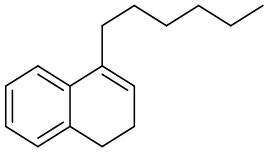
^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 161.0, 157.6, 156.1, 153.8, 131.7, 129.3, 125.4, 124.3, 124.2, 119.3, 117.4, 115.7, 113.9, 68.0, 31.7, 29.2, 29.1, 28.0, 24.9.

LR MS (EI, 70 eV, m/z): 356 $[M]^+$.

HR MS (ESI, 120 V, *m/z*): found 357.1252 $[M+H]^+$ (calculated: 357.1252).

FT-IR 3075(w), 2939(m), 2857(m), 1708(s), 1606(m), 1566(m), 1491(m), 1393(m), 1287(m), 1243(s), 1180(m) 1091(m), 1047(m), 935(m).

4-Hexyl-1,2-dihydronaphthalene



$C_{16}H_{22}$, 214.35 g/mol

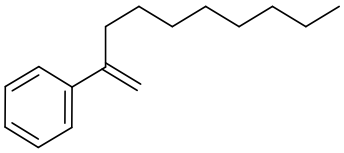
^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 7.27-7.13 (m, 4H), 5.85 (t, *J* = 4,5 Hz, 1H), 2.76-2.71 (m, 2H), 2.46-2.40 (m, 2H), 2.28-2.21 (m, 2H), 1.56-1.48 (m, 2H), 1.39-1.26 (m, 6H), 0.91-0.87 (m, 3H).

$^{13}C\{^1H\}$-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 136.8, 136.7, 135.1, 127.5, 126.4, 126.3, 124.6, 122.7, 32.8, 31.8, 29.3, 28.5, 28.4, 23.1, 22.7, 14.1.

LR MS (EI, 70 eV, m/z): 214 $[M]^+$.

HR MS (ESI, 120 V, *m/z*): found 214.1694$[M]^+$ (calculated: 214.1700).

2-Phenyl-dec-1-ene[49]



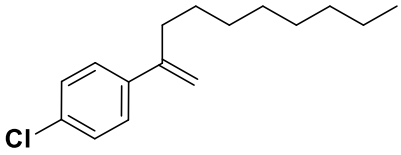
$C_{16}H_{24}$, 216.37 g/mol

^1H-NMR (400 MHz, $CDCl_3$): δ_H [ppm] = 7.46-7.38 (m, 2H), 7.36-7.22 (m, 3H), 5.276 (s, 1H), 5.06 (s, 1H), 2.50 (t, *J* = 7.6 Hz, 2H), 1.51-1.41 (m, 2H), 1.36-1.21 (m, 10H), 0.89 (t, *J* = 6.8 Hz, 3H).

$^{13}C\{^1H\}$-NMR (101 MHz, $CDCl_3$): δ_C [ppm] = 147.8, 140.5, 127.2, 126.2, 125.1, 111.0, 34.4, 30.9, 28.4, 28.33, 28.25, 27.3, 21.6, 13.1.

LR MS (EI, 70 eV, m/z): 216 $[M]^+$.

2-(4'-Chlorophenyl)-dec-1-ene[50]



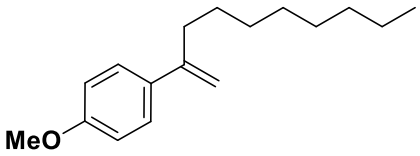
$C_{16}H_{23}Cl$, 250.81 g/mol

^1H-NMR (400 MHz, $CDCl_3$): δ_H [ppm] = 7.36-7.24 (m, 4H), 5.24 (d, *J* = 1.3 Hz, 1H), 5.07 (d, *J* = 1.3 Hz, 1H), 2.50-2.42 (m, 2H), 1.47-1.38 (m, 2H), 1.38-1.19 (m, 10H), 0.88 (t, *J* = 6.9 Hz, 3H).

$^{13}C\{^1H\}$-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 147.7, 139.9, 133.0, 128.4, 127.5, 112.6, 35.3, 31.9, 29.4, 29.30, 29.28, 28.2, 22.7, 14.1.

LR MS (EI, 70 eV, m/z): 250 $[M]^+$.

2-(4'-Methoxyphenyl)-dec-1-ene



$C_{17}H_{26}O$, 246.39 g/mol

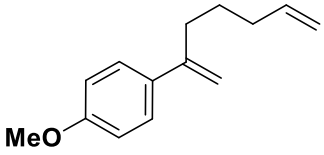
^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 7.43-7.33 (m, 2H), 6.92-6.83 (m, 2H) 5.21 (d, *J* = 1.5 Hz, 1H), 4.99 (d, *J* = 1.4 Hz, 1H), 3.83 (s, 3H), 2.53-2.42 (m, 2H), 1.53-1.40 (m, 2H), 1.40-1.19 (m, 10H), 0.89 (t, *J* = 6.7 Hz, 3H).

^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 158.9, 148.0, 133.9, 127.2, 113.6, 110.5, 55.3, 35.4, 31.9, 29.48, 29.43, 29.3, 28.4, 22.7, 14.2.

LR MS (EI, 70 eV, m/z): 246 $[M]^+$.

HR MS (ESI, 120 V, m/z): found 246.1947 $[M^+]$ (calculated: 246.1978).

2-(4'-Methoxyphenyl)-hepta-1,6-diene



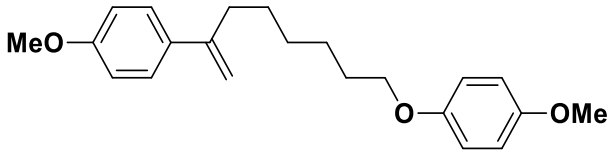
$C_{14}H_{18}O$, 202.30 g/mol

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 7.36 (d, *J* = 8.9 Hz, 2H), 6.87 (d, *J* = 8.9 Hz, 2H), 5.87-5.74 (m, 1H), 5.03-4.91 (m, 2H), 3.82 (s, 3H), 2.51-2.47 (m, 2H), 2.05-2.02 (m, 2H), 1.51-1.40 (m, 4H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 157.9, 146.7, 137.9, 126.1, 111.3, 112.8, 109.6, 54.2, 34.2, 32.6, 27.6, 26.7.

FT-IR 3050(w), 2950(w), 1703(s), 1496(w), 1454(w), 1414(w), 1373(m), 1288(m), 1224(s), 1138(m), 1050(m) 955(w), 829(w), 749(w).

1-Methoxy-4-(8‘-(4‘‘-methoxyphenoxy)oct-1‘-en-2‘-yl)benzene



$C_{22}H_{28}O_3$, 340.46 g/mol

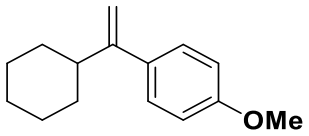
^{1}H-NMR (400 MHz, $CDCl_3$): δ_H [ppm] = 7.38-7.33 (m, 2H), 6.90-6.85 (m, 2H), 6.85-6.81 (m, 4H), 5.20 (d, *J* = 1.0 Hz, 1H), 4.98 (s, 1H), 3.89 (t, *J* = 6.5 Hz, 2H), 3.82 (s, 3H), 3.77 (s, 3H), 2.49 (t, *J* = 7.3 Hz, 2H), 1.75 (m, 2H), 1.54-1.36 (m, 6H).

^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 158.9, 153.7, 153.3, 147.9, 133.8, 127.2, 115.5, 114.6, 113.6, 110.6, 68.6, 55.8, 55.3, 35.4, 29.4, 29.1, 28.2, 25.9.

LR MS (EI, 70 eV, m/z): 340 $[M]^+$.

HR MS (CI, *m/z*): found 340.2016$[M]^+$ (calculated: 340.2033).

1-(1-Cyclohexylvinyl)-4‘-methoxybenzene[51]

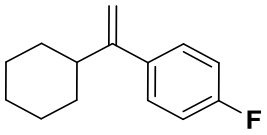


$C_{15}H_{20}O$, 216.32 g/mol

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 7.34-7.27 (m, 2H), 6.92-6.85 (m, 2H), 5.12 (d, *J* = 1.1 Hz, 1H), 4.98-4.94 (m, 1H), 3.83 (s, 3H), 2.41 (t, *J* = 11.7 Hz, 1H), 1.92-1.68 (m, 5H), 1.44-1.08 (m, 5H).

LR MS (EI, 70 eV, m/z): 216 $[M]^+$.

1-(1‘-Cyclohexylvinyl)-4-fluorobenzene



$C_{14}H_{17}F$, 204.29 g/mol

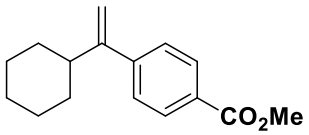
^{1}H-NMR (400 MHz, $CDCl_3$): δ_H [ppm] = 7.32-7.24 (m, 2H), 7.03-6.95 (m, 2H), 5.08 (s, 1H), 4.99 (s, 1H), 2.36 (t, *J* = 11.3 Hz, 1H), 1.86-1.65 (m, 5H), 1.38-1.08 (m, 5H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ_C [ppm] = 162.1, (d, *J* = 245.4 Hz), 154.0, 138.9 (d, *J* = 3.3 Hz), 128.1 (d, *J* = 7.8 Hz), 114.9 (d, *J* = 21.2 Hz), 110.4, 42.8, 32.6, 26.8, 26.4.

LR MS (EI, 70 eV, m/z): 204 $[M]^+$.

HR MS (EI, 70 eV, *m/z*): found 204.1315$[M]^+$ (calculated: 204.1314).

Methyl 4-(1‘-cyclohexylvinyl) benzoate



$C_{16}H_{20}O_2$, 244.33 g/mol

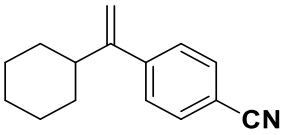
^{1}H-NMR (400 MHz, $CDCl_3$): δ_H [ppm] = 8.00-7.95 (m, 2H), 7.42-7.36 (m, 2H), 5.20 (s, 1H), 5.09 (s, 1H), 3.91 (s, 3H), 2.43 (t, *J* = 11.7 Hz, 1H), 1.86-1.67 (m, 5H), 1.39-1.10 (m, 5H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ_C [ppm] = 167.0, 154.2, 147.7, 129.5, 128.7, 126.6, 111.9, 52.0, 42.4, 32.6, 26.7, 26.4.

LR MS (EI, 70 eV, m/z): 220 $[M]^+$.

HR MS (EI, 70 eV, *m/z*): found 220.0736 $[M]^+$ (calculated: 220.0738).

4-(1'-Cyclohexylvinyl) benzonitrile[51]



$C_{15}H_{17}N$, 211.31 g/mol

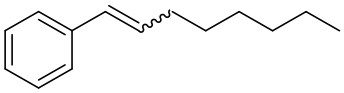
^{1}H-NMR (400 MHz, $CDCl_3$): δ_H [ppm] = 7.64-7.57 (m, 2H), 7.45-7.38 (m, 2H), 5.20 (s, 1H), 5.13 (s, 1H), 2.39 (t, *J* = 11.5 Hz, 1H), 1.85-1.66 (m, 5H), 1.38-1.09 (m, 5H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ_C [ppm] = 153.6, 147.7, 132.0, 127.3, 119.0, 112.9, 110.7, 42.3, 32.5, 26.7, 26.3.

LR MS (EI, 70 eV, m/z): 211 $[M]^{+\cdot}$.

Oct-1-enyl benzene[52,53]

The product was obtained as a *E*/*Z* = 13:1 mixure as deduced from ^{1}H-NMR.



$C_{14}H_{20}$, 188.31 g/mol

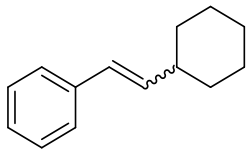
^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 7.37-7.26 (m, 4H), 7.22-7.16 (m, 1H), 6.38 (d, *J* = 15.8 Hz, 1H), 6.23 (dt, *J* = 15.8, 6.7 Hz, 1H (*E*)), 5.67 (dt, *J* = 11.7, 7.2 Hz, 1H (*Z*)), 2.25 (m, 2H), 1.56-1.27 (m, 8H), 0.92-0.87 (m, 3H).

^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 137.9, 131.3, 129.7, 128.5, 126.7, 125.9, 33.1, 31.9, 31.8, 29.7, 29.6, 29.3, 28.9, 22.7, 22.6, 14.1.

LR MS (EI, 70 eV, m/z): 188 $[M]^{+\cdot}$.

(2-Cyclohexylvinyl)benzene[54]

The product was obtained as a *E*/*Z* = 3.8:1 mixure as deduced from ^{1}H NMR.



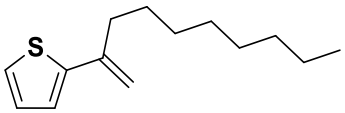
$C_{15}H_{20}$, 186.30 g/mol

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H [ppm] = 7.38-7.14 (m, 5H), 6.39-6.28 (m, 1H), 6.18 (d, *J* = 16.0, 6.9Hz, 1H (*E*)), 5.49 (m, *J* = 11.7, 10.2 Hz 1H (*Z)*), 2.65-2.51 (m, 1H (*Z*)), 2.20-2.06 (m, 1H (*E*)), 1.90-1.59 (m, 5H), 1.40-1.09 (m, 5H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ_C [ppm] = 139.0 (*Z*), 138.1 (E), 136.8 (E), 128.6 (Z), 128.4 (E), 128.2 (Z), 127.2 (E), 126.8 (Z), 126.7 (E), 126.4 (Z), 126.0 (E), 41.2 (E), 36.9(Z), 33.3 (Z), 33.0 (E), 26.2 (E), 26.1 (E), 25.7 (Z).

LR MS (EI, 70 eV, m/z): 186 $[M]^+$.

2-(Dec-1'-en-2'-yl)thiophene[52]



$C_{14}H_{22}S$, 222.39 g/mol

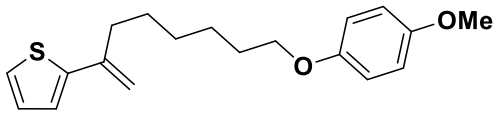
^{1}H-NMR (400 MHz, $CDCl_3$): δ_H [ppm] = 7.16 (dd, *J* = 5.1, 1.0 Hz 1H), 7.04 (dd, *J* = 3.6, 1.1 Hz 1H), 6.98 (dd, *J* = 5.1, 3.6 Hz, 1H), 5.38 (s, 1H), 4.95 (d, *J* = 0.9 Hz, 1H), 2.49-2.42 (m, 2H), 1.62-1.52 (m, 2H), 1.40-1.22 (m, 10H), 0.92-0.87 (m, 3H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ_C [ppm] = 145.6, 142.0, 127.3, 124.0, 123.2, 110.6, 35.6, 31.9, 29.4, 29.3, 28.5, 22.7, 14.1.

LR MS (EI, 70 eV, m/z): 222 $[M]^+$.

HR MS (EI, 70 eV, *m/z*): found 222.1441 $[M]^+$ (calculated: 222.1442).

2-(8'-(4''-Methoxyphenoxy)oct-1'-en-2'-yl)thiophene



$C_{19}H_{24}O_2S$, 316.46 g/mol

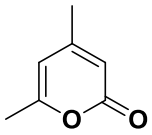
^{1}H-NMR (400 MHz, $CDCl_3$): δ_H [ppm] = 7.16 (dd, *J* = 5.1, 0.9 Hz 1H), 7.06-7.02 (m, 1H), 7.00-6.95 (m, 1H), 6.83 (s, 4H), 5.39 (s, 1H), 4.95 (s 1H), 3.90 (t, *J* = 6.5 Hz, 2H), 3.77 (s, 3H), 2.51-2.45 (m, 2H), 1.83-1.70 (m, 2H), 1.67-1.38 (m, 6H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ_C [ppm] = 153.9, 153.3, 145.5, 141.8, 127.3, 124.0, 123.3, 115.5, 114.6, 110.8, 68.6, 55.8, 35.5, 29.4, 29.1, 28.4, 25.9.

LR MS (EI, 70 eV, m/z): 317 $[M]^+$.

HR MS (CI, *m/z*): found 317.1570 $[M+H]^+$ (calculated: 317.1570).

4,6-Dimethyl-2-pyrone[55]

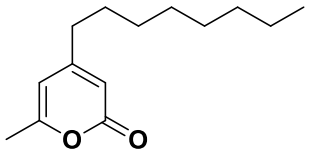


$C_7H_8O_2$, 124.14 g/mol

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 5.94 (s, 1H), 5.84 (s, 1H), 2.21 (s, 6H), 2.10 (d, *J* = 1.0 Hz, 3H).

LR MS (EI, 70 eV, m/z): 124 $[M]^+$.

6-Methyl-4-octyl-2-pyrone[56]



$C_{14}H_{22}O_2$, 222.33 g/mol

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 5.93 (s, 1H), 5.85 (s, 1H), 2.37-2.31 (m, 2H), 2.22 (s, 3H), 1.60-1.47 (m, 2H), 1.36–1.20 (m, 12H), 0.88 (t, *J* = 6.8, 3H).

LR MS (EI, 70 eV, m/z): 222 $[M]^+$.

3.8.2.2 Mechanistic Investigations

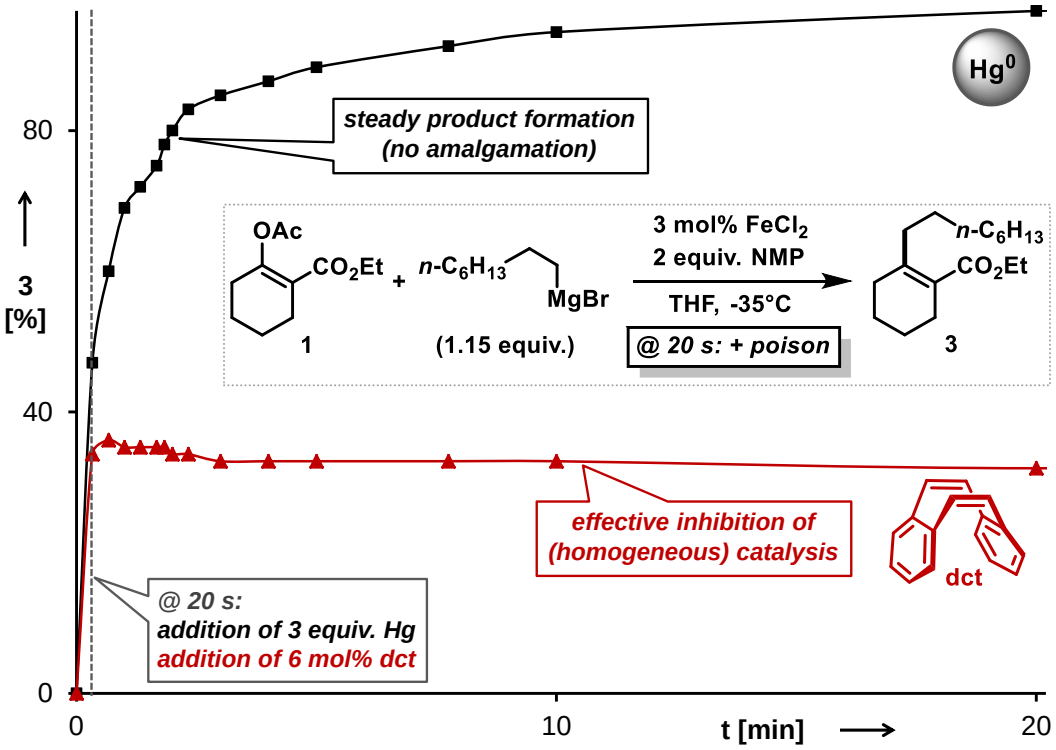
Reaction progress analysis by quantitative GC

The reaction was carried out under dry and inert conditions. First a $FeCl_2$-NMP-THF stock solution was prepared in a glovebox. Therefore a flask was charged with $FeCl_2$ (19.0 mg, 0.15 mmol) and dry NMP (96 µL, 10.0 mmol). Dry THF was added and the mixture was stirred until the iron salt was completely solved.

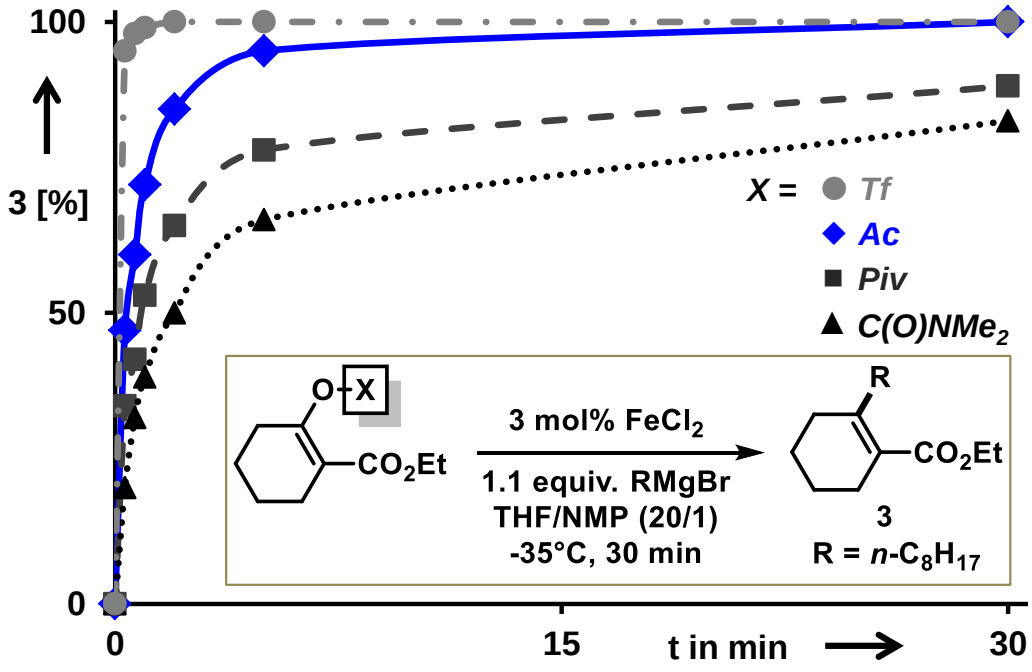
Representative procedure: In a glovebox, a reaction tube was charged with ethyl 2-acetoxycyclohexen-1-ene-carboxylate (212 mg, 1.00 mmol), *n*-pentadecane (50.0 µL, 0.18 mmol) as internal standard and 4.0 mL of a freshly prepared $FeCl_2$-NMP-stock solution. The reaction tube was sealed with a rubber septum and removed from the glovebox. The reaction mixture was cooled to 0 °C, -20°C or -35 °C and 1.15 mL of an *n*-octylmagnesium bromide solution in THF (1.15 mmol, 1.0 M) was added within 10 seconds. After defined time intervals, aliquots (aprox. 200 µL) have been taken and poured in a saturated aqueous NH_4Cl solution (0.5 mL). The mixtures were extracted with ethyl acetate (3 x 1.5 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solution was subjected to quantitative GC-FID.

Kinetic poisoning studies with mercury and dct

In difference to the general procedure for reaction progress analysis, mercury (44 µL, 3.0 mmol) or dct (12.2 mg, 0.06 mmol) in THF (100 µL) were added after 20 seconds after addition of the *n*-octylmagnesium bromide.



Comparison of reactivity of different leaving groups at ethyl cyclohexenoate

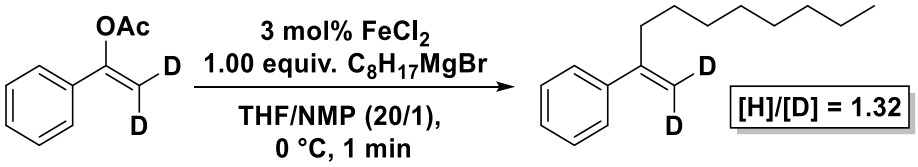


Determination of the secondary kinetic isotope effect (2° KIE)

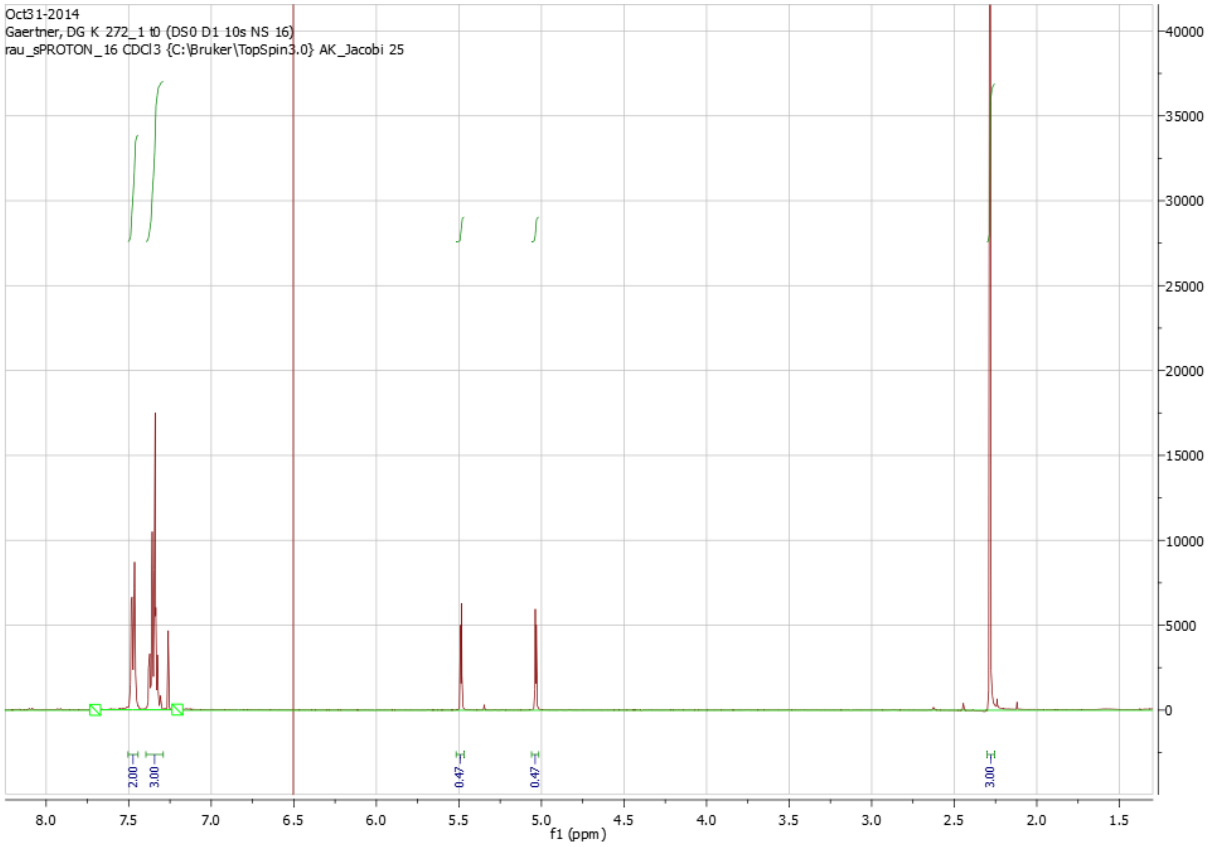
The reaction was carried out under dry and inert conditions. First a 0.25 M substrate stock solution of non-deuterated (375 µmol) and deuterated substrate (375 µmol) in dry THF (3 mL) was prepared in a glovebox.

In a glovebox, a reaction tube was charged with $FeCl_2$ (1.9 mg, 15 µmol) and dry NMP (96 µL, 1.00 mmol). Then 2 mL of the freshly prepared substrate stock solution were added. The residue of the stock solution was used for the determination of the initial H/D-ratio of the substrate mixture. The reaction tube was sealed with a rubber septum and removed from the glovebox. The reaction mixture was cooled to 0 °C and 0.50 mL of a *n*-octylmagnesium bromide solution in THF (500 µmol, 1.0 M) was added within 10 seconds. After 1 minute the reaction was hydrolyzed with a saturated aqueous NH_4Cl solution (0.5 mL). Ethyl acetate (2 mL) was added and the mixture was extracted with ethyl acetate (3 x 3 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The residue was purified by column chromatography using *n*-pentane as eluent. The isolated products and starting materials were subjected to quantitative NMR analysis.

In difference to standard NMR settings the delay time (D_1) was set to 10 seconds and the number of dummy scans (DS) was set to 0.

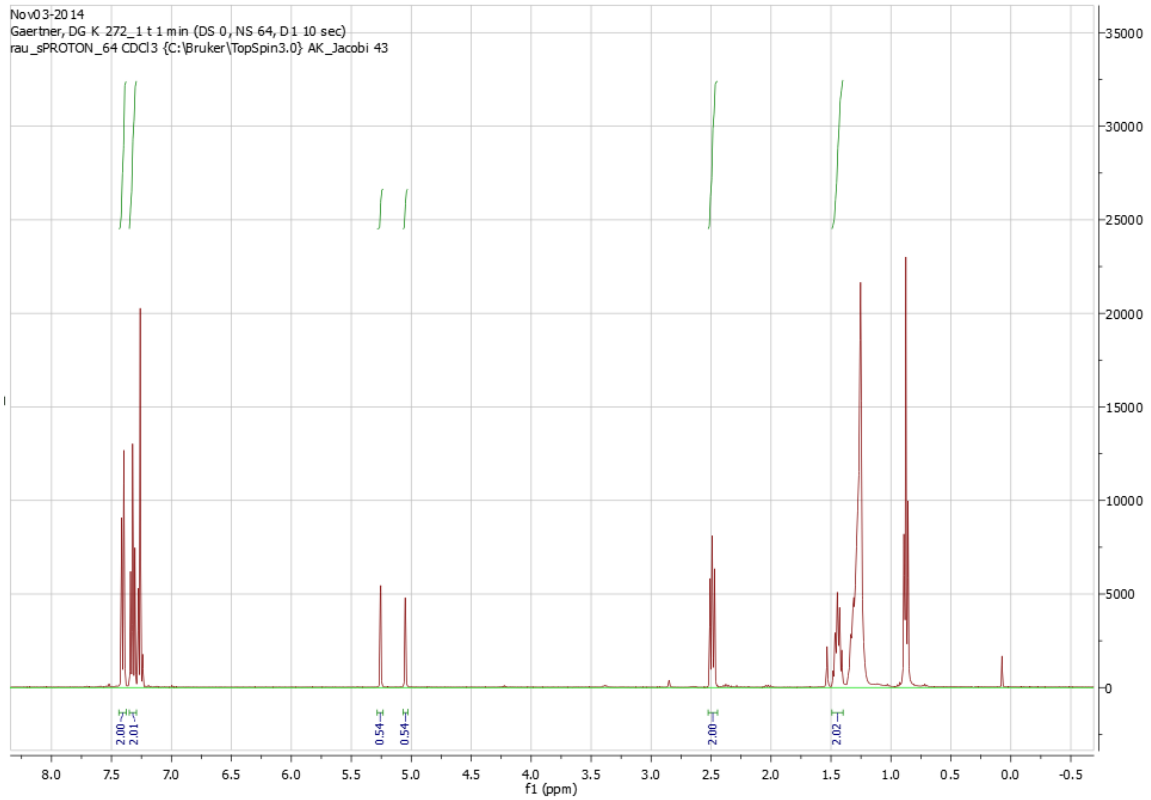


Initial H/D ratio of starting material



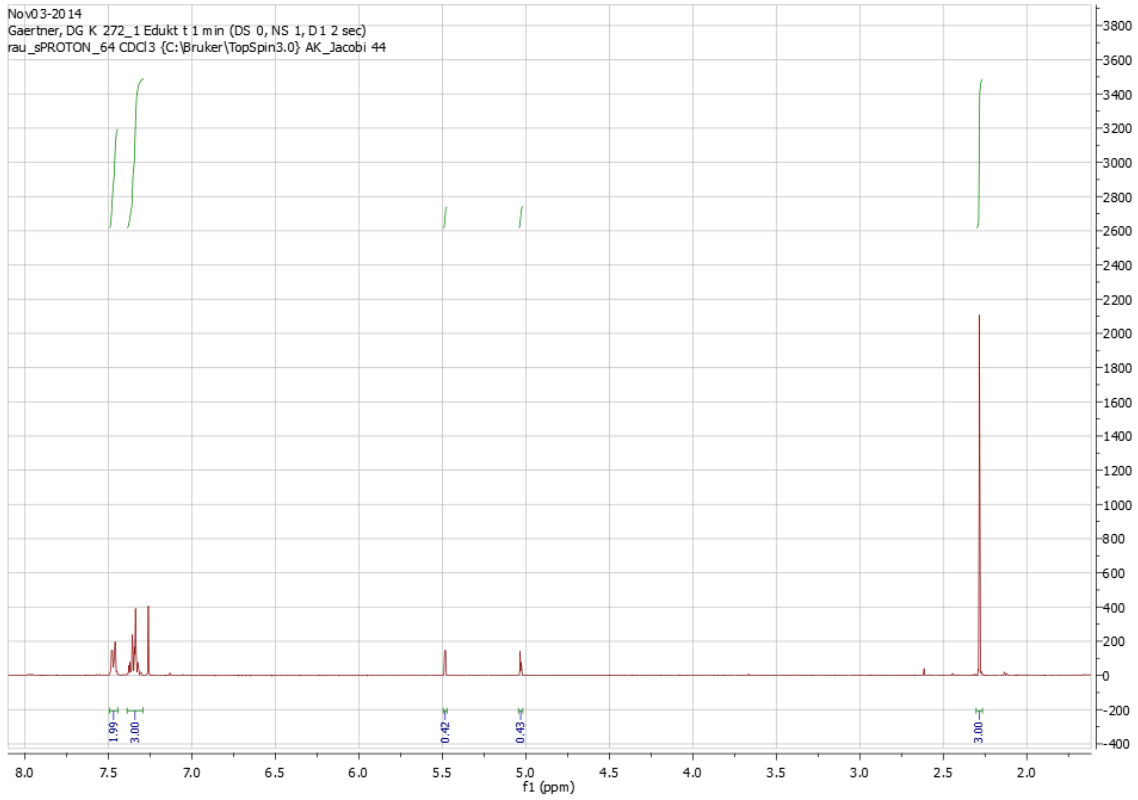
H/D ratio = 47/53

H/D ratio of product after 1 minute

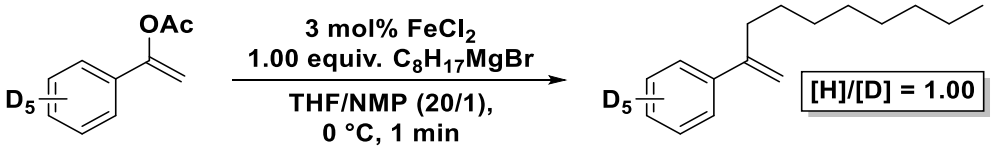


H/D ratio = 54/46

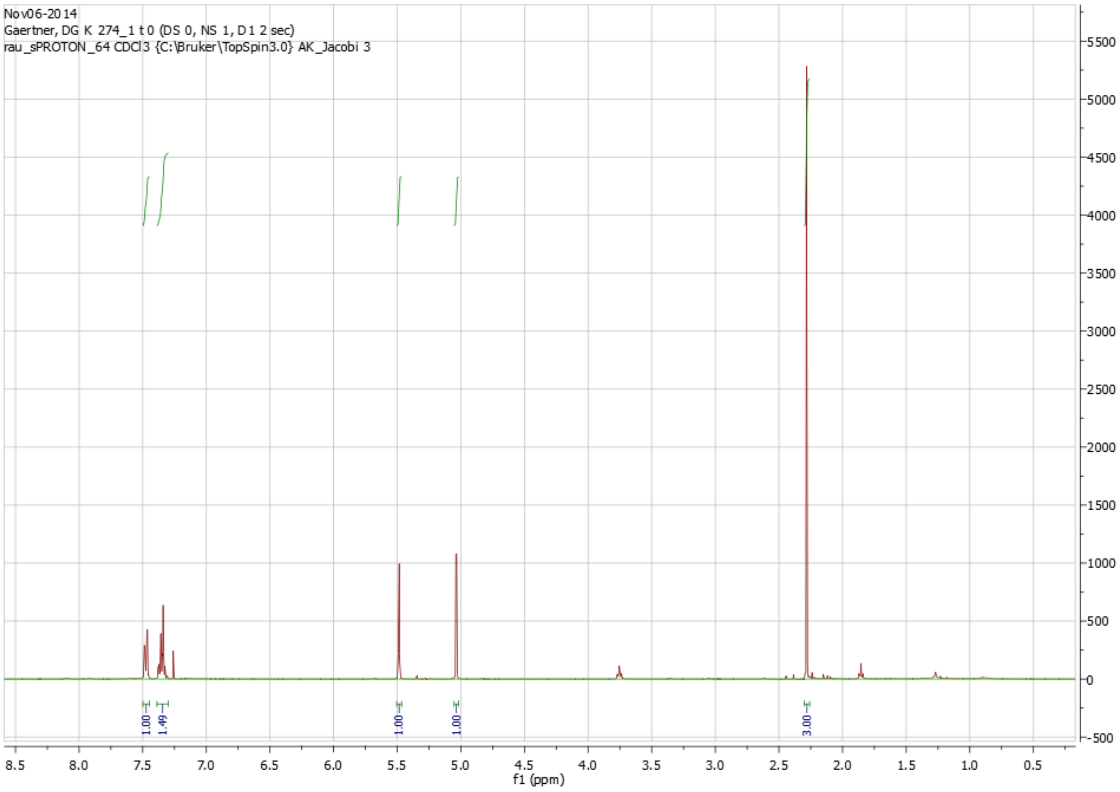
H/D ratio of starting material after 1 minute



H/D ratio = 43/57

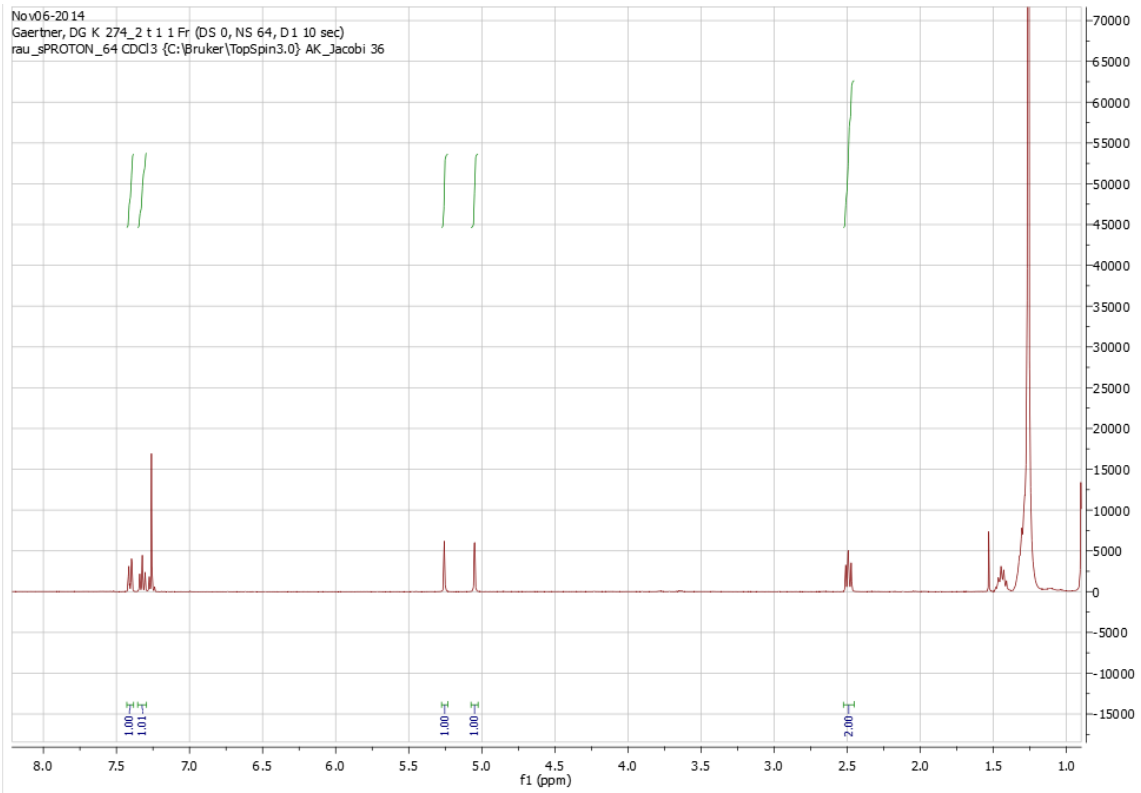


Initial H/D ratio of starting material



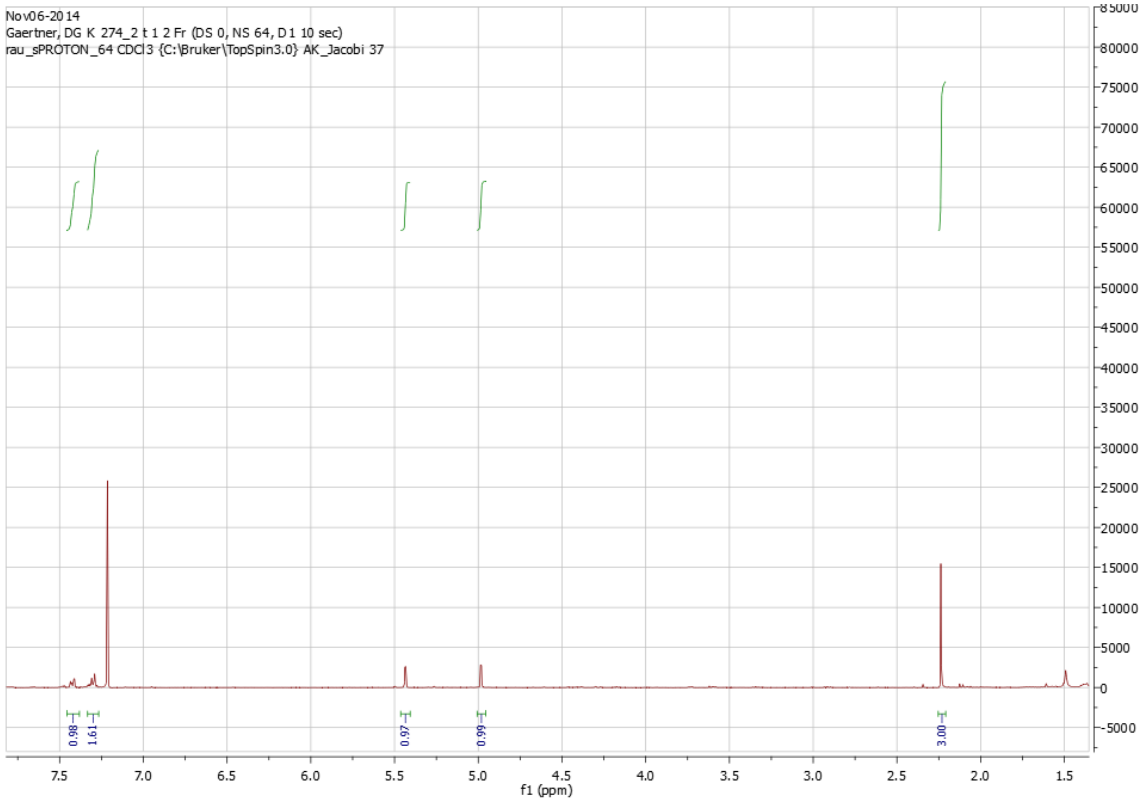
H/D ratio = 50/50

H/D ratio of product after 1 minute

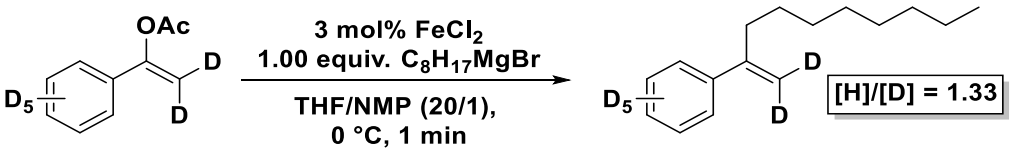


H/D ratio = 50/50

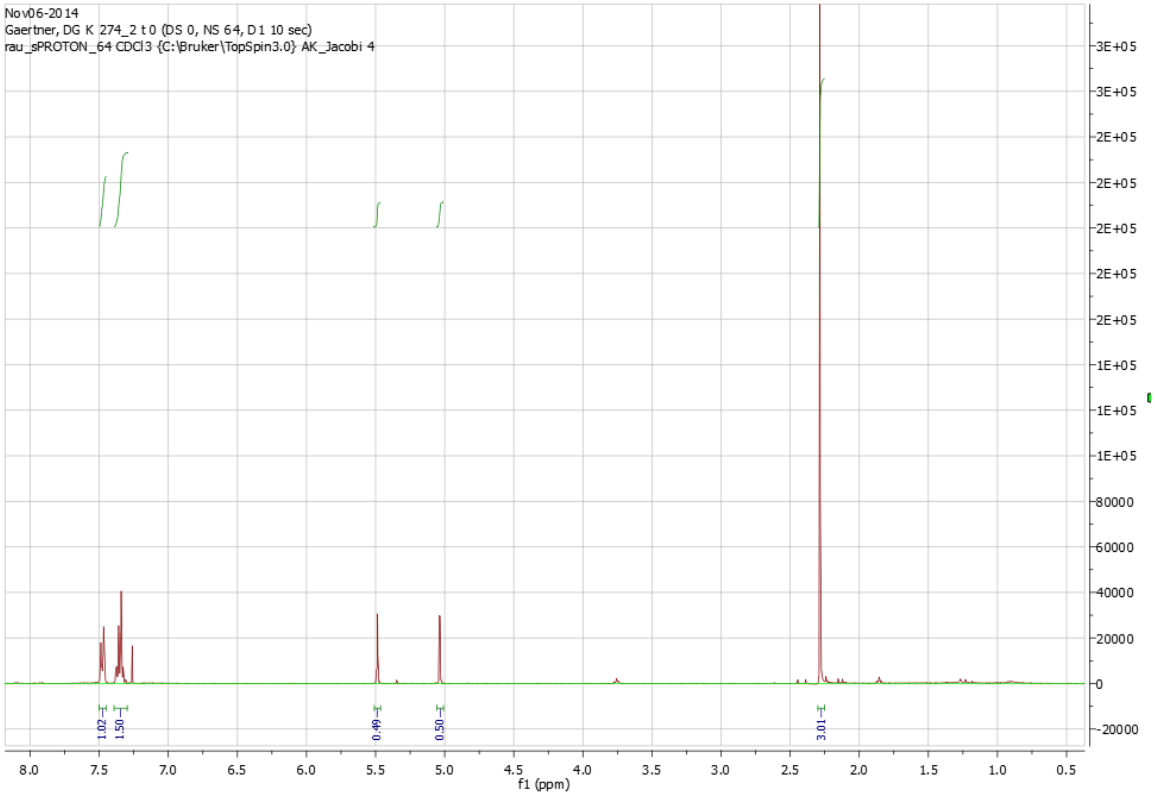
H/D ratio of starting material after 1 minute



H/D ratio = 48/52

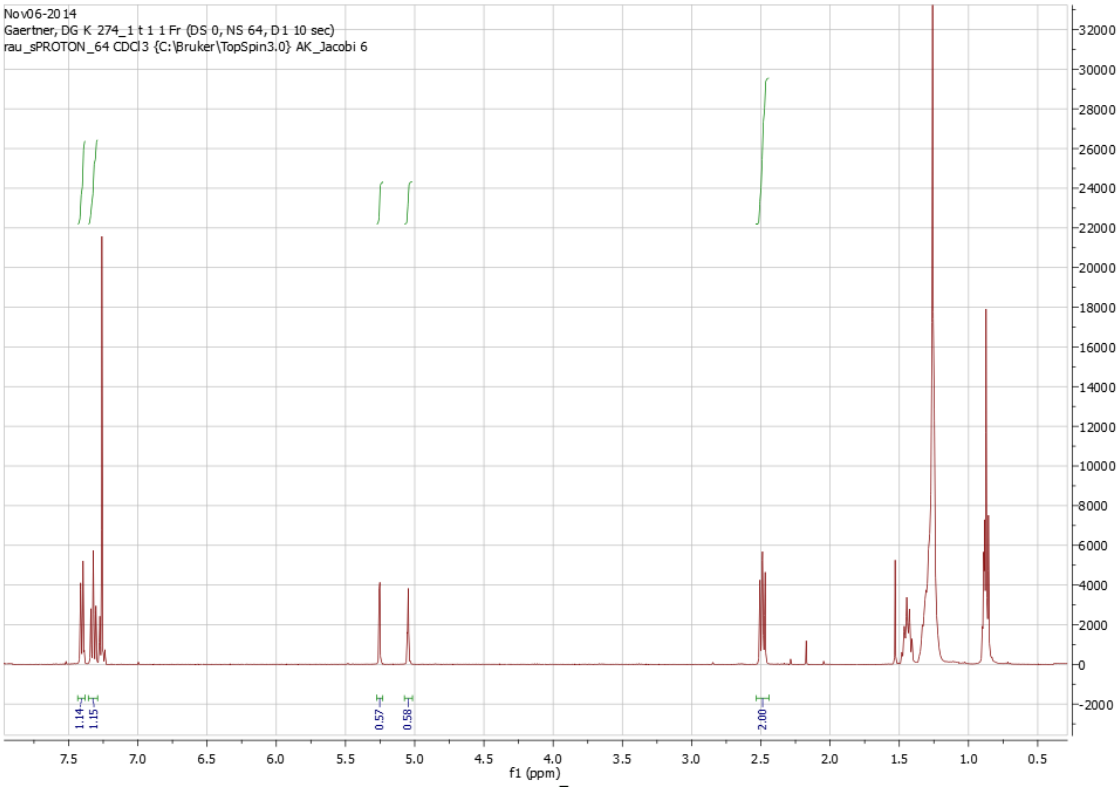


Initial H/D ratio of starting material



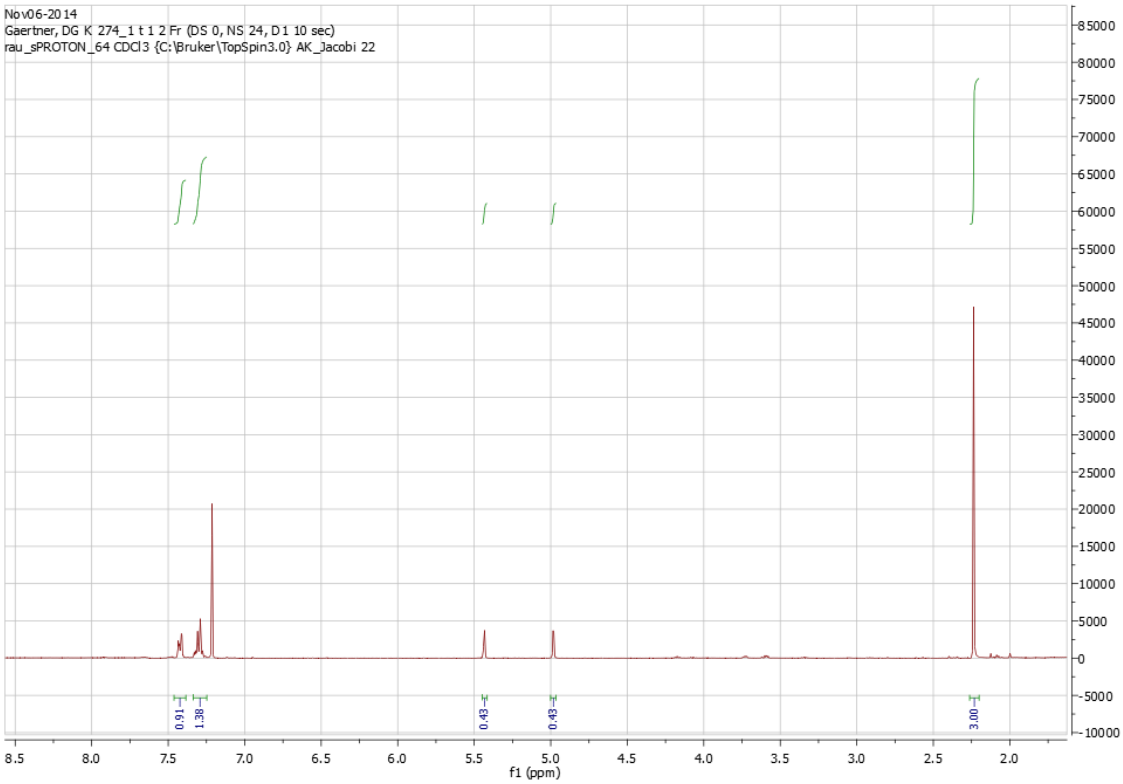
H/D ratio 50/50

H/D ratio of product after 1 minute



H/D ratio 57/43

H/D ratio of starting material after 1 minute



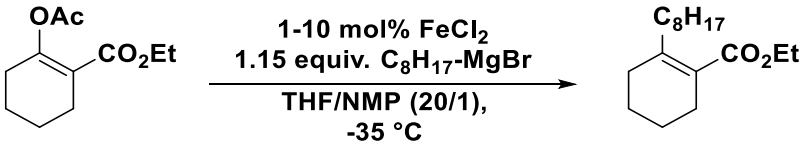
H/D ratio 43/57

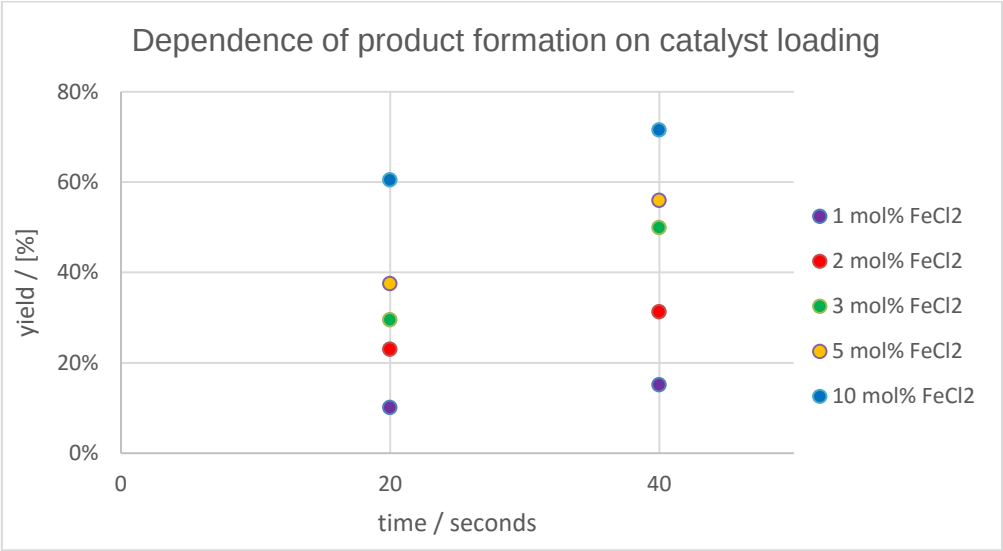
Determination of reaction orders

Dependence of catalyst concentration

The reactions were carried out under dry and inert conditions. First a $FeCl_2$-NMP-stock solution was prepared in a glovebox. Therefore a flask was charged with $FeCl_2$ (25.5 mg, 2.00 mmol). Dry NMP (0.38 mL) was added and the mixture was stirred until the iron salt was completely dissolved. In addition, a substrate stock solution was prepared in the glovebox. Therefore ethyl 2-acetoxycyclohexen-1-enecarboxylate (742.9 mg, 3.5 mmol) and *n*-pentadecane (350 µL, 1.26 mmol) as internal standard were solved in dry THF (14 mL) and stirred.

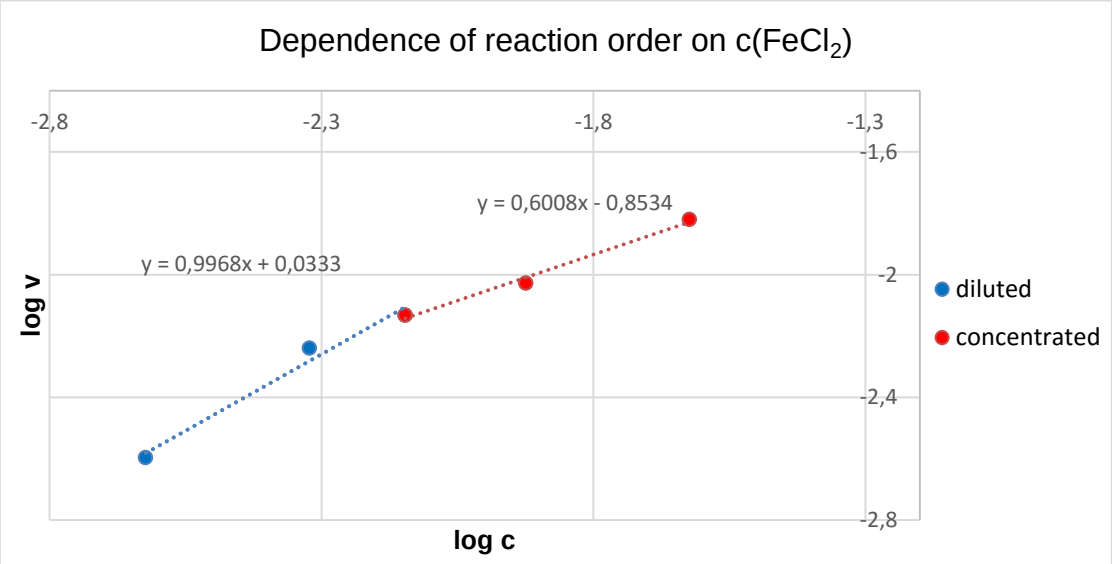
The reaction tubes were charged with 2 mL of the freshly prepared substrate solution and appropriate amounts of the $FeCl_2$ stock solution in NMP were added (9.4 µL for 1 mol%, 18.9 µL for 2 mol% etc.). Missing NMP amounts were added afterwards (to 1.0 mmol per reaction). The reaction tubes were sealed with a rubber septum and removed from the glovebox. The reaction mixture was cooled to -35 °C and 530 µL of a *n*-octylmagnesium bromide solution in THF (0.53 mmol, 1.0 M) was added within 5 seconds. 20 and 40 seconds after addition of the the *n*-octylmagnesium bromide solution, aliquots (aprox. 200 µL) have been taken and poured in a saturated aqueous NH_4Cl solution (0.5 mL). Ethyl acetate (1.5 mL) was added and the mixture was extracted with ethyl acetate (3 x 1.5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and the solution was subjected to quantitative GC-FID.





For the determination of the initial reaction rate only the amount of formed product after 20 seconds were considered.

[$FeCl_2$] [mol%]	c($FeCl_2$) [mmol/L]	log c ($FeCl_2$)	n (R-R') [mmol]	v (20 sec) [mmol/s]	log v
1	2,381	-2,62324929	0,050594779	2,529738928	-2,5969243
2	4,762	-2,32221929	0,115037322	5,751866119	-2,24019123
3	7,143	-2,14612804	0,147531861	7,376593037	-2,13214418
5	11,905	-1,92427929	0,187574206	9,378710296	-2,02785688
10	23,810	-1,62324929	0,302158246	15,10791232	-1,82079554

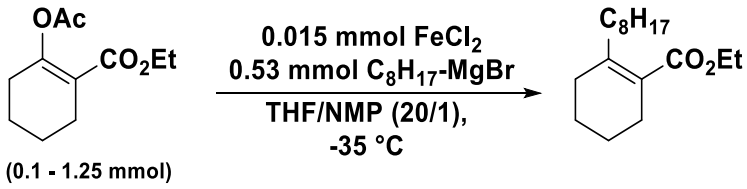


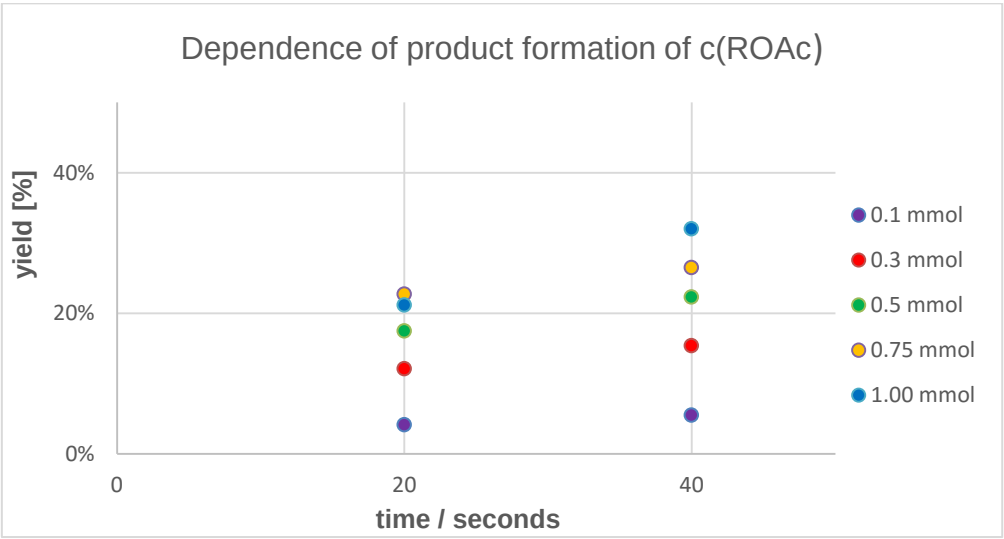
Data points at < 20 seconds are within the induction period of catalyst formation and were found to be poorly reproducible. However, the collected data points can still serve as lower limits of the “real” consumption rates so that the determined order in $FeCl_2$ are upper limits: < 1 at lower concentrations and <0.6 at higher concentrations.

Dependence of substrate concentration

The reactions were carried out under dry and inert conditions. First a $FeCl_2$-NMP-stock solution was prepared in a glovebox. Therefore a flask was charged with $FeCl_2$ (13.3 mg, 0.10 mmol). Dry NMP (0.67 mL) was added and the mixture was stirred until the iron salt was completely dissolved. In addition, a *n*-pentadecane (300 µL, 1.08 mmol)-THF (12 mL) stock solution was prepared in the glovebox.

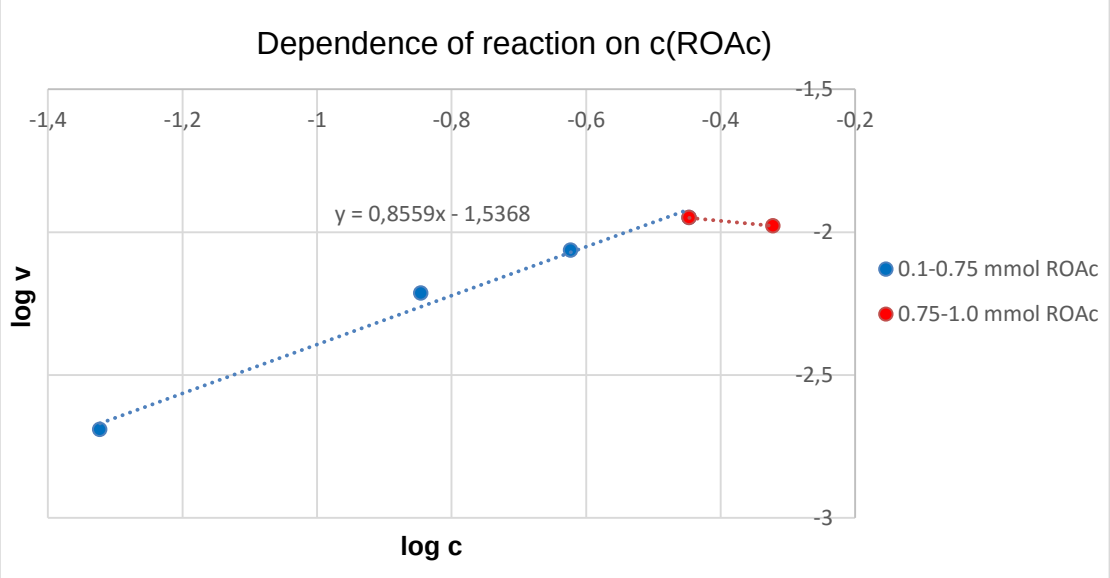
The reaction tubes were charged with appropriate amounts of ethyl 2-acetoxy-cyclohexen-1-ene-carboxylate (21.2 mg, 0.10 mmol; 63.6 mg, 0.30 mmol; etc.) and 2 mL of the freshly prepared *n*-pentadecane solution and 96 µL of the $FeCl_2$-NMP-stock solution were added. The reaction tubes were sealed with a rubber septum and removed from the glovebox. The reaction mixture was cooled to -35 °C and 530 µL of a *n*-octylmagnesium bromide solution in THF (0.53 mmol, 1.0 M) was added within 5 seconds. After 20 and 40 seconds after addition of the *n*-octylmagnesium bromide solution, aliquots (aprox. 200 µL) have been taken and poured in a saturated aqueous NH_4Cl solution (0.5 mL). Ethyl acetate (1.5 mL) was added and the mixture was extracted with ethyl acetate (3 x 1.5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and the solution was subjected to quantitative GC-FID.





For the determination of the initial reaction rate only the amount of formed product after 20 seconds were considered.

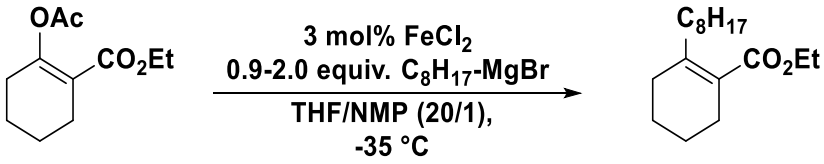
[ROAc] [mmol]	c(ROAc) [mmol/L]	log c ($FeCl_2$)	n (R-R') [mmol]	v (20 sec) [mmol/s]	log v
0.1	47.56296	-1.32273	0.041384	2.069184	-2,6842
0.3	142.6889	-0.84561	0.121141	6.057043	-2,21774
0.5	238.2635	-0.62294	0.174577	8.728828	-2,05904
0.75	357.3953	-0.44685	0.227072	11.35359	-1,94487
1.00	476.0783	-0.32232	0.211638	10.58188	-1,97544

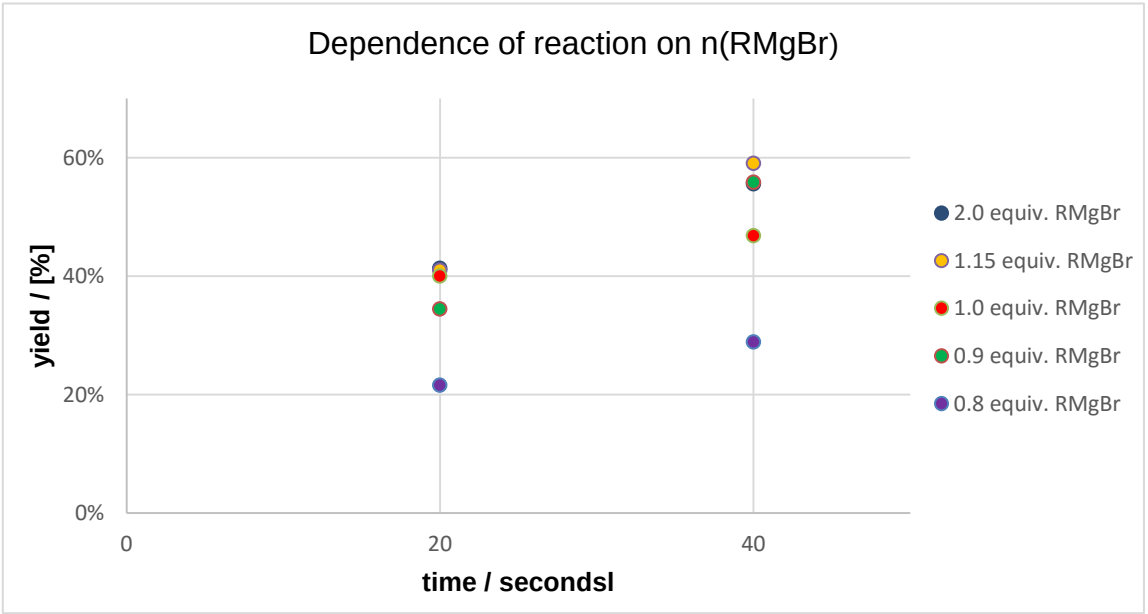


Data points at < 20 seconds are within the induction period of catalyst formation and were found to be poorly reproducible. However, the collected data points can still serve as lower limits of the "real" consumption rates so that the determined order in $FeCl_2$ are upper limits: < 1 at lower concentrations and <0.6 at higher concentrations.

Dependence of *n*-octylmagnesium bromide concentration

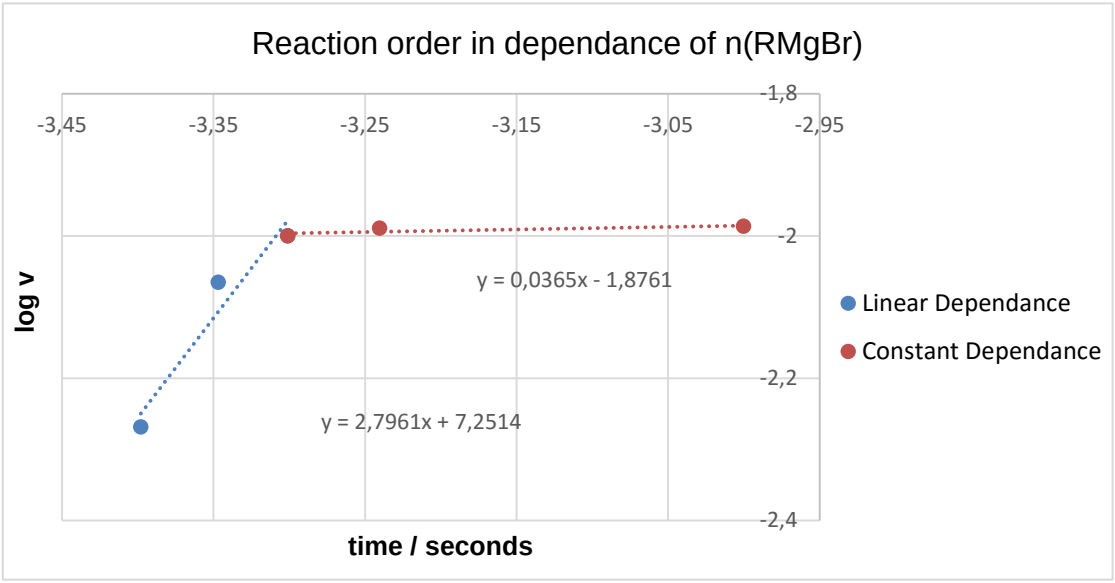
The reactions were carried out under dry and inert conditions. An oven dried reaction tube was charged with ethyl 2-acetoxycyclohexen-1-ene-carboxylate (106 mg, 0.5 mmol) and *n*-pentadecane (50 µL, 0.18 mmol) as internal standard under an atmosphere of argon. Then, 2.0 mL of a freshly prepared solution of $FeCl_2$ (19.0 mg, 0.15 mmol) in NMP (0.96 mL, 10.0 mmol) and THF (19 mL) were added. The reaction mixture was cooled to -35 °C and *n*-octylmagnesium bromide solution in THF (0.8-2.0 equiv., 0.4-1.0 mmol; 1.0 M) was added within 10 seconds. 20 and 40 seconds after addition of the *n*-octylmagnesium bromide solution, aliquots (aprox. 200 µL) have been taken and poured in a saturated aqueous NH_4Cl solution (0.5 mL). Ethyl acetate (1.5 mL) was added and the mixture was extracted with ethyl acetate (3 x 1.5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and the solution was subjected to quantitative GC-FID.





For the determination of the initial reaction rate only the amount of formed product after 20 seconds were considered.

[RMgBr] [equiv.]	n(RMgBr) [mmol]	log n (RMgBr)	n (R-R') [mmol]	v (20 sec) [mmol/s]	log v
0.8	0.4	-3.39794001	0.10766781	5.3833905	-2.26894412
0.9	0.45	-3.34678749	0.17206666	8.603333323	-2.06533326
1.0	0.5	-3.30103	0.19987665	9.99383267	-2.00026793
1.15	0.575	-3.24033216	0.20488915	10.2444575	-1.98951104
2.0	1.0	-3.0	0.16553476	10.3166824	-1.98645994



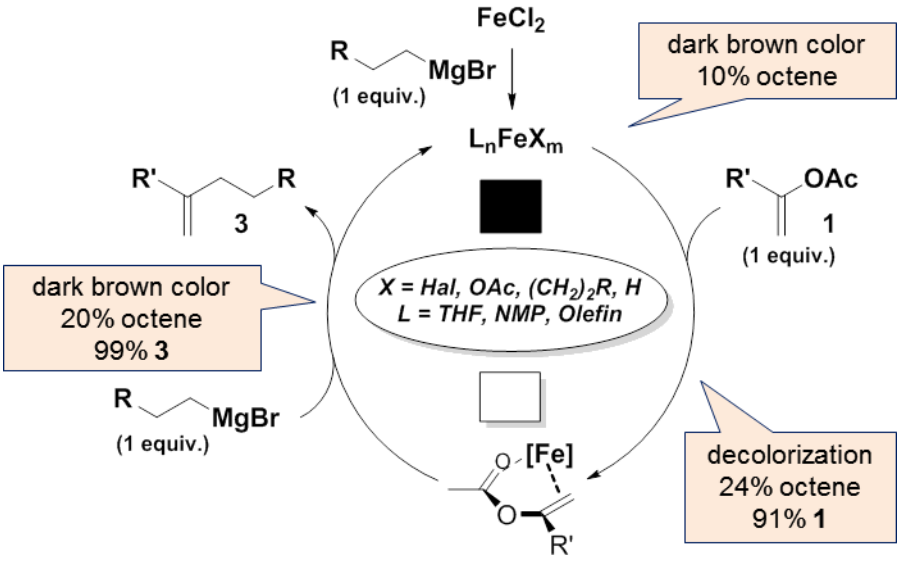
Data points at < 20 seconds are within the induction period of catalyst formation and were found to be poorly reproducible. However, the collected data points can still serve as lower limits of the “real” consumption rates so that the determined order in $FeCl_2$ are upper limits: < 1 at lower concentrations and <0.6 at higher concentrations.

Reaction progress and visual observation of a stoichiometric reaction

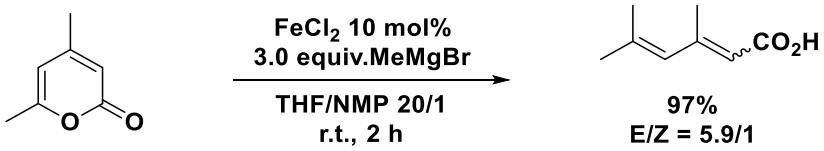
$FeCl_2$ (5 mmol) in THF/NMP (20 mL) at 0 °C; then slow addition of **2** (5 mmol, 1 M in THF) over 30 seconds afforded brown solution; after another 30 seconds a GC aliquot was taken. Addition of **1** (5 mmol) effected rapid decolorization and precipitation; after 1 minute another GC sample was taken. A second addition of **2** (5 mmol, 1 M in THF) over 30 seconds regenerated the brown solution. GC sample was taken after another 30 seconds. All GC samples were immediately hydrolyzed with aqueous NH_4Cl solution and analyzed by quantitative GC-FID vs. internal *n*-pentadecane.

Simplified mechanistic scheme based on a stoichiometric reaction:

Ethyl 2-acetyloxycyclohex-1-ene-carboxylate (**1**), *n*-octylmagnesium bromide (**2**), coupling product ethyl 2-octylcyclohex-1-en-carboxylate (**3**)



3.8.3 Ring-Opening/Cross-Coupling Reactions



This protocol is a slight modification of ref. [6]

The reaction was carried out under dry and inert conditions. First a *Schlenk*-flask was charged with $FeCl_2$ (6.3 mg, 0.05 mmol), 4,6-dimethyl-2-pyrone (62.0 mg, 0.50 mmol) and 10 mL of a solvent mixture of THF/NMP (20/1). The mixture was stirred until the iron salt was completely dissolved.

The reaction tube was sealed with a rubber septum and removed from the glovebox. Then 580 µL of a methylmagnesium bromide solution in THF (1.5 mmol, 2.6 M) was added via syringe pump over a period of 1 hour. After stirring at that temperature for an additional hour, the reaction was hydrolyzed with a saturated aqueous NH_4Cl solution (4 mL). The pH value of the hydrolyzed reaction mixture was adjusted to ~2 with a 1 M HCl solution. After extraction with ethyl acetate (3 x 50 mL), the combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. After removal of the solvent, the residue was subjected to quantitative NMR analysis (internal reference: *n*-pentadecane).

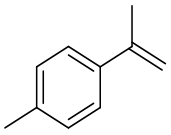
3.8.4 Iron catalyzed cross-coupling reactions of alkenyl acetates with aryllmagnesium halides

3.8.4.1 General procedure for iron catalyzed cross-coupling of alkenyl acetates with arylmagnesium bromides

A 10 mL *Schlenk* tube was charged with Mg turnings (1.5 equiv.) and anhydrous LiCl (1.5 equiv.) and heated under vacuum for 3 minutes. The *Schlenk* tube was purged with nitrogen and placed in an ice-water bath (0 °C). Dry THF (2 mL) was added *via* syringe. After addition of the arylbromide (1.25 equiv.) at 0 °C, the mixture was stirred for 2 hours allowing to warm to room temperature. Then, the mixture was cooled again to 0 °C and a solution of $FeCl_3$ (5 mol%) (and additive, if noted) in dry THF (0.5 mL) was added *via* syringe, followed by the alkenyl acetate (1 equiv.). The mixture was stirred for 3 hours at 0 °C, quenched with saturated aqueous NH_4Cl solution, and extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was subjected to quantitative GC-FID (internal reference: *n*-pentadecane), NMR (internal reference: hexamethyldisiloxane) or silica gel flash column chromatography.

2-(4'-Methylphenyl)propene[57]

According to general procedure, 1.35 equiv. 4-bromotoluene and 1.0 equiv. *iso*-propenyl acetate (110 µL, 1.00 mmol) were used.



$C_{10}H_{12}$, 132.21 g/mol

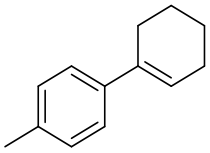
^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 7.38 (d, *J* = 8.2 Hz, 2H), 7.15 (d, *J* = 7.9 Hz, 2H), 5.35 (d, *J* = 0.6 Hz, 1H), 5.03 (m, 1H), 2.36 (s, 3H), 2.15 (dd, *J* = 1.2, 0.7 Hz, 3H).

^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 143.2, 138.5, 137.3, 129.0, 125.5, 111.7, 22.0, 21.2.

LR MS (EI, 70 eV, m/z): 132 $[M]^+$.

1-Cyclohex-1-enyl-4-methylbenzene[58]

According to general procedure, 1.35 equiv. 4-bromotoluene and 1.0 equiv. cyclohexenyl acetate (70.0 mg, 1.00 mmol) were used.



$C_{13}H_{16}$, 172.27 g/mol

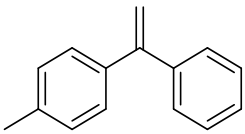
^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 7.27 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 6.07 (m, 1H), 2.37 (m, 2H), 2.32 (s, 3H), 2.19 (m, 2H), 1.75 (m, 2H), 1.65 (m, 2H).

^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 139.8, 136.4, 136.1, 129.0, 124.9, 124.1, 27.5, 26.0, 23.2, 22.3, 21.2.

LR MS (EI, 70 eV, m/z): 172 $[M]^+$.

1-Methyl-4-(1-phenylvinyl)benzene[58]

According to general procedure, 1.35 equiv. 4-bromotoluene and 1.0 equiv. 1-phenylvinyl acetate (81.0 mg, 0.50 mmol) were used.



$C_{15}H_{14}$, 194.28 g/mol

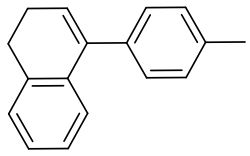
^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 7.31 (m, 5H), 7.22 (m, 2H), 7.12 (m, 2H), 5.42 (d, *J* = 1.3 Hz, 1H), 5.39 (d, *J* = 1.3 Hz, 1H), 2.35 (s, 3H).

^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 149.9, 141.7, 138.6, 137.5, 128.8, 128.3, 128.1, 128.1, 127.6, 113.6, 21.1.

LR MS (EI, 70 eV, m/z): 194 $[M]^+$.

4-(4'-Tolyl)-1,2-dihydronaphthalene[59]

According to general procedure, 1.35 equiv. 4-bromotoluene and 1.0 equiv. 3,4-dihydro-1-naphthyl acetate (94.0 mg, 0.50 mmol) were used.



$C_{17}H_{16}$, 220.32 g/mol

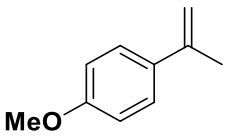
^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 7.48 (m, 1H), 7.23-7.07 (m, 6H), 7.01 (m, 1H), 6.07 (t, *J* = 4.7 Hz, 1H), 2.85 (t, *J* = 7.8 Hz, 2H), 2.40 (m, 2H), 2.39 (s, 3H).

^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 139.8, 138.0, 137.0, 136.9, 135.4, 129.6, 129.0, 128.8, 127.7, 127.4, 127.0, 127.0, 126.3, 125.6, 28.5, 23.6, 21.3.

LR MS (EI, 70 eV, m/z): 220 $[M]^+$.

2-(4'-Methoxyphenyl)propene[60]

According to general procedure, 1.35 equiv. 4-bromoanisol and 1.0 equiv. *iso*-propenyl acetate (110 µL, 1.00 mmol) were used.



$C_{10}H_{12}O$, 148.21 g/mol

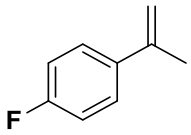
^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 7.43 (d, *J* = 8.9 Hz, 2H), 6.88 (d, *J* = 8.9 Hz, 2H), 5.30 (dd, *J* = 1.5, 0.7 Hz, 1H), 5.00 (m, 1H), 3.82 (s, 3H), 2.14 (dd, *J* = 1.4, 0.8 Hz, 3H).

^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 159.2, 142.7, 133.9, 126.7, 113.7, 110.8, 55.4, 22.1.

LR MS (EI, 70 eV, m/z): 148 $[M]^+$.

2-(4'-Fluorophenyl)propene[60]

According to general procedure, 1.35 equiv. 1-bromo-4-fluorobenzene and 1.0 equiv. *iso*-propenyl acetate (110 µL, 1.00 mmol) were used.



C_9H_9F, 136.17 g/mol

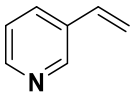
^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 7.43 (m, 2H), 7.08-6.94 (m, 2H), 5.32 (s, 1H), 5.11-5.00 (m, 1H), 2.14 (dd, *J* = 1.4, 0.8 Hz, 3H).

$^{13}C\{^1H\}$-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 162.4 (d, *J* = 246.2 Hz), 142.4, 137.4, 127.2 (d, *J* = 8.0 Hz), 115.1 (d, *J* = 21.3 Hz), 112.4, 22.1.

LR MS (EI, 70 eV, m/z): 136 $[M]^+$.

3-Vinylpyridine[61]

According to general procedure, 1.35 equiv. 3-bromopyridine and 1.0 equiv. vinyl acetate (1.00 mmol, 92.0 µL) were used.



C_7H_7N, 105.14 g/mol

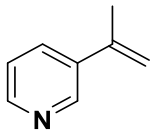
^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 8.53 (d, *J* = 2.1 Hz, 1H), 8.40 (dd, *J* = 4.8, 1.5 Hz, 1H), 7.66 (dt, *J* = 7.9, 2.0 Hz, 1H), 7.18 (dd, *J* = 7.9, 4.8 Hz, 1H), 6.63 (dd, *J* = 17.7, 11.0 Hz, 1H), 5.75 (dd, *J* = 17.7, 0.5 Hz, 1H), 5.30 (d, *J* = 11.0 Hz, 1H).

$^{13}C\{^1H\}$-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 148.7, 148.1, 133.4, 133.0, 132.6, 123.4, 116.1.

LR MS (EI, 70 eV, m/z): 105 $[M]^+$.

3-(Prop-1-en-2-yl)pyridine

According to general procedure, 1.35 equiv. 3-bromopyridine and 1.0 equiv. *iso*-propenyl acetate (110 µL, 1.00 mmol) were used.



C_8H_9N, 119.17 g/mol

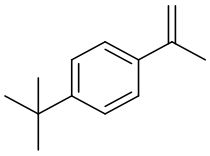
^{1}H-NMR (400 MHz, $CDCl_3$): δ_H [ppm] = 8.67 (d, *J* = 1.8 Hz, 1H), 8.45 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.69 (ddd, *J* = 8.0, 2.4, 1.7 Hz, 1H), 7.20 (ddd, *J* = 8.0, 4.8, 0.8 Hz, 1H), 5.37 (m, 1H), 5.13 (m, 1H), 2.11 (dd, *J* = 1.5, 0.8 Hz, 3H).

^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 148.5, 147.1, 140.5, 132.8, 136.6, 123.1, 114.2, 21.5.

LR MS (EI, 70 eV, m/z): 119 $[M]^+$.

2-(4'-*tert*-Butylphenyl)propene[62]

According to general procedure, 1.35 equiv. 1-bromo-4-*tert*-butylbenzene and 1.0 equiv. *iso*-propenyl acetate (110 µL, 1.00 mmol) were used.



$C_{13}H_{18}$, 174.29 g/mol

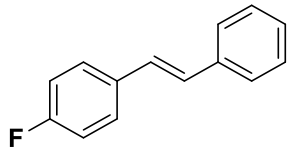
^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 7.67-7.40 (m, 4H), 5.49 (s, 1H), 5.17 (t, *J* = 1.5 Hz, 1H), 2.27 (s, 3H), 1.46 (s, 9H).

^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 150.3, 143.0, 138.3, 125.2, 125.1, 111.6, 34.5, 31.3, 21.7,

LR MS (EI, 70 eV, m/z): 174 $[M]^+$.

(*E*)-1-Fluoro-4-styrylbenzene[63]

According to general procedure, 1.35 equiv. 1-bromo-4-fluorobenzene and 1.0 equiv. (*E*)-styryl acetate (1.00 mmol, 162 mg) were used.



$C_{14}H_{11}F$, 198.24 g/mol

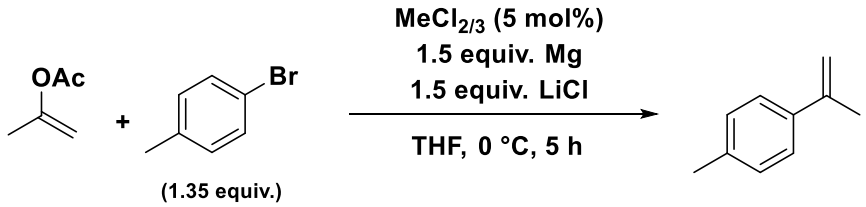
^{1}H-NMR (400 MHz, $CDCl_3$): δ_H [ppm] = 7.66-7.50 (m, 4H), 7.43 (t, *J* = 7.2 Hz, 2H), 7.28-7.36 (m, 1H), 7.23-7.04 (m, 4H).

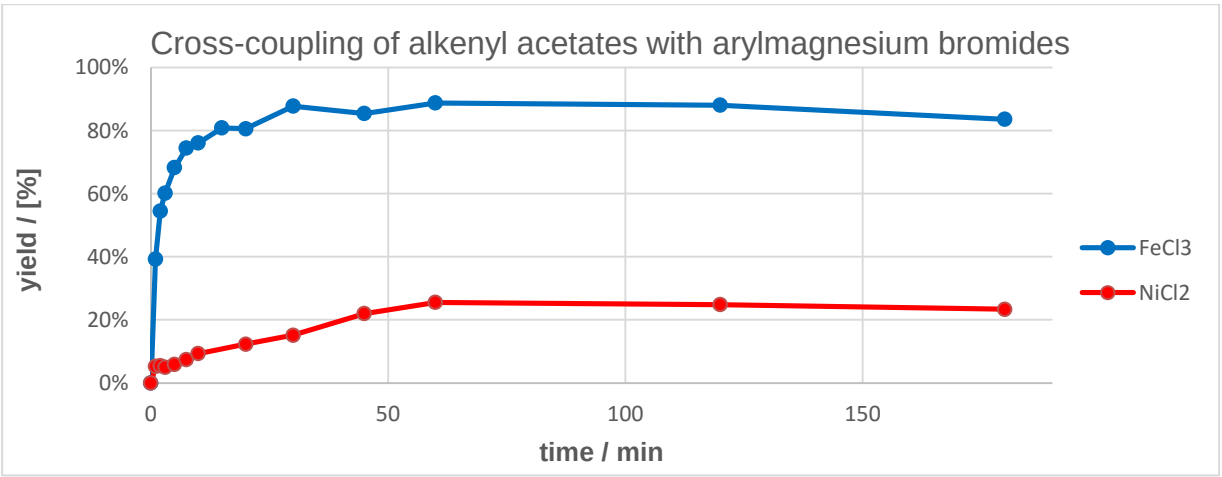
^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ_C [ppm] = 162.4 (d, *J* = 245.6 Hz), 137.2, 133.6 (d, *J* = 3.0 Hz), 128.8, 128.6, 128.1 (d, *J* = 7.9 Hz), 127.7, 127.5, 126.5, 115.6 (d, *J* = 21.5 Hz).

LR MS (EI, 70 eV, m/z): 198 $[M]^+$.

3.8.4.2 Kinetic experiments

In addition to the general procedure *n*-pentadecane (100 µL, 0.36 mmol) was added with the metal salt solution ($FeCl_3$ or $NiCl_2$) in THF. After defined periods of time, aliquots (aprox. 200 µL) were taken and poured into a saturated aqueous NH_4Cl solution (0.5 mL). The mixture was extracted with ethyl acetate (3 x 1.5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and the solution was subjected to quantitative GC-FID.





3.9 References

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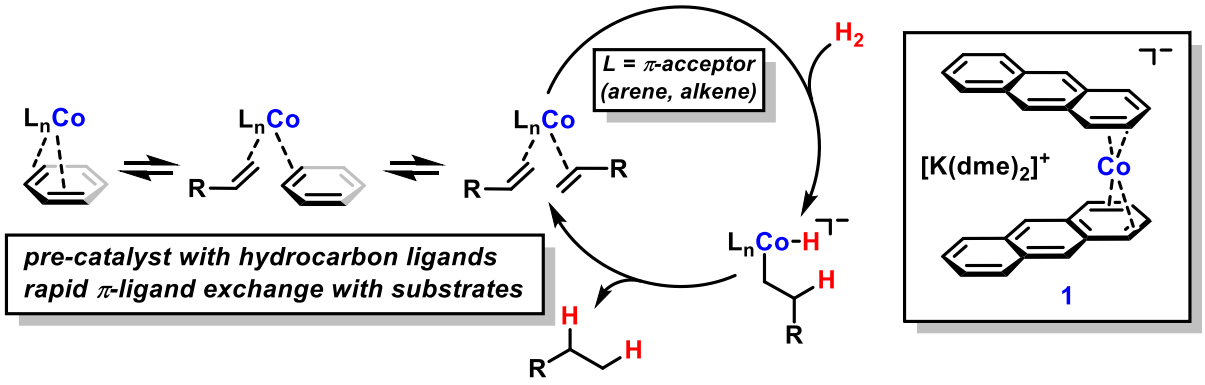
4 Heteroatom-Free Arene-Cobalt and Arene-Iron Catalysts for Hydrogenations



Abstract: 75 years after the discovery of hydroformylation, cobalt catalysts are now undergoing a renaissance in hydrogenation reactions. We have evaluated arene metalates in which the low-valent metal species is-conceptually different from heteroatom-based ligands-stabilized by π-coordination to hydrocarbons. Potassium bis(anthracene)cobaltate **1** and -ferrate **2** can be viewed as synthetic precursors of quasi-"naked" anionic metal species; their aggregation is effectively impeded by (labile) coordination to the various π-acceptors present in the hydrogenation reactions of unsaturated molecules (alkenes, arenes, carbonyl compounds). Kinetic studies, NMR spectroscopy, and poisoning studies of alkene hydrogenations support the formation of a homogeneous catalyst derived from **1** which is stabilized by the coordination of alkenes. This catalyst concept complements the use of complexes with heteroatom donor ligands for reductive processes.[I-IV]

[I] Reproduced with permission from: D. Gärtner, A. Welther, B. R. Rad, R. Wolf, A. Jacobi von Wangelin, *Angew. Chem. Int. Ed.* **2014**, *53*, 3722-3726. Copyright 2015 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim; schemes, figures and text may differ from published version.

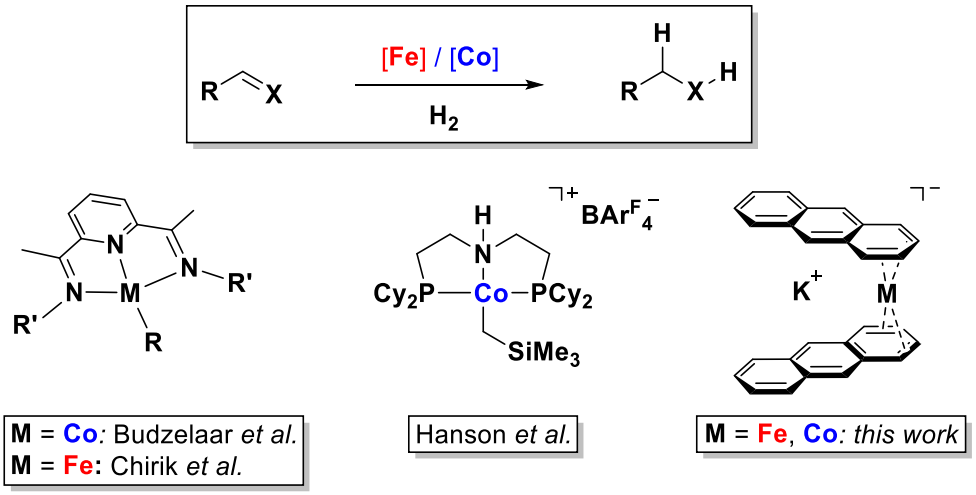
[II] Initial Investigations of *"Iron and Cobalt Catalyzed Hydrogenation Reactions"* were performed by A. Welther. See: A. Welther, *Dissertation*, University of Regensburg 2013.

[III] Complex synthesis and spectroscopic studies were performed by Dr. B. R. Rad, University of Regensburg.

[IV] Own workshare is about 60%

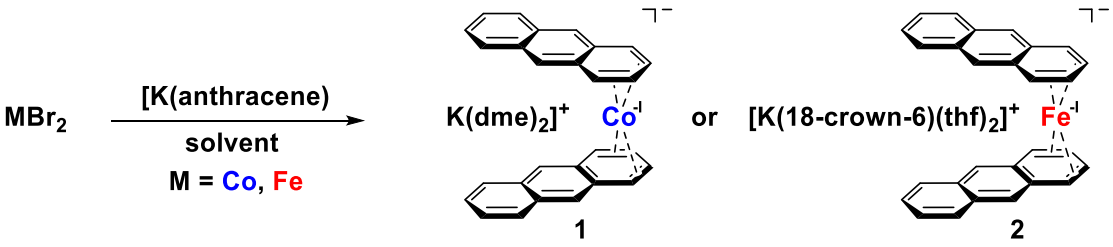
4.1 Introduction

Catalytic hydrogenations constitute one of the most important operations for the conversion of chemical raw materials and in the synthesis of fine chemicals and pharmaceuticals.[1] Noble metal catalysts display the widest substrate scope and functional group tolerance.[2] However, economic and environmental concerns have prompted an ever increasing demand for sustainable processes, including efficient hydrogenation methods with base-metal catalysts. Significant progress has only recently been made with the use of first-row transition-metal catalysts for the mild hydrogenation of olefins and carbonyl compounds.[3] Iron-catalyzed hydrogenations have only played a major role in bulk-scale reductions (Haber–Bosch, gas-to-liquid).[4] Early cobalt-catalyzed hydroformylations also included hydrogenation studies.[5] Careful ligand design has recently allowed the use of well-defined low-valent iron and cobalt catalysts.[6] Cobalt catalysts with redox-active bis(imino) pyridine ligands were applied to olefin hydrogenations by Budzelaar and co-workers.[6b,c] A PNP pincer ligand was recently used by Hanson and co-workers to stabilize a cobalt catalyst with 15 valence electrons that allowed hydrogenation of alkenes, ketones, and imines after activation by Brookhart`s acid.[7] Cobalt-catalyzed hydrogenations of styrenes were also developed by Chirik and co-workers.[8] The same research group reported high activities of bis(imino)pyridine- and bis(arylimidazol-2-ylidene)pyridine–iron and -cobalt catalysts bearing two labile N_2 ligands (Scheme 4.1).[9]



Scheme 4.1: Iron- and cobalt-based hydrogenation catalysts with an odd number of electrons.

We envisioned capitalizing on the presence of the labile arene ligands in potassium bis(anthra-cene)cobaltate **1** and ferrate **2** which render these complexes synthetic precursors quasi-“naked” anionic metal species(Scheme 4.2).[10,11]]



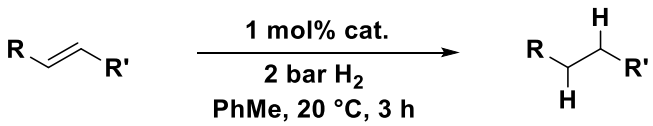
Scheme 4.2: Synthesis of bis(anthacene)metalates(-I) 1 and 2.[14]

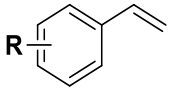
Unlike many catalytic reactions where this scenario would entail catalyst aggregation and deactivation, the presence of a large excess of π-acidic ligands in hydrogenations (of unsaturated molecules such as alkenes, arenes and carbonyl compounds) can effect rapid ligand exchange between π-ligands and thus assure prolonged catalyst activity in the homogeneous phase.[12] We tested this catalyst concept for the first time in hydrogenations.[13,14]

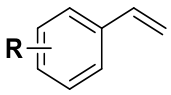
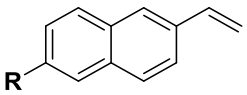
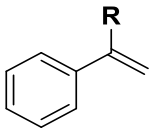
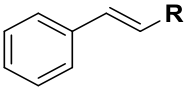
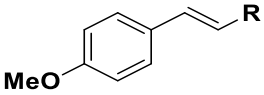
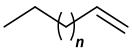
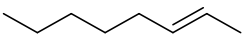
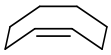
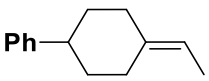
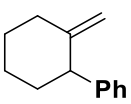
4.2 Hydrogenation of alkenes, alkynes and arenes

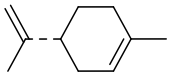
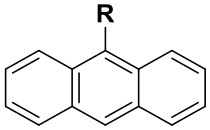
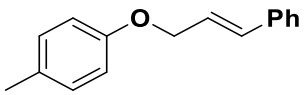
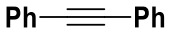
Initially, hydrogenations of styrenes-which are prone to competing polymerization[15] by anionic, redox-active catalysts-were studied under mild conditions (1 bar H_2, 20 °C,Table 4.1).[16]

Table 4.1: Hydrogenations of alkenes, alkynes and arenes.



Entry	Olefin	R	Yield [%]	
			Cat. 1	Cat. 2
1		H	95 (89)[a]	89
2		4-OMe	98	100[b]
3		4-F	100	100
4		4-NH_2	27	0

Entry	Olefin	R	Yield [%]	
			Cat 1	Cat 2
5		4-CO_2Me	89	2
6		2-OMe	95	50
7		2-CF_3	100	75[c]
8		2-Cl (2-Br)	0 (0)	0 (0)
9		3-Me	96	27
10		2-Me	100[d]	-
11		4-Me	100[d]	-
12		H	100[d]	-
13		OMe	97[d]	58
14		OAc	69	-
15		Me	100[b]	-
16		Ph	100[e]	-
17		Me	100[b]	-
18		Ph	100[b]	-
19		CO_2Et	76[e]	-
20		Me	99[e]	-
21		CO_2Et	86[e]	-
22		*n* = 4	88[e,f]	73[e,f]
23		*n* = 8	92[e,f]	72[e,f]
24			92[e]	-
25			89[b]	-
26			100[b]	-
27			60[e,g]	-
28			78(d.r. 1:1)[e,]	-

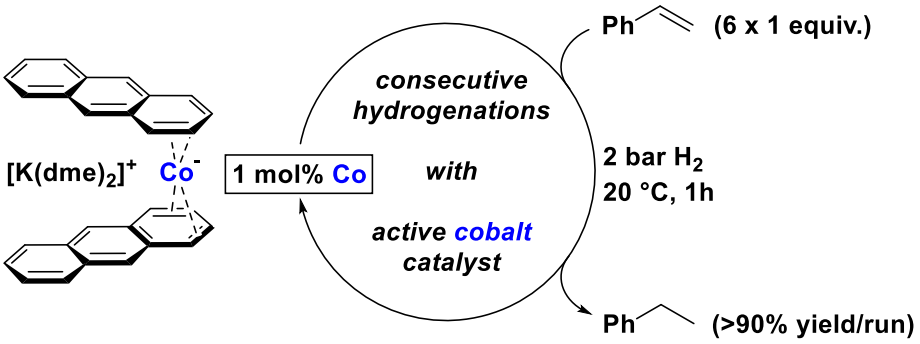
Entry	Olefin	R	Yield [%]	
			Cat 1	Cat 2
29			60[e,h]	-
30		H	99[e] (2:1)[i]	–
31		Cl	0[e]	–
32			79[e]	<5[e]
33			99[e,j]	<5[e,k]

[a] with 150 equiv. Hg/[Co]; [b] 60 °C, 2 bar, 24 h; [c] 2 mol% cat.; [d] 2 bar; [e] 5 mol% cat., 60 °C, 10 bar, 24 h; [f] <8% 2-alkene; [g] 80 °C; [h] 1-menthene; [i] 9,10-dihydro-/1,2,3,4-tetrahydroanthracene; [j] bibenzyl; [k] (*E*)-stilbene.

Cobaltate **1** exhibited far higher activity than the related ferrate **2**. This is likely a consequence of the higher propensity for oxidation of the latter, which has been shown to release the anthracenyl anion in ligand-exchange reactions.[10c] Excellent yields were obtained in hydrogenations of styrenes and alkenes with catalyst **1** at a H_2 pressure of 1–10 bar. Polymerization was observed only to a minor extent (< 5%). Aryl halides (Br, Cl) led to oxidation of the catalyst, as observed in cross-coupling reactions.[13,17] A comparative study of initial reaction rates revealed no significant electronic effect of the para substituent of different styrene derivatives (F, H, Me, OMe). The isomerization of alkenes was largely suppressed (entries 22, 23, and 28);[18] tri-substituted olefins reacted slower (entries 27 and 29). The hydrogenation of anthracene gave 9,10-dihydroanthracene and 1,2,3,4-tetrahydroanthracene (2:1, entry 30). Exchange of the cation by using $[K(18\text{-crown-6})\{Co(C_{14}H_{10})_2\}]$[10] instead of **1** afforded identical yields in reactions of various styrenes. The different activity of **1** and **2** was also reflected in hydrogenations of 1,2-diphenylacetylene. Catalyst **1** gave full conversion into bibenzyl (10 bar H_2,60 °C), whereas **2** led to low conversion to (*Z*)-stilbene.[16b] The reactions are chemoselective despite the presence of anionic catalyst species: the C-O bonds of esters and activated ethers were tolerated (entries 5, 14, 19, 21, and 32).

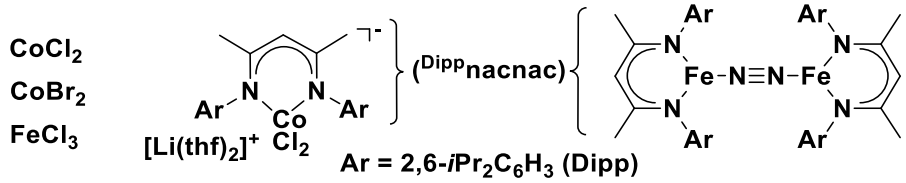
It is important to note that this protocol does not require pretreatment or activation of the precatalyst and operates under essentially ligand-free conditions.[6,7,9] The

standard conditions allowed consecutive catalyses of **1** by addition of another equivalent of styrene after each run (6 x 1 equiv, see Scheme 4.3).



Scheme 4.3: Consecutive hydrogenations with precatalyst 1.

The higher valent precursors $FeCl_3$, $CoCl_2$, $CoBr_2$, $[Li(thf)_2][Co(^{Dipp}nacnac)Cl_2]$,[19] and $[Fe_2(\mu\text{-}N_2)\text{-}(^{Dipp}nacnac)_2]$[20] exhibited no catalytic activity at 2 bar H_2(Scheme 4.4).



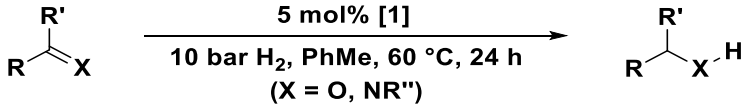
Scheme 4.4: Inactive precatalysts. Ar = 2,6-*i*$Pr_2C_6H_3$ (DIPP).

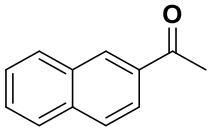
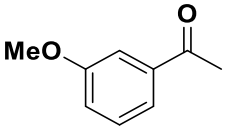
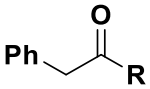
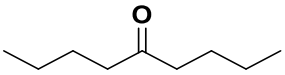
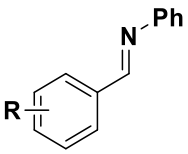
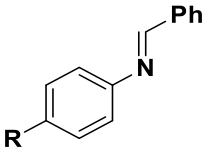
4.3 Hydrogenation of ketones and imines with cobaltate 1

Aiming at a broader substrate scope, we wondered whether anionic **1** would selectively catalyze hydrogenations of carbonyl compounds or instead engage in undesired nucleophilic addition or oligomerization with these electrophiles. Gratifyingly, **1** displayed excellent activity in the hydrogenation of various aromatic and aliphatic ketones and imines at 10 bar H_2 and 60 °C (Table 4.2).

No pinacol products were detected. The high chemoselectivity of cobaltate **1** also resides in its poor nucleophilicity: no direct reactions with styrenes and the more electrophilic cinnamyl ethers, ketones and imines were observed. Aldehydes engaged in oligomerizations and condensations.

Table 4.2: Hydrogenations of ketones and imines with cobaltate 1.[a]



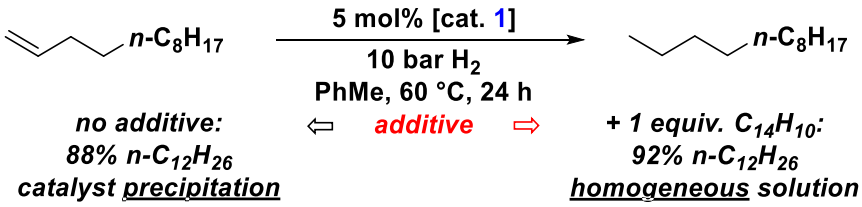
Entry	Carbonyl Compound		Yield [%]
1			88
2			71
3		R = Me	99
4		R = Bn	96 (36[b] 14)[c]
5			100
6		R = H	96
7		R = 2-Me	98
8		R = 3-Me	100
9		R = 4-OMe	100
10		R = CO_2Et	79[d]
11		R = Br	0

[a] standard conditions: 0.5 mmol substrate in 2 mL toluene; yields determined by ^{1}H NMR spectroscopy with HMDS as internal standard; [b] RT; [c] 2 bar H_2; [d] 7.5 mol% **1**, 70 °C.

4.4 Mechanistic studies

No catalyst precipitation or color change was observed by visual inspection of the olefin hydrogenation reactions. The loss of suitable π-acceptors after complete hydrogenation of 1-dodecene (and 2% anthracene from the precatalyst) resulted in catalyst precipitation. Under identical conditions, crude reactions containing an equimolar amount of anthracene remained homogeneous as a result of the slow

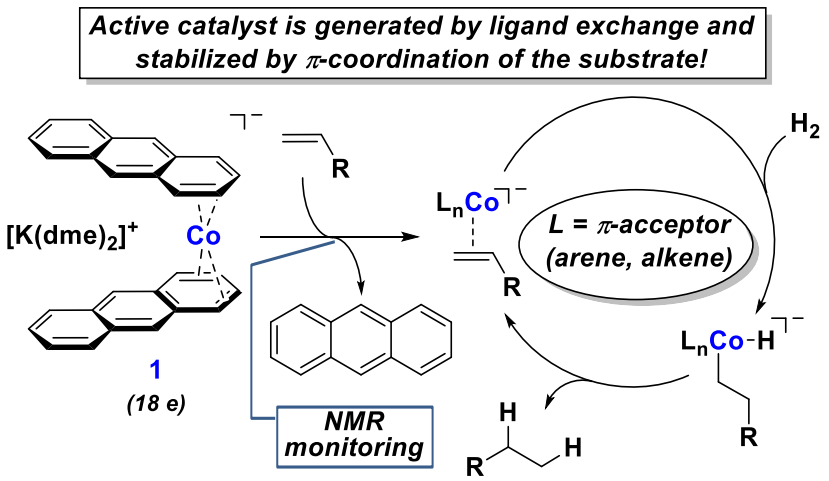
hydrogenation of anthracene (Scheme 4.5). This is consistent with the assumption that π-acceptors other than anthracene are also capable of stabilizing reactive low-valent homogeneous metal species.[10–12]



Scheme 4.5: Hydrogenations in the presence of anthracene.

Unambiguous distinction between homogeneous and heterogeneous catalysts is intricate,[21] yet our observations are consistent with a homogeneous mechanism. Hg poisoning (addition of 150 equiv. Hg per [Co] at the start of the reaction and at 25% conversion, respectively) showed no loss of activity (Table 4.1, entry 1, and see Figure S4 in the Experimental Section). The homogeneity of the catalyst was further indicated by experiments carried out in the presence of dibenzo[a,e]cyclo-octatetraene (dct).[22] Dct selectively binds homogeneous metal species as a consequence of its rigid tublike structure and π-acceptor ability, and it is resistant to hydrogenation. Complete inhibition of the catalytic activity was observed when adding **2** equiv. dct per [Co] to styrene hydrogenations at 20% conversion (see Figure S1 in the Experimental Section).

We postulate a mechanism initiated by the substitution of the labile anthracene molecules by π-acceptor substrates (Scheme 4.6).



Scheme 4.6: Proposed mechanism of 1-catalyzed hydrogenations.

Similar stoichiometric reactions were previously reported for cyclooctadiene and butadiene.[10] Reaction progress analyses (GC-FID) fully support the notion of an initial anthracene substitution which is hydrogenated only after the stoichiometric substrate (styrene) is entirely consumed (Figure 4.1).

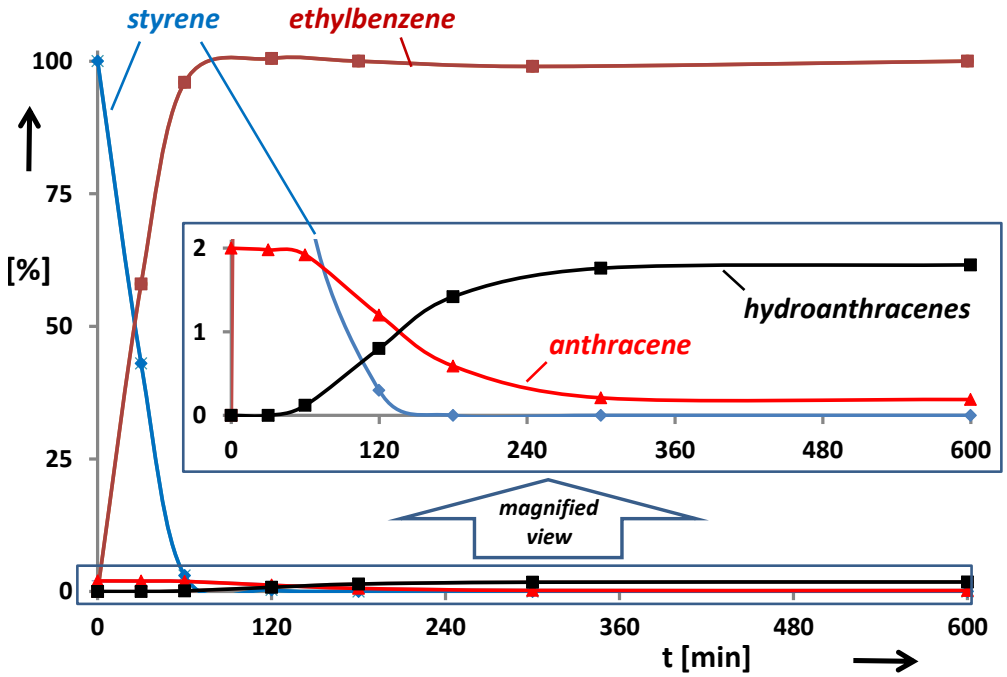
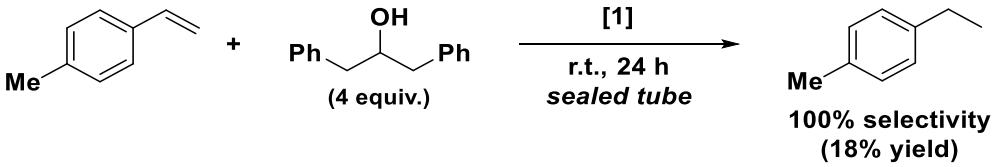


Figure 4.1: Ligand exchange is followed by ligand hydrogenation.

Quantitative analysis of the early reaction phase (< 20 min) showed neither an induction period nor a sigmoidal kinetic curve (see Figure S2 in the Experimental Section), which could indicate a nano-cluster nucleation step *en route* to particle formation (Figure S2).[21a]

Monitoring a mixture of **1** with 20 equiv. styrene by ^{1}H NMR spectroscopy revealed that anthracene is indeed rapidly exchanged by styrene (see Figure S3 in the Experimental Section). No direct reaction between **1** and H_2 in the absence of styrene (or alkenes) was observed under these conditions. The activation of H_2 at the catalyst species followed by alkene insertion into a hydridocobaltate gives an alkylcobalt(I) hydride.[23] Substitution of the hydrogenated product occurs by coordination of another olefin. The catalytic intermediates are apparently stabilized by π-acceptors which are present in large excess (arenes, olefins). Cobalt-catalyzed hydrogenations of styrene and 1,3-diphenylacetone followed by work-up with D_2O afforded no deuterated products (^{1}H, ^{2}H NMR). The reaction of styrene under 2 bar D_2 gave α,β-[D_2]-ethylbenzene. Treatment of **1** with alcohols (ethanol, 1,3-diphenyl-

propan-2-ol) at room temperature resulted in oxidation of the catalyst to another catalytic species, a color change (dark red to dark green), and H_2 evolution.[24] Transfer hydrogenation between 1,3-diphenyl-propan-2-ol (4 equiv.) and 4-methyl-styrene in the presence of **1** indeed afforded 1-ethyl-4-methylbenzene with 100% selectivity (18% yield) in the absence of an H_2 atmosphere (Scheme 4.7).



Scheme 4.7: Initial result of a transfer hydrogenation with secondary alcohols.

NMR studies confirmed the exchange of anthracene ligands with ketones in the coordination sphere of **1** (see Figure S5 in the Experimental Section). No direct reduction of diphenylacetone by an equimolar amount of **1** was observed. We thus postulate the initiation of carbonyl hydrogenation by cobaltate **1** and the operation of a cobalt(I) catalyst after the first turnover at elevated temperature and H_2 pressure.[24,25]

4.5 Summary

For the first time, homoleptic arene complexes were applied to catalytic hydrogenations. Catalysts **1** and **2** are readily accessible by reduction of metal halides with potassium-anthracene.[10] Bis(anthracene)cobaltate **1** was highly active in the hydrogenation of alkenes, ketones, and imines(1–5 mol% cat., 1–10 bar H_2, 20–60 °C). It displays comparable activity to Hanson`s ternary catalyst system PNP ligand/cobalt/$HB(Ar^F)_4$,[7] but does not require sophisticated ligands or further additives (e.g. Brookhart`s acid). Olefin hydrogenation catalysis with **1** is initiated by anthracene dissociation to release an active species which is homogeneous and stable in the presence of suitable π-acceptors. Consecutive reactions were performed without loss of activity. Current studies aim at the spectroscopic characterization of the intermediate cobalt species with labile π-acceptor ligands and applications of this new catalyst concept to other transformations with alkenes, carbonyl compounds, and arenes, including transfer hydrogenation.[26]

4.6 Experimental Section

Chemicals and Solvents. If not indicated, commercial reagents were used without purification. For catalytic reactions, exclusively dried solvents were used. Toluene was dried over sodium/benzophenone. Liquid substrates were distilled prior to use. THF-d_8 was dried over sodium/benzophenone and distilled. D_2O was purchased from *Deutero* (purity 99.8%), D_2 from *Linde* (purity 99.9%).

Hydrogenation Reactions. The reactions were carried out in 4 mL glass vials with a screw cap and PTFE septum. The reaction vessels were placed into a 300 or 160 mL high pressure reactor (*Parr*) (5-6 reactions parallel, 5.2 purity of H_2). The reactor was sealed and the hydrogenations were performed outside the glovebox. The reactions were magnetically stirred with an external magnetic stirrer. [K([18]crown-6)$(thf)_2${$Fe(C_{14}H_{10})_2$}] (**2**) was provided by Dr. B. Rezaei Rad and Prof. R. Wolf from the Institute of Inorganic Chemistry, University of Regensburg, and synthesized according to literature procedures.[10c] Reactions for NMR experiments were performed in an UniLab glovebox (*MBraun*) under an atmosphere of dry argon using J. Young NMR tubes. NMR spectra were recorded on a Bruker Avance 400 spectrometer at 300 K and internally referenced to residual solvent resonances.

Analytical thin-layer chromatography. TLC was performed using aluminium plates with silica gel and fluorescent indicator (Merck, $60F_{254}$). Thin layer chromatography plates were visualized by exposure to UV light and/or by immersion in an aqueous staining solution of $KMnO_4$.

Column chromatography. Flash column chromatography with silica gel 60 Å (220-240 mesh) from *Acros*. Pentane, hexanes or mixtures thereof with ethyl acetate were used as eluents.

Gas chromatography with mass-selective detector. *Agilent* 6890N Network GC-System, mass detector 5975 MS. Column: BPX5 (30 m x 0.25 mm x 0.25 µm, from *SGE*, carrier gas: H_2. Standard heating procedure: 50 °C (2 min), 25 °C/min -> 300 °C (5 min).

Gas chromatography with FID

Agilent 7820A GC-Systems. Column: HP 5 19091J 413 (30 m x 0.32 mm x 0.25 µm) from *Agilent*, carrier gas: N_2. GC-FID was used for catalyst screening (Calibration with internal standard *n*-pentadecane and analytically pure samples).

NMR. ^{1}H and ^{13}C nuclear magnetic resonance spectra were recorded on a *Bruker* Avance 300 (300 MHz ^{1}H; 75 MHz ^{13}C) and *Bruker* Avance 400 (400MHz ^{1}H, 101 MHz ^{13}C) spectrometers Chemicals shifts are reported in ppm (δ) relative to internal tetramethylsilane (TMS). Coupling constants (J) are reported in Hertz (Hz). Following abbreviations are used for spin multiplicities:
s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, dt = doublet of triplet, dq = doublet of quartet, ddt = doublet of doublet of triplet. For yield determinations, hexamethyldisiloxane was used as internal standard.

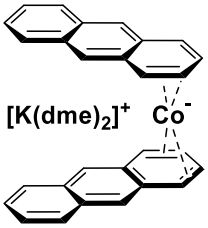
IR spectroscopy. Infrared spectra were recorded on a *Varian* Scimitar 1000 FT-IR equipped with a ATR unit. Wavenumbers are indicated in cm^{-1}. Intensive absorption bands are indicated with „s“ (strong), medium bands with „m“ (medium), and weak bands with „w“ (weak).

High resolution mass spectrometry (HRMS). The spectra were recorded by the Central Analytics Lab at the Department of Chemistry, University of Regensburg, on a MAT SSQ 710 A from *Finnigan*.

Preparation of [K(dme){Co($C_{14}H_{10}$)$_2$}] (1). All manipulations were performed under an atmosphere of dry argon using standard *Schlen*k and glovebox techniques. Cobaltate **1** was prepared by modification of the literature procedures for [K([18]crown-6)(thf)$_2$][Co($C_{14}H_{10}$)$_2$] and [K([2.2.2]cryptand)][Co($C_{14}H_{10}$)$_2$].[10a]
A suspension of anhydrous $CoBr_2$ (25.00 mmol 5.46 g) in 1,2-dimethoxyethane (DME, 350 mL, –78 °C) was added by cannula to a freshly-prepared, deep blue solution of $KC_{14}H_{10}$ (75.00 mmol) in DME (300 mL, –78 °C). The reaction mixture turned deep red during the transfer and was allowed to warm to room temperature overnight. After filtration, *n*-heptane (150 mL) was added and the solvent was concentrated *in vacuo* until the deep red mixture became turbid and a dark precipitate began to form. Then, diethyl ether (ca. 450 mL) was added, whereupon a

dark solid precipitated. Recrystallization from DME/diethyl ether (1/3) afforded dark red, X-ray quality crystals of $[K(dme)_2\{Co(C_{14}H_{10})_2\}]$. The crystals lose one DME molecule upon drying in high vacuum to give $[K(dme)_2\{Co(C_{14}H_{10})_2\}]$ (**1**).

$[K(dme)\{Co(C_{14}H_{10})_2\}]$



$C_{40}H_{52}CoKO_4$, 694.88 g/mol

Yield: 7.89 g (15.62 mmol, 63% based on $CoBr_2$).

M.p.: 104-107 °C.

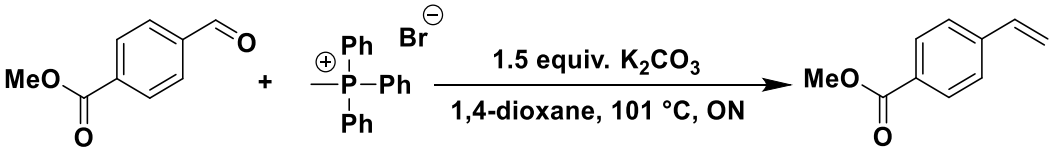
^{1}H NMR (400 MHz, d_8THF): δ_H [ppm] = 6.93 (br s, 4H, $H_{6,7}$ or $H_{5,8}$ of anthracene), 6.73 (br s, 4H, $H_{5,8}$ or $H_{6,7}$ of anthracene), 6.27 (br s, 4H, $H_{9,10}$ of anthracene), 5.05 (br s, 4H, $H_{2,3}$ of anthracene), 3.43 (s, 8H, DME, OCH_2), 3.27 (s, 12H, DME, OCH_3), 3.05 (br s, 4H, $H_{1,4}$ of anthracene).

^{13}C{^{1}H}-NMR (101 MHz, d_8THF): δ_H [ppm] = 145.7 ($C_{11,12}$ of anthracene), 133.5 ($C_{13,14}$ of anthracene), 124.9 (s, $C_{5,8}$ or $C_{6,7}$ of anthracene), 122.0 (s, $C_{5,8}$ or $C_{6,7}$ of anthracene), 109.4 (s, $C_{9,10}$ of anthracene), 74.8 (br, $C_{2,3}$), 72.6 (s, DME, OCH_2), 58.8 (s, DME, OCH_3), 54.2 (br, $C_{1,4}$ of anthracene).

Superscripts behind compound names are literature references.

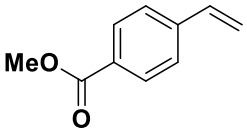
4.6.1 Preparation of Starting Materials

Preparation of methyl 4-vinylbenzoate[27]



In a 50 mL round bottom flask, methyl (4-formylbenzoate) (10 mmol, 1.64 g) was dissolved in 1,4-dioxane (10 mL). To this mixture, potassium carbonate (2.07 g, 15mmol) and methyl triphenylphosphonium bromide (5.33 g, 15 mmol) were added. The reaction mixture was refluxed at 101 °C overnight (~18 h). After cooling down to room temperature and filtration, the solvent was removed under reduced pressure. The residue was then purified by column chromatography (hexanes/ethyl acetate 95/5). The product was obtained as white solid.

Methyl 4-vinylbenzoate[27]



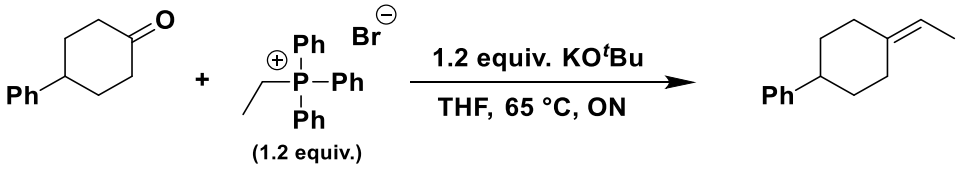
$C_{10}H_{10}O_2$, 162.19 g/mol

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 8.01-7.98 (m, 2H), 7.48-7.45 (m, 2H), 6.8-6.71 (dd, *J* = 17.7, 10.9 Hz, 1H), 5.86 (d, *J* = 17.6 Hz, 1H), 5.38 (d, *J* = 10.9 Hz, 1H), 3.92 (s, 3H).

^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 160.5, 152.1, 136.2, 131.4, 129.2, 128.8, 126.0, 120.9.

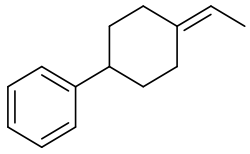
LR MS (EI, 70 eV, m/z): 227 $[M]^+$.

Preparation of 4-ethylidene cyclohexylbenzene[28]



The reaction was carried out under an inert atmosphere (Ar). To a suspension of ethyl triphenylphosphonium bromide (12 mmol, 4.46 g) in THF (25 mL) was added KO^{t}Bu (12 mmol, 1.35 mL) at 0 °C. The suspension was stirred for 10 minutes and 4-phenylcyclohexanone (10 mmol, 1.74 g) was added slowly. The reaction was stirred over night at reflux conditions. The reaction mixture was hydrolyzed with water (10 mL) and extracted with Et_2O (2 x 10 mL). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure and purified by column chromatography (hexanes/ethyl acetate 10/1).

4-Ethylidene cyclohexylbenzene[28]



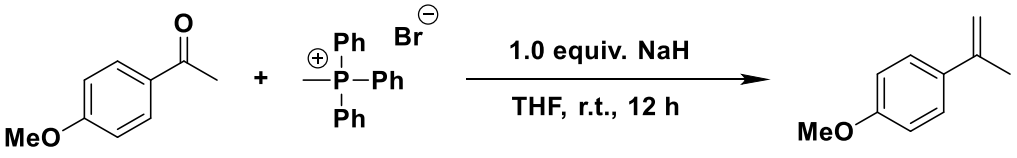
$C_{14}H_{18}$, 186,30 g/mol

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H [ppm] = 7.38-7.17 (m, 5H), 5.32-5.22 (m, 1H), 2.80 (d, *J* = 13.5 Hz, 1H), 2.72 (td, *J* = 12.2, 2.7 Hz, 1H), 2.35 (d, *J* = 13.0 Hz, 1H), 2.22 (t, *J* = 13.2 Hz, 1H), 2.00 (t, *J* = 10.5 Hz, 2H), 1.89 (t, *J* = 13.4 Hz, 1H), 1.72–1.62 (m, 3H), 1.61–1.43 (m, 2H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): 147.2, 138.8, 128.4, 126.9, 126.0, 116.0, 44.9, 36.87, 35.9, 34.9, 28.0, 12.80.

LR MS (EI, 70 eV, m/z): 186 $[M]^+$.

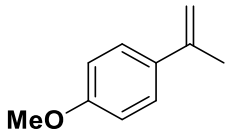
General procedure for the preparation of styrenes from carbonyl compounds[29]



Representative procedure for the olefination of 4-methoxyacetophenone: The reaction was carried out under an inert atmosphere (N_2). To a suspension of methyl triphenylphosphonium bromide (10 mmol, 3.59 g) in THF (14 mL) was added a 60% dispersion of NaH (10 mmol, 406 mg) in mineral oil and the resulting mixture was stirred for 2 h at room temperature. 4-Methoxyacetophenone (10 mmol) was added

dropwise and the reaction was stirred over night at room temperature. The reaction mixture was hydrolyzed with water (15 mL) and extracted with *n*-pentane (3 x 30 mL). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure and purified by column chromatography (hexanes/ethyl acetate 10/1).

4-Methoxy *α*-methylstyrene[30]

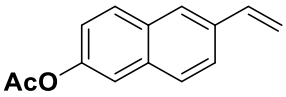


$C_{10}H_{12}O$, 148.20 g/mol

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 7.42 (d, *J* = 8.9 Hz, 2H), 6.89 (d, *J* = 8.9 Hz, 2H), 5.30-5.27 (m, 1H), 4.99 (quint, *J* = 1.5 Hz, 1H), 3.82 (s, 3H), 2.14 2.12 (m, 3 H).

LR MS (EI, 70 eV, m/z): 148 $[M]^+$.

6-Vinylnaphthyl-2-acetate



$C_{14}H_{12}O_2$, 212.25 g/mol

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H [ppm] = 7.82 (d, *J* = 8.8 Hz, 1H), 7.75 (d, *J* = 8.3 Hz, 1H), 7.65 (d, *J* = 8.7 Hz, 1H), 7.52 (d, *J* = 2.3 Hz, 1H), 7.22 (dd, *J* = 8.8, 2.3 Hz, 1H), 6.87 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.87 (dd, *J* = 17.6, 0.6 Hz, 1H), 5.34 (dd, *J* = 10.9 Hz, 1H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 169.7, 148.4, 136.7, 129.5, 127.9, 126.2, 124.0, 121.5, 118.5, 114.4, 21.3.

LR MS (EI, 70 eV, m/z): 212 $[M]^+$.

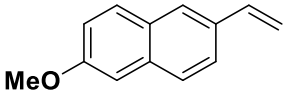
HR MS (CI, *m/z*): found 212.0836 (calculated: 212.0837)

FT-IR: 3050(w), 2900(w), 1754,(s), 1630(m), 1599(m), 1506(m), 1475(m), 1433(m), 1371(s), 1338(m), 1207(m), 1142(m), 1015(m).

M.p.: 98-99 °C

2-Methoxy-6-vinylnaphthalene[31]

The product was purified by column chromatography using a solvent mixture of hexanes/ethyl acetate (98/2).



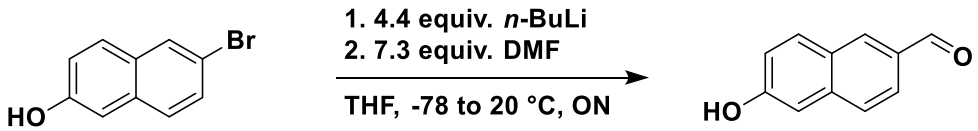
$C_{14}H_{12}O_2$, 184.24 g/mol

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 7.76–7.57 (m, 4H), 7.19–7.09 (m, 2H), 6.86 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.83 (dd, *J* = 17.6, 0.8 Hz, 1H), 5.28 (dd, *J* = 10.9, 0.8 Hz, 1H), 3.93 (s, 3H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 157.8, 137.0, 134.3, 133.0, 129.6, 127.0, 126.2, 123.8, 119.0, 113.1, 105.8, 55.3.

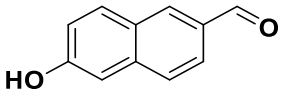
LR MS (EI, 70 eV, m/z): 212 $[M]^+$.

Preparation of 6-hydroxy-2-naphthaldehyde[32]



Under an inert atmosphere, 5-bromo-2-naphthol (20 mmol, 4.46 g) was dissolved in dry THF (200 mL). The solution was cooled to -78 °C and 4.4 equiv. of a 1.6 M solution of *n*-BuLi in hexane (88 mmol, 55 mL) was added slowly. After 5 hours of stirring at this temperature, dry DMF (146 mmol, 113 mL) was added so that the temperature remained below -50 °C. After 45 minutes, the mixture was poured into an iced aqueous HCl-solution. The mixture was allowed to reach room temperature overnight and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed twice with water and dried over Na_2SO_4. Solvents were removed under reduced pressure and the crude product purified by column chromatography (hexanes/ethyl acetate 2/1).

6-Hydroxy-2-naphthaldehyde[32]



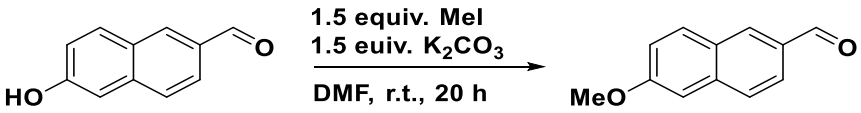
$C_{11}H_8O_2$, 172.18 g/mol

^{1}H-NMR (400 MHz, d^6-DMSO): δ_H [ppm] = 10.33 (s, 1H), 10.04 (s, 1H), 8.43 (s, 1H), 8.02 (d, *J* = 8.5 Hz, 1H), 7.86–7.74 (m, 2H), 7.26–7.17 (m, 2H).

^{13}C{^{1}H}NMR (75 MHz, d_6DMSO): δ_C [ppm] = 192.3, 158.4, 138.0, 134.7, 131.5, 131.2, 126.9, 126.5, 122.6, 119.7, 109.1.

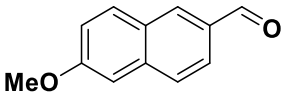
LR MS (EI, 70 eV, m/z): 172 $[M]^+$.

Preparation of 6-methoxy-2-naphthaldehyde[33]



To a solution of 6-hydroxy-2-naphthaldehyde (1.21 g, 7.03 mmol) and MeI (10 mmol, 659 µL) in DMF (6 mL) was added K_2CO_3 (10.5 mmol, 1.46 g). The mixture was stirred for 20 hours, hydrolyzed with water (20 mL) and extracted with diethylether (3 x 20 mL). The organic layers were dried (Na_2SO_4), solvents removed in vacuu and the crude product purified by column chromatography (hexanes/ethyl acetate 9/1).

6-Methoxy-2-naphthaldehyde[34]

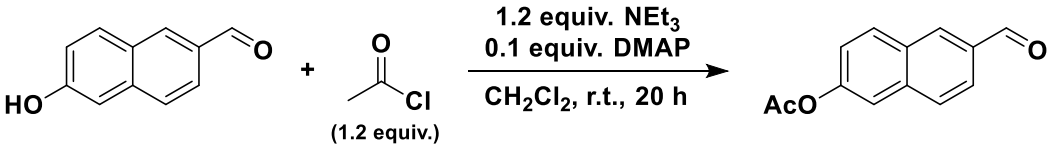


$C_{12}H_{10}O_2$, 186.21 g/mol

^{1}H-NMR (300 MHz, d_6-DMSO): δ_H [ppm] = 10.10 (d, *J* = 0.5 Hz, 1H), 8.26 (s, 1H), 7.91 (dd, *J* = 10.1, 8.7 Hz, 2H), 7.81 (d, J = 8.5 Hz, 1H), 7.26-7.17 (m, 2H), 7.22, 3.96 (s, 3H).

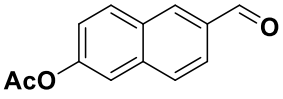
LR MS (EI, 70 eV, m/z): 186 $[M]^+$.

Preparation of 6-formyl-2-naphthyl acetate[35]



To a solution of 6-hydroxy-2-naphthaldehyde (5 mmol, 0.86 g) in CH_2Cl_2 (19 mL) was added triethylamine (6 mmol, 0.83 mL) and 4-dimethylaminopyridine (0.5 mmol, 56 mg). Then acetyl chloride (6 mmol, 0.43 mL) was added dropwise. The reaction mixture was stirred at room temperature for 20 hours and hydrolyzed by aqueous saturated solution of $NaHCO_3$. The layers were separated and the aqueous layer was extracted with diethylether (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (hexanes/ethyl acetate 4/1).

6-Formyl-2-naphthyl acetate



$C_{13}H_{10}O_3$, 214.22 g/mol

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 10.10 (s, 1H), 8.29 (s, 1H), 8.01–7.84 (m, 3H), 7.59 (d, *J* = 2.2 Hz, 1H), 7.30 (dd, *J* = 8.9, 2.3 Hz, 1H), 2.33 (s, 3H).

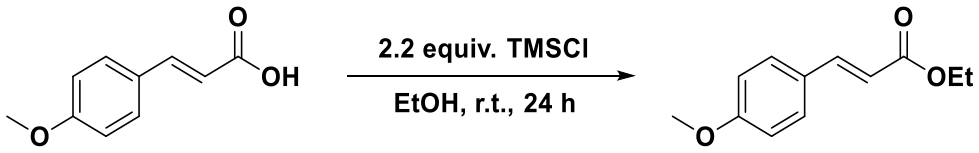
^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 192.1, 169.4, 150.8, 137.1, 134.2, 134.0, 131.1, 130.6, 128.9, 123.6, 122.5, 119.0, 21.3.

HR MS (CI, *m/z*): found 214.0627 (calculated: 214.0630)

FT-IR: 2980(w), 2930(w), 2880(w), 1702/s), 1607(m), 1508(m), 1460(w), 1386(m), 1280(s), 1226(m), 1179(m), 1179(m), 1109(s), 1034(m).

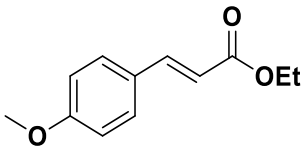
M.p.: 114-115 °C.

Preparation of ethyl 4-methoxycinnamate[36]



To a solution of 4-methoxycinnamic acid (26.6 mmol, 4.74 g) in ethanol (130 mL) was added trimethylsilyl chloride (59 mmol, 7.5 mL). The solution was stirred for 24 hours at room temperature. The product was concentrated under vacuum. A purification process was not necessary.

Ethyl 4-methoxy cinnamate[37]



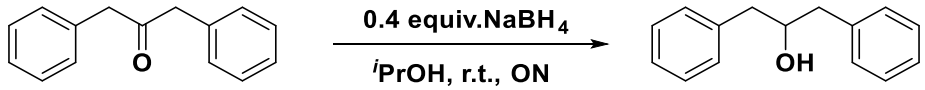
$C_{12}H_{14}O_3$, 206.24 g/mol

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 7.64 (d, *J* = 16.0 Hz, 1H), 7.50-7.44 (m, 2H), 6.94-6.87 (m, 2H), 6.31 (d, *J* = 16.0 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.83 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 167.4, 161.3, 144.3, 129.7 2, 127.2, 115.8, 114.3, 60.4, 55.38, 14.4.

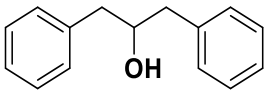
LR MS (EI, 70 eV, m/z): 206 $[M]^+$.

Synthesis of 1,3-diphenyl-2-propanol[29]



To a solution of 1,3-diphenylacetone (10 mmol, 2.10 g) in *iso*-propanol (12 mL) was added carefully $NaBH_4$ (4 mmol, .151 mg). The reaction mixture was stirred at room temperature overnight and hydrolyzed with water. The aqueous layer was separated and extracted with diethyl ether (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and after evaporation of the solvent the crude product was purified by column chromatography (hexanes/ethyl acetate 9/1).

1,3-Diphenyl-2-propanol[38]



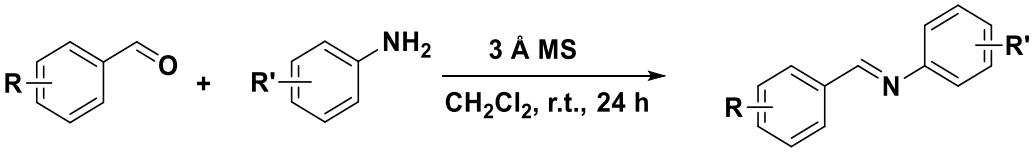
$C_{15}H_{16}O$, 212.29 g/mol

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H [ppm] = 7.43 (m, 4H), 7.33 (m, 6H), 4.11 (m, 1H), 2.88 (m, 4H), 1.97 (s, 1H).

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ_C [ppm] = 138.7, 129.6, 128.6, 126.6, 73.7, 43.5.

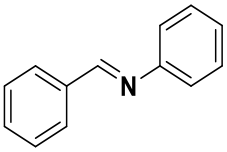
LR MS (EI, 70 eV, m/z): 212 $[M]^+$.

General procedure for the preparation of imines[39]



A modified procedure by Taguchi *et al.* was used: A dry 50 mL round bottom flask was charged with 3 Å MS (pre-activated by heating under vacuum), 40 mL of dry CH_2Cl_2 and equipped with a rubber septum and purged with nitrogen. Then, 10 mmol of the aniline and 10 mmol of the aldehyde were added via syringe and the reaction mixture stirred at room temperature for 24 hours. Then, the reaction mixture was filtered off and the solvent completely removed under reduced pressure. The residual aldehyde was removed by washing with an aqueous saturated $NaHSO_3$ solution, if necessary. The obtained solids were recrystallized from ethanol (ice bath or r.t.).

***N*-Benzylidene aniline**[40]



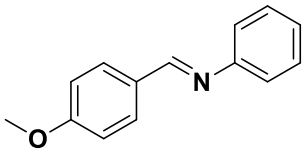
$C_{13}H_{11}N$, 181.23 g/mol

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 8.46 (s, 1H), 7.94-7.87 (m, 2H), 7.52-7.45 (m, 3H), 7.43-7.36 (m, 2H), 7.28-7.18 (m, 3H).

$^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 160.5, 152.1, 136.2, 131.4, 129.2, 128.8, 126.0, 120.9.

LR MS (EI, 70 eV, m/z): 181 $[M]^+$.

***N*-(4-Methoxybenzylidene) aniline**[41]



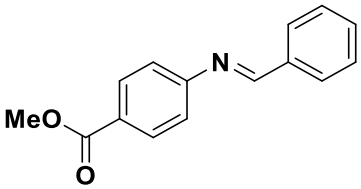
$C_{14}H_{13}NO$, 211.26 g/mol

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 8.38 (s, 1H), 7.87-7.84 (m, 2H), 7.41-7.36 (m, 2H), 7.23-7.18 (m, 3H), 6.99-6.97 (m, 2H), 3.87 (s, 3H).

$^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 162.3, 159.8, 152.4, 130.5, 129.3, 129.1, 125.6, 120.9, 114.2, 55.5

LR MS (EI, 70 eV, m/z): 211 $[M]^+$.

Methyl 4-(benzylidene amino) benzoate[42]



$C_{15}H_{13}NO_2$, 239.27 g/mol

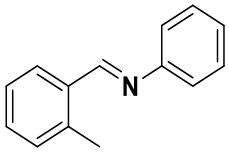
^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 8.44 (s, 1H), 8.08 (m, 2H), 7.9 (m, 2H), 7.49 (m, 3H), 7.2 (m, 2H), 3.93 (s, 3H).

$^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 161.7, 156.3, 135.8, 130.9, 129.1, 128.9, 127.3, 120.7, 52.1.

LR MS (EI, 70 eV, m/z): 239 $[M]^+$.

M.p.: 106-107 °C.

***N*-(2-Methylbenzylidene) aniline**



$C_{14}H_{13}N$, 195.26 g/mol

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 8.73 (s, 1H), 8.08-8.06(m, 1H), 7.41-7.18 (m, 8H), 2.57 (s, 3H).

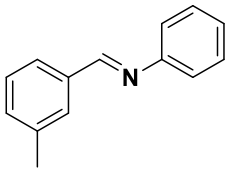
$^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 159.2, 152.8, 138.7, 134.2, 131.1, 129.2, 127.9, 126.4, 125.9, 121.0, 19.5.

LR MS (EI, 70 eV, *m/z*): 195 $[M]^+$.

HR MS (CI, *m/z*): found 195.1052 (calculated: 195.1048)

FT-IR: 3063(w), 3024(w), 2921(w), 1622(s), 1588(s), 1490(m), 1453(w), 1372(w), 1286(w), 1201(m), 972(w), 909(w), 873(w), 761(s), 714(s), 692(s), 547(m).

***N*-(3-Methylbenzylidene) aniline**



$C_{14}H_{13}N$, 195.26 g/mol

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 8.34 (s, 1H), 7.71 (bs, 1H), 7.9 (m, 2H), 7.62-7.60 (d, *J* = 7.79 Hz, 1H), 7.36-7.13 (m, 7H), 2.36 (s, 3H)

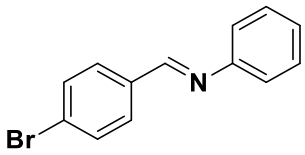
$^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 160.7, 152.3, 138.6, 136.3, 132.4, 129.3, 129.1, 128.8, 126.6, 121.0, 21.3.

LR MS (EI, 70 eV, *m/z*): 195 $[M^+]$

HR MS (CI, *m/z*): found 195.1050 (calculated: 195.1048)

FT-IR: 3058(w), 3023(w), 2863(w), 1626(s), 1584(s), 1486(s), 1450(w), 1367(w), 1281(w), 1205(m), 974(w), 904(w), 857(w), 785(m), 693(s), 635(w), 544(w).

_N_-Benzylidene-4-bromoaniline[43]



$C_{13}H_{10}BrN$, 260.13 g/mol

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 8.43 (s, 1H), 7.91-7.88 (m, 2H), 7.52-7.44 (m, 5H), 7.12-7.08 (m, 2H).

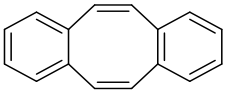
$^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 160.8, 151.0, 135.9, 132.2, 131.7, 128.9, 128.9, 122.6, 119.3.

LR MS (EI, 70 eV, m/z): 260 $[M]^+$.

M.p.: 63-64 °C.

Preparation of dibenzo[*a*,*e*]cyclooctatraene (dct)[26]

dct was synthesized in a 3-step synthesis according to a recent literature report.[26]



$C_{16}H_{12}$, 204.27 g/mol

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 7.19–7.13 (m, 4H), 7.10–7.02 (m, 4H), 6.76 (s, 4H).

$^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 137.1, 133.3, 129.1, 126.8.

LR MS (EI, 70 eV, m/z): 204 $[M]^+$.

4.6.2 Hydrogenation Reactions

General procedure for the hydrogenation of styrenes

In an argon-filled glovebox, a dry 5 mL vial with a screw cap and PTFE septum was charged with a magnetic stir bar and a solution of complex **1** (0.005 mmol, 3.2 mg) or of complex **2** (0.005 mmol, 4.3 mg) in 2 mL toluene. Then, 0.5 mmol of the corresponding styrene were added. The vial was placed into a high pressure reactor (*Parr Instr.*) and the septum punctured with a short needle (*Braun*). The reactor was sealed, discharged from the glovebox, placed on a magnetic stirrer plate, and purged with hydrogen. After 3 hours at room temperature under an atmosphere of hydrogen

(2 bar), the pressure was released, the vial removed, and the reaction hydrolyzed with saturated aqueous $NaHCO_3$-solution (1 mL). The mixture was extracted with diethyl ether and the organic phases were dried over Na_2SO_4. For quantitative GC-FID analysis, *n*-pentadecane was added as internal standard. For preparative work-up, the solvents were removed in vacuum and the residue was flash-chromatographed (SiO_2, pentane/ethyl acetate).

Hg-poisoning experiments

A comparative sample w/o mercury was prepared and hydrogenated in a parallel run. In an argon-filled glovebox a dry 5 mL vial with a screw cap and PTFE septum was charged with a magnetic stir bar and a solution of complex **1** (0.005 mmol, 3.2 mg) in 2 mL toluene. Then, styrene (0.5 mmol, 57 µL) and mercury (1.50 mmol, 300 mg) was added. The vial was placed into a high-pressure reactor (*Parr Instr.)* and the septum punctured with a short needle (*Braun*). The reactor was sealed, discharged from the glovebox, placed on a magnetic stirrer plate, and purged with hydrogen. After 3 hours at room temperature under an atmosphere of hydrogen (2 bar), the pressure was released, the vial removed, and the reaction hydrolyzed with saturated aqueous $NaHCO_3$-solution (1 mL). The mixture was extracted with diethyl ether and the organic phases were dried over Na_2SO_4. For quantitative GC-FID analysis, *n*-pentadecane was added as internal standard.

A similar experiment was performed where the high-pressure reactor was depressurized, transferred into a glovebox (argon), and 150 mol% Hg were added. Quantitative GC-FID analysis just before Hg addition indicated conversion of styrene to be ~25%. The reactor was sealed, eliminated from the glovebox and pressurized again with 2 bar H_2.

Hg poisoning and dct addition at 20%/25% conversion:

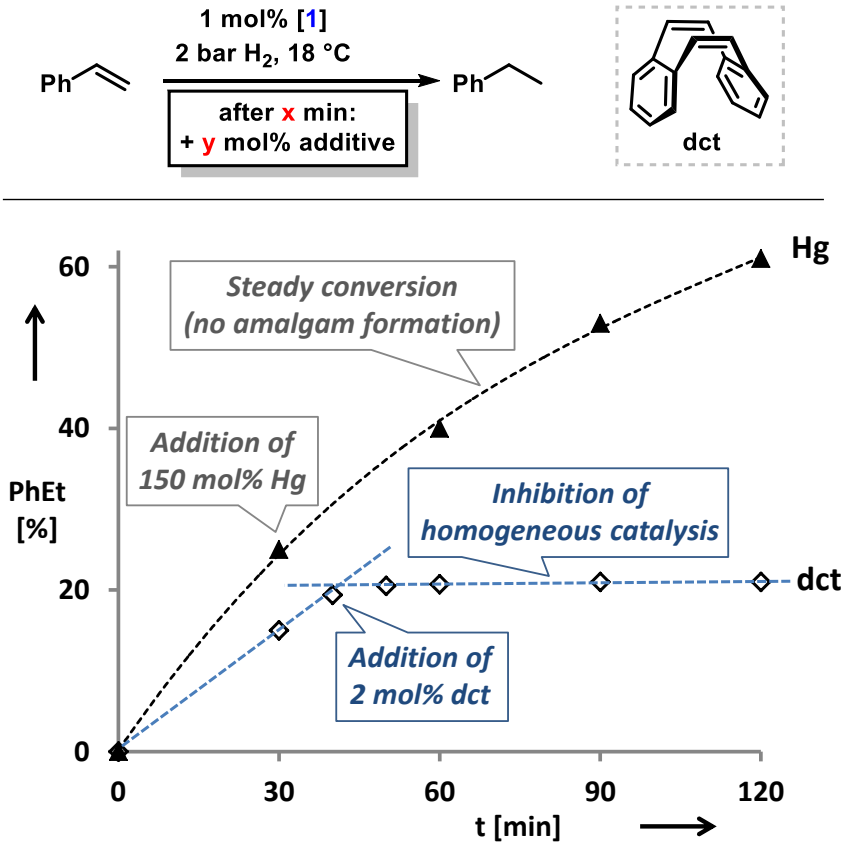


Figure S1: Poisoning experiments with mercury (Hg) and dibenzo[*a*,*e*]-cyclooctatraene (dct). Standard conditions (2 bar H_2, 18 °C, 1 mol% catalyst **1**).

Consecutive hydrogenation cycles with styrene

In an argon-filled glovebox, a dry 5 mL vial with a screw cap and PTFE septum was charged with a magnetic stir bar and a solution of complex **1** (0.005 mmol, 3.2 mg) in 2 mL toluene. Then, styrene (0.5 mmol, 57 µL) was added. The reaction vessel was placed into a 100 mL high pressure reactor (*Parr*), the vial was punctured with a short needle (*Braun*), and the reactor sealed. The reactor was purged three times with hydrogen and stirred with an external magnetic stirrer at room temperature under 2 bar of H_2 for 1 h. After depressurizing the reactor slowly, another portion of styrene (0.5 mmol) was added to the reaction mixture (in the glovebox) and the hydrogenation repeated following the same procedure as for the first hydrogenation. After five hydrogenation cycles, the reaction was hydrolyzed with saturated aqueous $NaHCO_3$ (approx. 1 mL). For quantitative GC-FID analysis *n*-pentadecane was added as internal standard.

Reaction progress analysis by quantitative GC-FID

In an argon-filled glovebox, a 50 mL glass reactor (*Büchi*) was charged with a magnetic stir bar and a solution of 32 mg (0.05 mmol) of complex **1** in 20 mL toluene. Then styrene (5.0 mmol, 570 µL) was added. The reactor was sealed, purged three times with hydrogen and stirred with an external magnetic stirrer at room temperature under 2 bar. After specified periods of time the reactor was slowly depressurized and an aliquot was taken (0.5 mL). The reactor was sealed again, and the hydrogenation was repeated following the same procedure as for the first hydrogenation. The aliquot was hydrolyzed with a saturated aqueous $NaHCO_3$-solution (1 mL). The mixture was extracted with diethyl ether and the organic phases were dried over Na_2SO_4. For quantitative GC-FID analysis, *n*-pentadecane was added as internal standard.

Reaction progress analysis of styrene hydrogenations and of Hg poisoning experiments were performed using a 25 mL *Schlenk* tube with a rubber septum through which addition/sampling was performed with gastight syringes under a stream of argon/hydrogen..

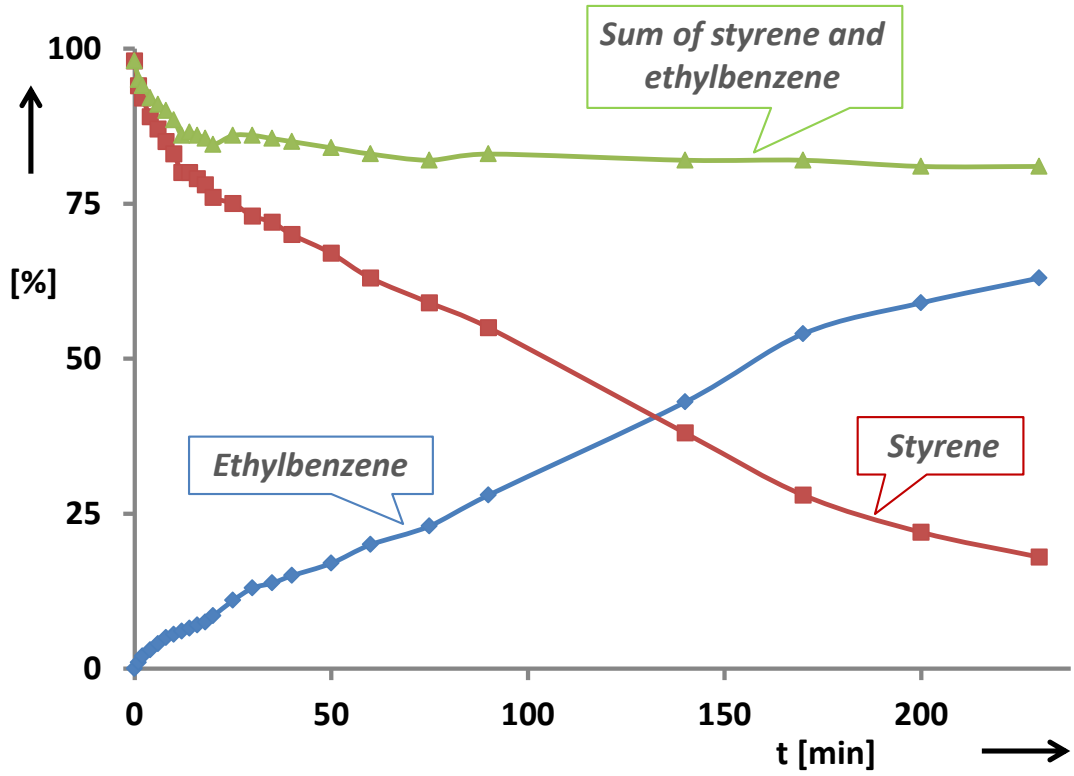


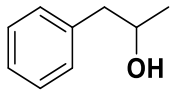
Figure S2: Kinetic curve of standard reaction of styrene to ethylbenzene shows no induction period nor sigmoidal behavior. Conditions: 1 mol% [**1**], 18 °C, 1.5 bar H_2. Reaction was performed in a 25 mL *Schlenk* tube capped with a rubber septum. Samples were taken after x min, quenched with $NaHCO_3/H_2O$ and quantitatively analyzed by GC-FID (vs. internal reference *n*-pentadecane). The loss of material (sum of styrene and ethylbenzene) of aprox. 20% over 4 hours is a consequence of the multiple sample taking under a strong stream of argon/hydrogen and the lower boiling points of styrene (145 °C) and ethylbenzene (136 °C; cf. *n*-pentadecane, 270 °C).

General procedure for the hydrogenation of ketones and imines

In an argon-filled glovebox, a dry 5 mL vial with a screw cap and PTFE septum was charged with a magnetic stir bar and a solution of complex **1** (0.025 mmol, 16 mg) in 2 mL toluene. Then, 0.5 mmol of the corresponding imine or ketone were added. The vial was placed into a high pressure reactor (*Parr Instr.*) and the septum punctured with a short needle (Braun). The reactor was sealed, discharged from the glovebox and placed on a magnetic stirrer plate The reactor was purged three times with hydrogen, pressurized with 10 bar H_2, heated to 60 °C and stirred at this temperature for 24 h (pressure at 60 °C, 10.7 bar). Stirring was carried out with an external magnetic stirrer. Then, the reactor was slowly depressurized, the vial removed and the reaction quenched with saturated aqueous $NaHCO_3$-solution (1 mL). The organic layer was separated and the aqueous extracted with *n*-pentane. The solvent was

removed and hexamethyldisiloxane (11.8 µL) was added as internal standard for quantitative ^{1}H-NMR analysis.

1-Phenylpropan-2-ol[44]



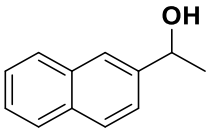
$C_9H_{12}O$, 139.19 g/mol

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 7.33-7.19 (m, 4H), 4.05-3.95 (m, 1H), 2.80-2.64 (m, 2H), 1.70 (m, 1H), 1.23 (d, *J* = 6.14 Hz, 3H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 138.6, 129.4, 128.6, 126.5, 68.9, 45.8, 22.8.

LR MS (EI, 70 eV, m/z): 121 $[M\text{-}H_2O]^+$.

1-(Naphthalen-2-yl)ethanol[45]



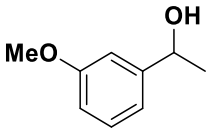
$C_{12}H_{12}O$, 172.22 g/mol

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 7.85-7.79 (m, 4H), 7.52-7.42 (m, 3H), 5.10-5.03 (q, 1H), 1.93 (s, 1H), 1.58 (d, *J* = 6.4 Hz, 3H)

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 143.2, 133.3, 132.9, 128.4, 128. , 127.7, 126.2, 125.8, 123.8, 70.6, 25.2

LR MS (EI, 70 eV, m/z): 172 $[M]^+$.

1-(3-Methoxyphenyl)ethanol[46]



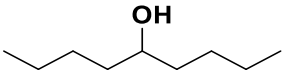
$C_9H_{12}O_2$, 152.19 g/mol

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 7.28-7.23 (t, *J* = 8.1 Hz, 1H), 6.95-6.92 (m, 2H), 6.83-6.79 (m, 2H), 4.91-4.82 (q, *J* = 6.3 Hz, 1H), 3.81 (s, 3H), 1.92 (bs, 1H), 1.48 (d, *J* = 6.6 Hz, 3H)

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 159.8, 147.6, 117.7, 112.9, 110.9, 70.4, 55.3, 25.2

LR MS (EI, 70 eV, m/z): 152 $[M]^+$.

Nonan-5-ol[47]



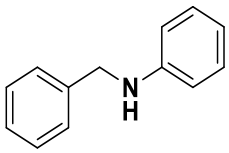
$C_9H_{20}O$, 144.25 g/mol

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 3.58 (m, 1H), 1.50-1.26 (m, 13H), 0.91 (m, 6H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 72.0, 37.2, 27.9, 22.8, 14.1.

LR MS (EI, 70 eV, m/z): 126 $[M\text{-}H_2O]^+$.

***N*-Benzylaniline**[48]



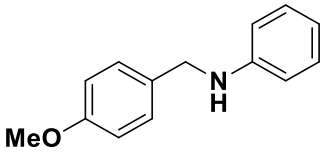
$C_{13}H_{13}N$, 183.25 g/mol

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 7.37-7.27 (m, 5H), 6.73-6-69 (m, 1H), 6.63-6.60 (m, 2H), 4.31 (s, 2H), 4.00 (bs, 1H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 148.2, 139.5, 129.3, 128.7, 127.6, 127.3, 117.6, 112. 9, 48.4

LR MS (EI, 70 eV, m/z): 183 $[M]^+$.

***N*-(4-Methoxybenzyl) aniline**[48]



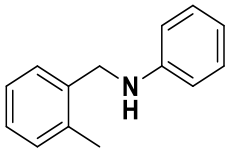
$C_{14}H_{15}NO$, 213.28 g/mol

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 7.34-7.30 (m, 2H), 7.25-7.19 (m, 2H), 6.94-6.90 (m, 2H), 6.80-6.74 (m, 1H), 6.69-6.66 (m, 2H), 4.28 (s, 2H), 3.98 (bs, 1H), 3.83 (s, 3H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 158.9, 148.3, 131.5, 129.3, 128.9, 117.5, 114.1, 112.9, 55.3, 47.8.

LR MS (EI, 70 eV, m/z): 213 $[M]^+$.

***N*-(2-Methylbenzyl) aniline**[48]



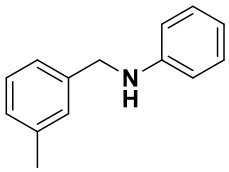
$C_{14}H_{15}N$, 197.28 g/mol

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 7.33-7.30 (m, 1H), 7.20-7.15 (m, 5H), 6.73-6.68 (m, 1H), 6.63-6.60 (m, 2H), 4.25 (s, 2H), 3.80 (bs, 1H), 2.36 (s, 3H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 148.3, 137.0, 136.3, 130.6, 129.3, 128.2, 127.4, 126.1, 117.4, 112.6, 46.3, 18.9,

LR MS (EI, 70 eV, m/z): 197 $[M]^+$.

_N_-(3-Methylbenzyl) aniline[49]



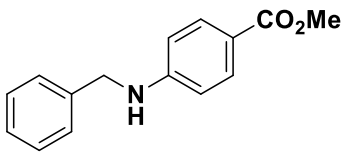
$C_{14}H_{15}N$, 197.28 g/mol

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 7.23-7.08 (m, 6H), 6.74-6.69 (m, 1H), 6.65-6.62 (m, 2H), 4.27 (s, 2H), 4.08 (bs, 1H), 2.31 (s, 3H)

$^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C [ppm] = 148.2, 139.3, 138.4, 129.3, 128.6, 128.4, 128.1, 124.7, 117.6, 113.0, 48.5, 21.5.

LR MS (EI, 70 eV, m/z): 197 $[M]^+$.

Methyl 4-(benzylamino) benzoate[24]



$C_{15}H_{15}NO_2$, 241.29 g/mol

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 7.88-7.84 (m, 2H), 7.36-7.27 (m, 5H), 6.62-6.57 (m, 2H), 4.57 (bs, 1H), 4.39 (s, 2H), 3.84 (s, 3H).

LR MS (EI, 70 eV, m/z): 241 $[M]^+$

NMR experiments

Reaction of $[K(dme)_2\{Co(C_{14}H_{10})_2\}]$ (**1**) with styrene and dihydrogen: Complex **1** (0.032 mmol, 20.4 mg) was dissolved in THF-d_8 in a *J. Young* NMR tube. The ^{1}H-NMR spectrum was recorded at room temperature (Figure **S3a**). Then styrene (0.65 mmol, 68 mg, 20 equiv.) was added to this solution. A ^{1}H NMR spectrum (Figure **S3b**) was recorded after a reaction time of 3 hours which shows the formation of free anthracene. The NMR tube was subsequently cooled carefully in liquid nitrogen and the argon was replaced by H_2. The ^{1}H-NMR spectrum (Figure

S3c) was recorded at room temperature after 3 hours, showing the formation of ethylbenzene.

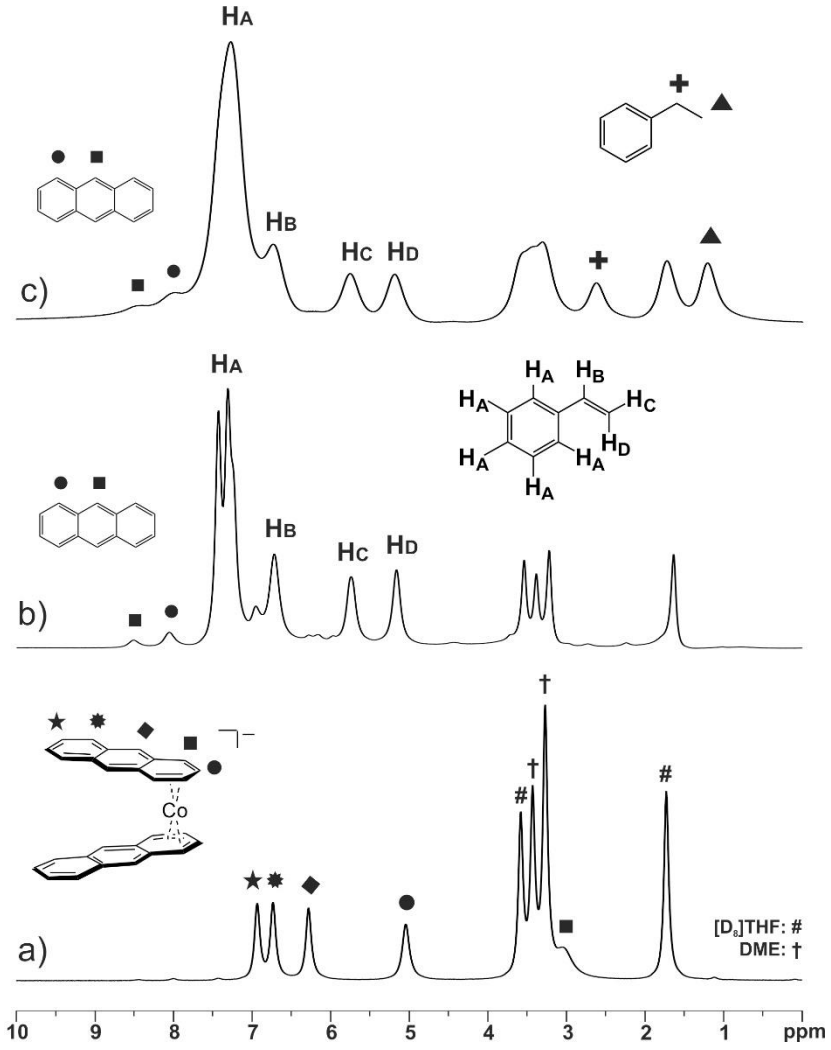


Figure S3: ^{1}H-NMR monitoring (400.13 MHz, 300 K, THF-d_8) of the reaction of **1** with styrene and H_2; a) ^{1}H-NMR spectrum of pure **1**; b) mixture of **1** and 20 equiv. styrene after 3 hours, the formation free anthracene is apparent from the signals at 8.00 and 8.44 ppm, c) mixture **1** and 20 equiv. styrene after storage under an H_2 atmosphere (4 bar) for 3 hours, the signals of ethylbenzene appear at 1.21 and 2.62 ppm.

Reaction of $[K(dme)_2\{Co(C_{14}H_{10})_2\}]$ (**1**) with 1,1-diphenylethylene: Complex **1** (0.016 mmol, 10 mg,) was dissolved in THF-d_8 in a *J. Young* NMR tube. A ^{1}H-NMR spectrum (Figure S4a) was measured at room temperature. 1,1-diphenylethylene (0.5 mmol, 90 mg, 31 equiv.) was then added. The ^{1}H-NMR spectrum (Figure **S4b**) recorded after 30 minutes showed no signals for free anthracene. An analogous experiment was carried out using **1** (0.016 mmol, 10 mg,) and 4.1 equiv.

1,1-diphenylethylene (0.066 mmol,12 mg). The ^{1}H-NMR spectrum of this mixture (Figure **S4c**) also did not the show the formation of free anthracene.

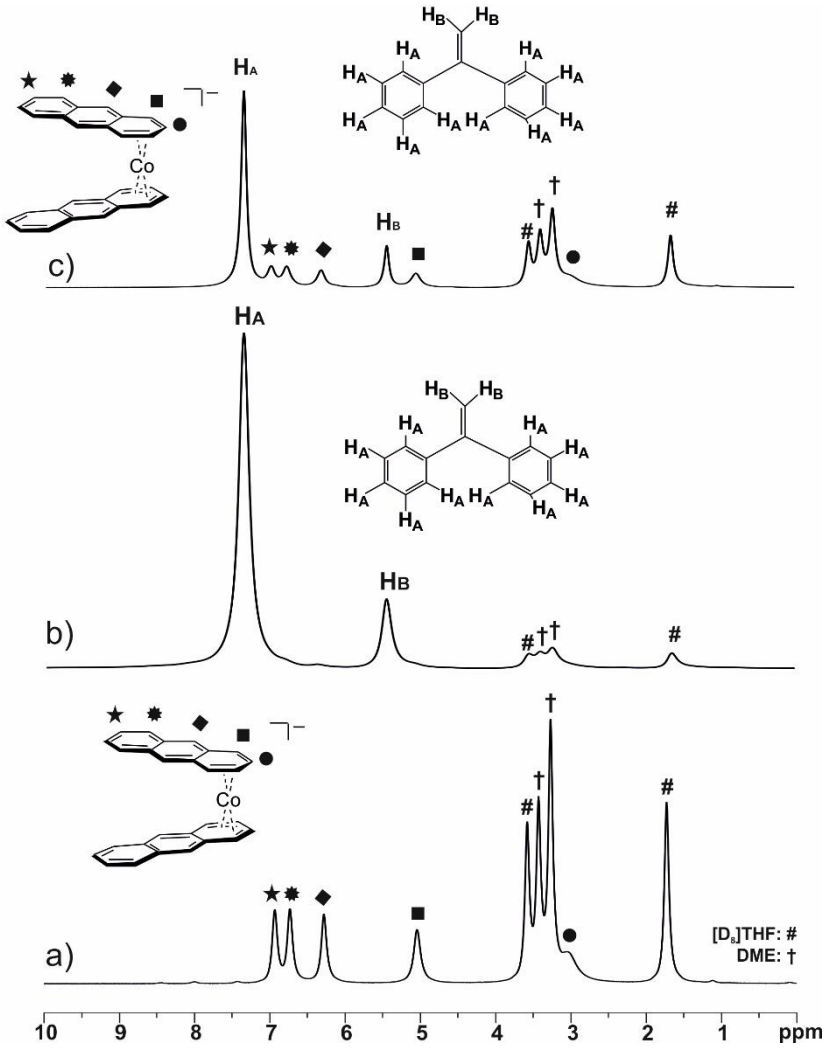


Figure S4: ^{1}H-NMR monitoring (400.13 MHz, 300 K, THF-d_8) of the reaction of **1** with 1,1-diphenylethene; a) ^{1}H-NMR spectrum pure **1**; b) mixture of **1** and 31 equiv. 1,1-diphenylethene after 30 minutes, no signals for free anthracene are apparent, c) mixture **1** and 4 equiv. 1,1-diphenylethene after 30 minutes, again, no signals for free anthracene are apparent.

Reaction of $[K(dme)_2\{Co(C_{14}H_{10})_2\}]$ (**1**) with 1,3-diphenylacetone: Complex **1** (0.025 mmol, 16 mg,) was dissolved in THF-d_8 in a *J. Young* NMR tube, and the ^{1}H-NMR spectrum (Figure **S5a**) was recorded at room temperature. 1,3-Diphenylacetone (0.5 mmol, 105 mg, 20 equiv.) was then added to this solution. The ^{1}H-NMR spectrum (Figure **S5b**) recorded after 30 minutes showed no signals for free anthracene. An analogous experiment (Figure **S5c**) was carried out using **1** (0.020 mmol, 13 g) and 5 equiv. 1,3-diphenylacetone (0.1 mmol, 21 mg).

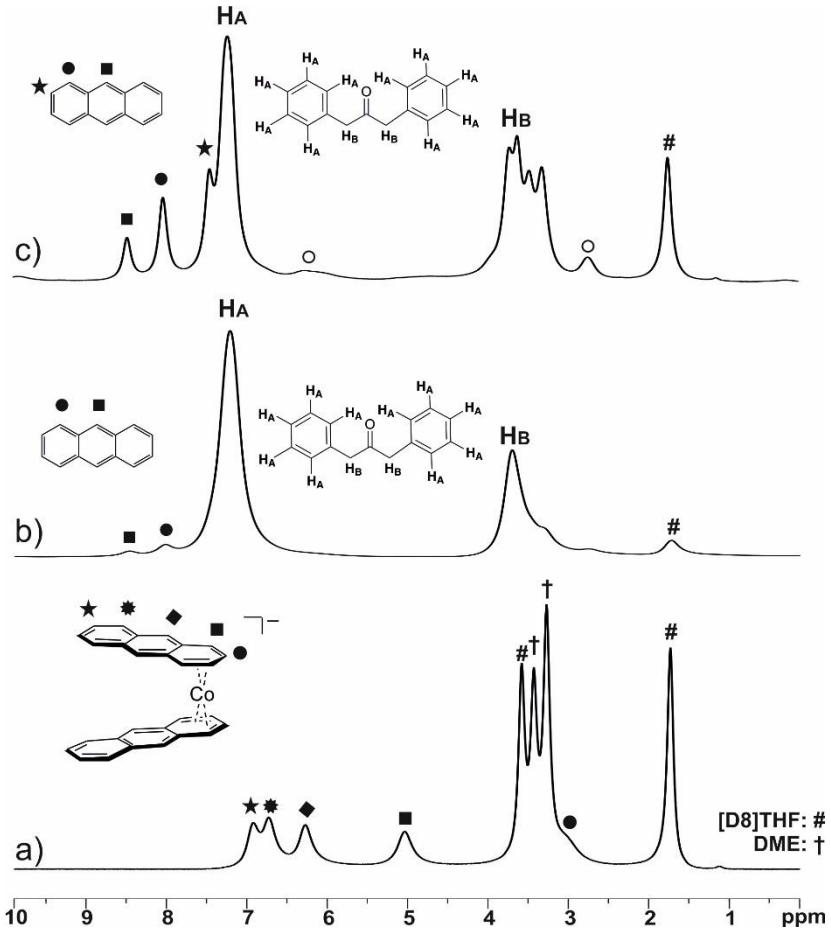
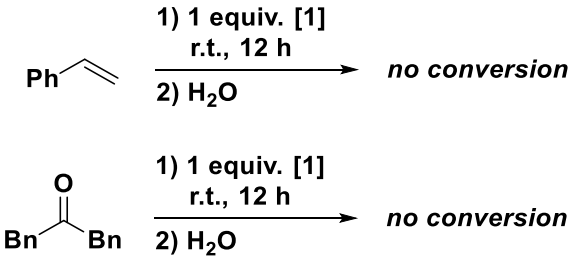


Figure S5: ^{1}H-NMR monitoring (400.13 MHz, 300 K, THF-d_8) of the reaction of **1** with diphenylacetone; a) ^{1}H-NMR spectrum pure **1**; b) mixture of **1** and 20 equiv. diphenylacetone after 30 minutes, the formation free anthracene is apparent, c) mixture **1** and 5 equiv. diphenylacetone after 30 minutes, again, signals for free anthracene are apparent, signals for other, unidentified species formed in this reaction are marked with an open circle.

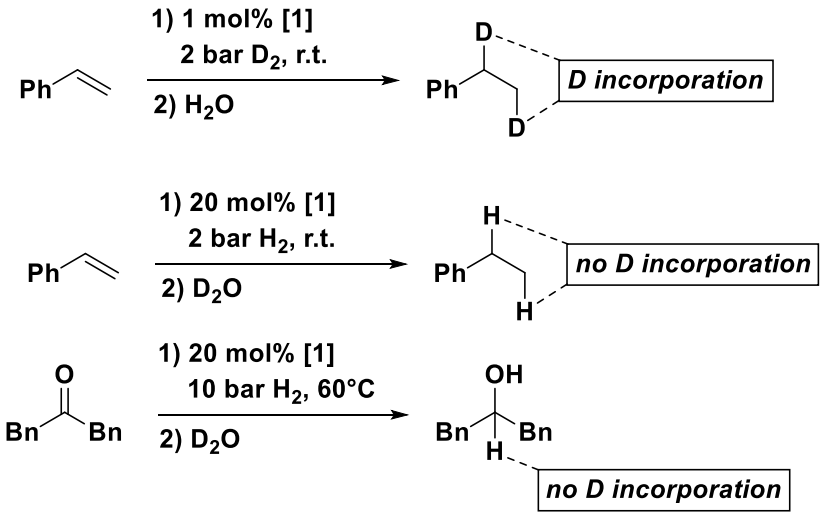
4.6.3 Further mechanistic studies

(Note: if no further details given, standard conditions for styrenes/ketones apply!)

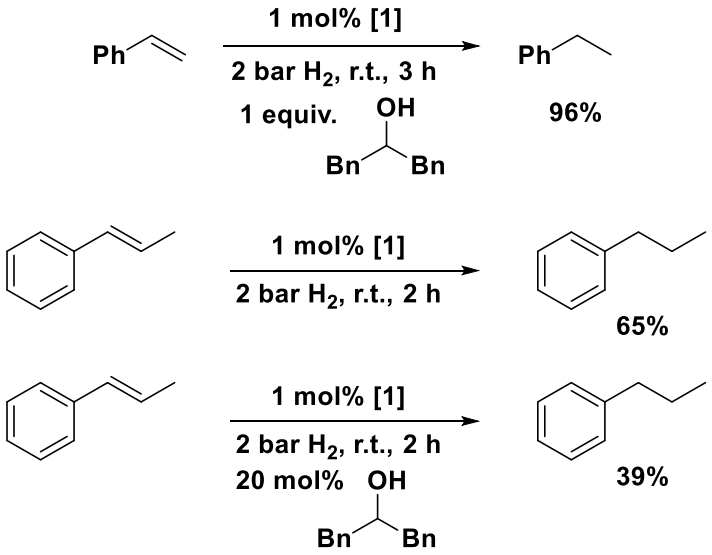
Low nucleophilicity of cobaltate 1: No direct reaction with styrene or dibenzyl ketone:



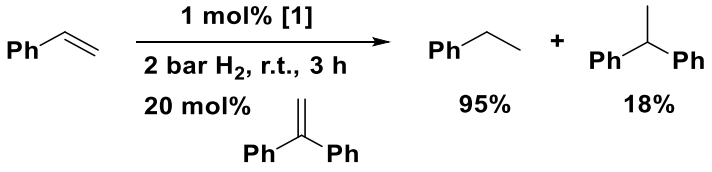
Deuteration experiments with D_2O and D_2:



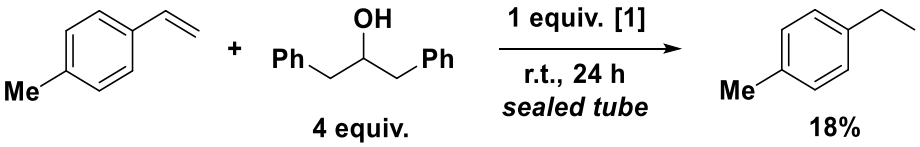
Alcohol-modified catalyst of higher oxidation state is catalytically competent, but less active than cobaltate(-I):



Reaction in the presence of radical probe:



Transfer hydrogenation between 1,3-diphenyl-2-propanol and 4-methylstyrene:



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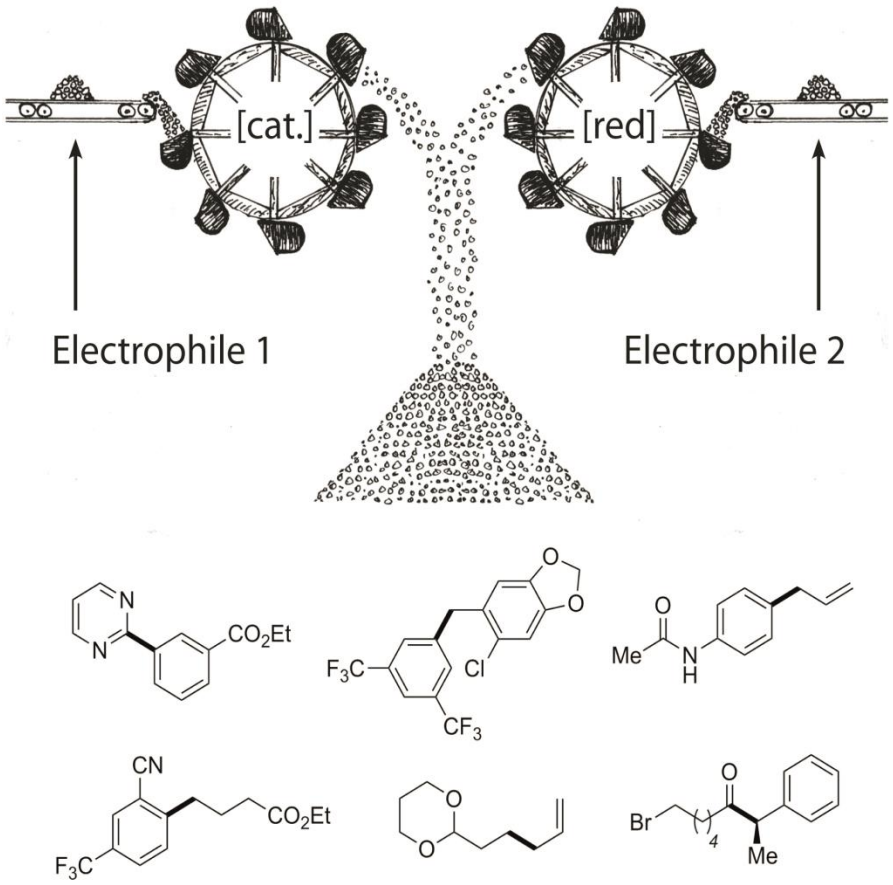
5 Reductive Cross-Coupling Reactions between Two Electrophiles



Abstract: Reductive cross-electrophile coupling reactions have recently been developed to a versatile and sustainable synthetic tool for selective C-C bond formation. The employment of cheap and abundant electrophiles avoids the pre-formation and handling of organometallic reagents. *In situ* reductive coupling is effected in the presence of a transition metal catalyst (Ni, Co, Pd, Fe) and a suitable metallic reductant (Mn, Zn, Mg). This concept article assesses the current state of the art and summarizes recent protocols with various combinations of alkyl, alkenyl, allyl, and aryl reagents and highlights key mechanistic studies. [I,II]

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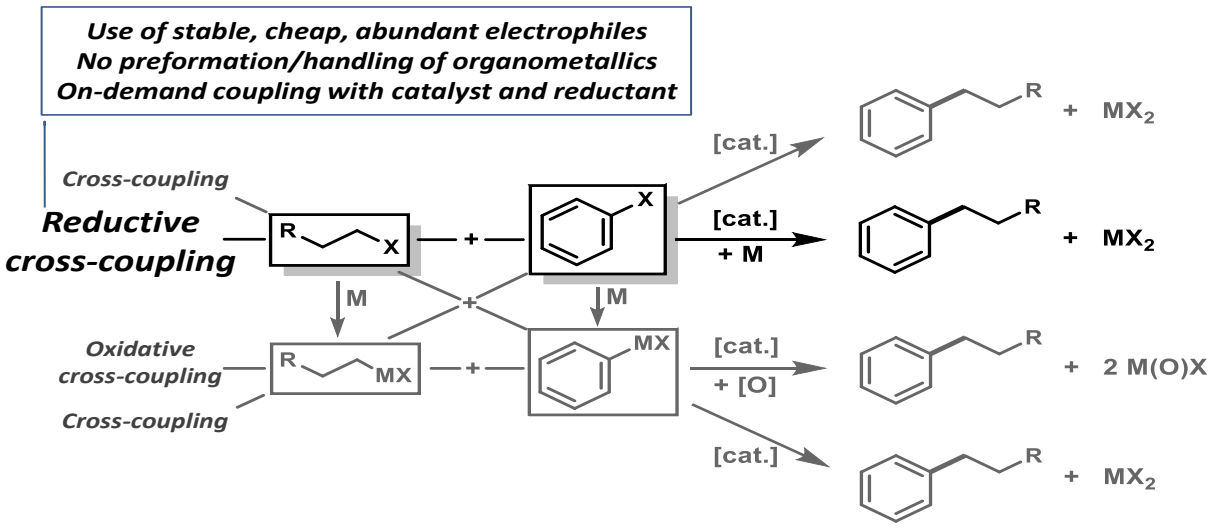
[II] The own workshare of this article is about 25%

5.1 Introduction

The construction of carbon-carbon linkages is of utmost importance for the generation of structural complexity and diversity in organic molecules. The advent of transition-metal catalysis in the last century has shaped the art of C-C bond fusion like no other synthetic tool in the past decades. Today, cross-coupling protocols find numerous applications in the manufacture of fine chemicals, pharmaceuticals, agrochemicals, and materials, and the synthesis of versatile organic building blocks and complex natural products.[1] Their pivotal relevance became recently manifest in the bestowal of the 2010 Chemistry Nobel prizes.[2] The general reactivity pattern of cross-coupling reactions equates with a formal nucleophilic substitution of an organic electrophile bearing a suitable leaving group (mostly halides, sulfonates, carboxylates) with an organometallic reagents in the coordination sphere of a transition metal catalyst. Most reactions proceed by a cascade of organometallic elemental steps (oxidative addition, transmetalation, reductive elimination), or single electron transfer (SET) processes.[3] Significant research efforts are currently being directed at the development of sustainable protocols with cheap and benign catalyst systems that allow the activation of strong and abundant C-X bonds within the electrophile (X = Cl, OC(O)R, OR instead of Br, I, OTf) with weakly nucleophilic organometallics (e.g. Zn, B, Si) under mild conditions.[4] A conceptually different approach is the reductive cross-electrophile coupling reaction between two electrophilic reagents which avoids the individual preparation and intricate handling of hazardous organometallics (Scheme 5.1).



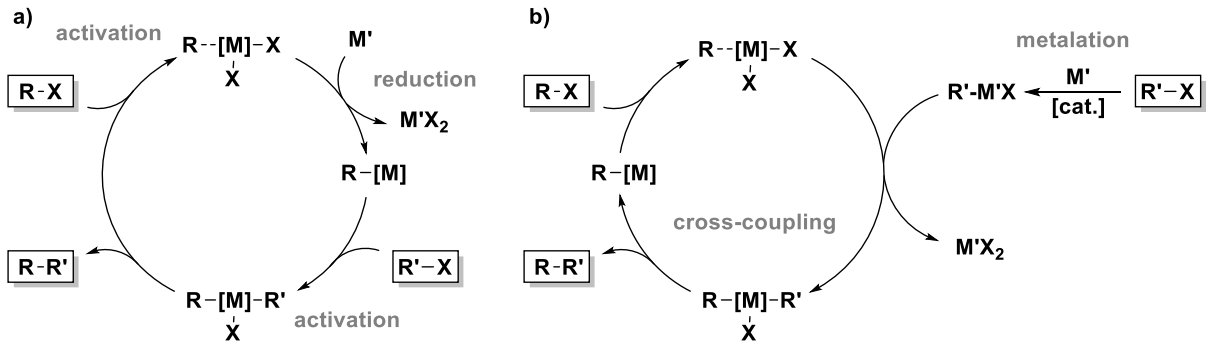
Scheme 5.1: Modes of C(sp^2)-C(sp^3)-cross-coupling reactions.

The foremost advantage of this strategy lies within the wide availability of diverse electrophiles, which are inherently more stable than their organometallic counterparts derived by (trans)metalation under ambient aerobic and aqueous conditions.[5] Most electrophilic coupling partners (e.g. organohalides, sulfonates, carboxylates) can be easily stored and handled, even under ambient aerobic and moist conditions and on larger scales.

Their Umpolung into organometallics mostly affords highly nucleophilic/basic species, which often react spontaneously with air and moisture and require stringent safety arrangements.[6]

The use of pre-formed organometallic reagents is even more inefficient when considering that the laborious preparation and handling of organometallic reagents often takes more effort and time than the actual cross-coupling operation. In the past years, several protocols of oxidative cross-coupling reactions between two organometallic reagents have been reported. Such strategies exhibit rather low redox efficiency as they involve up to three Umpolung steps for which two equivalents of metal-based reductants (to generate the organometallic nucleophiles from the two electrophiles) and one equivalent of an oxidant (for the oxidative coupling) are required.[7] On the other hand, reductive cross-coupling reactions between two stable and available electrophiles that utilize an *in situ* formed reductant exhibit high operational simplicity, sustainability, and cost-efficiency. The use of the same reductant for many combinations of electrophiles makes such methods an ideal platform for rapid library synthesis and large-scale preparations. In general, the reductant can play two mechanistic roles (Scheme 5.2): It either triggers the (slow) formation of one nucleophilic reactant under the coupling conditions (Scheme 5.2b). This “just in time” delivery often assures a low, steady-state concentration of the organometallic species if the following cross-coupling step is fast. High selectivities can be reached if the electronics and/or sterics of the electrophilic reagents differ sufficiently. Alternatively, the (mostly metallic) reductant can reduce the oxidized catalyst after the initial reductive activation of one electrophile (i.e. oxidative addition or SET oxidation at catalyst metal) to effect another reductive C-X bond cleavage (Scheme 5.2a). Both mechanistic scenarios can involve covalently bound substrate-catalyst complexes or proceed through SET processes via radical species. However, high chemoselectivity of the reduction steps in the presence of several electrophiles (i.e. oxidants: electrophile 1, electrophile 2, metal salts, catalyst species) is key to the

success of a cross-coupling event. Potential side reactions include reductive homo-coupling, hydrodefunctionalization, and catalyst deactivation. The reaction selectivity is mostly assured by the subtle fine-tuning of reductant/catalyst combinations and the employment of electrophiles with significantly different redox potentials and/or sterical properties.



Scheme 5.2: General mechanistic scenarios of *in situ* reductive cross-couplings.

Table 5.1 lists selected standard redox potentials of organic halides and metal species which are commonly employed in direct cross-coupling reactions.[8]

Table 5.1: Redox potentials of selected organohalide and metal couples.[8]

Ox/Red couple	*E* vs. SCE [V]
Ph-Cl / $Ph^{\bullet}$ + Cl^{-}	-2.39
Ph-Br / $Ph^{\bullet}$ + Br^{-}	-2.07
Ph-I / $Ph^{\bullet}$ + I^{-}	-1.47
CH_3CH_2-Cl / $CH_3CH_2^{\bullet}$ + Cl^{-}	-1.13
CH_3CH_2-Br / $CH_3CH_2^{\bullet}$ + Br^{-}	-0.88
CH_3CH_2-I/$CH_3CH_2^{\bullet}$ + I^{-}	-0.80
$PhCH_2$-Cl / $PhCH_2^{\bullet}$ + Cl^{-}	-0.67
Zn^{2+} / Zn	-1.02
$[Ni(bpy)_3]^{2+}$ / $[Ni(bpy)_3]^{+}$	-1.24
Mn^{2+} / Mn	-1.44
Mg^{2+} / Mg	-2.62

Metallic zinc and manganese are often used as stoichiometric reductants, with the latter exhibiting the higher reductive power. Organochlorides have a lower potential

and therefore are less easily reduced than the corresponding bromides and iodides. Benzylic halides undergo rather facile reduction due to the mesomeric stabilization of the resultant radical species. It is important to note that standard redox potentials refer to (electrochemical) one-electron reductions which by no means mirror the individual conditions and mechanistic course of cross-coupling reactions. However, a comparison of redox potentials might allow a rough estimation of the thermodynamic feasibility of redox-triggered coupling reactions in many cases.

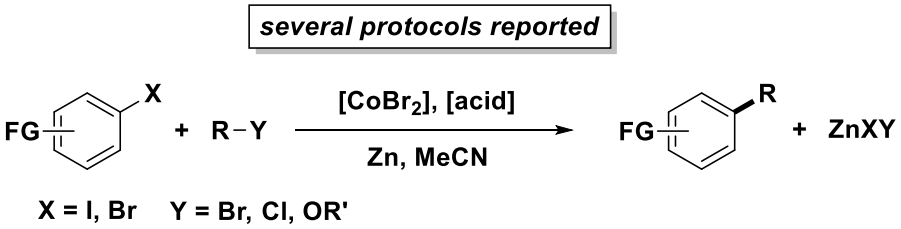
Over the past decade, reductive cross-coupling reactions have been developed to a versatile and operationally simple synthetic tool for selective C-C bond formations. Various combinations of alkyl, alkenyl, allyl, and aryl reagents bearing diverse leaving groups have been successfully employed. Despite the presence of metallic reductants, many reductive cross-coupling protocols achieve high chemoselectivity and show good tolerance of capricious keto, ester, nitrile, halide, and nitro groups. This Concept article is intended to provide a timely review of major developments in the area of C-C bond forming cross-coupling reactions between two electrophiles under reductive conditions. The article is categorized by the nature of the metal species involved (catalyst, reductant). For reasons of clarity, the newly formed C-C bond is sketched **bold**. Conceptionally different methods of reductive coupling reactions (e.g., dimerizations, electrochemical reactions, alkyne/alkene additions) are beyond the scope of this treatise.

5.2 Cobalt Catalysis

Cobalt has a rather low natural abundance, but its direct exploitation as by-product from the mining of copper and nickel minerals makes cobalt a relatively cheap transition metal. Cobalt was one of the first transition metals to be used in catalytic reactions on large scales (Roelen's hydroformylation from 1938).[9] The facile accessibility of the oxidation states 0, +1, +2, and +3 is central to the use as effective cross-coupling catalyst.[10] Stable water-free cobalt(II) halides are often employed; in situ reduction provides the catalytically active species (mostly Co^0 and Co^I). The majority of in situ reductive cross-coupling reactions were reported with cobalt catalysts in combination with zinc or manganese as stoichiometric reductants.

5.2.1 Zinc-Mediated Reaction

Zinc is a widely used reducing agent in direct cross-coupling reactions. Its use in combination with cobalt was pioneered by Gosmini and Perichon. They initially developed a cobalt-catalyzed reaction of aryl halides with stoichiometric zinc dust in acetonitrile, which provides an easy access to highly functionalized arylzinc species (Scheme 5.3).[11]

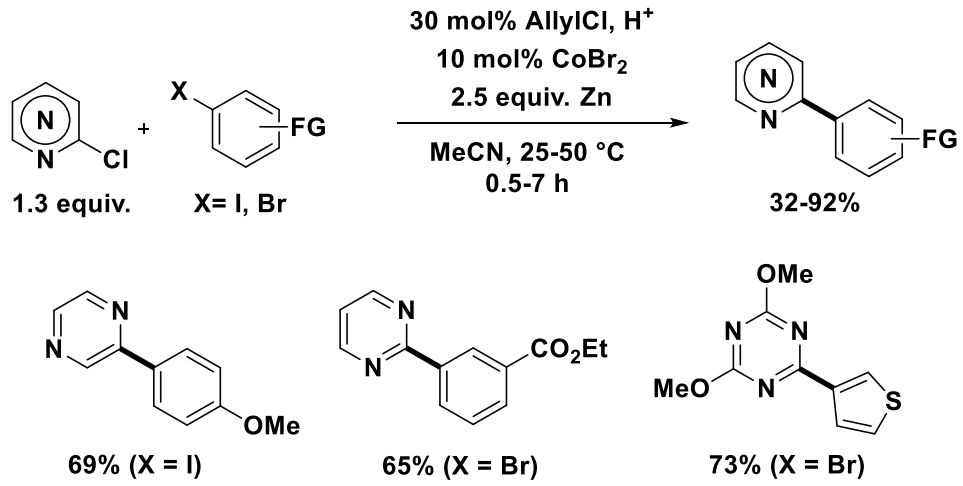


Scheme 5.3: General scheme of various cobalt-catalyzed reductive arylations.

This method constitutes not only a practical synthesis of arylzinc halides with improved yields but has been further exploited in Barbier type reactions by operating the aryl-zinc formation in combination with a cross-coupling step. Such Barbier type reactions can follow a cobalt-centered reductive coupling mechanism or a Negishi type cross-coupling via in situ generated arylzinc species. Activation by Brønsted acids and enhancement of selectivity by addition of allyl chloride was often observed. The latter acts as sacrificial oxidant, which reduces the formation of unwanted homobiaryl and hydrodehalogenation products. Allyl chloride is converted to minor amounts of propene, hexadiene, and allylation products under the reaction conditions. Four mechanistic roles of the added allyl chloride have been discussed: (i) enhancement of cobalt(II) salt reduction to a low-valent cobalt(I) species by coordination, (ii) facilitation of oxidative zinc(II) formation and generation of the arylzinc species, (iii) suppression of cobalt species in too low oxidation states which rapidly hydrodehalogenate the starting materials, and (iv) the scavenging of traces of acidic protons by the allylcobalt intermediates.[11,12,13] The last effect allows the use of off-shelf non-distilled solvents. The functional group tolerance of such cobalt-catalyzed zinc-mediated cross-coupling reactions is usually high (esters, nitriles, ketones, sulfones, chloride). However, substrates with acidic protons (OH, SH, etc.) are not tolerated.

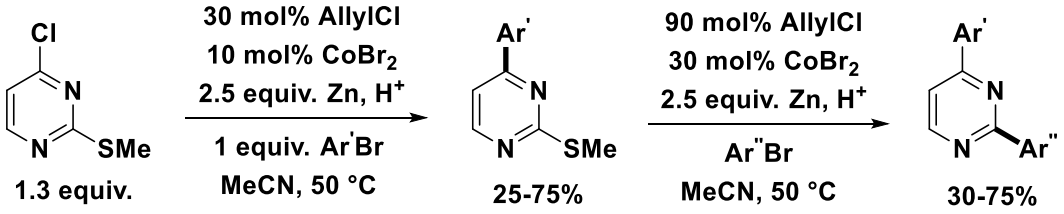
5.2.1.1 Formation of Biaryls

Gosmini and co-workers used the aforementioned methodology for reductive couplings of *N*-heteroaryl chlorides with aryl halides. Using 10 mol% $CoBr_2$ as catalyst and 1.5-2.5 equiv. of Zn dust as reducing agent, 2-chloropyrimidine was reacted with aryl iodides and bromides at 50 °C;[12] 2-chloropyrazine with an aryl iodide at 50 °C; and 2-chloro-1,3,5-triazine with aryl bromides as well as with thienyl bromide at room temperature (Scheme 5.4).[14]



Scheme 5.4: Cobalt-catalyzed arylation of 2-chlorodiazines.

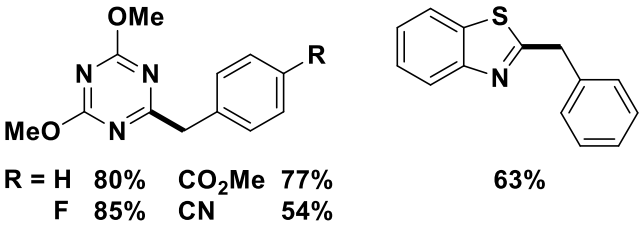
The direct reductive cross-coupling is only selective when the electronic properties of the electrophiles differ sufficiently. On the aryl halide, electron-donating and withdrawing substituents in *meta*- or *para*-position produce the desired cross-coupling products in moderate to good yields; *ortho*-substituents are not well tolerated. A related protocol was applied to sequential chloride and thiomethyl substitutions at 4-chloro-2-methylsulfanyl pyrimidine (Scheme 5.5).[15]



Scheme 5.5: Cobalt-catalyzed arylations of 4-chloro-2-methylsulfanyl pyrimidine.

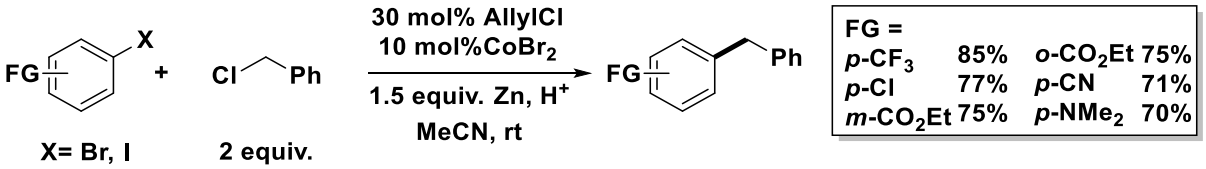
5.2.1.2 Benzylation and Allylations

Similarly, benzylations of chlorotriazine and 2-methylthiobenzo[*b*]thiazole with benzyl chlorides can be performed.[14,15] The reaction conditions are identical to those reported above (Scheme 5.4) and gave moderate yields (Scheme 5.6).



Scheme 5. 6: Cobalt-catalyzed benzylation products.

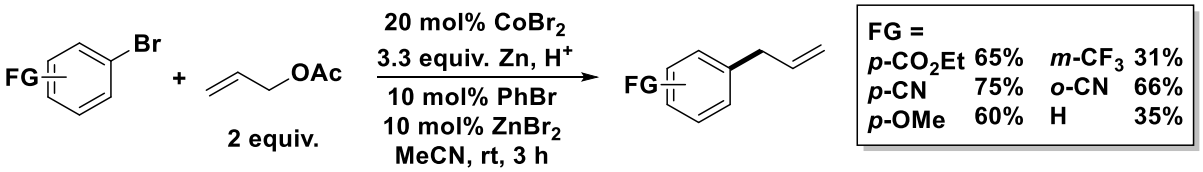
Benzylations of aryl iodides and bromides can also be effected with the same $CoBr_2$/Zn system.[16] An excess of the more reactive benzyl chloride is necessary to prevent major dibenzyl formation. Aryl iodides and bromides react smoothly to give the corresponding diarylmethanes in good yields at room temperature (Scheme 5.7).



Scheme 5.7: Reductive benzylation to diarylmethanes (similar yields with X = Br, I).

Electron-donating and -withdrawing substituents and *ortho*-substituents were tolerated. Employment of aryl chlorides or *α*-substituted benzyl chlorides resulted in slow reductive coupling but rapid benzyl dimerization.

One of the earliest examples of cobalt-catalyzed reductive coupling is the allylation of aryl bromides with cheap allyl acetate.[17] This reaction uses the combination of $CoBr_2$ in acetonitrile and zinc (3 equiv.) as reductant, but requires high catalyst loading (Scheme 5.8).

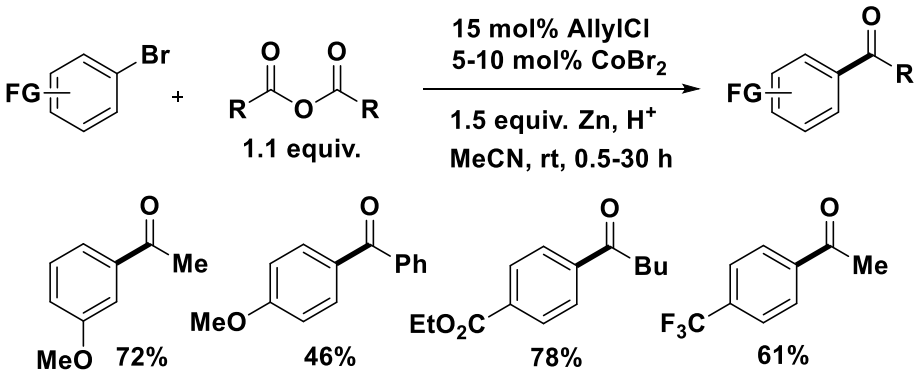


Scheme 5.8: Cobalt-catalyzed allylation of aryl bromides.

Allyl acetate is also employed in excess amounts (2 equiv.); the addition of 10 mol% bromobenzene was shown to suppress hydrodehalogenation, higher yields were obtained in the presence of 10 mol% $ZnBr_2$. The protocol allows the selective formation of allylbenzenes at room temperature and exhibits wide functional group tolerance. However, variations at the allyl acetate are limited; crotyl and cinnamyl acetates gave low yields (<30%).

5.2.1.3 Acylations

The acylation of aryl halides is another formal sp^2-sp^2 cross-coupling process which results in the formation of aromatic ketones (phenones). One notable example was reported by Perichon *et al.* using the standard system $CoBr_2$/Zn/allyl chloride. Various aryl bromides and acyl anhydrides could be coupled in moderate yields (Scheme 5.9).[13]



Scheme 5.9: Cobalt-catalyzed reductive acylation of aryl bromides.

Allyl chloride was again shown to suppress hydrodehalogenation of the aryl bromide. Acyl chlorides underwent rapid decomposition under the reaction conditions, but could be coupled in good yields when resorting to a standard cross-coupling protocol with preformed arylzinc species.

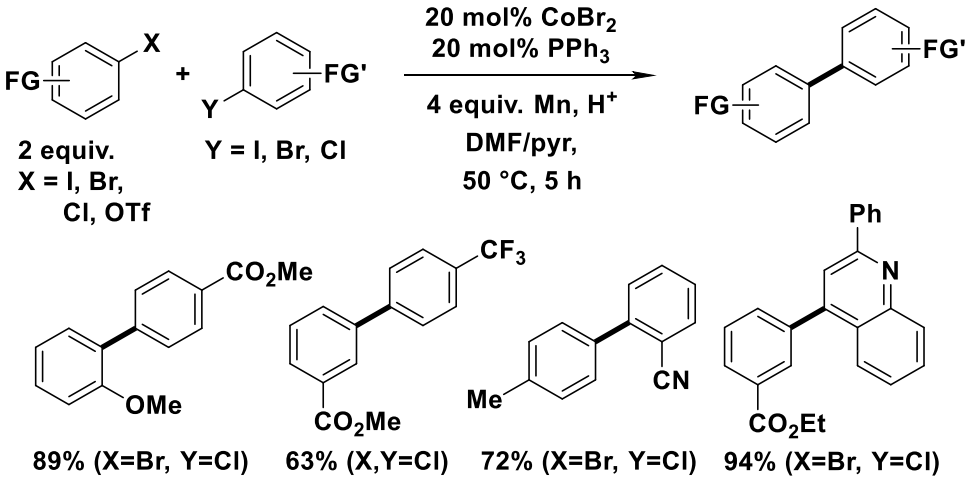
5.2.2 Manganese Mediated Reactions

With manganese as reductant, most reductive cross-coupling reactions of aryl halides were postulated to proceed through a sequence of catalyst reduction,

oxidative addition, catalyst reduction, oxidative addition steps. This type of mechanism has first been supported by DFT calculations on the reductive homo-coupling of aryl bromides.[18] In contrast, reactions with alkyl halides operate via a single-electron transfer (SET) mechanism as evidenced by radical clock and scavenging experiments.[19,20][20] However, unambiguous characterization of the open-shell intermediates has not yet been achieved. Pyridine is often used as co-solvent to stabilize low-valent cobalt(I) species, especially in DMF solutions. The Mn-mediated reactions display similar substrate scope and functional group tolerance as those with zinc.

5.2.2.1 Biaryl Formation

The reductive cobalt-catalyzed synthesis of unsymmetrical biaryls proceeds most selectively if the two aryl electrophiles exhibit sufficient electronic differentiation.[21] Aryl halides (I, Br, Cl) and triflates have been successfully employed, including a range of heteroaryl halides (Br, Cl) (Scheme 5.10).

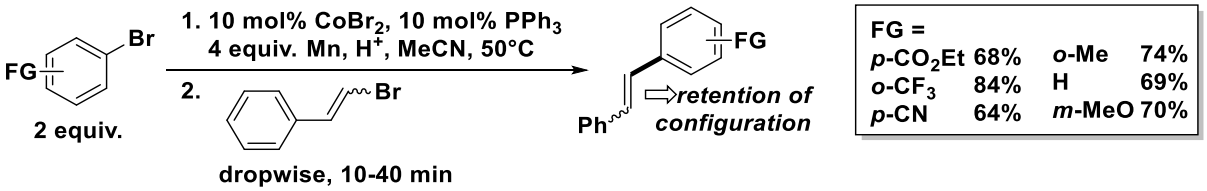


Scheme 5.10: Cobalt-catalyzed reductive biaryl coupling with Mn as reducing agent.

The more electrophilic reactant is employed in excess amounts (mostly 2 equiv.). High selectivities were obtained in DMF/pyridine and by addition of catalytic triphenylphosphine. The addition of radical scavengers showed no effect and indicated the operation of cobalt-centered insertion and reduction steps.

5.2.2.2 Alkenylations

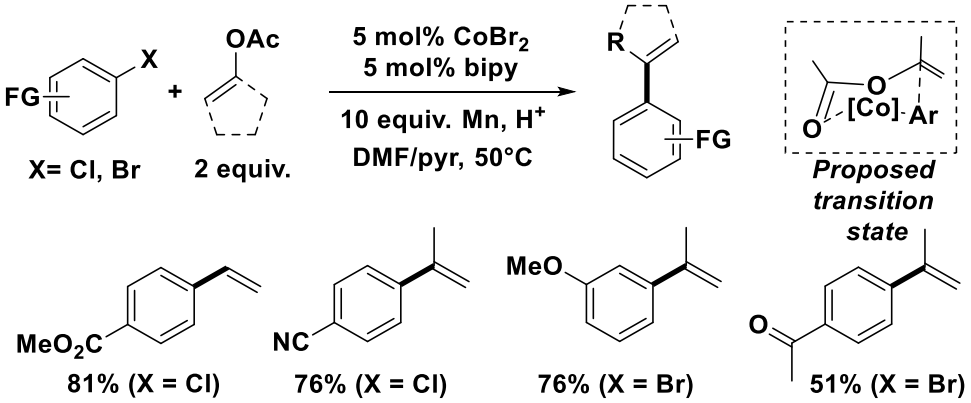
The related cobalt-catalyzed alkenylation of aryl halides with *β*-halostyrenes readily produces functionalized stilbenes. In the presence of triphenylphosphine as ligand, this reaction proceeded with retention of double-bond configuration: pure *cis*-*β*-bromo-styrene gave exclusively *cis*-stilbene (Scheme 5.11).[22]



Scheme 5.11: Cobalt-catalyzed formation of unsymmetrical stilbenes with retention of the double bond configuration.

Aryl iodides require an excess of the styrene derivative, whereas aryl bromides show better selectivity when employed in excess and upon slow addition of the styryl halide. The absence of organomanganese and free-radical intermediates was proven by scavenging experiments and DFT studies. Addition of acetic anhydride gave no ketone formation; the presence of galvinoxyl free-radicals had no impact on rate and selectivity. Competitive reactions with bromostyrene and aryl bromides documented the faster consumption of the latter. A potential vinylcobalt intermediate would be prone to rapid isomerization and thus cannot account for the configurational conservation.

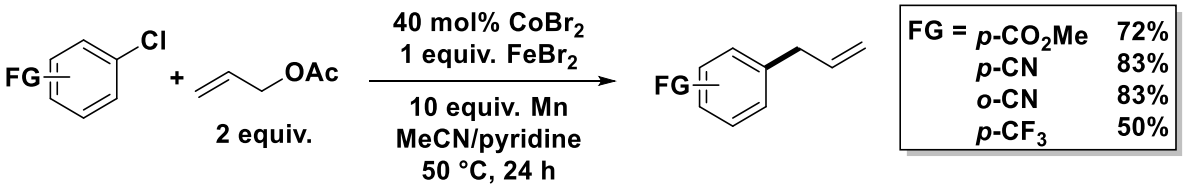
Vinyl acetates are a cheap and halide-free class of electrophiles and were successfully employed in the reductive formation of styrenes from aryl halides.[23] Electron-deficient aryl chlorides and aryl bromides showed good reactivity with various acyclic and cyclic alkenyl acetates (Scheme 5.12). Vinyl acetate was used in excess (2 equiv.) with 2,2'-bipyridine being added as ligand to ensure high catalyst activity; *ortho*-substituents were generally not tolerated. The reaction is proposed to proceed through a cyclic six-membered transition state involving carbonyl coordination to the arylcobalt intermediate.



Scheme 5.12: Cobalt-catalyzed reaction of aryl halides with vinyl acetates.

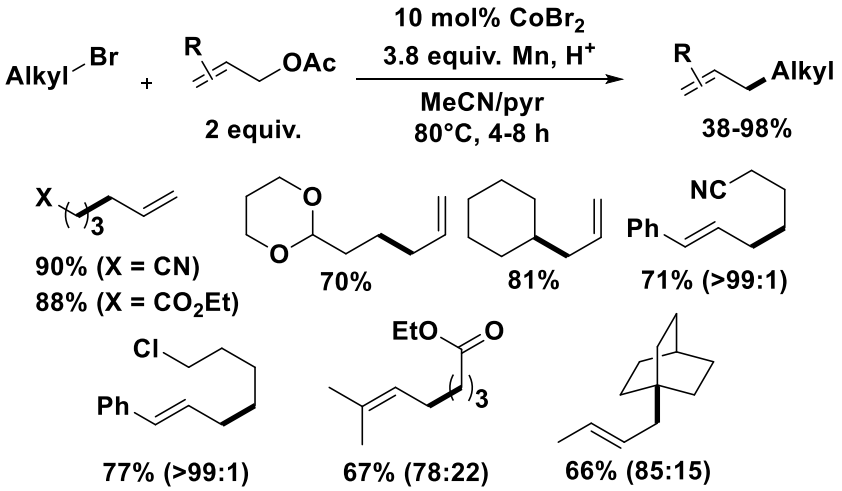
5.2.2.3 Allylations

Conceptually related is the formal sp^3-sp^2 bond forming allylation of aryl halides, which has been reported to occur similarly under cobalt catalysis. Electron-poor aryl chlorides were reacted with allyl acetate in the presence of a large excess of Mn and stoichiometric $FeBr_2$ (Scheme 5.13).[17]



Scheme 5.13: Cobalt-catalyzed allylation of aryl chlorides.

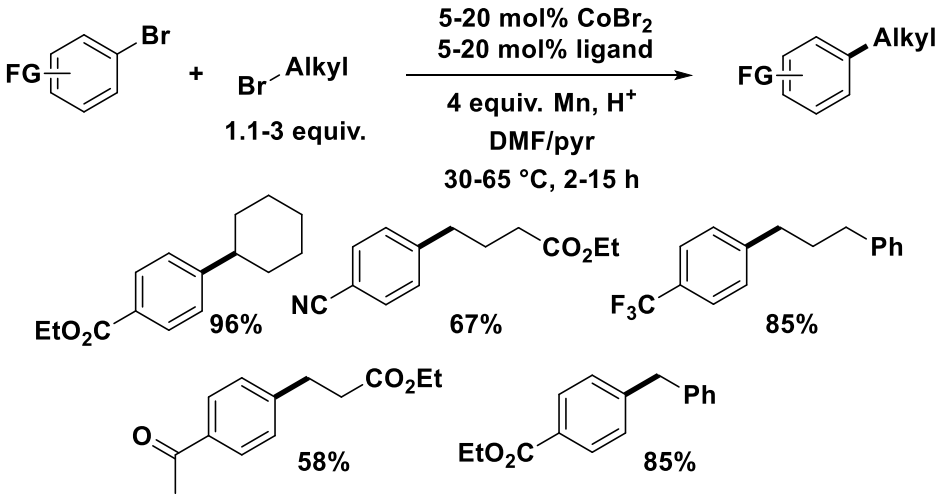
The formal sp^3-sp^3 cross-coupling between alkyl halides (1°, 2°, 3°; Br, Cl) and allyl acetates or carbonates occurs likewise. Moderate to excellent yields were obtained in a refluxing mixture of acetonitrile and pyridine (Scheme 5.14).[20] Substitution on the allyl acetate decreases the yield significantly. Under these conditions, formation of the linear products is favored. Activated alkyl halides (benzyl chlorides, EWG-substituted alkyl bromides) also reacted with allyl carbonates. Experimental evidence (inhibition by addition of TEMPO; ring-opening with (bromomethyl)cyclopropane exists for a mechanism involving radical intermediates.



Scheme 5.14: Allylation of alkyl bromides. Ratio of linear (*α*-substitution on allyl acetate) to branched (*γ*-substitution) products formed from *γ*-substituted allyl acetates.

5.2.2.4 Alkylations

Cobalt complexes were also found to catalyze the direct alkylation of activated aryl halides (Br, Cl) with alkyl bromides bearing *ß*-hydrogen atoms under mild conditions (Scheme 5.15).[19]



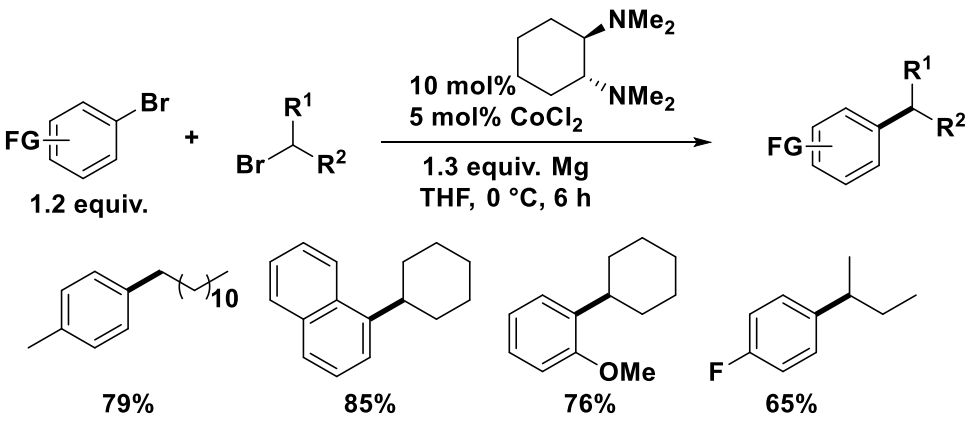
Scheme 15. Cobalt-catalyzed alkylation of aryl bromides using Mn as reductant.

The alkyl bromide is mostly used in excess (1.1-3.0 equiv.). Diisopropyl-phenylphosphine is usually employed as ligand with the exception of couplings with more reactive alkyl halides (3-bromopropionate, benzyl chloride) where 2,2'-bi-

pyridine was used. (Bromomethyl)cyclopropane underwent ring-opening, wich is indicative of an SET mechanism.

5.2.3 Magnesium-Mediated Reactions

Since their discovery at the dawn of the 20th century, Grignard reagents have been extensively used for a wide variety of reactions. In particular, cobalt-catalyzed reactions of arylmagnesium halides have been already reported in 1941.[24] Reactions with magnesium metal usually occur through formation of the Grignard reagent, and thus share the features usually associated with these species: acidic protons and highly electrophilic functionalities such as ketones or nitriles are not tolerated; THF is used as solvent. Ether, amine, halogen, and (when forming the Grignard reagent by transmetalation, for example with *iso*-PrMgCl) ester substituents are mostly compatible with the presence of Grignard reagents.
Jacobi von Wangelin *et al.* reported a cobalt-catalyzed cross-coupling of aryl bromides with alkyl bromides in the presence of catalytic *N*,*N*,*N'*,*N'*-tetramethyl-1,2-diaminocyclohexane (Me_4-DACH) and 1.3 equiv. Mg (Scheme5.16).[25]



Scheme 5.16: Cobalt-catalyzed alkylation of aryl bromides with Mg as reductant.

The amine ensures slow formation of the arylmagnesium species which is key to a high cross-coupling selectivity and only minor homo-biaryl formation. The catalytically active species is assumed to be an ate-complex of cobalt(0), which forms with excess arylmagnesium bromide. Asymmetric cross-coupling of a racemic secondary alkyl halide using enantiopure (*R*,*R*)-Me_4-DACH afforded only low stereoinduction (ca. 20%).

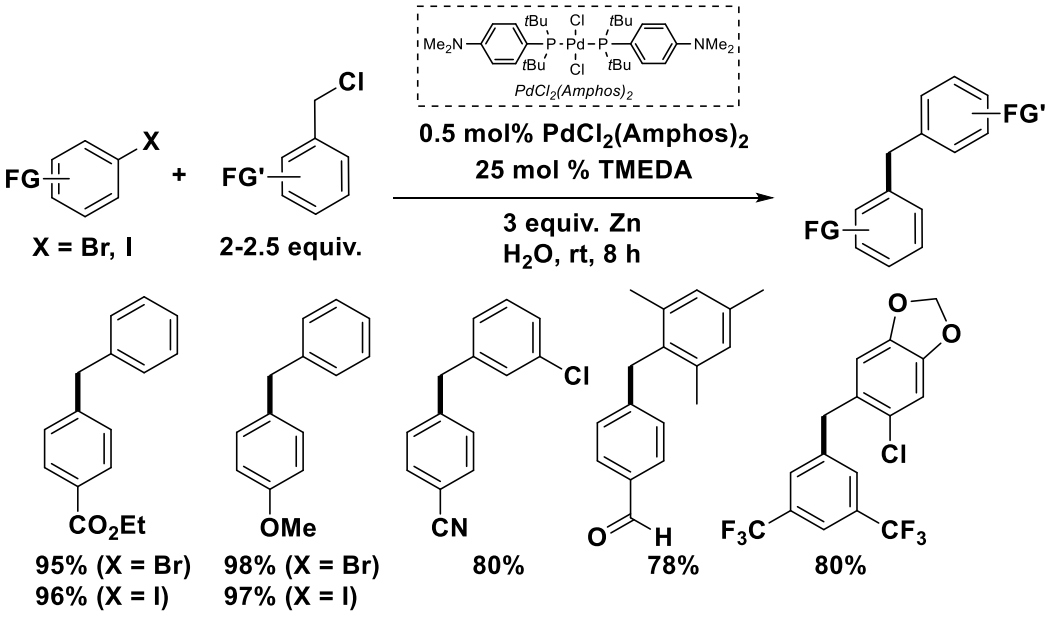
5.3 Palladium Catalysis

Palladium-catalyzed cross-coupling reactions are among the most versatile methods for the construction of C-C bonds. There are numerous protocols in the literature which operate under mild conditions and exhibit high functional group tolerance including reactions in aqueous solution. Most of the research effort of the past 35 years has been devoted to the development of heteropolar coupling reactions between organometallic reagents and organic electrophiles (mostly halides and pseudohalides). Only recently, some researchers have turned their attention to reductive cross-coupling reactions with palladium catalysts and in most cases with zinc as reducing agent.

5.3.1. Zinc-Mediated Reactions

5.3.1.1 Benzylations

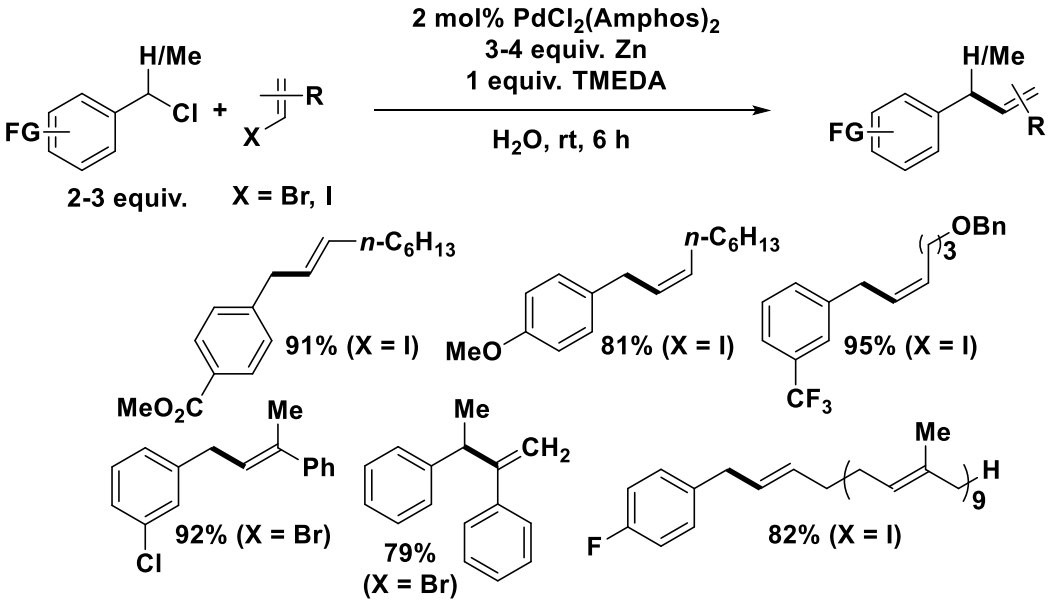
Lipshutz *et al.* reported a practical method for the synthesis of unsymmetrical diarylmethanes in water. A palladium(II) pre-catalyst in the presence of tetramethyl-enediamine (TMEDA) and in combination with zinc as reducing agent allows for the coupling of various aryl bromides and aryl iodides with benzyl chlorides at room temperature (Scheme 5.17).



Scheme 5.17: Palladium-catalyzed reductive benzylation of aryl halides "on water".

The benzyl chloride is used in excess (ca. 2.5 equiv.). The reaction features remarkably broad functional group tolerance. Presumably, TMEDA acts as surface-cleaning and/or activating agent and stabilizes the organozinc intermediate, which is formed *in situ*.[26]

Lipshutz *et al.* later modified the method to also facilitate cross-coupling between benzyl chlorides and alkenyl halides (I, Br) (Scheme 5.18).



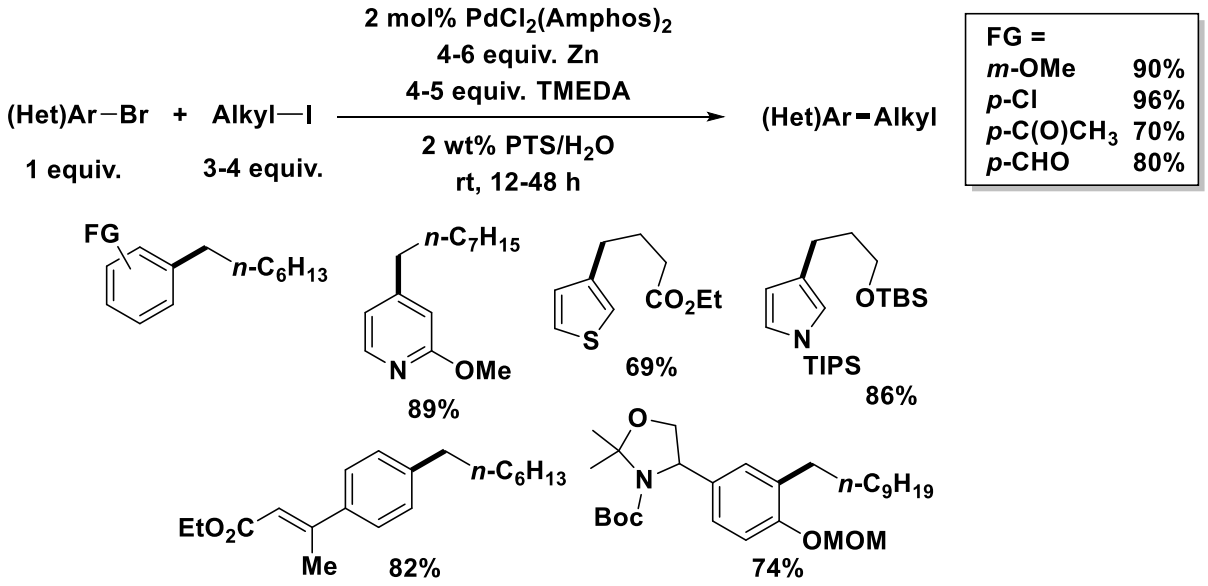
Scheme 5.18: Palladium-catalyzed benzylation of alkenyl halides "on water".

Higher catalyst loading and one equivalent of TMEDA were required for good to excellent selectivities. Almost perfect retention of olefin configuration was observed in all studied cases. Competition experiments showed that (*E*)-alkenyl bromides reacted faster than the *Z* isomer and both of them much faster than bromobenzenes. Therefore, selective cross-coupling sequences with arylvinyl dibromides became feasible.[27]

5.3.1.2 Alkylations

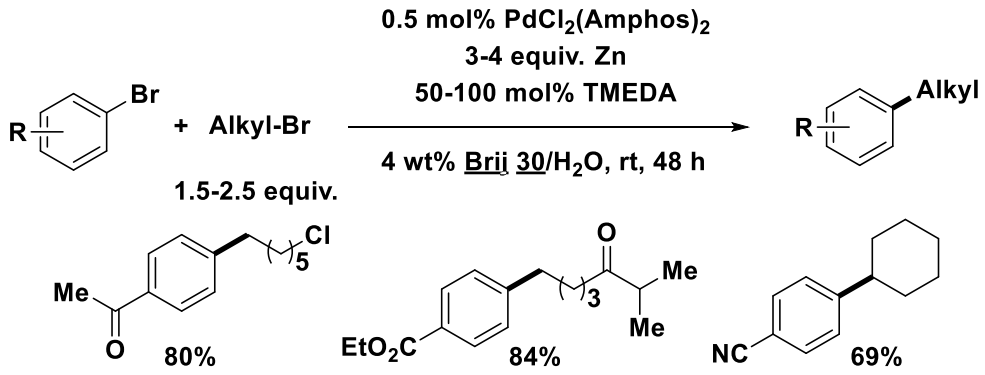
The same group disclosed the first aqueous micellar catalytic reaction with a designer surfactant applied to a moisture-sensitive, zinc-mediated, Pd-catalyzed cross-coupling. Upon addition of the commercial surfactant PTS (PEG-600/alpha-tocopherol-based diester of sebacic acid) to water, spontaneous formation of

micelles occurs which has been used as nanoreactors within the aqueous solution. Primary alkyl iodides were successfully coupled with aryl and heteroaryl bromides at room temperature employing a palladium catalyst, Zn as reducing agent, and TMEDA as activator and stabilizer of the *in situ* formed organozinc species. A wide range of functional groups and heteroaromatic systems were tolerated (Scheme 5.19).



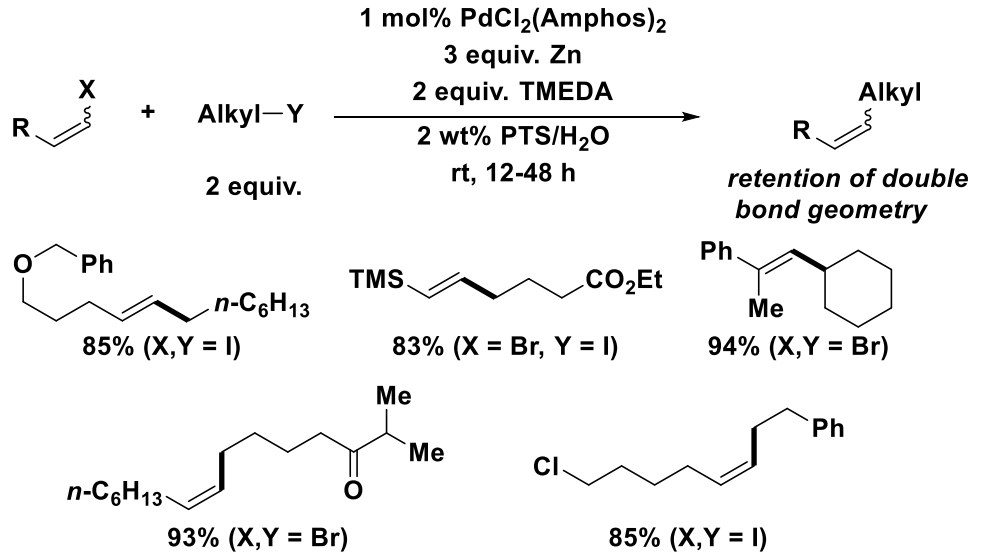
Scheme 5.19: Palladium-catalyzed alkylation with alkyl iodides in micelles.

The reaction selectivity is based on the selective oxidative insertion of Pd into the C(sp^2)-halide bond while Zn inserts into the C(sp^3)-halide bond.[28] For reactions with primary and secondary alkyl bromides, Brij 30 (commercially available non-ionic surfactant consisting of polyoxyethylated lauryl ether) showed better characteristics as surfactant and allowed aryl-alkyl couplings in good yields (Scheme 5.20).[29]



Scheme 5.20: Palladium-catalyzed alkylation with alkyl bromides in micelles.

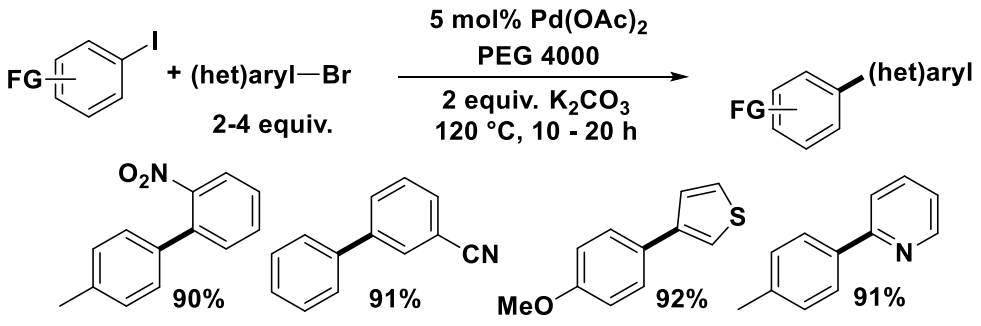
Micellar catalysis was also applied to Negishi type reactions between stereodefined alkenyl halides (Br, I) and alkyl halides (Br, I). Primary and secondary alkyl halides could be reacted; sec. bromides fared better than the corresponding iodides. In most cases, full retention of double bond geometry was observed (Scheme 5.21).[30]



Scheme 5.21: Palladium-catalyzed alkenylation of alkyl halides in micelles.

5.3.2 Non-metallic Reductant

Under thermal conditions, a direct coupling reaction between electron-rich aryl iodides and electron-deficient (hetero)aryl bromides was reported by Zhang and Wang *et al.* to proceed in the absence of an obvious reductant (Scheme 5.22).



Scheme 5.22: Synthesis of unsymmetrical biaryls using PEG as reducing agent.

$Pd(OAc)_2$ was employed as catalyst in polyethylene glycol (PEG-4000). The unsymmetric biaryls were obtained in excellent yields at 120 °C with the aryl iodide

being the limiting substrate. Based on previous works, the authors suggest that the terminal hydroxyl groups of PEG act as reductant. The selective formation of biaryls proved to be very sensitive to the concentration of these terminal groups on the PEG polymer. Interestingly, the catalyst system could be recycled and re-used up to five times with no loss of activity.[31]

5.4 Nickel Catalysis

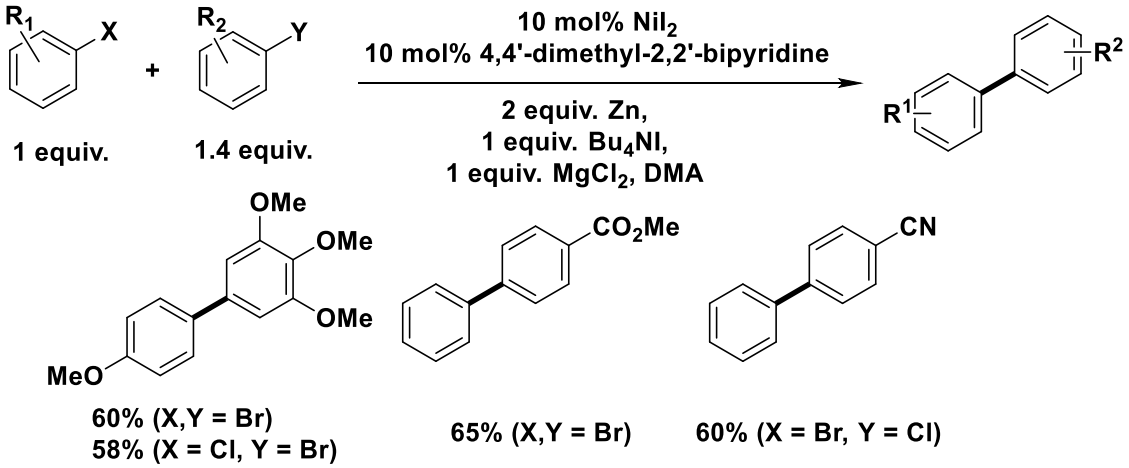
Together with palladium, nickel catalysts dominate the field of heteropolar cross-coupling reactions between organic electrophiles and organometallic reagents.[32] Much of the early work on reductive cross-couplings centered around cobalt catalysts, whereas most of the recent reports favour nickel catalysts. Catalysts comprising a nickel(II) precursor and chelating nitrogen-based ligands (bipyridine, phenanthroline) were shown to be especially active. Metallic manganese as reductant seemed to be best suited for the postulated reduction of the nickel(I) and nickel(II) catalyst intermediates. The most advanced mechanistic studies have also been performed under these conditions which indicate the presence of radical intermediates in alkylation reactions. In the presence of chiral ligands, enantioselective reactions have been realized.

5.4.1 Zinc-Mediated Reactions

5.4.1.1 Biaryl formations

Qian and Lin *et al.* recently reported a nickel-catalyzed reductive cross-coupling between aryl halides (Br, Cl). The optimized set of conditions involve catalytic NiI2 and the ligand 4,4’-dimethyl-2,2’-bipyridine, two equiv. of Zn as reducing agent and the additives tetrabutylammonium iodide and magnesium chloride. The additives presumably activate the zinc powder by removing residual salts from its surface. The reaction is performed in DMA at room temperature for 12 hours. The mild reaction conditions tolerate a range of functional groups (esters, nitriles, ketones and CF_3). The yields are usually higher when the electron-poor reactant is employed in excess amounts (ca. 1.4 equiv.). The reaction also allows the cross-coupling of two electron-

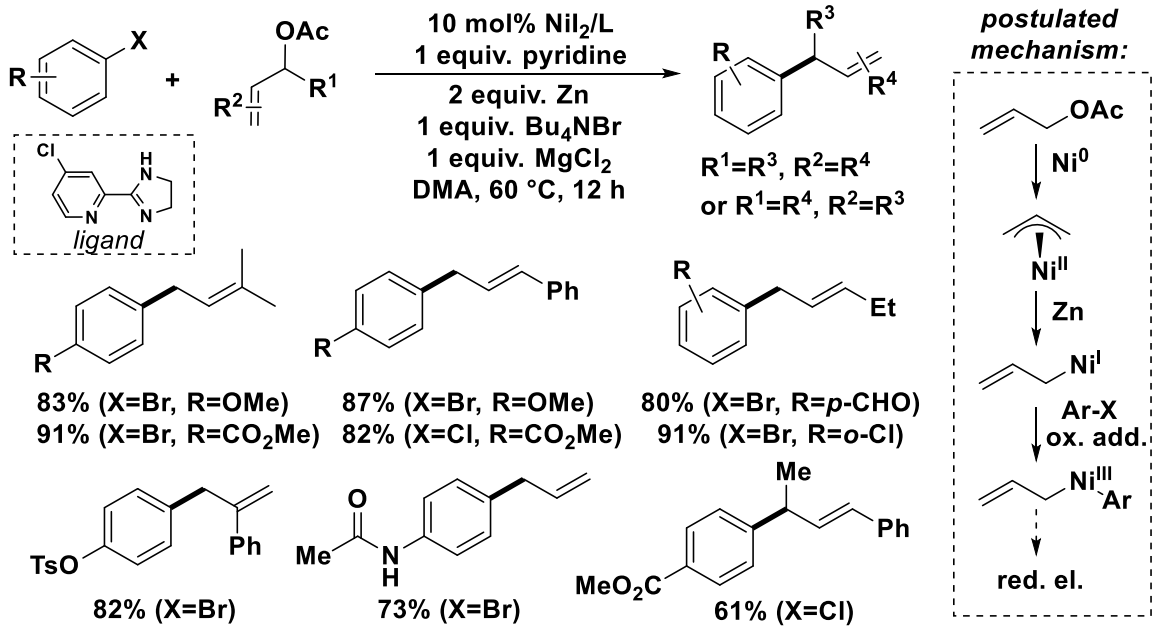
rich aryl halides. *N*- heteroaryl halides fared equally well, however, 2-bromothiophene gave no coupling product (Scheme 5.23).[33]



Scheme 5.23: Nickel/bipyridine-catalyzed reductive biaryl formation.

5.4.1.2 Allylations

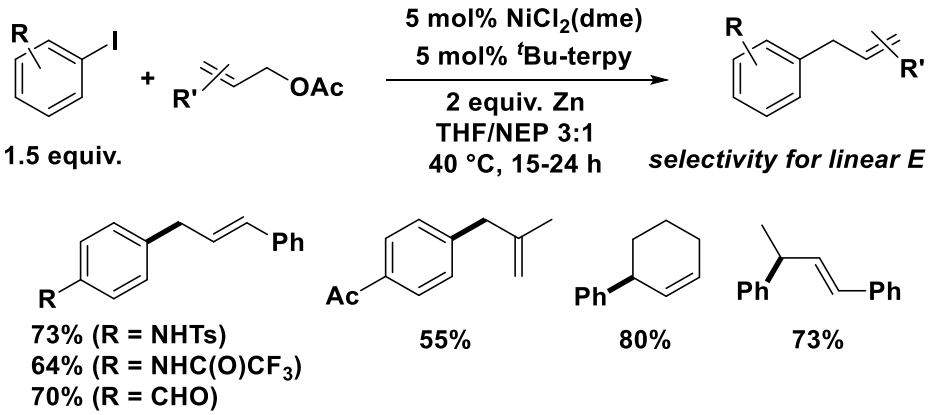
A similar protocol was reported by the same group for a nickel-catalyzed reaction between allyl acetates and aryl halides (Br, Cl). 2-(2-Pyridyl)-1,3-imidazole acts as ligand and pyridine, tetrabutylammonium bromide, and magnesium chloride were employed as additives. The reactions at 60 °C afforded the desired allylbenzenes in good to excellent yields (Scheme 5.24).



Scheme 5.24: Nickel-catalyzed reductive allylation of aryl halides.

Electron-rich aryl bromides and electron-deficient aryl bromides or chlorides were competent reactants. The coupling occurs selectively at the less hindered position of substituted allyl acetates producing exclusively (*E*)-alkenes. A wide range of functional groups (aldehydes, esters, amides, tosylates) were tolerated. Experimental evidence points at a mechanism which does not include the intermediate formation of an organozinc species, but the reduction of an initially formed Ni(II)-π-allyl complex.[34]

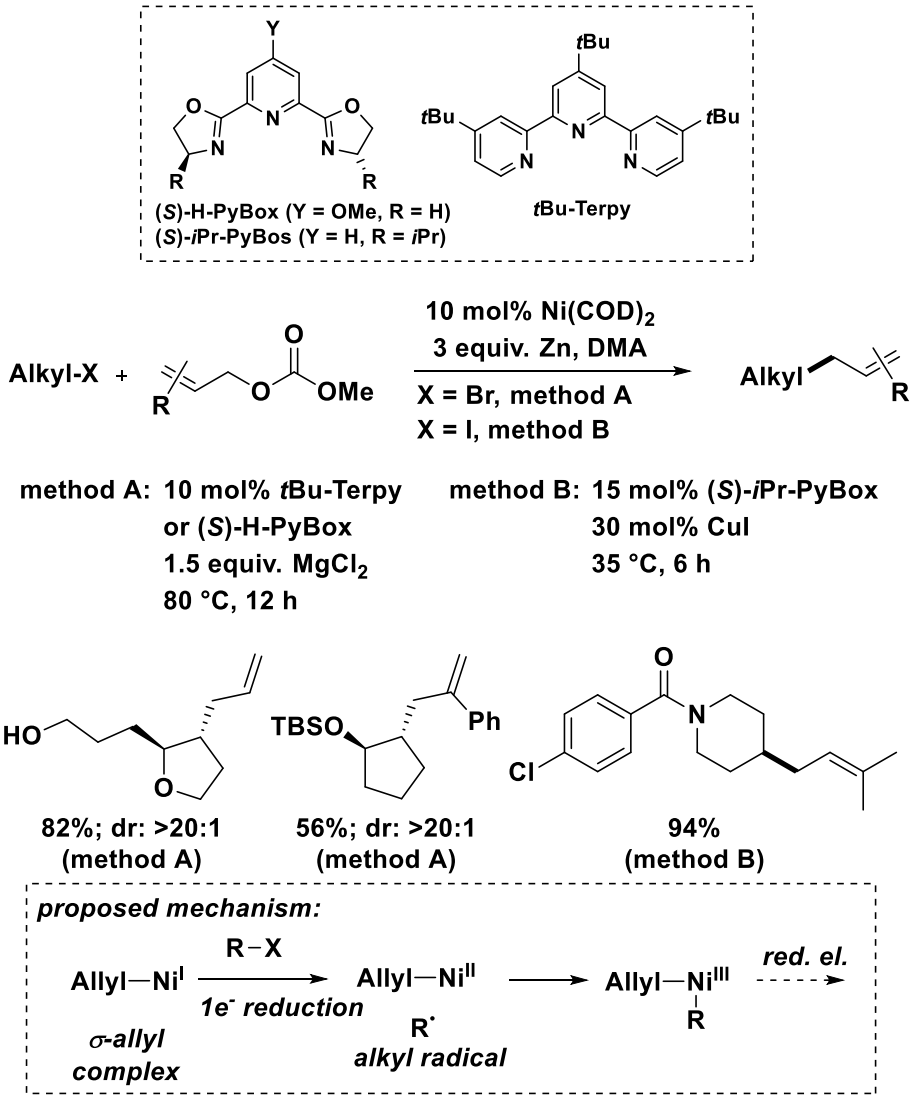
Weix *et al.* reported the mild allylation of aryl halides (Br, I) with a catalyst system comprising 5 mol% $NiCl_2$(dme) and 5 mol% *tert*-Bu-terpy (see Scheme 5.25) as ligand. The reactions run in THF/NEP (*N*-ethylpyrrolidinone) at 40 °C and require an excess of the aryl halide (1.5 equiv.) and zinc (2 equiv.) for moderate to good selectivity. Substituted allyl acetates selectively give linear (*E*)-alkenes as products. The reaction conditions tolerate aldehydes, ketones, halides, and the fairly acidic protons of trifluoroacetamides and sulphonamides (Scheme 5.25).[35]



Scheme 5.25: Nickel-catalyzed allylation of aryl halides by Weix *et al*.

The Gong group developed a method for the nickel-catalyzed coupling of allyl carbonates with secondary alkyl halides (Br, I). Unsymmetrical allyl substrates were regioselectively attacked at the less hindered terminus and gave (*E*)-alkenes. The carbonate was used in excess (2 equiv.). A mixture of $Ni(cod)_2$ and tri-dentate *N*-ligands was employed as pre-catalyst. The reactions of alkyl bromides and alkyl iodides followed different protocols. Alkyl bromides were reacted at 80 °C in the presence of pyridinebis(oxazoline) (pybox) or terpyridine ligands. Alkyl iodides were coupled with addition of catalytic copper(I) iodide at 35 °C (Scheme 5.26). Various functional groups are tolerated (amides, esters and alcohols!). Initial mechanistic

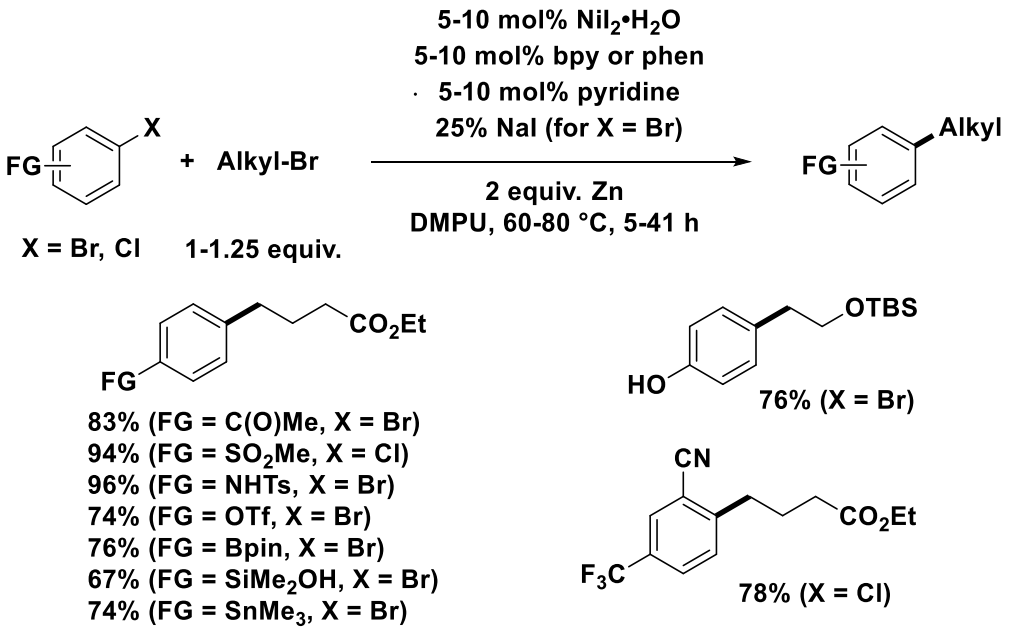
investigations support the absence of intermediate organozinc species but indicate the presence of radical intermediates (Scheme 5.26).[36]



Scheme 5.26: Nickel-catalyzed reductive allylation of alkyl halides.

5.4.1.3 Alkylations

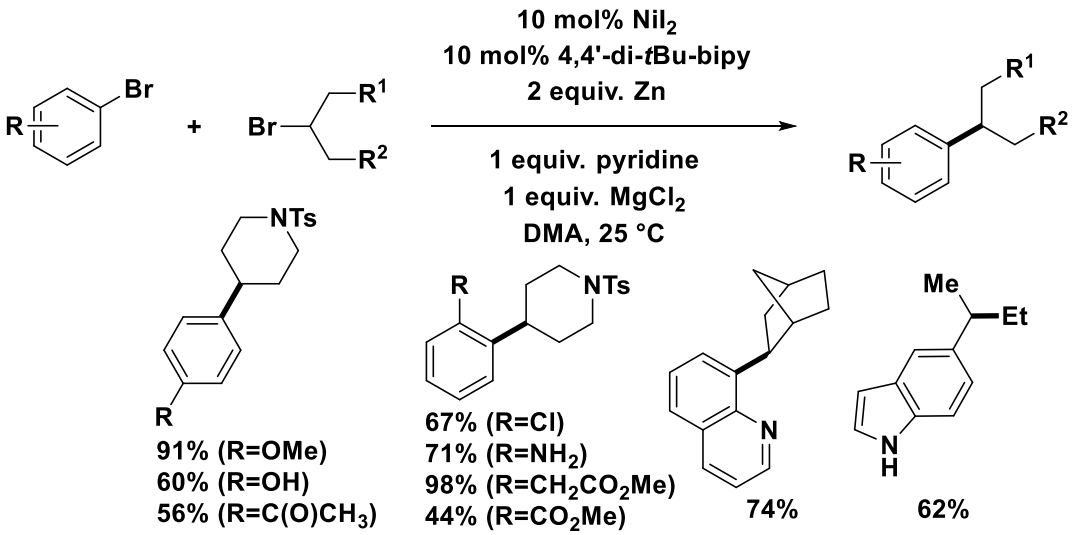
A multicatalyst system was applied to reductive couplings of primary alkyl bromides with a wide range of aryl bromides. Nicikel(II) iodide, bipyridine or phenanthroline, and pyridine were employed as pre-catalyst mixture which allowed the alkylation of aryl bromides and chlorides at elevated temperature in the presence of zinc and *N*,*N*-dimethylpropylene urea (DMPU, Scheme 5.27).



Scheme 5.27: Nickel-catalyzed reductive alkylation of aryl halides.

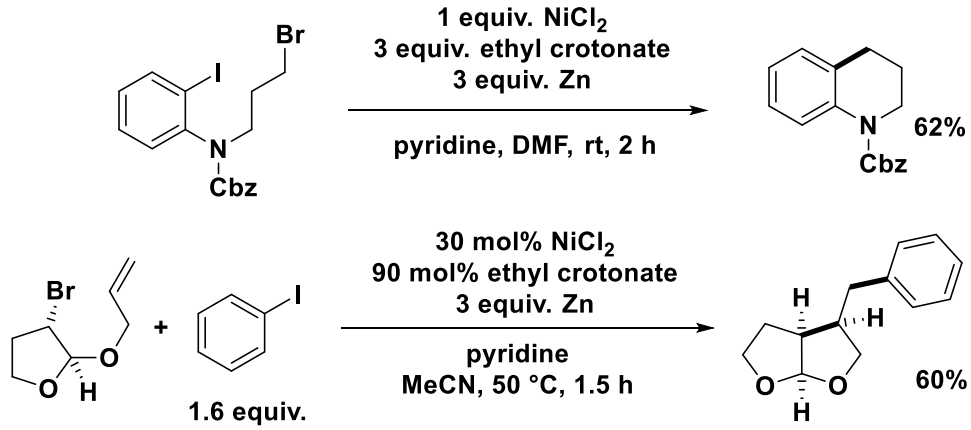
In the case of aryl chlorides, a slight excess of the alkyl bromide (1.25 equiv.) was used. The reaction tolerates a wide range of functional groups and can be performed without the exclusion of air and moisture. The reaction conditions are orthogonal to conventional heteropolar cross-couplings: substrates bearing electrophilic and nucleophilic carbon positions were selectively modified at the electrophilic site (R-X) while no reaction occurred at the nucleophilic site. Mechanistic studies render the intermediacy of organozinc species highly unlikely.[37]

Gong *et al.* reported a similar protocol for the nickel-catalyzed reductive coupling of secondary alkyl bromides with aryl halides at 25-60 °C in DMA (Scheme 5.28). Equimolar amounts of the reactants can be used. Electron-rich ArBr give better yields than electron-poor ones; electron-poor aryl chlorides can be reacted under slightly modified conditions (addition of 1 equiv. Bu_4NBr and 50 °C required). The tolerance of functional groups (hydroxyl, nitrile, ester, amide groups) and one *ortho*-substituent is good. 2,6-Disubstituted aryl halides were inert. The addition of TEMPO inhibited the reaction indicating a possible radical mechanism.[38]



Scheme 5.28: Reductive coupling between aryl halides and 2° alkyl bromides.

An interesting expansion of this method to intramolecular reductive cross-couplings of unactivated alkyl bromides with aryl iodides was reported by Peng *et al.* (Scheme 5.29).

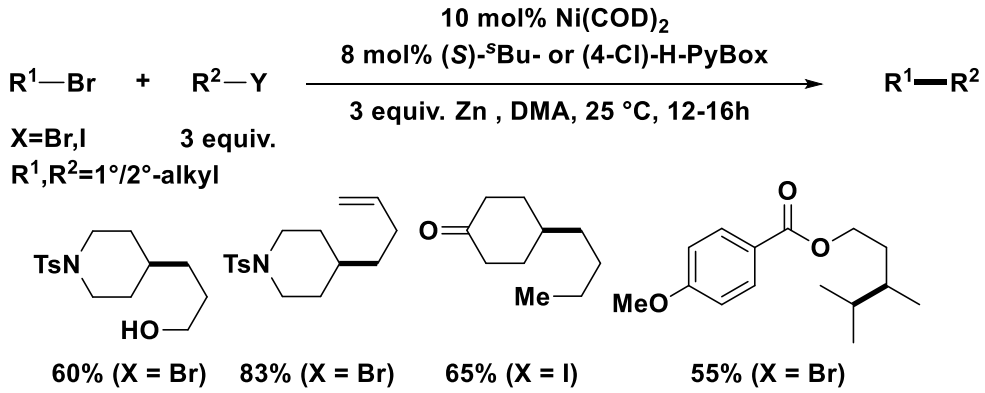


Scheme 29: Reductive cross-coupling and domino cyclization/cross-coupling.

The reaction is mediated by $NiCl_2$/Zn in combination with ethyl crotonate and pyridine at room temperature to provide access to indolines, tetrahydroquinolines, dihydrobenzofurans, and chromane with moderate to good yields. The role of ethyl crotonate is unclear. However, no reaction was observed without addition of ethyl crotonate. Similar tolerance of functional groups as in the Weix and Gong protocols was established. Catalytic $NiCl_2$ can be used for domino cyclization/cross-coupling processes with excellent diastereoselectivities of the formed four contiguous

stereocenters (Scheme 5.29). The reaction can be rationalized by an initial 5-*exo*-trig cyclization, which is in accordance with the assumption of a radical process.[39]

Alkyl-alkyl cross-coupling processes are still highly challenging due to the competition of elimination and radical dimerization pathways. An effective cross-coupling between two non-activated alkyl halides has been devised by Gong *et al.* (Scheme 5.30).

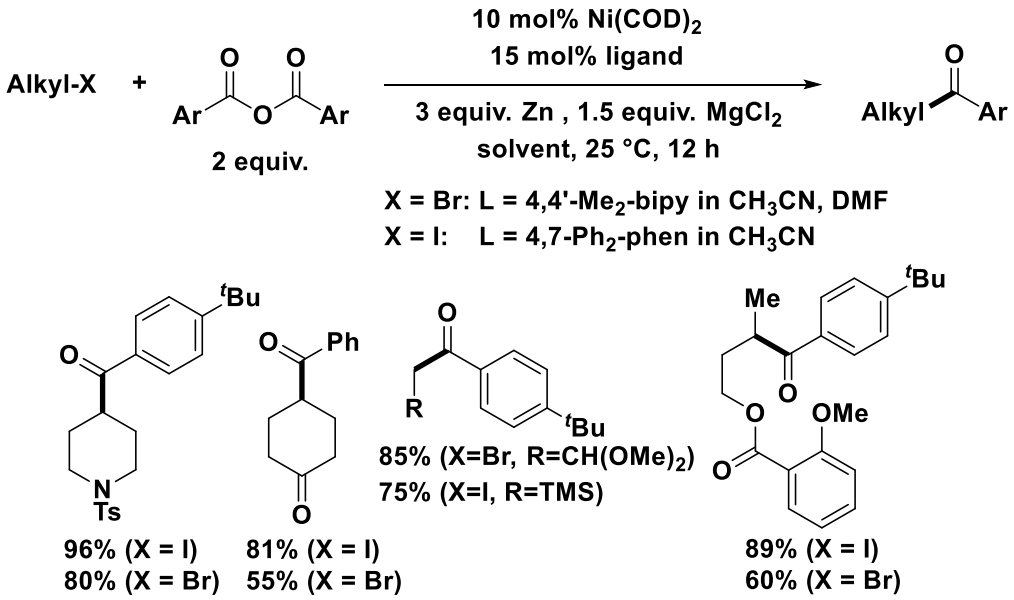


Scheme 5.30: Nickel-catalyzed alkyl-alkyl cross-coupling.

Alkyl bromide (1° or 2) as the limiting reagent can be coupled with another alkyl bromide or iodide (1° or 2°) which is used in excess (3 equiv.) to grant high selectivity. The mild conditions allow useful functional group tolerance (e.g., ester, alcohol, amide, ketone). The pybox-type ligand was shown to govern cross-coupling selectivity and suppress homo-coupling. Nevertheless, homo-coupling is a significant side reaction. A radical mechanism has been proposed without the formation of intermediate organozinc species.[40]

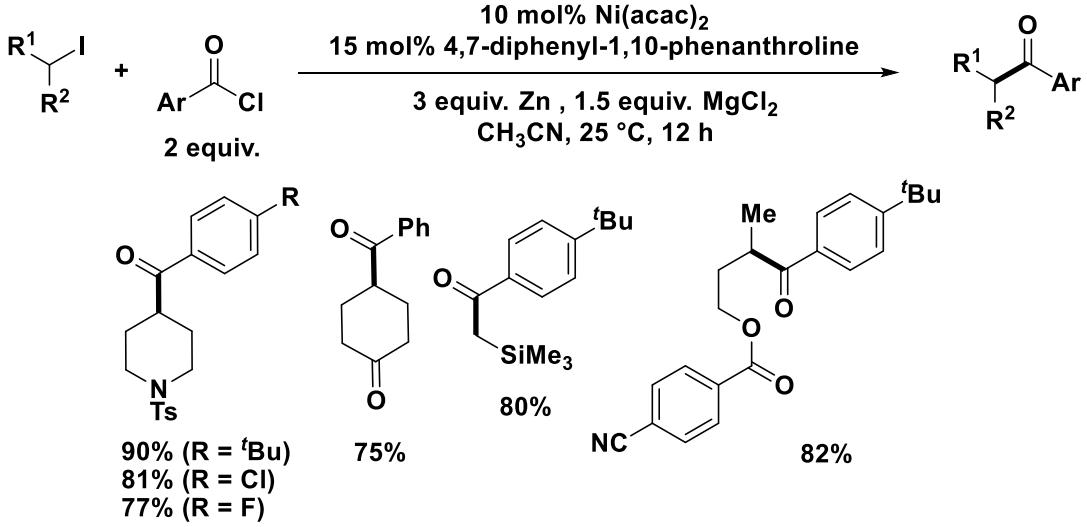
5.4.1.4 Ketone formation

Lin and Gong *et al.* developed methods for the reductive coupling of unactivated primary and secondary alkyl halides RX with aroyl anhydrides using a nickel catalyst, 4,4'-dimethyl-2,2'-bipyridine (X=Br) or 4,7-diphenylphenanthroline (X=I) as ligands, and zinc as reducing agent (Scheme 5.31). The anhydride was used in excess (2 equiv.). It is assumed that the mechanism for alkyl bromides is different from that with alkyl iodides. Under slightly modified conditions and with lower yields, secondary alkyl iodides also react with benzoic acids in the presence of di-*tert*-butyl carbonate (Boc_2O) via intermediate anhydrides.[41]



Scheme 5.31: Nickel-catalyzed reductive ketone formation from aroyl anhydrides.

An alternative approach to alkyl aryl ketones employs benzoyl chlorides under similar conditions (Scheme 5.32).



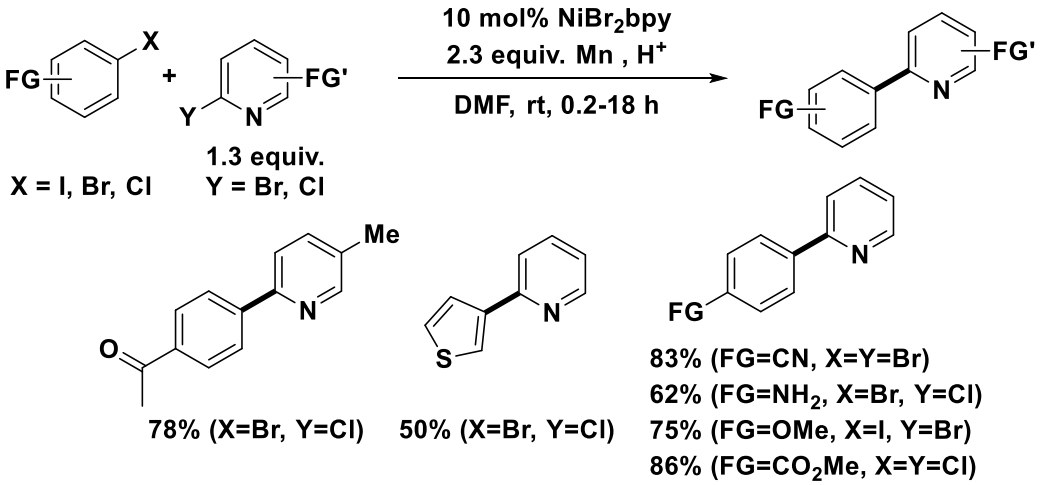
Scheme 5.32: Nickel-catalyzed reductive coupling of alkyl halides with aroyl chlorides.

Unactivated primary and secondary alkyl iodides and activated alkyl bromides and chlorides (benzyl, allyl) undergo aroylation with good tolerance of functional groups (ketone, chloride, nitrile, ester). The presence of *ortho*-substituents and electron-withdrawing groups results in decreased yields. A radical mechanism was postulated.[42]

5.4.2 Manganese-mediated reactions

5.4.2.1 (Hetero)biaryl formation

An early protocol by Gosmini *et al.* reported the nickel-catalyzed reductive cross-electrophile coupling for the synthesis of functionalized 2-arylpyridines using manganese as reductant (Scheme 5.33).

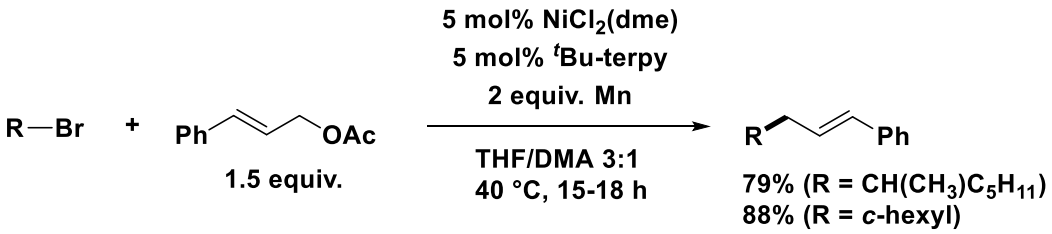


Scheme 5.33: Nickel-catalyzed reductive formation of functionalized 2-arylpyridines.

2-Halopyridines (Cl, Br) were coupled with aryl halides (Cl, Br, I) at room temperature under catalysis of $NiBr_2$(2,2'-bipyridine). Moderate to excellent yields were obtained when the halopyridine was employed in moderate excess (1.3 equiv.). A wide range of functional groups was tolerated such as amines, esters, nitriles and ketones.[43]

5.4.2.2 Allylations

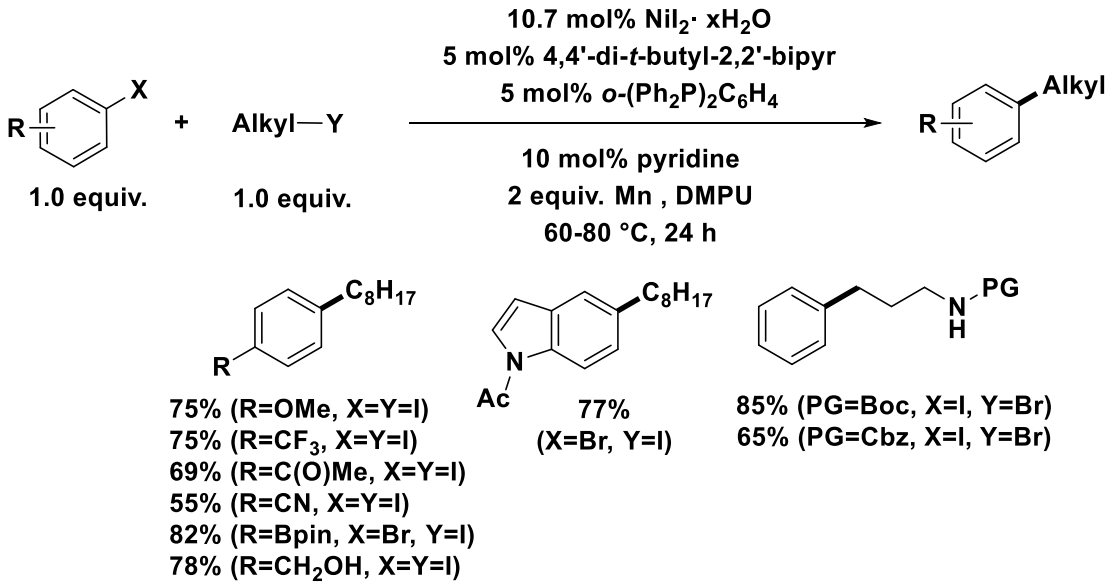
Weix *et al.* reported a process for the nickel catalyzed allylation of alkyl and vinyl bromides. They used similar conditions as for the related allylation of aryl halides but with manganese instead of zinc as reductant. [$NiCl_2$(dme)] and *tert*-Bu-terpy (see Scheme 5.26) were used as pre-catalysts. The reactions run in THF/DMA at 40 °C and require an excess of the allyl acetate (1.5 equiv.) and manganese (2 equiv., Scheme 5.34). Application of this method to 2-bromocyclohex-2-enone as a vinyl bromide showed good selectivity towards the formation of the desired diene. Neocuproine was used as ligand in these reactions.[35]



Scheme 5.34: Nickel-catalyzed allylations of alkyl and vinyl bromides by Weix *et al.*

5.4.2.3 Alkylations

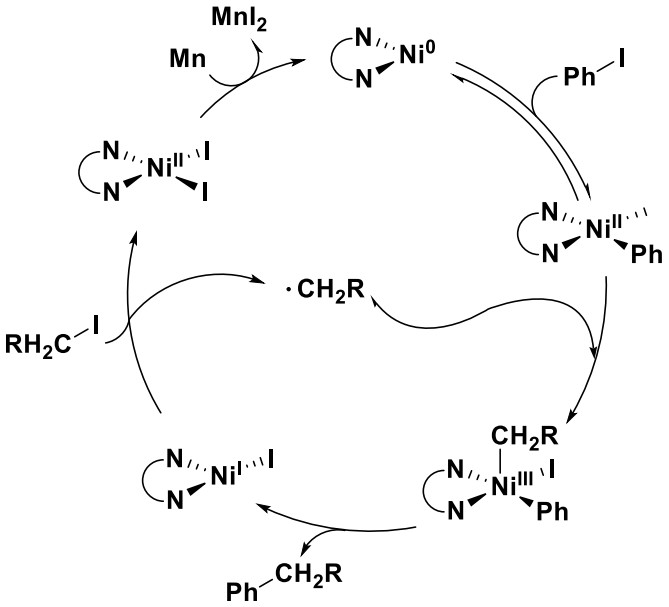
A cocktail of various catalysts enabled the reductive cross-coupling of aryl halides (I, Br) with alkyl halides (I, Br) without the intermediacy of a stoichiometric organometallic reagent. In this work by the Weix group, the pre-catalyst NiI_2 was most active in the presence of bipyridine, pyridine, and arylphosphine ligands. Both organohalides were employed in equimolar amounts and could contain various substituents including ketones, nitriles, alcohols, and boronic esters (Scheme 5.35).[44]



Scheme 5.35: Reductive nickel-catalyzed alkylation of aryl halides.

The same group published a thorough mechanistic study of the mechanism of such nickel-catalyzed reductive alkyl-aryl cross-coupling reaction.[45a] The authors provide conclusive evidence that no organomanganese reagent is formed. The operation of a transmetalation between two different organonickel species and sequential formal

oxidative addition at a single nickel center was excluded. The mechanism rather seems to involve a radical pathway where the rapidly formed arylnickel(II) species combines with the free alkyl radical to give a nickel(III) species that undergoes reductive elimination (Scheme 5.36).

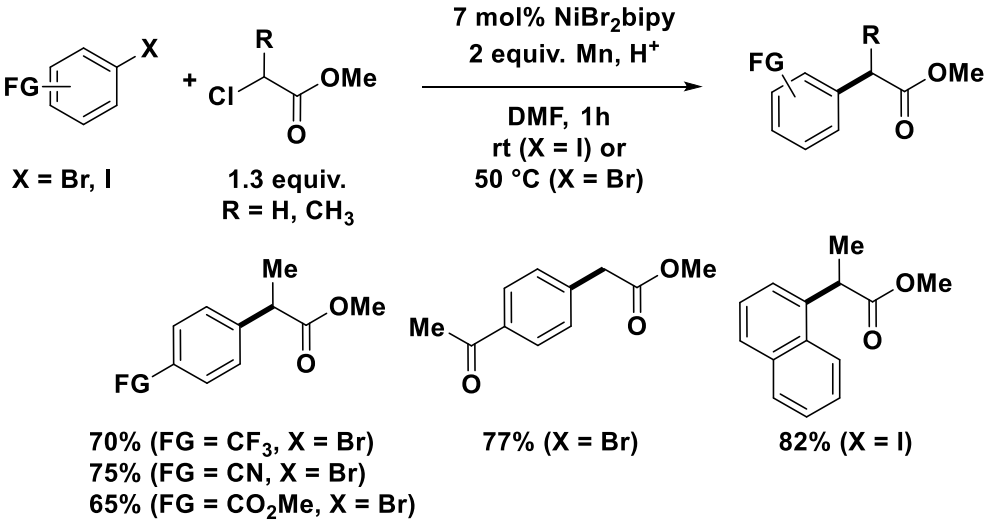


Scheme 5.36: Coexisting polar and radical steps in nickel-catalyzed aryl-alkyl couplings.

The resulting nickel(I) intermediate engages in an SET reductive cleavage of another alkyl halide to generate a new alkyl radical and a nickel(II) complex. The latter is reduced by equimolar Mn to give Ni(0), which activates another aryl halide molecule. An alternative off-cycle process for the formation of the alkyl radicals was also proposed.

In similar manner, reductive alkylations of 2-chloropyridines with various alkyl bromides bearing ester, amide, and ether groups in moderate yields were accomplished. A catalyst formed from $NiBr_2 \cdot 3H_2O$ and 4,7-diphenylphenanthroline (each 5 mol%) and Mn (1.5 equiv.) were used in DMF at 40 °C.[45b]

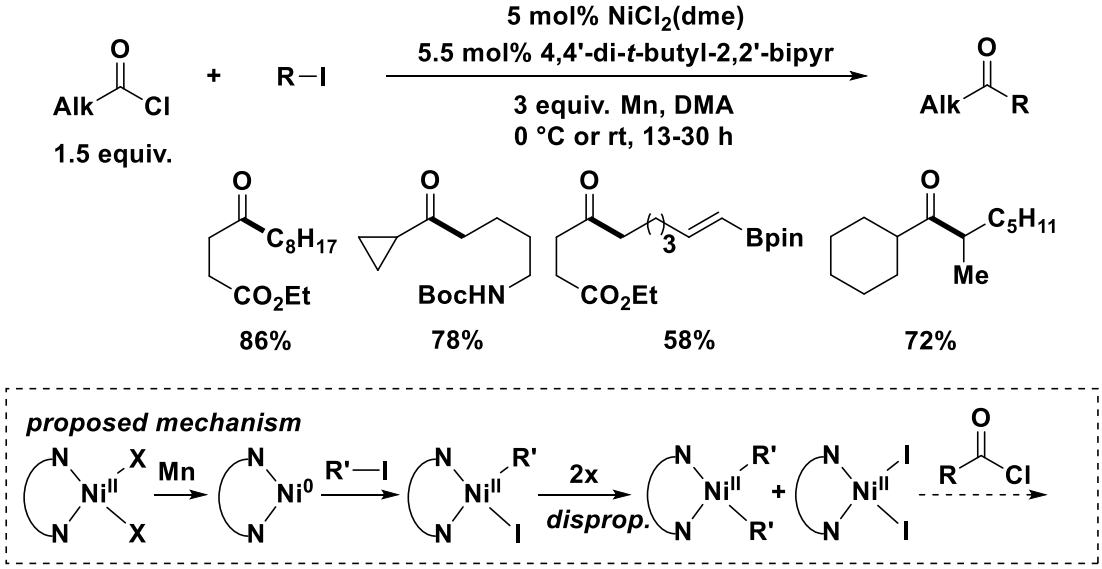
Another class of activated organochlorides were used by Durandetti *et al.* in a nickel-catalyzed reductive alkylation of aryl halides (Br, I) (Scheme 5.37). *α*-Chloroesters were coupled with various aryl halides bearing electron-donating or electron-withdrawing substituents using manganese as reductant.[46]



Scheme 5.37: Nickel-catalyzed reductive coupling with *α*-chloroesters or allyl acetate.

5.4.2.4 Ketone formation

Weix *et al.* further reported reductive conditions for the synthesis of unsymmetrical dialkyl ketones from acyl chlorides and alkyl iodides with manganese (Scheme 5.38).

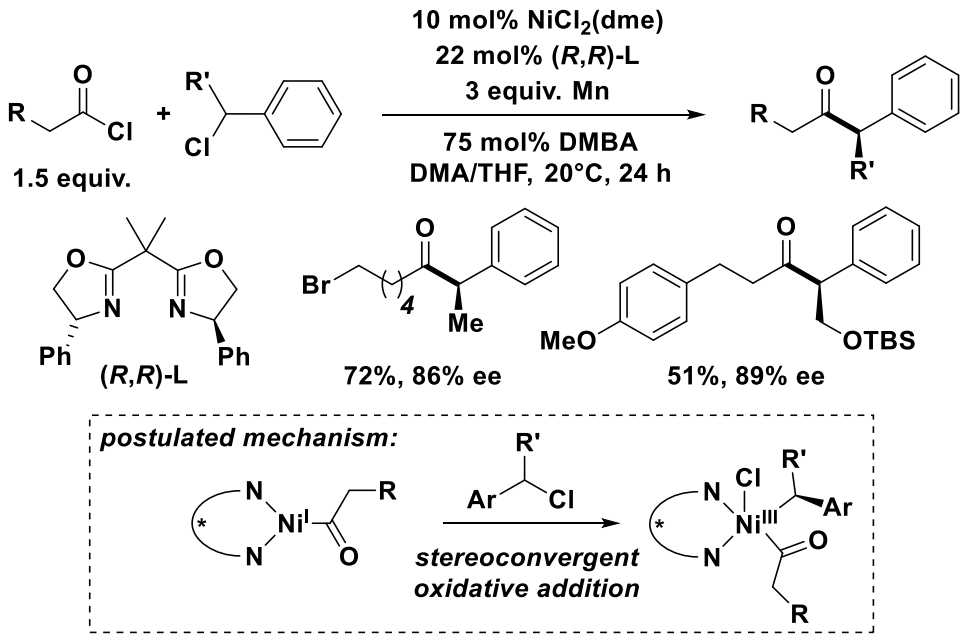


Scheme 5.38: Nickel-catalyzed reductive dialkyl ketone synthesis.

The acyl chloride was used in excess (1.5 equiv.). Replacement of Mn with Zn allowed coupling of (2-pyridyl)thioesters under otherwise identical conditions. A wide variety of functional groups is tolerated, including carboxamides, esters, and alkyl borane moieties.[47] A mechanistic proposal was presented which suggests the

reduction of [Ni(dtbpy)Cl_2] (dtbp = 4,4'-di-*tert*-butyl-2,2'-bipyridine) by metallic manganese or zinc to a nickel(0) complex. Alkyl iodide activation and disproportionation affords [Ni(dtbpy)I_2] and [Ni(dtbpy)(R')$_2$]. The latter is believed to react with the acyl chloride to form the ketone (Scheme 5.38).

The first enantioselective version of such carbonyl alkylation was recently reported by Reisman *et al.* A nickel catalyst with a chiral bis(oxazoline) (box) ligand allows the employment of secondary benzyl chlorides and acyl chlorides to give *α*-chiral ketones in good yields and enantiomeric excess. Key to success seems to be a stereoconvergent oxidative addition of the racemic benzyl chloride to the postulated complex (box)Ni(I)-acyl. The addition of 2,6-dimethylbenzoic acid decreased the amount of homocoupling products. Manganese (3 equiv.) served as reductant of the catalytic Ni(I) or Ni(II) intermediates (Scheme 5.39).[48]



Scheme 5.39: Enantioselective *α*-alkyl-*α*-arylketone synthesis.

5.5 Iron catalysed reactions

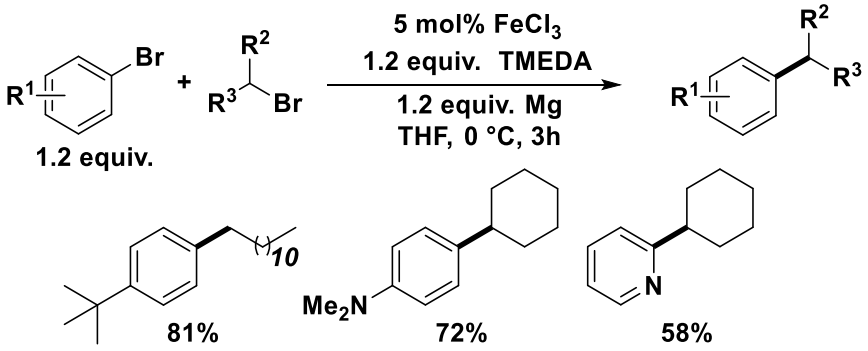
Iron is much less used as catalyst in cross-coupling reactions than nickel and palladium despite its low toxicity, high abundance and low price. More than 30 years after the pioneering work of Kochi in the 1970, iron-catalyzed cross-coupling reactions were rediscovered and applied to several highly efficient C-C bond formations. However, the use of iron catalysts in C-C cross-couplings requires strongly reducing conditions for the formation of a reactive low valent catalyst

species. This resulted in Grignard reagents being the most widely used organometallics in such reactions. The low functional group tolerance that is usually associated with the use of stoichiometric amounts of preformed highly basic and nucleophilic organomagnesium halides makes direct reductive cross-coupling reactions an especially attractive alternative.

5.5.1 Magnesium mediated reactions

5.5.1.1 Arylation of alkyl bromides

The first protocol for direct iron-catalyzed cross-coupling between two electrophiles was published in 2009 by Jacobi von Wangelin *et al.* Aryl bromides were successfully coupled with alkyl bromides (and chlorides) using a simple pre-catalyst mixture comprising iron(III) chloride and TMEDA (Scheme 5.40).

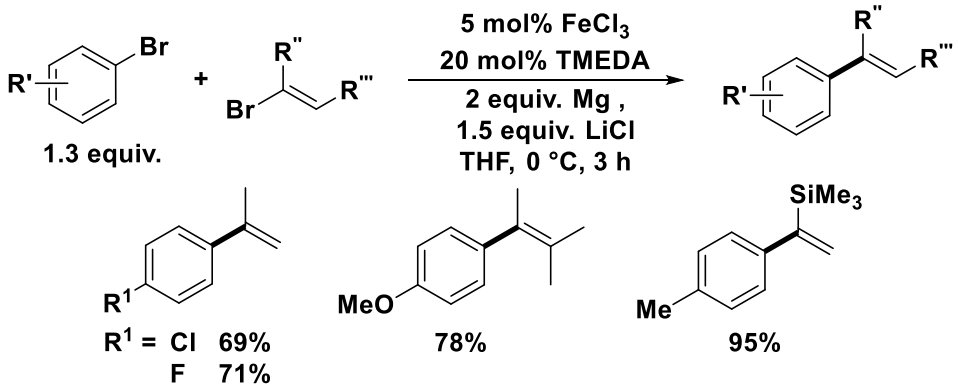


Scheme 5.40: Iron-catalyzed reductive cross-coupling of aryl and alkyl bromides.

Under mild conditions, the Grignard reagent is formed *in situ* and undergoes rapid coupling with the second electrophile. Kinetic investigations revealed that the Grignard formation and the cross-coupling step proceed under iron catalysis. The functional group tolerance is much lower than in zinc or manganese-mediated reactions.[49] The role of TMEDA as additive is not fully understood but is believed to involve deceleration of the Grignard forming step by blocking the Mg surface, enhancement of transmetalation, and coordination to the active iron species.

5.5.1.2 Arylation of alkenyl halides

A related iron-catalyzed cross-coupling without pre-formation of organomagnesium species was realized between activated aryl bromides and alkenyl bromides (Scheme 5.41).



Scheme 5.41: Reductive sp^2-sp^2 cross-coupling between aryl and alkenyl bromides.

Catalytic amounts of TMEDA were sufficient. The aryl bromide was used in slight excess (1.3 equiv.), possibly due to the consumption in pre-catalyst reduction with traces of *in situ* formed arylmagnesium halides.[50]

5.6 Summary and Outlook

Reductive cross-coupling reactions between two electrophiles (or reductive cross-electrophile coupling reactions) have recently gained a strong foothold among the arsenal of cross-coupling reactions. Unlike the conventional coupling protocols involving stoichiometric amounts of pre-formed organometallic species, the employment of bench-stable and abundantly available electrophiles results in much safer handling and operational simplicity. Furthermore, similar substrate scopes and functional groups can be tolerated. Complexes of 3d transition metals with suitable ligands have been demonstrated to be the most active catalyst species (Ni, Co, Fe). Cheap and non-toxic metals (Zn, Mn, Mg) can be used as stoichiometric reductants. However, the mechanistic details of many reductive cross-coupling protocols are not sufficiently explored. The most advanced studies have been performed at nickel-catalyzed aryl-alkyl couplings with manganese. The activation of the aryl halide appears to follow a two-electron oxidative addition pathway while the alkyl halide is

subject to a single electron reduction. The stoichiometric reductant effects catalyst reduction after each formal oxidative activation step. In comparison with the recently developed oxidative cross-couplings between two organometallic species, reductive cross-couplings exhibit a higher redox economy and sustainability as no preceeding Umpolung steps are required. Further mechanistic understanding of the underlying reductive elemental steps and radical intermediates will certainly fuel wider applications of this general concept. Iron catalysts are likely to play a key role in the near future and will further emphasize the superior sustainability of reductive cross-coupling reactions over the conventional heteropolar procedures. Significant effort should also be devoted to the optimization of reaction conditions which mostly require high catalyst loadings, large excess amounts of one reactant and the metallic reductant, and an often complex catalyst cocktail. Many reported protocols also suffer from high halogen contents in the starting materials, additives, and catalysts which ultimately poses the question of waste treatment. The development of enantioselective versions will advocate further applications in the context of complex molecule synthesis. Finally, it should be noted that cross-coupling reactions also bear a conceptual advantage over the rapidly developing field of cross-dehydro-coupling processes involving some type of CH activation event. Generally, cross-coupling reactions (oxidative, reductive or heteropolar) exhibit perfect regioselectivity and site specificity and a much lower dependence on substitution patterns.

The field of reductive couplings has already come a long way from the early metal-mediated and electrochemical homo-coupling reactions between electrophiles to the most recent highly selective cross-coupling protocols which tolerate acidic protons, carbonyls and halides. We are convinced that reductive cross-coupling reactions will fledge in the very near future and soon be on a par with the conventional cross-coupling reactions which were given a considerable headstart. The recent reports on highly selective reductive cross-couplings have casted serious doubts on the accepted imperative to prepare and handle sensitive and hazardous organometallic reagents when performing cross-coupling reactions.

5.7 References

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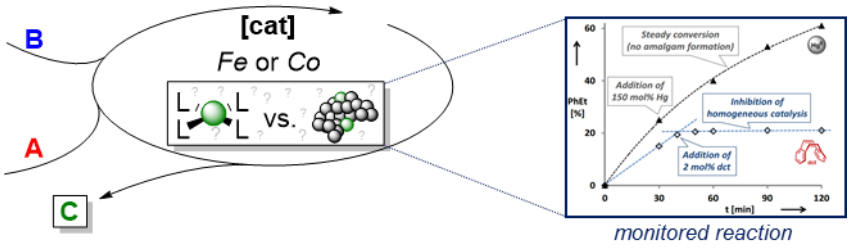
6 Summary

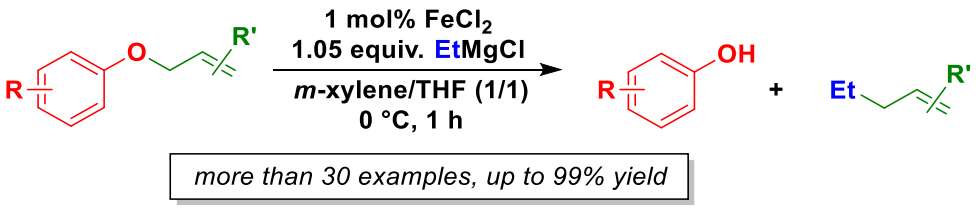
The application of sustainable, abundant and non-toxic catalytic processes becomes more and more important. Especially 3d-metals like iron and cobalt based catalysts constitute to be an interesting alternative to well-established noble metal catalysts. But several limitations (e.g. lifetime, selectivity, etc.) still prevent their industrial application. Mechanistic understanding is the key for further catalyst adjustments. *Chapter 1* contains a review about two of the most important techniques that can be used to distinguish between homotopic and heterotopic catalysts.



Scheme 6.1: How to distinguish between homotopic and heterotopic catalysts.

The highlighted so called *in operando* techniques are kinetics, reaction progress analyses and poisoning experiments. Since there is not a single test that can proof homo- or heterotopicity of catalytic system, always various tests should be performed to validate results.

In *chapter 2*, a facile iron-catalyzed deallylation protocol has been described.[2]

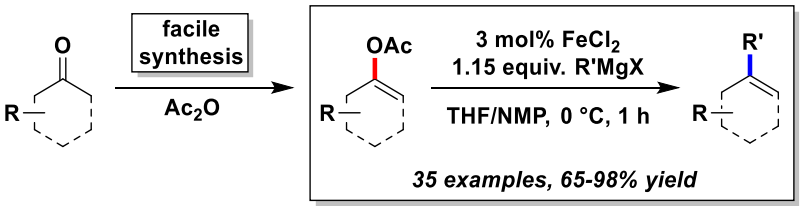


Scheme 6.1 Iron-catalyzed deallylation of allyl ethers.

The described protocol utilizes iron(II)-chloride as pre-catalyst under mild reaction conditions (0 °C). A selective deallylation process occurs in less than one hour for a variety of compatible substrates. Tolerable functional groups are halides, olefins, esters, methylthio, allylamine, and benzylether groups. The only by-products (propene, pentene, CO_2, etc.) obviates the need for laborious product separation. The use of

NHC-ligands enhanced the reaction rate. Beside allyl ethers, also benzylic ethers and carbonates could be successfully cleaved.

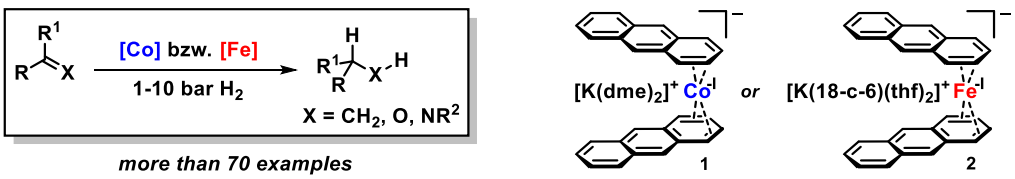
Chapter 3 contains a practical iron-catalyzed protocol for the chemoselective cross-coupling of alkenyl acetates with Grignard reagents.



Scheme 6.2 Iron-catalyzed cross-coupling of alkenyl acetates and Grignard reagents.

The combination of iron(II)-chloride and Grignard reagents under mild reaction conditions (0 °C) enabled the selective cross-coupling of alkenylacetates as electrophiles with nucleophilic Grignard reagents. Thermodynamically preferred deprotonation and acylation reactions are suppressed by the highly active catalyst system. A *post*-isomerization (even to thermodynamically more favored olefins) does not occur. Several primary and secondary Grignard reagents can be utilized and numerous functional groups, like halides, nitriles, esters, acetals, ethers and thioethers are tolerated. Kinetic studies and poisoning experiments support a homogeneous mechanism. An observed secondary KIEs suggest a rate-determining coordination of the conjugated alkenyl acetate.

The catalytic hydrogenations of alkenes, ketones and imines with homoleptic iron- and cobalt arene complexes are described in *chapter 4*.



Scheme 6.3: Cobalt- and Iron-catalyzed hydrogenation of alkenes, ketones and imines.

For the first time bis(anthracene)cobaltate and bis(anthracene)ferrate, have been utilized in catalytic hydrogenation reactions. Bis(anthracene)cobaltate was highly active in the hydrogenation of alkenes, ketones, and imines(1–5 mol% cat., 1–10 bar

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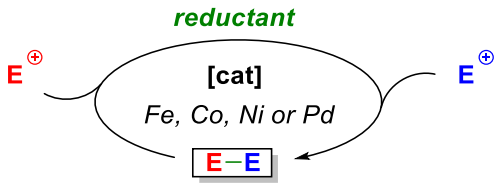
H_2, 20–60 °C). The corresponding ferrate revealed a lower activity and stability; only olefins could be hydrogenated. Kinetic studies and poisoning experiments suggest a homogeneous catalyst. The hydrogenation is initiated by the substitution of arene ligand by two olefins. Consecutive hydrogenation reactions showed that the catalytic system is stable as long as π-acceptors are present. Consecutive reactions were performed without loss of activity.

In *chapter 5* a detailed review about reductive cross-coupling reactions between two electrophiles (or reductive cross-electrophile coupling reactions) is included.



Scheme 6.5: Metal-catalyzed reductive cross-coupling between two electrophiles.

Compared to oxidative cross-coupling protocols, with two organometallic partners, reductive cross-couplings have a better redox potential economy and sustainability. Most active catalysts for these transformations are 3d-metal complexes (Ni, Co, Fe). As stoichiometric reductants, cheap and non-toxic metals (Zn, Mn, Mg) can be utilized. Further mechanistic understanding of the underlying reductive elemental steps and radical intermediates will certainly fuel wider applications of this general concept. Most mechanistic studies have been done for Ni-catalyzed aryl-alkyl-coupling reactions with manganese as reductant. Promising are especially Fe-based catalysts, due to their superior sustainablility. The need of high catalyst loadings, large amounts of one reactant and reductants and a frequent use of halogen containing substrates are disadvantageous and further optimizations are worthwhile.

7 List of Abbreviations

Ac	acetyl
acac	acetylacetonate
AH	asymmetric hydrogenation
Alloc	allyloxycarbonyl group
approx.	approximately
Ar	aryl
ATH	asymmetric transfer hydrogenation
ATR	attenuated total reflection
Bu	buthyl
°C	degree Celsius
DABCO	1,4-diazabicyclo[2.2.2]octane
Dct	dibenzo[a,e]cyclooctatetraene
DIAD	diisopropyl azodicarboxylate
DIBAL-*H*	diisopropyaluminium hydride
DIPP	2,6-diisopropylphenyl
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
EI	electron impact
Et	ethyl
eV	electronvolt
equiv.	equivalents
FID	flame ionization detector
GC	gas chromatography
h	hour(s)
HMDSO	hexamethyldisiloxane
HR MS	high resolution mass spectrometry

Hs	high spin
IPr·HCl	1,3-bis(2,6-diisopropylphenyl)imidazolium chloride
IR	infrared
J	coupling constant
KHMDS	potassium bis(trimethylsilyl)amide
KIE	kinetic isotope effect
L	liter
LHMDS	lithium bis(trimethylsilyl)amide
LR MS	low resolution mass spectrometry
Ls	low-spin
Nacnac	1,3-diketimine
NBS	*N*-bromosuccinimide
NMP	*N*-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
NP	nanoparticles
m	meter
M	mol per liter
Me	methyl
min	minute(s)
MHz	megahertz
Mp.	melting point
MS	molecular sieves
NHC	*N*-heterocyclic carbene
ON	overnight
Ph	phenyl
Piv	pivaloyl
ppm	parts per million
Pr	propyl

r.t.	room temperature
SET	single electron transfer
SIMes·HCl	1,3-bis(2,4,5-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene
TBC	4-*tert*-butylcatechol
TBHP	*tert*-butylhydroperoxide
Tf	trifluoromethanesulfonyl
THF	tetrahydrofurane
TMEDA	bis(2-(*N*,*N*-dimethylamino)ethyl)ether
TMDSO	1,1,3,3-tetramethyldisiloxane
TLC	thin-layer chromatography
TMS	tetramethylsilane
TMSCl	trimethylsilyl chloride
TON	turnover number
TOF	turnover frequency
p-TSA	para-toluenesulfonic acid
UV	ultraviolet

8 Acknowledgements

Mein ganz besonderer Dank gilt Herrn Prof. Dr. Axel Jacobi von Wangelin für die interessanten Aufgabenstellungen, die wertvollen Anregungen und Tipps, die hervorragende Betreuung während der letzten 4 Jahre, sowohl für die Masterarbeit als auch für die Promotion und für die sehr angenehme Arbeitsatmosphäre.

Frau Prof. Dr. Olga Garcia Mancheño danke ich für die Übernahme des Zweitgutachtens.

Herrn Prof. Dr. Robert Wolf danke ich für die wertvolle Unterstützung und Diskussionsbereitschaft während unserer gemeinsamen Kooperationen sowie für die Übernahme des Amtes des Drittprüfers.

Herrn Prof. Dr. Achim Göpferich danke ich für die Übernahme des Amtes des Prüfungsvorsitzenden. Danke auch für die herzlichen Worte am Gang.

Der Arbeitsgruppe Wolf, insbesondere Philipp Büschelberger, Stefan Pelties und Dr. Babak Rezaei Rad, danke ich für die sehr gute Zusammenarbeit und die rege Diskussionsbereitschaft.

Den Arbeitsgruppen Fleischer und Garcia danke ich für die zahlreichen schönen Abende im Bierzelt. Besonders erwähnen möchte ich noch Vera Hirschbeck für die abendliche Korrekturarbeit.

Von der Arbeitsgruppe Geschwind danke ich besonders Julian Greindl und Florian Hastreiter für die vielen Kicker- und Bierabenteuer.

Mein Dank gilt den Mitarbeitern der Zentralen Analytik, der Glasbläserei und Werkstätten. Frau Ulrike Weck danke ich für ihre wertvolle und schnelle Hilfe bei organisatorischen Fragen.

Ich danke allen Forschungspraktikanten und Bacheloranden für die von Ihnen geleistete Arbeit.

Mein ganz großer Dank gilt natürlich den jetzigen und ehemaligen Mitarbeitern der Arbeitsgruppe Jacobi:
Dr. Raul Perez-Ruiz für die hervorragenden Rotweine, den guten Serranoschinken und die vielen Steuerbescheide. Meinem Laborkollegen Efrain *Elfi* Reyes-Rodriguez für das nächtliche Korrekturlesen, die sehr angenehme Arbeitsatmosphäre, die interessanten Diskussionen, die tollen gemeinsamen Abende und prägende Lebensweisheiten: „Viel Spaß, viel Erfolg“. Tim N. Gieshoff für die interessanten Diskussionen, schönen Tagungen und gemeinsamen Feiern. Josef *Sepp* Schachtner für die gewinnbringenden Schafkopfabende. Michal *Jesus* Majek für die berauschenden Nächte und die konstruktiven, bereichernden Gespräche. Matteo Villa für Fritti Scampi, Pizza, Pasta und Luca Toni. Diesen und allen anderen für die vielen unvergesslichen, die über den Laboralltag hinausgehenden, Momente.

Herzlich möchte ich mich bei Michaela Lutz für die hervorragende Arbeit und Unterstützung, den guten Kaffee und die interessanten Gespräche bedanken.

Ich möchte allen meinen Bundesbrüdern der K.St.V. Agilolfia im KV zu Regensburg für die berreichernde Gemeinschaft danken. Besonderer Dank gilt meinem Leibburschen Benno Ehrl und meinem Leibfuxen Christian *Paulchen* Hartl.

Meinen ehemaligen Studienkollegen, Fachschaftskollegen und guten Freunden Justus *„the lone wolf“* Back, Dominik *Dô* Kellner und Mathias OneT Schwedes danke ich für eine unvergesslich schöne Studienzeit.

Allen Freunden, die mich über die gesamte Studienzeit unterstützt und begleitet haben möchte ich danken, dass sie immer für mich da waren sowie für die vielen unvergesslichen Momente. Besonders erwähnen möchte ich Thomas *Bob* Ranner, Sebastian Henneberger, Felix Schell, Nicola Faidt, Christian Lössner, Larissa Neumann, Loi Vo und Julia Gartner

Ganz besonders möchte ich meinem *Bro* und Dr. in spe Nils *Dils* Sorgenfrei danken, der mir hoffentlich nicht wie angekündigt die Freundschaft kündigt, sollte ich vor ihm die Promotion abschließen. Die zahlreichen Diskussionen, sowohl fachlicher als auch

privater Natur, die sehr schönen gemeinsamen Momente, vor allem während der letzten 4 Jahre, haben mich sehr geprägt.

Ich danke meiner Mutter Beate Wolbert, meinem Papa Nils Wolbert, meiner Schwester Miriam Reichenberger und meinen Großeltern Elfriede und Ingo Jürgenliemk für die bedingungslose Unterstützung die sie mir während meiner gesamten Studienlaufbahn entgegengebracht haben.

Meiner Freundin Julia Märsch danke ich von ganzem Herzen für die unvergessliche Zeit und die wunderschönen Momente, die wir bereits miteinander verbracht haben. Ich freue mich auf unsere gemeinsame Zukunft.

9 Curriculum Vitae

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(Master of Science)

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List of Publications

(1) *"Highly Practical Iron-Catalyzed C-O Cleavage Reactions"*, D. Gärtner, H. Konnerth, A. Jacobi von Wangelin, *Catal. Sci. Technol.* **2013**, *3*, 2541.

(2) *"Heteroatom-Free Arene Cobalt and Iron Catalysts for Hydrogenations"*, D. Gärtner, A. Welther, B. R. Rad, R. Wolf, A. Jacobi von Wangelin, *Angew. Chem. Int. Ed.* **2014**, *53*, 3722.

(3) *"Reductive Cross-Coupling Reactions between Two Electrophiles"*, C. E. I. Knappke, S. Grupe, D. Gärtner, M. Corpet, C. Gosmini, A. Jacobi von Wangelin, *Chem. Eur. J*. **2014**, *20*, 6828.

(4) *"Iron-Catalyzed Cross-Coupling of Alkenyl Acetates*", D. Gärtner, A. L. Stein, S. Grupe, J. Arp, A. Jacobi von Wangelin, *Angew. Chem. Int. Ed.* **2015**, *54,* 10545-10549.

(5) "*Transition Metal-Free Reductive Silylation of (Het)Aryl Bromides*", S. Gülak, , E. Reyes-Rodriguez, D. Gärtner, A. Jacobi von Wangelin, **2015**, *manuscript in preparation*.

(6) "Polyarene and Alkene Metalates as Precatalysts in Hydrogenations", P. Büschelberger, D. Gärtner, A. Jacobi von Wangelin, R. Wolf, **2015**, *manuscript in preparation*.

(7) "How to Distinguish Between Homotopic and Heterotopic Fe- or Co-Catalysts". D. Gärtner, A. Jacobi von Wangelin, **2015**, *manuscript in preparation*.

Presentations (Poster, Oral)

(1) D. Gärtner, A. Jacobi v. Wangelin, "*Iron-Catalyzed Deprotection of Allyl Ethers"*, FeUR, **2012,** Regensburg (Germany). (Poster)

(2) D. Gärtner, A. Jacobi v. Wangelin, "*Iron-Catalyzed Deprotection of Allyl Ethers"*, Liebig-Vereinigung für Organische Chemie (ORCHEM), **2012,** Weimar (Germany). (Poster)

(3) D. Gärtner, H. Konnerth, A. Jacobi von Wangelin, "*Chemoselective Iron-Catalyzed Deprotection of Allyl Ethers"*, Wissenschaftsforum Chemie (WiFO), **2013**, Darmstadt (Germany). (Vortrag und Poster)

(4) D. Gärtner, H. Konnerth, A. Jacobi von Wangelin, "*Chemoselective Iron-Catalyzed Deprotection of Allyl Ethers*", 2nd Bi-national South African–German Organic Chemistry Conference (BOCC), **2013**, Tutzing (Germany). (Poster).

(5) D. Gärtner, P. Büschelberger, R. Wolf, A. Jacobi v. Wangelin, "*Heteroatom-Free Arene- and Alkene-Cobalt and Iron Catalysts for Hydrogenations*", International Symposium on Relations between Heterogeneous and Homogenous Catalysis (ISHHC), **2015**, Utrecht (Netherlands). (Poster)

(6) D. Gärtner, A. L. Stein, S. Gruppe, J. Arp, A. Jacobi von Wangelin, "*Chemoselective Iron-Catalyzed Cross-Coupling* of Organo Acetates*"*, Wissenschaftsforum Chemie (WiFO), 2015, Leipzig (Germany). (Poster)

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Regensburg, den 16.10.