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"Base-Metal Catalyzed Hydroamination of Dienes"

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Thomas Maier, BSc

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Abstract

To improve the transition metal catalyzed hydroamination of dienes with secondary amines, the possibility to conduct this reaction with catalysis through complexes of the base metals iron, cobalt, manganese and nickel was investigated. To do so, a benchmark system consisting of morpholine and cyclohexadiene was reacted by catalysis with *in situ* generated phosphine and phosphite complexes of the mentioned metals. The resulting mixtures were analyzed with a GC-FID method.

No reactivity was found in the tested Manganese, Iron and Cobalt containing systems.

For the Nickel based reactions, a trend could be observed which leads to the assumption, that ligands, which are sterically not demanding, strong σ-donors are beneficial for the reaction. Additionally, multidentate ligands seem to improve the reaction as well.

Zusammenfassung

Um die übergangsmetallkatalysierte Hydroaminierung von Dienen mit sekundären Aminen zu verbessern, wurde die Möglichkeit untersucht, diese Reaktion mit Komplexen der Grundmetalle Eisen, Cobalt, Mangan und Nickel zu katalysieren. Dazu wurde ein Standardsystem bestehend aus Morpholin und Cyclohexadien mit *in situ* erzeugten Phosphin und Phosphit Komplexen ebenjener Metalle zur Reaktion gebracht. Die so erhaltenen Reaktionmischungen wurden mittels GC-FID untersucht.

Es konnte keine Reaktivität in den getesteten, mangan-, eisen- und cobaltbasierenden Systemen festgestellt werden.

Bei den durch Nickel katalysierten Reaktionen konnte dagegen ein Trend beobachtet werden, der daraufhin deutet, das sterisch wenig anspruchsvolle, Liganden, die einen starken σ-Donor darstellen für die Reaktion förderlich sind. Außerdem scheinen multidentate Liganden die untersuchte Reaktion zu fördern.

"The story so far:

In the beginning the Universe was created.

This has made a lot of people very angry and been widely regarded as a bad move."

Douglas Adams, The Restaurant at the End of the Universe

Abbreviations

acac ..... *acetylacetonate*
CHD *1,3-cyclohexadiene*
COD ..... *1,6 -cyclooctadiene*
DCM ..... dichloromethane
DEAD .. *ethyl(NZ)-N-ethoxycarbonyliminocarbamate*
DI ..... *deionized*
DPPF ..... *bi(diphenylphosphino)ferrocene*
ee ..... *enantiomeric excess*
EtOH ..... *ethanol*
FID ..... *flame ionisation detector*
GC ..... *gaschromatography*
HA ..... *hydroamination*
IMes ... *1,3-Bis(2,4,6-trimethylphenyl)imidazolinium chloride*
iPr ..... *iso-propyl*
MeOH ..... *methanol*
MES ..... *mesitylene*
MS ..... *mass spectrometry*
nBu ..... *n-butyl*
tBu ..... *tert-Butyl*
TFA ..... *trifluoroacetic acid*
UV ..... *ultra violett light*

Table of contents

1. Introduction

1.1 Amines

Amines are a versatile compound class found throughout nature. Since they are such a large group of substances, they have a diverse range of (bio)chemical properties. Amines are found in recreational drugs and pharmaceutical drugs like caffeine and morphine as well as in amino acids like glycine and of course in poisonous substances such as strychnine, as well as in common biochemical substances used as nutritional supplements like creatine (Figure 1).[1–5]

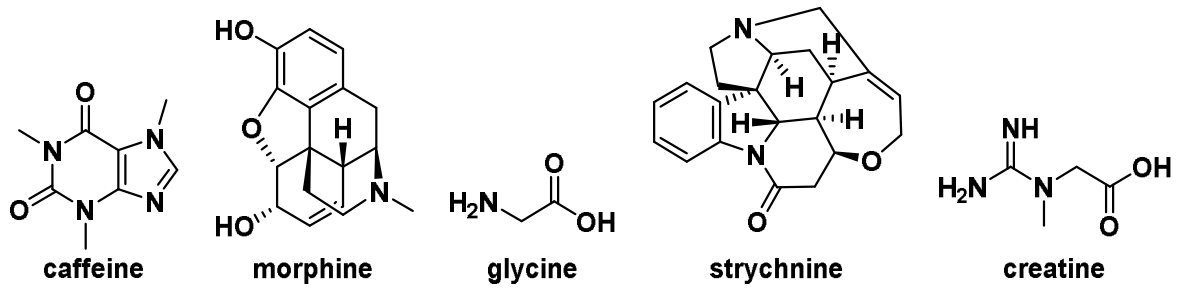


Figure 1: Natural compounds containing amine group.[1–5]

Since they play a vital role in many (bio)chemical processes, they are not only of interest for the organic chemist but for pharmaceuticals as well. Therefore it is no surprise that all top five grossing pharmaceuticals in the USA in 2013 contained an amine group or a derivative thereof.[6]

For the organic chemist, they are of interest not only as products but as reactants as well. Many amines, often of simple structure, are used in synthesis not only as building blocks but for example as bases as well. This is probably due to their tunable basicity and the fact that many of them are easily soluble in common organic solvents.

Another established use of amines is the use as catalysts for example in phase transfer catalysis in the form of an ammonium salt (see Figure 2).[7]

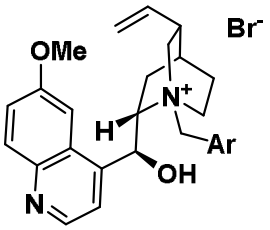


Figure 2: An example of a quartery ammonium salt for phase transfer catalysis.[8]

Furthermore, they can be used as catalysts in Michael reactions to achieve enantio- and chemoselectivity.[9]

Additionally, they offer interesting properties as ligands in transition metal catalyzed reactions for example as PNP pincer type ligands (Figure 3).

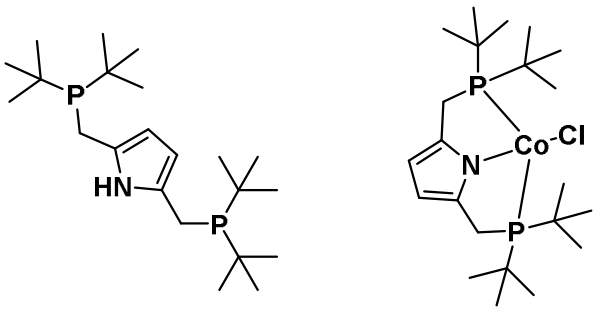


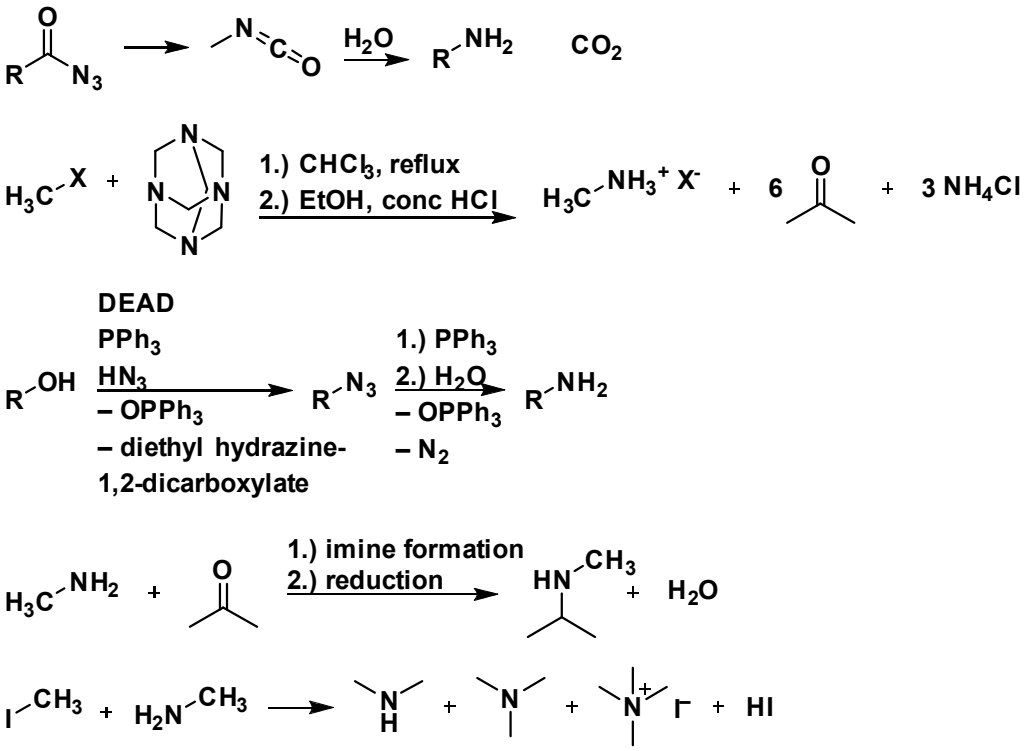
Figure 3: An example for an amine as a Ligand in a PNP complex.[10]

In summary, amines play a vital role not only in chemistry but in biochemistry and pharmacy as well. Thus, methods to synthesize amines are quite an interesting and important topic.

1.2 Traditional Synthesis of Amines

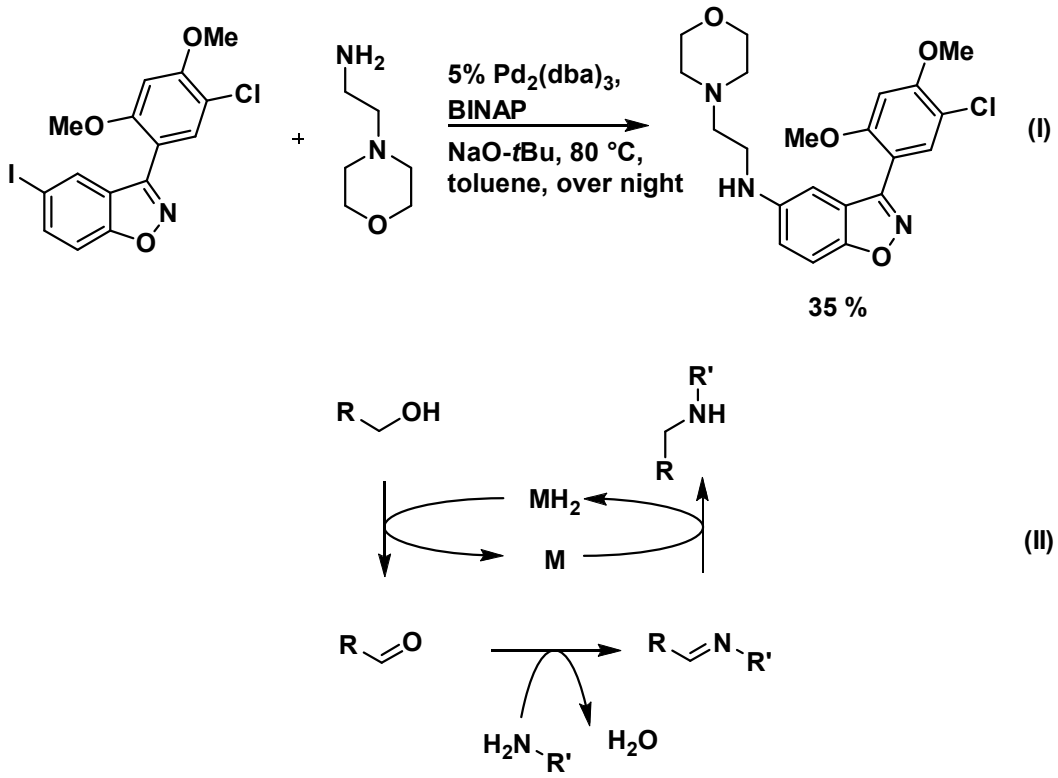
Nowadays, amines can be produced through various reactions, each with its various disadvantages, for example, most – if not all – are not waste free.

Methods to synthesize amines in traditional organic syntheses include, but are not limited to the Curtius reaction[11] and the Delépine reaction[12] as well as two step syntheses like the Mitsunobu reaction.[13] Other possibilities include the formation of an imine from an amine and a ketone followed by a reduction step or the treatment of an amine with an alkylation reagent like methyl iodine to obtain a more highly substituted amine (Scheme 1).



Scheme 1: Traditional amine syntheses.

Of course, there are also transition metal-catalyzed pathways like the Buchwald-Hartwig amination[14] or the borrowing-hydrogen type reactions (Scheme 2).[15]



Scheme 2: Buchwald Hartwig amination[16] (I) and the borrowing hydrogen method (II).[15]

As seen by the number of reactions, the synthesis of amines is quite developed, which again highlights the importance of that substance class. However, all of the shown reactions share a disadvantage, which is the production of stochiometric amounts of byproducts, resulting in large amounts of waste. This is, of course, not desirable in terms of green chemistry methods[17] as well in terms of costs.

Another disadvantage is, that some of them use toxic and hazardous chemicals.

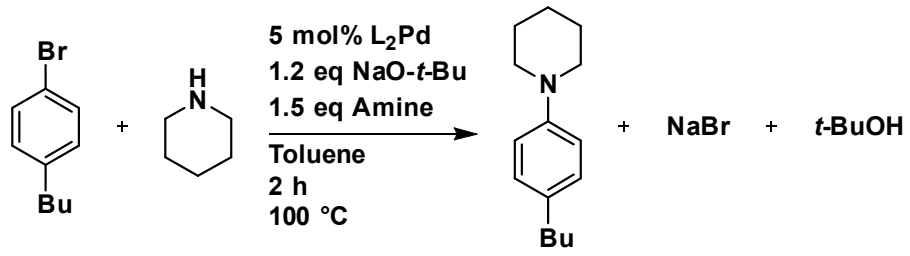
Hydroamination is a promising method to overcome these drawbacks. In this process, a simple amine or even ammonia is reacted with a C-C double or triple bond to generate a C-N and a C-H bond. Advantages and disadvantages of this potentially useful method will be discussed in the next section.

1.3 Hydroamination

Since this work is focused on transition metal catalyzed hydroamination, the following section will highlight different aspects of this method, like its benefits and disadvantages. Although it should be noted that other metal-catalyzed and non-metal-catalyzed methods exist.[18]

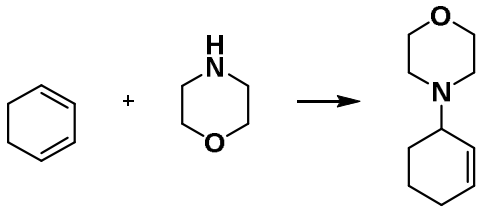
As already mentioned, a prominent disadvantage of traditional amine syntheses is, that they often require the use of hazardous chemicals like methyl iodide or formaldehyde. Therefore, an atom economic process using only an amine and another readily available reagent is quite desirable for generating higher value amines. Other than the hydroamination reaction, it is possible to synthesize amines *via* the hydrogen borrowing methodology. This method is virtually waste free as H_2O is the only by-product. A flaw of this process is the use of alcohols. Of course, they are a common functional group, but the use of olefins would be even more convenient since they are easier to access. Also, an additional method to perform this transformation offers the benefit of versatility.

Although already quite sophisticated, catalyzed methods like the Buchwald-Hartwig amination are not atom economical. In addition, this method needs a bromine or iodine on the coupling partner, which is another disadvantage, because this means more byproducts and the need of a specific element in a defined place (Scheme 3).



Scheme 3: Products of the Buchwald-Hartwig cross coupling were, typically, the tertiary amine is the desired product and NaBr and t-BuOH are the byproducts.[19]

The most ideal approach to tackle the mentioned problems is the direct addition of an amine to an unsaturated C-C bond (Scheme 4).



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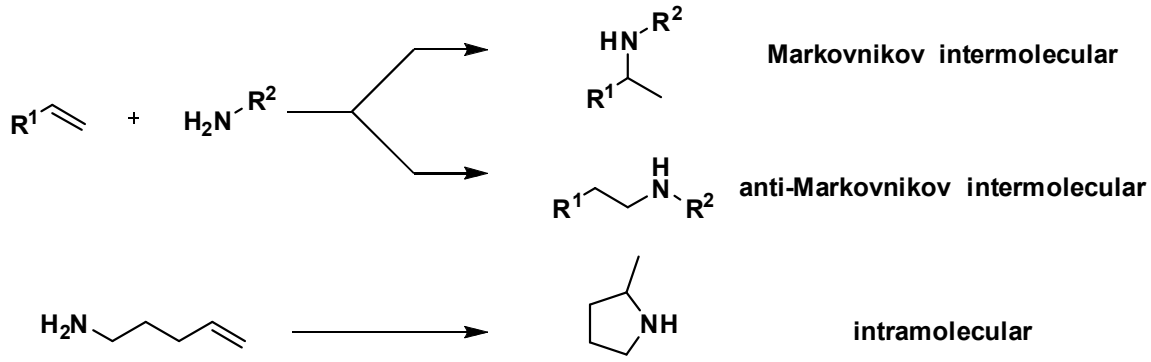
*Scheme 4: Hydroamination of the benchmark system 1,3-cyclohexadiene (CHD) and morpholine yielding 4-(cyclohex-2-en-1-yl)morpholine **1**.*

This process would be highly atom economic and would only use readily available starting materials, olefins and simple amines or even ammonia.

Of course, this process also has its drawbacks. Although the reaction is thermodynamically feasible ($\Delta G^0 \approx 14.7$ kJ mol^{-1} for the addition of ammonia to ethylene) with a slightly exothermic to thermoneutral reaction enthropy,[20] the repulsion between the amine's free electron pair and the electrons of the double bond generates a high activation barrier which hinders the reaction. Since the reaction has a negative reaction entropy, raising the temperature cannot overcome this problem because it would shift the equilibrium towards the starting compounds.[20] This is highlighted in Table 1. A way to overcome this barrier is to use a suitable catalyst.

Table 1: Thermodynamic data for the HA of ethene.[21]

Reaction	ΔG^0 (kJ mol^{-1})	$\Delta_R H^0$ (kJ mol^{-1})	$\Delta_R S^0$ (kJ mol^{-1} K^{-1})
$C_2H_4 + NH_3 \longrightarrow EtNH_3$	–14.7	–52.7	–127.3
$C_2H_4 + EtNH_2 \longrightarrow Et_2NH$	–33.4	–78.2	–152.2
$C_2H_4 + Et_2NH \longrightarrow Et_3N$	–30.0	–79.5	–166.3



Scheme 5: Intra and intermolecular HA; Markovnikov and anti-Markovnikov products.

A few variations of the HA reaction are known; it can be distinguished between an intermolecular HA and an intramolecular HA. Additionally, there are differences in regioselectivity, since Markovnikov or anti- Markovnikov product can be formed (see Scheme 5).[18]

The intramolecular HA is more feasible than the intermolecular variant because of the general entropic advantages of intramolecular reactions, as well as the proximity of the two reacting parts. A lot of work has been done in this field, especially in the last two decades,[20] therefore, some interesting points are highlighted in the next sections.

1.3.1 Hydroamination of dienes

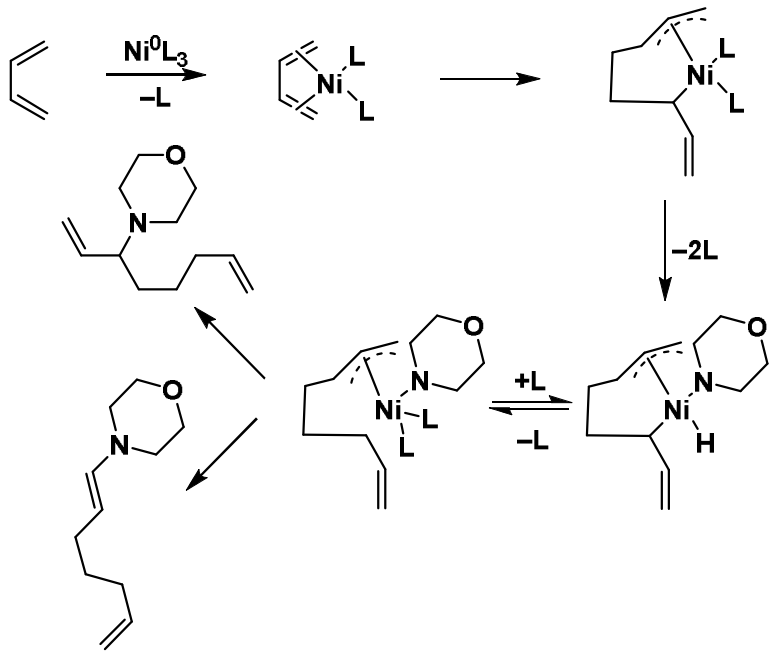
The hydroamination of dienes is different from the hydroamination of a non-conjugated olefin in a few aspects. Since those differences are important for this work, they will be discussed out in detail in this part.

One important trait of alkenes pertinent to this work is the different reactivity of different double bond arrangements.

A few different double bond arrangements can be distinguished, the most important of these for this work are monoenes and dienes. Dienes can, again, be grouped in cumulated, conjugated and non-conjugated, isolated dienes, which all show distinct reactivities. Among these groups, allenes are the most reactive and isolated dienes tend to have the same reactivities as their monoene counterparts. Conjugated dienes tend to have intermediate reactivity.[18]

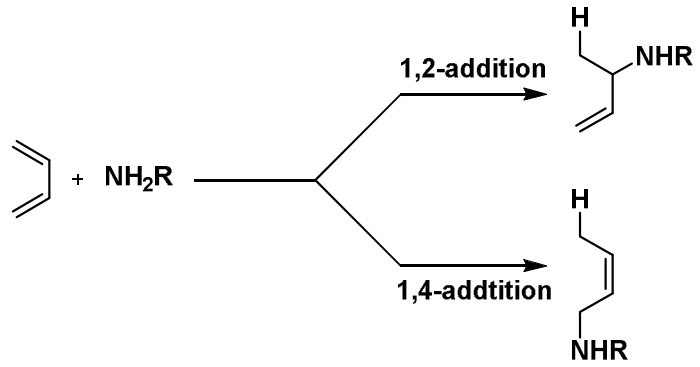
Since conjugated dienes are more reactive,[18] they are more suitable in the search for active systems since they show activity even for systems which are not very active; some of these systems might be worth looking into and could be overlooked using only regular olefins.

Their main disadvantage is that they often undergo side reactions which are not seen when reacting monounsaturated olefins. Dienes tend to oligomerize and form telomers (see Scheme 6) in the presence of an amine under HA conditions.[22]

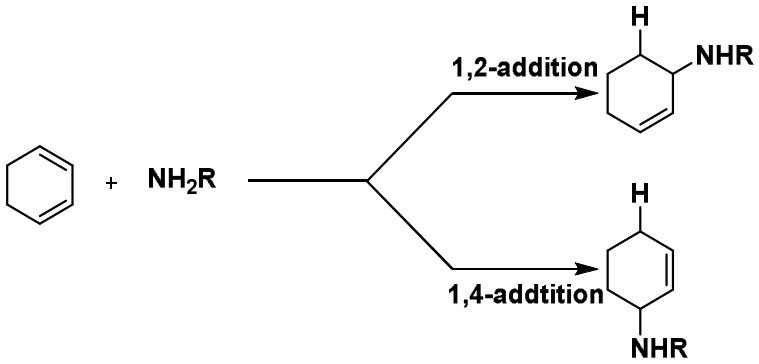


Scheme 6: The telomerization of dienes.

Furthermore, they display a more challenging regio-selectivity; they can react to give a 1,4-adduct and a 1,2-adduct, whereas regular olefins only undergo 1,2-additions (Scheme 7).



Scheme 7: Regioselectivity problem of the hydroamination of butadiene.[23]



Scheme 8: 1,3-cyclohexadiene's hydroamination products are identical.

If the olefin substrate is a cyclic diene like in Scheme 8, 1,4- and 1,2-addition give the same product. Furthermore, probably due to sterical reasons, 1,3-cyclohexadiene does not give telomers. Therefore, the obtained reaction mixtures are simpler, thus easier to analyze.

Additionally, 1,3-cyclohexadiene is easier to use because of its higher boiling point of 80.3 °C[24] compared to butadiene with –4.6 °C.[24]

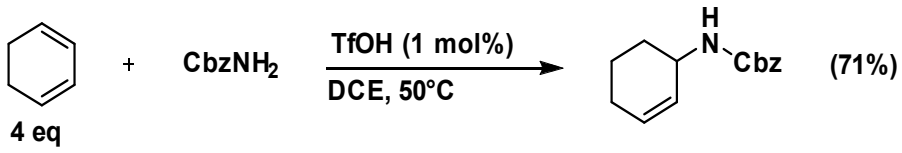
Other simple, conjugated dienes might be used as well for a benchmark reaction, but these two are the most interesting because they are quite prominent among the literature.

Although the intramolecular HA is easier to achieve, the next parts will focus on the intermolecular reaction since it is the topic of this work.

1.4 Hydroamination catalysts

A vast number of different catalysts for different substrate classes are known. Therefore, the following is only an example to highlight the broad versatility of conditions used. The base metals iron, nickel, manganese and cobalt are discussed in more detail in chapter 1.4.1.

Acid catalyzed, metal free methods are established for activated amines with lower basicity, such as *N*-protected amines (Scheme 9) or hydrazines, azoles and anilines.[18] For other substrates, metal catalyzed processes are necessary.



Scheme 9: An example of a HA without transition metal catalysis.

Alkali, alkaline earth and rare-earth metals are also known to catalyze HA reactions.[18,20] The HA reaction of basic primary and secondary amines can be catalyzed, for example, using alkali metals and their readily available derivatives like metal hydrides and alkyl amides.[18] An example for this reaction is the Takasago menthol process, which is used to add diethylamine to myrcene on a multiton scale.[18]

Other examples include clays and zeolites, which are not too reactive for unprotected amines and ammonia but can be used in the reaction between protected amines and higher olefins like cyclohexene.[18] Examples with rare earth metals exist as well. Catalytically active systems containing samarium,[20] yttrium, lanthanum, and lutetium[25] and others are known in the literature. Early transition metals work especially well for the cyclisation of aminoalkenes.[18]

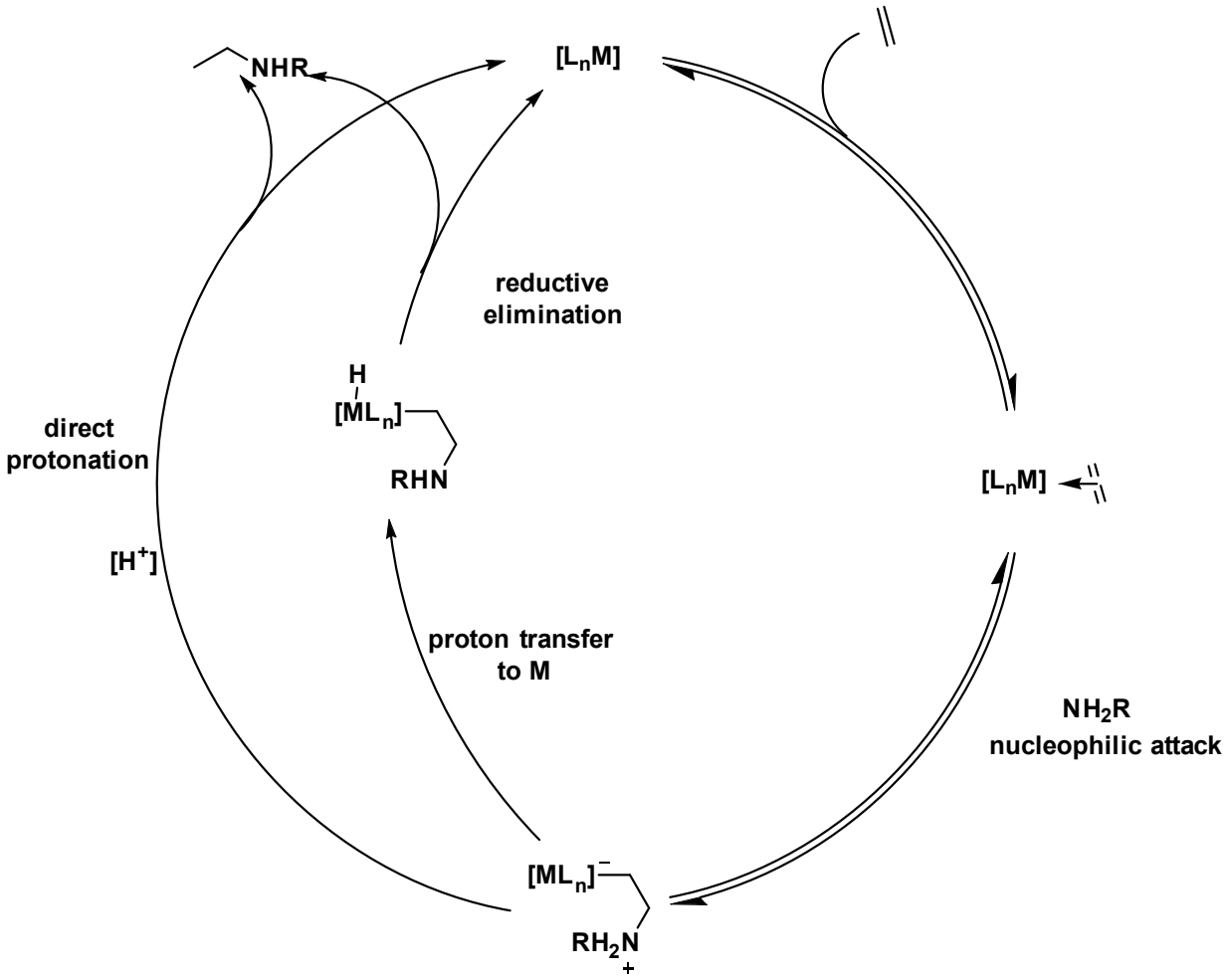
Late transition metals are known to catalyze the HA of dienes and primary or secondary amines. They include rhodium, iridium, ruthenium, platinum and palladium.[18] Palladium (II) is known to be able to catalyze the hydroamination of 1,3-cyclohexadiene with arylamines under mild conditions with a good enantiomeric ratio of up to 96.0:4.0 with a corresponding yield of 63 %.[26]

Gold(I) can catalyze the reaction of a diene with a carbamate or a sulfonamide in a regioselective way under mild conditions. [27–29] Similar systems with bismuth[30] and copper[31] are known as well.

Another example for a gold catalyzed hydroamination is the addition of ammonia to olefins. This reaction can be achieved *via* an Au(I) carbene catalyst.[32] Obviously, the drawbacks of this reaction are the use of a gold catalyst as well as the need for activated HA targets like allenes and alkynes.

1.4.1 Metals covered in this work

For late transition metals, two modes of activation are established, depending on the substrates and the catalyst. The first one includes amine activation, whereas the second one includes olefine activation. For the chosen benchmark reaction, an olefin activation pathway as shown in Scheme 10 is more plausible.[18]



Scheme 10: Hydroamination via olefine activation.

1.4.1.1 Iron

$FeCl_3$ is known to catalyze the addition of an amine to a double bond under certain conditions.[18]

A system utilizing $FeCl_2$, a ligand and a reducing agent is known to catalyze hydroamination reactions. This system uses the higher reactivity of styrene derivatives and an N-protected amine.[33] The drawback of the high amount of Grignard reagent as reducing agent should be noted; the proposed mechanism suggests one equivalent although the authors used four equivalents.

To the best of my knowledge, there are no systems known to date that utilize iron complexes for catalytic hydroamination of dienes. The only exception to this are systems such as DPPF, were iron functions as a part of the ligand. This is described to work for the nickel catalyzed hydroamination of 1,3-cyclohexadiene and morpholine.[21,34]

1.4.1.2 Nickel

Many reports concerning the HA catalyzed by nickel are known;[18] therefore, the next section is highlighting mostly the features, which are important for this work. Until now, there are different approaches to this reaction. Utilizing Ni^{2+} catalysts, mostly with multidentate, ferrocene bridged ligands, Togni and co-workers were able to perform HA reactions in a enantioselective way for amines bearing electron withdrawing groups (Aza-Michael reaction).[21]

Starting from Ni^{2+}, Baker *et al.* managed to get up to 95% yield for a system of $NiCl_2$, $NaBH_4$ phosphine ligand and butadiene and morpholine as substrates, although they mostly observed the telomerized product (Table 2, Entries 1-6). [35]

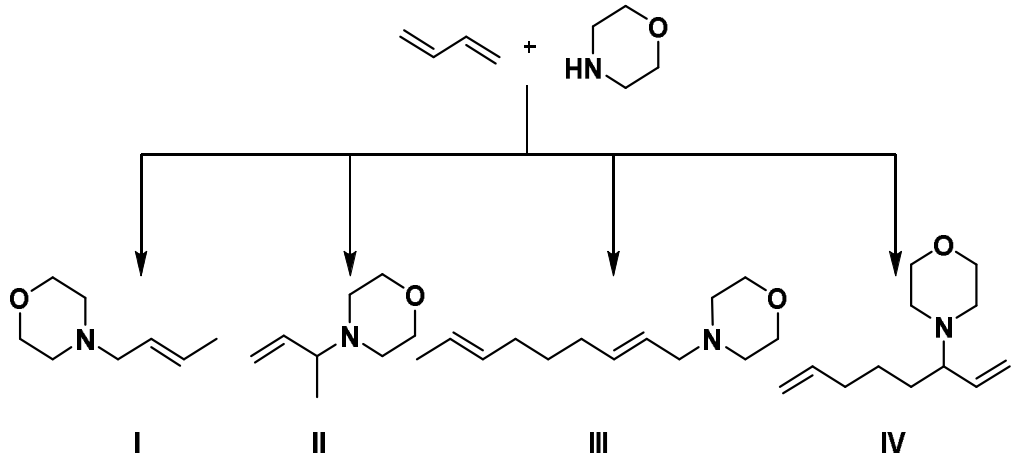
In another work, Baker *et al.* used different Ni^0 and Ni^{2+} systems generated *in situ* to achieve up to 100% yield ($NiBr_2$ in $HCONMe_2$ at 100°C), although again, there were huge amounts of telomers observed.[36]

Hartwig *et al* used a screening approach with a colorimetric assay a to identify $Ni(COD)_2$ with DPPF as a very active system at room temperature.[34] An example can be seen in Table 2, Entry 9, although the same system was used for other dienes and other amines as well.

Tolstikov *et al.* used $Ni(acac)_2$ and phosphorous ligands with triethyl aluminum as reductant to catalyze the reaction of butadiene with morpholine, where they could, at least partially, influence the composition of the product mixture (Table 2 entries 7 and 8).[23] They noticed, that

the composition of the product mixture depends on the nature of the used phosphorous ligand as well as on the use of triethyl aluminum instead of $NaBH_4$.[23] Additionally, the use of TFA suppresses the formation of telomers (Table 2, Entry 10)

Another work by the same authors shows, that this reaction is transferable to other morpholine and piperidine with 1,3-cyclohexadiene as well as with cyclopentadiene. In this work, they stated, that they could not transfer this reaction to 1,3-cyclooctadiene.[37]



Scheme 11: Exemplary products of the hydroamination reaction starting from butadiene and morpholine as mentioned in Table 2.

The different products as mentioned in Table 2 are shown in Scheme 11; I and II result from 1,2 and 1,4 addition of 1,3-butadiene to morpholine, whereas III and IV result from telomerization as described in Scheme 6. For entry one, the same products are generated with the only difference of having to isopropyl moieties on the nitrogen instead of the ring.

Table 2: Exemplary hydroamination reactions with nickel catalysts.

Entry	Precursor	Ligand	Temperature [°C]	Time [h]	Solvent	Additive	Amine	Diene	Yield [%]	Product ratio I:II:II:IV
1[35]	8 mol% $NiCl_2$	32 mol% PPh_3	20	6	EtOH	32 mol% $NaBH_4$	(*n*-Pr)$_2$NH	Butadiene	46	5:2:84:9
2[35]	2 mol% $NiCl_2$	4 mol% P(i-PrO)$_2$Ph	20	9	EtOH	2 mol% $NaBH_4$	Morpholine	Butadiene	11	14:77:8:1
3[35]	2 mol% $NiCl_2$	4 mol% P(2-MeC$_6$H$_4$O)$_3$	20	8	EtOH	2 mol% $NaBH_4$	Morpholine	Butadiene	44	3:27:64:6
4[35]	2 mol% $NiCl_2$	4 mol% P(2-MeC$_6$H$_4$O)$_3$	20	9	EtOH	2 mol% $NaBH_4$	Morpholine	Butadiene	18	0:0:85:15
5[35]	2 mol% $NiCl_2$	4 mol% PPh_3	20	6	EtOH	2 mol% $NaBH_4$	Morpholine	Butadiene	85	2:6:75:17
6[35]	8 mol% $NiCl_2$	16 mol% PPh_3	20	6	EtOH	32 mol% $NaBH_4$	Morpholine	Butadiene	95	8:8:65:19

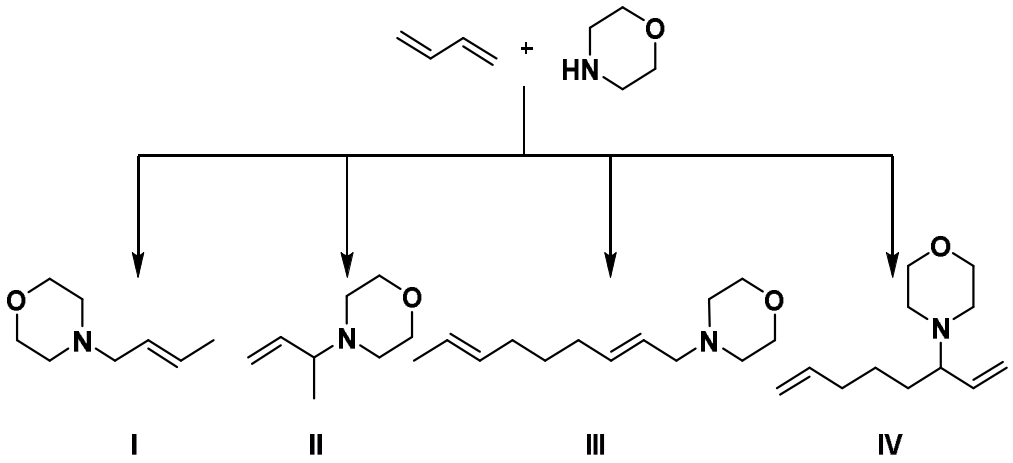
Entry	Precursor	Ligand	Temperature [°C]	Time [h]	Solvent	Additive	Amine	Diene	Yield [%]	Product ratio I:II:II:IV
7[23]	5 mol% $Ni(acac)_2$	5 mol% $(n\text{-}Bu)_3P$	80	3	Benzene	3 mol% Et_3Al	Morpholine	Butadiene	98	93:4:3:0
8[23]	5 mol% $Ni(acac)_2$	5 mol% $(n\text{-}Bu)_3P$	80	3	Benzene	3 mol% Et_3Al	Morpholine	Butadiene	98	0:15:61:24
9[34]	5 mol% $Ni(COD)_2$	5 mol% DPPF	rt	20	Toluene	20 mol% TFA,	Morpholine	Cyclohexadiene	82	-
10[37]	1 mol% $Ni(COD)_2$	3 mol% $P(n\text{-}Bu)_3$	80	5	Benzene	20 mol% TFA,	Morpholine	Cyclohexadiene	80	-

For Entries 1-8, three equivalents of cyclohexadiene were used. For Entries 9 and 10, 2 and 1 respectively.

The different products are described in Scheme 11.

1.4.1.3 Cobalt

There are some reports concerning the cobalt catalyzed hydroamination (of dienes). The work of Baker *et al* shows the reactivity of morpholine, di-*N*-propylamine and diethylamine towards HA of butadiene catalyzed by a cobalt PPh_3 species (Table 3, entry 1).[35] For the morpholine reactions, the yields are very good (up to 98%) with no or almost no telomerization observed for the system utilizing $CoCl_2$, $NaBH_4$ and PPh_3. An interesting trait of this system is that upon addition of $Al(i\text{-}OPr)_3$ to the mixture, the amount of telomere increases drastically. It should be noted as well, that in this experiment, the amount of Co catalyst was reduced, and the temperature was increased drastically as well as the reaction time (see Table 3).[35]



Scheme 12: Exemplary products of the hydroamination reaction starting from butadiene and morpholine as mentioned in Table 3.

Table 3: Hydroamiantion reactions with cobalt catalysts.[35]

Entry	Precursor	Ligand	Temperature [°C]	Time [h]	Solvent	Additive	Amine	Diene	Yield [%]	Product ratio I:II:II:IV
1	2.5 mol% $CoCl_2$	7.5 mol% PPh_3	100	16	EtOH	40 mol% Al(OiPr)	Et_2NH	Butadiene	44	14:42:42:3
2	2.5 mol% $CoCl_2$	7.5 mol% PPh_3	100	16	EtOH	40 mol% Al(OiPr)	$(n\text{-Pr})_2NH$	Butadiene	35	22:20:54:4
3	40 mol%$CoCl_2$	40 mol% PPh_3	20	11	EtOH	60 mol% $NaBH_4$	$(n\text{-Pr})_2NH$	Butadiene	66	29:55:8:8
4	2.5 mol%$CoCl_2$	7.5 mol% PPh_3	75	15.5	EtOH	5 mol% $NaBH_4$	Morpholine	Butadiene	37	8:13:71:8
5	2.5 mol%$CoCl_2$	7.5 mol% PPh_3	100	15.5	EtOH	5 mol% $NaBH_4$	Morpholine	Butadiene	60	12:29:54:5
6	15 mol%$CoCl_2$	45 mol% PPh_3	20	8	EtOH	8 mol% $NaBH_4$	Morpholine	Butadiene	98	9:83:7:
7	40 mol%$CoCl_2$	60 mol% PPh_3	20	8	EtOH	40 mol% $NaBH_4$	Morpholine	Butadiene	98	10:90:0:0
8	40 mol%$CoCl_2$	40 mol% PPh_3	rt	11	EtOH	60 mol% $NaBH_4$ 40 mol% Al(OiPr)	$PhNH_2$	Butadiene	5	0:1:0:0

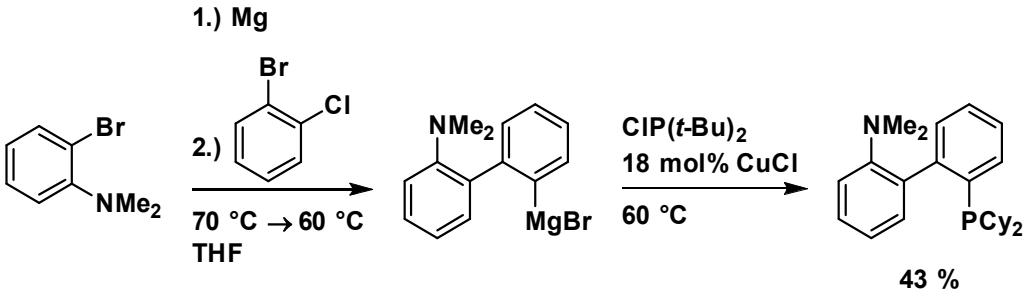
Three equivalents of butadiene were used for each reaction. The different products are described in Scheme 12.

1.4.1.4 Manganese

To the best of my knowledge, no HA reactions utilizing manganese have been reported to date.

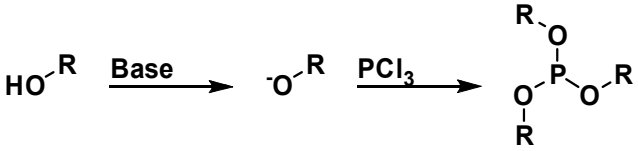
1.5 Phosphine and Phosphite Ligands

Phosphines as well as phosphites have quite interesting features and have grown in use in catalysis. One of the reasons is that they are quite easy to synthesize. Phosphines are accessible e. g. through Grignard reactions (see Scheme 13). [38]



Scheme 13: Example of a (biaryl)phosphine synthesis.[38]

It is easy to build up the carbon backbone of the phosphine and put together all the fragments in the final stages of the synthesis. This makes them easily modifiable in a steric and electronic fashion. Another beneficial feature of phosphines is that they are easily tunable with respect to their steric and electronic properties. The same is true for phosphites, which are accessible e.g. through a substitution reaction on PCl_3 through a deprotonated alcohol (see Scheme 14).[39]



Scheme 14: General example for a phosphite synthesis.[39]

The tunability of phosphines and phosphites in respect to their electronic and steric influence can be seen visualized clearly in Tolman's landmark review, where he described a method to measure those effects accurately.[40] This topic will be explained in more detail in chapter 1.5.1.

Of course, other useful traits of this kind of ligand also exists. Looking at multidentate ligands, features like hapticity and bite angle play a huge role as well.

For the Nobel Prize winning contributions to transition metal catalysis from 2001 (Knowles, Noyori and Sharpless), 2005 (Chauvin, Grupps and Schrock) and 2010 (Heck, Negishi and Suzuki), several P(III) ligands play an important role.[41–45] This highlights the significance of this kind of ligands and their huge impact in the field of catalysis.

1.5.1 Tolman prarameters

In his landmark review from 1977, Tolman described a method to determine the electronic and steric influence of different phosphorous ligands. His data is used in this work to make assumptions about the nature of the ligands and rationalize the outcome. Figure 4 shows an overview over different phosphorous ligands as reported by Tolman.[40]

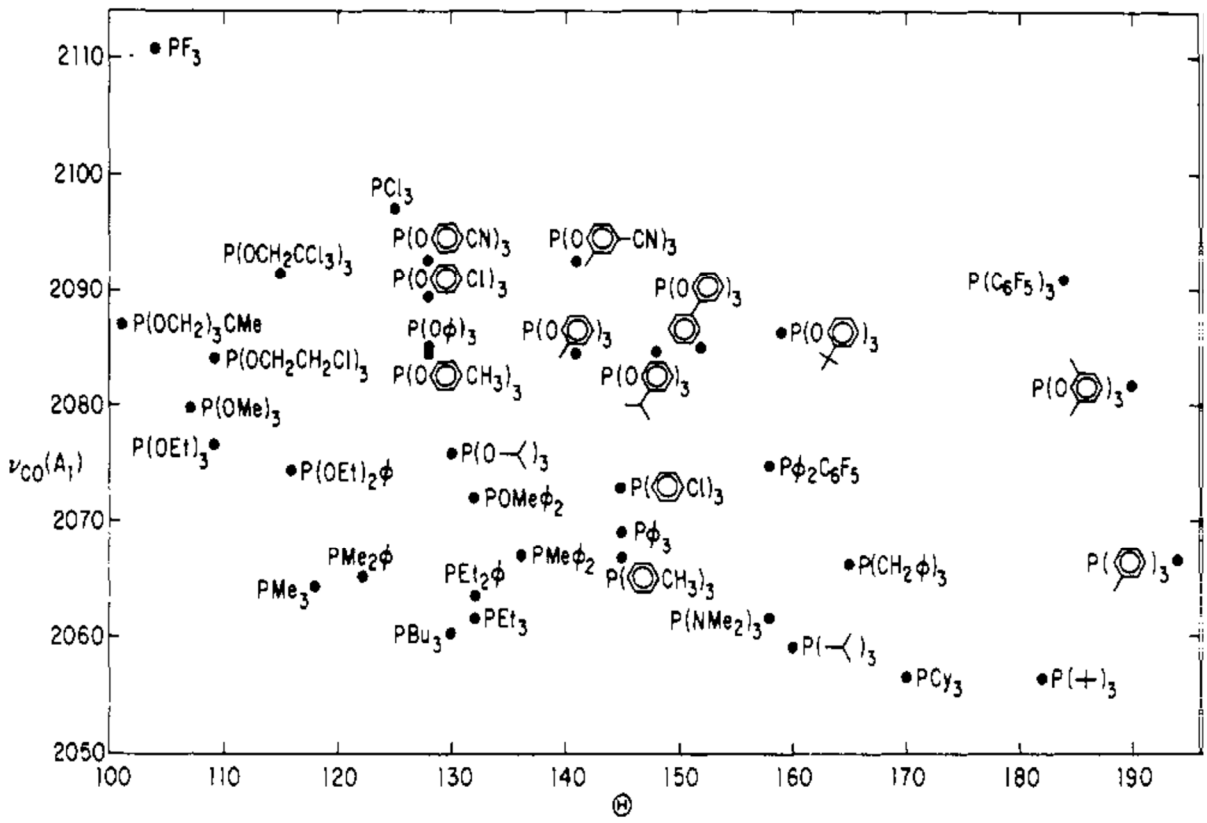


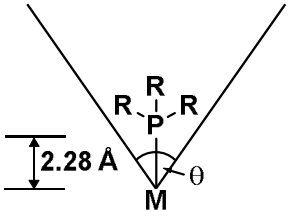
Figure 4: Tolman's steric and electronic parameter.[40]

To assess the electronic effect, he measured the IR frequency ν of the A_1 normal mode of a $Ni(CO)_3L$ species, where L is the tested ligand. This species is easily obtained upon mixing $Ni(CO)_4$ and L in a 1:1 ratio. For ligands he did not measure, he suggested a calculation method,

$$\nu = 2056.1 + \sum_{i=1}^{3} \chi_i$$

with χ_i an increment value given in his review.[40]

Since this aspect alone did not explain the differences in competition for various phosphorous ligands towards Ni (0), the cone angle Θ was introduced. This parameter is defined as the apex angle of a cylindrical cone, centered 2.28 Å (translates to 2.57 cm in the CPK model) from the center of the phosphorous atom which just touches the van der Waals radii of the outermost atoms of a CPK molecular model (Scheme 15). This definition is only for symmetric molecules, meaning all three substituents on the phosphorous are the same.[40]



Scheme 15: Schematic drawing of the Tolman cone angle.

Additionally, he introduced a method to calculate the cone angle for unsymmetric ligands,

$$\theta = 2/3 \sum_{i=1}^{3} \theta_i$$

with Θ_i as an increment value given in his review.[40]

2. Scope

This work aims to investigate the possibility of using complexes of the non-precious metals iron, cobalt, nickel and manganese as catalysts for the hydroamination of dienes.

To achieve this, a benchmark system consisting of morpholine and 1,3-cyclohexadiene was reacted with different *in situ* generated complexes, mostly phosphines and phosphites, of said metals. The resulting crude product mixtures were analyzed using GC-FID with mesitylene as an internal standard.

3. Results and Discussion

3.1 Analysis

3.1.1 First analytical trials

For the analysis a quick colorimetric assay was tried (Figure 4). The method of Hartwig et al.[34] was tried and found not to be suitable. This method includes the treatment of aliquots of the crude product solutions with acetaldehyde and a nitroprusside solution in saturated $NaHCO_3$. This method was found to be quite unreliable because of the fast evaporation of the acetaldehyde, even at 18 °C room temperature.

Therefore, another method was tried, where instead of direct addition of acetaldehyde, stock solutions were used. This method provides the benefit of being very fast and easy, therefore, being a good method for fast evaluation and high throughput, but it only determines the concentration of one substrate; thus, it does not show the formation of product nor the consumption of the second substrate and cannot indicate whether side reactions occurred. Another disadvantage is, that this method is not quantitative, but more an estimation *via* eyesight.

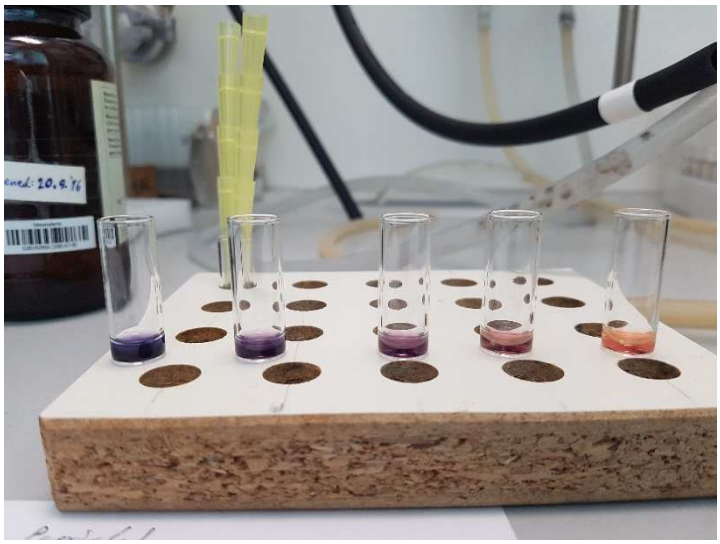


Figure 5: Example for a colourimetricassay.

A possibility to perform this reaction in a more quantitative fashion would be to set up a photometric analysis, but this would not solve the problem that it only shows the absence of

morpholine and since e.g. a GC set up is essentially as fast and yields more information, a GC-FID analysis is more reasonable.

Quantification *via* ^{1}H-NMR spectroscopy against a ferrocene standard was tried as well. This proved to be inaccurate, especially since the peaks were not completely resolved, making it difficult to integrate precisely.

Finally, GC-MS was investigated as an analysis method since it would be easy to determine the nature of possible side products with the given MS-spectra. Unfortunately, the MS seems to be inappropriate for the analytes since the determined areas and area ratios were not reproducible.

Thus, GC-FID was chosen as the final method since the FID detector is versatile and responds well to most organic compounds. As showed below, the measurements on such a setup were reproducible and could be used as a metric to assess the activity. Additionally, side products could be detected, because they should give rise to additional peaks.

3.1.2 Final analytical method

3.1.2.1 Conversion

To determine the conversion and for ease of use, stock solutions of the substrates were used. These contained a 1:1:0.33 (molar ratio) mixture of 1,3-cyclohexadiene, morpholine, and mesitylene; additionally, it contained toluene to adjust the volume. The samples were prepared in a volumetric flask and stored in a vial in the glove box freezer –35 °C. The used stock solutions had a concentration of 4.25 mmol/mL of morpholine and 1,3-cyclohexadiene respectively and of 1.42 mmol/mL of mesitylene.

These mixtures were measured with the same GC-FID program as the samples; to determine the conversion, the following equation was used:

$$1 - \frac{A_{sample\ substrate}}{A_{sample\ MES}} : \frac{A_{0\ substrate}}{A_{0\ MES}} = \text{conversion (\%)}$$

With A as the peak area, with the index 0 for the stock solution; substrate represents morpholine and 1,3-cyclohexadiene respectively. Therefore, two values of conversion could be determined.

3.1.2.2 Determination of the calibration curve

To determine the yield of the HA reactions directly, a calibration curve prepared made from five measurements containing different concentrations of 4-(cyclohex-2-en-1-yl)morpholine (**1**) and constant concentrations of mesitylene. This has the advantage, that the yield is accessed directly, and possible side reactions can be found more easily by comparing the yield and the conversion(s). An exemplary GC-FID trace is shown in Figure 6. The retention times of the standard, the substrates and the product are listed in Table 4.

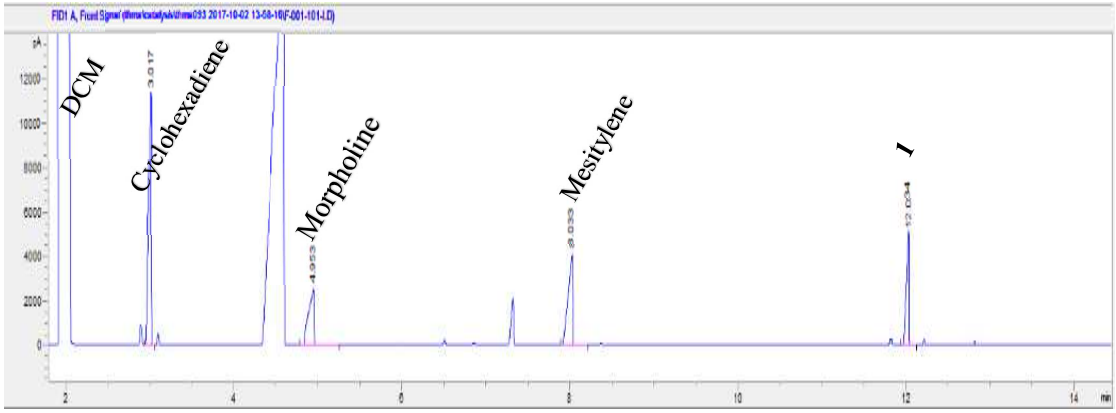


Figure 6: Example GC-FID trace of a reaction under standard conditions using P(O-o,p-tBu-Ph)$_3$ as a ligand. The not labeled peaks were not determined.

To determine the conversion of 1,3-cyclohexadiene and morpholine, the chromatogram was compared to the chromatogram of the used stock solution. Although **1** was thoroughly purified, the purity did not exceed 67% (m/m) according to NMR spectroscopy and GC-MS. Although purified twice *via* column chromatography, followed by an acid base extraction, no pure product could be obtained. According to analysis, the impurity is the oxidized ligand used in the synthesis (see Figure 7). Since the tri-*n*-butyl phosphine oxide has a high boiling point of 150 °C at 1.5 mm Hg,[46] a distillation or vacuum transfer of the impure product would probably remove the impurity. This method would still need experimental conformation.

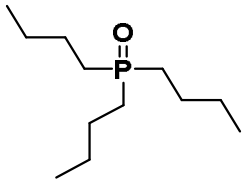


Figure 7: Tri-n-butyl phosphine oxide

This was taken into account by preparing the calibration curve with the weighed amount corrected by a factor of 0.67 to obtain the real weighed amount.

Table 4: Retention time of the used peaks.

Compound	Retention Time [min]
1,3-cyclohexadiene	2.98
morpholine	4.84
mesitylene	8.04
1	12.09

Gas chromatograms were recorded on an agilent 7890A gas chromatograph with a 7633b autosampler and an HP-5 (30m × 0.32mm × 0.25µm) column and detected with a flame ionization detector with H_2 as carrier gas. The temperature program started at 35 °C with a hold time of 2.25 min followed by a slope of 10 °C/min to 100 °C and 25 °C/min from 100 °C to 300 °C followed by a post run at 300 °C for 5 min.

The differences in 1,3-cyclohexadiene conversion and morpholine conversion can be accredited, at least to a certain degree, to the difference in volatility. Although 1,3-cyclohexadiene is probably more prone to side reactions than morpholine, only traces of other products were found. This can be seen especially in the tables in chapter 3.2.1, where discrepancies in the conversion according to cyclohexadiene and morpholine and the conversion can be noted. This might indicate, that the calculation of the purity of **1** are wrong, or that side products were generated that were lost during the workup or which were not visible on the GC-FID; although the latter is highly unlikely.

3.1.2.3 Calculations

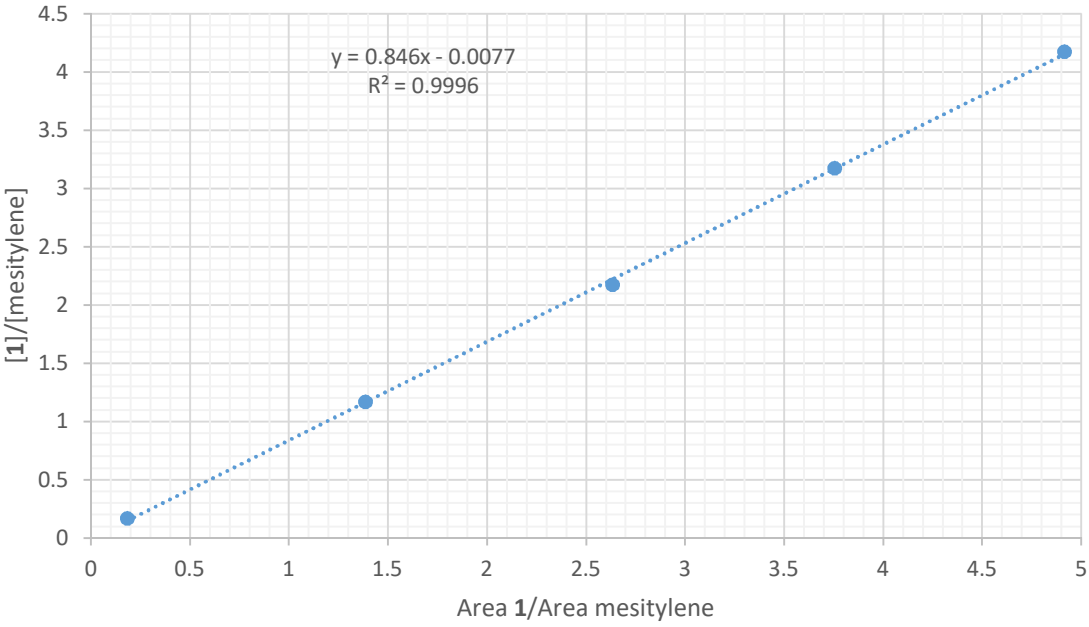


*Figure 8: The calibration curve shows the ratio of the area of **1** and mesitylene peaks against the corresponding concentration ratio.*

Table 5: Concentrations used for the calibration curve.

Measurement	c_{MES} [mol/L]	c_1 [mol/L]	C_1/C_{MES}	A_{MES}	A_1	A_1/A_{MES}
1	0.018	0.003	0.1667	6330.30	1152.35	0.182036531
2	0.018	0.021	1.1682	6688.75	9263.82	1.384985384
3	0.018	0.040	2.1695	8560.67	22539.20	2.632878357
4	0.018	0.058	3.1708	5923.73	22243.00	3.754897066
5	0.018	0.076	4.1721	5905.97	29015.80	4.91296443

c equals the concentration of the compound and A the area of the corresponding peak.

The calibration curve in Figure 8 using the GC yield shows the ratio of the concentrations of **1** and mesitylene ([**1**]/[mesitylene]) against the ratio of the areas of the GC peaks of **1** and mesitylene (Area **1**/Area mesitylene).

The calibration curve yields the following relationship between the ratio of the areas and the ratio of the concentrations.

$$\frac{A_1}{A_{MES}} = 0.846 \times \frac{c_1}{c_{MES}} - 0.0077$$

This makes it easy to determine the concentration ratio of mesitylene and **1** in any given sample. Since

$$\frac{c_{\mathbf{1}}}{c_{(\mathrm{MES})}} = \frac{\frac{n_{\mathbf{1}}}{V_{\mathbf{1}}}}{\frac{n_{MES}}{V_{MES}}}$$

and

$$V_{\mathbf{1}} = V_{MES}$$

and since both are dissolved in the same solution we can conclude that

$$\frac{n_{\mathbf{1}}}{n_{MES}} = \frac{c_{\mathbf{1}}}{c_{MES}}$$

and therefore

$$\frac{n_{\mathbf{1}}}{n_{MES}} = 0.846 \times \frac{A_{\mathbf{1}}}{A_{MES}} - 0.0077$$

Therefore, we can calculate the amount of **1** by multiplying the determined molar ratio with the amount of mesitylene. This value divided by the amount of possible **1** (which equals the amount of 1,3-cyclohexadiene or morpholine depending on which limits the reaction) represents the GC yield.

A problem arises when one compares the conversion according to 1,3-cyclohexadiene and morpholine and the yield determined *via* the calibration curve, as they are not the same. The difference in conversion of 1,3-cyclohexadiene and morpholine can be explained mostly through the different volatilities of morpholine and 1,3-cyclohexadiene. Furthermore, 1,3-cyclohexadiene is more prone to side reactions, but this should play only a minor role since no significant amounts of side products were observed.

An interesting fact is, that the generated calibration curve is always way lower compared to the substrate amounts and almost always by a similar factor. This might indicate that the **1** used to make the calibration curve was purer then assumed from the ^{1}H-NMR spectrum. Even if this is the case, the calculated values still represent activities of the systems and are comparable.

3.1.2.4 Workups

For the Ni(0) containing systems, quenching with NaOH solution was sufficient to stop the reaction and precipitate the metal containing substances. This was desired for two reasons. The first is the possibility to determine the exact point in time when the reaction is stopped; the other was, to be able to remove the metal containing species to protect the GC instrument from contamination. But for other reactions, e.g. the ones starting from $Mn(CO)_5Br$ or $Fe(CO)_5$, no precipitation or other changes of the reaction mixtures were observed after adding NaOH. Therefore, the reaction mixtures were treated with H_2O_2 (30 % w/w) to destroy the active compounds. Addition of NaOH to basify the mixtures and destroy excess H_2O_2, followed by extraction with dichloromethane (DCM) proved to be a reproducible, high throughput method.

Table 6: GC-FID signal intensities of mixtures of substrates, standard and product with and without treatment with H_2O_2.

Sample	A_{MES}	A_{CHD}	A_{CHD}/A_{MES}	A_{Morph}	A_{Morph}/A_{MES}	A_1	A_1/A_{MES}
uI	6870.32	6075.75	0.88	2068.93	0.30	709.92	0.10
uII	8419.98	7485.05	0.89	2445.90	0.29	851.92	0.10
uIII	6382.23	5630.67	0.88	1911.77	0.30	662.41	0.10
oI	6750.75	6001.11	0.89	2146.57	0.32	687.63	0.10
oII	7038.06	6273.26	0.89	2173.02	0.31	710.05	0.10
oIII	4971.65	4373.88	0.88	1631.68	0.33	517.07	0.10

A solution containing 0.7 mmol/l of each substrate and product and 0.2 mmol/l of mesitylene was split in 6 samples. Samples uI, uII and uIII were quenched with aq. NaOH (30 % w/w), filtrated and then extracted with DCM, Samples oI, oII and oIII were treated with H_2O_2 before adding NaOH. uI, uII and uIII are treated the same as are oI, oII and oIII

The reproducibility of the method can be seen in Table 6. Here, a stock mixture containing substrates, standard and product in DCM was split in six samples and those were furthermore split in two groups. The constant ratios of substrates and product to the standard indicate the use of H_2O_2 does not affect the relative concentrations of the components in the mixture.

Additionally, real reaction mixtures were investigated as well. The results can be seen in Table 7, where entry 3 shows a reaction where the workup involved only quenching with NaOH and entry 1 and 2 are workups involving treatment with H_2O_2, followed by NaOH. The difference between entries 1 and 2 is the time between addition of H_2O_2 and NaOH. While entry 1 is after approximately 5 minutes and entry 2 after 16 h.

Additionally, no difference in the peaks (amount nor shape) of the chromatograms was observed. This can be seen in Figures 9 and 10, whereas the analysis for that can be seen in Table 6; the shown chromatograms correspond to entry 3 (Figure 9) and entry 1 (Figure 10) of Table 7. Entry 2 is essentially the same as 1 but the mixture of Entry 1 stood over night at room temperature after adding H_2O_2 and was not extracted immediately after the quenching.

It should be noted, that, especially for the cobalt containing systems, it was crucial to perform the work up under ice cooling, since cobalt can catalyze the self-decomposition of H_2O_2[47] which leads to a vigorously bubbling, hot mixture, which, most likely, would interfere with the analysis.

Table 7: Influence of H_2O_2 on the reaction outcome

			Conversion		
Entry	H_2O_2	Time	CHD	Morpholine	Yield of **1**
1	Yes	5 min	93 %	90 %	66 %
2	Yes	o/n	93 %	90 %	62 %
3	no	-	94 %	91 %	63 %

Entry one was quenched with H_2O_2 and worked up after 5 min, entry two was worked up after sitting overnight and entry three was not quenched with H_2O_2 but only with NaOH. Each mixture consists of 0.03 mmol $Ni(COD)_2$, 0.09 mmol $P(nBu)_3$, 4.6 µL TFA, 141 µL substrate stock solution and 240 µL toluene heated for 24 h.

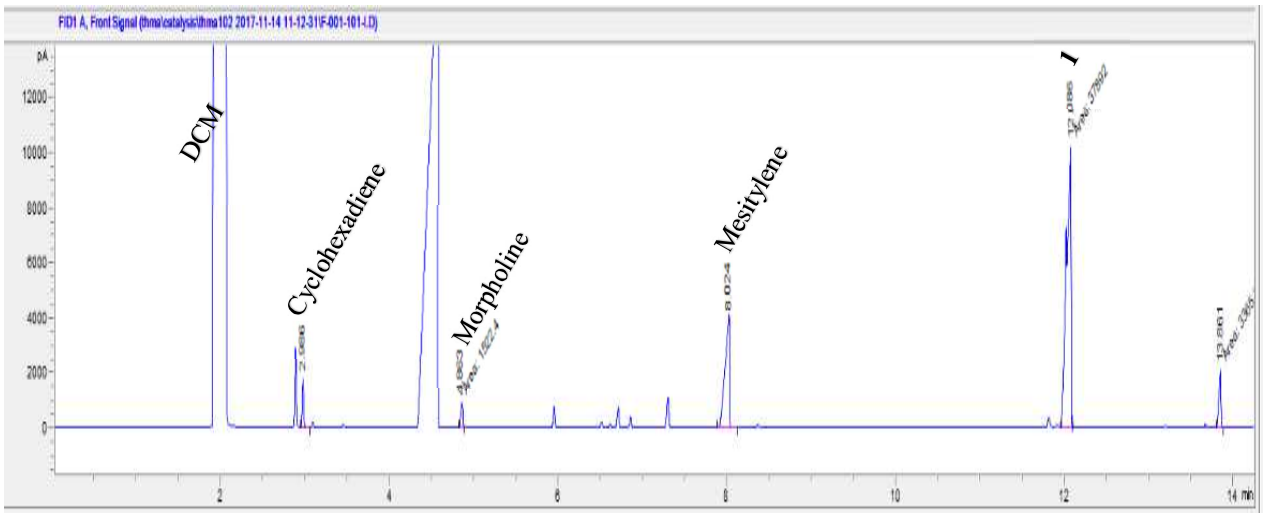


Figure 9: Example GC-trace of workup without H_2O_2 as described in Table 7, entry 3.

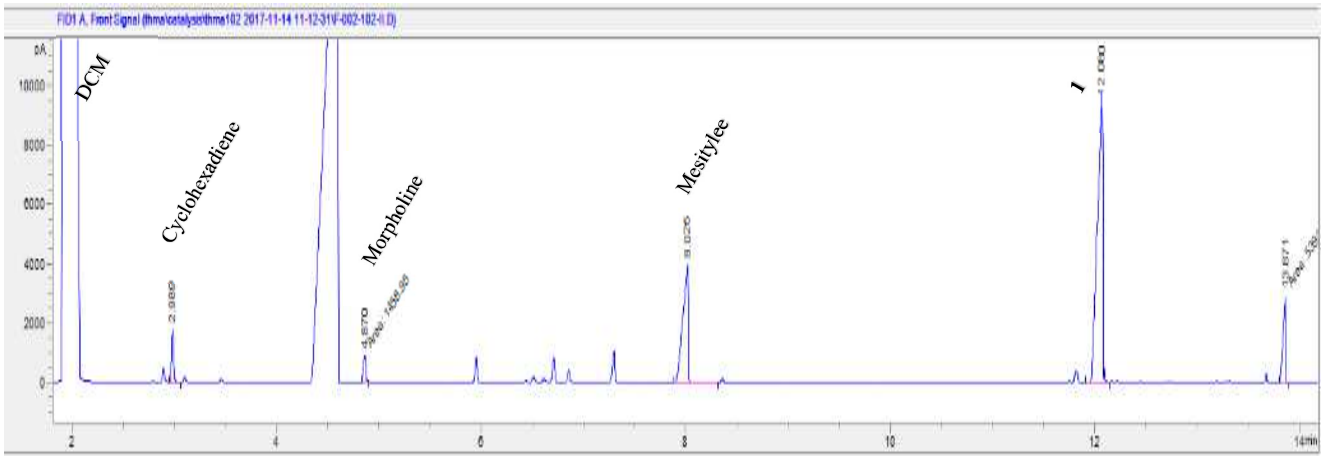


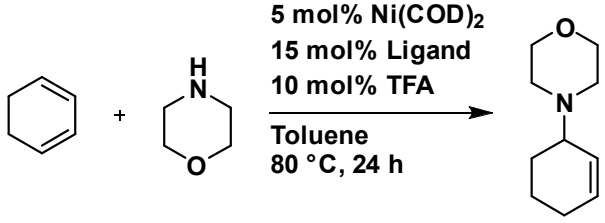
Figure 10: Example GC-trace of workup with 400 µL H_2O_2 as described in Table 7, entry 1.

3.2 Catalysis

3.2.1 Catalysis with nickel compounds

3.2.1.1 Ligands under benchmark conditions

Different phosphines, phosphites and the N-heterocyclic carbene IMes with distinct steric and electronic parameters were tested as ligands. The results can be seen in Table 8.



Scheme 16: Reaction as described in Table 8.

Table 8: Tested Ligands.

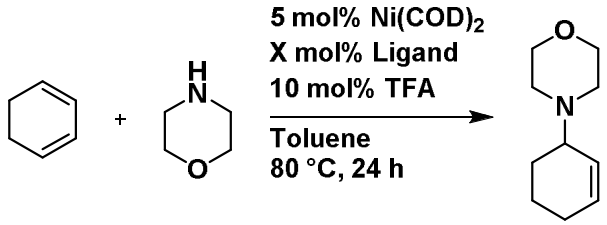
Ligand	Θ [°][40]	ν [cm^{-1}][40]	Conversion		Yield **1**
			CHD	Morpholine	
P(*i*Pr)$_3$	160	2059.2	24 %	10 %	0 %
P(*n*Pr)$_3$	132	2075.9	94 %	88 %	62 %
P(*t*Bu)$_3$	182	2056.1	44 %	6 %	0 %*)
P(*n*Bu)$_3$	132	2060.3	96 %	80 %	67 %
P(C$_6$F$_5$)$_3$	184	2090.9	26 %	34 %	0 %
L1	-	-	18 %	5 %	0 %
(C$_6$F$_5$)$_2$PCH$_2$CH$_2$P(C$_6$F$_5$)$_2$	-	-	4 %	38 %	0 %
P(*o*Tol)$_3$	194	2066.6	15 %	4 %	0 %
Brettphos	-	-	35 %	27 %	18 %
Triphos	-	-	8 %	7 %	3 %
LiBTriphosTMEDA$_2$	-	-	56 %	56 %	10 %
LiBTtriphosTMEDA$_2$	-	-	87 %	89 %	56 %**)
PMe$_2$Ph	122	2065.3	94 %	86 %	60 %
P(OPh *o*-Ph)$_3$	152	2085.0	92 %	81 %	60 %
P(OEt)$_3$	109	2076.3	59 %	48 %	36 %
P(OPh)$_3$	130	2085.3	43 %	36 %	26 %
P(OCH$_2$)$_3$CHEt	101	2086.8	31 %	38 %	16 %
P(O-*o*,*p*-tBu-Ph)$_3$	-	-	35 %	27 %	18 %
P(O*i*Pr)$_3$	131	2075.9	88 %	86 %	62 %
P(NMe$_2$)$_3$	157	2061.9	8 %	10 %	0 %
(PhO)$_2$PCH$_2$CH$_2$P(OPh)$_2$	-	-	43 %	40 %	26 %
IMes	--	2050.5	89 %	35 %	2 %

*Each mixture consists of 0.03 mmol Ni(COD)$_2$, 0.09 mmol ligand,0.06 mmol TFA, 141 µL substrate stock solution (0.6 mmol morpholine and 0.6 mmol 1,3-cyclohexadiene and 0.2 mmol mesitylene) and 240 µL toluene heated to 80 °C for 24 h. For the sake of clarity, the ligands are drawn in chapter 4.3. (page 60). The corresponding reaction can be seen in Scheme 16. *) Traces **) only 1 equivalent used*

As can be seen in Table 8, the yield was the highest for the benchmark reaction using the P(*n*Bu)$_3$ ligand. A similar system was already used by Tolstikov *et al.*,[37] where they achieved a slightly higher yield in 5 h in benzene. (see Table 2, Entry 10).

Comparing the activity of this ligand with that of other ligands with either another electronic or steric parameter is useful. The most similar cone angle is the one of P(O*i*Pr)$_3$ with a difference of only 1°; therefore, the difference in yield for **1** of 5 % arises most likely from the difference in the electronic parameter. This hints to the fact, that the best electronic value should be between 2060.3 cm^{-1} and 2075.9 cm^{-1}. If we look at a ligand with similar electronic properties and different steric properties, we can see a sharp loss of activity. This can be seen e. g. in the yield when using P(*i*Pr)$_3$, which gave no product at all.

Therefore, it was postulated that a sterically not too demanding ligand with high electron density is beneficial for the reaction. This led to the experiments shown in Table 9, where a sterically hindered ligand was used with only two equivalents instead of three. Unfortunately, decreasing the amount of ligand did not increase the activity for the P(tBu)$_3$ ligand.



Scheme 17: Reaction as described in Table 9.

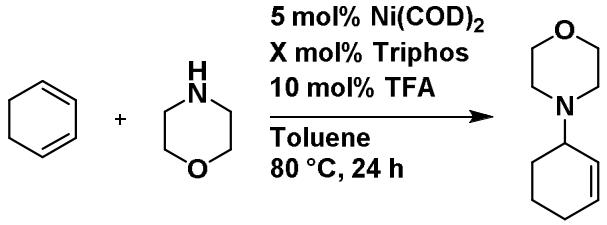
Table 9: Varied amounts of P(tBu)$_3$ and P(nBu$_3$).

Entry	Ligand	X	Conversion		Yield **1**
			CHD	Morpholine	
1	P(*t*Bu)$_3$	10	39 %	13 %	0 %
2	P(*t*Bu)$_3$	15	44 %	6 %	0 %
3	P(*n*Bu)$_3$	10	24 %	64 %	2 %
4	P(*n*Bu)$_3$	15	96 %	80 %	67 %

Each mixture consists of 0.03 mmol Ni(COD)$_2$, the stated amount ligand (0.06 mmol or 0.09 mmol respectively), 0.06 mmol TFA, 141 µL substrate stock solution (0.6 mmol morpholine and 0.6 mmol 1,3-cyclohexadiene and 0.2 mmol mesitylene) and 240 µL Toluene heated to 80 °C for 24 h. The corresponding reaction can be seen in Scheme 17.

The same trend in activity was observed when less P(nBu)$_3$ is used in toluene (see Table 9, entries 3 and 4). Different outcomes are observed in EtOH, which will be discussed in chapter 3.1.1.4.

The influence of the amount of used multidentate ligand is also interesting. Thus, the benchmark reaction was run with different amounts of Triphos, as shown in Table 10.



Scheme 18: The reaction as described in Table 10.

Table 10: Different amounts of Triphos.

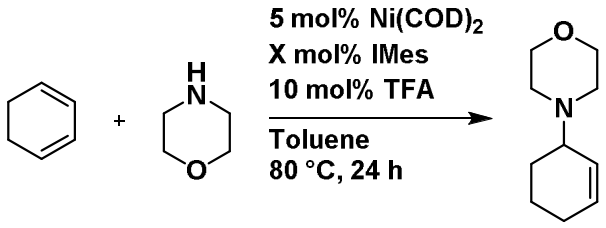
Entry	Ligand	X	Conversion		Yield **1**
			CHD	Morpholine	
1	Triphos	9	8 %	7 %	3 %
2	Triphos	4.5	86 %	88 %	62 %
3	Triphos	3	90 %	88 %	65 %

Each mixture consists of 0.03 mmol Ni(COD)$_2$, the stated amount ligand, 0.06 mmol TFA, 141 µL substrate stock solution (0.6 mmol morpholine and 0.6 mmol 1,3-cyclohexadiene and 0.2 mmol mesitylene) and 240 µL Toluene heated to 80 °C for 24 h. The corresponding reaction can be seen in Scheme 18.

The yields for the reactions with 1 and 1.5 equivalents are similar to the data from the reactions with P(OiPr)$_3$ and P(nBu)$_3$ from Table 8. Interestingly, the reactivity rises sharply when less Triphos is used (Table 10, entry 2 and entry 3 compared to entry 1).

3.2.1.2 *N*-Heterocyclic Carbenes

N-Heterocyclic carbenes were tested as they are particularly strong σ-donor ligand. An important difference to phosphine ligands is that they do not dissociate well from the metal center, contrary to the tested phosphorous species. This might influence the reaction since it is necessary that ligands dissociate to generate free binding sites.[23]



Scheme 19: The reaction as described in table 11.

Table 11: Conversion and yield for the reactions with IMes.

Entry	X	Amount of $P(OiPr)_3$ [mol%]	Conversion		Yield **1**
			CHD	Morpholine	
1	15*)	0	89 %	35 %	2 %
2	15	0	55 %	15 %	1 %
3	10	0	45 %	16 %	1 %
4	5	0	56 %	13 %	2 %
5	15**)	0	14 %	65 %	0 %
6	5	10	64 %	57 %	38 %

*Each mixture consists of 0.03 mmol $Ni(COD)_2$, the stated amount(s) of ligand(s), 0.06 mmol TFA, 141 µL substrate stock solution (0.6 mmol morpholine and 0.6 mmol 1,3-cyclohexadiene and 0.2 mmol mesitylene) and 240 µL THF heated to 80 °C for 24 h. *) in Toluene **) without $Ni(COD)_2$. IMes was generated by treatment of its acidic form with KH in THF. The corresponding reaction can be seen in Scheme 19.*

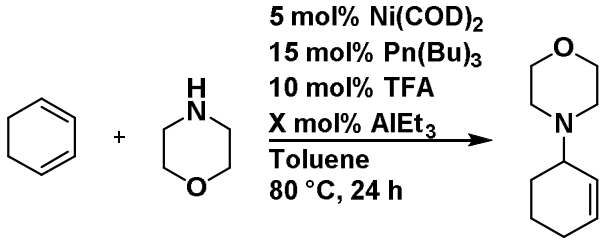
The first entry, 3 equivalents 1,3-Bis(2,4,6-trimethylphenyl)imidazolinium chloride (IMes) in toluene suggests, these complexes may be active. This procedure was performed in toluene, as similar to the benchmark reaction as possible. Since the literature known procedures for releasing the IMes from its HCl adduct are in THF, the conditions were adjusted to make sure all IMes is released. This was done by performing the reaction in THF, since the used base, KH is insoluble in toluene, which leads to almost no reaction in toluene. As can be seen in Table 13, the yield does not change drastically when switching the solvent to THF, the resulted difference in reactivity can be accounted to a different amount of IMes released. As seen in Table 11, the reactivity does not change much, upon changing the amount of IMes, but the yield is a bit better when only 1 equivalent of IMes is used. Although this interpretation is maybe too farfetched.

The last entry in Table 11 shows the combination of IMes and a phosphorous ligand; the yield was drastically improved compared to the system which only had an IMes ligand. Although the yield was lower compared to the P(O*i*Pr)$_3$ system with 3 equivalents phosphorous, (62% yield) this indicates an interesting possibility for combining a carbene and a phosphorous system.

Since all carbene reactions were done *in situ* without isolation of the complex and without removal of the byproduct KCl it might be that this interferes with the reaction. Additionally, unreacted KH might hamper the reaction by reacting with the added TFA, but this seems unlikely since no bubbling was observed when the TFA was added.

3.2.1.3 Precursor

Reducing Ni(acac)$_2$ to form a Ni^0 species hindered the reaction drastically (Table 12). This is in contrast to the results of Dzhemilev et al,[37] who obtained good result utilizing a similar method to react morpholine with butadiene and in another work morpholine with 1,3-cyclohexadiene using a different ligand.[23]



Scheme 20: The reaction as described in Table 12.

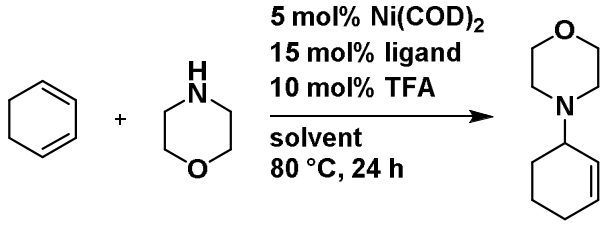
Table 12: Different precursors tested.

Precursor	X	Conversion		Yield **1**
		CHD	Morpholine	
Ni(COD)$_2$	0	96 %	80 %	67 %
Ni(acac)$_2$	15	71 %	15 %	1 %

Each mixture consists of 0.03 mmol Ni precursor, 0.015 mmol AlEt$_3$ (solution in hexane), 0.09 mmol P(nBu)$_3$, 0.06 mmol TFA, 141 µL substrate stock solution (0.6 mmol morpholine and 0.6 mmol 1,3-cyclohexadiene and 0.2 mmol mesitylene) and 240 µL toluene heated to 80 °C for 24 h. The corresponding reaction can be seen in Scheme 20.

3.2.1.4 Solvent

Changing the solvent from toluene to THF resulted in no significant difference; this can be seen in Table 13. Additionally, the reaction outcome does not change when conducted neat.



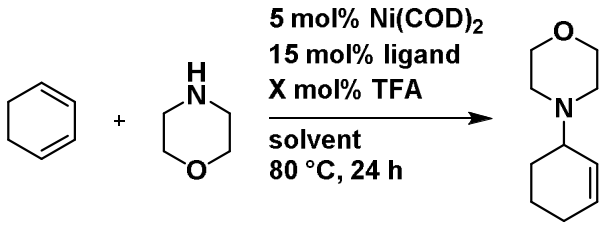
Scheme 21: The reaction as described in Table 13.

Table 13: The influence of different solvent on the reactions.

Entry	Ligand	Solvent	Conversion		Yield **1**
			CHD	Morpholine	
1	P(*n*Bu)$_3$	Toluene	96 %	80 %	67 %
2	P(*n*Bu)$_3$	THF	93 %	90 %	67 %
3	P(*n*Bu)$_3$	EtOH	85 %	81 %	51 %
4	P(OPh *o*-Ph)$_3$	toluene	92 %	81 %	60 %
5	P(OPh *o*-Ph)$_3$	Neat	92 %	83 %	60 %

Each mixture consists of 0.03 mmol Ni(COD)$_2$, 0.09 mmol ligand, 0.06 mmol TFA, 141 µL substrate stock solution (0.6 mmol morpholine and 0.6 mmol 1,3-cyclohexadiene and 0.2 mmol mesitylene) and 240 µL toluene heated to 80 °C for 24 h. The corresponding reaction can be seen in Scheme 21.

Contrary to the aforementioned solvent substitutions, using EtOH decreases the activity. An interesting effect is that when using EtOH without TFA the decrease in activity is lower compared to the decrease when toluene is used without TFA. This can be seen in Table 14. This might be due to weakly acidic proton in EtOH compared to the aprotic toluene. Since the effect is only small and the ligands are different in the tested setups, more testing is necessary here.

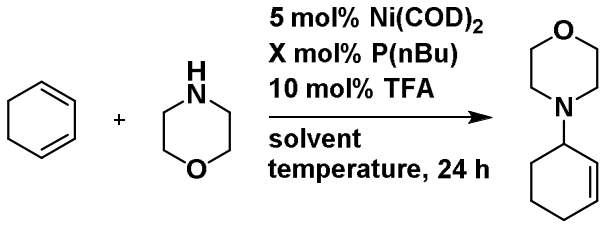


Scheme 22: The reaction as described in table 14.

Table 14: Influence of solvent on the need of acid cocatalyst.

Entry	Solvent	Ligand	X	Conversion		Yield **1**
				CHD	morpholine	
1	Toluene	P(OPh *o*-Ph)$_3$	10	92 %	81 %	60 %
2	Toluene	P(OPh *o*-Ph)$_3$	0	40 %	6 %	1 %
3	EtOH	P(*n*Bu)$_3$	10	85 %	81 %	51 %
4	EtOH	P(*n*Bu)$_3$	0	80 %	72 %	8 %

Each mixture consists of 0.03 mmol Ni(COD)$_2$, 0.09 mmol ligand, if used,0.06 mmol TFA, 141 µL substrate stock solution (0.6 mmol morpholine and 0.6 mmol 1,3-cyclohexadiene and 0.2 mmol mesitylene) and 240 µL toluene or EtOH respectively heated to 80 °C for 24 h. The corresponding reaction can be seen in Scheme 22.



Scheme 23: Reaction as described in Table 15.

Table 15: Influence of temperature and amount of ligand on the reaction).

Entry	Solvent	X	Temperature [°C]	Conversion		Yield **1**
				CHD	morpholine	
1	Toluene	15	80	96 %	80 %	67 %
2	Toluene	10	80	24 %	64 %	2 %
3	EtOH	15	80	85 %	81 %	51 %
4	EtOH	15	20	57 %	57 %	28 %
5	EtOH	10	80	57 %	54 %	7 %
6	EtOH	10	20	83 %	79 %	48 %

Each mixture consists of 0.03 mmol $Ni(COD)_2$, the stated amount of $P(nBu)_3$, 0.06 mmol TFA, 141 µL substrate stock solution (0.6 mmol morpholine and 0.6 mmol 1,3-cyclohexadiene and 0.2 mmol mesitylene) and 240 µL toluene or EtOH respectively heated to 80 °C or stirred at rt respectively for 24 h. The corresponding reaction can be seen in Scheme 23.

As expected, the yield decreases with decreasing temperature. Comparing entry 5 and 6 in Table 15 shows, that this relationship is reversed when less ligand is used. This might indicate a labile complex which decomposes in the presence of the alcohol, especially at elevated temperatures.

3.2.1.5 Water/O_2

Since the reaction needs a proton source, it was considered to perform the reaction in the presence of water. Unfortunately, the reaction did not work when TFA was exchanged with water.

As an additional simplification of the reaction it was postulated, that the reaction might be conductible under non-inert conditions. Therefore, the reaction was set up as usual in an argon glove box, and after the complex had formed, and the substrates were added, the mixture was brought outside, opened to air and air was bubbled through the system with a pipette. As expected, no product formation was observed, and a white precipitate formed. Only 2% yield could be achieved with this method for a system using EtOH as solvent and $P(O\textit{i}Pr)_3$ as ligand at room temperature.

3.2.1.6 Comparison

The highest yielding system is $Ni(COD)_2$ and $P(n\text{Bu})_3$ as ligand with 67 % gc yield. This was true as well in the work of Tolstikov *et al.*[23], although the used butadiene instead of 1,3-cyclohexadiene and only 5 % catalyst loading. To the best of my knowledge, the hydroamination of 1,3-cyclohexadiene with morpholine was not reported under these conditions to date.

Triphos shows a similar activity, but it is not quite as active.

Some interesting features of the reaction can be seen when EtOH is used as a solvent at room temperature. Here, different amounts of acid might be needed compared to the toluene systems, because EtOH is already weakly acidic compared to toluene.

Double hydroamination was not observed for any of the tested systems.

Therefore, it might be interesting to look at ligands containing both traits, for example Triphos like ligands with alkyl groups instead of phenyl groups to increase the donor strength to similar levels as $P(n\text{Bu})_3$ has but incorporating the tridentate nature of Triphos. Similar properties can be seen e.g. in the high activity of $Ni(COD)_2$ DPPF (and similar) systems.[34] Of course, the effect of the bite angle would need research as well.

The results from mixing a phosphite and a carbene may indicate, that PCP ligands could be quite active. However, the reactivity could also come from $P(O\text{i}Pr)_3$ alone, which needs to be ruled out.

3.2.2 Catalysis with iron compounds

According to Knölker[48], $Fe(CO)_5$ undergoes complexation of 1,3-cyclohexadiene under UV-irradiation. This reaction is initiated by the loss of CO. With this in mind, the desired HA *via* a UV irradiation of $Fe(CO)_5$ and $P(nBu)_3$ in hexane was trialed, combining the method of Knölker with the known reactivity of the nickel complexes. Unfortunately, this did not yield any significant amounts of the desired HA product; but it should be stated that the GC-MS chromatograms showed traces of a compound at the right retention time that might fit. And the ^{31}P-NMR suggests the generation of an iron phosphine complex.

Another method that was tried was to employ the known Knölker complex as catalyst (Figure 11). This catalyst, known to work for the reductive amination of alkyl aldehydes and amines,[49] was used with similar conditions as the working nickel complexes. One of the two reactions was conducted with addition of TFA and the other without, but none yielded any product.

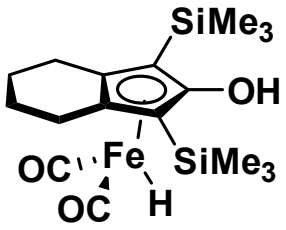
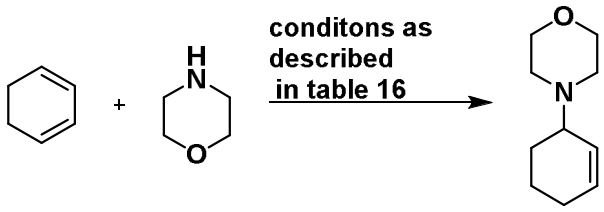


Figure 11: The utilized iron compound (Knölker complex).

Another approach was the use of $FeCl_2$ in THF. By heating a mixture of $FeCl_2$ and $P(OMe)_3$ in THF, Tolman et al.[50] synthesized a $Fe\{P(OMe)_3\}_3Cl_2$ species. Therefore, a similar approach was taken by refluxing $FeCl_2$ in THF with $P(nBu)_3$. The generated species was used *in situ* in the benchmark reaction. Unfortunately, no hydroamination was observed.

The other catalytic trials presented in Table 16 are under the conditions which worked for the nickel system unless noted differently.



Scheme 24: The reaction as described in Table 16.

Table 16: Tested iron systems.

Precursor	Ligand	Reductant	solvent	condition	Yield **1**	remarks
$FeCl_2$	P(*n*Bu)$_3$	-	THF	I	0 %	in THF heated 3 h before addition of substrates and TFA
$Fe(CO)_5$*)	P(*n*Bu)$_3$	-	Hexan	-	0 %	UV irradiation
$FeCl_2$	P(*n*Bu)$_3$	-	Toluene	I	0 %	heated to 80° for 0.5 h before adding substrate
$FeCl_2$	P(O*i*Pr)$_3$	-	Toluene	I	0 %	heated to 80° for 0.5 h before adding substrate
$Fe(acac)_2$	P(O*i*Pr)$_3$	-	Toluene	I	0 %	-
$Fe(acac)_2$	P(O*i*Pr)$_3$	$NaBH_4$	EtOH	II	0 %	larger scale (0.1 mmol metal) at 20 °C
$Fe(acac)_2$	P(O*i*Pr)$_3$	-	EtOH	II	0 %	20 °C
$Fe(acac)_2$	P(O*i*Pr)$_3$	-	EtOH	II	0 %	10% catalyst loading
Knölker**)	-	-	Toluene	I	0 %	10 % catalyst loading
Knölker**)	-	-	Toluene	I	0 %	without TFA 10 % catalyst loading

The corresponding reaction can be seen in Scheme 24.

Condition I and II: Each mixture consists of 0.03 mmol metal precursor, 0.09 mmol ligand, 4.6 µL TFA, 141 µL substrate stock solution (0.6 mmol morpholine and 0.6 mmol 1,3-cyclohexadiene and 0.2 mmol mesitylene) and 240 µL toluene or degassed EtOH respectively heated to 80 °C for 24 h. Reactions with EtOH were prepared by mixing everything besides EtOH in the box, transferring the reaction vessel outside and adding EtOH under argon flow on a Schlenk line. Reactions with $NaBH_4$ were performed with 0.1 mmol of metal and everything else adjusted accordingly (marked with the comment larger scale).

Condition III: $CoCl_2$, PPh_3, 1,3-cyclohexadiene and $NaBH_4$ were mixed in the box, EtOH was added under dry ice isopropanol cooling; substrate was added outside of the box, too.

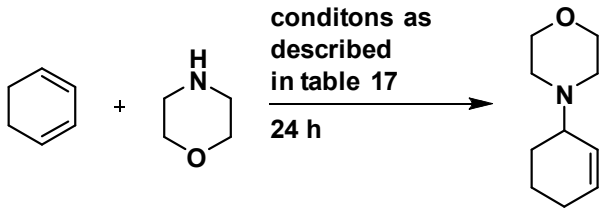
Condition IV: $Co(acac)_3$ and triphos were dissolved in THF in a glovebox, substrate mix and TFA were added and the mixture was transferred to the outside and EtOH was added under argon flow on a Schlenk line.

Conditions I, II, III and IV are further explained in chapter 4.2.

3.2.3 Catalysis with manganese compounds

Similar to the iron containing systems, different methods which worked for the tested nickel reactions were tried on different manganese containing precursors (Table 17).

Different conditions for manganese were tried. Although some (especially the ones starting from $Mn(CO)_5Br$) indicated a complexation by changing color, none of the systems showed any catalytic activity in the benchmark reaction.



Scheme 25: The reaction as described in Table 17.

Table 17: Tested manganese systems.

Precursor	Ligand	Reductant	solvent	condition	remarks	Yield **1**
$MnCl_2$	$P(OiPr)_3$	-	Toluene	I	no TFA	0 %
$MnCl_2$	$P(OiPr)_3$	-	EtOH	II	no TFA	0 %
$MnCl_2$	$P(OiPr)_3$	-	EtOH	II	no TFA 20 °C	0 %
$MnCl_2$	$P(OiPr)_3$	$NaBH_4$	EtOH	II	no TFA larger scale	0 %
$MnCl_2$	$P(OiPr)_3$	$NaBH_4$	EtOH	II	no TFA larger scale, 20 °C	0 %
$MnCl_2$	$P(OiPr)_3$	-	Toluene	I	-	0 %
$MnCO_5Br$	$P(n\text{Bu})_3$	-	Toluene	I	-	0 %
$MnCO_5Br$	$P(OiPr)_3$	-	Toluene	I	-	0 %
$MnCO_5Br$	$P(NMe_2)_3$	-	Toluene	I	-	0 %
$MnCO_5Br$	$P(t\text{Bu})_3$	-	Toluene	I	-	0 %
$MnCO_5Br$	$P(o\text{-Tol})_3$	-	Toluene	I	-	0 %
$MnCO_5Br$	IMes	-	Toluene	I	-	0 %

$MnCO_5Br$	P(OPh *o*-Ph)$_3$	-	Toluene	I	no TFA	0 %
$MnCO_5Br$	P(OEt)$_3$	-	Toluene	I	no TFA	0 %
$MnCO_5Br$	P(OPh)$_3$	-	Toluene	I	no TFA	0 %
$MnCO_5Br$	P(*n*Bu)$_3$	-	Toluene	I	no TFA	0 %
$MnCO_5Br$	P(OPh *o*-Ph)$_3$	-	Toluene	I	-	0 %
$MnCO_5Br$	P(OEt)$_3$	-	Toluene	I	-	0 %
$MnCO_5Br$	P(OPh)$_3$	-	Toluene	I	-	0 %
$MnCO_5Br$	P(nBu)$_3$	-	Toluene	I	-	0 %

The corresponding reaction can be seen in Scheme 25.

Condition I and II: Each mixture consists of 0.03 mmol metal precursor, 0.09 mmol ligand, 4.6 µL TFA, 141 µL substrate stock solution (0.6 mmol morpholine and 0.6 mmol 1,3-cyclohexadiene and 0.2 mmol mesitylene) and 240 µL toluene or degassed EtOH respectively heated to 80 °C for 24 h. Reactions with EtOH were prepared by mixing everything besides EtOH in the box, transferring the reaction vessel outside and adding EtOH under argon flow on a Schlenk line. Reactions with $NaBH_4$ were performed with 0.1 mmol of metal and everything else adjusted accordingly (marked with the comment larger scale).

Condition III: $CoCl_2$, PPh_3, 1,3-cyclohexadiene and $NaBH_4$ were mixed in the box, EtOH was added under dry ice isopropanol cooling; substrate was added outside of the box, too.

Condition IV: $Co(acac)_3$ and triphos were dissolved in THF in a glovebox, substrate mix and TFA were added and the mixture was transferred to the outside and EtOH was added under argon flow on a Schlenk line.

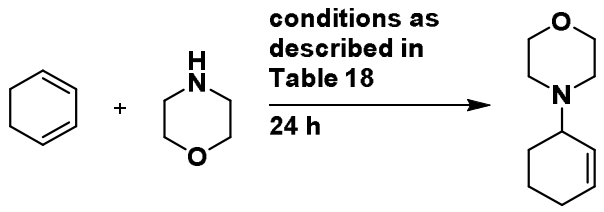
Conditions I, II, III and IV are further explained in chapter 4.2.

3.2.4 Catalysis with cobalt compounds

As for iron and manganese, no cobalt complexes were found to be active either. This is curious, since Baker *et al.*[35] found a cobalt(II) system containing $CoCl_2$, PPh_3 and $NaBH_4$ to be active for the addition of morpholine, di-*N*-propylamine and diethylamine to butadiene. (For examples, see Table 3) This reactivity was not the same as the benchmark system of morpholine and 1,3-cyclohexadiene.

A Co(III) system using $Co(acac)_3$ as a metal precursor was prepared and used *in situ* according to the procedure of Beller et al,[51] with TFA instead of $HNTf_2$. This system did not show any activity.

Other systems based on cobalt, as seen in Table 18, were also inactive. These were prepared in a similar manner to the active nickel systems.



Scheme 26: The reaction as described in Table 18.

Table 18: Tested cobalt systems.

Precursor	Ligand	Reductant	Solvent	Condition	remarks	Yield **1**
$Co(OAc)_2$	P(OPh *o*-Ph)$_3$	TEA	Toluene	I	neat	0 %
$Co(OAc)_2$	P(OPh *o*-Ph)$_3$	TEA	-	I	-	0 %
$Co(OAc)_2$	$P(NMe)_2$	TEA	Toluene	I	-	0 %
$Co(OAc)_2$	P(*t*Bu)$_3$	TEA	Toluene	I	-	0 %
$Co(OAc)_2$	P(*o*-Tol)$_3$	TEA	Toluene	I	-	0 %
$Co(OAc)_2$	IMes	TEA	Toluene	I	-	0 %
$CoCl(PPh_3)_3$	P(*n*Bu)$_3$	-	Toluene	I	-	0 %
$CoCl_2$	P(*n*Bu)$_3$	$NaBH_4$	Toluene	I	larger scale	0 %
$CoCl_2$	$P(NMe_2)_3$	$NaBH_4$	Toluene	I	larger scale	0 %
$CoCl_2$	P(*o*-Tol)$_3$	$NaBH_4$	Toluene	I	larger scale	0 %
$CoCl_2$	P(OPh *o*-Ph)$_3$	$NaBH_4$	Toluene	I	larger scale	0 %
$CoCl_2$	$P(OPh)_3$	$NaBH_4$	Toluene	I	larger scale	0 %
$CoCl_2$	P(*t*Bu)$_3$	$NaBH_4$	Toluene	I	larger scale	0 %
$CoCl_2$	$P(OEt)_3$	$NaBH_4$	Toluene	I	larger scale	0 %
$CoCl_2$	$P(OCH_2)_3CHEt$	$NaBH_4$	Toluene	I	larger scale	0 %
$CoCl_2$	$((C_6F_5)_2PCH_2)_2$	$NaBH_4$	Toluene	I	larger scale	0 %
$CoCl_2$	$((PhO)_2PCH_2)_2$	$NaBH_4$	Toluene	I	larger scale	0 %
$CoCl_2$	PPh_3	$NaBH_4$	Toluene	I	larger scale	0 %
$CoCl_2$	P(*i*Pr)$_3$	$NaBH_4$	EtOH	II	larger scale, no TFA	0 %
$CoCl_2$	P(*i*Pr)$_3$	$NaBH_4$	EtOH	II	larger scale	0 %
$CoCl_2$	PPh_3	$NaBH_4$	EtOH	II	larger scale, no TFA	0 %
$CoCl_2$	PPh_3	$NaBH_4$	EtOH	II	larger scale,	0 %
$Co(acac)_2$	P(O*i*Pr)$_3$	-	Toluene	I	-	0 %

$Co(acac)_3$	$P(OiPr)_3$	-	Toluene	I	-	0 %
$CoCl_2$	PPh_3	$NaBH_4$	EtOH	II	larger scale, 20 °C	0 %
$CoCl((PPh_3)$	-	-	EtOH	II	240 µL Substrate mix instead of 141 µL, 20 °C	0 %
$Co(acac)_2$	$P(OiPr)_3$	--	EtOH	II	20 °C	0 %
$Co(acac)_3$	$P(OiPr)_3$	--	EtOH	II	20 °C	0 %
$Co(acac)_2$	$P(OiPr)_3$	$NaBH_4$	EtOH	II	larger scale, 20 °C	0 %
$Co(acac)_3$	$P(OiPr)_3$	$NaBH_4$	EtOH	II	larger scale, 20 °C	0 %
$CoCl_2$	PPh_3	$NaBH_4$	EtOH	III	additional 95 µL CHD, 20 °C	0 %
$Co(acac)_2$	$P(OiPr)_3$	$NaBH_4$	EtOH	II	80 °C, 10 % cat loading	0 %
$Co(acac)_3$	$P(OiPr)_3$	$NaBH_4$	EtOH	II	80 °C, 10 % cat loading	0 %
$Co(acac)_3$	Triphos	--	EtOH/THF	IV	according to Beller et al.[51]	0 %

Condition I and II: Each mixture consists of 0.03 mmol metal precursor, 0.09 mmol ligand, 4.6 µL TFA, 141 µL substrate stock solution (0.6 mmol morpholine and 0.6 mmol 1,3-cyclohexadiene and 0.2 mmol mesitylene) and 240 µL toluene or degassed EtOH respectively heated to 80 °C for 24 h. Reactions with EtOH were prepared by mixing everything besides EtOH in the box, transferring the reaction vessel outside and adding EtOH under argon flow on a Schlenk line. Reactions with $NaBH_4$ were performed with 0.1 mmol of metal and everything else adjusted accordingly (marked with the comment larger scale).

Condition III: $CoCl_2$, PPh_3, 1,3-cyclohexadiene and $NaBH_4$ were mixed in the box, EtOH was added under dry ice isopropanol cooling; substrate was added outside of the box, too.

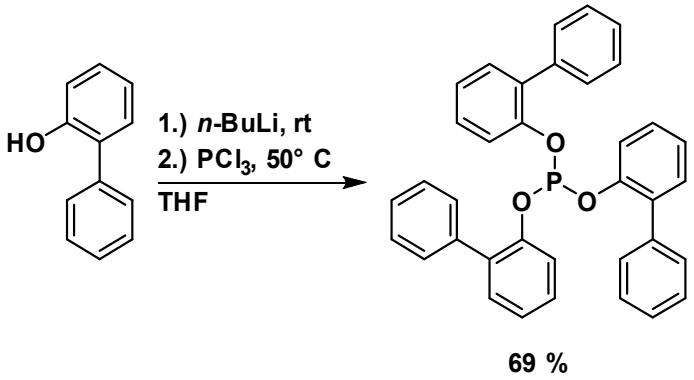
Condition IV: $Co(acac)_3$ and triphos were dissolved in THF in a glovebox, substrate mix and TFA were added and the mixture was transferred to the outside and EtOH was added under argon flow on a Schlenk line.

Conditions I, II, III and IV are further explained in chapter 4.2.

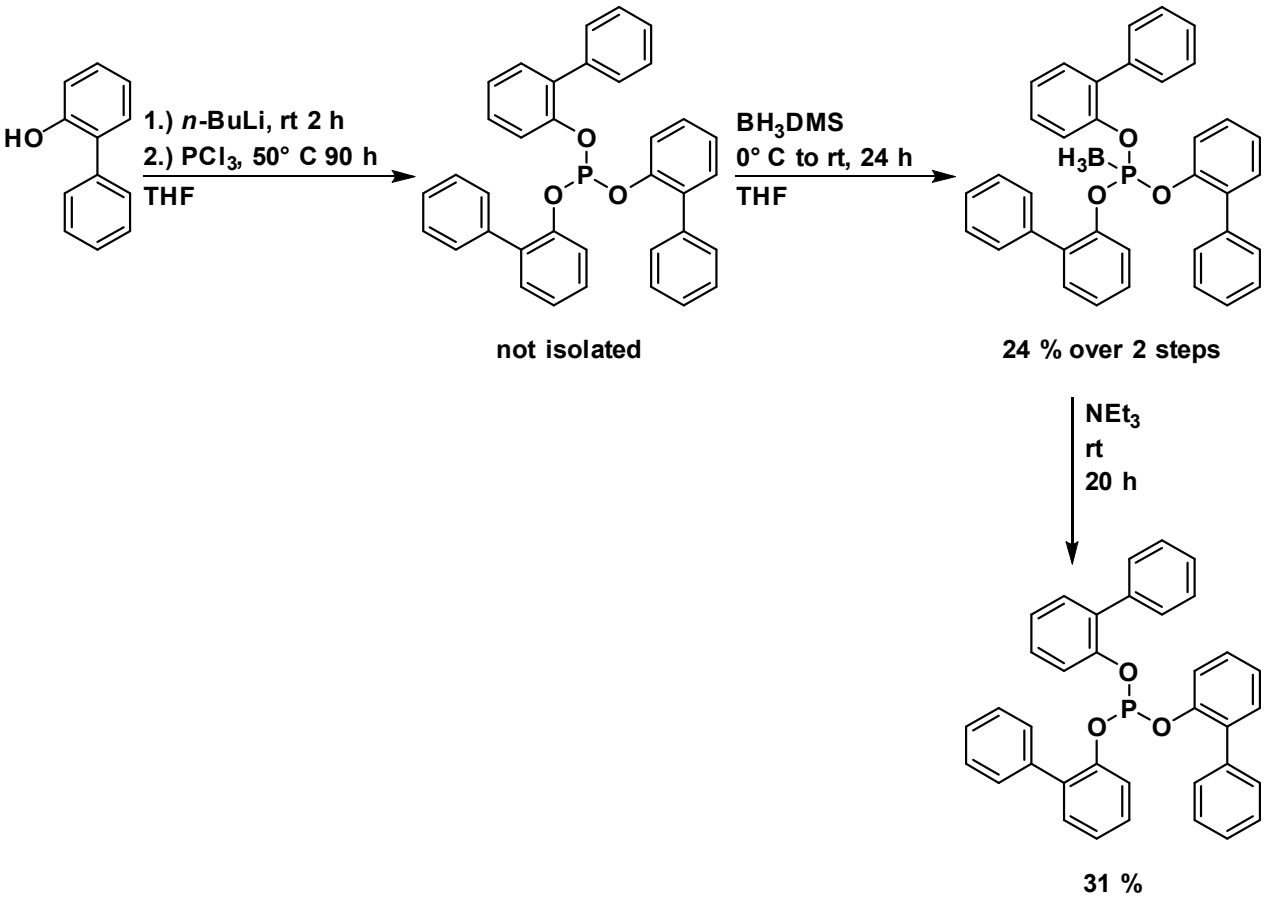
The corresponding reaction can be seen in Scheme 26.

3.3 Syntheses of ligands

The ligand P(OPh *o*-Ph)$_3$ was prepared according to the procedure of Kownacki et al.[39] as shown in Scheme 27.



Scheme 27: Synthesis of tri([1,1'-biphenyl]-2-yl) phosphite.[39]

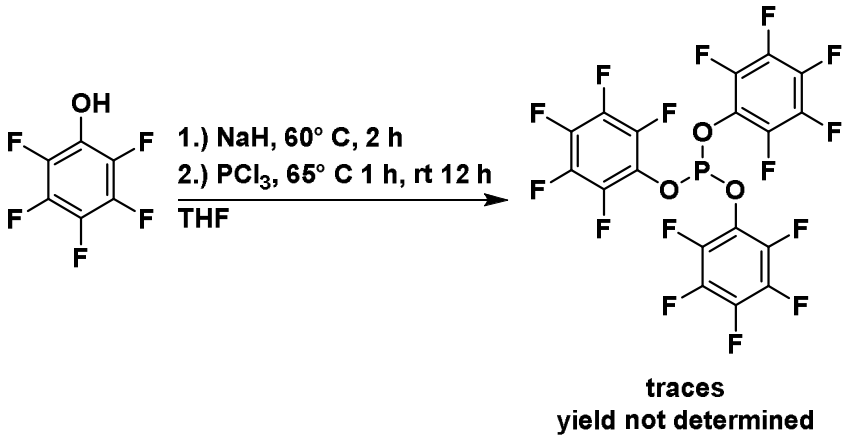


Scheme 28: Synthesis of tri([1,1'-biphenyl]-2-yl) phosphite via the BH_3 adduct.[39]

For the first synthesis (see chapter 4.1.1), this method was varied to achieve a higher yield as seen in Scheme 28. Since the desired product was thought to be highly air sensitive and purification *via* column chromatography was desired, the crude product was transformed into the BH_3 adduct. This was done to achieve an easier purification, because the borane protected product would be air stable. The resulting adduct was then purified *via* column chromatography and from that pure product, the pure phosphite should be isolated. But under the chosen column conditions, the protecting group was not fully stable and a large amount of deprotected product was already obtained in some of the collected fractions. The fraction containing protected phosphite was then treated with degassed NEt_3, which lead to a yield of 31 %. The fractions from the column chromatography, which contained deprotected ligand, gave additionally 15 % yield. Therefore, the total yield of product over 3 steps is 23 %.

The air stability of the ligand was assessed by performing ^{31}P NMR spectroscopy on the ligand before and after exposure to air over night. Since no differences were detected, the regular synthesis according to the literature was performed, followed by column chromatography. For this method, a yield of 69 % was obtained whereas the literature yield is 87 %. This might be explained by slow decomposition of the ligand in the presence of oxygen. The rate of decomposition might be accelerated due to higher oxygen levels in the solvent which were used for the chromatography. To a achieve a higher yield, the column chromatography could be performed under inert conditions with degassed solvents.

As second ligand, $P(OC_6F_5)_3$ was prepared according to the same publication (Scheme 29).[39] The product was lost before it could be weighed. The NMR data is in agreement with the literature.[39]



Scheme 29: Synthesis of tris(perfluorophenyl) phosphite.[39]

4. Conclusion and Outlook

The electric and steric needs of the nickel system were assessed. According to the results strong electron donors which are sterically undemanding are beneficial for the reaction. Particularly strong σ donors like *N*-heterocyclic carbenes, seem to hinder the reaction as well. Although this effect might arise from the fact, that carbenes cannot dissociate from the metal center.

An interesting possibility is to test PCP systems. The carbon bond might function as a strong electron donor, and the phosphorous might be a sterically not demanding, electron deficient ligand. This combination of strongly donating carbene and weakly donating phosphorous might be able to tune the electron density even precisely.

Another interesting trait of the nickel system is its high activity with Triphos as a ligand. Since this type of ligand is not only defined by the parameters of cone angle and electron donation but offers an adjustable bite angle as well, it would be very interesting to investigate the influence of the bite angle on the reaction outcome. Similar ligands would be interesting as well.

Since there are already working methods for $Co(PPh_3)_3Cl$,[35] further investigation is needed to utilize 1,3-cycloheadiene in this reaction. Another approach would be to utilize another benchmark system to investigate the reactivity of cobalt; since Baker et al.[35] were able to achieve this transformation for butadiene and morpholine, it might be possible to try this combination as a benchmark system for the cobalt catalyzed reaction.

An interesting starting point for iron phosphine compounds might be the work of Keiter et al.[52] Their method utilizing 1-BuOH might be used directly to generate the iron phosphine complexes *in situ* for further testing.

The UV-induced reaction of $Fe(CO)_5$ (or the *via* UV generated complexes thereof with phosphorous compounds) with 1,3-cyclohexadiene requires further investigation as well.

There are still plenty of procedures to generate complexes *in situ* which could be tested for this reaction. One the one hand, different metal precursor should be evaluated. On the other hand, other ligands, especially sophisticated ones, like described by Buchwald[53] pose an interesting possibility. Additionally, there are other methods, to form complexes of the used metals. It might still be an interesting try, to make other complexes based on $Fe(CO)_5$ in a fashion as described in 4.2.5.

Additionally, other iron compounds are interesting. Fe(I) and Fe(0) compounds are accessible by the method of Bhadbhade *et al.*[54].

For Manganese, other phosphines starting from $Mn(CO)_5Br$ are probably not as promising, because they were tried enough in this work. Therefore, other Mn(I) complexes might be of more interest; a *in situ* synthesis and reduction of Mn(II) complexes might be good starting point.

Other Cobalt complexes then the ones tried should most likely work as well in the benchmark system, considering Baker *et al.* reported a working cobalt system[35]. Therefore, it might be interesting to test different *in situ* generated cobalt compounds with the system as described by Baker *et al.*[35], starting with other phosphines and phosphites as well.

Of course, the given procedures are only examples.

5. Experimental Section

All manipulations were carried out using either standard Schlenk techniques or in a Braun Argon glovebox. All ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker Ultrashield™ 400 Plus instrument. All chemical shifts are noted in ppm relative to tetramethylsilane and were referenced to residual signals of the solvent (^{1}H NMR ($CDCl_3$): 7.26 ppm, ^{1}H NMR (CD_2Cl_2): 5.32 ppm, ^{1}H NMR (C_6D_6): 7.16 ppm, ^{13}C NMR ($CDCl_3$): 77.0 ppm).

Unless stated differently, commercially available chemicals were used as bought. Benzene and toluene were distilled from sodium benzophenone ketyl. Liquids used in the glovebox were dried over CaH_2 overnight, vacuum transferred and dried again over CaH_2 followed by a second vacuum transfer before they were brought into the glove box. TFA was dried over molecular sieves overnight, twice. All synthesized solids were freeze dried from benzene. PCl_3 was vacuum transferred from a still and stored at 4 °C in a Schlenk flask outside of the glovebox.

$Ni(COD)_2$ was kindly derived from Prof. Michael Widhalm. It was recrystallized in the glovebox from warm toluene. After crystallization in the freezer at –35°C for approx 24 h, the orange crystals were dried in full vacuum outside of the box. After drying, they were brought into the glovebox again and kept in the dark at –35°C.

Knölker's complex was kindly derived from Natalie Hofmann, MSc. of the Hultzsch group. It was prepared by the procedure of Knölker *et al*.[55,56]

$Mn(CO)_5Br$ was kindly derived from Leonard Homberg, MSc. of the Hultzsch group. It was prepared according to the patent of Motterlini *et al*.[57]

Vials were used one time and thrown out, vial caps were washed with DCM, acetone and water and dried in a desiccator.

Stir bars were washed by subsequent sonication in DCM, acetone and water, 15 min each, rinsing with acetone and drying for at least an hour in a drying oven at 120 °C.

Glassware was cleaned by submerging in a base bath consisting of KOH solution in isopropanol for two days. After rinsing with water, the glassware was submerged in diluted HCl solution for two days, washed with deionized (DI) water and dried in a drying oven at 120 °C.

Gas chromatograms were recorded on an agilent 7890A gas chromatograph with a 7633b autosampler and an HP-5 (30m × 0.32mm × 0.25µm) column and detected with a flame ionization detector with H_2 as carrier gas. The temperature program started at 35 °C with a hold

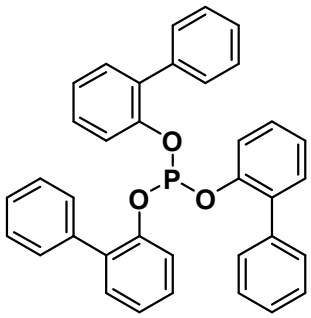
time of 2.25 min followed by a slope of 10 °C/min to 100 °C and 25 °C/min from 100 °C to 300 °C followed by a post run at 300 °C for 5 min.

n-BuLi was titrated before use against *N*-pivaloyl-*o* -benzylaniline.[58]

5.1 Ligand synthesis

5.1.1 Synthesis of tri([1,1'-biphenyl]-2-yl) phosphite *via* BH_3 complex

5.1.1.1 Synthesis of tri([1,1'-biphenyl]-2-yl) phosphite[39]



A flame dried Schlenk flask equipped with a stir bar was charged with anhydrous THF (40 mL) and of 2-phenylphenol (1.013 g, 6 mmol). n-BuLi (2.7 mL, 2.4 mol L^{-1} in hexanes, 6.5 mmol) was added and the mixture was stirred at room temperature for 2 h. Afterwards, PCl_3 (171 µL, 2.1 mmol) was added and the reaction was allowed to stir for 90 h at 50 °C. Subsequently, all volatiles were removed *in vacuo*.

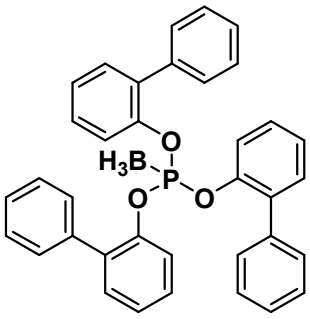
Yield: not isolated

^{1}H-NMR (400.3 MHz, $CDCl_3$): 7.29 ppm (m, 6H), 7.10 ppm (m, 1H), 7.02 ppm (dt, 1H), 6.73 ppm (tt, 1H)

^{31}P-NMR (162.0 MHz, CD_2Cl_2): 130.3 ppm (s,1P)

^{13}C{^{1}H}-NMR (100.7 MHz, CD_2Cl_2): 149.5 (d, 1C, *J*=2.70 Hz), 13.4 ppm (s, 1C), 134.6 ppm (d, J=2.89 Hz, 1C), 131.6 ppm (s, 1C), 130.1 ppm (s, 2C), 129.0 ppm (s, 1C), 128.6 ppm (s, 2C), 127.7 ppm (s, 1C), 124.8 ppm (s, 1C), 121.4 ppm (d, 1C, *J*=11.52 Hz)

5.1.1.2 Synthesis of the BH_3 adduct[59]



The crude product of 4.1.1.1 was dissolved in THF (40 mL) and borane dimethyl sulfide (276 µL, 2.9 mmol) were added at 0 °C. After the addition was completed, the mixture was allowed to stir for 24 h at rt. This crude product was attempted to purify by column chromatography. From the chromatography fractions, unprotected ligand could be isolated.

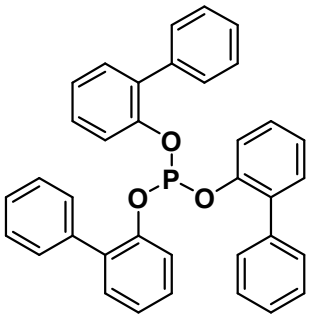
Yield of the deprotected ligand over two steps: 171 mg (15 %)

Yield of the BH_3 adduct over two steps: 251 mg (24 %)

^{1}H-NMR (400.3 MHz, $CDCl_3$): 7.27 ppm (m, 6H), 7.18 ppm (tt, 1H), 7.05 ppm (dt, 1H), 6.78 ppm (tt, 1H)

^{31}P-NMR (162.0 MHz, $CDCl_3$): 106.4 ppm (d, 1P, *J*=82.6 Hz)

5.1.1.3 Release of tri([1,1'-biphenyl]-2-yl) phosphite[60]

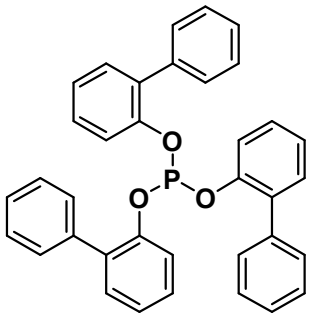


The fractions of 4.1.1.2 which contained the borane adduct were collected and refluxed in degassed NEt_3 (5 mL, 36 mmol) for 20 h. Subsequently, all volatiles were removed *in vacuo* on a Schlenk line and the product was freeze dried.

Yield: 75 mg (31 %)

The spectroscopic data is in agreement with the data obtained in section 4.1.1.1.

5.1.2 Synthesis of tri([1,1'-biphenyl]-2-yl) phosphite[39]

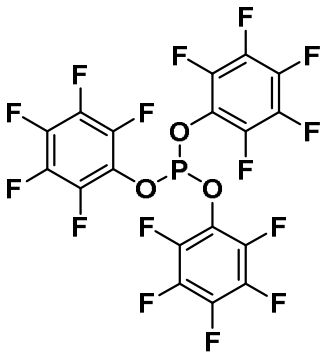


A flame dried Schlenk flask equipped with a stir bar was charged with anhydrous THF (24 mL). After adding 2-phenylphenol (4.012 g, 24 mmol), freshly titrated n-BuLi (10.0 mL, 2.4 mol L^{-1}, 24 mmol) was added and the mixture was allowed to stir for 2 h. PCl_3 (622 µL, 7 mmol) was added and the reaction mixture was allowed to stir for 90 h. The volatiles were removed under reduced pressure under inert atmosphere. The crude product was purified via column chromatography and freeze dried.

Yield: 3.154 g (69 %)

The spectroscopic data is in agreement with the data obtained in section 4.1.1.1.

5.1.3 Synthesis of tris-(pentafluorophenyl)-phosphite[39]



Pentafluorophenol (500 mg, 2.7 mmol) was dissolved in anhydrous THF (3.15 mL) in a flame dried Schlenk flask. This solution was added to a suspension of NaH (130 mg, 5.4 mmol) in anhydrous THF (2.25 mL) in a flame dried Schlenk flask equipped with a stir bar *via* a cannula. The mixture was allowed to stir for 2 h at 60 °C. Subsequently, the mixture was filtered off by a canula in a flame dried Schlenk flask equipped with stir bar and PCl_3 (70.7 µL, 0.8 mmol) was added to the filtrate. The mixture was then stirred at 65 °C for 1 h and at rt for 12 h. Afterwards, the solution was evaporated to dryness and anhydrous hexane was added. The suspension was filtered with a canula into another flame dried Schlenk flask. The filtrate was concentrated and left to crystallize. The solvent was decanted from the crystals via canula. The crystals were freeze dried from benzene and transferred to an argon glove box.

Yield: not determined; enough for NMR.

^{1}H-NMR (C_6D_6, 400.3 MHz): no signals

^{31}P-NMR (C_6D_6, 162.0 MHz): 130.85 (hept, J = 30.1 Hz)

5.2 Catalysis

5.2.1 Catalysis condition (I)

0.03 mmol of the metal precursor are weighed in a 4 mL screw-capped vial in an argon filled glovebox. Subsequently, the vial was charged with a stir bar, ligand (0.09 mmol) and toluene (240 µL). If a reductant was used, it was added now. After stirring the closed vial for 30 min, substrate mix (141 µL; consisting of 0.6 mmol morpholine, 0.6 mmol 1,3-cyclohexadiene and 0.2 mmol mesitylene) and TFA (4.6 µL, 0.06 mmol) were added. The closed vial was then heated for 24 h in an aluminum block on a stir plate in the box.

Afterwards, of H_2O_2 (400 µL, 30 % w/w) was added under ice cooling outside of the box. As soon as the evolution of gas stopped (after approx 30 min), NaOH (1 mL, 15 % w/w) was added dropwise while maintaining the cooling. After the bubbling seceded, the mixture was filtered using a syringe equipped with a glass fiber filter. The filtrate was then extracted five times with DCM (1 mL). The organic phases were collected and measured *via* GC-FID.

5.2.2 Catalysis condition (II)

The metal precursor (0.03 mmol) was weighed in a 4 mL screw-capped vial. Subsequently, a stir bar, substrate stock solution (141 µL; consisting of 0.6 mmol morpholine, 0.6 mmol 1,3-cyclohexadiene and 0.2 mmol mesitylene), the ligand (0.09 mmol) and the reducing agent (0.05 mmol) were added.

The vial was brought out of the box, put in a glass tube connected to an argon line under an argon stream. The cap of the vial was removed, EtOH (240 µL) was added and the cap was closed again, still with an argon stream. The vial was placed in an aluminum block outside of the box and stirred at 80 °C for 24 h.

Afterwards, of H_2O_2 (400 µL, 30 % w/w) was added under ice cooling outside of the box. As soon as the evolution of gas stopped (after approx 30 min), NaOH (1 mL, 15 % w/w) was added dropwise while maintaining the cooling. After the bubbling seceded, the mixture was filtered using a syringe equipped with a glass fiber filter. The filtrate was then extracted five times with DCM (1 mL). The organic phases were collected and measured *via* GC-FID.

5.2.3 $CoCl_2$ with additional 1,3-cyclohexadiene according to Baker et al. (Conditon III)[35]

$CoCl_2$ (26 mg, 0.2 mmol), PPh_3 (50.25 mg, 0.2 mmol), 1,3-cyclohexadiene (95.3 µL, 1.0 mmol) and $NaBH_4$ (3.8 mg, 0.1 mmol) were mixed in a screw cap vial, equipped with a stir

bar, in an argon glovebox. The mixture was transferred to the outside, cooled in a bath of dry ice and isopropanol and EtOH (500 µL) and substrate stock solution (117 µL; consisting of 0.50 mmol morpholine, 0.50 mmol 1,3-cyclohexadiene and 0.17 mmol mesitylene), transferred out of the box in a GC vial with a septum) were added through a septum. The mixture was allowed to stir for 24 h at room temperature.

Afterwards, of H_2O_2 (400 µL, 30 % w/w) was added under ice cooling outside of the box. As soon as the evolution of gas stopped (after approx 30 min), NaOH (1 mL, 15 % w/w) was added dropwise while maintaining the cooling. After the bubbling seceded, the mixture was filtered using a syringe equipped with a glass fiber filter. The filtrate was then extracted five times with DCM (1 mL). The organic phases were collected and measured *via* GC-FID.

5.2.4 $Co(acac)_3$-Triphos system according to Beller et al. (Condition IV)[51]

$Co(acac)_3$ (12.98 mg, 0.036 mmol) and Triphos (37.48 mg, 0.06 mmol) were dissolved in THF (175 µL) in a 4 mL screw cap vial equipped with a stir bar. Substrate mix (141 µL; consisting of 0.6 mmol morpholine, 0.6 mmol 1,3-cyclohexadiene and 0.2 mmol mesitylene) and TFA (4.6 µL, 0.06 mmol) were added and the closed vial was removed from the box. Under argon flow on the Schlenk line, the vial was opened and EtOH (65 µL) were added. The resulting mixture was stirred at 80 °C in an aluminum block for 24 h.

Afterwards, of H_2O_2 (400 µL, 30 % w/w) was added under ice cooling outside of the box. As soon as the evolution of gas stopped (after approx 30 min), NaOH (1 mL, 15 % w/w) was added dropwise while maintaining the cooling. After the bubbling seceded, the mixture was filtered using a syringe equipped with a glass fiber filter. The filtrate was then extracted five times with DCM (1 mL). The organic phases were collected and measured *via* GC-FID.

5.2.5 Carbene complexes

In an argon glovebox, KH (3.61 mg, 0.09 mmol) was weighed in a 4 mL threaded vial, a stir bar, 240 µL toluene or THF respectively and IMes precursor (27.4 mg) were added. The mixture was closed and put in an aluminum block. Subsequently, it was stirred for 2 h and then, $Ni(COD)_2$ (8.25 mg, 0.03 mmol) was added, the mixture was allowed to stir for 30 min and substrate stock solution (141 µL; consisting of 0.6 mmol morpholine, 0.6 mmol 1,3-cyclohexadiene and 0.2 mmol mesitylene) and TFA (4.6 µL, 0.06 mmol) were added. Subsequently, the reaction mixture was allowed to stir for 24 h in an aluminum block at 80 °C.

Afterwards, of H_2O_2 (400 µL, 30 % w/w) was added under ice cooling outside of the box. As soon as the evolution of gas stopped (after approx 30 min), NaOH (1 mL, 15 % w/w) was added

dropwise while maintaining the cooling. After the bubbling seceded, the mixture was filtered using a syringe equipped with a glass fiber filter. The filtrate was then extracted five times with DCM (1 mL). The organic phases were collected and measured *via* GC-FID.

5.2.6 Catalysis with $FeCl_2$ in THF

In a 4 mL screw capped vial charged with a stir bar, $FeCl_2$ (3.81 mg, 0.03 mmol) was suspended in THF (240 µL) in an argon glovebox. Subsequently, $P(nBu)_3$ (29.6 µL, 0.12 mmol) was added. Afterwards, the vial was placed in an aluminum block and brought to reflux for 3 h. The mixture was allowed to cool to rt and substrate stock solution (141 µL; consisting of 0.6 mmol morpholine, 0.6 mmol 1,3-cyclohexadiene and 0.2 mmol mesitylene) were added, followed by TFA (4.6 µL, 0.06 mmol). The vial was closed again, and the mixture was refluxed for 24 h.

Afterwards, of H_2O_2 (400 µL, 30 % w/w) was added under ice cooling outside of the box. As soon as the evolution of gas stopped (after approx 30 min), NaOH (1 mL, 15 % w/w) was added dropwise while maintaining the cooling. After the bubbling seceded, the mixture was filtered using a syringe equipped with a glass fiber filter. The filtrate was then extracted five times with DCM (1 mL). The organic phases were collected and measured *via* GC-FID.

5.2.7 Catalysis with $Fe(CO)_5$ under UV-light irradiation

A quartz tube was charged with of $Fe(CO)_5$ (8.06 µL, 0.06 mmol), a stir bar, hexanes (480µL), $P(nBu)_3$ (44.4 µL, 0.18 mmol), substrate stock solution (282 µL; consisting of 1.2 mmol morpholine, 1.2 mmol 1,3-cyclohexadiene and 0.4 mmol mesitylene) and TFA (9.2 µL, 0.12 mmol). The vessel was sealed with an unpierced rubber septum and parafilm and brought out of the box. The tube was then placed next to a mercury UV lamp and irradiated for 24 h at rt.

Afterwards, of H_2O_2 (400 µL, 30 % w/w) was added under ice cooling outside of the box. As soon as the evolution of gas stopped (after approx 30 min), NaOH (1 mL, 15 % w/w) was added dropwise while maintaining the cooling. After the bubbling seceded, the mixture was filtered using a syringe equipped with a glass fiber filter. The filtrate was then extracted five times with DCM (1 mL). The organic phases were collected and measured *via* GC-FID.

5.2.8 Stock solutions

Stock solutions were prepared from 1,3-cyclohexadiene, morpholine and mesitylene in a volumetric flask. A molar ratio of 1:1:0.33 morpholine:cyclohexadiene:mesitylene was used; the volumetric flask was made up to volume with toluene. The concentrations can be seen in Table 19.

GC-FID spectra of the standards were made by diluting a few drops in approx 1.5 mL DCM and measuring the prepared mixture with the GC-FID instrument.

Table 19: Concentrations of 1,3-cyclohexadiene, morpholine and mesitylene in the substrate stock solutions.

Compound	Concentration [mmol/mL]
Morpholine	4.25
Cyclohexadiene	4.25
Mesitylene	1.42

6. Literature

(1) Caffeine | The Merck Index Online https://www.rsc.org/Merck-Index/monograph/m2909/caffeine?q=unauthorize (accessed Apr 1, 2018).

(2) Morphine | The Merck Index Online https://www.rsc.org/Merck-Index/monograph/m7631/morphine?q=unauthorize (accessed Apr 1, 2018).

(3) Glycine | The Merck Index Online https://www.rsc.org/Merck-Index/monograph/m5796/glycine?q=unauthorize (accessed Apr 1, 2018).

(4) Strychnine | The Merck Index Online https://www.rsc.org/Merck-Index/monograph/m10255/strychnine?q=unauthorize (accessed Apr 1, 2018).

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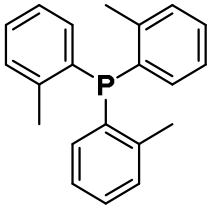
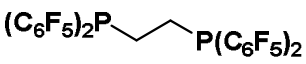
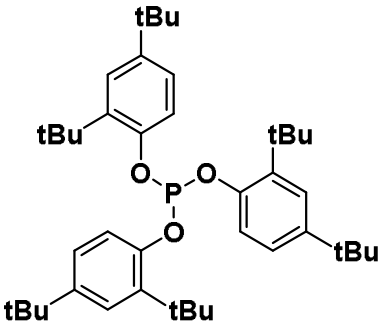
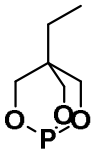
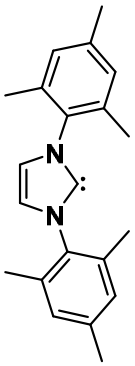
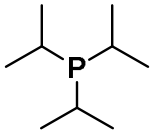
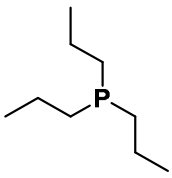
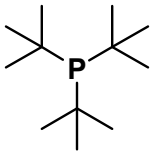
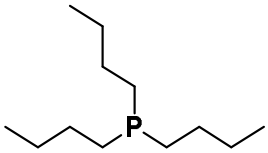
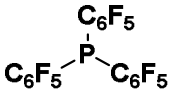
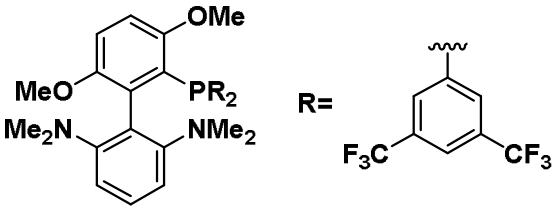
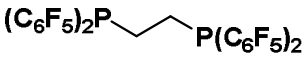
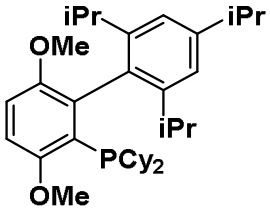
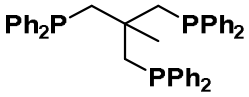
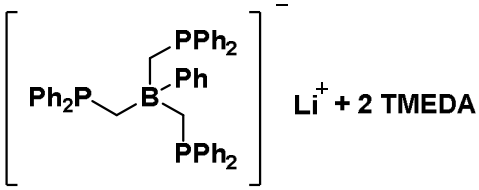
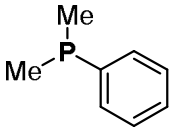
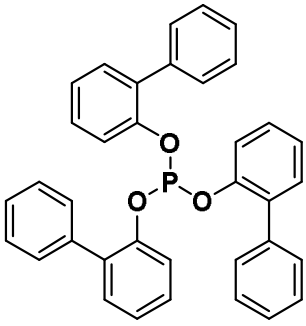
7. Appendix

7.1 Table of ligands

Abbreviation	Structure
P(*o*Tol)$_3$	
$(C_6F_5)_2PCH_2CH_2P(C_6F_5)_2$	
P(O-*o*,*p*-*t*Bu-Ph)$_3$	
P(OCH$_2$)$_3$CHEt	
IMes	
P(*i*Pr)$_3$	
P(*n*Pr)$_3$	

P(*t*Bu)$_3$	
P(*n*Bu)$_3$	
P(C_6F_5)$_3$	
L1	
(C_6F_5)$_2$PCH_2CH_2P(C_6F_5)$_2$	
Brettphos	
Triphos	
LiBTriphosTMEDA$_2$	
PMe_2Ph	
P(OPh *o*-Ph)$_3$	

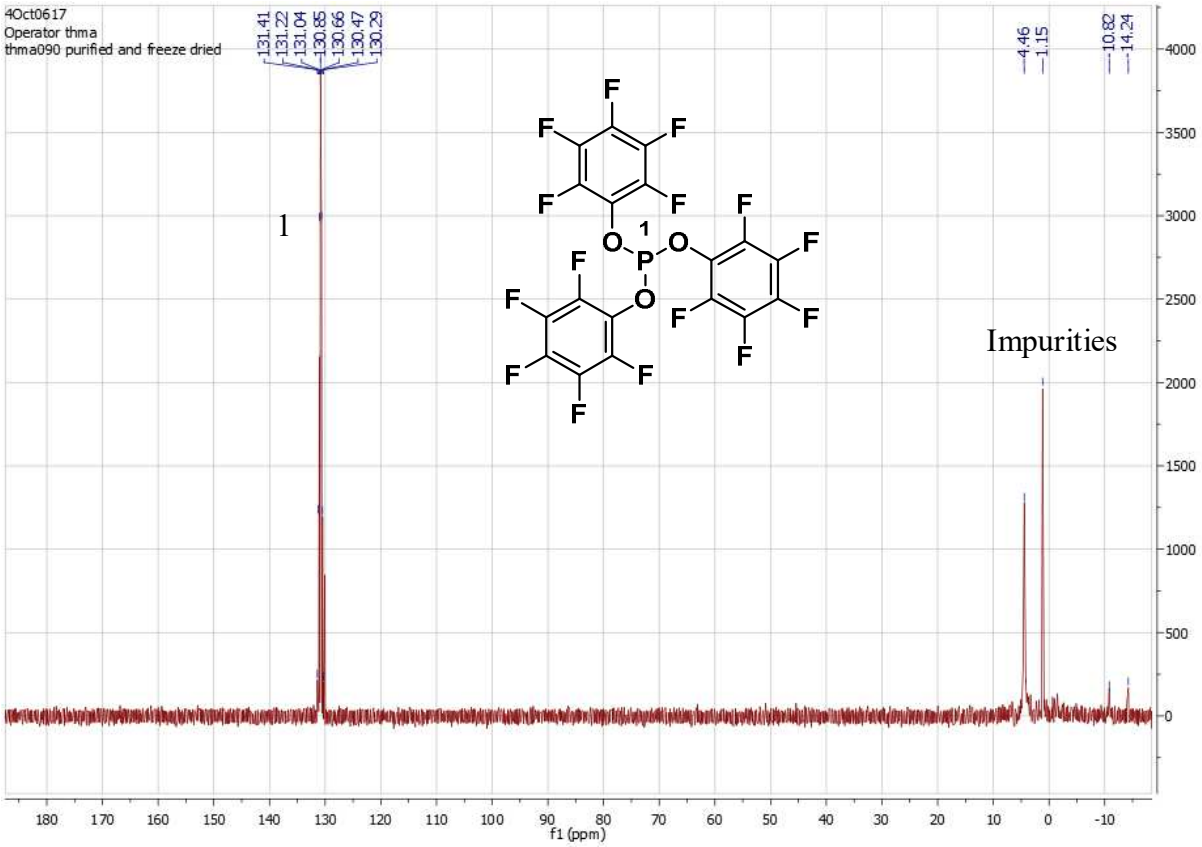
$P(OEt)_3$	
$P(OPh)_3$	
$P(O\mathit{i}Pr)_3$	
$P(NMe_2)_3$	
$(PhO)_2PCH_2CH_2P(OPh)_2$	

7.2 List of figures

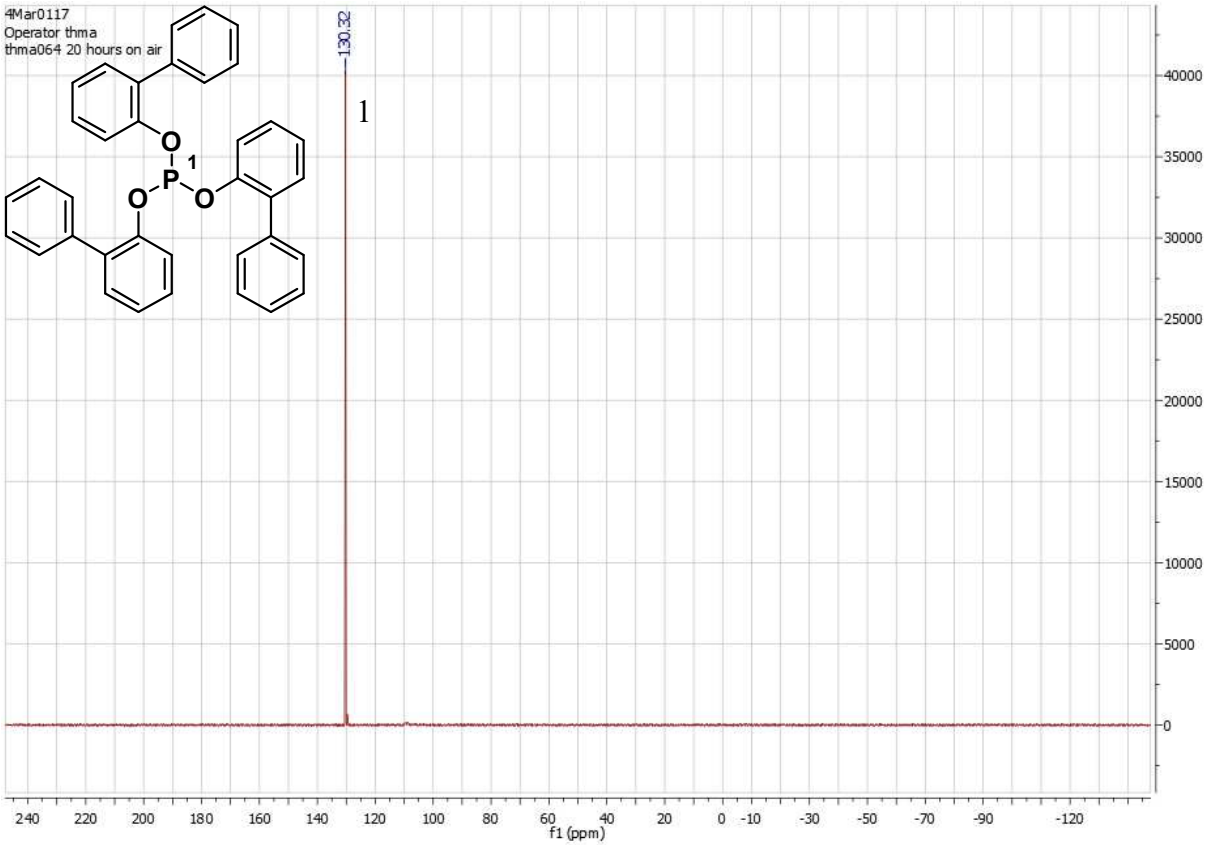
7.3 List of schemes

7.4 List of tables

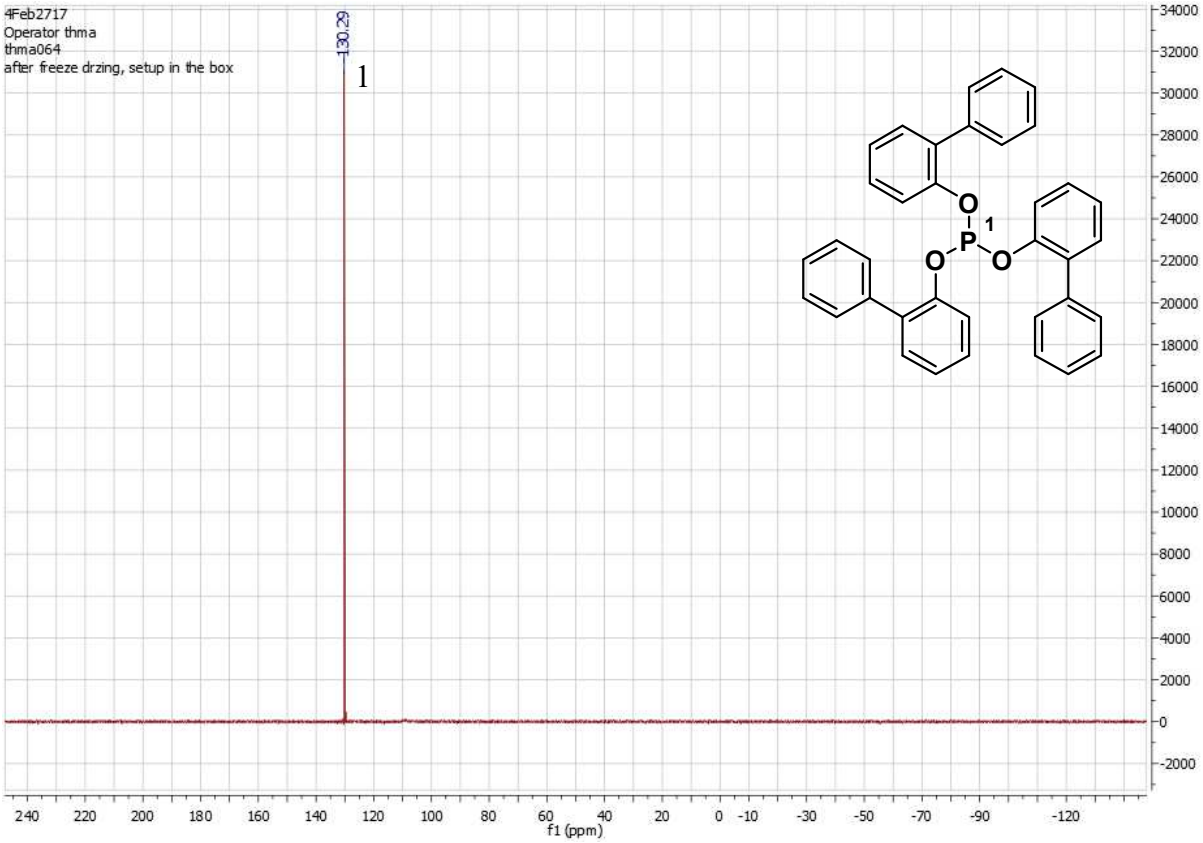
7.5 Supplementary information



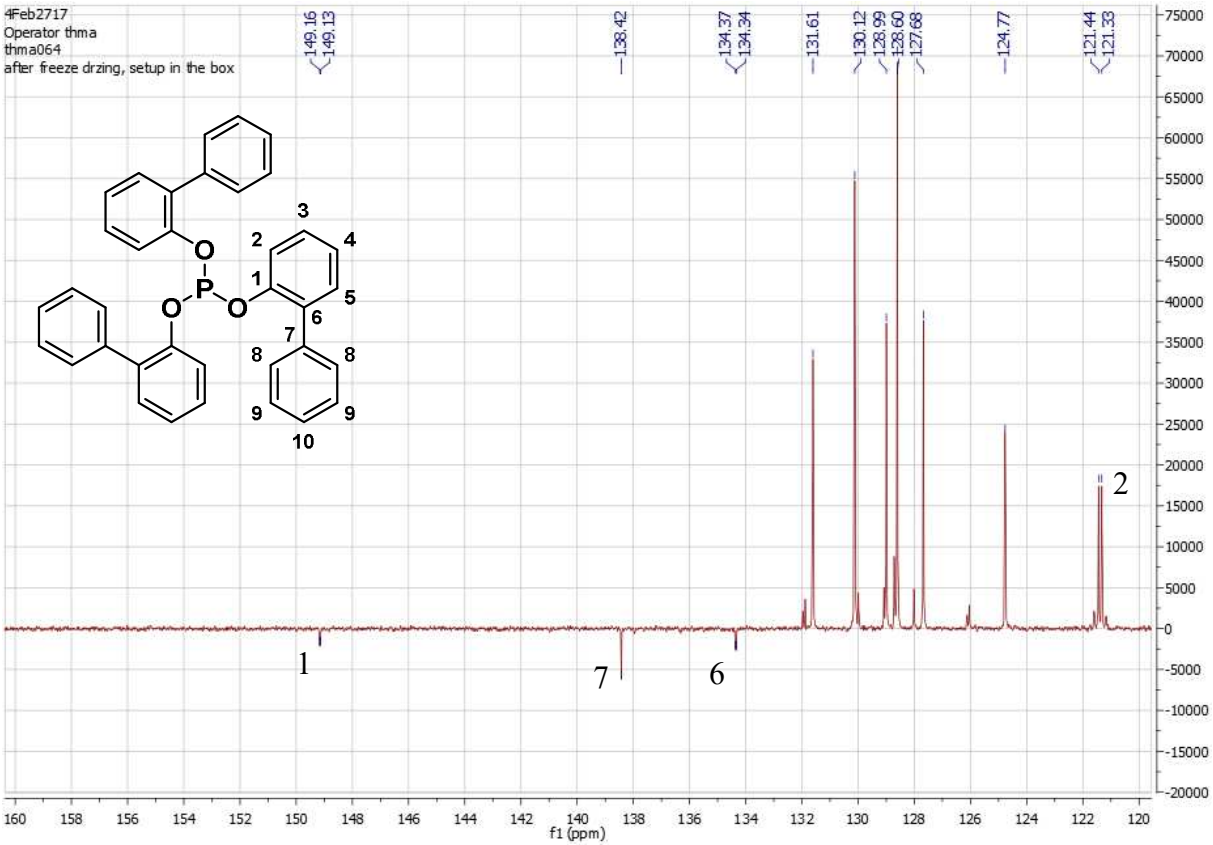
SI 1 $^{31}P\{^{1}H\}$-NMR (162.0 MHz, C_6D_6) of tris-(pentafluorophenyl)-phosphite at 25 °C.



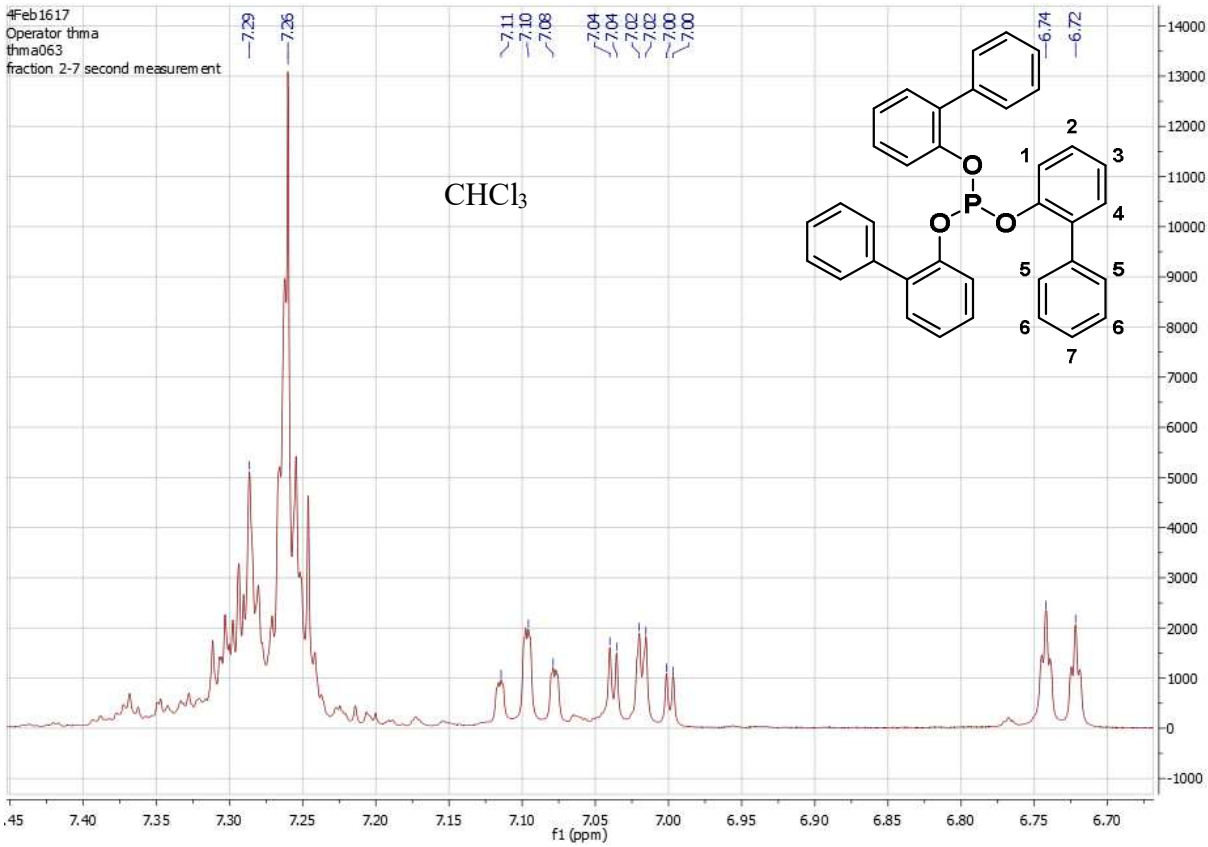
SI 2 $^{31}P_{\{^{1}H\}}$-NMR (162.0 MHz, CD_2Cl_2) of tri([1,1'-biphenyl]-2-yl) phosphite at 25 °C after exposure to air for20 h rt.



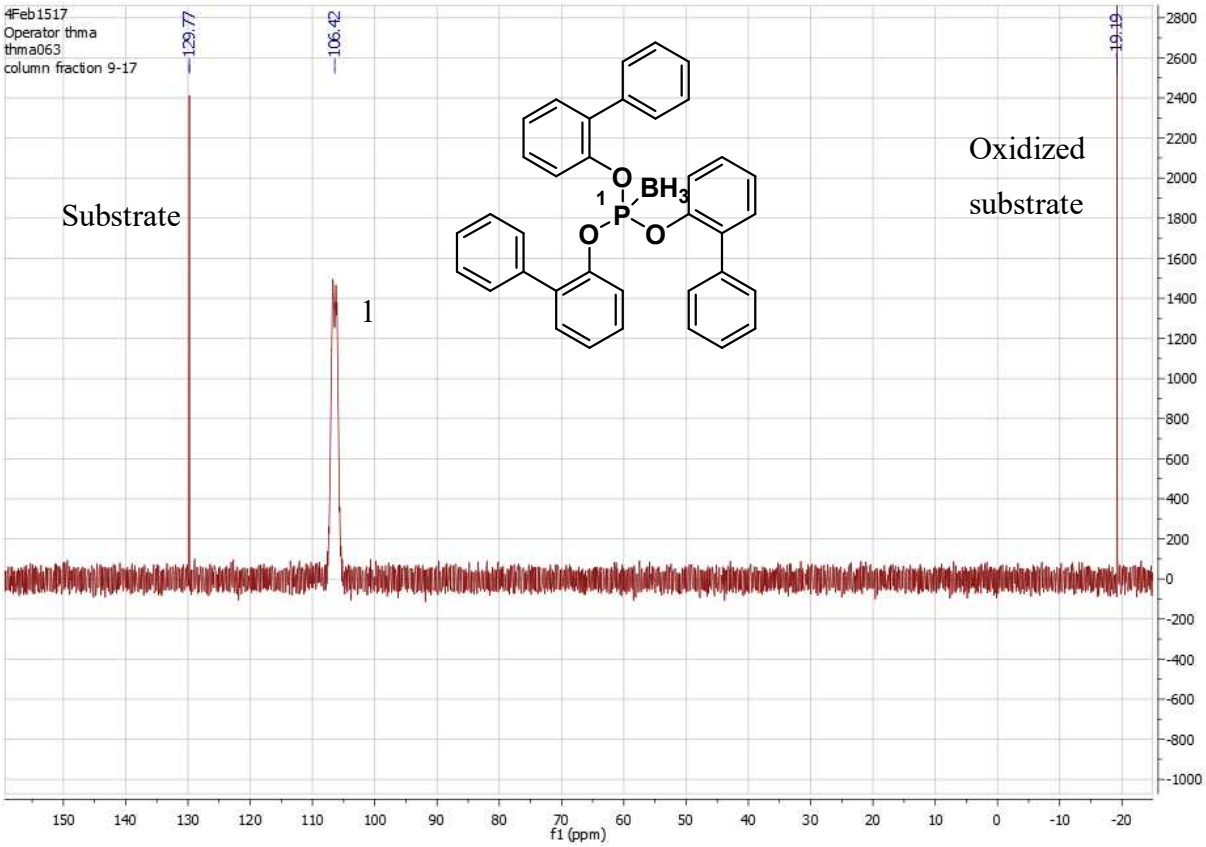
SI 3 $^{31}P\{^{1}H\}$-NMR (162.0 MHz, CD_2Cl_2) of tri([1,1'-biphenyl]-2-yl) phosphite at 25 °C.



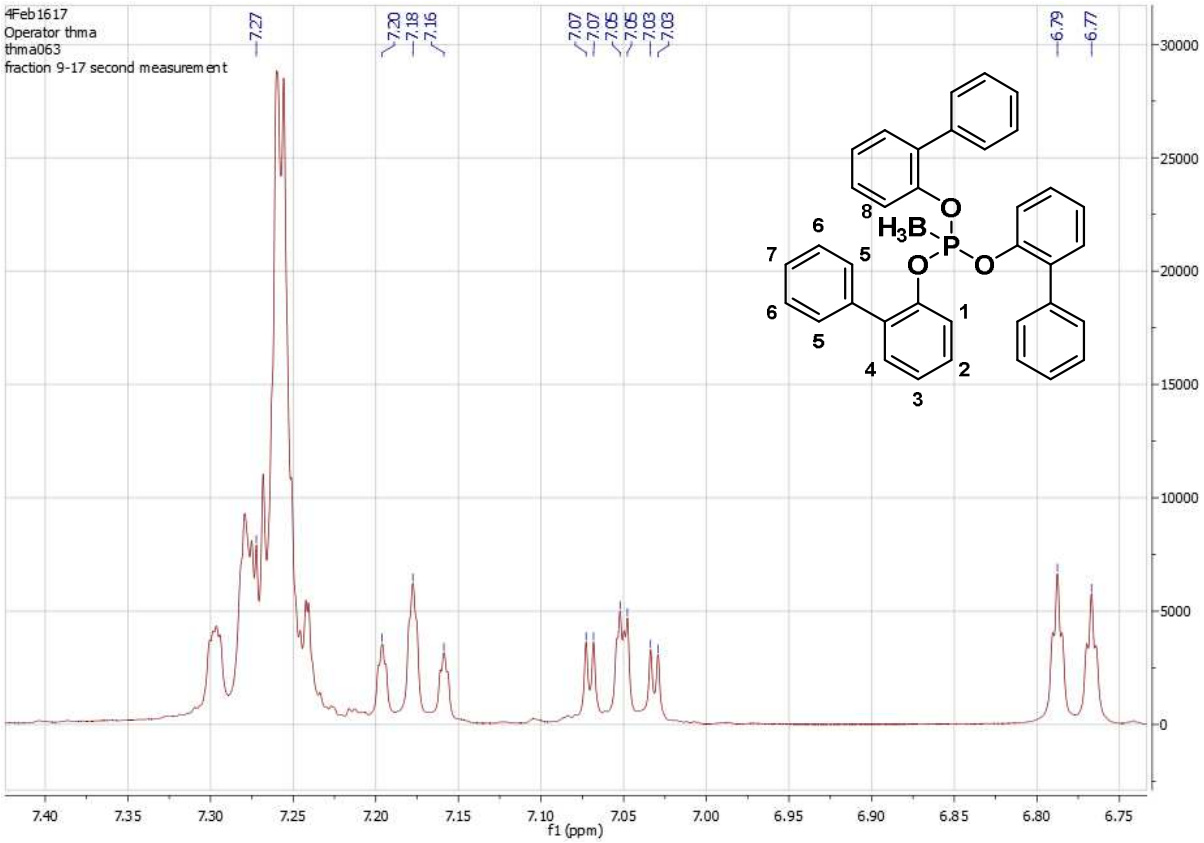
SI 4 $^{13}C\{^{1}H\}$-NMR (100. 7 MHz, CD_2Cl_2, APT) of tri([1,1'-biphenyl]-2-yl) phosphite at 25 °C.



SI 5 ^{1}H-NMR (400.3 MHz, $CDCl_3$) of tri([1,1'-biphenyl]-2-yl) phosphite at 25 °C.



SI 6 $^{31}P_{\{^1H\}}$-NMR (162.0 MHz, $CDCl_3$) of the tri([1,1'-biphenyl]-2-yl) phosphite BH_3 adduct at 25 °C.



SI 7 ^{1}H-NMR (400.3 MHz, $CDCl_3$) of the tri([1,1'-biphenyl]-2-yl) phosphite BH_3 adduct at 25 °C.