Alpha-Arylation of Acetophenones via a Radical Mechanism

Masterthesis
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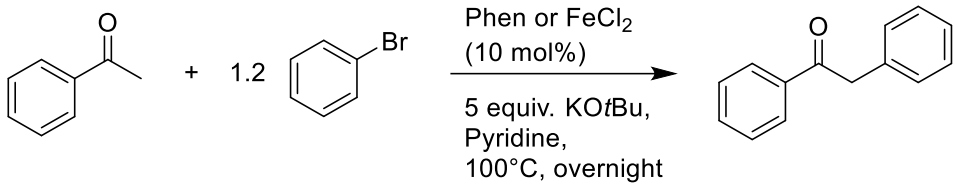
Abstract

Alpha-arylation is an important reaction which is commonly used in the synthesis of many pharmaceuticals. To catalyze these reactions palladium catalysts are usually used, however copper and nickel also can be used. Alpha-arylation is also possible without any transition metal via the $S_{RN}1$ reaction. Recently, Klein Gebbink *et al.* found an alpha-arylated side product, namely 1-(4-Phenylphenyl)-2-(4-acetylphenyl)ethanone, in the direct arylation reaction between 4-bromoacetophenone and benzene.

Using their conditions as a starting point, different conditions were tried in order to optimize the reaction between acetophenone and bromobenzene. Yields of up to 49% of 2-phenylacetophenone were obtained when using bromobenzene and 57% of 2-(1-naphthyl)-1-phenylethanone when using 1-bromonapthtalene.



Alpha-arylation of an ester was attempted, which did not yield any arylated product. This was most likely due to KO*t*Bu not being strong enough to deprotonate *tert*-butyl acetate. Furthermore, in an alpha-arylation reaction in the presence of carbon monoxide, a diketone was obtained in 6% yield. This shows that the used system is able to perform free-radical carbonylation.

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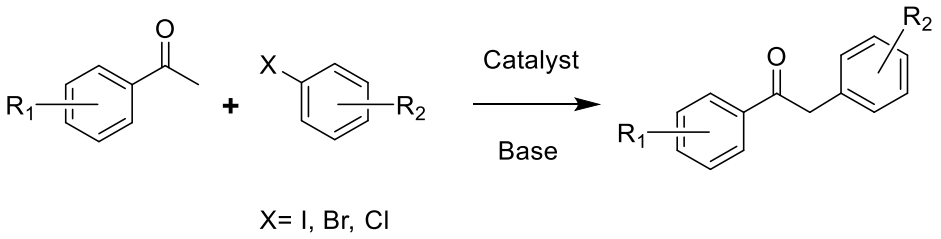
List of abbreviations

δ	-	Chemical Shift, given in ppm
^{1}H-NMR	-	Proton Nuclear Magnetic Resonance
^{13}C-NMR	-	Carbon Nuclear Magnetic Resonance
DCM	-	Dichloromethane
DMF	-	Dimethylformamide
DMSO	-	Dimethylsulfoxide
GC	-	Gas Spectrometry
h	-	Hour
Hz	-	Hertz
KO*t*Bu	-	Potassium tert-butoxide
MHz	-	Mega Hertz
MS	-	Mass Spectrometry
NMR	-	Nuclear Magnetic Resonance
Phen	-	1,10-Phenanthroline
ppm	-	Parts per million
RT	-	Room Temperature
THF	-	Tetrahydrofurane

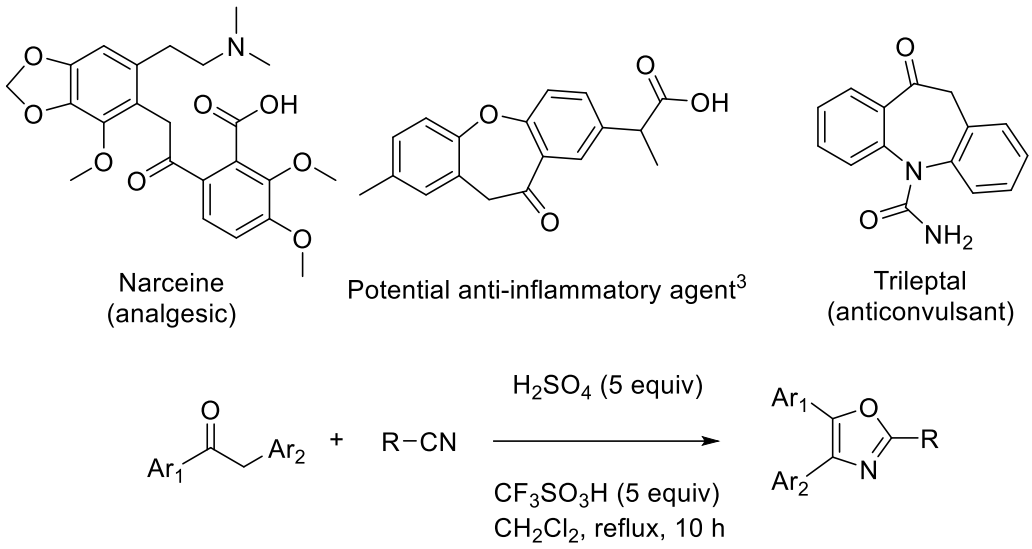
Chapter 1. Introduction

1.1. Background information

Alpha-arylation is an important reaction in organic chemistry to create alpha-aryl-substituted ketones, esters, nitriles, carboxyamides, etc.[1] When acetophenone or one of its derivatives is used in the reaction, a motif is formed (deoxybenzoin) which is commonly found in many pharmaceuticals such as painkillers (analgesics)[2], anti-inflammatory drugs[3,4], antimicrobial drugs[5] and anti-epileptic drugs (anticonvulsants).[6,7] These deoxybenzoins can also be used as building blocks for the formation of heterocyclic molecules such as indoles,[8] isoxazoles[9] and pyrazoles.[10]

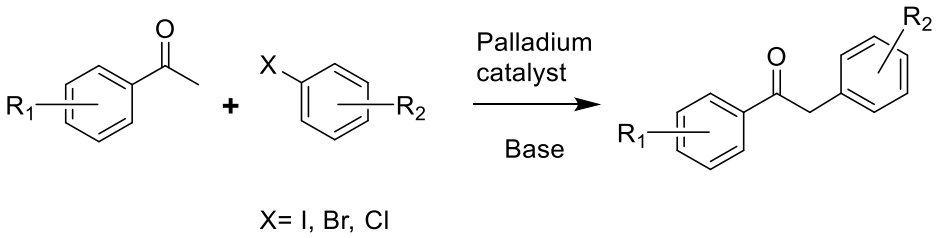


Scheme 1: General reaction scheme of alpha-arylation of an aryl ketone



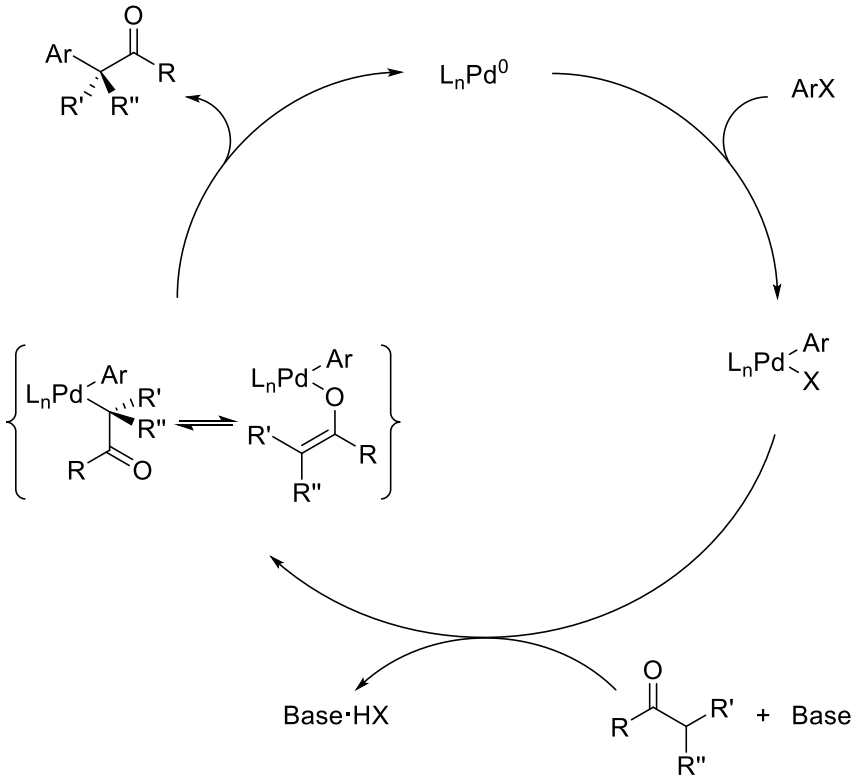
Scheme 2: Top, examples of compounds that have the deoxybenzoin motive, bottom, synthesis utilizing deoxybenzoins as starting materials.

1.2. Palladium catalyzed alpha-arylation



Scheme 3: General palladium catalyzed alpha-arylation

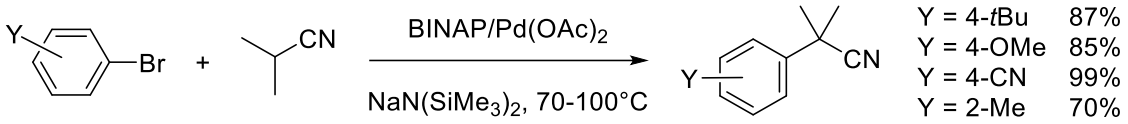
Alpha-arylation catalyzed by palladium has been pioneered by the groups of Buchwald,[11] Hartwig,[12] and Natsume.[13] These reactions need an aryl halide and an enolizable ketone to work. Ketones such as benzophenone are not able to undergo tautomerization and therefore cannot undergo alpha-arylation. However, other functional groups are also possible such as nitriles, but they will still need a hydrogen at the alpha position. The catalysts used in palladium catalyzed alpha-arylation are a combination of either $Pd(OAc)_2$ and $Pd(dba)_2$ with a phosphine ligand. A likely catalytic cycle is shown in Scheme 4 which starts with oxidative addition of the aryl halide to the palladium. This is followed by substitution of the halide by the enolate formed from the ketone in the presence of the base. The last step is a reductive elimination of the product. ·



Scheme 4: Reaction mechanism of palladium catalyzed alpha-arylation[12,14–17]

Alpha-arylation via palladium catalyst can be done efficiently, yields of over 80% are easily feasible. Hamann and Hartwig[18] reported highly active catalysts that are able to do the alpha-arylation quantitatively.

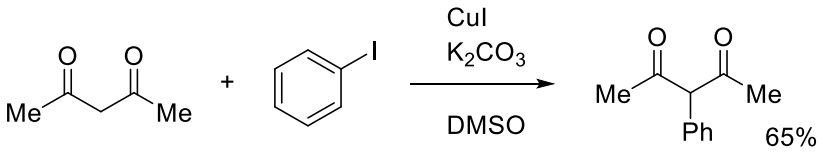
Besides the high yields of this reaction, the substrate scope is very wide. Alpha-arylation can be done with carbonyls and nitriles, which both can be aromatic or aliphatic. Furthermore, the aryl halide can have electron withdrawing substituents, such as cyano groups or electron donating substituents such as methoxy groups.[1,17] An example of alpha-arylation of a nitrile using different aryl halides is show in Scheme 5.



Scheme 5: Alpha-arylation of a nitrile using different aryl bromides[17]

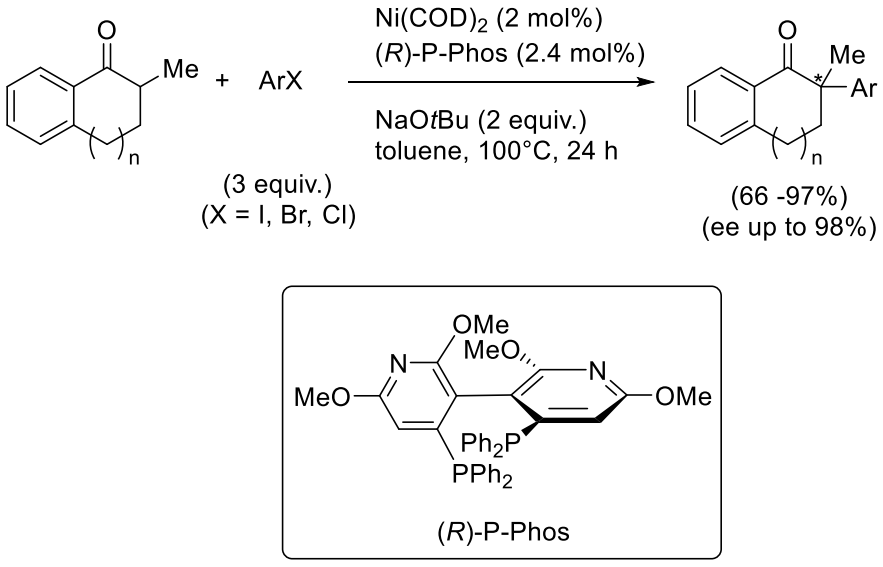
1.3. Copper and Nickel catalyzed alpha arylation

Using a less precious metal than palladium comes with the usual beneficial effects of lower costs, higher abundancy and lower toxicity. These advantages for copper also came with a price of a reduced substrate scope. Copper catalyzed alpha-arylation needed specific functional groups such as a diketone, dinitrile, diester or a combination of these groups to work.[19,20] However, Taillefer *et al.* reported alpha-arylation of non-activated or non-protected ketones (deoxybenzoins).[21]



Scheme 6: Alpha-arylation using a copper catalyst

Scheme 6 shows the copper catalyzed arylation of a diester that has been reported by Miura *et al.*[19] While the yield of these reactions is not as good as with palladium, they can still be considered good yields as they vary mostly between 50-80%.



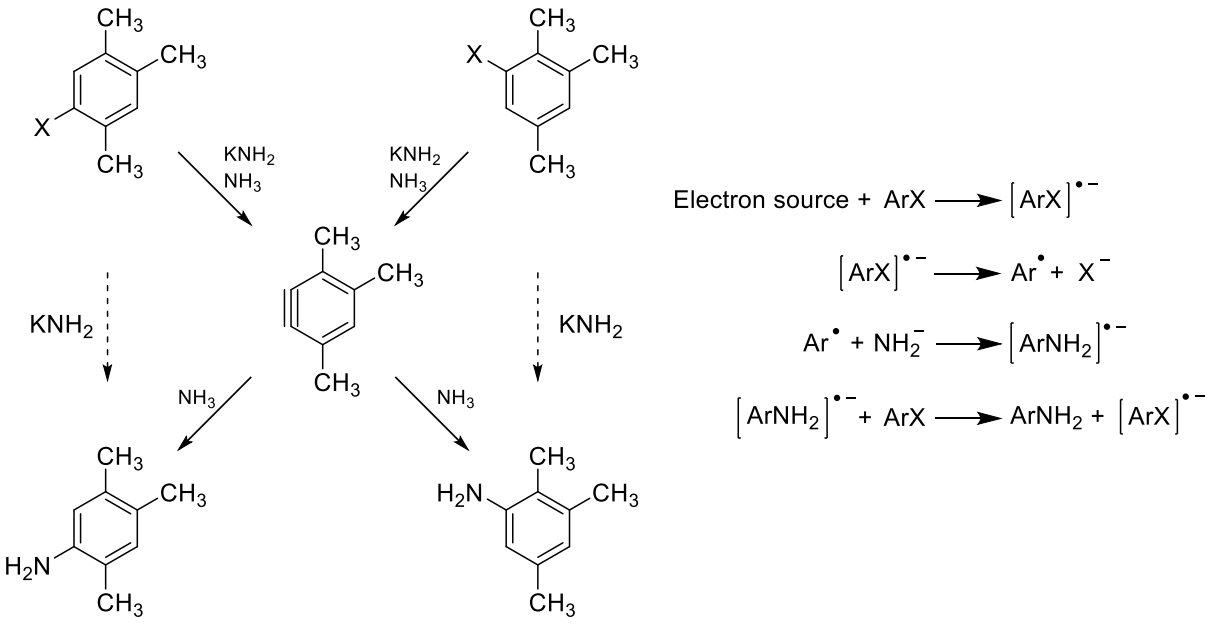
Scheme 7: Alpha-Arylation using Nickel with a chiral ligand

An example of nickel catalyzed alpha-arylation is shown in Scheme 7. Kwong and Chen[22] reported a nickel catalyzed arylation of cyclic ketones with aryl halides in excellent yields, up to 97%. The ligand used in this reaction was a dipyridyldiphosphine (P-Phos), this P-Phos displays axial chirality, meaning that there is hindered rotation around a single bond which locks the molecule in a particular conformation. Due to this chiral ligand the product was obtained in excellent yields and with an enantiomeric excess up to 98%.

However, while nickel catalyzed alpha-arylation are very interesting, the high toxicity of the Ni catalyst can pose a serious problem for using nickel catalyzed arylation reaction in industrial applications.[1]

1.4. $S_{RN}1$ Reactions

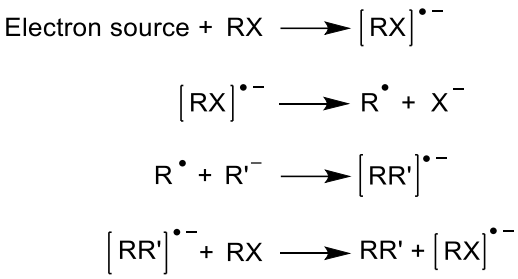
Another method to achieve alpha-arylation is via the $S_{RN}1$ mechanism, which stands for *substitution, radical-nucleophilic, unimolecular*. The $S_{RN}1$ reaction was discovered in 1970 by Kim and Bunnett[23] when they examined the reaction between 5- and 6-halopseudocumenes with potassium amide in liquid ammonia (Scheme 8). If the reaction would proceed through an aryne intermediate, both the 5- and 6-halopseudocumenes would have the same aryne intermediate. This would result in both isomers having the same product distribution, however, significant more product was formed with the amide group at the same position as were the halide was before the reaction.



Scheme 8: Left, reaction pathways of 5- and 6-halopseudocumenes, right, proposed reaction mechanism by Kim and Bunnett[23]

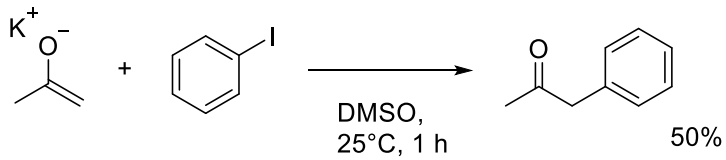
The reaction instead of going through an aryne intermediate, proceeds via aryl radicals, which are generated using the solvated electrons of sodium or potassium in liquid ammonium. These aryl radicals react with a nucleophile (NH_2^-) to form an arylamide radical anion. The radical can then be transferred to an aryl halide and the mechanism can be repeated. An important feature of the $S_{RN}1$ reaction is the affinity of the aryl radicals for certain strong nucleophiles,[24] such as the amide

ion.[23,25,26] However, quickly after the first report, many other nucleophiles were reported that also reacted in the $S_{RN}1$ reaction. Nucleophiles such as the cyanomethyl[25], carbanions[24] and in 1973 Rossi and Bunnett reported that even acetone enolate could be arylated with yields up to 95%.[27] In many of these cases photostimulation was used to start the initial electron transfer. The mechanism of the $S_{RN}1$ reaction shown in Scheme 8 can be generalized as shown in Scheme 9.



Scheme 9: General mechanism of the $S_{RN}1$ reaction

While there were enough examples of ketone enolates able to participate in the reaction,[28–30] arylation of an aromatic ketone was not reported until 1980 when Semmelhack and Bargar reported arylation of acetophenone via the $S_{RN}1$ process,[31] this was done with excellent yields up to 96%. While alpha-arylation of acetophenone was now possible, the reactions were still limited in use due to the need of several hours of photostimulation and the use of liquid ammonia as solvent. The problem with the solvents was quickly solved when it was discovered that DMSO also could be used as solvent.[29] That only left the photostimulation as a potential hindrance, however, Scamehorn *et al.* reported in 1984 thermally initiated $S_{RN}1$ reactions of ketone enolates with iodobenzene in DMSO.[32]

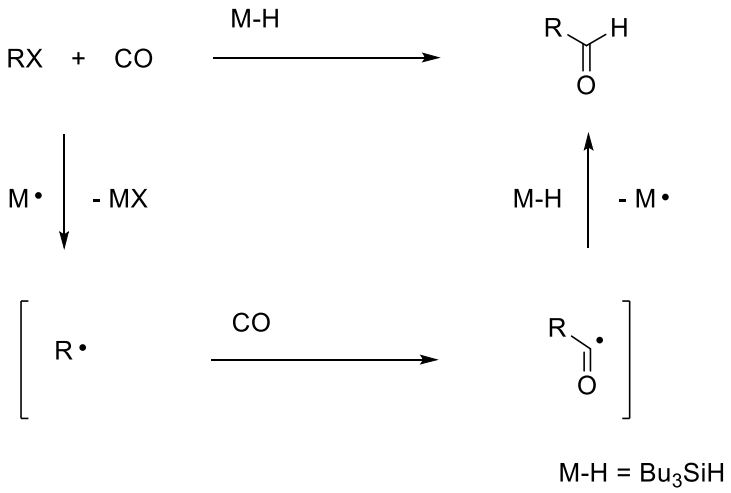


Scheme 10: Thermally initiated alpha-arylation reported by Scamehorn *et al.*[32]

The thermally initiated reactions suffered from a rather small substrate scope, aromatic ketones such as acetophenone where not arylated under these conditions. This stayed the same for a long time until in 2014 Peñéñory *et al.* reported alpha-arylation of ketones by microwave induced thermal $S_{RN}1$ reactions.[33] While previous reactions utilizing photostimulation usually had very high yields of more than 90%, the yields of these microwave induced reactions where typically around 50% yield. Another method of circumventing photostimulation is when the reaction is performed in presence of iron[34] or samarium.[35] However these methods suffer from the problem of a limited substrate scope (e. g. no acetophenone).

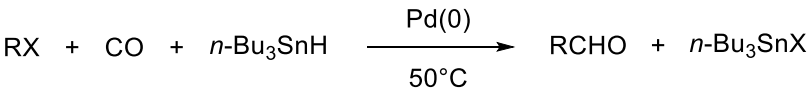
1.5. Carbonylation reactions

Carbonylation reactions are great methods for making aldehydes and ketones.[48] Free-radical carbonylation reactions can be catalyzed via a tin hydride. The initiation is done with a radical initiator like 2,2'-azobis(isobutyronitrile) (AIBN), which generates the tin radicals needed to do an abstraction of the halogen from compounds such as 1-iodohexane or iodobenzene. The radicals then add to carbon monoxide and these acyl radicals can abstract a hydrogen from the tin hydride creating the product and also a tin radical which can be used further in the reaction.[48] Scheme 11 shows this process, when a ketone is desired than an alkene is needed to react with the acyl radical.



Scheme 11: Reaction mechanism of the formylation using tributyltin hydride[48]

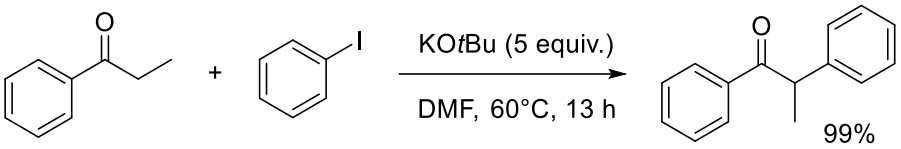
Besides a radical initiator like AIBN, transition metals can also be used, a good example is the Stille carbonylative cross-coupling.[49,50] Using similar reagents as the free-radical carbonylation reactions however needing no initiator to start this reaction due to this not being a radical reaction but a cross coupling reaction. Other transition metals that are used in carbonylation/formylation reactions include molybdenum[51] and iron.[52]



Scheme 12: Stille carbonylative cross-coupling[49]

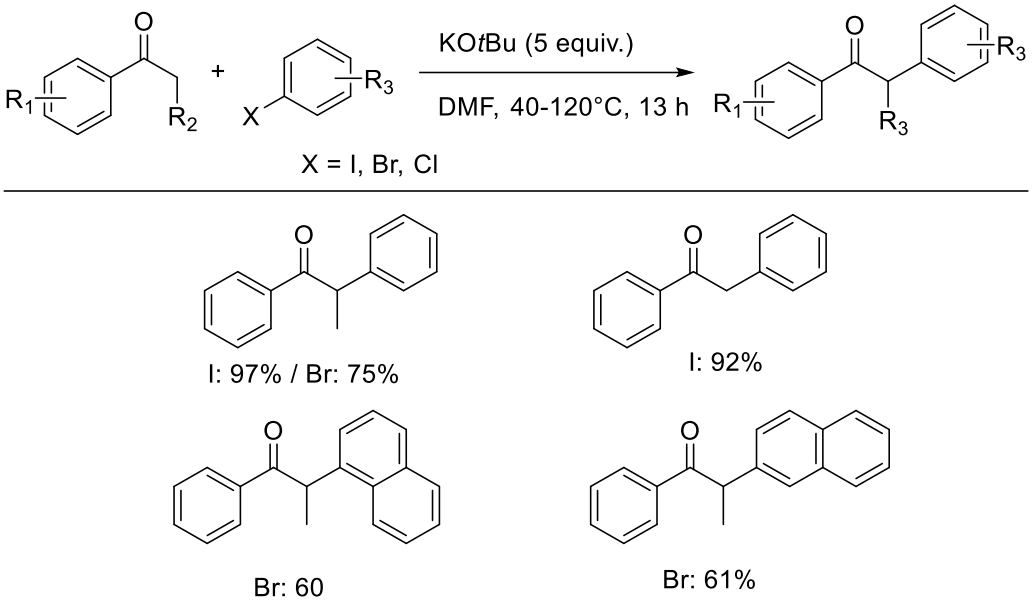
1.6. Alpha-arylation with DMF/KO*t*Bu

During this project, Taillefer *et al.* published an article on the subject of alpha-arylation[36] which is very similar to the work described in this thesis. In this article they describe how they found that KO*t*Bu in DMF is able to catalyze alpha-arylation. They tested the reaction between propiophenone and iodobenzene (1.2:1) and got moderate yields. Increasing the temperature from 40°C to 60°C gave a moderate increase in yield while changing the ratio between propiophenone and iodobenzene to 2.0:1.0 while at 60°C, drastically increased the yield to 99%. This quantitative conversion of iodobenzene is only possible when using KO*t*Bu in DMF, changing one of these conditions leads to little to no product being formed.



Scheme 13: Alpha-arylation of propiophenone reported by Taillefer *et al.*[36]

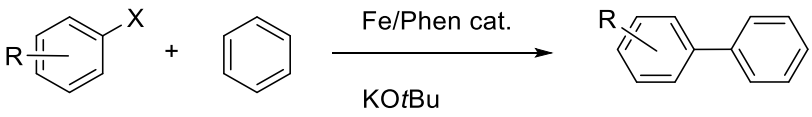
Taillefer *et al.* also investigated the scope of this reaction. Using the same conditions while replacing iodobenzene for iodotoluene still gave good yields (~70%), however needed more propiophenone (4 equivalents) to reach quantitative yields. Other substituents usually gave yields in the range of 50-70%, even when more equivalents of propiophenone was used.



Scheme 14: Small part of the substrate scope of the alpha-arylation reaction reported by Taillefer *et al.*[36]

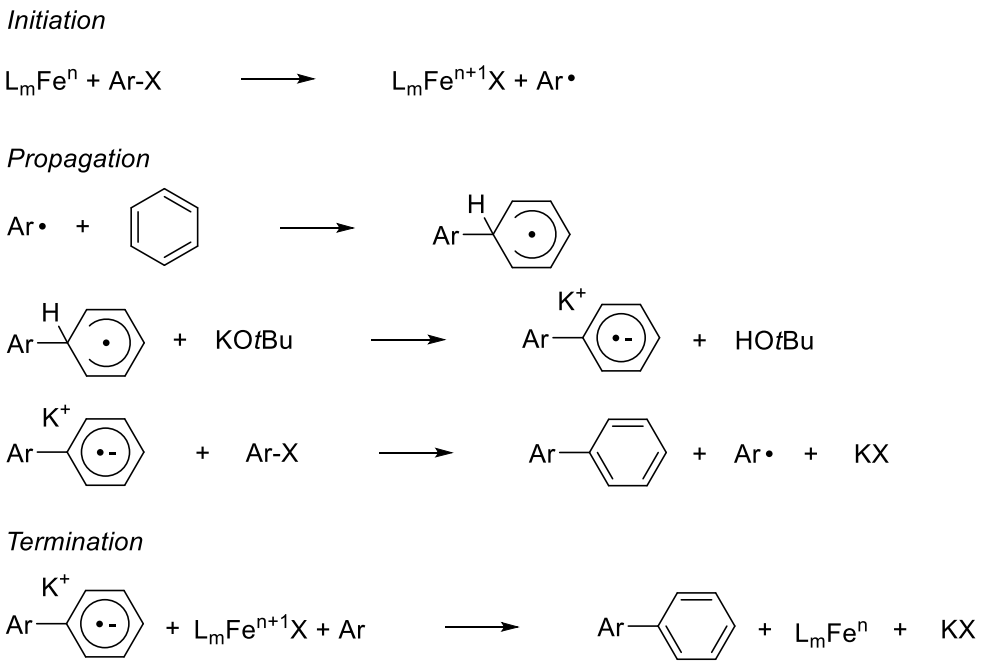
1.7. Iron-mediated alpha-arylation

From the well over a century old Ullmann coupling[37] to the modern day transition metal catalyzed direct arylations,[38] the formation of aryl-aryl bonds is an important reaction due to the high presence of the biaryl moieties in natural and synthetic products.[39] However, many of the successful applications of these reactions still rely on metals such as palladium and ruthenium, i.e. precious metals. Replacing these precious metals with base metals would give the same advantages as discussed section 1.2.



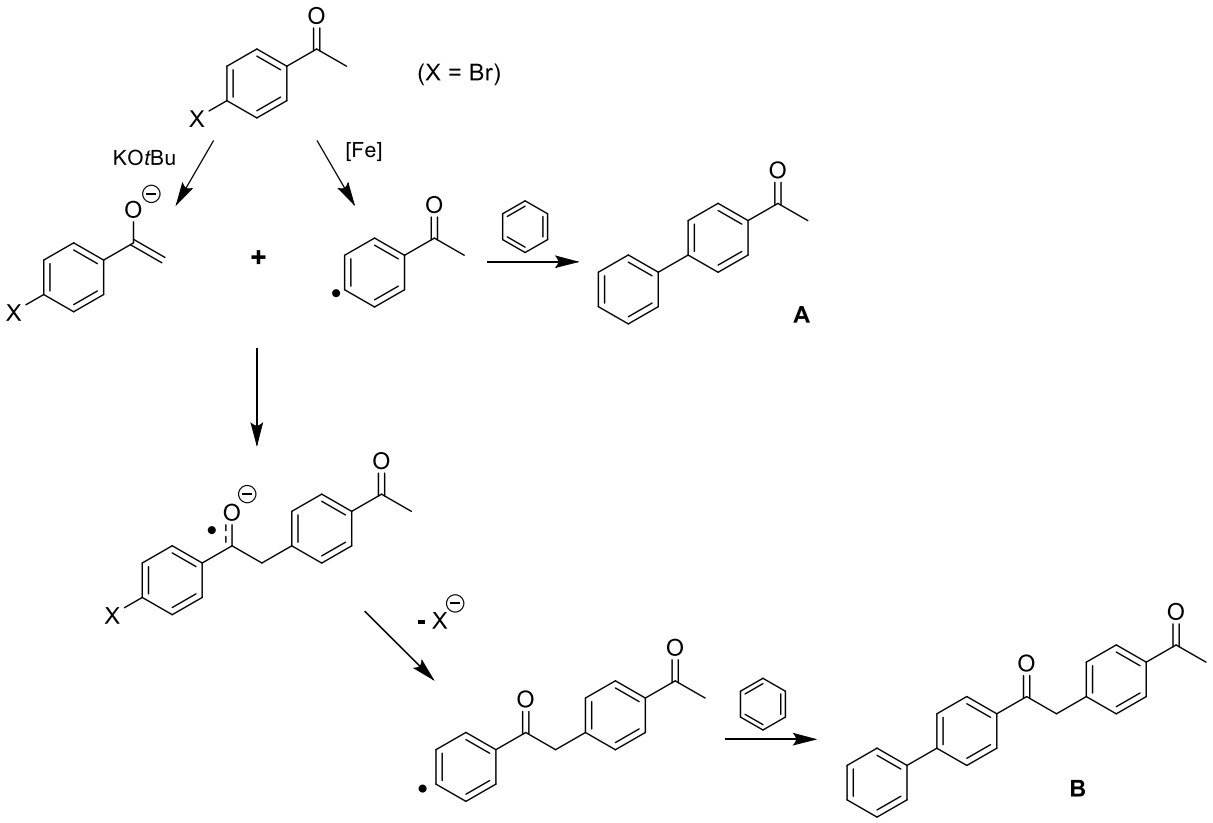
Scheme 15: General reaction scheme of the work reported by Klein Gebbink *et al.*[40]

Klein Gebbink *et al.* reported iron-mediated direct arylation of unactivated arenes in air[40] which was inspired by the work of Charette *et al.*[41] and Lei *et al.*[42] They were able to do direct arylation of various aryl halides with benzene under air in moderate to excellent yields. They used an iron/1,10-phenanthroline catalyst and KO*t*Bu as base and propose a radical chain mechanism shown in Scheme 16. The reaction is initiated by halogen abstraction, generating the aryl radical. This radical then attacks the arene, forming an intermediate cyclohexadienyl radical. The next step of the propagation is proton transfer to the KO*t*Bu and the last step is electron transfer to the aryl halide to produce the arylated arene and a radical anion which fragments into an aryl radical and halide anion.



Scheme 16: Proposed radical chain mechanism for iron-mediated direct arylation[40]

Going back to the subject of alpha-arylations, they were also able to isolate an interesting side product in the reaction between 4-bromoacetophenone and benzene. Not only was the expected product found (Scheme 17, product A), also an alpha-arylated product was found (Scheme 17, product B)

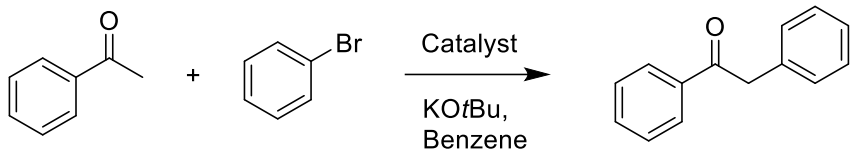


Scheme 17: Reaction pathways of 4-iodobenzene with benzene in presence of an iron/phen catalyst and base reported by Klein Gebbink *et al.*[40]

The reaction mechanism described by Klein Gebbink *et al.* bears some similarities when comparing it with the mechanism of the $S_{RN}1$ reaction (Scheme 9). Both start with generation of the aryl radical, followed by a reaction with the nucleophile, which is in the case of alpha-arylation the ketone enolate. While in $S_{RN}1$ reaction the resulting compound transfers its radical to another aryl halide, the coupled product of two 4-bromoacetophenones is able to relocated the radical to the place of the bromide by releasing the bromide anion, creating a new aryl radical. This new radical can than do direct arylation to form product B (Scheme 17). While the alpha-arylated product was obtained in only 11% yield, it does show promise as a gateway to new alpha-arylation reaction of aromatic ketones that do not rely on photostimulation or are microwave induced.

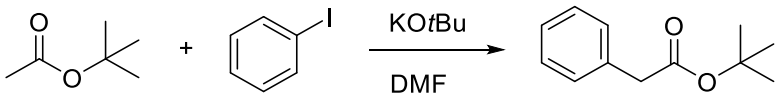
Chapter 2. Research aims

The aim of this project is to find a method to efficiently synthesize alpha-arylated aromatic ketones without the use of photostimulation or precious metals. Acetophenone and bromobenzene will be used as model substrates and work from Klein Gebbink *et al.*[40] will be used as a starting point from which different conditions, catalysts and reagents will be tested to optimize the alpha-arylation reaction.



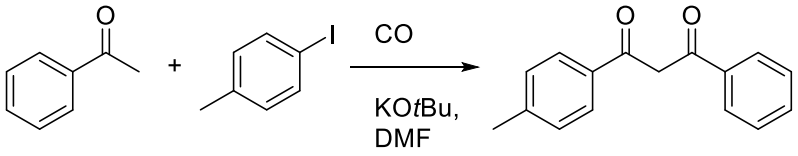
Scheme 18: The reaction scheme of the proposed alpha-arylation reaction

Furthermore, to extent the substrate scope, alpha-arylation of an ester will be attempted. *Tert*-butyl acetate and iodobenzene will be used as reagents and the conditions will be the same as the KO*t*Bu/DMF system of Taillefer *et al.*



Scheme 19: The reaction scheme of the alpha-arylation of an ester

As these reaction start by generating the aryl radical, it was hypothesized that these could add to carbon monoxide before reacting with the enolated, resulting in a diketone rather than a deoxybenzoin. This will be tested using acetophenone and 4-iodotoluene in the presence of CO in an autoclave.

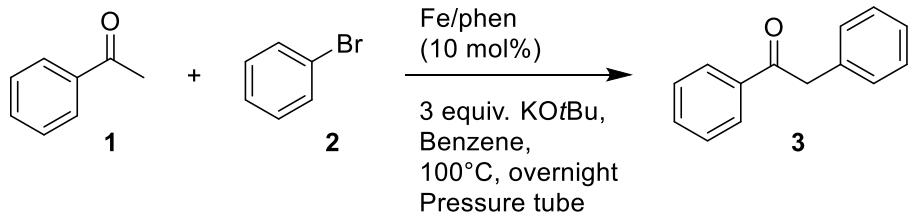


Scheme 20: The reaction of acetophenone and 4-iodobenzene in presence of CO

Chapter 3. Alpha-arylation of acetophenone

3.1. Optimization of the alpha-arylation reaction

In order to optimize the alpha-arylation reaction, acetophenone and bromobenzene were chosen as model substrates. The first reaction between acetophenone and bromobenzene was performed using conditions shown in Scheme 21 and was performed in a pressure tube to reach a temperature of 100°C.



Scheme 21: Alpha-arylation of acetophenone with bromobenzene in benzene using an iron/phen catalyst with base

The workup consisted of adding 1M HCl to quench and neutralize the reaction mixture and was wash three times with DCM. The collected organic layers were concentrated using a rotary evaporator. After the workup a ^{1}H-NMR spectrum (Figure 1) was taken of the resulting mixture. Two peak stand out, the large one at 2.6 ppm, which belongs to the methyl group of acetophenone (^{1}H-NMR of acetophenone is shown in appendix A1) and the very small peak at 4.3 ppm, which is from the –CH_2- of compound **3** (^{1}H-NMR and ^{13}C-NMR spectrum of pure compound **3** is shown in appendix A2 and A3 respectively).

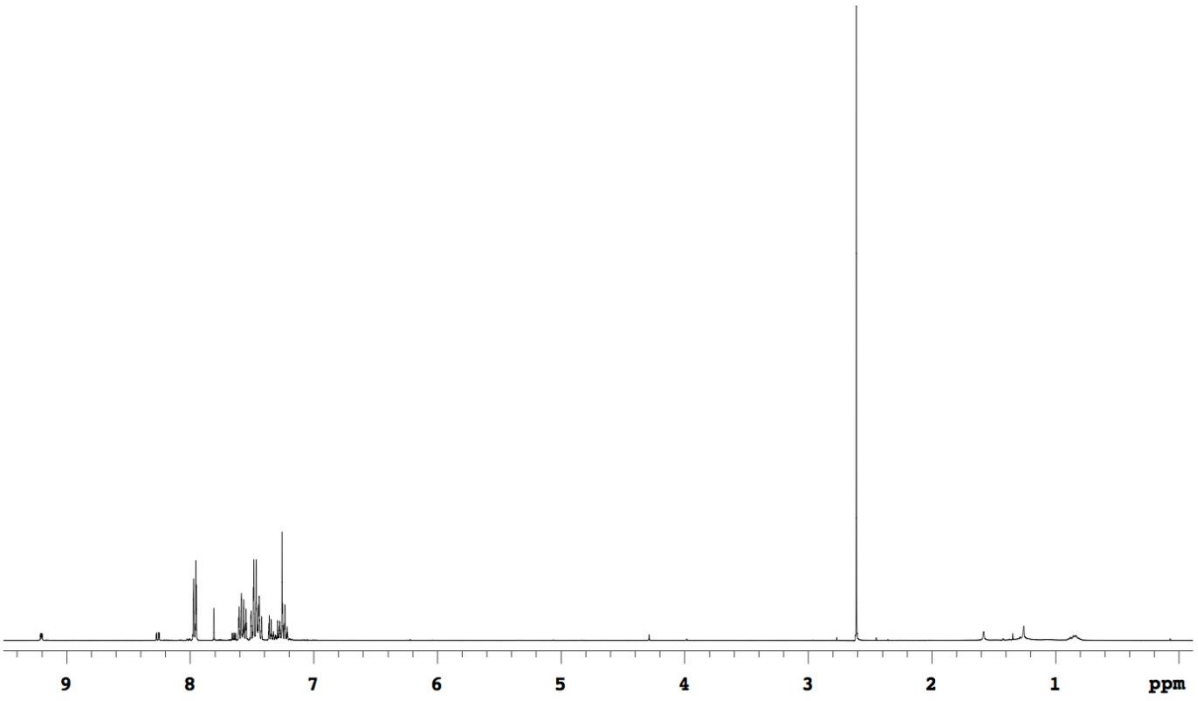


Figure 1: ^{1}H-NMR spectrum of the alpha-arylation shown in Scheme 21

Acetophenone and bromobenzene were chosen because they should do alpha-arylation and not arylation of an arene. However, benzene was used as solvent which means that arylation of benzene still could happen. Detecting the formed biphenyl via ^{1}H-NMR can be challenging due to the already crowded aromatic region. GC-MS gave the solution, as the biphenyl was detected using GC-MS. This arylation of benzene is most likely the cause of the very small product peak due to the significant higher amount of benzene (50 mmol, 4.5 mL) versus the amount of acetophenone (0.5 mmol, 58.5 µL) and also explains the high amount of acetophenone in the NMR spectrum, as there was almost no bromobenzene to react with. The reaction was repeated but this time with much less benzene, 1 mL instead of 4.5 mL. This decrease in amount of solvent increased the peak at 4.3 ppm of compound **3** as seen in Figure 2. The yield of this reaction equates to 12% and was determined via GC with pentadecane as internal standard.

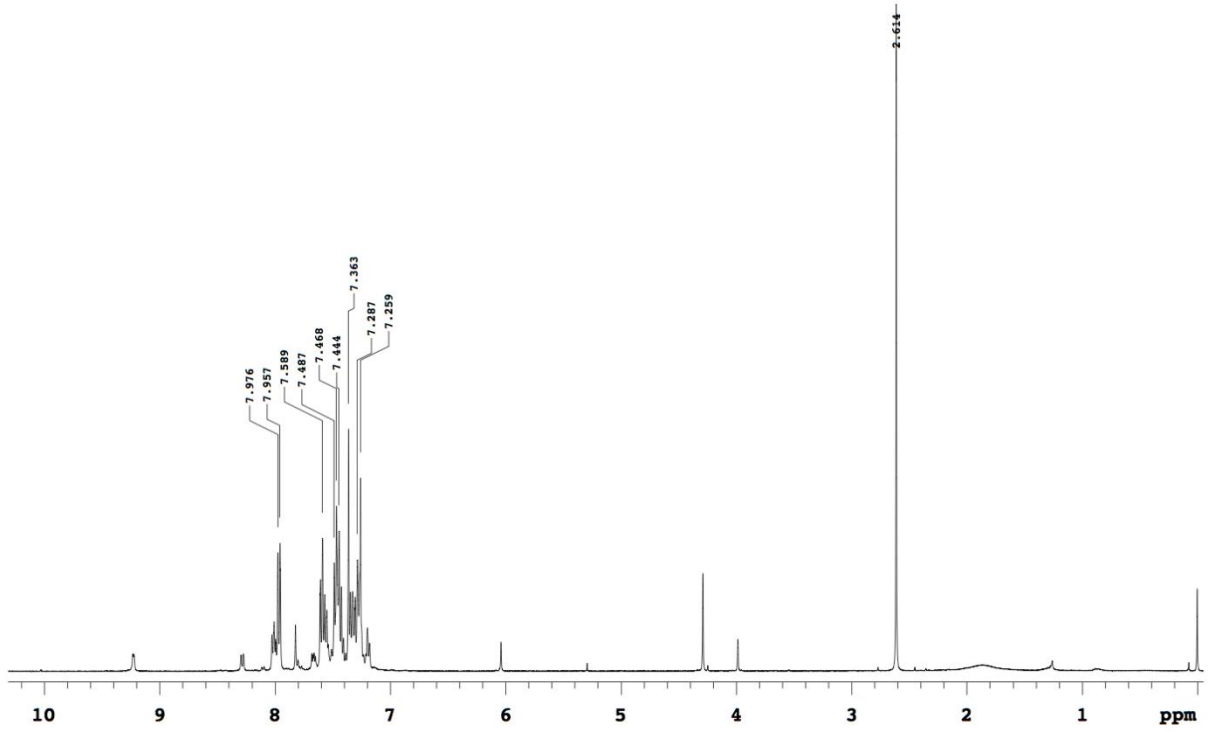


Figure 2: ^{1}H-NMR spectrum of the alpha-arylation shown in Scheme 21 with only 1 mL benzene

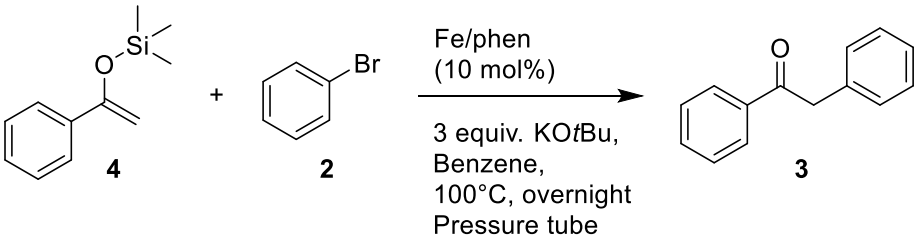
The other compounds in the mixture were also analyzed with GC and GC-MS. The amount of biphenyl formed in the reactions was monitored via GC but was lower than expected, only ±10 % of the amount of bromobenzene was converted to biphenyl. Furthermore there was also about 5% of product which has been arylated twice (1,2,2-triphenylethanone). However, when combining all products and accounting for the amount of bromobenzene is consumed in producing these compounds, the mass balances does not even comes close to 100%

Using a different solvent where the formation of biphenyl is not possible would be beneficial as the bromobenzene used there could be used to form the product. Therefore, other solvents were tested in the reaction of Scheme 21, and the results are shown in Table 1.

Entry	Solvent	Yield
1	Benzene	12%
2	Hexane	0%
3	Heptane	0%
4	Carbon Tetrachloride	0%
5	Acetophenone	0%
6	Hexafluorobenzene	0%
7	Mesitylene	0%
8	*Tert*-butanol	0%
9	THF	1%
10	Dioxane	6%

Table 1: Yields of the various solvents used in the reaction depicted in Scheme 21, analyzed via GC

Table 1 shows that benzene is still the best solvent thus far, mainly due to that almost no other solvent showed any activity, as only in THF and dioxane compound 3 is even observed. To limit the formation of biphenyl and increase the overall low yield, an increase in reaction speed of forming compound 3 could be beneficial. This could be done by, instead of generating the enolate of acetophenone *in situ* with KO*t*Bu, by adding acetophenone as a silyl enol ether (compound **4**) to increase the reaction rate of forming compound **3**, and therefore limiting side reactions.



Scheme 22: Alpha-arylation of the silyl enol ether of acetophenone

Entry	Yield	Notes
1	27%	-
2	13%	New batch of catalyst
3	13%	Same conditions as entry 1
4	14%	2x amount of bromobenzene
5	4%	Half the amount of KO*t*Bu
6	12%	1,10-Phenanthroline used as catalyst

Table 2: Yields of the reaction shown in Scheme 22 with varied conditions, analyzed via GC

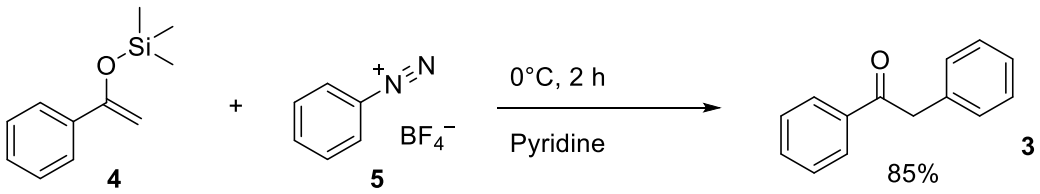
With a yield of 27% (via GC, 21% isolated yield) of compound **3**, this result would support the above mentioned theory. However, another reaction with a new batch of catalyst only yielded 13% and a repeat of the original experiment yielded 13% (same "old" catalyst was used), showed that the first experiment may have some error in it which is responsible for the high yield.

In all reactions a lot of acetophenone is left after the reaction, usually ranging from 20-30% but increasing the amount of bromobenzene only had a very small effect on the yield of compound **3** (Table 2, entry 4, calculated the yield with the amount of acetophenone), while halving the amount of KO*t*Bu severely hampers the reaction (Table 2, entry 5). Interestingly, 1,10-phenanthroline is able to catalyze the reaction even without the presence of iron (Table 2, entry 6). That 1,10-phenanthroline alone can catalyze the reaction should however not be too surprising as phen is able to catalyze arylation of arenes,[43] and the conditions used here stem from direct arylation of arenes. What is surprising that phen catalyzes the reaction almost as good as the iron/phen catalyst.

Entry	Solvent	Yield
1	Dioxane	10%
2	Propanol	0%
3	DMSO	13%
4	Pyridine	29%

Table 3: Yields of the reaction shown in Scheme 22 with different solvents, analyzed via GC

Using dioxane in the reaction shown in Scheme 22 gives 10% yield (Table 3, entry 1), when using acetophenone instead of its silyl enol ether the yield was 6% (Table 1, entry 10). $S_{RN}1$ reactions mainly use liquid ammonia and DMSO as solvents,[31,32] the former was not tested due to practical reasons, while the latter gave a yield of 13% which is the same as when using benzene (Table 3, entry 3).



Scheme 23: Alpha-arylation of the silyl enol ether of acetophenone using benzenediazonium tetrafluoroborate in pyridine

Tanaka *et al.*[44] showed that the reaction between the silyl enol ether of acetophenone and benzenediazonium tetrafluoroborate proceeds with a yield of 85%, but only when using pyridine. They have strong indications that this happens via a radical mechanism. Due to similarities of having a phenyl radical with the silyl enol ether, pyridine was also used as a solvent in the reaction. As seen in Table 3, entry 4, pyridine gave the relatively high yield of 29%. The product was purified using column chromatography (100% DCM), leading to an isolated yield of 21%. The ^{1}H-NMR spectrum is shown in Figure 3 and the ^{13}C-NMR in appendix A4.

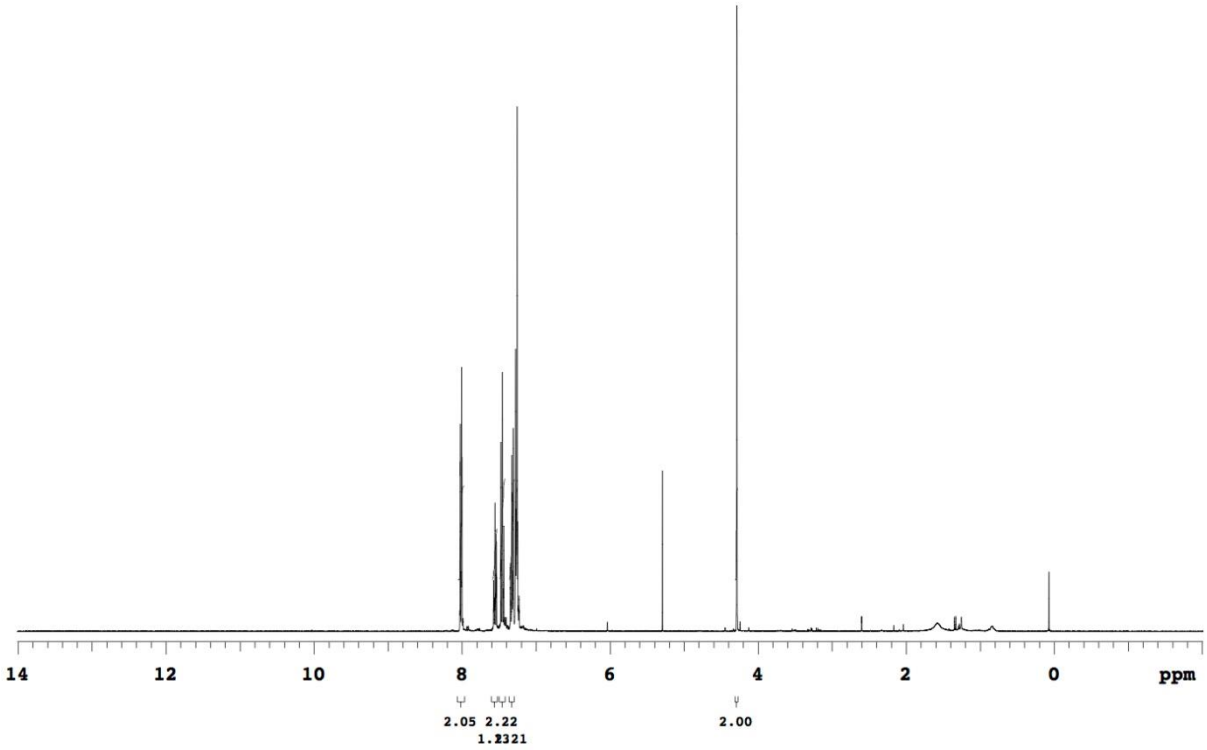
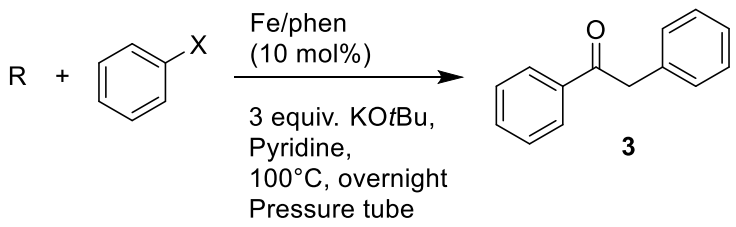


Figure 3: Compound 13, synthesized via alpha-arylation in pyridine

Looking back at the use of the silyl enol ether of acetophenone reveals that is does has an effect, however the magnitude of this effect is not very impactful. Especially when using benzene as solvent as it only increased the yield by 1-2%, in dioxane the effect is a more noticeable as there the increase is from 6% to 10%.

3.2. Alpha-arylation in pyridine

Pyridine as solvent generates a significant better yield then when using benzene in the alpha-arylation reaction (Table 3). First some conditions that were tested with benzene were also tested with pyridine. Using less benzene increased the yield of the reaction, to see whether pyridine showed the same behavior, the reaction was performed in 3 mL pyridine. As expected, using more pyridine decreased the yield from 29% to 23%. When using 1,10-phenathroline as catalyst in benzene, the yield stayed relatively the same (Table 2, entry 3 versus 6). However, in pyridine the difference is more noticeable, decreasing from 29% to 24%.



Scheme 24: Alpha-arylation of either acetophenone or its silyl enol ether

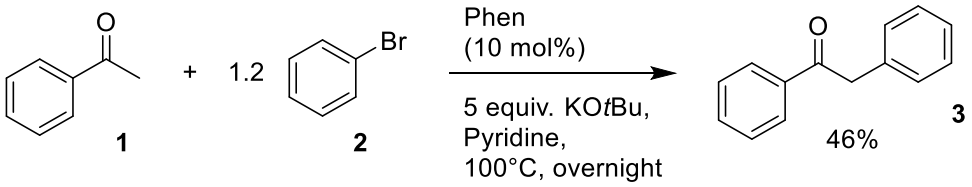
Entry	R	Aryl halide	Yield	Notes
1	Silyl enol ether	Bromobenzene	29%	-
2	Silyl enol ether	Bromobenzene	23%	3 mL of pyridine
3	Silyl enol ether	Bromobenzene	24%	1,10-phenathroline as catalyst
4	Acetophenone	Bromobenzene	21%	2 mL of pyridine
5	Acetophenone	Iodobenzene	22%	2 mL of pyridine

Table 4: Yields of the reaction shown in Scheme 24 with varied conditions, analyzed via GC

When switching from the silyl enol ether of acetophenone to just regular acetophenone the yield decreases a bit. A reaction of acetophenone and bromobenzene in pyridine only yielded 21% of compound **3**. This reaction was performed in 2 mL pyridine which makes it not possible to fully compare it with the reaction of Table 3, entry 4 but the reaction with 3 mL pyridine showed 23% yield, which is still higher even though increasing the amount of solvent should decrease the yield, meaning that using the silyl enol ether could increase the yield. This would be true if not considering an additional effect that comes from using the silyl enol ether, as in both reactions using acetophenone or the silyl enol ether of acetophenone, the same amount of KO*t*Bu is used. Studies show that KO*t*Bu is involved in the generation of the radical[45] or even responsible for it.[46] When using acetophenone, the KO*t*Bu is also needed to generate the enolate, meaning that a part of the 3 equivalents is used, which could explain the drop in the yield. This is supported by the reaction in Table 2, entry 5 where only half of the normal amount of KO*t*Bu was used and leading to a significant reduced yield.

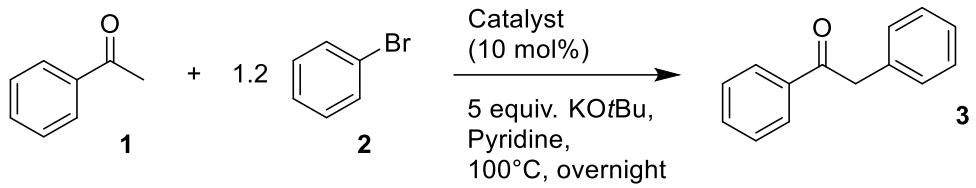
These reactions are usually performed at 100°C, the use of a pressure tube was necessary when using benzene as solvent due to its boiling point being 80°C. The boiling point of pyridine is a bit higher, namely 115°C, meaning that there is no need of using a higher pressure to reach 100°C. The reaction of acetophenone and bromobenzene in a reflux setup failed to yield any product. While this reaction has some of the limitations named above, such as 3 equivalents of KO*t*Bu in combination with acetophenone and more solvent than usual (3 mL), the reaction still should had yielded some product as none of these things should completely shut down the reaction. However, this was only 1 reaction and could very well be just a failed attempt. Another problem that could impact the reaction is air, while the reactions in the pressure tube are also exposed to air, after sealing the pressure tube the amount of air is limited, while in a reflux setup this is not the case.

All things mention above were taken in to account to create the optimized reaction. 1.2 equivalents of bromobenzene were used because in all reactions a bit of acetophenone was left after the reaction and no bromobenzene. 5 equivalents of KO*t*Bu were used to counteract the loss of KO*t*Bu due to the formation of the enolate of acetophenone. Schlenk conditions and dried, degassed pyridine was used to limit any side reaction due to air or water. 10 Mol% 1,10-phenanthroline was used as catalyst instead of the usual Fe/phen catalyst.



Scheme 25: Reaction done with the optimized conditions

Using the conditions described above, a yield of 46% of compound **3** was obtained. While this is a very high yield compared to the other obtained yields, still improvements could be made. Besides the already tested 1,10-phenanthroline, some metal salts were also tested, as well as using no catalyst/additive. Stoichiometric amounts of $FeCl_2$ and $FeCl_3$ were used, however $FeCl_3$ reacted violently when added to a mixture of KO*t*Bu and pyridine. This reaction is likely due to formation of iron complexes with KO*t*Bu and/or pyridine and due to this, the reaction with $FeCl_3$ was not conducted. $FeCl_2$ showed promise as it yielded 35% of compound **3** and when decreasing the amount of $FeCl_2$ used to a catalytic amount (10 mol%), the yield increased to 49%. This yield is even higher then when using 1,10-phenanthroline as catalyst. Interestingly, when using no additive, just KO*t*Bu and pyridine, the yield is still 20%.

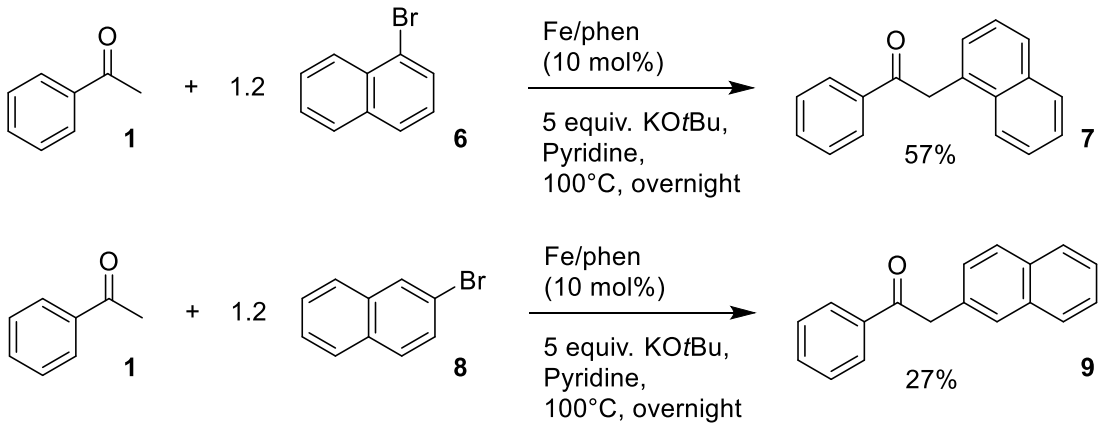


Scheme 26: General reaction used in Table 5

Entry	Catalyst	Yield
1	1,10-Phenanthroline	46%
2	$FeCl_2$	49%
3	-	20%

Table 5: Yields of different catalyst used in the reaction depicted in Scheme 26

Different aryl halides than bromobenzene were also tested. At the moment only 1-bromonaphthalene and 2-bromonaphthalene were used, however, both gave different results, 1-bromonaphthalene gave a slight increased yield of 57% (Table 5, entry 4, ^{1}H-NMR shown in appendix A5). 2-Bromonaphthalene gave the opposite effect, not increasing the yield but significantly reducing the yield to 24% (Table 5, entry 5, ^{1}H-NMR shown in appendix A6).



Scheme 27: Reactions using 1-bromonaphthalene and 2-bromonaphthalene as aryl halide

3.3. Comparison

The results in section 3.2 can be compared with the article of Taillefer *et al.* which was published during this project (section 1.6).

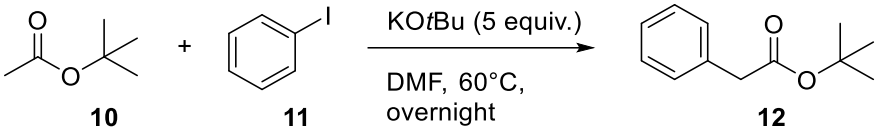
When Taillefer *et al.* did the reaction with acetophenone to synthesize compound **3**, they got a yield 92%, however, they used only iodobenzene in this reaction. In reactions with propiophenone they showed that when going from iodobenzene to bromobenzene, their yield decreased from 97% to 75%. In our work there have also been tests with iodobenzene, these showed minimal difference in yields. However, this was not done on the optimized reaction, which could have influenced the result as the problem could have been with other conditions rather than if bromobenzene or iodobenzene was used. In conclusion, synthesis of compound **3** using bromobenzene via our conditions gave a yield of 49% and using the conditions of Taillefer *et al.* would result in likely a little less than 75% yield because going from propiophenone to acetophenone decreases the yield a bit (when using iodobenzene).

The results of the reactions with the 1-bromonaphthalene and 2-bromonaphthalene can also be compared with the results reported by Taillefer *et al.* (section 1.6). However, unlike the previous comparison, these result come closer to each other. Using 1-bromonaphthalene they got a yield of 60%, this is very close to the 57% obtained in our work, but in our work acetophenone is used instead of propiophenone. Although looking at the results obtained by Taillefer *et al.* it looks that alpha-arylation of propiophenone proceeds better than that of acetophenone. However going from 1-bromonaphthalene to 2-bromonaphthalene they got a yield of 61%, which is almost identical with their result with 1-bromonaphthalene. In our work when performing the reaction with 2-bromonaphthalene the yield drops to 24%. This could be just be a failed experiment, but in the work of Peñéñory *et al.*[33] where they do alpha-arylation in DMSO using microwave irradiation, they also got a significant difference between 1- and 2-bromonaphthalene. They also had their highest yield when using 1-bromonaphthalene, 55% and when using 2-bromonaphthalene the yield is only 35%.

Chapter 4. Additional reactions using the DMF/KO*t*Bu system

4.1. Attempted alpha-arylation of an ester

In an attempt to extend the scope of the alpha-arylation reaction beyond trying compounds with different substituents, an ester was tried in the reaction. Semmelhack *et al.* showed that alpha-arylation of an ester is possible, although they used photostimulation.[31]



Scheme 28: Attempted alpha-arylation of *tert*-butyl acetate

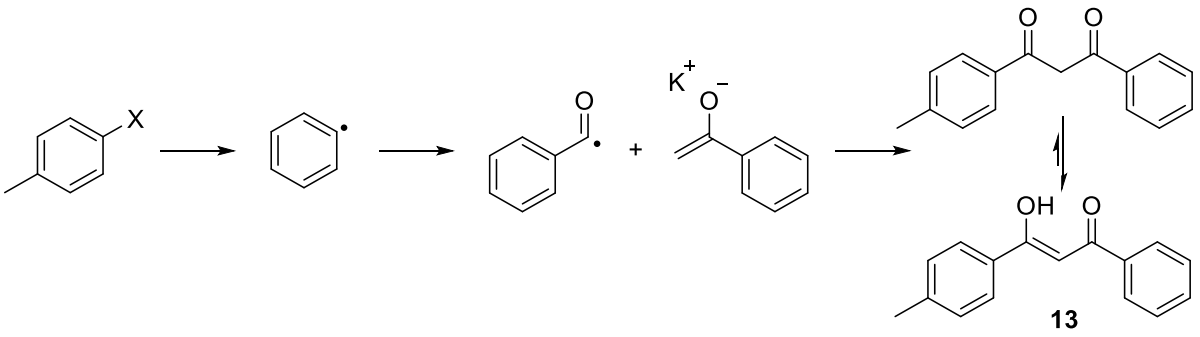
In Scheme 28 the intended reaction is shown, unfortunately no product was observed. This comes as no surprise as Semmelhack *et al.* did not used KO*t*Bu as base for the reactions with an ester. Those reactions needed a lithium amide base, which was generated out of n-butyllitium and ammonia. For the alpha-arylation in Scheme 28 to work a stronger base is needed. However, KO*t*Bu is needed for the reaction to proceed and other bases usually show little to no reactivity in these reactions.

Compound	pKa (water)	pKa (DMSO)
Acetophenone	-	24.7
KOtBu	17.0	29.4
Tert-butyl acetate (**11**)	24.5	30.3
NH_3	38	41

Table 6: pKa values of relevant compounds[47]

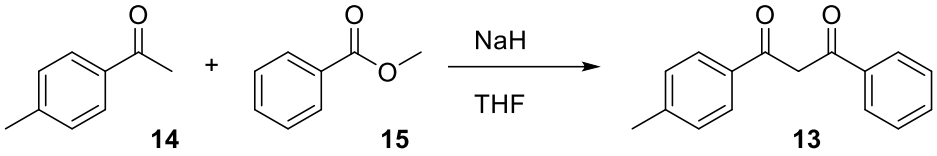
4.2. CO trapping and intermolecular bond formation

The alpha-arylation reaction starts with generating the aryl radical,[36] this radical than reacts with the enolate to form the product after release of the radical. However, when carbon monoxide is present the phenyl radicals could also add to this to form a benzoyl radical (Scheme 29). After this the radical could react with the enolate to produce the product, this time not being a deoxybenzoin (such as compound **3**) but a diketone. The diketone exits mainly as its enol tautomer due to it being more stable than the ketone tautomer because of the formation of intramolecular hydrogen bonding.[53,54]



Scheme 29: Proposed mechanism of the formation of compound

To aid in identification, compound **13** was synthesized via a different method. The synthesis was done via a Claisen condensation of 4-methylacetophenone and methyl benzoate using NaH in THF. The ^{1}H-NMR spectrum of the purified product is shown in Figure 4. The features described in literature, the peak at 6.8 and 16.9 ppm of the enol form are present, as well as the rest of the peaks. When comparing Figure 4 with Figure 5, all the peaks from compound **13** are present in Figure 5. This is the same story with the GC-MS, leading to the conclusion that compound **13** was indeed synthesized in the reaction between 4-iodobenzene and acetophenone in the presence of CO.



Scheme 30: Claisen condensation to synthesize compound 13

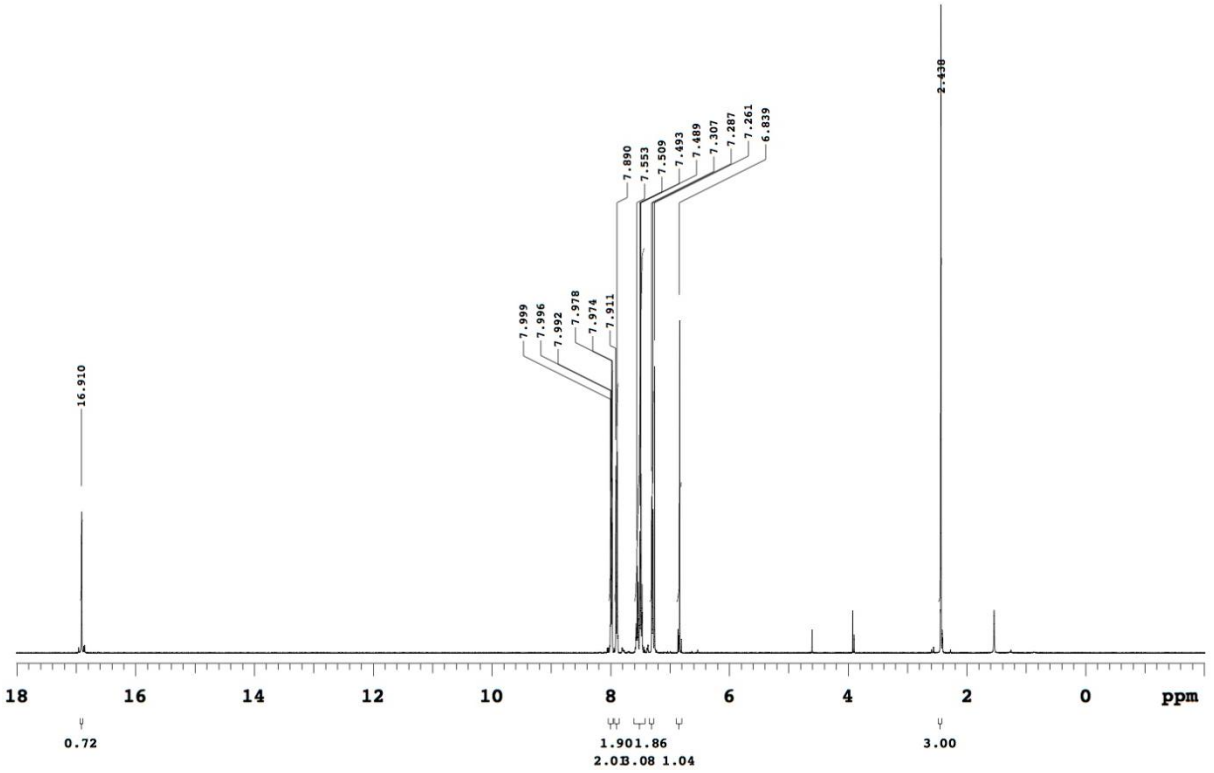
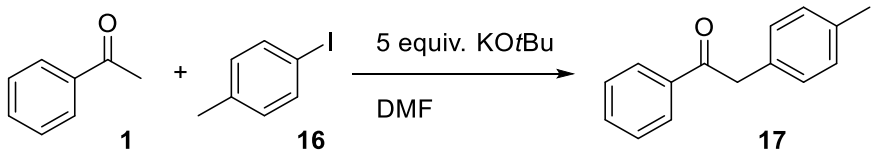


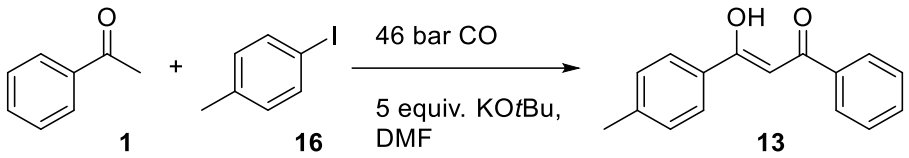
Figure 4: ^{1}H-NMR spectrum of compound 13, synthesized via a Claisen condensation

The other possible product, compound **17** (reaction without CO) was also synthesized in order to aid identification. The synthesis was done via an alpha-arylation of acetophenone with 4-iodotoluene. The reaction scheme is shown in Scheme 31 and the ^{1}H-NMR spectrum of the purified product in the appendix A7.



Scheme 31: Synthesis of compound 15 using the method reported by Taillefer *et al.*[36]

4-Iodotoluene was chosen as aryl halide to be able to exclude any possibility that the product could be form due to a combination of two acetophenone molecules. Radical carbonylation are usually performed at high pressures to efficiently trap the phenyl radical because otherwise decarbonylation (back reaction) would be a serious problem.[55] For this reason, the pressure/Schlenk tubes used in other reactions were exchanged for an autoclave, which is able to handle the high amount of pressure needed.



Scheme 32: Synthesis of compound 13 using CO in an autoclave

The autoclave was loaded with anhydrous DMF, KO*t*Bu, 4-iodotoluene and acetophenone. After flushing with carbon monoxide for 15 minutes, the pressure was raised to 46 bar and heated to 100°C for 4 hours. The reaction was left to cool and stir overnight, followed by the addition of 1M HCl to quench and neutralize the reaction mixture. After 10 minutes of stirring, diethyl ether was added and was washed with water (3 times) and brine (1 time). The organic layer was dried over anhydrous $MgSO_4$ and the solvents was evaporated using a rotary evaporator. The resulting residue was analyzed with NMR and GC-MS, the NMR spectrum is shown in Figure 5.

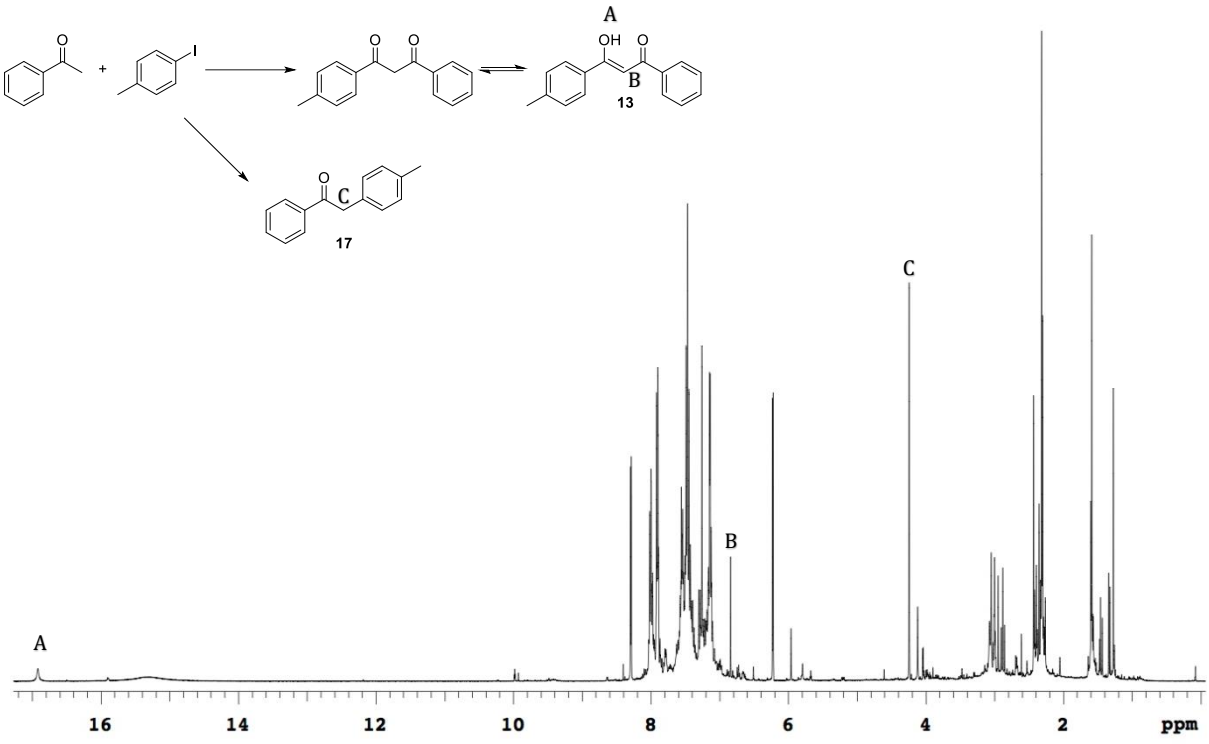


Figure 5: ^{1}H-NMR spectrum of the reaction mixture alpha-arylation in presence of CO

Of the many peaks present in Figure 5, there are some important peaks visible. The peak at 4.25 ppm corresponds with the $-CH_2-$ of compound **17**. Features of compound **13** are also visible, namely the peak at 16.9 and 6.8 ppm. The rest of the peaks of compound **13** and **17** are present, however they are not as prominent as the previously mentioned peaks because they either coincide with other peaks (e.g. the aromatic peaks) or are close to other peaks (e.g. the methyl peaks at 2.4 ppm). The GC-MS spectrum also confirms the NMR results as there is a peak which MS spectrum belongs to compound **13**. With triphenylmethane as internal standard the yield of compound **13** was determined to be 6%.

In an attempted to improve the yield a higher CO pressure was chosen to increase the formation of the benzoyl radical. Also the temperature was lowered from 100°C to 50°C since the reaction that happens without CO (Scheme 31) is more efficient at higher temperatures.[36] However, no product was observed in ^{1}H-NMR, giving the impression that lowering the temperature to 50°C completely shuts down the reaction pathway towards compound **13**. Another experiment at the same temperature of the successful reaction (100°C) was executed, but with this time with an increased pressure (66 bar). The ^{1}H-NMR spectrum of the reaction mixture (Figure 6) showed that again no product had been formed just as with the reaction at 50°C. Further analysis of Figure 6 however shows that also the peak at 4.3 ppm of compound **17** is also missing, meaning that that reaction also did not happened. This missing peak of compound **17** is also missing when looking at the spectrum of the reaction at 50°C (appendix A8). More proof of the reaction not happening comes from the GC-MS, there is a massive peak present which belongs to 4-iodobenzene.

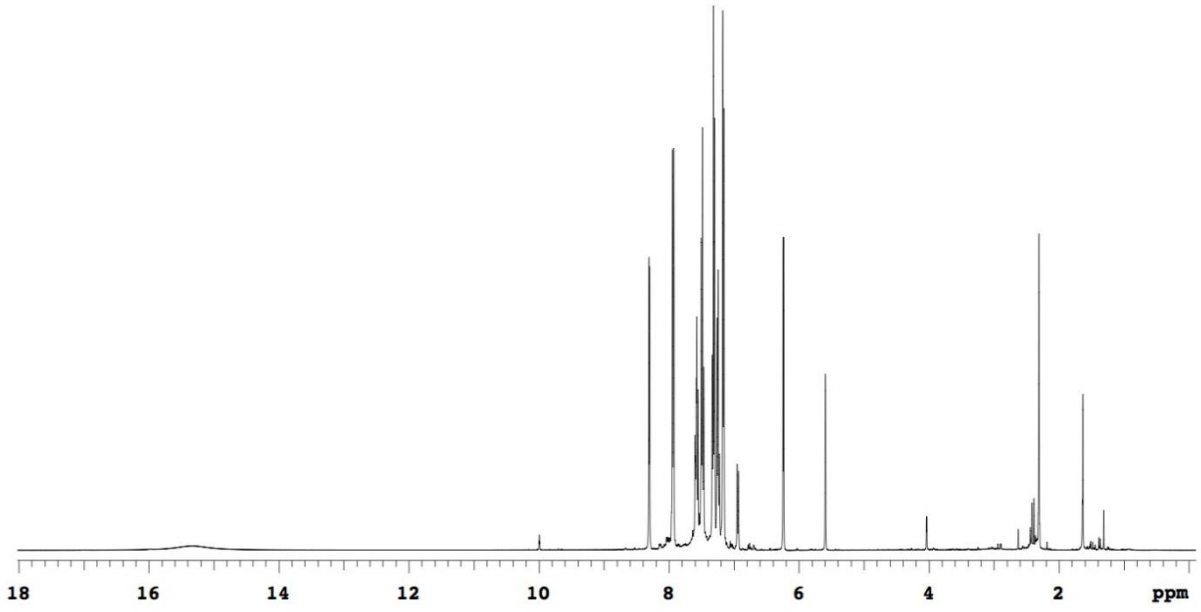


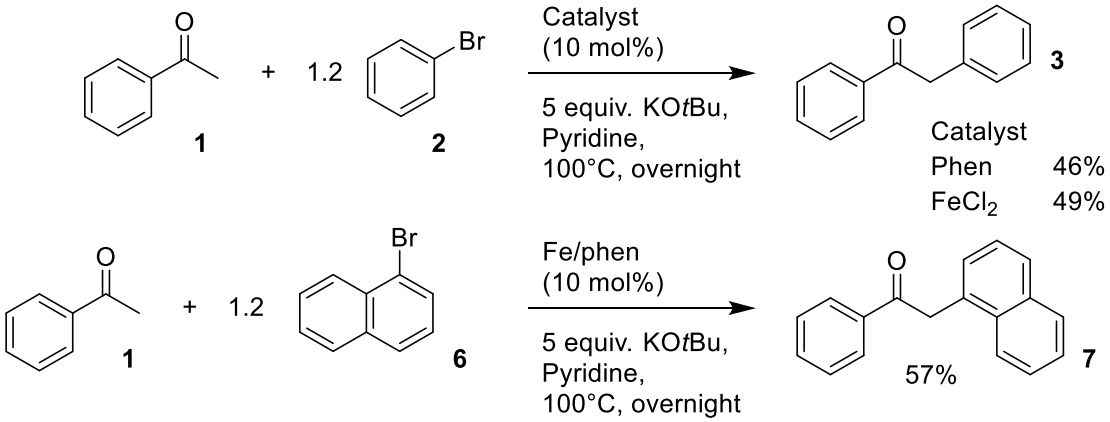
Figure 6: ^{1}H-NMR spectrum of the second attempted of the synthesis of compound 13 at 100°C

That the reaction without CO did not happen is strange because this reaction should even be able to happen under air or in undistilled DMF,[36] meaning that it should still happen even if there was somehow air or water present that could hinder the formation of compound **13**. The most likely explanation is that something has changed during the time between the first (successful) reaction and the subsequent (failed) reactions. There are indeed a few things that have happened, the first one being that a new bottle of anhydrous DMF was used for both the failed reactions because the last one was empty. It could be that some impurity could stop both reactions, however, this seems

quite unlikely. Another possibility is that between the first and second reaction the autoclave was used in a reaction that involved Raney nickel, which could influence the reaction. The change in pressure should not be left out when talking about differences but the increase in CO concentration (i.e. the pressure) should not stop both reaction. At most it should stop the formation of compound **17** if the phenyl radicals are all converted to the benzoyl radical. Unfortunately, due to time constraints, no further investigation into the problems was possible.

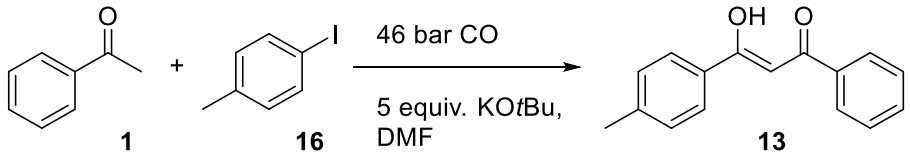
Chapter 5. Conclusions

The optimization of arylation of acetophenone has led to a reaction with yields up to 49% when using bromobenzene as the other reagent or 57% when using 1-bromonapthtalene. This was achieved using 5 equivalents of potassium *tert*-butoxide and using either 1,10-phenanthroline or $FeCl_2$ as catalyst (both 10 mol%). Pyridine was used as solvent for this reaction as it gave the best results. In many other solvents the yield of the alpha-arylation has shown to be 0%, only reactions performed in benzene, DMSO, pyridine, dioxane and THF were successful with mixed results. However the latter two had significant lower yield than the other solvents. The alpha-arylation reaction in pyridine has been shown to work without the use of a catalyst, only in presence of the base, potassium *tert*-butoxide. However, the yield improves from 20% to 46% or 49% when 1,10-phenanthroline or $FeCl_2$ is used respectively. Different aryl halides gave mixed results, while 1-bromonaphthalene gave an increase yield of 57%, 2-bromonaphthalene only yielded 24%.



In order to expand the substrate scope, alpha-arylation of an ester was tried using the KO*t*Bu/DMF system. However no product was found, which is likely due to the base being too weak to deprotonate the ester.

The KO*t*Bu/DMF system was also used to perform an alpha-arylation in presence of carbon monoxide. The product with carbon monoxide incorporated (compound **13**), was obtained in a yield of 6% via NMR. Subsequent reactions however had no yield at all for both compound **13** and **17**. This is quite unusual as the reaction without CO, just the regular alpha-arylation is able to proceed even while under air or undistilled DMF.



Chapter 6. Outlook

Alpha-arylation of aromatic ketones with aryl iodides can be done with yields over 90%. With aryl bromides the yields do not exceed 75% and aryl chlorides have even lower yields. However, these aryl halides could be interesting to investigate further due to their lower costs when compared to aryl iodides. Another interesting improvement to alpha-arylation could be using esters. While this work showed that when using the normal conditions, arylation of esters is not possible, it could be that if the deprotonation is done by a stronger base (e.g. lithium diisopropylamide) the reaction is able to proceed.

Further research towards the alpha-arylation in presence of CO would be interesting. As it stands now, 6% yield shows that the aryl radical can first react with the CO to form a benzoyl radical and then react further with the ketone enolate to form a diketone. There are two reaction pathways an aryl radical can take, the first one is a reaction with the ketone enolate to form the deoxybenzoin. The second one is the desired one, which is a reaction with CO followed by the reaction with the ketone enolate. To increase the yield of the reaction, the first pathway needs to shut down or suppressed. This could be achieved by increasing the CO concentration (i.e. the pressure) or lowering the concentration of the ketone, and thus lowering the reaction rate of the first pathway. Another way to increase the yield could be by addition of chemicals that could stabilize the benzoyl radical making the second pathway more favorable. Maybe even 1,10-phenanthroline or $FeCl_2$ could stabilize the benzoyl pathway. Compounds that have been showed to be able to catalyze direct arylation reaction could also be tried as additive because these reaction bear quite some similarities. These compounds include, but are not limited to: L-proline, DMEDA, ethylenediamine or ethanolamine.[56]

Chapter 7. Experimental

7.1. Materials and instrumental

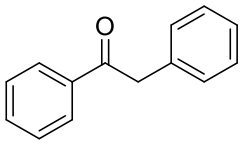
Reaction utilizing a pressure tube used chemicals that were obtained from commercial suppliers without further purification. Reactions were Schleck techniques where applied, mainly reaction with pyridine and DMF, were carried out in dry, degassed solvent and under a N_2 atmosphere. All chemicals were obtained from commercial sources unless stated otherwise. The NMR spectra were recorded on a Mercury (400 MHz) spectrometer or Agilent (400 MHz) at 298 K and referenced internally against the residual ^1H signal of the deuterated solvent, which is in all cases deuterated chloroform. The NMR-results are shown in δ (ppm). GC analysis was done on a Perkin Elmer Clarus 500 Gas Chromatograph equipped with an Agilent HP-5 column (30m od 0.32 id 0.25 µm 5% phenyl-95% methylpolysiloxane). GC-MS spectra were recorded on a Perkin Elmer Clarus 680 Gas Chromatograph, equipped with a Perkin Elmer Elite 5MS column (15m x 0.25 mm ID x 0.25µm), and a Perkin Elmer Clarus SQ 8 T Mass Spectrometer.

7.2. Methods

Preparation of Fe/Phen catalyst:

Procedure from Klein Gebbink *et al.*[40] was used. A solution of $FeCl_3$ (2.50 mmol) in ethanol (30mL) was added dropwise to a stirred solution of 1,10-phenanthroline (5.00 mmol) in the same solvent (60 mL). The orange suspension was stirred for 1 hour and the resulting solid was collected through centrifugation ad dried under vacuum for 20 min.

General procedure for pressure tube reactions:



In a glove box a pressure tube was charged with KO*t*Bu (168 mg, 1.5 mmol, 3.0 equiv.) and a stirring bar. The tube was brought out of the glove box and the catalyst was added (10 mol%). To this, a mixture of acetophenone or the silyl enol ether of acetophenone (58.5 µL, 0.5 mmol, 1.0 equiv.), bromobenzene (52.5 µL, 0.5 mmol, 1.0 equiv.) and solvent were added. The mixture was stirred at room temperature for 2 minutes and at 100°C for 18 hours (overnight). After cooling the reaction was quenched by the addition of water (30 mL) and the mixture was extracted with DCM (3x20 mL). The combined organic extracts were concentrated and analyzed with GC. Further purification was done via column chromatography (100% DCM). ^1H-NMR (400 MHz, $CDCl_3$) δ = 8.02 (2H, m, Ar), 7.56 (1H, m, Ar), 7.46 (2H, m, Ar), 7.33 (2H, m, Ar), 7.27 (3H, m, Ar), 4.29 (2H, s, $-CH_2-$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 197.6, 136.6, 134.5, 133.2, 129.5, 128.67, 128.64, 128.62, 126.9, 45.5.

General procedure for Schlenk tube reactions in pyridine:

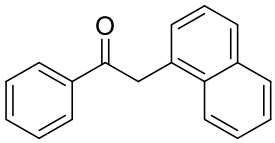
In a glove box a Schlenk tube was charged with KO*t*Bu (280 mg, 2.5 mmol, 5.0 equiv.) and a stirring bar. The Schlenk tube was brought out of the glove box and the catalyst was added (10 mol%). To this, acetophenone (58.5 µL, 0.5 mmol, 1.0 equiv.), bromobenzene (63.1 µL, 0.6 mmol, 1.2 equiv.)

and pyridine (1 mL) were added. The mixture was stirred at room temperature for 2 minutes and at 100°C overnight. After cooling the reaction was quenched by the addition of water (30 mL) and the mixture was extracted with DCM (3x20 mL). The combined organic extracts were concentrated and analyzed with GC. Further purification was done via column chromatography (100% DCM).

General procedure for autoclave reactions:

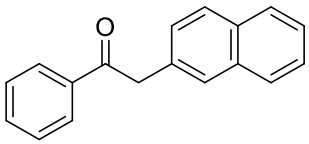
KO*t*Bu (2.8 g, 25 mmol), 25 mL anhydrous DMF, 4-iodotoluene (1.09 g, 5.0 mmol) and acetophenone (±10 mmol, 1.2 mL) was added to the autoclave. The autoclave was closed and flushed with CO for 15 minutes. The pressure was raised to the desired one and stirred and heated for the given time. After cooling the reaction was quenched with 4M HCl (10 mL). After addition of diethylether (10 mL), the mixture was washed with water (3x2 mL) and brine (1x2 mL). The organic layer was dried with anhydrous MgSO4 and concentrated in vacuo. Triphenylmethane was added as internal standard and the product was analyzed via NMR.

Synthesis of 2-(1-naphthyl)-1-phenylethanone (compound **7**)



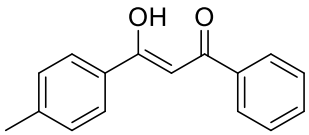
In a glove box a Schlenk tube was charged with KO*t*Bu (280 mg, 2.5 mmol, 5.0 equiv.) and a stirring bar. The Schlenk tube was brought out of the glove box and the catalyst was added (10 mol%). To this, acetophenone (58.5 µL, 0.5 mmol, 1.0 equiv.), 1-bromonaphthalene (83.9 µL, 0.6 mmol, 1.2 equiv.) and pyridine (1 mL) were added. The mixture was stirred at room temperature for 2 minutes and at 100°C overnight. After cooling the reaction was quenched by the addition of water (30 mL) and the mixture was extracted with DCM (3x20 mL). The combined organic extracts were concentrated and analyzed with GC. Further purification was done via column chromatography (100% DCM). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.05 (2H, m, Ar), 7.80 (3H, m, Ar), 7.73 (1H, s, Ar), 7.44 (5H, m, Ar), 4.45 (2H, s, -CH_2-).

Synthesis of 2-(2-naphthyl)-1-phenylethanone (compound **9**)



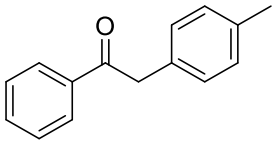
In a glove box a Schlenk tube was charged with KO*t*Bu (280 mg, 2.5 mmol, 5.0 equiv.) and a stirring bar. The Schlenk tube was brought out of the glove box and the catalyst was added (10 mol%). To this, acetophenone (58.5 µL, 0.5 mmol, 1.0 equiv.), 1-bromonaphthalene (124.2 mg, 0.6 mmol, 1.2 equiv.) and pyridine (1 mL) were added. The mixture was stirred at room temperature for 2 minutes and at 100°C overnight. After cooling the reaction was quenched by the addition of water (30 mL) and the mixture was extracted with DCM (3x20 mL). The combined organic extracts were concentrated and analyzed with GC. Further purification was done via column chromatography (100% DCM).^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.09 (2H, m, Ar), 7.88 (2H, m, Ar), 7.80 (1H, m, Ar), 7.59 (1H, m, Ar), 7.44 (6H, m, Ar), 4.75 (2H, s, -CH_2-).

Synthesis of 1-(4-methylphenyl)-3-phenyl-1,3-propanedione (compound **13**):



The synthesis method was based on work from Tang *et al.*[57] In a glove box, sodium hydride (0.3 g, 12.5 mmol) was added to a to a 50 mL, three-necked, round-bottom flask. The flask was brought out of the glove box (keeping the N_2 atmosphere intact) and cooled with an ice bath to 0°C. Distilled THF (17.5 mL), 4-methylacetophenone (0.67, 5 mmol) and methyl benzoate (0.068 g, 0.5 mmol) were added. After stirring for 20 min at 0°C, more methyl benzoate was added (0.68 g, 5.0 mmol). The ice bath was removed and the mixture was refluxed for 16 hours. After cooling to room temperature, 3.2 mL 4M HCl solution was slowly added. Ethyl acetate was added and the organic layer was washed 3x with brine followed by column chromatography with petroleum ether-ethyl acetate (80:1) to obtain the product in a yield of 59.5% (0.7084 g). Note: using a column with a ratio of 80:1 seamed to give some solubility issues inside the column. Using a ratio with a bit more ethyl acetate removes this problem while still retaining good separation. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 16.91 (1H, s, OH). 7.99 (2H, m, Ar), 7.90 (2H, m, Ar), 7.50 (3H, m, Ar), 7.30 (2H, m, Ar), 6.84 (1H, s, =CH-) 2.44 (3H, s, -CH_3).

Synthesis of 1-phenyl-2-(4-methylphenyl)-ethanone (compound **17**)



This synthesis was based on work of Taillefer *et al.*[36] In a glove box a Schleck tube was charged with KO*t*Bu (5.0 mmol, 5.0 equiv.) and a stirring bar. The Schleck tube was brought out of the glove box and DMF (3 mL) was added and left to stir at RT for 10 min. Then, acetophenone (0.24 g, 2.0 mmol) and 4-iodotoluene (0.218 g, 1.0 mmol) were added. The mixture was stirred at 60°C overnight. After cooling the reaction was quenched with 1M HCl (2 mL) and stirred for 10 min. After addition of diethylether (10 mL), the mixture was washed with water (3x2 mL) and brine (1x2 mL). The organic layer was dried with anhydrous $MgSO_4$, concentrated in vacuo and purified via column chromatography with petroleum ether-ethyl acetate (80:1) to obtain the product in 76% yield (0.1611 g). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.01 (2H, m, Ar), 7.48 (3H, m, Ar), 7.15 (4H, m, Ar), 4.25 (2H, s, -CH_2-), 2.32 (3H, s, -CH_3).

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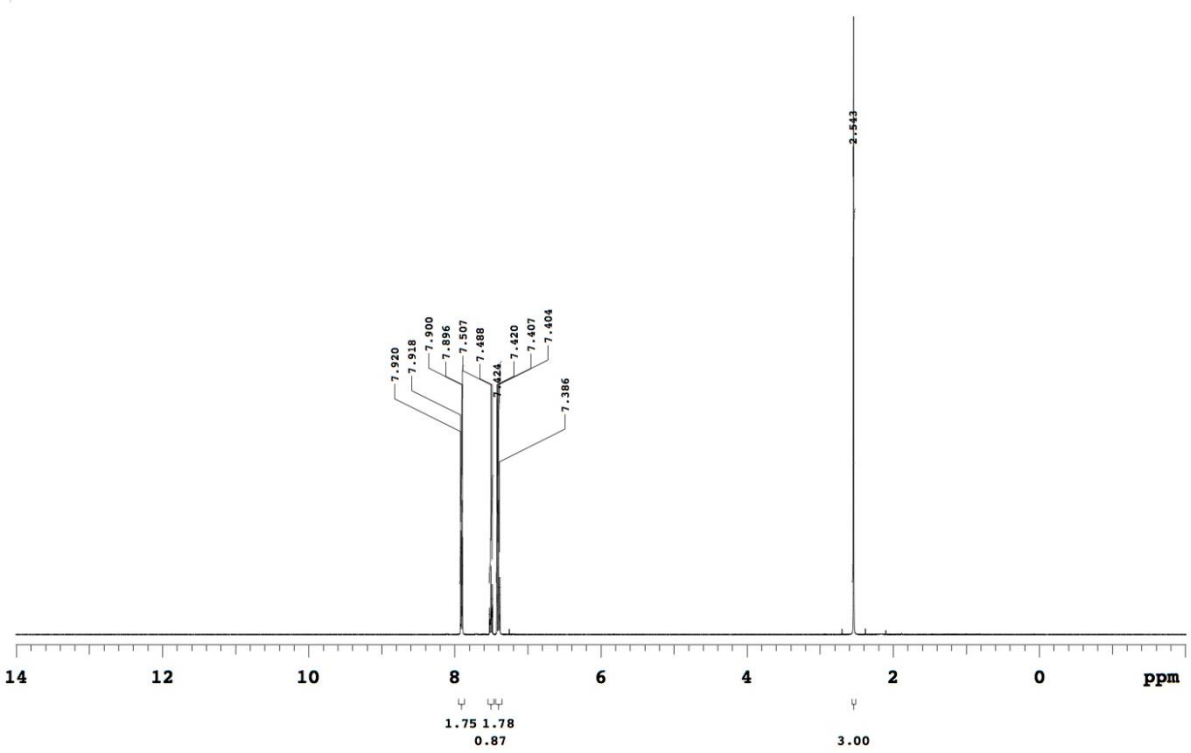
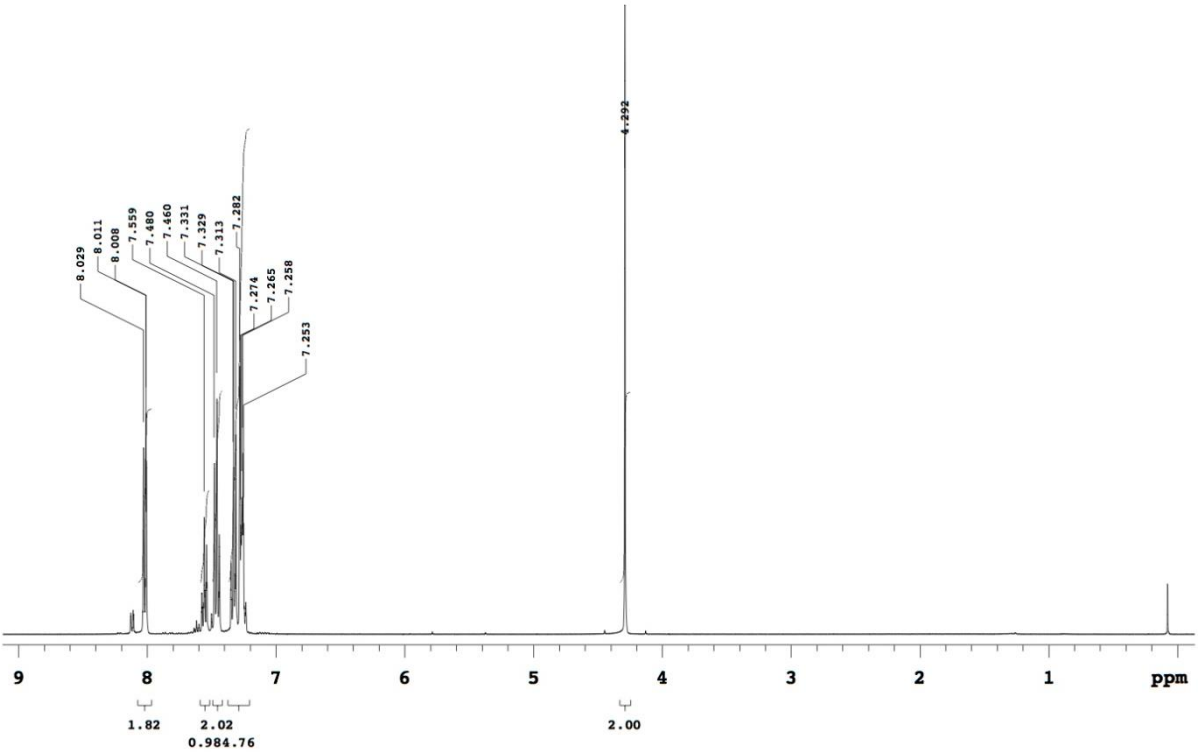
Appendices

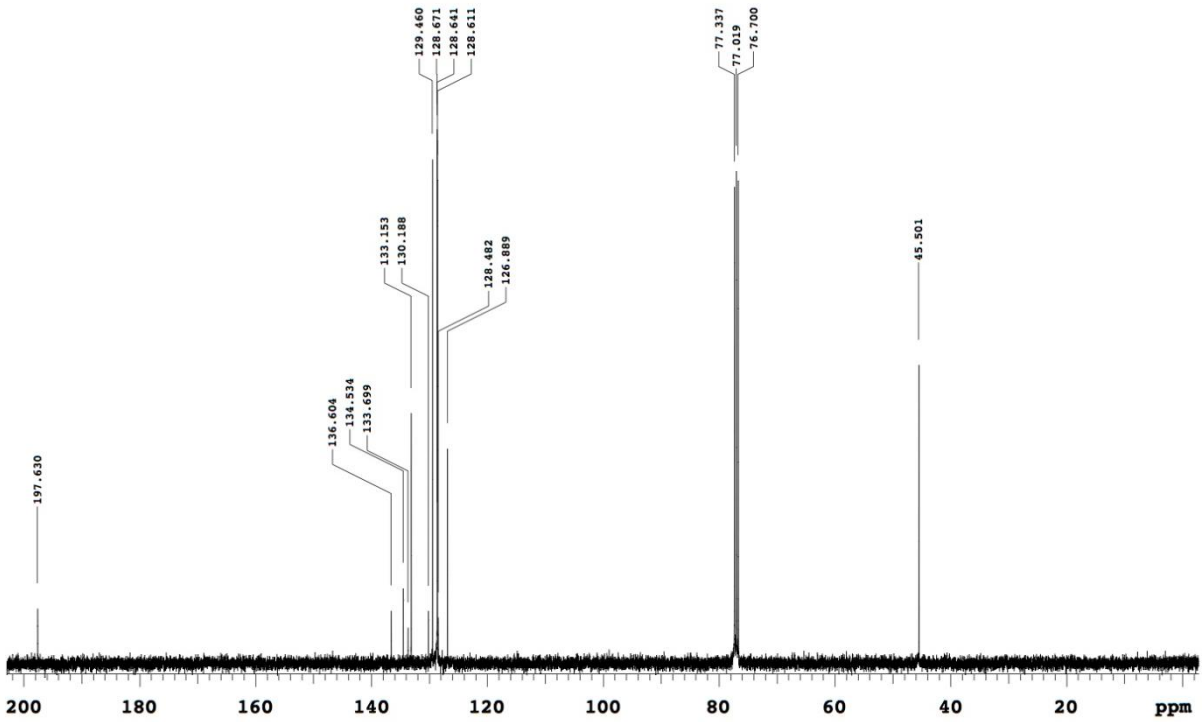
A1. ^{1}H-NMR spectrum of acetophenone



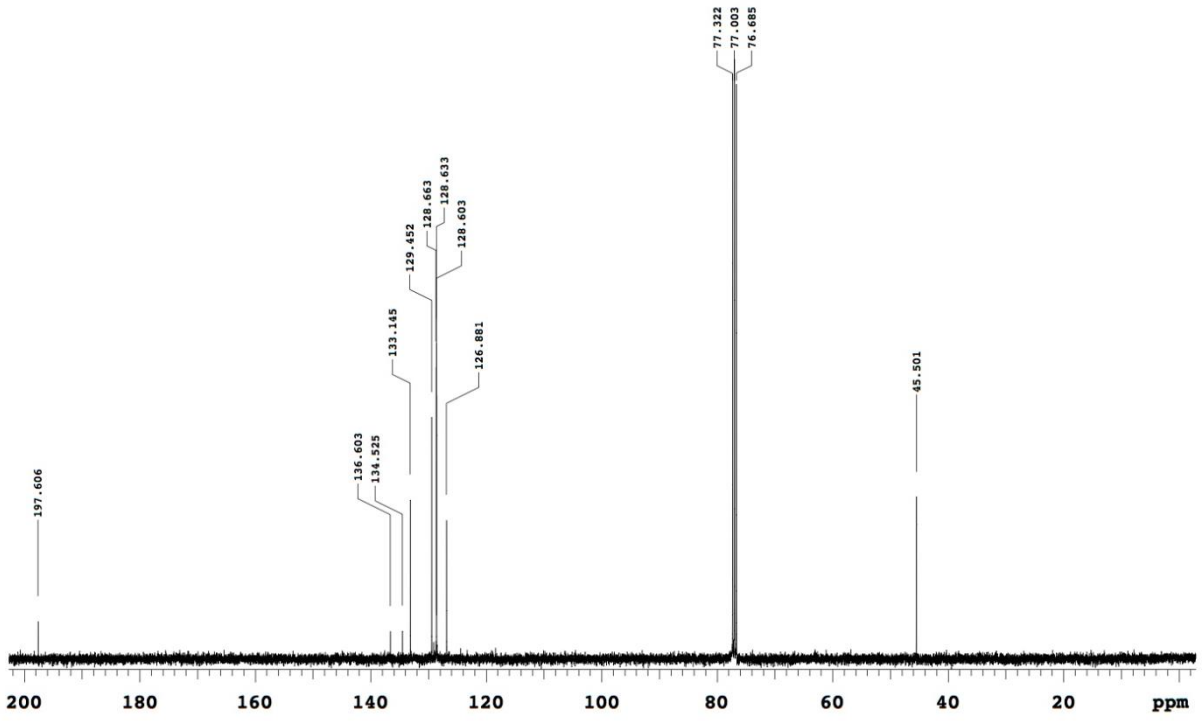
A2. ^{1}H-NMR spectrum of 2-phenylacetophenone (compound 3)



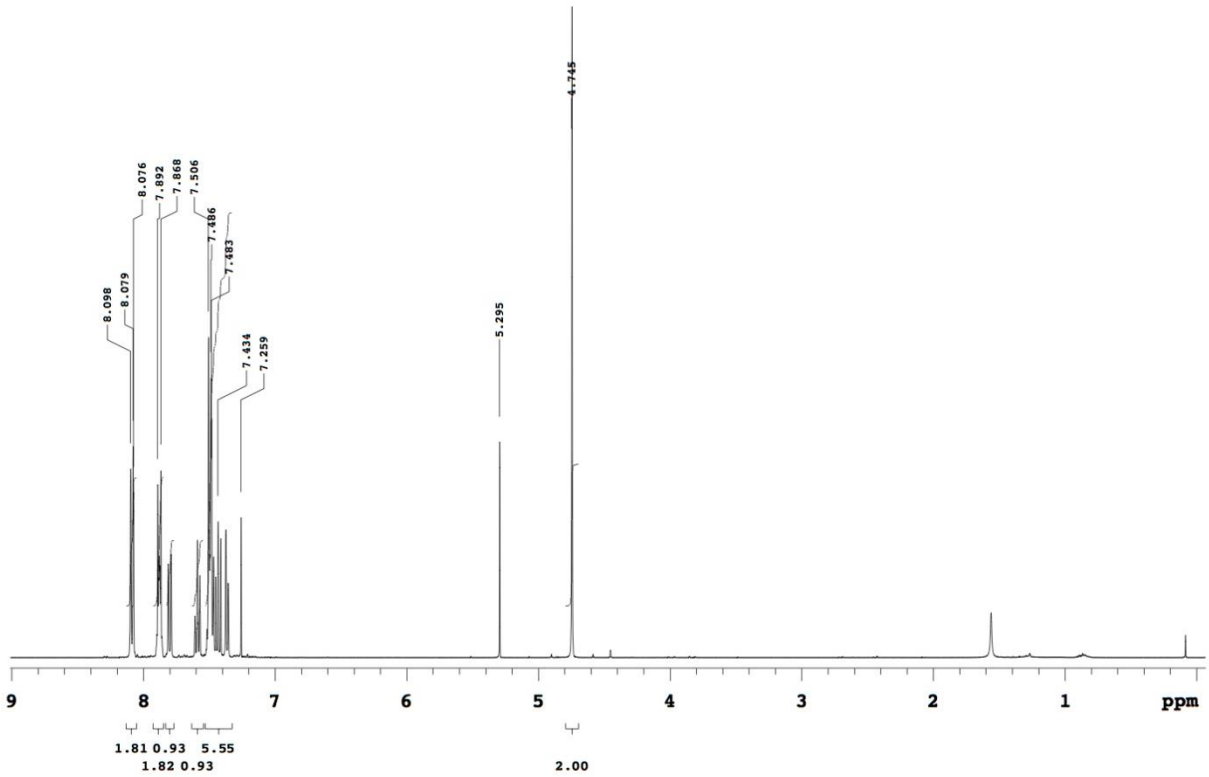
A3. ^{13}C-NMR spectrum of 2-phenylacetophenone (compound 3)



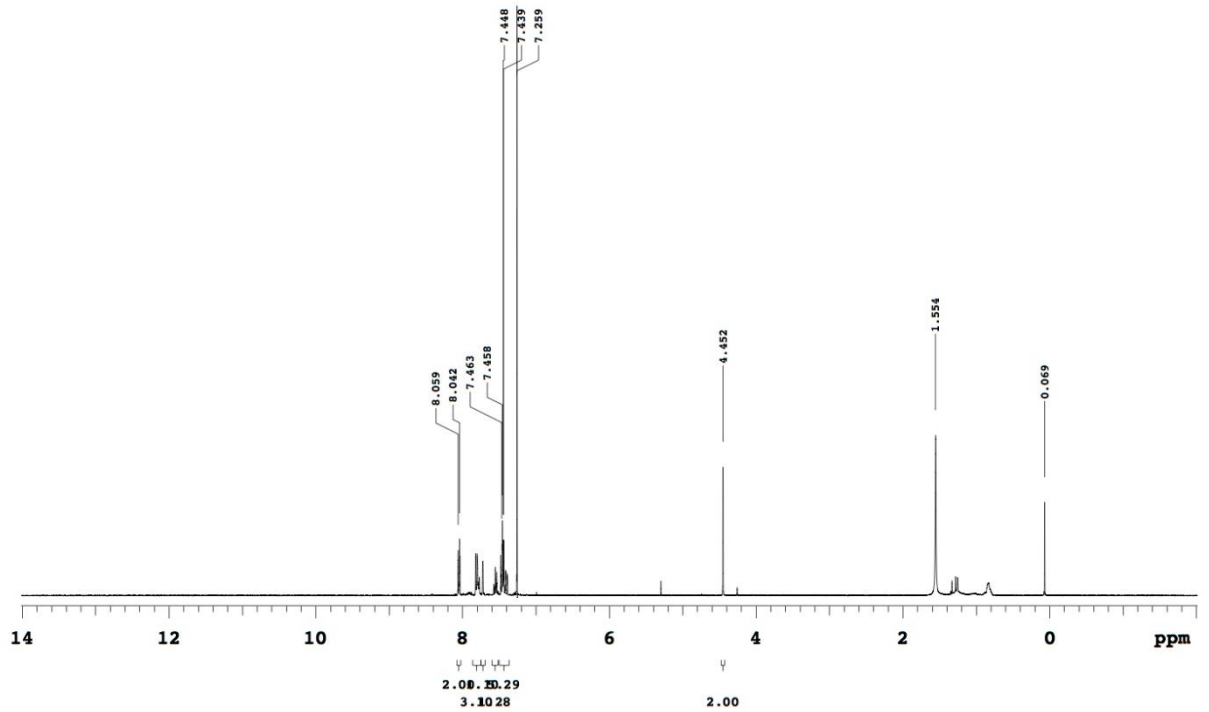
A4. ^{13}C-NMR spectrum of 2-phenylacetophenone (compound 3) synthesized via alpha-arylation in pyridine



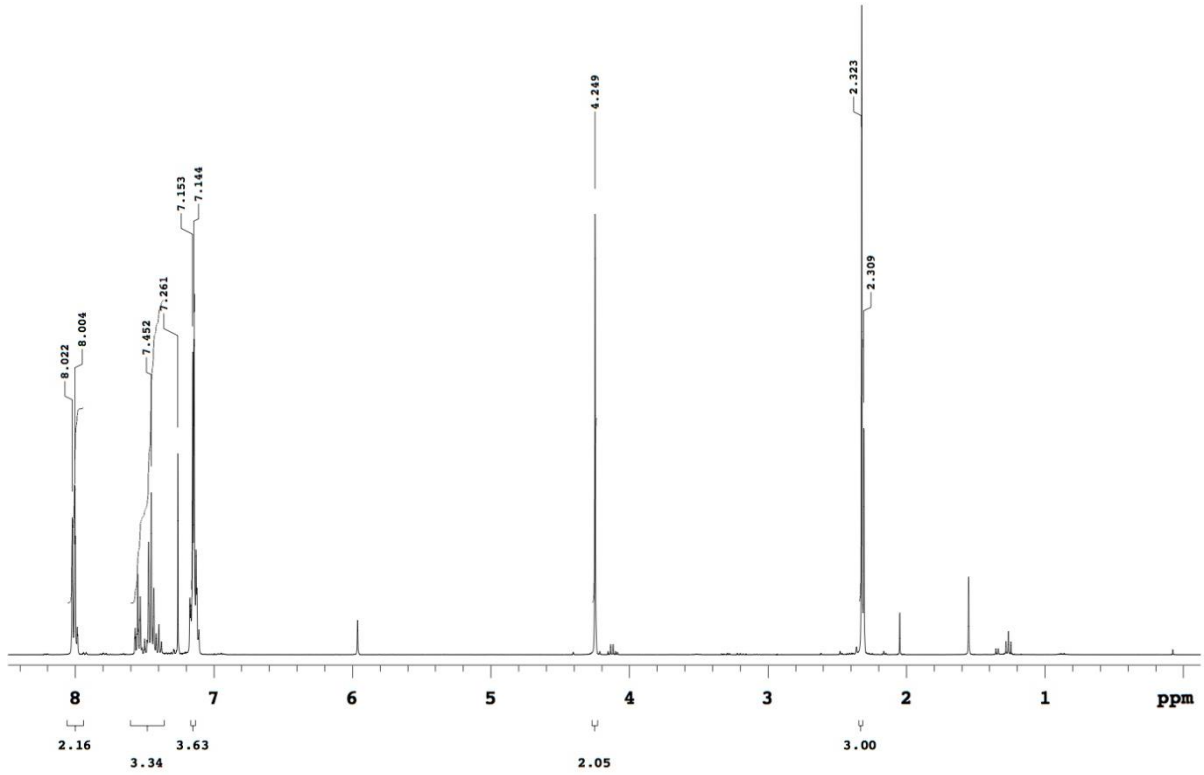
A5. ^{1}H-NMR spectrum of 2-(1-naphthyl)-1-phenylethanone (compound 7)



A6. ^{1}H-NMR spectrum of 2-(2-naphthyl)-1-phenylethanone (compound 9)



A7. ^{1}H-NMR spectrum of 1-phenyl-2-(4-methylphenyl)-ethanone (compound 17)



A8. ^{1}H-NMR spectrum of the reaction mixture of the attempted alpha-arylation in the presence of CO at 50°C