DIPLOMARBEIT

QUATERNARY AMMONIUM SALTS AS ALKYLATING AGENTS IN C-H ACTIVATION CHEMISTRY

ausgeführt am

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Meinen Eltern gewidmet.

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Abstract

This thesis focuses mainly on Rh(I)-catalyzed C-H alkylation reactions. Transition metal catalyzed direct alkylation reactions of benzylic amines using alkyl halides and olefins were already investigated in our group. Preliminary results showed, that it is possible to use quaternary ammonium salts as alkylating reagents in this reaction. The olefin is generated *in-situ* by Hofmann elimination. The formed olefin is able to undergo a direct C-H alkylation reaction of benzylic amines at the benzylic carbon atom directed by 3-substituted pyridin-2-yls.

Olefins as alkylating agents are often used in organic chemistry, however short chained olefins like ethylene, propylene or butylene are gaseous at room temperature and highly flammable. Overcoming these drawbacks by substituting olefins with quaternary ammonium salts was the goal of this thesis. Quaternary ammonium salts are solid at room temperature, not particular dangerous and cheap. Therefore this compounds are easy to work with in the organic lab.

In the progress of this thesis, we managed to find a working protocol exploiting quaternary ammonium salts as alkylating agents. Furthermore, the reaction conditions were optimized allowing us to perform this reaction with longer chained salts up to C8, generating in that case 1-octene in the reaction mixture upon elimination. Furthermore, a scope of different substituted benzylic amines could be successfully alkylated.

Moreover we tried our newly developed method with other literature known C-H alkylation reactions using olefins as alkylating agents. Different substrates and catalysts could be successfully alkylated by our method, showing that this reaction has more applications in the field of direct C-H alkylation reactions.

Additional studies to gain a deeper understanding of this reaction were conducted. Kinetic studies into the Hofmann elimination step gained insight on the needed conditions to perform an efficient elimination. Also, experiments towards the correct catalytic active species were performed in cooperation with the Institute of Chemical Technologies and Analytics. Giving us further hints towards proposed reaction mechanism of this Rh(I)-catalyzed alkylation reaction.

Deutsche Kurzfassung

Diese Arbeit fokussierte vorallem auf Rh(I)-katalysierte C-H Alkylierungs Reaktionen. Übergangsmetall katalysierte C-H Alkylierungs Reaktionen von benzylischen Aminen mit Alkylhalogeniden oder Olefinen wurde bereits von unserer Gruppe untersucht. Erste Resultate zeigten jedoch, dass es möglich ist, quartäre Ammonium Salze als Alkylierungs Reagenzien in dieser Reaktion zu nutzen. Das Olefin wird dann *in-situ* durch eine Hofmann Eliminierung generiert. Die Alkylierungs Reaktion kann dann dieses Olefin als Alkylquelle nutzen, um benzylische Amine an ebendiesem benzylischen Kohlenstoffatom mit Unterstützung einer dirigierenden Gruppe, in diesem Fall 3-substituierten Pyridin-2-yl, zu alkylieren.

Olefine werden in der organischen Chemie oft genutzt. Jedoch vor allem kurzkettige Olefine wie Ethen, Propen und Buten sind gasförming bei Raumtemperatur und zudem noch leicht entflammbar. Diese Nachteile können überwunden werden, wenn das Olefin durch quartäre Ammonium Salze ausgetauscht wird. Diese sind fest bei Raumtemperatur, billig und nicht besonders schädlich. Deshalb kann mit diesen Salzen im Labor einfach gearbeitet werden.

Im Zuge der Arbeit, konnte ein neues Protokoll entwickelt werden, welches quartäre Ammonium Salze as Alkylierungsreagenzien nutzt. Weiters wurden die Reaktionsparameter optimiert, welches uns erlaubt, auch länger-kettige Salze zu verwenden, was bis zum Tetraoctylammoniumsalz gezeigt wurde. In diesem Fall entsteht dabei während der Elimierung 1-Octen in der Reaktionsmischung. Weiters konnte eine Reihe von verschieden substituierten benzylischen Aminen erfolgreich alkyliert werden.

Diese neue C-H Alkylierungsmethode wurde auch an bereits Literatur bekannten C-H Alkylierungsreaktionen getestet, welche Olefine als Alkylierungsreagenzien nutzt. Verschiedene Substrate und Katalysatoren konnten auf diese Weise mit unserer Methode getestet werden. Dies zeigte, dass diese Reaktion potentiell breite Anwendung auf dem Feld der C-H Alkylierungschemie finden kann.

Zudem wurden mehrere Experimente durchgeführt um diese Reaktion und deren Konditionen besser zu verstehen. Ein Temperaturprofil für den Hofmann Eliminierungsschritt zeigte ab welcher Temperatur die Elimination effizient ist. Auch wurden eine Reihe von Versuchen angestellt in Kooperation mit dem Institut für Chemische Technologien und Analytik, um weitere Hinweise in Richtung der katalytisch aktiven Spezies zu erhalten. Mit diesen Experimenten konnten weitere Hinweise für den vorgeschlagenen Reaktionmechanismus dieser Rh(I)-katalysierten C-H Alkylierungsreaktion gefunden werden.

Key

All compounds synthesized in this thesis are labelled with Arabic bold numbers. Byproducts generated in some reactions or compounds that are intended to be grouped together are labelled with Arabic bold numbers followed by Latin alphabetic characters.

Literature citations are indicated by superscript Arabic numbers in square brackets. Footnotes in tables, figures or schemes are indicated with superscript Latin characters and are found directly below the respective table, figure or scheme.

Contents

1. General Synthetic Scheme

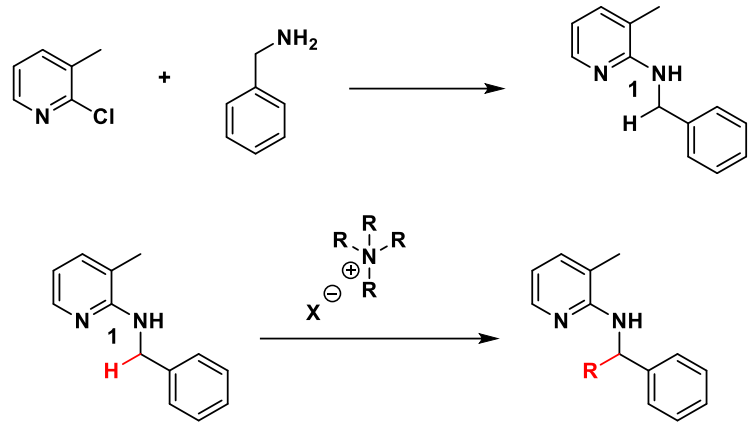


Table 1.1: Isolated yields of compounds using different chained tetraalkylammonium salts up to C8.

Compound Number	R	Isolated Yield [%]
2	ethyl	68
3	propyl	62
4	butyl	60
5	pentyl	58
6	hexyl	61
7	octyl	40

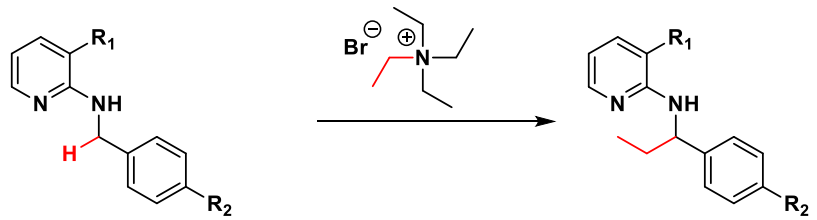
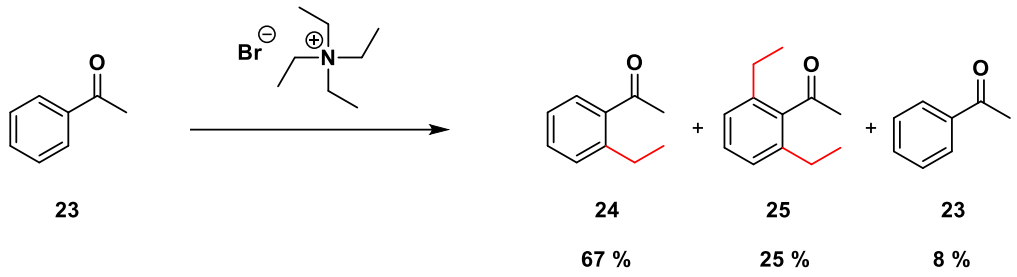


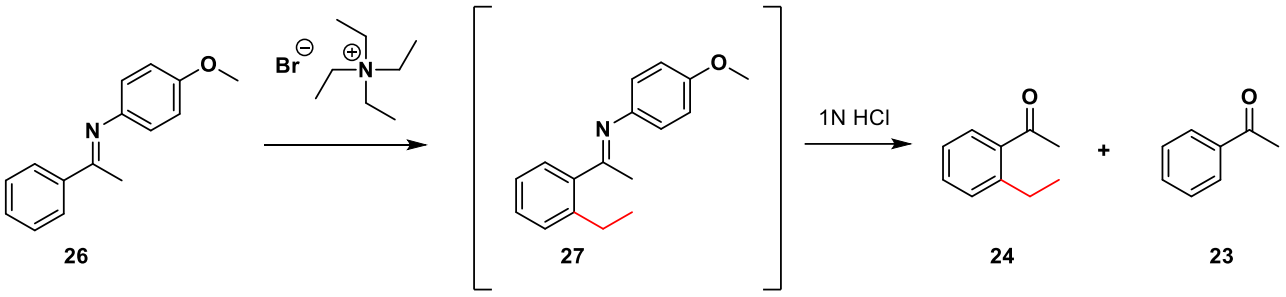
Table 1.2: Isolated substrate scope on the target compound.

Compound Number	R_1	R_2	Isolated Yield [%]
8	phenyl	H	63
9	phenyl	CH_3	65
10	mesityl	H	64
11	4-$(CH_3)_2$CHO-phenyl	H	59
12	CH_3	$(CH_3)_2N$	61
13	CH_3	$(CH_3)_2$CHO	69
14	CH_3	F_3C	53
15	CH_3	CH_3O	71
16	CH_3	F	50



23 **24** **25** **23**

67 % **25 %** **8 %**



26 **27** **24** **23**

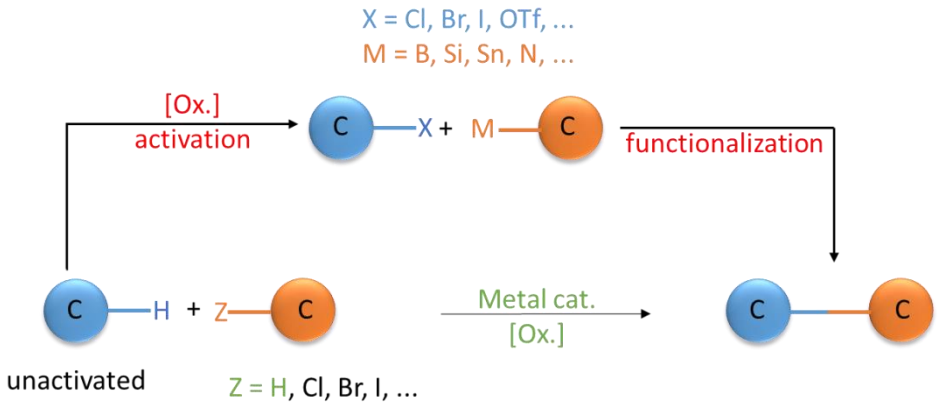
40 % **60 %**

2. Introduction

Carbon-carbon bond (C-C) formation is a fundamental, and thus often encountered problem in chemistry. Today, there is a vast number of C-C bond forming reactions and these transformations take a central part in many chemical syntheses.[1-3] Cross-coupling reactions, the coupling between two differently substituted hydrocarbon fragments with the aid of a metal catalyst, are high priority syntheses in the immense field of C-C bond formation. Cross-couplings between a nucleophile and an alkylating agent (generally an electrophile) clearly constitute one of the most widely employed reactions for compounds of various purposes, and every year more and more reactions utilizing different metals are reported.[4-8] The most well-established type is the coupling between an organometal species RM (R = organic fragment, M = metal) and an organic halide in presence of a metal catalyst. In fact, the 2010 Nobel Prize in Chemistry has been given to Richard F. Heck, Ei-ichi Negishi and Akira Suzuki for developing palladium catalyzed cross coupling reactions.[9-11] Moreover, palladium is not the only metal that is available for such reactions. A variation of metals like copper, nickel, iron, and others are common and widely established in organic chemistry. However, the required organometallic reagents are often not commercially available and if so, rather expensive. One way to overcome this drawback is to introduce new functional groups directly by transforming C-H bonds. This gives rise to new opportunities and different synthetic strategies for every organic chemist. In the last decades, considerable advances have been achieved in transition-metal-catalyzed C-H functionalization and such transformations became highly attractive.

2.1. C-H Activation

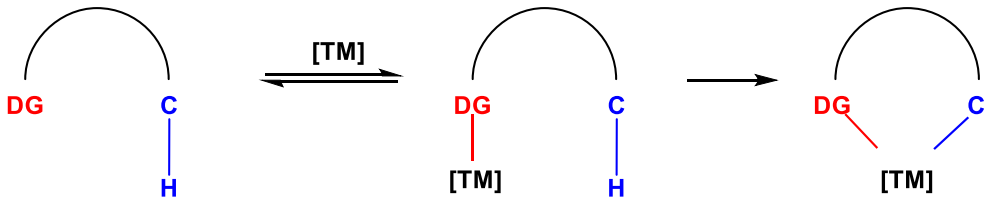
The development of synthetic strategies which are more economical and environmentally friendly generated intense interest in recent years. Decreasing the number of steps in a given synthesis is one of the simplest ways for achieving this general goal in chemistry. Reducing the functional group manipulations, which are typically required to obtain a reactive substrate to directly perform the key C-C or C-heteroatom bond formation in the desired position of the C-H precursor, is the easiest way to take a shortcut to the product (Scheme 2.1).[12] Therefore, direct C-H bond functionalization has emerged as powerful tool and gained lots of attention in organic chemistry.



Scheme 2.1: C-H activation / functionalization synthesis in comparison to traditional approach involving an oxidation step

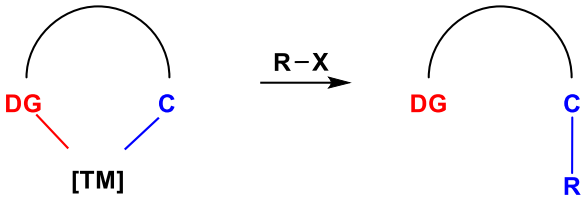
Direct functionalization of a C-H bond, enables to use in principal the simplest and cheapest feedstock of molecules in the lab for the synthesis of complex organic molecules. Metal catalyzed C-H activation chemistry is a rapidly expanding field.[13-18] Research is going into a wide area of many different directions. Thus, in the last decades, C-H activation processes for assembly and functionalization of organic molecules could greatly simplify the synthesis of pharmaceuticals, natural products and general feedstock chemicals.[19-21] However, due to the manifold of different C-H bonds in organic molecules, selective activation of a specific C-H bond can be an arduous task. An isolated C-H bond in a molecule has, in general, a very low reactivity. The bond has a very apolar nature and therefore a large kinetic barrier to bond cleavage. The bond dissociation energies decreases from C(sp)-H < C(sp^2)-H < C(sp^3)-H.[12] Therefore direct functionalization of C(sp^3)-H bonds is a challenging task, but a very attractive one. No wonder that there are plenty developed methods from literature on sp^2 C-H bonds, but not as much on the challenging C(sp^3)-H bond.

Cyclometalation is a solution to achieve selective C(sp^3)-H activation. In general, cyclometalation is the formation of a cyclic ring system, which contains at least one metal atom (Scheme 2.2).[22]



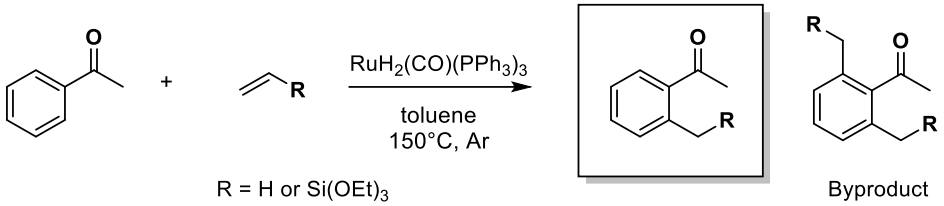
Scheme 2.1: Cyclometalation step. Directing groups allow to selectively activate a C-H bond

Heteroatoms influence the electron density of different C-H positions. Therefore, using heteroatoms to guide the regioselectivity is an often used strategy and also applies to C-H activation chemistry. In particular, making use of directing groups (DGs) can be powerful in selectively activating the desired position in the target molecule (Scheme 2.3).



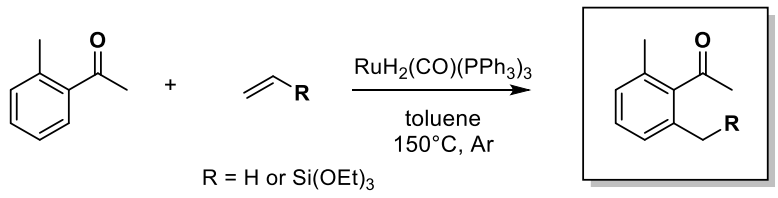
Scheme 2.2: Selective C-C bond formation after C-H activation via cyclometalation

About three decades ago, the group of Shinji Murai set a landmark in directing group assisted C-H activation.[23] In this contribution a ketone was used as directing group to guide the alkylation in a specific position. More specific, the group used acetophenone to activate the aromatic *ortho*-position, exploiting a Ru(II) catalyst and using olefins as alkylating agents (Scheme 2.4).



Scheme 2.4: Murai's direct C-H alkylation reaction of acetophenone with olefins. The ketone DG allows selective activation of the ortho-position.

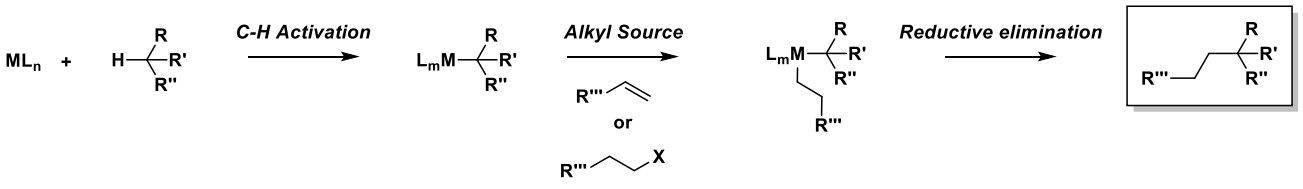
This showed that regioselectivity problems can be overcome when the metal catalyst is precoordinated to a directing group. This allows selective C-H cleavage in proximity to these groups. Olefins as alkylating reagents achieved very good yields in this reaction. The group was also able to overcome the problem of using gaseous short chained olefins by using vinylsilanes instead. The dialkylated byproduct can never be completely suppressed in this kind of reactions, but blocking the position can help overcoming this problem (Scheme 2.5).



Scheme 2.5: Adding a methyl group in one of the ortho-positions allows to get rid of the byproduct formation.

2.2. Direct C-H Alkylation

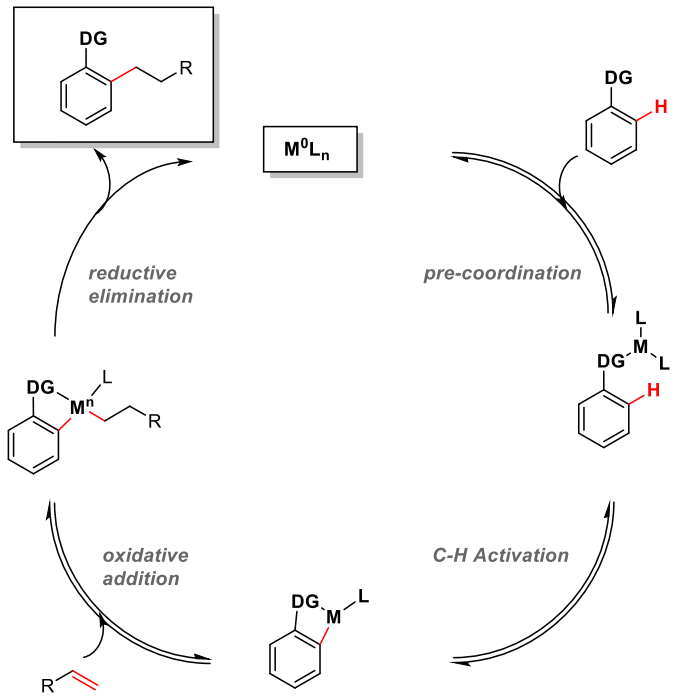
Direct C-H alkylation reactions are a subgroup of C-H functionalization, where a C-H group is substituted for an alkyl group. Needless to say, a substrate is required which is able to donate the desired alkyl group. Conventionally, such transformations rely on using reactive alkylating agents. Very commonly used are alkyl halides or sulfonates. While these reactions can be efficient, they suffer from the downside of producing stoichiometric amounts of byproducts. With advances of transition metal catalyzed chemistry during the last decades, it became possible to use another very potent alkylating agent: The olefin. A number of attractive benefits can be achieved exploiting the double bond of an olefin. First of all, the reaction would become byproduct-free, leading to a more atom-efficient and environmental friendly reaction.[24, 25] Moreover, olefins are generally cheaper and readily available than the alkyl halides, as these alkyl halides are most likely synthesized from the corresponding olefin in the first place. A very general scheme for a classic C-H alkylation reaction is shown in Scheme 2.6.



Scheme 2.6: Direct C-H alkylation reaction scheme

In general, C-H activation reaction pathways have a lot in common to cross coupling mechanisms. Once substrate and alkylating agent are bound to the metal center, the alkyl group is transferred to the carbon atom by reductive elimination and a new C-C bond is formed. Mostly depending on what alkyl source is used, different intermediates can be formed. In case of alkyl halides, the metal center gets inserted into the C-X bond of the halide. However olefins, usually form a π-complex where then the olefin is inserted into a M-H bond to form the reactive metal alkyl complex which then can undergo the reductive elimination step to form the alkylated product.[26]

As mentioned in the previous section, when Murai reported his Ru-catalyzed alkylation reaction of aromatic ketones with olefins, he used the ketone functionality as DG to selectively activate a specific C-H bond for an alkylation.[23] In fact, the proposed reaction pathway is illustrated in Scheme 2.7. The reaction is initiated by oxidative addition into the *ortho*-C-H bond, assisted by the ketone moiety.



Scheme 2.7: Example of directing group assisted C-H alkylation reaction of aromatic systems using olefins. In case of Murai-tpye reactions[23]: DG = CO-CH3; catalyst: RuH2(CO)(PPh3)3; M = Ru; L = H; R = e.g. Si(OEt)3

2.3. C-H Activation Reactions of Benzylic Amines in Literature

The following section summarizes the knowledge gained from literature and investigations in our group on C-H activation reactions on benzylic amine substrates with 3-substituted pyridine derivatives as directing groups.

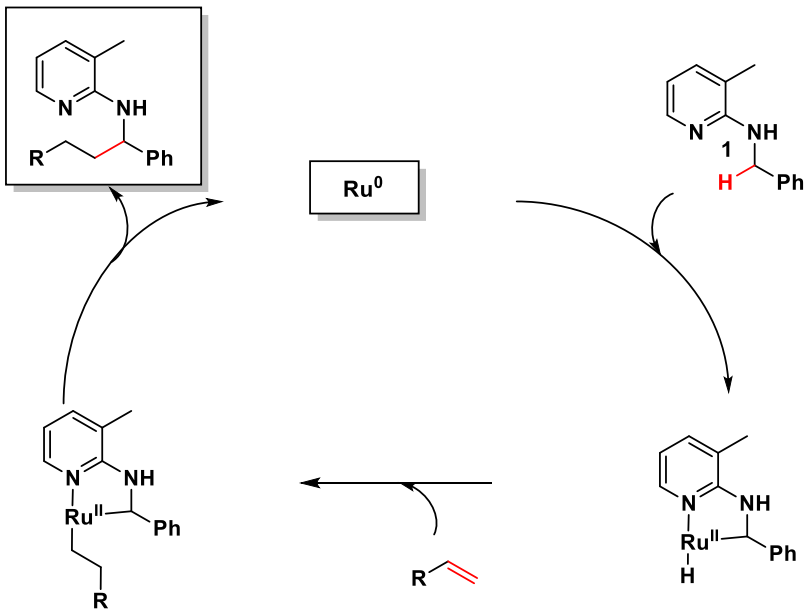
In 1998, Jun and his group reported their work of a Ru(0)-catalyzed C-H alkylation reaction of 2-(benzylamino)pyridines with alkenes as alkylating reagents.[27] And later, in 2011, the group of Shibata was able to use a chiral Ir(I) catalyst that led to an enantioselective reaction mechanism (see following chapter 2.3.1).[28]

In more recent years, our group showed different C(sp^3)-H activation reactions on these benzylic amines substrates using palladium, rhodium and ruthenium catalysts (see following chapter 2.3.2).[29-33]

2.3.1. Direct Alkylation of Benzylic Amines

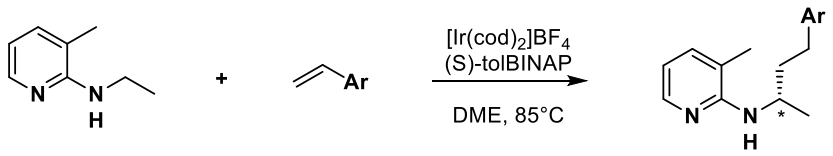
As aforementioned, already in 1998 the group of Jun reported the alkylation of N-benzyl-3-methylpiridin-2-amine. A Ru(0)-catalyzed reaction was described, testing various olefins and showing the scope of substrates that arises with that.[27] The proposed reaction mechanism followed the most straightforward route (Scheme 2.9). Meaning, first, cyclometalative C-H

activation, then insertion of the olefin into the Ru-H bond completed by reductive elimination to form the reaction product. The possibility of an imine intermediate was not mentioned and the report did only focus on a ruthenium catalyst.



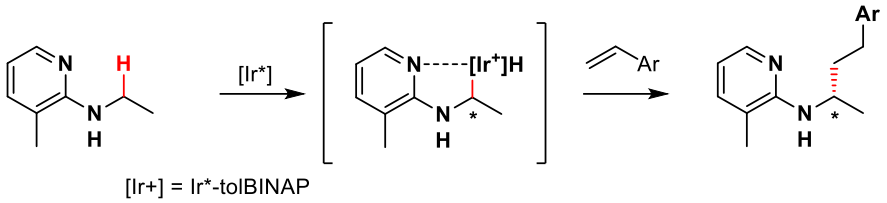
Scheme 2.9: Direct C-H alkylation with olefins on N-Benzyl-3-methyl-2-pyridin-2-amine

And later, in 2011, Shibata and his group was able to make this reaction enantioselective. In that case they used N-ethyl-3-methylpyridin-2-amine as starting material.[28] They were able to use a cationic Ir(I) catalyst and added a chiral ligand to the reaction mixture (e.g. *(S)*-tolBINAP). Scheme 2.10 shows a general setup for this enantioselective reaction.



Scheme 2.10: Reaction scheme for enantioselective C-H alkylation reaction.

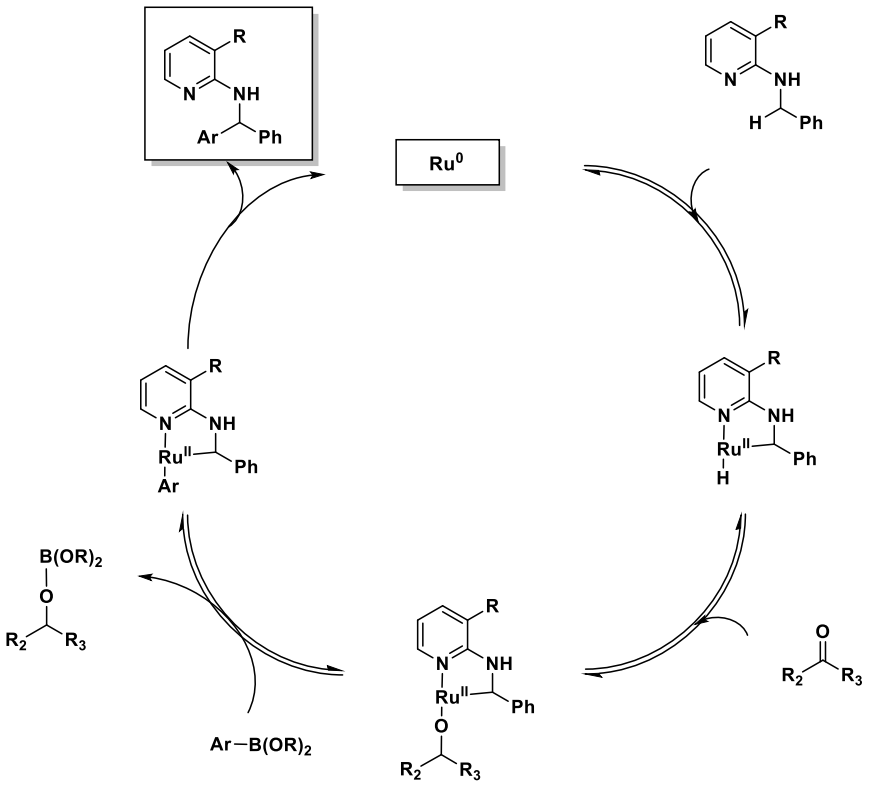
They described good yields with different substituted aryls at the olefin (e.g. around 70 – 80%). But more importantly, they obtained enantiomeric excess (*ee*) up to 90%. The group also performed some preliminary mechanistic studies. With that, they assume, that the cleavage of the secondary C(sp^3)-H bond is an initiation step. This would generate an asymmetric carbon atom. After the alkene is inserted to the cyclometalated intermediate, the reductive elimination step gives the chiral amine as an alkylated product (Scheme 2.11).



Scheme 2.11: Proposed mechanism for this enantioselective C-H alkylation reaction.

2.3.2. Direct Arylation of Benzylic Amines

In 2012, a Ru-catalyzed arylation using boronic acid esters has been reported.[32] The proposed reaction mechanism follows the previously mentioned reaction pathway. Initiated by a cyclometalation C-H activation step, a transmetalation of the aryl boronic acid ester is possible. The final product is then formed by reductive elimination. Moreover, it was found, that the substitution in 3-position of the pyridine directing group has high influence on the reaction and is crucial for good conversions. Computational studies revealed, that the conformation of the molecule is important for the outcome of the reaction. With a substituent in 3-position of the pyridine, the molecules prefers a conformation in which the pyridine nitrogen atom and the benzylic methylene group are aligned favorably for the crucial C-H activation step. The general proposed pathway for this transformation is illustrated in Scheme 2.12.

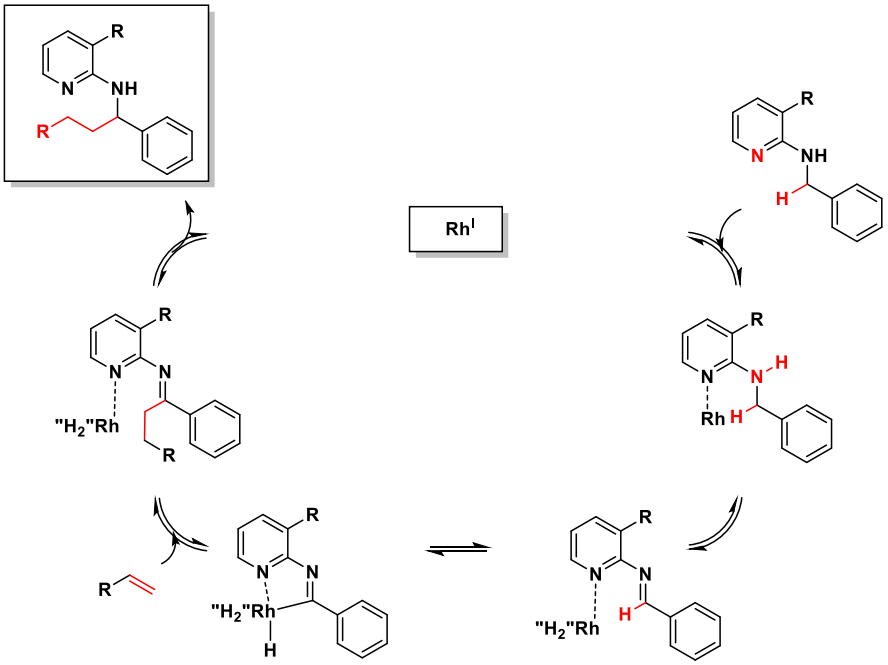


Scheme 2.12: Proposed mechanism for Ru-catalyzed direct C-H arylation of benzylic amines with aryl boronic acid esters.[32]

This reaction could be further improved. Additional studies with this benzylic amines substrates showed that also aryl halides could be used for this type of reaction. In detail, aryl chlorides and bromides were reported to undergo this type of reaction.[31, 33] Furthermore, a rather important step in understanding the reaction mechanism has been achieved at the time. The corresponding imines of both substrate and product could be isolated as byproducts. It was considered, that the reaction pathway might lead in some extend through an intermediary imine. Since this was only a hypothesis at that time, the general straightforward mechanistic approach was published.

2.4. Direct Alkylation of Benzylic Amines in our Group

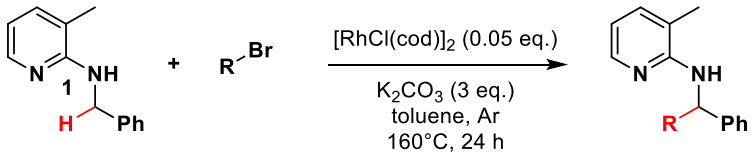
With the knowledge our group already gained on direct C-H arylation reactions of benzylic amines, we set our focus on alkylation reactions. In 2014, a Rh(I)-catalyzed alkylation protocol was reported.[29] Using alkyl halides and later also olefins as alkyl source. Furthermore, ongoing kinetic and mechanistic investigations showed that the reaction did not proceed directly over the amines, but instead over the corresponding imines. This proved, that the formal C(sp^3)-H activation reactions did indeed proceed over and C(sp^2)-H transformation pathway. This led directly to a new mechanistic proposal for the direct C-H alkylation reactions of benzylic amines (Scheme 2.11).



Scheme 2.11: Direct alkylation reaction of benzylic amines. New mechanistic proposal reveals the reaction proceeds over the corresponding imines.

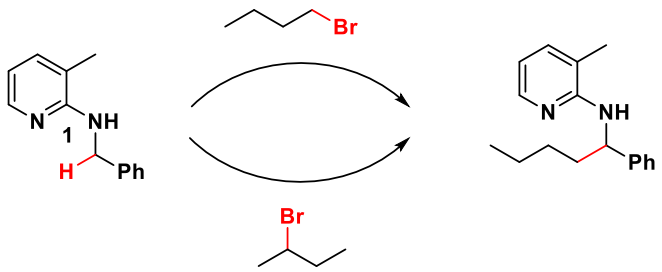
The catalytic cycle starts with precoordination of the benzylic amine to the rhodium species. After a reversible transformation to the corresponding imine complex, a cyclometalation step occurs. Then, alkylation of this cyclometalated imine intermediate complex by an olefin and reductive elimination leads to the product formation and reactivation of the catalytic active species.

For the development of direct alkylation reactions, our group focused mainly on rhodium(I)-catalyzed C-H activation reactions. First, the possibility of using alkyl halides as alkylating agents was considered. Intensive screenings revealed the optimized conditions shown in Scheme 2.12.



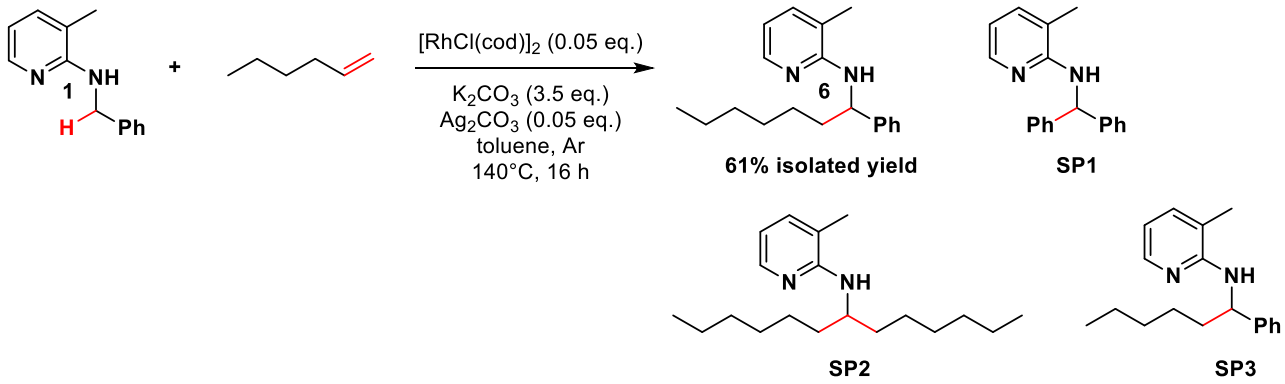
Scheme 2.12: Optimized reaction conditions for a direct C-H alkylation approach using alkyl halides.

The optimized reaction led to 20-50% product, in respect to the used alkyl halide. At the time, the overall synthetic plan also included using secondary alkyl bromides for this reaction. And interestingly enough, both primary and secondary alkyl bromides gave rise to the same product. Instead of forming the new C-C bond to the internal carbon, again the terminal position reacted (Scheme 2.13).



Scheme 2.13: Alkylation reactions using primary and secondary alkyl bromides led to the same product.

These findings led to the hypothesis that the olefin has to be an intermediate in this reaction, since β-H eliminations are not uncommon in transition metal alkyl complexes.[34, 35] In that case, using directly the olefin instead of generating it *in-situ* by elimination of an alkyl halide should be beneficial for the reaction. And moreover, benefits of using an olefin instead of an alkyl halide have been mentioned previously in this work (see Chapter 2.2). So further studies and optimization were focused on using olefins. Soon after, optimized conditions using olefins in this direct alkylation reactions were identified (Scheme 2.14). Noteworthy, the yield of the desired product plateaued at around 60% due to the formation of a series of side products (SP). Several studies towards the formation of these side products have been carried out already.



Scheme 2.14: Optimized reaction conditions for direct alkylation reaction using olefins. Also, showing the typical side products that are formed.

The first major improvement in the reaction rate for this reaction was adding Ag_2CO_3 (0.05 equiv.). Further improvements focused on 2 main goals: Decreasing the reaction temperature and at the same time decreasing the amount of side products and with that the overall selectivity. It was the addition of Et_3N that showed positive results on both goals. The reaction temperature could be reduced to 140°C and the formation of side products, especially SP3 could be significantly reduced. However, when Et_3N was available in the reaction mixture, a new byproduct was formed (Figure 2.1).

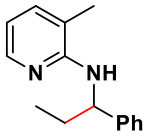
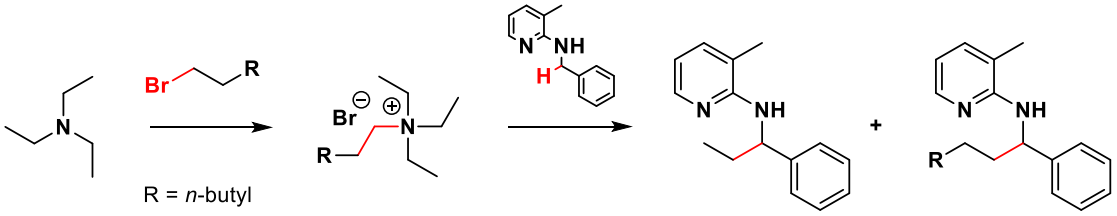


Figure 2.1: The ethylated side product was formed once Et3N was added to the reaction mixture.

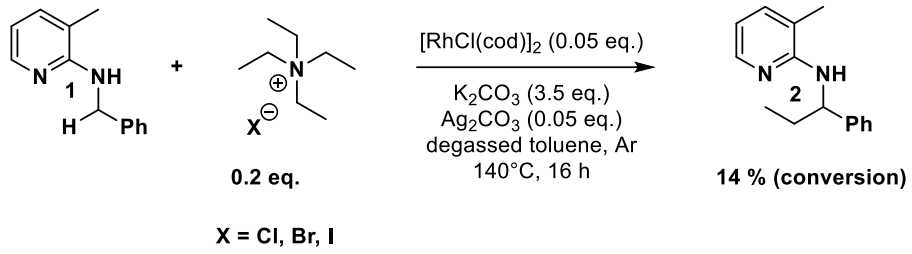
Somehow, when Et_3N is available, ethylene has to be generated in the reaction mixture. Which can then undergo the direct C-H alkylation transformation leading to the ethylated side product instead of the desired hexylated one. A theory was crafted, which hypothesized that to some extent, a quaternary ammonium salt has to be generated *in-situ.* This could further undergo a Hofmann elimination towards ethylene, giving rise to the alkylation side product with an ethyl group (Scheme 2.15).



Scheme 2.15: Proposed reaction scheme for generating triethylhexylammonium bromide in the reaction mixture and generating both ethylene and 1-hexene upon Hofmann elimination. Both ethylated and hexylated product are expected.

2.5. Motivation for this Thesis

The aforementioned knowledge built the basis for this thesis. Investigations into the side products (Scheme 2.14 and Figure 2.1) became the starting point for further experiments. The hypothesis of generating an olefin *in-situ* from the corresponding quaternary ammonium salt by Hofmann elimination became a very promising theory. Additional experiments revealed, that it is possible to convert some substrate to the desired C-H alkylated product going towards the route of the Hofmann elimination, already when using only small amounts (0.2 eq.) of quaternary ammonium salts (Scheme 2.16).



Scheme 2.16: First experiments to show that C-H alkylation reactions are possible using quaternary ammonium salts as alkyl source und optimized reaction conditions for reactions using olefins.

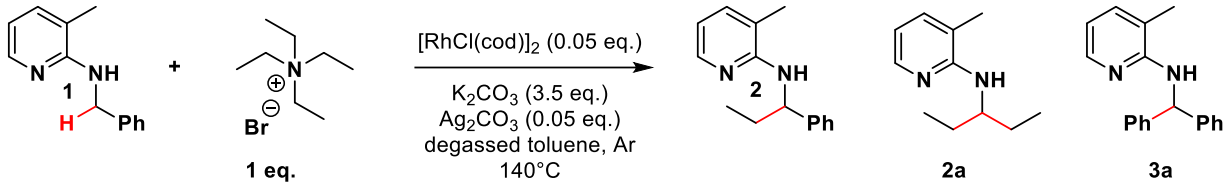
In earlier chapters, only benefits very mentioned when using olefins instead of e.g. alkyl halides (see Chapter 2.2). But also olefins have drawbacks, especially when using short chained olefins like ethylene, propylene or butylene. These molecules are gaseous at room temperature and are highly flammable, therefore they have to be used with caution. Thus, they are not desired in the organic lab. When substituting these short chained olefins with the corresponding quaternary ammonium salts, these drawbacks disappear. These salts are stable solids at room temperature, not particular dangerous or hazardous. Therefore easy to handle in the lab. Hence, establishing quaternary ammonium salts as alternative alkylating agents was the ultimate goal of this thesis.

3. Results and Discussion

3.1. Direct C-H Alkylation of Benzylic Amines Exploiting Tetraalkylammonium Salts as Alkyl Source

3.1.1. First Results

With optimized reaction conditions in hand for a direct alkylation approach on benzylic amines using olefins, these conditions were applied on first experiments exploiting tetraethyl ammonium bromide as alkyl source (Scheme 3.1). These experiments showed, that the reaction indeed delivers the ethylated product accompanied by the same type of byproducts mentioned previously (Chapter 2.4; Scheme 2.14). The reaction was followed by taking samples and analyzing them with GC (Figure 3.1).



Scheme 3.2: First experiments using tetraethyl ammonium bromide as alkyl source with optimized reaction conditions for direct alkylation protocol using olefins. Analyzed with GC and GC/MS

The experiment gave a lot of insight. First the reaction seem to work as intended, similarly to using olefins. About 80% product and 90% consumption of starting material could be detected by calibrated GC-analysis. This is an outstanding finding, since it shows that olefins can be substituted for quaternary ammonium salts, seemingly without any further optimization. It has to be mentioned that the reaction was quite slow, since reactions using olefins (e.g. 1-hexene) were finished after 3 h already. After 28 h the reaction stopped and did not further react with remaining substrate. It seemed as it might come to some sort of an equilibrium between product, starting material and byproducts.

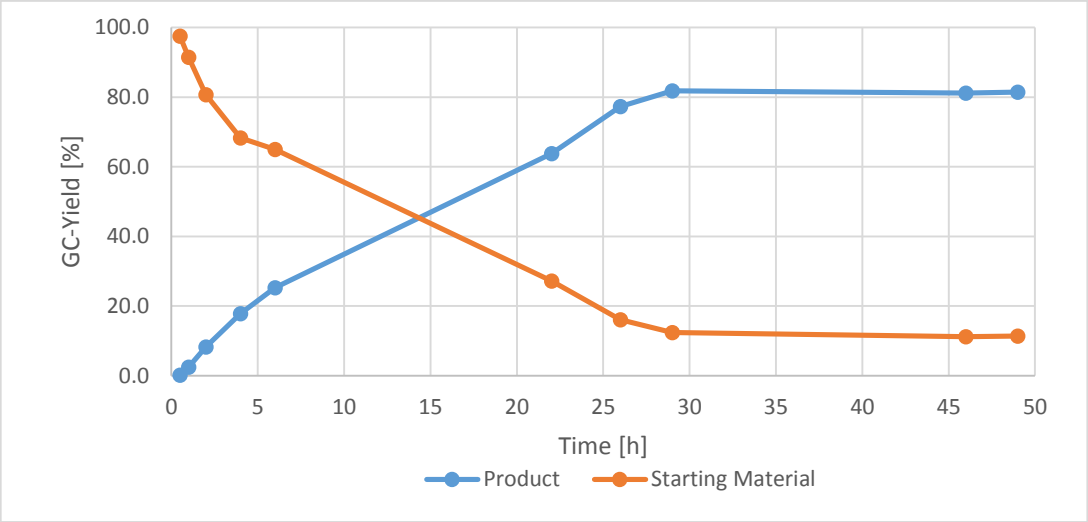


Figure 3.1: Time screening using tetraethyl ammonium bromide as alkyl source. Analyzed with GC and GC/MS

The next step was to investigate using longer chained quaternary ammonium salts (Table 3.1). A series was started testing tetraalkylammonium salts up to C8. Moreover, to prove the Hofmann elimination and with that the reaction pathway *via* olefin, tetramethylammonium chloride was tested, since there is no possibility for generating an olefin.

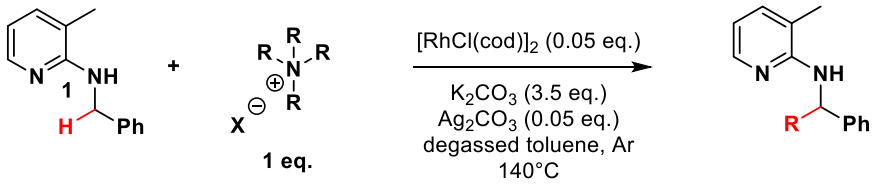


Table 3.1: A variation of longer chained alkylation reactions using tetraalkylammonium salts as alkylating reagents was tested.

Entry	R	Conversion to Product [%][a]	Consumption of 1 [%][a]
1	methyl	7.9[b]	17.5
2	ethyl	79.0	89.2
3	propyl	3.3[b]	12.7
4	butyl	3.3	14.9
5	pentyl	11.7[c]	21.2
6	hexyl	3.1[c]	15.1
7	octyl	7.2[c]	27.0

[a] Determined by GC-analysis.

[b,c] The conversion is determined relative to dodecane as internal standard assuming the compound has the same conversion factor as the ethylated[b] or butylated[c] product, which have been calibrated.

The obtained results were quite unexpected. First of all, the enormous downfall in conversion and consumption by adding one carbon atom from ethyl to propyl was very puzzling (cf. Table 3.1, Entries 2 and 3). It seemed, that the reaction was nearly inhibited by prolonging the alkyl chain with 1 carbon atom. Furthermore, adding more carbon atoms up to chains with 8 carbon atoms seemed to not have any further effect on the reaction outcome (cf. Table 3.1, Entries 2 -7). Moreover, experiments using tetramethylammonium chloride led to the most unexpected result. The reagent that has no possibility of forming an olefin still managed to show at least some conversion to the methylated product (Table 3.1, Entry 1). A hypothesis at this time is, that under the harsh reaction conditions, a Rh-carbene species can be formed which is able to act as a nucleophile.[36-39] Further investigations have to be conducted to either prove or disprove this theory. The topic was put aside, since this was not the direction this thesis had intended to go.

Thinking about where the problem of this reaction with longer chains might be, a paper was found where calculated Gibbs free energy values for the Hofmann anti-elimination step have been reported.[40] This gave insight in the elimination step of tetraalkylammonium salts. And in fact, the Gibbs free energy increases significantly when adding one carbon atom from tetraethyl- to tetrapropylammonium salts. In fact the energy increases from around 17.5 kcal/mol for tetraethyl- to nearly 24 kcal/mol for tetrapropylammonium salts. This correlates to a 37% increase in needed energy per mol for the elimination step. But interestingly, adding more carbon atoms, prolonging the chains, does not further increase the required energy for an elimination significantly. This led to the hypothesis that it is indeed the Hofmann elimination step which is rate limiting at this point and hence, further optimization needs to address this issue.

3.1.2. Reaction Optimization

Thinking about what could improve the elimination to the olefin, brought us to the following optimization steps (cf. Table 3.2). Since we already achieved good conversion using tetraethylammonium bromide as alkylating agent, further optimization was carried out using the tetrabutylammonium chloride as alkyl source.

The first step was increasing the reaction temperature from 140 °C to 160 °C. However this showed no impact on conversion (Entry 1). Since the base has a big influence in Hofmann elimination reactions,[41, 42] different bases were tested in our reaction protocol. Switching from K_2CO_3 to potassium tert-butoxide showed the first beneficial impact on the conversion, increasing the amount of detected product from 4% to 24% (Entry 2). On the other hand, using NaH was counterproductive, since in this case only traces of product were detected (Entry 3). According to literature,[42] hydroxide ions can have a rather large influence on Hofmann elimination reactions. So we tried NaOH, arguably the most common base in chemistry. We gained further improvement to 56% (Entry 4), which was even further surpassed by using KOH instead (Entry 5, 72%).

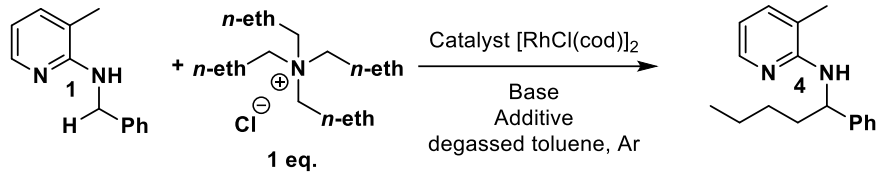


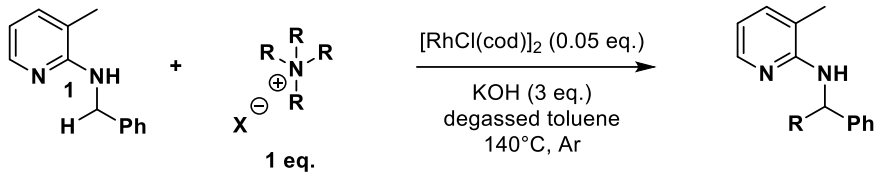
Table 3.2: Selected reaction optimization steps to accelerate the Hofmann elimination step and overall improve the conversion.

Entry	Base	Additives	Catalyst (mol%)	Temperature [°C][a]	Time [h]	Conversion to 4 [%][b]
1	K_2CO_3 (3.5 eq.)	Ag_2CO_3 (5 mol%)	5	160	28	4
2	C_4H_9KO (3.5 eq.)	Ag_2CO_3 (5 mol%)	5	140	28	24
3	NaH (3.5 eq.)	Ag_2CO_3 (5 mol%)	5	140	28	traces
4	NaOH (3.5 eq.)	Ag_2CO_3 (5 mol%)	5	140	28	56
5	KOH (3.5 eq.)	Ag_2CO_3 (5 mol%)	5	140	28	72
6	KOH (3.5 eq.)	-	5	140	28	71
7	KOH (0.5 eq.)	-	5	140	3	11
8	KOH (1 eq.)	-	5	140	3	14
9	KOH (2 eq.)	-	5	140	3	42
10	KOH (3 eq.)	-	5	140	3	72
11	KOH (3 eq.)	-	5	160	3	70
12	KOH (3 eq.)	TBA Cl (2 eq.)	5	140	3	71
13	KOH (3 eq.)	TBA Cl (1 eq.) added after 3 h	5	140	6	70
14	KOH (3 eq.)	-	5 + 5 after 3 h	140	6	73
15	KOH (3 eq.)	-	7,5	140	3	71
16	KOH (3 eq.)	-	10	140	3	72

[a] Reaction block temperatures and not inside temperatures of the reaction mixtures. [b] Determined by GC-analysis. [c,d] The conversion is determined relative to dodecane as internal standard assuming the compound has the same response factor as the ethylated[c] or butylated[d] product, which have been calibrated.

Since the peculiar combination of additives (Ag_2CO_3, K_2CO_3) was derived from a protocol using alkyl halides as alkyl source, it was tested whether these compounds were required in the present protocol. Indeed, it turned out that the addition of Ag_2CO_3 is obsolete (Entry 6), giving basically the same yield in its absence. Next, it was tested whether the reaction really requires 3.5 equiv. of KOH and whether the reaction time could be reduced. Using 0.5 equiv. KOH, only low conversion was observed in 3 hours (Entry 7). Keeping the reaction time constant, the amount of KOH was gradually increased and at 3.0 equiv. the same conversion as before (Entry 5) was obtained, but now within a much shorter reaction time (Entry 10). Noteworthy, 3 hours is also the reaction time needed for the direct C-H alkylation approach using olefins directly, with respect to this substrate.[29] Additional reaction optimization tried to push the conversion

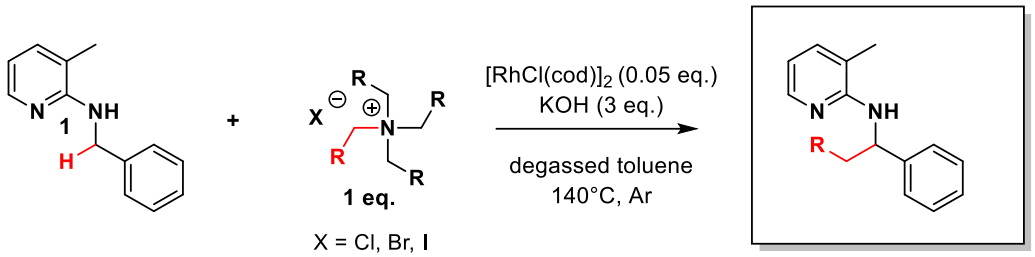
to 100% or generally increase the substrate consumption. However, all further experiments failed on that regard. Adding more tetrabutylammonium chloride from start (2 equiv., Entry 12), or adding a second portion after 3 hours of reaction time (Entry 13), had no beneficial impact. Also, increasing the catalyst loading, or adding new catalyst after 3 hours reaction time resulted in the same conversion (Entries 14-16). Thus, the hypothesis that there is an equilibrium between product, substrate and byproducts seems to be justified.
The optimal reaction conditions found are summarized in Scheme 3.4. These conditions were, if not otherwise noted, used in all further experiments conducted in this thesis.



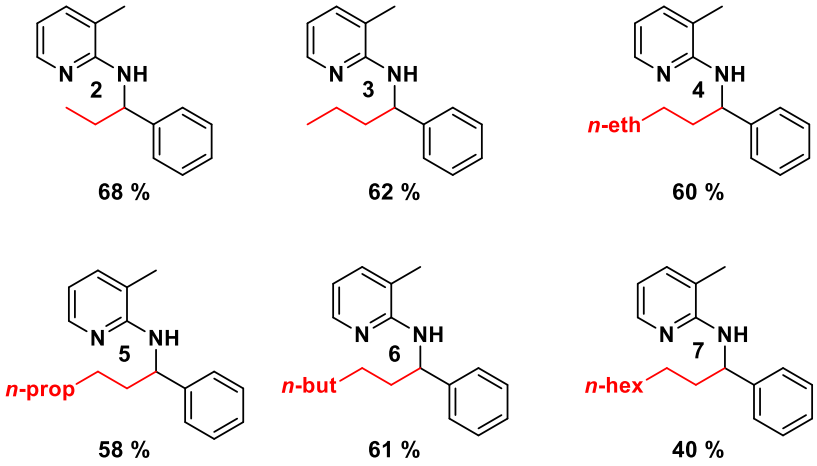
Scheme 3.3: Optimized reaction conditions for direct C-H alkylation reaction using tetraalkyl ammonium salts as alkylating agents.

3.1.3. Substrate Scope – Tetraalkylammonium Salts

With the optimized protocol in hand, next we wanted to show the scope of this reaction. First the goal was to isolate a variation of different compounds with alkyl chains of different length. We decided to use longer chains up to C8 (Scheme 3.5). All reactions worked according to the standard protocol.



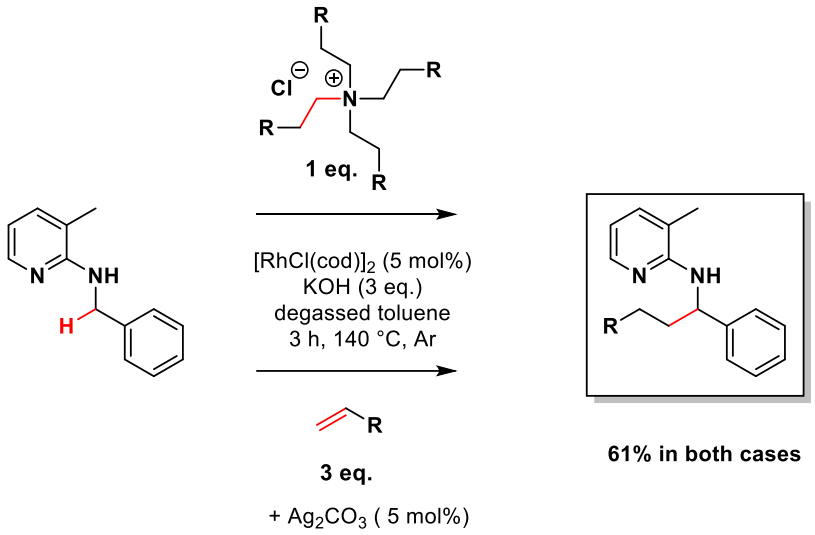
Scheme 3.4: Reaction scheme for isolating a scope of different compounds using the optimized direct C-H alkylation protocol exploiting a variation of chains at the tetraalkylammonium salts.



Using tetraethylammonium bromide in order to ethylate substrate **1** showed best results towards the desired product **2**. However also longer chained ammonium salts worked with good yields up to the hexylated product (**3-6**). Since with longer chained ammonium salts get sterically more hindered, a decrease in conversion and yield could have been expected with increasing chain length. However, a significant drop in yield was only observed when applying our reaction protocol for a C8 alkylation, exploiting tetraoctylammonium bromide as alkyl source. In this case, the reaction did not proceed as smooth as when using shorter chained salts. Meaning, the reaction slowed down, and had to be heated over 3 days in order to gain 40 % isolated yield. There are 2 hypotheses when thinking about this octylation protocol. First, it might very well be, that the steric hindrance between substrate **1** and olefin, which obviously has to be generated *in-situ* for this alkylation protocol, starts to become a relevant factor and

prevents a better conversion. Another theory could be that the properties of tetraoctylammonium bromide become more ionic liquid like.[43] Meaning that this salt may very well be much more stable to Hofmann elimination, than shorter chained salts. Nevertheless, **7** could be isolated with reasonable yields of 40%.

Furthermore, it had to be proved, that using solid quaternary ammonium salts has no large downside as opposed to using the olefin directly. For that case, we compared using tetrahexylammonium chloride with using 1-hexene in the reaction mixture (Scheme 3.6).



Scheme 3.6: Comparing both alkylating reagents in our optimized C-H alkylation reactions. No difference in reaction time, temperature or isolated yield.

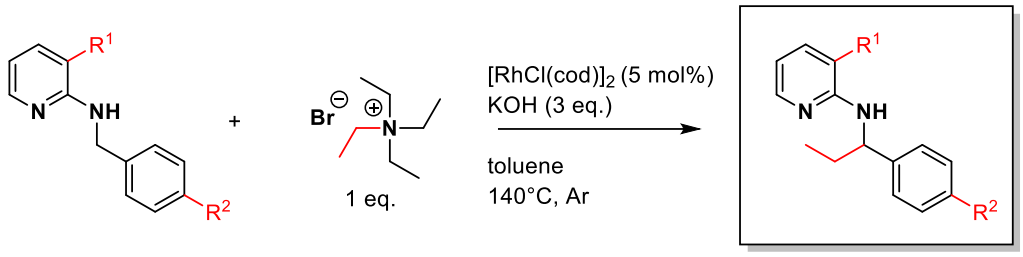
As aforementioned, we already optimized the reaction conditions up to the point, that both reactions are finished after 3 hours. But also the reaction outcome is obviously very important. We could prove, that substituting 1-hexene with the corresponding tetrahexylammonium chloride resulted in the same amount of isolated product in comparison to use 1-hexene directly. The only difference besides the alkylating reagent is Ag_2CO_3, which has to be added when using the olefin directly. Besides that, both reactions led to 61% isolated yield. Reaction temperature and time was the very same. So we could prove, that using the corresponding tetraalkylammonium salt has no major drawback to using the olefin directly. However, no additives (Ag_2CO_3) are needed in the reaction with quaternary ammonium salts, and furthermore, we can use solid starting reagents.

3.1.4. Substrate scope – Benzylic Amines

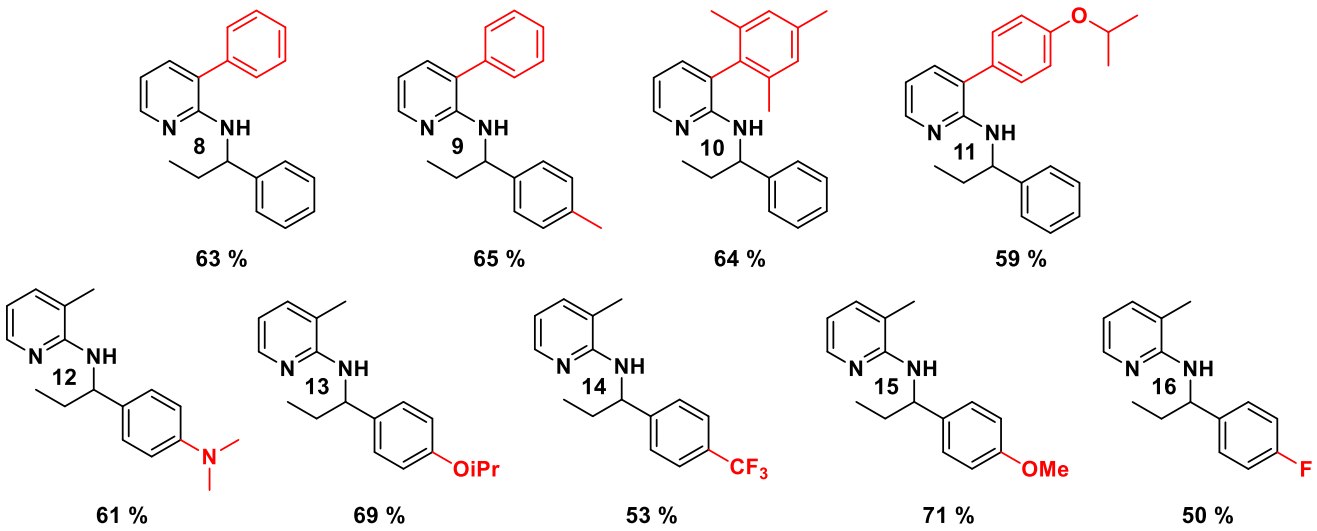
Next, different substrates were tested in order to extend the scope of this reaction protocol further. First, it was tested whether substituents other than methyl are tolerated in position 3 of the pyridine directing group. We decided to use tetraethylammonium bromide as alkylating agent, because substituting ethylene by a solid reagent is most attractive and additionally, the ethylation showed best conversions at substrate **1** before (see Scheme 3.5). It was found that bulkier substituents at position 3 of pyridine had only a neglible influence on the yield (Scheme 3.7, **8-11**). Even the mesitylen group did not diminish the isolated yield significantly (**10**).

Furthermore, the electronic influence of different substituents at the benzylic para position (**12-16**) was investigated. In our previously disclosed arylation protocols, it was found that electron withdrawing substituents led to decreased yields in case of para substituted phenyl bromides as aryl source. When using 4-fluoro substituted phenyl bromide the yield decreased to 55% from 69% when using bromobenzene directly as aryl source. When applying the strongly electron withdrawing nitro group in para position, no product formation was observed.
However electron donating groups had no, or little influence on the reaction outcome. A weakly electron donating methyl group in para-position still gave 65% yield. But moreover, also a rather strong electron donating methoxy group gave 63% yield, only decreasing the overall outcome of the reaction by 6%.

We expected a similar trend in our alkylation protocol. In case of the alkylation, electron-donating groups at this position seemed to be even beneficial for the conversion under these conditions (**13, 16**). On the other hand electron-withdrawing substituents gave slightly lower yields. However, the effect was not dramatic at all and comparable to the findings in our arylation protocol.



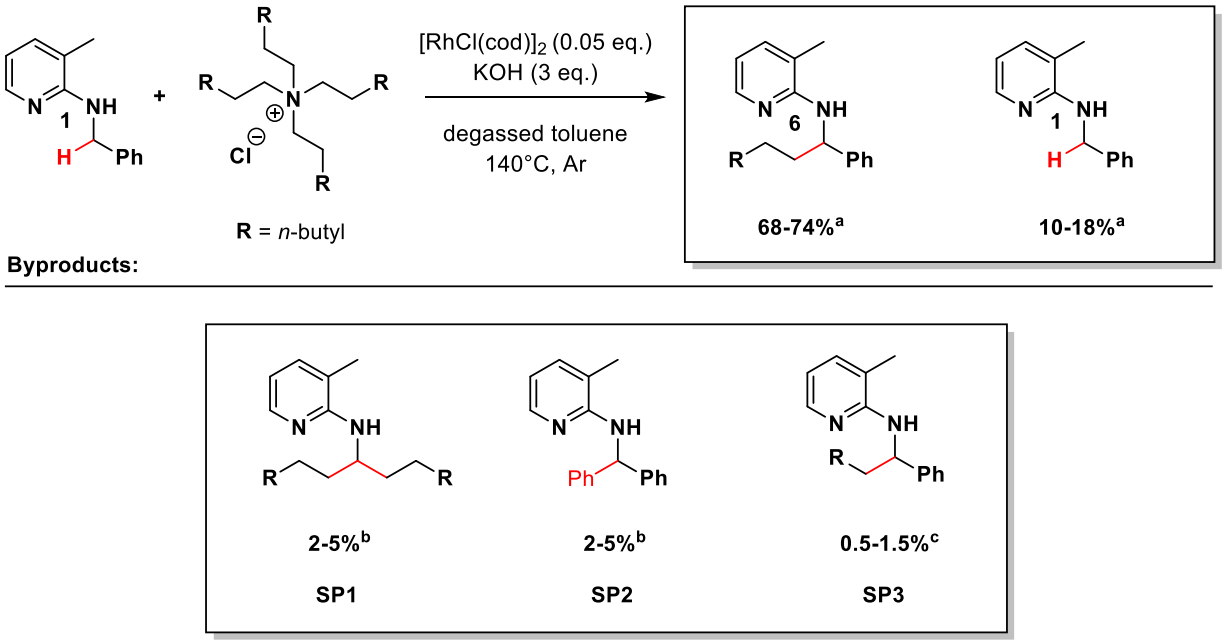
Scheme 3.7: Substrate scope in respect to the amine.



Overall this substrate scope shows the broad applicability of the optimized reaction conditions. A variety of different benzylic amines has been successfully alkylated selectively at the desired C-H bond.

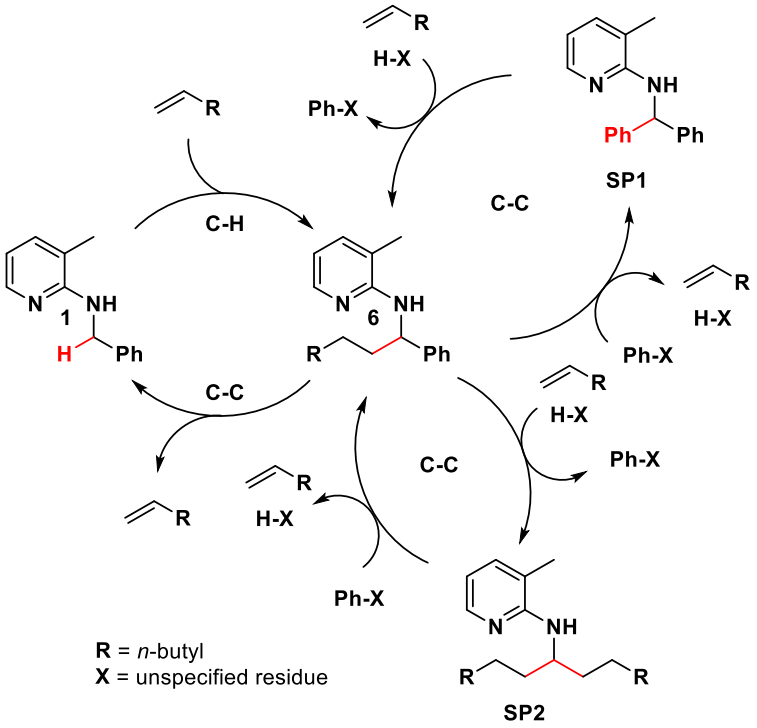
3.1.5. Byproducts Studies

As already mentioned in earlier chapters, byproducts are a common thing in this kind of C-H alkylation reaction (see Chapter 2.4 – Scheme 2.11). Using the olefin directly, byproduct studies have already been conducted in previous work of our group.[36] Also when using quaternary ammonium salts as alkyl source, the same byproducts are generated. When optimizing the reaction conditions, in every experiment the same byproducts could be observed (Scheme 3.8).



Scheme 3.8: Byproducts that are generated in every experiment using quaternary ammonium salts as alkyl source under the optimized reaction conditions. aYields determined by GC-Analysis. b The conversion is determined relative to dodecane as internal standard assuming a conversion factor of 1. cThe conversion is determined relative to dodecane as internal standard assuming the compound has the same response factor as the ethylated product.

At the stage of intensively screening for the optimal reaction conditions, some interesting observations could be made. First of all, the reaction could never be optimized towards 100% conversion, or at least 100% consumption of the starting material. At some point, the reaction simply seemed to stop. Any additional efforts in time and heating, did not further impact the reaction outcome. Furthermore, under the optimized reaction conditions, the same 3 byproducts could be observed, respectively. In case of the hexylation protocol the 3 byproducts are illustrated in Scheme 3.8. The dihexylated **SP1** and diarylated **SP2** benzylic amines are generated and, interestingly enough, the pentylated product **SP3** is observed as well. And with all other tested chain lengths, the corresponding byproducts appear (e.g. for pentylation, the butylated compound is the byproduct). This leads to the thoughts, that under these harsh reaction conditions the catalyst has to be very reactive. The catalytic active species must be able to cut C-C bonds to some extent, in order to generate these byproducts.
And moreover, as already mentioned previously, the fact that the reaction just simply seems to stop always around the same amount of product, starting material and byproducts led to think that there must be some sort of an equilibrium adjusted. Our group propose a reaction scheme that could then look more like Scheme 3.9.[29]



Scheme 3.9: Equilibrium reaction scheme. Formation and interconversion of 1 and reaction products 2, SP1 and SP2 in the direct C-H alkylation reaction. (C-H = C-H activation, C-C = C-C activation).

Substrate **1** gets alkylated in a C-H activation mechanism with the olefin present in the reaction mixture. But at the very harsh reaction conditions, the catalyst is able to not only react with substrate **1**, but also able to attack the generated product **6**, to some extent at least. Then, in a C-C activation reaction, either the starting material **1** or a side product (**SP1** or **SP2**) is generated.

This leaves us with what looks like an equilibrium between starting material **1**, product **6** and byproducts. This would explain, that every reaction stops at nearly the same ratio between compounds **1, 6, SP1** and **SP2**.

3.2. Different Quaternary Ammonium Salts

With the positive results of the developed C-H alkylation reaction using tetraalkylammonium salts in mind, a variation of different quaternary ammonium salts was tested in the reaction protocol (Figure 3.2). We synthesized 6 rather different quaternary ammonium salts, which properties tend to go in the direction of ionic liquids.

The goal and thought process behind these experiments was to specifically attach one desired alkyl chain to a common available feed stock chemical, which could then selectively C-H alkylate the desired substrate. For example in later stages of a multi-step synthesis, one does not want to generate a tetraalkylammonium salt of a very complex olefin, because obviously 4 equivalents of the desired alkyl chain would be needed and only one could be used for alkylation.

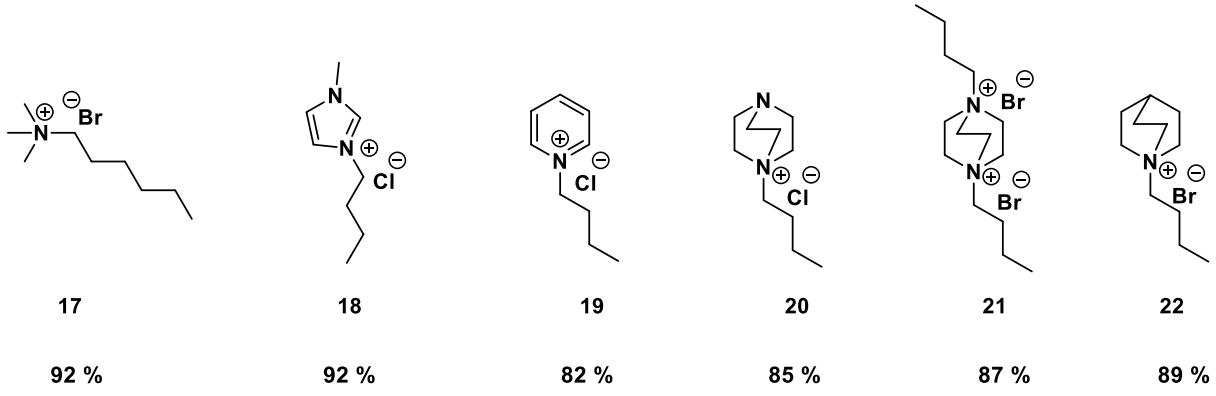


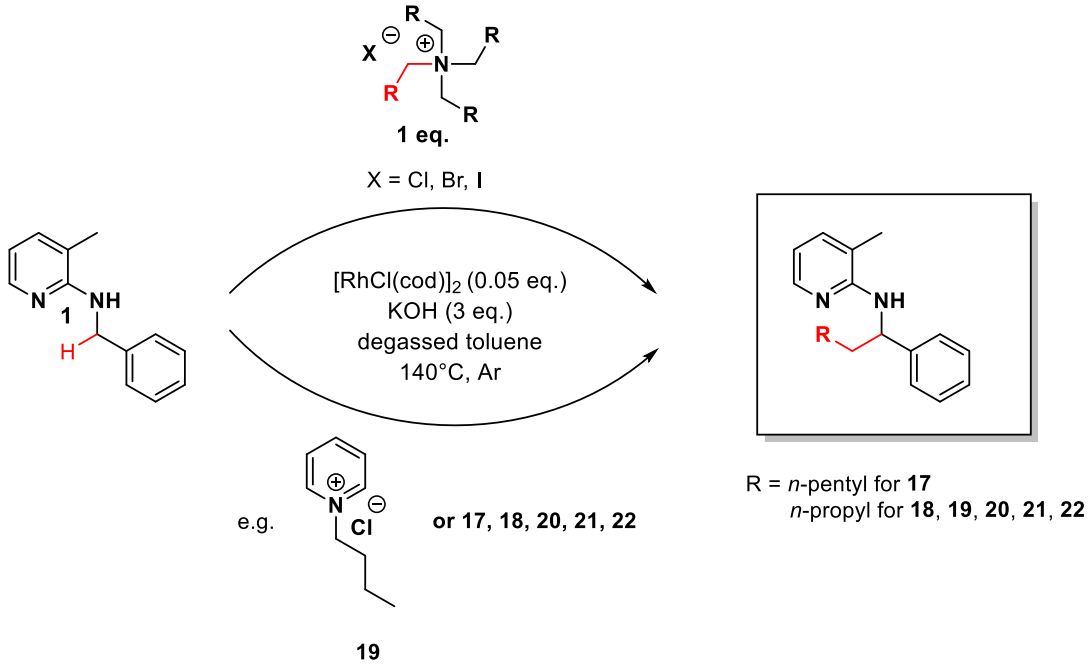
Figure 3.2: A variation of different quaternary ammonium salts was synthesized to test the found C-H alkylation protocol.

We choose to attach a hexyl chain to trimethylamine in order to generate 1-hexene upon elimination (**17**), since methyl elimination was considered to be impossible. Furthermore, we attached a butyl chain to 1-methylimidazole (**18**), pyridine (**19**), DABCO (**20**) and chinuclidine (**22**). Also, we managed to successfully attach 2 butyl chains to DABCO (**21**). In all these cases, 1-butene elimination should be the massively favored process over any other side reaction. With those ammonium salts in hand, we tried to butylate our standard substrate **1** (Scheme 3.10).

When we used trimethylhexylammonium bromide **17** in our optimized C-H alkylation reaction we detected only 8 % hexylated product, but interestingly enough, 12 % methylated byproduct. We then performed an experiment, to see if 1-hexene is generated in the reaction mixture when using salt **17**. After heating up compound **17** with KOH in d_8-toluene to 140 °C for 1 hour, we could detect generated 1-hexene in the reaction mixture by NMR. Since we already know that rhodium is able to form carbene species [36-39], we hypothesize, that if some carbene is formed, this species might react irreversible with our catalyst, and thus inhibit his catalytic capability.

However, none of the other aforementioned quaternary ammonium salts (**18-22**) worked under the optimized reaction conditions with tetraalkylammonium salts. This was definitely not expected. We anticipated, that at least some of these salts should be able to successfully alkylate the substrate in this reaction protocol.

We synthesized the imidazole and pyridine salts (**18**, **19**), because at least in our minds they seemed to be the most likely to work. When they failed the reaction, we decided to try DABCO salts (**20**, **21**), thinking that maybe the aromatic system in **18** and **19** made the salts too stable or somehow interfered with the elimination step. Thus, when both the single and double alkylated DABCO failed, we decided to give the butylated chinuclidine salt (**22**) a last try. However also this salt did not do the trick.



Scheme 3.10: General reaction scheme for substituting tetraalkylammonium salts in our working protocol with different quaternary ammonium salts.

It might be, that these salts already go too far in the direction of ionic liquids, which are known to be very stable. Especially to elimination processes. So perhaps, these salts are also at the reaction conditions too stable to undergo Hofmann elimination to a significant extent. Moreover we observed, that these salts are quite insoluble in toluene, also at 140 °C. In either case, no or surely not enough olefin could be produced in the reaction mixture. Obviously, since there is no alkyl source in the reaction mixture then, an alkylation process is impossible. Another theory was, that the elimination products of the salts are good ligands for our catalytic active species. Resulting in forming a permanent bond with the catalyst and thus inhibit its power to perform the C-H alkylation reaction.

However, since all these aforementioned other quaternary ammonium salts failed to deliver any results, we put this chapter aside. This study was conducted for the sake of knowledge

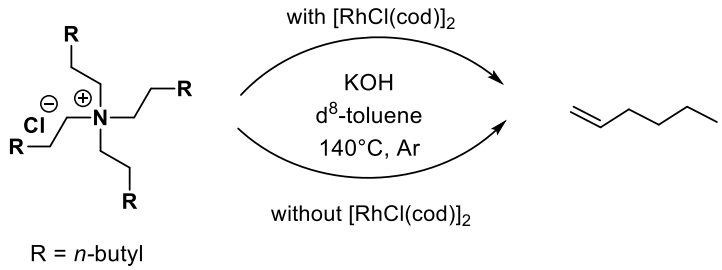
and would have been a good asset to this thesis. But when this set of experiments failed with no outlook of positive results, we decided to focus on the main part of the thesis. Further investigations into why the reaction did not deliver considerable amounts of product would have to be conducted in order to optimize it. Also aforementioned statements about the failure of the reaction would have to be proved (or disproved) in order to gain more insight and thus know which part of the reaction has to be optimized.

3.3. Additional Studies

This chapter summarizes all the additional studies that were performed during the time of the thesis. Mainly these investigations were conducted along the way to gain more insight over the reaction and its mechanism. More knowledge over a certain reaction mechanism means easier and more efficient optimization. With that in mind, we tried to learn as much as possible for every step of the reaction. Leading us to a better understanding and easier reaction optimization for this, and similar projects, in the future.

3.3.1. Hofmann Elimination of Tetraalkylammonium Salts under the Optimized Reaction Conditions

Since the first results were obtained (see Chapter 3.1.1) it was quite clear that the Hofmann elimination step plays a crucial role in this reaction. Reaction optimization focused mainly on accelerating the elimination step in order to generate more olefin in the reaction mixture. To gain more insight over the elimination step at the reaction conditions, several experiments were performed. At first we checked if the Hofmann elimination step is benefitting from the very reactive catalyst $[RhCl(cod)]_2$ to some extent. Therefore we set up 2 reactions without adding substrate to it. One of them with $[RhCl(cod)_2$, the other without – both otherwise with unchanged reaction conditions (Scheme 3.11).



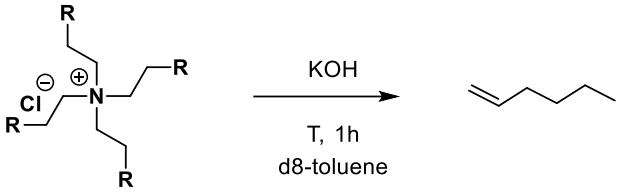
Scheme 3.11: Reaction scheme in order to check if the Hofmann elimination is benefitting from catalyst [RhCl(cod)]2

Analyzing both reactions with NMR revealed, that in both cases similar amount of 1-hexene is produced in the reaction mixture. Therefore it is safe to say, that the Hofmann elimination does not benefit from the presence of catalyst.

Further investigations focused on the reaction temperature. Since experiments showed that no catalyst is needed, it was interesting to know which temperature is needed for an efficient elimination step. Therefore, experiments with different temperature were set up (Figure 3.3). Tetrahexylammonium chloride was stirred with KOH in d_8-toluene for 1 hour at room temperature. After ^{1}H-NMR was measured, the mixture transferred back into a 8 ml glass vial

and stirred at 40 °C for 1 h. We proceeded this experiments up to 140 °C, the reaction temperature of our alkylation protocol. We quantified the results by comparing the NMR signals of generated 1-hexene to the remaining tetrahexylammonium salt.

We could prove, that at r.t. only traces of 1-hexene is available in the reaction mixture. The salt is stable at r.t. also in presence of KOH. When increasing the temperature to the 40 °C, already about 2% of 1-hexene is present. The tendency keeps up, at 60 °C already 5-6% of the olefin is generated. When increasing the temperature from 60 to 80 °C, we could detect a significant increase of 1-hexene in reaction mixture. The next temperature we tested was 140 °C, the reaction temperature for our alkylation protocol. But at 140 °C we detected the same amount of 1-hexene as compared to 80 °C.



R = *n*-butyl

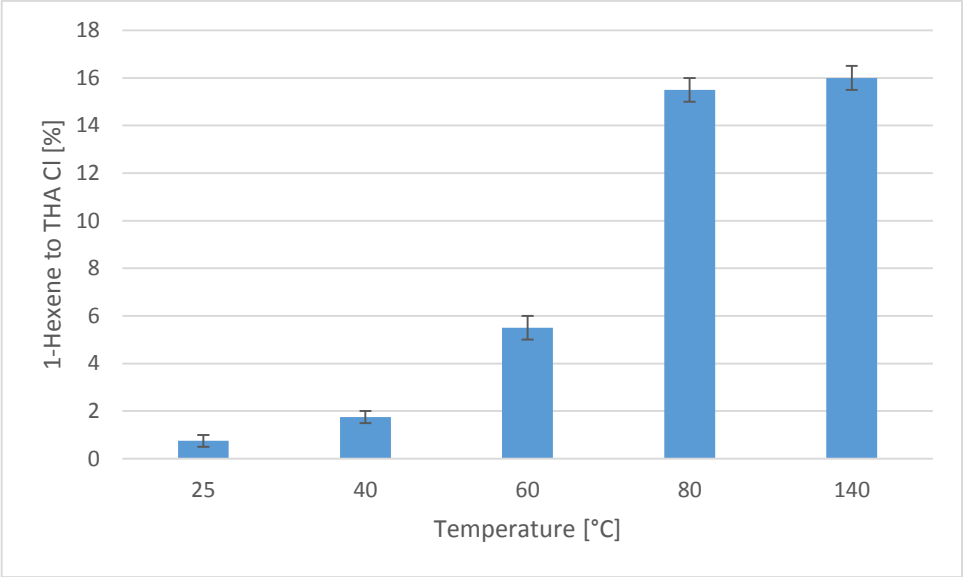


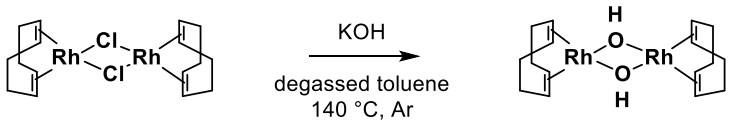
Figure 3.3: Simulating the Hofmann elimination step at reaction conditions without catalyst. Percentage values are determined via NMR by comparing integrals of generated 1-hexene to tetrahexylammonium chloride peaks.

This experiments revealed, that at least 80 °C are required for optimal results in the Hofmann elimination step at the reaction conditions, with respect to eliminating 1-hexene. This knowledge has influence on further projects. In theory it should be possible to substitute any olefin in a direct C-H alkylation reaction with the corresponding tetraalkylammonium salt, as long as the temperature is at 80 °C or higher, naturally, as long as the catalytic system and substrate tolerates the presence of KOH, which is the crucial reagent for the elimination step.

3.3.2. Catalytic Active Species

As mentioned already, catalysts play an enormous role in C-H activation chemistry. In order to understand these reactions, it is important to gain insight into the mechanism. However, gaining this knowledge proved to be not simple at all. Transition metal catalysts are very reactive, and often soluble in the solvent used in the reaction. Ligands that are bound to the catalyst when weighting it into the reaction flask, may never be bound again once the reaction started. In most cases, it is hard to find the correct catalytic active species. The most effective way would be to crystallize this species directly out of the reaction mixture, but this is very time consuming and often times bond to luck.

In fact, along the way of this thesis, several attempts to crystallize the catalytically active species (or any species formed in course of the reaction) were committed. Unfortunately, no progress was obtained at that front. However, a change of plan gained some hints. Various experiments were performed to conclude to the right catalytic species out of the reaction mixture directly. In cooperation with the Institute of Chemical Technologies and Analytics, we managed to gain an important hint with Tandem MS-MS technology. Analyzing the mass pattern revealed following theory: Upon heating the catalyst with KOH to 140 °C in degassed toluene, the dichloro rhodium dimer is actually transformed into a dihydroxy rhodium dimer species (Scheme 3.12). Figure 3.4 shows the detected mass pattern.



Scheme 3.12: Catalyst [RhCl(cod)]2 gets transformed into [RhOH(cod)]2 at reaction conditions.

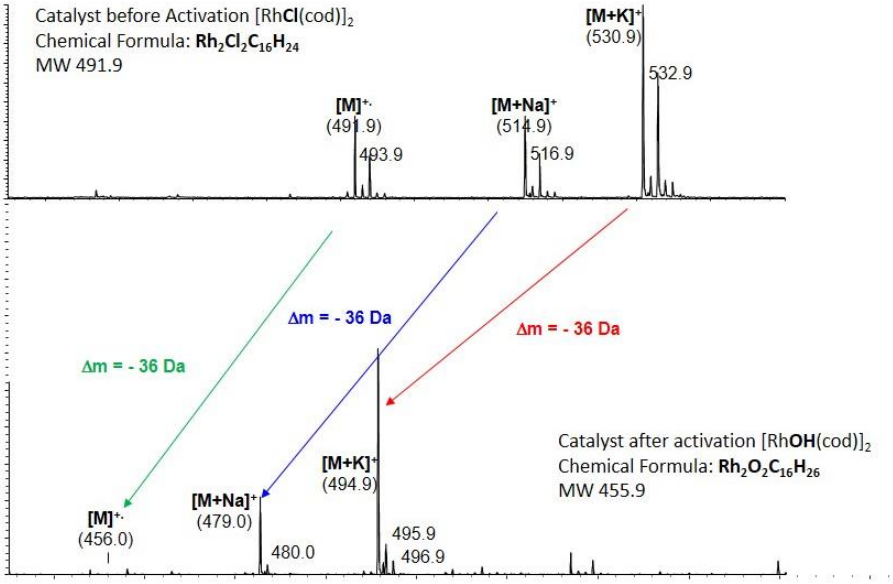
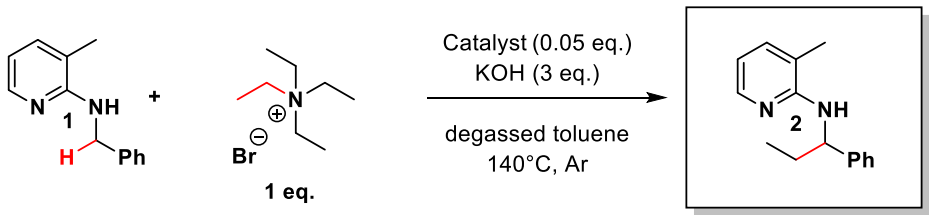


Figure 3.4: Comparison of the mass spectra taken before and after activation of the catalyst. The mass pattern reveals the substitution of both chloride species and indicates 2 hydroxy species instead.

However, this only gives a hint towards the correct catalytically active species. Because, all these measurements were performed after the reaction mixture cooled down again to room temperature. But, since not only the dichloro rhodium cyclooctadiene dimer catalyst is commercially available, but also the corresponding dihydroxy one, we could perform our reaction at the optimized conditions, only substituting $[RhCl(cod)]_2$ with $[RhOH(cod)]_2$ (Figure 3.4).



Catalyst = $[RhCl(cod)]_2$ or $[RhOH(cod)]_2$

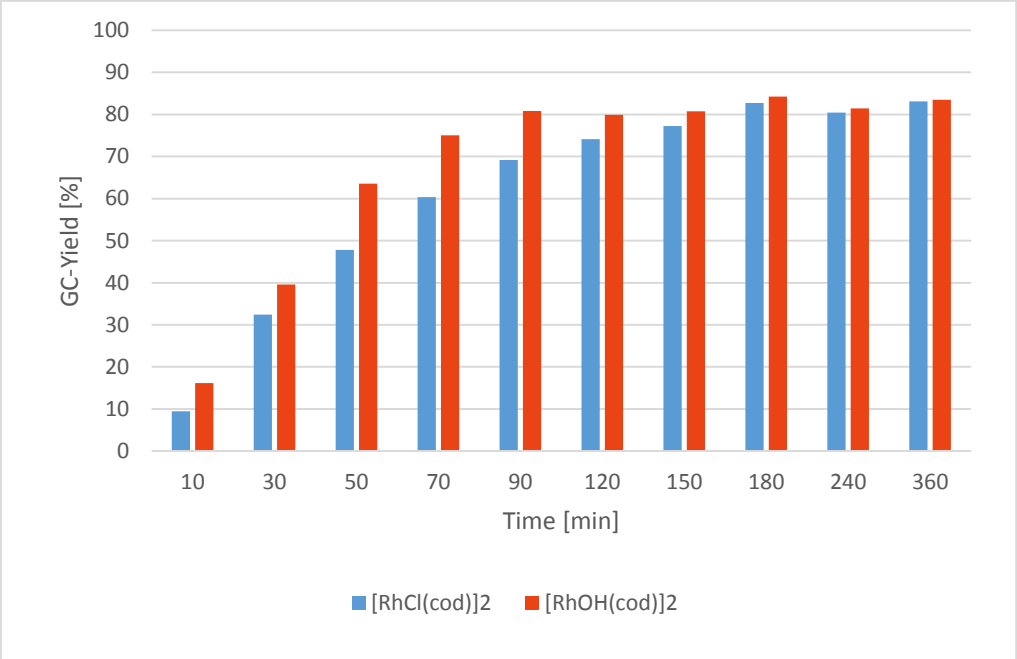


Figure 3.4: Comparison between catalysts [RhCl(cod)]2 and [RhOH(cod)]2

Comparison of the data shown in Figure 3.4 leads to the conclusion, that the 2 catalysts perform nearly identical in this reaction. This was expected and further shows, that the dihydroxy catalyst is able to accomplish at least the same results than the corresponding dichloro substituted catalyst. But moreover, the dihydroxy catalyst performed this reaction even faster than its dichloro homologue. Also this makes sense. Because it may take some time to substitute the 2 chloro moieties with hydroxyl species in order to gain the active species. Additionally, the chloro and hydroxyl version might be in equilibrium, so that in case the hydroxyl catalyst is used directly, it is the only species present and hence available in larger concentration.

These experiments lead to think, that the $[RhOH(cod)]_2$ is at some point formed in the reaction mixture, at least after cooling down to room temperature. At 140 °C and our reaction conditions, it is much more likely, that the corresponding monomer RhOH(cod) is the catalytic active species. In the monomer form, rhodium has one obvious coordination site free to coordinate to the pyridine nitrogen from the directing group of our substrate. With good conscience it can be assumed, that the dihydroxy rhodium cyclooctadiene species is involved in the catalytic mechanism for this reaction.

Proven in last chapter, we know that the olefin gets produced in the reaction mixture already at lower temperatures than 140°C. With that in mind, experiments were performed to analyze the required reaction temperature for the transition metal catalyzed C-H alkylation reaction. Basically we performed the same reaction but varied the reaction temperature. These studies showed, that product formation starts at 120 °C, but accelerates further when going up to 140 °C and also peaks at 140 °C. Further increasing temperature to 160 °C showed no

improvement. Keeping those additional studies in mind, the following catalytic reaction mechanism is proposed, aligned to already mentioned previous studies our group performed (Figure 3.5).[29]

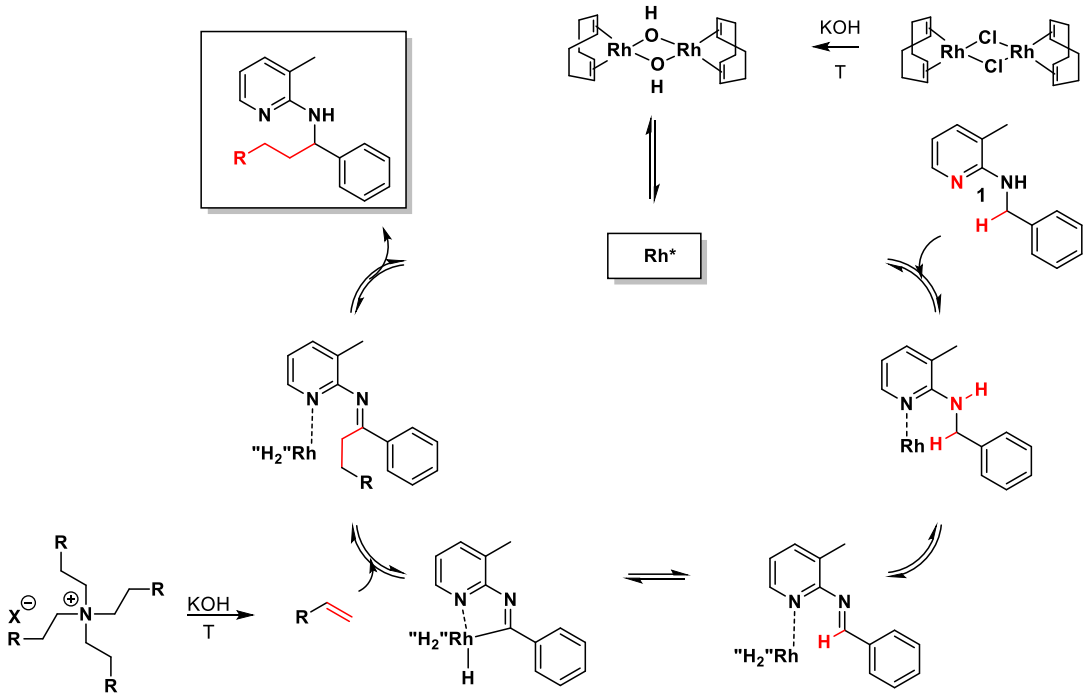


Figure 3.5: Proposed catalytic reaction mechanism. "H2" implies that it is not known how the 2 hydrogen atoms are bond to the catalyst or ligand. "Rh" emphasizes that the actual catalytic active species has not been identified unequivocally.*

3.3.3. Influence of Counterions

In the very beginning of the screening experiments we checked the influence of different counterions when using tetraethylammonium salts (cf. Table 3.3, entries 1-3). We performed the same reaction with chloride, bromide and iodide as counterion species. All 3 salts performed at the same level, and the reaction outcome was the same, leading to about 79% of ethylated product.

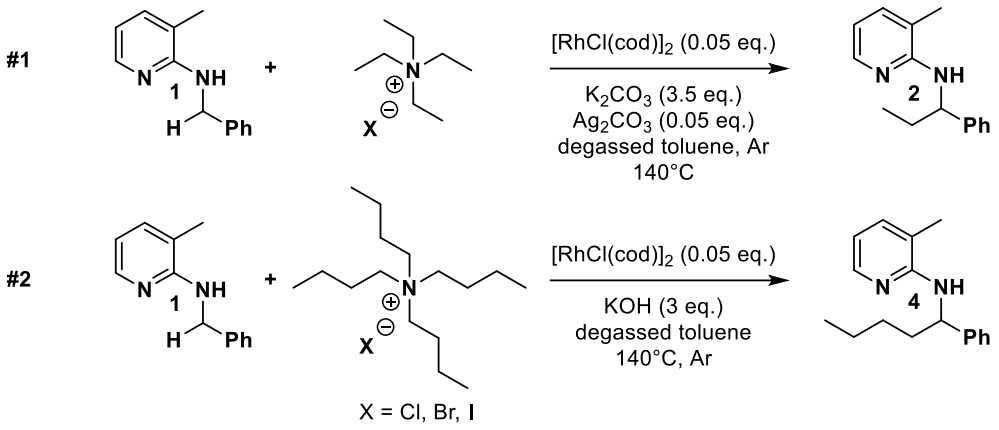


Table 3.3: Experiments were performed to check the influence of the counterion of the quaternary ammonium salt. At the beginning of the screening with the starting conditions (#1), and after the reaction conditions have been optimized (#2).

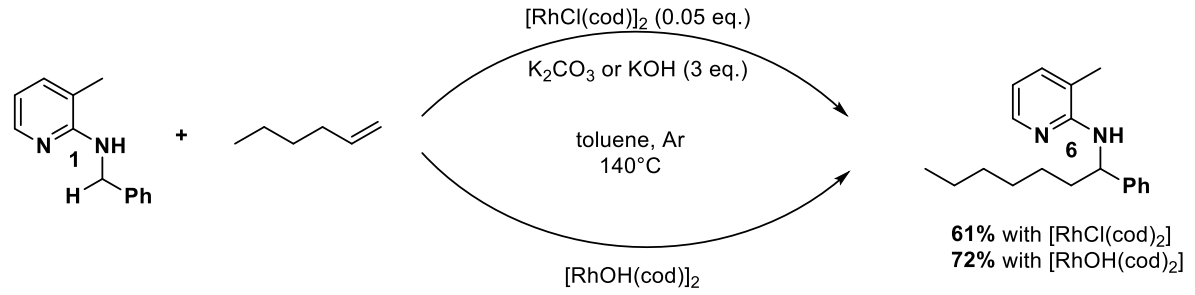
Entry	Reaction	X	Conversion to Product [%][a]	Consumption of 1 [%][a]
1	#1	chloride	78.4	89.1
2	#1	bromide	79.0	89.2
3	#1	iodide	78.3	88.7
4	#2	chloride	72.0	86.3
5	#2	bromide	72.1	85.9
6	#2	iodide	70.2	87.0

[a] Determined by GC-Analysis. The conversion is determined relative to dodecane as internal standard.

And also after the reaction conditions were optimized using tetrabutylammonium chloride, these different counterions have been tested (cf. Table 3.3, entries 4-6). No significant influence on the reaction outcome could be detected. All 3 counterion showed similar yields around 72% and starting material consumption around 86%. So for all reactions of this thesis, the cheapest, or readily available salts were used.

3.3.4. Further Reactions with [RhOH(cod)]$_2$

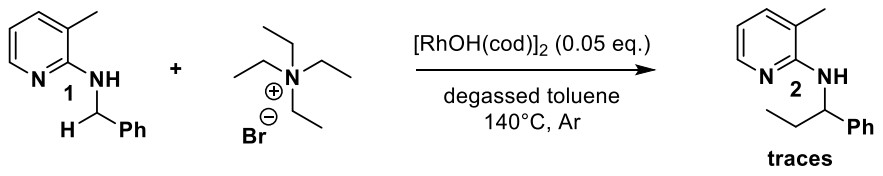
After gaining positive results when experimenting with cyclooctadiene rhodium hydroxy dimer [RhOH(cod)]$_2$ as catalyst, new ideas came up. It was interesting to know, if we actually need a base additive in the reaction when using the olefin directly. Since the hypothesis at this point is, that the base is only generating the catalytic active species. So we performed the same reaction either with [RhCl(cod)]$_2$ and base additive, or with [RhOH(cod)]$_2$ without any additive (Scheme 3.13).



Scheme 3.13: Experiments to prove the hypothesis that K2CO3/KOH is only needed for generating the catalytic active species and has indeed no influence on the reaction mechanism if the olefin is readily available in the reaction mixture.

The experiment showed that K_2CO_3 (or base generally) is only needed for generating the catalytic active species. The reaction does not further benefit from the base. And moreover, even the isolated yield could be improved by about 10%, respectively.

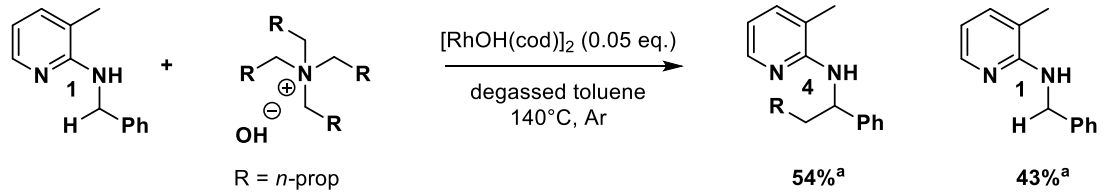
Obviously, we also wanted to exploit the hydroxyl catalyst when using tetraalkylammonium salts. But we already know that we need KOH to perform the elimination step efficiently. At first, we thought that we are able to observe some product when using tetraethylammonium bromide as alkyl source. Since the ethylation protocol also worked with K_2CO_3, maybe we are able to eliminate enough ethylene at 140 °C without any base to convert at least some amounts of the starting material toward the product (Scheme 3.14).



Scheme 3.14: Reaction scheme without base. Only traces of the product could be observed.

Unfortunately only traces of the product could be observed. The starting material did not undergo the transformation. It seems, that also tetraethylammonium bromide is not able to

eliminate ethylene without base. Another hypothesis led to thinking, that the cationic potassium is actually needed to bind the free bromide in the reaction mixture, which would be generated along the olefin in stoichiometric amounts. The active hydroxyl catalytic species could then be substituted to some extent by a catalytically inactive rhodium bromide species. As we already knew from literature research towards the Hofmann elimination step, tetraalkylammonium hydroxide salts are highly unstable and eliminate quite easily[41]. So we hypothesized that the corresponding hydroxide salts might do the trick. However, those salts are even unstable at air. Therefore, they are commercially available either as hydrates or in solution. Nevertheless we bought tetrabutylammonium hydroxide 30-hydrate. The presence of such large quantities of water inhibits the reaction, but we were able to get rid of the crystal water by azeotropic distillation in toluene. After distillation the highly unstable tetrabutylammonium hydroxide salt was handled in the glovebox.
Gratifyingly, the reaction worked as intended. At 140 °C 1-butene gets eliminated and starting material **1** gets transformed to the corresponding product **4** (Scheme 3.15).



Scheme 3.15: Reaction scheme for C-H alkylation reaction with tetrabutylammonium hydroxide as alkyl source. No KOH is needed in this reaction. aCalibrated GC-Yield.

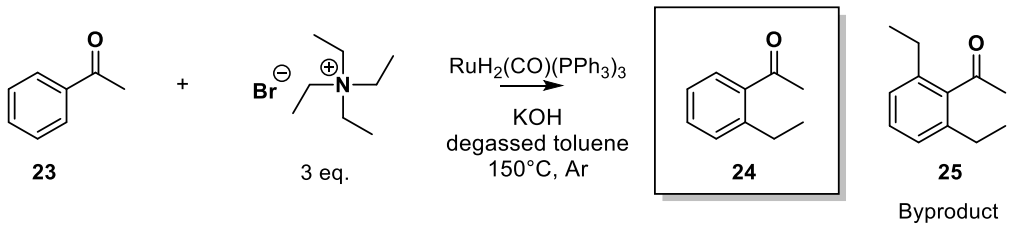
54% of the butylated product was observed with calibrated GC analysis. 43% of the starting material was not consumed. As we already expected, if the olefin is available from the start of the reaction (see Scheme 3.13), or gets generated in the mixture without base (see Scheme 3.15), no additional base is needed. So there could be definitely potential for optimizing this reaction, in cases when large quantities of KOH are not tolerated by the substrate. However, the practicability of the transformation is significantly reduced.

3.4. Alternative Substrates

Up to this point, we always used the same kind of starting parameters in this C-H alkylation reaction. We performed our reactions using rhodium as transition metal catalyst and pyridine derivatives as directing groups. As earlier mentioned (chapter 3.3.1), we know the parameters required for the Hofmann elimination, and in principal also other substrates and catalysts should be compatible with our protocol. To prove this, we selected Murai's C-H alkylation reaction of acetophenone as second example. This could show that also ruthenium catalysts are no problem with our protocol, and also ketone directing groups can work. Furthermore, we tried also an imine directing group with a different rhodium catalyst *(vide infra)*.

3.4.1. Acetophenone

In earlier chapters the name Shinji Murai was already mentioned with his C-H alkylation reaction using olefins as alkyl source.[23] This reaction started enormous investigations into directing group assisted C-H activation reactions of all kinds. No wonder, that we choose this very exemplary reaction to further test our new protocol. Using the 1993 published reaction conditions, but substituting olefins in this reaction by tetraethylammonium bromide and adding KOH (Scheme 3.16).

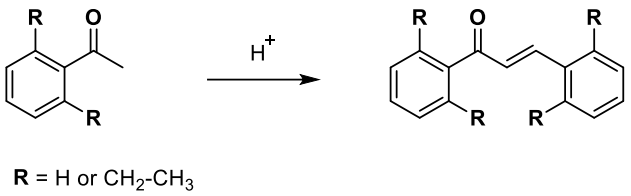


Scheme 3.16: Reaction scheme using acetophenone as substrate, adapting our protocol using tetraethylammonium bromide as alkyl source. Formation of byproduct 25 was expected since also Murai's group reported this byproduct. [23]

The reaction looked straight forward at first. After a few optimization steps (adding 3 eq. tetraethylammonium bromide and adjusting the catalyst loading to 0.04 eq.), the reaction showed good conversion. Expected byproduct formation (**25**) could not be prevented and was already observed in the literature protocol.

However purification of the product turned out to be a quite hard task. Literature[23] used distillation as purification tool. Although with our small scale experiments distillation is obviously not an option. So flash column chromatography was the next best option, as up to this point every C-H alkylated product was purified by flash column chromatography using LP and EtOAc as solvents. Although after column a mixture of a lot of different compounds was detected. It was GCMS that led us to the conclusion that on column the acetophenone derivatives are able to perform an Aldol condensation (Scheme 3.17). The acidity of the silica

gel is enough for the compounds to undergo this condensation step.

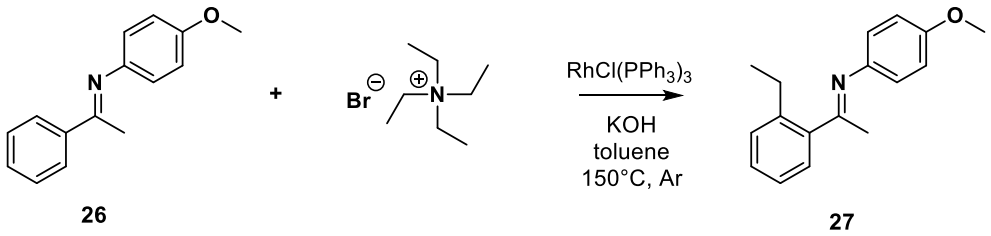


Scheme 3.17: Acidic catalyzed Aldol condensation of acetophenone derivates.

Neutralizing the acidic groups on the silica was the obvious choice in order to prevent the condensation. Adding 1% triethylamine to both solvents (LP and EtOAc) prevented compounds **23**, **24** and **25** from condensation. Although the next problem followed. When adding triethylamine to the column it was not possible anymore to separate the reaction mixture. So we isolated a mixture of product **24**, byproduct **25** and remaining starting material **23**. The ratio between this compounds could be determined by ^{1}H-NMR. Good calculated yield of 67% product, 1-(2-ethylphenyl)ethanone **24,** was obtained. Respectable amounts of byproduct **25** (25%) was detected. 92% starting material acetophenone **23** was consumed. Remarkably also this reaction followed the trend, that it is not possible to reach 100% consumption of the starting material.

3.4.2. N-(4-Methoxybenzyl)-1-phenylmethanimine

Our group previously investigated C-H alkylation reactions supported by imine directing groups. We picked imine **26** as potential candidate for the ethylation protocol with tetraethylammonium bromide as alkylation reagent (Scheme 3.12).

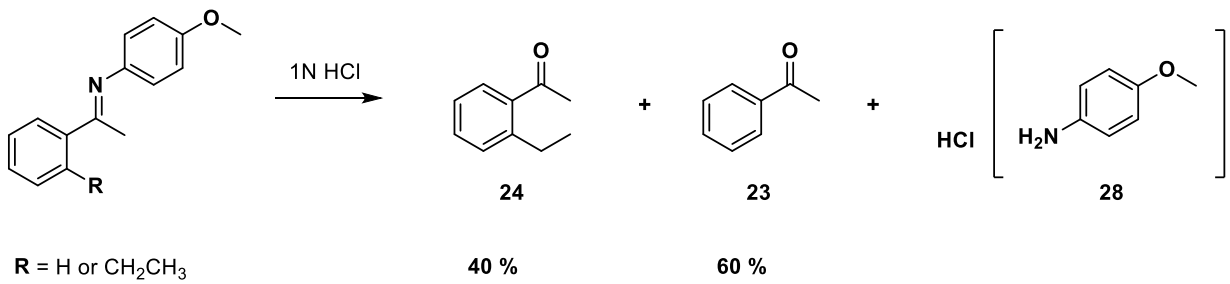


Scheme 3.12: Reaction scheme using imine 26 as substrate. Exploiting tetraethylammonium bromide as alkyl source leads us to product 27.

Following the reaction with GCMS showed promising results. Although the reaction always seemed to stop at 50% conversion to the product. With that in mind, we checked whether we got a mixture of E/Z isomers in our starting material **26**. This would have made sense, as in that case it could be possible that only the E-isomer is able to undergo the transformation.

Unfortunately, after checking the NMR data again, we could not detect any hints towards the presence of the Z-isomer in ^{1}H- and ^{13}C-NMR.

Also in this reaction, purification was problematic. Because it was not possible to purify the compound with column chromatography, as on column both imine **26** and **27** hydrolyzed. Unfortunately, adding 1% triethylamine to the solvents on column chromatography did not do the trick in this case. The compound still hydrolyzed. So we headed for another option. Hydrolyzing the imines after the reaction on purpose led us back to the acetophenone derivatives we already encountered (see Chapter 3.4.1) and we could isolate a mixture of acetophenone **23** and 1-(2-ethylphenyl)ethanone **24** (Scheme 3.13).



Scheme 3.13: Hydrolyzing imines 26 and 27 to the corresponding acetophenone derivates.

After hydrolysis with 1N HCl, the mixture was extracted with Et_2O. The resulting amine **28** is generated upon hydrolysis, but fortunately is staying in the aqueous layer as a hydrochloride salt upon workup. The ratio between these compounds could be determined by ^{1}H-NMR. A calculated yield of 39.4% 1-(2-ethylphenyl)ethanone **24** was obtained. 60.6% acetophenone **23** was found in the mixture. Meaning that only 60.6% of the imine starting material **26** was converted to the product.

Obviously this yield is not satisfying and there is possibility for optimizing this reaction. But in case of this thesis we were only interested if the reaction is working with our alkylation protocol with quaternary ammonium salts. We could show that olefins could also be substituted by tetraalkylammonium salt when using Wilkinson's catalyst ($RhCl(PPh_3)_3$) and imine starting materials as directing groups. And with that, we put this chapter aside without further optimizing this reaction.

4. Conclusion

In conclusion, benzylic amines could be alkylated at the benzylic C(sp^3)-H bond using quaternary ammonium salts as alkylating reagents. It was found, that tetraalkylammonium salts are able to substitute an olefin by generating the free olefin *in-situ* after a Hofmann elimination step. Not only short chained olefins such as ethylene or propylene but also longer chained ones like hexene or octene could be successfully replaced by the corresponding ammonium salts. The reaction was optimized and a practical protocol was found to use solid materials instead of gaseous or liquid olefins.

Moreover, a scope of different benzylic amines with a variety of functional groups could be alkylated with this method. And not only benzylic amines could be used as substrates in this kind of reaction. In examples of literature known reactions on other types of substrates using also different catalysts and directing groups, the olefin could be successfully replaced by our method.

Potassium hydroxide was found as crucial reagent for an efficient Hofmann elimination step. Temperature screening experiments led to a greater understanding into the elimination step at our reactions conditions. With that in mind, it is possible to pick literature known reactions and replace an olefin with the corresponding tetraalkylammonium salt with our method. If the Hofmann elimination is possible at the given conditions from literature.

Additional studies revealed a potential catalytic active species. With this knowledge it was possible to gain new hints leading to a deeper understanding of the catalytic mechanism. For future studies, DFT calculation can be conducted to verify the potential mechanism we have suggested. This is under way within the laboratory of Prof. Andras Stirling of the Hungarian Academy of Science.

5. Experimental

List of Abbreviations

BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
but	butyl
cod	1,5-cyclooctadiene
d	doublet
DABCO	1,4-Diazabicyclo[2.2.2]octan
DCPTPB	2-Dicyclohexyl-phosphino-2',4',6'-triisopropylbiphenyl
eth	ethyl
eq.	equivalent(s)
Et_2O	diethyl ether
EtOAc	ethyl acetate
hex	hexyl
LP	light petroleum
m	multiplet
mp	melting point
n.i.	not isolated
prop	propyl
q	quartet
rac	racemic
r.t.	room temperature
s	singlet
t	triplet
TEA	triethylamine
WP	weighed portion

5.1. General Methods

In general, unless noted otherwise, chemicals were purchased from commercial suppliers and used without further purification. Cyclooctadiene rhodium chloride dimer $[RhCl(cod)]_2$ was handled in the glovebox under argon. Dry and degassed toluene was stored over molecular sieves in the glovebox under argon. Other dry solvents were obtained by passing pre-dried material through a cartridge containing activated alumina (solvent dispensing system) and stored under nitrogen atmosphere until usage.

^{1}H-NMR, C^{13}-NMR and HSQC spectra were recorded on a Bruker Avance 400, chemical shifts are reported in ppm, using Me_4Si as internal standard. NMR signals were assigned according to Figure 5.1 with different aromatic systems marked as a, b and c and numbers without labels assigned to the aliphatic molecule part.

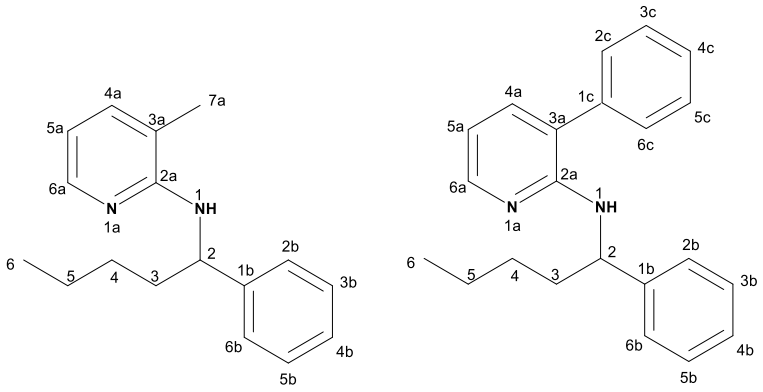


Figure 5.2: Scheme for assigning NMR Signals

GC-MS was performed on a Thermo Trace 1300 GC/ MS ISQ LT (quadrupole, EI+) with a TR-5 capillary column (7m x 0.32 mm, 0.25µm film, achiral). Temperature program: Start at 100 °C (hold 2 min), 35 °C/min, 300 °C (hold 4 min).

GC spectra were recorded on a Thermo Focus GC using a BGB-5 capillary column (30m x 0.32 mm, 1.0µm film, achiral) with the following oven temperature program: Start at 100 °C (hold 2 min), 35 °C/min, 300°C (hold 4 min).
GC yields were calculated by using the response factor of the corresponding compound relative to dodecane as internal standard, which was determined by calibration.

Microwave reactions were performed on a Biotage Initiator Sixty™ microwave unit.

For TLC aluminum backed silica gel 60 with fluorescence indicator F254 was used. Column chromatography was performed on Silica 60 from Merck (40 µm – 63 µm). Flash chromatography, was carried out on a Büchi Sepacore™ MPLC system.

Melting points were determined on an automated melting point system (Büchi Melting Point B-545) and are uncorrected.

High-resolution mass spectrometry (HRMS) for literature-unknown compounds was performed by liquid chromatography in combination with hybrid ion trap and high-resolution time-of-flight mass spectrometry (LC-IT-TOF-MS) in only positive-ion detection mode with the recording of standard (MS) and tandem (MS/MS) spectra.

5.2. General Procedures

5.2.1. General procedure A for C-H activation reactions

Solid starting materials (except the catalyst) were placed in an oven-dried 8 ml glass vial with a septum screw cap and a magnetic stirring bar. The vial was transferred into the glovebox under argon. Catalyst, solvent and dodecane were added in the glovebox. Finally, the vial was closed and the reaction mixture was heated in a heating block for the desired time at the desired temperature.

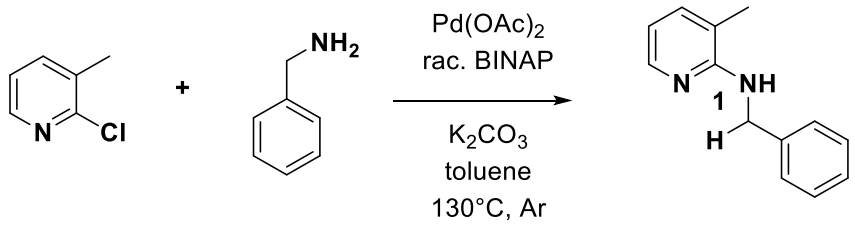
5.2.2. General work-up procedure B for C-H activation reactions

After cooling the reaction mixture to room temperature, the solid material was removed by filtration using a Pasteur pipette with cotton and silica. The residue was washed with CH_2Cl_2. The combined organic filtrate was concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (LP/EtOAc) with, unless otherwise noted, one of the following setups: Gradient A: 1% EtOAc isocratic for 5min, then setting up a gradient which varies the solvents from 1% to 10% EtOAc within 1 hour. Gradient B: 1% EtOAc isocratic for 5min, then setting up a gradient which varies the solvents from 1% to 20% EtOAc within 1 hour. Flow rate was set to 30 ml/min for all separations.

5.3. Synthetic Procedures

5.3.1. Precursor Synthesis

5.3.1.1. N-Benzyl-3-methylpiridin-2-amine (1)

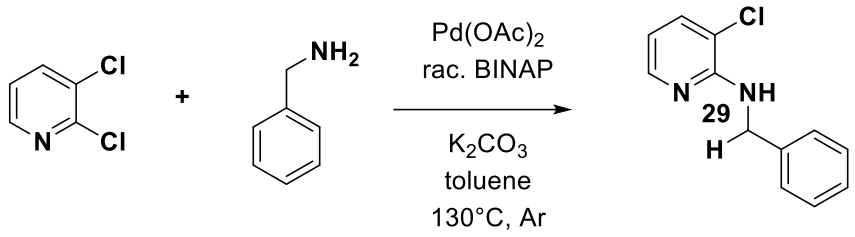


$Pd(OAc)_2$ (67 mg, 0.3 mmol, 0.02 eq.), rac. BINAP (187 mg, 0.3 mmol, 0.02 eq.) and K_2CO_3 (7.256 g, 52.5 mmol, 3.5 eq.) were placed in a 100 ml 3-necked-flask, evacuated, and flushed with argon 3 times. Then 2-chloro-3-methylpyridine (1.64 ml, 15 mmol, 1 eq.), freshly distilled benzylamine (1.97 ml, 18 mmol, 1.2 eq.) and finally toluene (38 ml) were added through the septum with a syringe. The mixture was heated to 130 °C maintaining the argon atmosphere with a balloon. The reaction was stopped after 18 h (TLC). After cooling to r.t. the solid material was removed by filtration and washed with CH_2Cl_2 (150 ml). The combined organic layers were evaporated and the resulting crude product was purified by flash column chromatography (LP/EtOAc) starting with 3 % EtOAc. The pure product was dried under reduced pressure and isolated in 92% yield.
Analytical data is in accordance to literature.[44]

N-Benzyl-3-methylpiridin-2-amine (1) Colorless to beige solid (2.736 g, 92%)
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.09 (s, 3H, C[7a]-H_3), 4.37 (s, 1H, N[1]-H), 4.70 (d, J = 5.3 Hz, 2H, C[2]-H_2), 6.57 (dd, J = 7.1, 5.1 Hz, 1H, C[5a]-H), 7.23 – 7.44 (m, 6H, C[4a]-H, C[2-6b]-H), 8.06 (dd, J = 5.1, 1.7 Hz, 1H, C[6a]-H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 17.1 (q, C[7a]), 46.0 (t, C[2]), 113.0 (d, C[5a]), 116.7 (s, C[3a]), 127.3 (d, C[4b]), 128.0 (d, C[2b]; C[6b]), 128.7 (d, C[3b]; C[5b]), 137.0 (d, C[4a]), 140.1 (s, C[1b]), 145.5 (d, C[6a]), 156.7 (s, C[2a]).

MP: 48-49 °C
TLC: 0.51 (LP/EtOAc 5:1)

5.3.1.2. N-Benzyl-3-chloropyridin-2-amine (29)

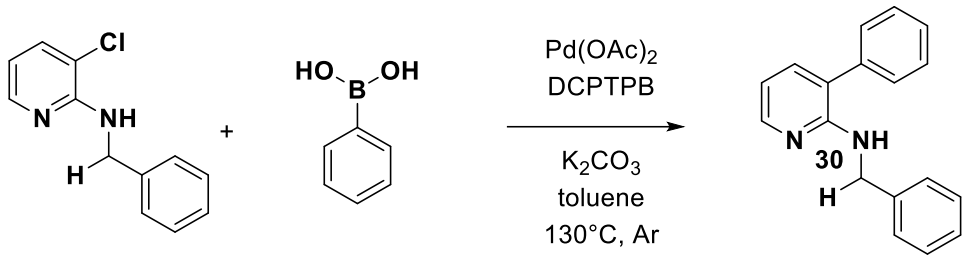


$Pd(OAc)_2$ (67 mg, 0.3 mmol, 0.02 eq.), rac. BINAP (187 mg, 0.3 mmol, 0.02 eq.) and K_2CO_3 (7.256 g, 52.5 mmol, 3.5 eq.) were placed in a 100 ml 3-neck-flask and evacuated and flushed with Argon 3 times. Then 2,3-dichloropyridine (2.22 g, 15 mmol, 1 eq.), freshly distilled benzylamine (1.97 ml, 18 mmol, 1.2 eq.) and finally toluene (38 ml) were added. The mixture was heated to 130 °C maintaining the argon atmosphere with a balloon. The reaction was stopped after 16 h (TLC). After cooling to r.t. the solid material was removed by filtration and washed with CH_2Cl_2 (150 ml). The combined organic layers were evaporated and the resulting crude product was purified by flash column chromatography (LP/EtOAc) starting with 3 % EtOAc. The pure product was dried under reduced pressure and isolated in 90% yield.
Analytical data is in accordance with literature.[45]

N-Benzyl-3-chloropyridin-2-amine (29) Yellow oil (2.95 g, 90 %)
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.68 (d, J = 5.6 Hz, 2H, C[2]-H_2), 5.28 (s, 1H, N[1]-H), 6.56 (dd, J = 7.7, 4.9 Hz, 1H, C[5a]-H), 7.26 – 7.41 (m, 5H, C[2-6b]-H), 7.47 (dd, J = 7.6, 1.6 Hz, 1H, C[4a]-H), 8.06 (dd, J = 4.9, 1.6 Hz, 1H, C[6a]-H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 45.6 (t, C[2]), 113.2 (d, C[5a]), 115.5 (s, C[3a]), 127.4 (d, C[4b]), 127.8 (d, C[2b]; C[6b]), 128.8 (d, C[3b]; C[5b]), 136.2 (d, C[4a]), 139.4 (s, C[1b]), 146.2 (d, C[6a]), 154.0 (s, C[2a]).

TLC: 0.65 (LP/EtOAc 5:1)

5.3.1.3. N-Benzyl-3-phenylpyridin-2-amine (30)



N-Benzyl-3-chloropyridin-2-amine (1.095 g, 5 mmol, 1 eq.), phenylboronic acid (1.830 g, 15 mmol, 3 eq.), K_2CO_3 (1.380 g, 10 mml, 2 eq.), $Pd(OAc)_2$ (20 mg, 0.1 mmol, 0.02 eq.) and DCPTPB (50 mg, 0.1 mmol, 0.02 eq.) were placed in a 100 ml 3-necked-flask. The flask was evacuated and flushed with argon 3 times. The mixture was heated to 130 °C maintaining the argon atmosphere with a balloon. The reaction was stopped after 16 h (TLC). After cooling to r.t. the solid material was removed by filtration and washed with CH_2Cl_2 (100 ml). The combined organic layers were evaporated and the resulting crude product was purified by flash column chromatography (LP/EtOAc) starting with 5 % EtOAc. The pure product was dried under reduced pressure and isolated in 87% yield.
Analytical data is in accordance with literature.[33]

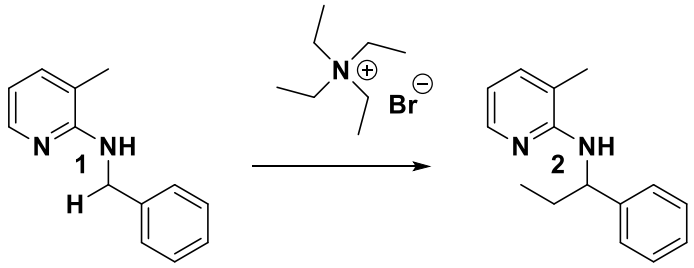
N-Benzyl-3-phenylpyridin-2-amine (30) Colorless to beige solid (1.13 g, 87 %)
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.67 (d, J = 5.6 Hz, 2H, C[2]-H_2), 4.91 (s, 1H, N[1]-H), 6.69 (dd, J = 7.2, 5.1 Hz, 1H, C[5a]-H), 7.20 – 7.48 (m, 11H, C[4a]-H; C[2-6b]-H; C[2-6c]-H), 8.16 (dd, J = 5.1, 1.8 Hz, 1H, C[6a]-H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 45.7 (t, C[2]), 113.1 (d, C[5a]), 122.5 (s, C[3a]), 127.1 (d, C[4b]), 127.6 (d, C[2b]; C[6b]), 127.9 (d, C[2c]; C[6c]), 128.6 (d, C[3b]; C[5b]), 129.0 (d, C[4c]), 129.4 (d, C[3c]; C[5c]), 137.4 (d, C[4a]), 137.9 (s, C[1c]), 140.0 (s, C[1b]), 147.0 (d, C[6a]), 155.4 (s, C[2a]).

MP: 58-60 °C
TLC: 0.80 (LP/EtOAc 5:1)

5.3.2. Substrate Scope – Tetraalkylammonium Salts

Unless otherwise noted, experiments were performed on a 0.50 mmol scale with an initial concentration of 0.25 mol/l of **1** in the reaction mixture.

5.3.2.1. 3-Methyl-N-(1-phenylpropyl)pyridin-2-amine (2)

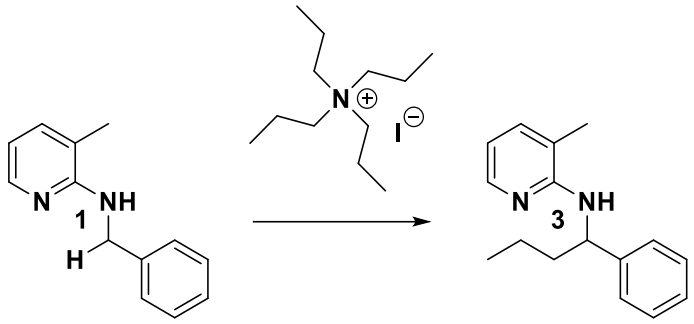


The reaction was carried out according to general procedure A with **1** (100 mg, 0.50 mmol, 1 eq.), tetraethylammonium bromide (105 mg, 0.50 mmol, 1 eq.), KOH (84 mg, 1.50 mmol, 3 eq.) and $[RhCl(cod)]_2$ (12 mg, 0.025 mmol, 0.05 eq.) in dry and degassed toluene (2 ml). The reaction mixture was heated for 16 h at 140 °C. The general work-up procedure B for C-H activation reactions was followed using gradient A. Product **2** was isolated in 68 % yield.

3-Methyl-N-(1-phenylpropyl)pyridin-2-amine (2) Colorless solid (77 mg, 68 %).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.94 (t, J = 7.4 Hz, 3H, C[4]-H_3), 1.82 – 2.04 (m, 2H, C[3]-H_2), 2.12 (s, 3H, C[7a]-H_3), 4.40 (d, J = 7.7 Hz, 1H, N[1]-H), 5.19 (q, J = 7.2 Hz, 1H, C[2]-H), 6.48 (dd, J = 7.1, 5.1 Hz, 1H, C[5a]-H), 7.17 – 7.41 (m, 6H, C[4a]-H, C[2-6b]-H), 7.97 (dd, J = 5.1, 1.7 Hz, 1H, C[6a]-H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 10.9 (q, C[4]), 17.2 (q, C[7a]), 30.3 (t, C[3]), 56.1 (d, C[2]), 112.7 (d, C[5a]), 116.4 (s, C[3a]), 126.7 (d, C[2b]), 126.9 (d, C[6b]), 127.7 (d, C[4b]), 128.5 (d, C[3b]), 128.6 (d, C[5b]), 136.9 (d, C[4a]), 144.3 (s, C[1b]), 145.6 (d, C[6a]), 156.3 (s, C[2a]).

MP: 41.5-42.5 °C
TLC: 0.54 (LP/EtOAc 5:1)
GCMS: Retention time: 6.55 min. Main fragments: 226 (M^+, 20), 211 (8), 197 (100), 108 (22), 92 (42), 65 (35).
HRMS: calculated for $C_{15}H_{19}N_2$ $[M+H]^+$ 227.1543; found 227.1554; Δ = 5.22 ppm.

5.3.2.2. 3-Methyl-N-(1-phenylbutyl)pyridin-2-amine (3)

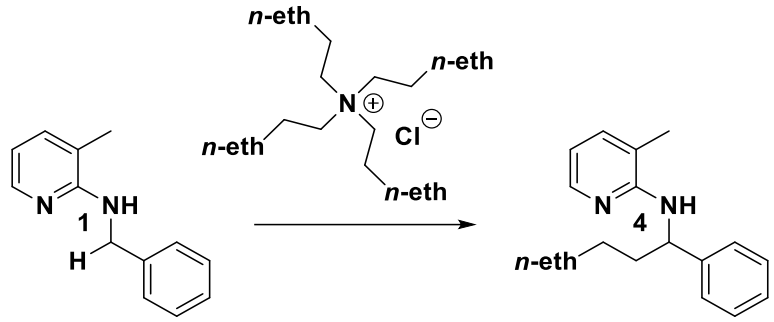


The reaction was carried out according to general procedure A with **1** (100 mg, 0.50 mmol, 1 eq.), tetrapropylammonium iodide (157 mg, 0.50 mmol, 1 eq.), KOH (84 mg, 1.50 mmol, 3 eq.) and $[RhCl(cod)]_2$ (12 mg, 0.025 mmol, 0.05 eq.) in dry and degassed toluene (2 ml). The reaction mixture was heated for 16 h at 140 °C. The general work-up procedure B for C-H activation reactions was followed using gradient A. Product **3** was isolated in 62 % yield.

3-Methyl-N-(1-phenylbutyl)pyridin-2-amine (3) Colorless oil (75 mg, 62 %).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.85 (t, J = 7.4 Hz, 3H, C[5]-H_3), 1.16 – 1.43 (m, 2H, C[4]-H_2), 1.68 – 1.88 (m, 2H, C[3]-H_2), 2.02 (s, 3H, C[7a]-H_3), 4.29 (d, J = 7.7 Hz, 1H, N[1]-H), 5.18 (q, J = 7.4 Hz, 1H, C[2]-H), 6.37 (dd, J = 7.1, 5.0 Hz, 1H, C[5a]-H), 7.06 – 7.33 (m, 6H, C[4a]-H, C[2-6b]-H), 7.87 (dd, J = 5.2, 1.8 Hz, 1H, C[6a]-H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 14.2 (q, C[5]), 17.2 (q, C[7a]), 19.7 (t, C[4]), 39.9 (t, C[3]), 54.5 (d, C[2]), 112.6 (d, C[5a]), 116.2 (s, C[3a]), 126.6 (d, C[2b; 6b]), 126.8 (d, C[4b]), 128.5 (d, C[3b; 5b]), 136.8 (d, C[4a]), 144.7 (s, C[1b]), 145.7 (d, C[6a]), 156.3 (s, C[2a]).

TLC: 0.57 (LP/EtOAc 5:1)
GCMS: Retention time: 6.77 min. Main fragments: 240 (M^+, 12), 211 (20), 197 (100), 108 (28), 92 (41), 65 (24).
HRMS: calculated for $C_{16}H_{21}N_2$ $[M+H]^+$ 241.1699; found 241.1698; Δ = 0.49 ppm.

5.3.2.3. 3-Methyl-N-(1-phenylpentyl)pyridin-2-amine (4)

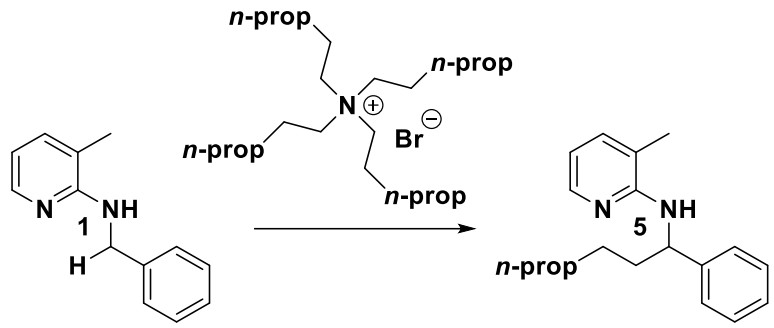


The reaction was carried out according to general procedure A with **1** (100 mg, 0.50 mmol, 1 eq.), tetrabutylammonium chloride (139 mg, 0.50 mmol, 1 eq.), KOH (84 mg, 1.50 mmol, 3 eq.) and $[RhCl(cod)]_2$ (12 mg, 0.025 mmol, 0.05 eq.) in dry and degassed toluene (2 ml). The reaction mixture was heated for 16 h at 140 °C. The general work-up procedure B for C-H activation reactions was followed using gradient B. Product **4** was isolated in 60 % yield.

3-Methyl-N-(1-phenylpentyl)pyridin-2-amine (4) Colorless oil (76 mg, 60 %).
^{1}H-NMR (400 MHz, $CDCl_3$): δ= 0.88 (t, J = 7.1 Hz, 3H, C[6]-H_3), 1.24 – 1.43 (m, 4H, C[4-5]-H_2), 1.80 – 1.99 (m, 2H, C[3]-H_2), 2.12 (s, 3H, C[7a]-H_3), 4.38 (d, J = 7.7 Hz, 1H, N[1]-H), 5.25 (q, J = 7.3 Hz, 1H, C[2]-H), 6.47 (dd, J = 7.1, 5.0 Hz, 1H, C[5a]-H), 7.16 – 7.40 (m, 6H, C[4a]-H, C[2-6b]-H), 7.96 (dd, J = 5.1, 1.7 Hz, 1H, C[6a]-H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 14.1 (q, C[6]), 17.2 (q, C[7a]), 22.8 (t, C[5]), 28.7 (t, C[4]), 37.4 (t, C[3]), 54.7 (d, C[2]), 112.6 (d, C[5a]), 116.3 (s, C[3a]), 126.6 (d, C[2b; 6b]), 126.8 (d, C[4b]), 128.5 (d, C[3b; 5b]), 136.9 (d, C[4a]), 144.7 (s, C[1b]), 145.7 (d, C[6a]), 156.3 (s, C[2a]).

TLC: 0.60 (LP/EtOAc 5:1)
GCMS: Retention time: 7.01 min. Main fragments: 254 (M^+, 13), 211 (20), 197 (100), 108 (30), 92 (43), 65 (22).

5.3.2.4. 3-Methyl-N-(1-phenylhexyl)pyridin-2-amine (5)

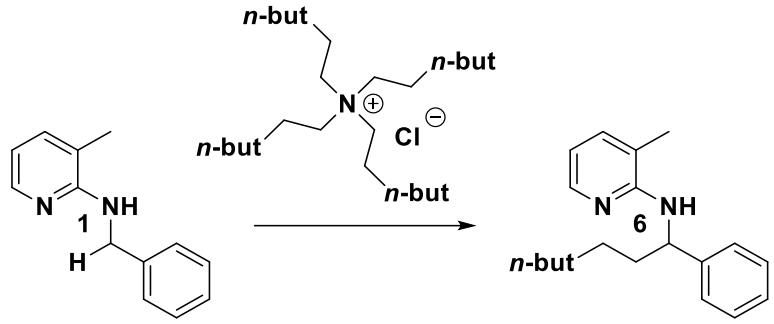


The reaction was carried out according to general procedure A with **1** (100 mg, 0.50 mmol, 1 eq.), tetrapentylammonium bromide (189 mg, 0.50 mmol, 1 eq.), KOH (84 mg, 1.50 mmol, 3 eq.) and $[RhCl(cod)]_2$ (12 mg, 0.025 mmol, 0.05 eq.) in dry and degassed toluene (2 ml). The reaction mixture was heated for 16 h at 140 °C. The general work-up procedure B for C-H activation reactions was followed using gradient B. Product **5** was isolated in 58 % yield.

3-Methyl-N-(1-phenylhexyl)pyridin-2-amine (5) Colorless solid (78 mg, 58 %).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.86 (d, J = 6.9 Hz, 3H, C[7]-H_3), 1.24 – 1.45 (m, 6H, C[4-6]-H_2), 1.78 – 1.97 (m, 2H, C[3]-H_2), 2.12 (s, 3H, C[7a]-H_3), 4.38 (d, J = 7.6 Hz, 1H, N[1]-H), 5.25 (q, J = 7.3 Hz, 1H, C[2]-H), 6.47 (dd, J = 7.1, 5.1 Hz, 1H, C[5a]-H), 7.17 – 7.40 (m, 6H, C[4a]-H, C[2-6b]-H), 7.96 (dd, J = 5.1, 1.7 Hz, 1H, C[6a]-H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 14.2 (q, C[7]), 17.2 (q, C[7a]), 22.7 (t, C[6]), 26.2 (t, C[5]), 31.9 (t, C[4]), 37.6 (t, C[3]), 54.8 (d, C[2]), 112.6 (d, C[5a]), 116.3 (s, C[3a]), 126.6 (d, C[2b; 6b]), 126.8 (d, C[4b]), 128.5 (d, C[3b; 5b]), 136.9 (d, C[4a]), 144.7 (s, C[1b]), 145.7 (d, C[6a]), 156.3 (s, C[2a]).

MP: 40-41 °C
TLC: 0.60 (LP/EtOAc 5:1)
GCMS: Retention time: 7.28 min. Main fragments: 268 (M^+, 8), 211 (19), 197 (100), 108 (31), 92 (27), 65 (20).
HRMS: calculated for $C_{18}H_{25}N_2$ $[M+H]^+$ 269.2012; found 269.2033; Δ = 7.79 ppm.

5.3.2.5. 3-Methyl-N-(1-phenylheptyl)pyridin-2-amine (6)

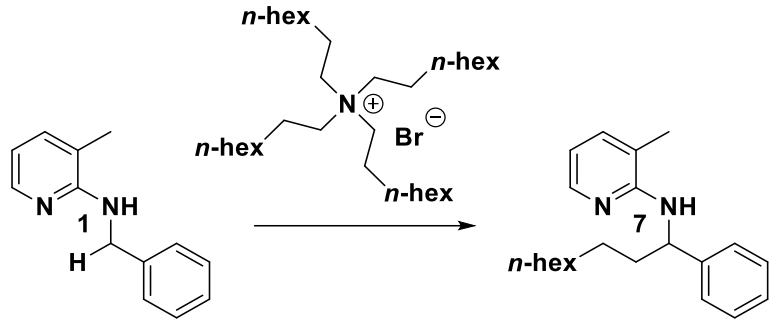


The reaction was carried out according to general procedure A with **1** (100 mg, 0.50 mmol, 1 eq.), tetrahexylammonium chloride (195 mg, 0.50 mmol, 1 eq.), KOH (84 mg, 1.50 mmol, 3 eq.) and $[RhCl(cod)]_2$ (12 mg, 0.025 mmol, 0.05 eq.) in dry and degassed toluene (2 ml). The reaction mixture was heated for 16 h at 140 °C. The general work-up procedure B for C-H activation reactions was followed using gradient B. Product **6** was isolated in 61 % yield.

3-Methyl-N-(1-phenylheptyl)pyridin-2-amine (6) Colorless oil (86 mg, 61 %).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, J = 6.7 Hz, 3H, C[8]-H_3), 1.23 – 1.45 (m, 8H, C[4-7]-H_2), 1.80 – 1.99 (m, 2H, C[3]-H_2), 2.13 (s, 3H, C[7a]-H_3), 4.39 (d, J = 7.7 Hz, 1H, N[1]-H), 5.26 (q, J = 7.3 Hz, 1H, C[2]-H), 6.48 (dd, J = 7.1, 5.0 Hz, 1H, C[5a]-H), 7.14 – 7.45 (m, 6H, C[4a]-H, C[2-6b]-H), 7.97 (dd, J = 5.1, 1.8 Hz, 1H, C[6a]-H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 14.2 (q, C[8]), 17.2 (q, C[7a]), 22.7 (t, C[7]), 26.5 (t, C[6]), 29.4 (t, C[5]), 31.9 (t, C[4]), 37.7 (t, C[3]), 54.7 (d, C[2]), 112.6 (d, C[5a]), 116.2 (s, C[3a]), 126.6 (d, C[2b; 6b]), 126.8 (d, C[4b]), 128.5 (d, C[3b; 5b]), 136.8 (d, C[4a]), 144.7 (s, C[1b]), 145.7 (d, C[6a]), 156.3 (s, C[2a]).

TLC: 0.63 (LP/EtOAc 5:1)
GCMS: Retention time: 7.54 min. Main fragments: 282 (M^+, 7), 211 (17), 197 (100), 108 (32), 92 (30), 65 (14).

5.3.2.6. 3-Methyl-N-(1-phenylnonyl)pyridin-2-amine (7)



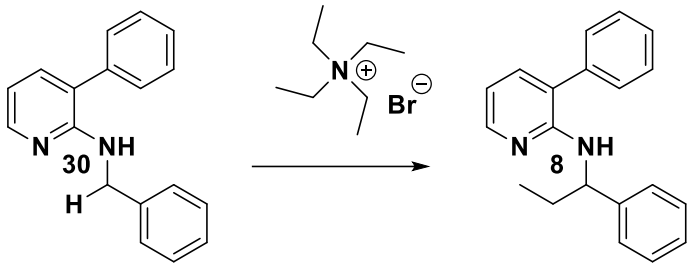
The reaction was carried out according to general procedure A with **1** (100 mg, 0.50 mmol, 1 eq.), tetraoctylammonium bromide (273 mg, 0.50 mmol, 1 eq.), KOH (84 mg, 1.50 mmol, 3 eq.) and $[RhCl(cod)]_2$ (12 mg, 0.025 mmol, 0.05 eq.) in dry and degassed toluene (2 ml). The reaction mixture was heated for 84 h at 140 °C. The general work-up procedure B for C-H activation reactions was followed using gradient B. Product **7** was isolated in 40 % yield.

3-Methyl-N-(1-phenylnonyl)pyridin-2-amine (7) Colorless oil (63 mg, 40 %).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, J = 6.8 Hz, 3H, C[9]-H_3), 1.22 – 1.43 (m, 12H, C[4-8]-H_2), 1.79 – 1.97 (m, 2H, C[3]-H_2), 2.12 (s, 3H, C[7a]-H_3), 4.38 (d, J = 7.7 Hz, 1H, N[1]-H), 5.25 (q, J = 7.3 Hz, 1H, C[2]-H), 6.47 (dd, J = 7.1, 5.1 Hz, 1H, C[5a]-H), 7.14 – 7.42 (m, 6H, C[4a]-H, C[2-6b]-H), 7.96 (dd, J = 5.1, 1.7 Hz, 1H, C[6a]-H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 14.2 (q, C[9]), 17.2 (q, C[7a]), 22.8 (t, C[8]), 26.5 (t, C[7]), 29.4 (t, C[6]), 29.7 (t, C[5]), 32.0 (t, C[4]), 37.7 (t, C[3]), 54.7 (d, C[2]), 112.6 (d, C[5a]), 116.3 (s, C[3a]), 126.6 (d, C[2b; 6b]), 126.8 (d, C[4b]), 128.5 (d, C[3b; 5b]), 136.9 (d, C[4a]), 144.7 (s, C[1b]), 145.7 (d, C[6a]), 156.3 (s, C[2a]).

TLC: 0.63 (LP/EtOAc 5:1)
GCMS: Retention time: 8.07 min. Main fragments: 310 (M^+, 5), 211 (17), 197 (100), 108 (33), 92 (28), 65 (10).
HRMS: calculated for $C_{21}H_{31}N_2$ $[M+H]^+$ 311.2482; found 311.2505; Δ = 7.53 ppm.

5.3.3. Substrate Scope – Target Compound

5.3.3.1. 3-phenyl-N-(1-phenylpropyl)pyridin-2-amine (8)

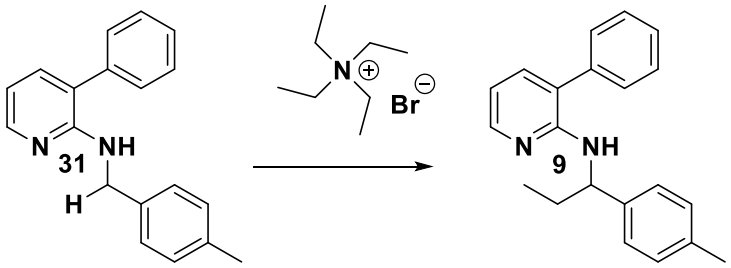


The reaction was carried out according to general procedure A with N-benzyl-3-phenylpyridin-2-amine (**30**) (130 mg, 0.50 mmol, 1 eq.), tetraethylammonium bromide (105 mg, 0.50 mmol, 1 eq.), KOH (84 mg, 1.50 mmol, 3 eq.) and $[RhCl(cod)]_2$ (12 mg, 0.025 mmol, 0.05 eq.) in dry and degassed toluene (2 ml). The reaction mixture was heated for 16 h at 140 °C. The general work-up procedure B for C-H activation reactions was followed using gradient A. Product **8** was isolated in 63 % yield.

3-Phenyl-N-(1-phenylpropyl)pyridin-2-amine (8) Yellowish oil (91 mg, 63 %).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.85 (t, J = 7.4 Hz, 3H, C[4]-H_3), 1.72 – 1.84 (m, 2H, C[3]-H_2), 4.88 (d, J = 8.0 Hz, 1H, N[1]-H), 5.14 (q, J = 7.2 Hz, 1H, C[2]-H), 6.59 (dd, J = 7.2, 5.1 Hz, 1H, C[5a]-H), 7.17 – 7.50 (m, 11H, C[4a]-H, C[2-6b]-H, C[2-6C]-H), 8.05 (dd, J = 5.0, 1.8 Hz, 1H, C[6a]-H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 10.9 (q, C[4]), 30.3 (t, C[3]), 56.2 (d, C[2]), 112.7 (d, C[5a]), 122.4 (s, C[3a]), 126.6 (d, C[4b]), 128.0 (d, C[2c; 6c]), 128.4 (d, C[2b; 6b]), 128.6 (d, C[4c]), 129.0 (d, C[3b; 5b]), 129.4 (d, C[3c; 5c]), 137.2 (s, C[4a]), 138.2 (d, C[1c]), 144.1 (s, C[1b]), 147.1 (d, C[6a]), 155.0 (s, C[2a]).

TLC: 0.57 (LP/EtOAc 5:1)
GCMS: Retention time: 7.80 min. Main fragments: 288 (M^+, 11), 259 (100), 181 (26), 154 (21), 129 (27), 127 (36), 115 (12), 91 (28), 77 (11).
HRMS: calculated for $C_{20}H_{21}N_2$ $[M+H]^+$ 289.1699; found 289.1704; Δ = 2.06 ppm.

5.3.3.2. 3-Phenyl-N-(1-(4-methylphenyl)propyl)pyridin-2-amine (9)

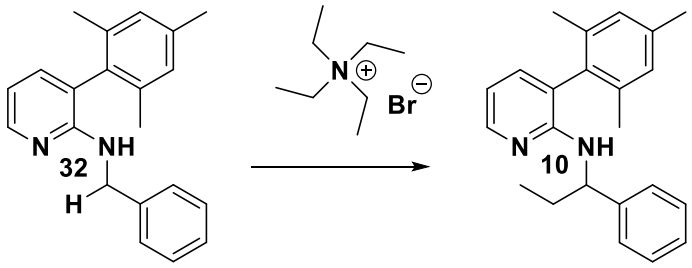


The reaction was carried out according to general procedure A with N-(4-methylbenzyl)-3-phenylpyridin-2-amine (**31**) (137 mg, 0.50 mmol, 1 eq.), tetraethylammonium bromide (105 mg, 0.50 mmol, 1 eq.), KOH (84 mg, 1.50 mmol, 3 eq.) and $[RhCl(cod)]_2$ (12 mg, 0.025 mmol, 0.05 eq.) in dry and degassed toluene (2 ml). The reaction mixture was heated for 16 h at 140 °C. The general work-up procedure B for C-H activation reactions was followed using gradient A. Product **9** was isolated in 65 % yield.

3-Phenyl-N-(1-(4-methylphenyl)propyl)pyridin-2-amine (9) Yellowish oil (98 mg, 65 %).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, J = 7.4 Hz, 3H, C[4]-H_3), 1.27 (s, 1H, C[3]-H), 1.68 – 1.88 (m, 2H, C[3]-H_2), 2.31 (s, 3H, C[7b]-H_3), 4.87 (d, J = 7.4 Hz, 1H, N[1]-H), 5.12 (q, J = 7.3 Hz, 1H, C[2]-H), 6.60 (dd, J = 7.2, 5.0 Hz, 1H, C[5a]-H), 7.06 – 7.53 (m, 10H, C[4a]-H, C[2-3b;5-6b]-H, C[2-6C]-H)), 8.07 (dd, J = 5.1, 1.8 Hz, 1H, C[6a]-H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 10.9 (q, C[4]), 21.2 (q, C[7b]), 29.9 (t, C[3]), 30.3 (t, C[3]), 56.0 (d, C[2]), 112.7 (d, C[5a]), 122.4 (s, C[3a]), 126.8 (d, C[2b; 6b]), 127.9 (d, C[2c; 6c]), 129.0 (d, C[4c]), 129.1 (d, C[3b; 5b]), 129.4 (d, C[3c; 5c]), 136.3 (d, C[4a]), 137.2 (s, C[4b]), 138.3 (d, C[1c]), 141.1 (s, C[1b]), 147.2 (d, C[6a]), 155.1 (s, C[2a]).

TLC: 0.57 (LP/EtOAc 5:1)
GCMS: Retention time: 8.05 min. Main fragments: 302 (M^+, 12), 273 (100), 181 (30), 154 (24), 129 (27), 127 (32), 115 (12), 106 (28), 91 (13), 77 (10).
HRMS: calculated for $C_{21}H_{23}N_2$ $[M+H]^+$ 303.1856; found 303.1881; Δ = 8.37 ppm.

5.3.3.3. 3-Mesityl-N-(1-phenylpropyl)pyridin-2-amine (10)

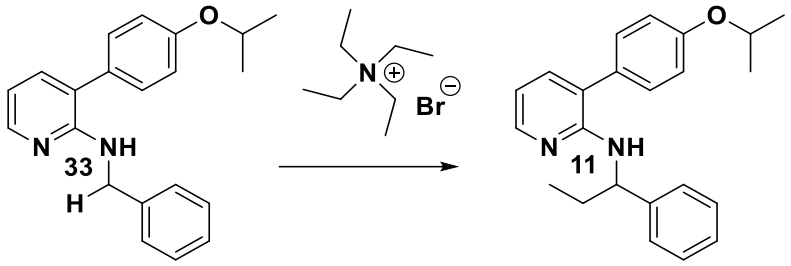


The reaction was carried out according to general procedure A with N-benzyl-3-mesitylpyridin-2-amine (**32**) (151 mg, 0.50 mmol, 1 eq.), tetraethylammonium bromide (105 mg, 0.50 mmol, 1 eq.), KOH (84 mg, 1.50 mmol, 3 eq.) and $[RhCl(cod)]_2$ (12 mg, 0.025 mmol, 0.05 eq.) in dry and degassed toluene (2 ml). The reaction mixture was heated for 16 h at 140 °C. The general work-up procedure B for C-H activation reactions was followed using gradient A. Product **10** was isolated in 64 % yield.

3-Mesityl-N-(1-phenylpropyl)pyridin-2-amine (10) Yellowish oil (106 mg, 64 %).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.84 (t, J = 7.4 Hz, 3H, C[4]-H_3), 1.60 – 1.79 (m, 2H, C[3]-H_2), 1.91 (s, 3H, C[7c]-H_3), 2.06 (s, 3H, C[9c]-H_3), 2.36 (s, 3H, C[8c]-H_3), 4.27 (s, 1H, N[1]-H), 5.15 (d, J = 7.7 Hz, 1H, C[2]-H), 6.61 (dd, J = 7.2, 5.1 Hz, 1H, C[5a]-H), 7.00 (d, J = 6.0 Hz, 2H, C[3c; 5c]), 7.10 (dd, J = 7.2, 1.9 Hz, 1H, C[4a]-H), 7.15 – 7.30 (m, 5H, C[2-6b]-H), 8.08 (dd, J = 5.1, 1.9 Hz, 1H, C[6a]-H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 10.9 (q, C[4]), 20.2, (q, C[7c]), 20.2, (q, C[9c]), 21.3 (q, C[8c]), 30.4 (t, C[3]), 55.8 (d, C[2]), 112.7 (d, C[5a]), 116.5 (s, C[3a]), 126.7 (d, C[4b]), 128.4 (d, C[2b; 6b]), 128.9 (d, C[3c; 5c]), 129.0 (d, C[3b; 5b]), 136.2 (d, C[4a]), 137.1 (s, C[1c]), 137.3 (s, C[2c; 6c]), 137.9 (s, C[4c]), 140.7 (s, C[1b]), 146.5 (d, C[6a]), 155.0 (s, C[2a]).

TLC: 0.61 (LP/EtOAc 5:1)
GCMS: Retention time: 7.99 min. Main fragments: 330 (M^+, 15), 301 (100), 209 (29), 197 (13), 181 (25), 143 (14), 91 (39).
HRMS: calculated for $C_{23}H_{27}N_2$ $[M+H]^+$ 331.2169; found 331.2180; Δ = 3.38 ppm.

5.3.3.4. 3-(4-Isopropoxyphenyl)-N-(1-phenylpropyl)pyridin-2-amine (11)

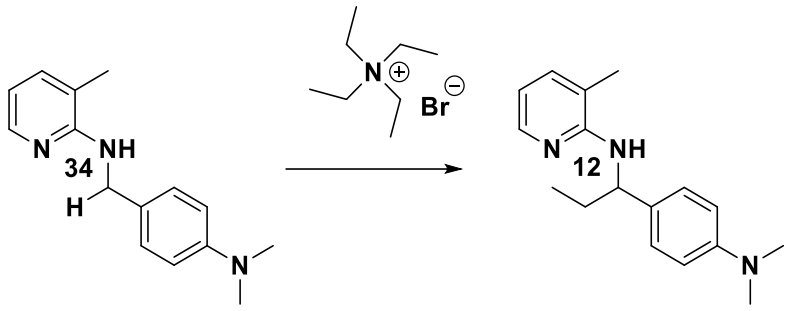


The reaction was carried out according to general procedure A with N-benzyl-3-(4-isopropoxyphenyl)pyridin-2-amine (**33**) (159 mg, 0.50 mmol, 1 eq.), tetraethylammonium bromide (105 mg, 0.50 mmol, 1 eq.), KOH (84 mg, 1.50 mmol, 3 eq.) and $[RhCl(cod)]_2$ (12 mg, 0.025 mmol, 0.05 eq.) in dry and degassed toluene (2 ml). The reaction mixture was heated for 16 h at 140 °C. The general work-up procedure B for C-H activation reactions was followed using gradient A. Product **11** was isolated in 59 % yield.

3-(4-Isopropoxyphenyl)-N-(1-phenylpropyl)pyridin-2-amine (11) Yellow oil (103 mg, 59 %).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, J = 7.4 Hz, 3H, C[4]-H_3), 1.38 (d, J = 6.1 Hz, 6H, C[9-10c]-H_3), 1.71 – 1.84 (m, 2H, C[3]-H_2), 4.60 (p, J = 6.0 Hz, 1H, C[8c]-H), 4.90 (d, J = 8.0 Hz, 1H, N[1]-H), 5.14 (q, J = 7.2 Hz, 1H, C[2]-H), 6.56 (dd, J = 7.2, 5.1 Hz, 1H, C[5a]-H), 6.92 – 7.04 (m, 2H, C[3c; 5c]-H), 7.15 – 7.34 (m, 8H, C[4a]-H, C[2-6b]-H, C[2c; 6c]), 8.02 (dd, J = 5.1, 1.8 Hz, 1H, C[6a]-H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 10.9 (q, C[4]), 22.2 (q, C[9-10c]), 30.4 (t, C[3]), 56.2 (d, C[2]), 70.1 (d, C[8c]), 112.7 (d, C[5a]), 116.5 (d, C[3c; 5c]), 122.2 (s, C[1c]), 126.6 (d, C[2b; 6b]), 126.7 (d, C[4b]), 128.4 (d, C[3b; 5b]), 130.2 (d, C[2c; 6c]), 137.1 (s, C[4a]), 140.7 (s, C[1b]), 146.7 (d, C[6a]), 155.3 (s, C[4c]), 157.7 (s, C[2a]).

TLC: 0.51 (LP/EtOAc 5:1)
GCMS: Retention time: 8.68 min. Main fragments: 346 (M^+, 19), 317 (100), 275 (32), 197 (25), 185 (26), 170 (11), 115 (21), 91 (45).
HRMS: calculated for $C_{21}H_{31}N_2$ $[M+H]^+$ 347.2118; found 347.2138; Δ = 5.95 ppm.

5.3.3.5. N-(1-(4-(Dimethylamino)phenyl)propyl)-3-methylpyridin-2-amine (12)



The reaction was carried out according to general procedure A with N-(4-(dimethylamino)benzyl)-3-methylpyridin-2-amine (**34**) (121 mg, 0.50 mmol, 1 eq.), tetraethylammonium bromide (105 mg, 0.50 mmol, 1 eq.), KOH (84 mg, 1.50 mmol, 3 eq.) and $[RhCl(cod)]_2$ (12 mg, 0.025 mmol, 0.05 eq.) in dry and degassed toluene (2 ml). The reaction mixture was heated for 16 h at 140 °C. The general work-up procedure B for C-H activation reactions was followed using gradient A. Product **12** was isolated in 61 % yield.

N-(1-(4-(Dimethylamino)phenyl)propyl)-3-methylpyridin-2-amine (12) Yellow oil (82 mg, 61 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.91 (t, J = 7.4 Hz, 3H, C[4]-H_3), 1.77 – 1.89 (m, 1H, C[3]-H), 1.93 – 2.05 (m, 1H, C[3]-H), 2.07 (s, 3H, C[7a]-H_3), 2.92 (s, 6H, C[8-9b]-H_3), 4.32 (d, J = 7.6 Hz, 1H, N[1]-H), 5.09 (q, J = 7.2 Hz, 1H, C[2]-H), 6.46 (dd, J = 7.1, 5.1 Hz, 1H, C[5a]-H), 6.67 – 6.75 (m, 2H, C[3b; 5b]-H), 7.17 (ddt, J = 6.3, 1.8, 0.9 Hz, 1H, C[4a]-H), 7.21 – 7.30 (m, 2H, C[2b; 6b]-H), 7.98 (dd, J = 5.1, 1.8 Hz, 1H, C[6a]-H).

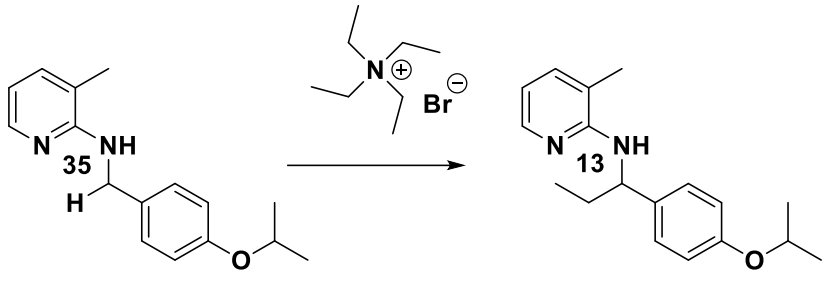
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 11.0 (q, C[4]), 17.2 (q, C[7a]), 29.8 (t, C[3]), 40.8 (q, C[8-9b]), 55.6 (d, C[2]), 112.3 (d, C[5a]), 112.8 (d, C[3b; 5b]), 116.4 (s, C[3a]), 127.6 (d, C[2b; 6b]), 132.0 (s, C[1b]), 136.8 (d, C[4a]), 145.5 (d, C[6a]), 149.7 (s, C[4b]), 156.4 (s, C[2a]).

TLC: 0.29 (LP/EtOAc 5:1)

GCMS: Retention time: 7.82 min. Main fragments: 269 (M^+, 13), 240 (47), 162 (72), 147 (30), 134 (100), 122 (82), 107 (26), 92 (58), 65 (36).

HRMS: calculated for $C_{21}H_{31}N_2$ $[M+H]^+$ 270.1965; found 270.1985; Δ = 7.17 ppm.

5.3.3.6. N-(4-isopropoxybenzyl)-3-methylpyridin-2-amine (13)

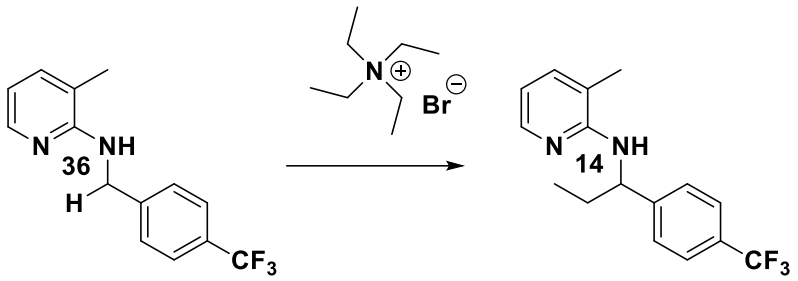


The reaction was carried out according to general procedure A with N-(4-isopropoxybenzyl)-3-methylpyridin-2-amine (**35**) (128 mg, 0.50 mmol, 1 eq.), tetraethylammonium bromide (105 mg, 0.50 mmol, 1 eq.), KOH (84 mg, 1.50 mmol, 3 eq.) and $[RhCl(cod)]_2$ (12 mg, 0.025 mmol, 0.05 eq.) in dry and degassed toluene (2 ml). The reaction mixture was heated for 16 h at 140 °C. The general work-up procedure B for C-H activation reactions was followed using gradient A. Product **13** was isolated in 69 % yield.

N-(1-(4-isopropoxyphenyl)propyl)-3-methylpyridin-2-amine (13) Yellow oil (99 mg, 69 %).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = δ 0.92 (t, J = 7.4 Hz, 3H, C[4]-H_3), 1.32 (d, J = 6.1 Hz, 6H, C[9-10b]-H_3), 1.79 – 1.89 (m, 1H, C[3]-H), 1.91 – 2.03 (m, 1H, C[3]-H), 2.10 (s, 3H, C[7a]-H_3), 4.33 (d, J = 7.7 Hz, 1H, N[1]-H), 4.51 (hept, J = 6.1 Hz, 1H, C[8b]-H), 5.13 (q, J = 7.2 Hz, 1H, C[2]-H), 6.48 (dd, J = 7.1, 5.1 Hz, 1H, C[5a]-H), 6.80 – 6.88 (m, 2H, C[3b; 5b]-H), 7.19 (ddt, J = 7.1, 1.9, 1.0 Hz, 1H, C[4a]-H), 7.23 – 7.32 (m, 2H, C[2b; 6b]-H), 7.98 (dd, J = 5.1, 1.8 Hz, 1H, C[6a]-H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 10.9 (q, C[4]), 17.2 (q, C[7a]), 22.3 (q, C[9-10b]), 30.1 (t, C[3]), 55.6 (d, C[2]), 69.9 (d, C[8b]), 112.5 (d, C[5a]), 115.8 (d, C[3b; 5b]), 116.4 (s, C[3a]), 127.8 (d, C[2b; 6b]), 136.0 (s, C[1b]), 136.8 (d, C[4a]), 145.6 (d, C[6a]), 156.4 (s, C[4b]), 156.9 (s, C[2a]).

TLC: 0.34 (LP/EtOAc 5:1)
GCMS: Retention time: 7.52 min. Main fragments: 284 (M^+, 19), 255 (74), 213 (66), 177 (10), 135 (69), 119 (38), 107 (100), 92 (86), 77 (13), 65 (29).
HRMS: calculated for $C_{21}H_{31}N_2$ $[M+H]^+$ 285.1961; found 285.1989; Δ = 9.91 ppm.

5.3.3.7. 3-Methyl-N-(1-(4-(trifluoromethyl)phenyl)propyl)pyridin-2-amine (14)



The reaction was carried out according to general procedure A with 3-methyl-N-(4-(trifluoromethyl)benzyl)pyridin-2-amine (**36**) (133 mg, 0.50 mmol, 1 eq.), tetraethylammonium bromide (105 mg, 0.50 mmol, 1 eq.), KOH (84 mg, 1.50 mmol, 3 eq.) and $[RhCl(cod)]_2$ (12 mg, 0.025 mmol, 0.05 eq.) in dry and degassed toluene (2 ml). The reaction mixture was heated for 16 h at 140 °C. The general work-up procedure B for C-H activation reactions was followed using gradient A. Product **14** was isolated in 53 % yield.

3-Methyl-N-(1-(4-(trifluoromethyl)phenyl)propyl)pyridin-2-amine (14) Yellow oil (78 mg, 53 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.97 (t, J = 7.4 Hz, 3H, C[4]-H_3), 1.85 – 1.96 (m, 2H, C[3]-H_2), 2.15 (s, 3H, C[7a]-H_3), 4.41 (d, J = 7.3 Hz, 1H, N[1]-H), 5.21 (q, J = 7.1 Hz, 1H, C[2]-H), 6.50 (dd, J = 7.1, 5.1 Hz, 1H, C[5a]-H), 7.22 (ddd, J = 7.2, 1.9, 0.9 Hz, 1H, C[4a]-H), 7.45 – 7.58 (m, 4H, C[2-3b; 5-6b]-H), 7.92 (dd, J = 5.1, 1.7 Hz, 1H, C[6a]-H)).

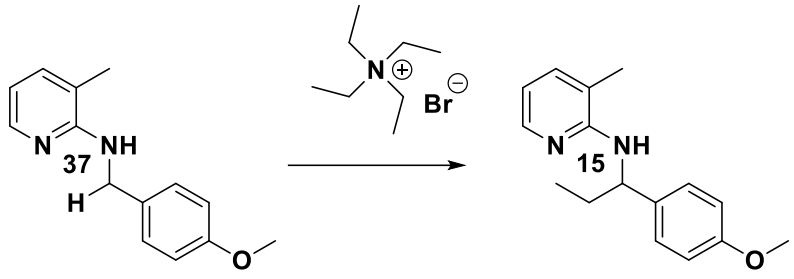
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 10.9 (q, C[4]), 17.2 (q, C[7a]), 30.4 (t, C[3]), 56.0 (d, C[2]), 113.1 (d, C[5a]), 116.4 (s, C[3a]), 124.4 (s, J_{CF} = 271.9 Hz, C[7b]), 125.4 (d, J_{CF} = 3.8 Hz, C[3b; 5b]), 127.0 (d, C[2b; 6b]), 129.0 (s, J_{CF} = 32.0 Hz, C[4b]), 137.1 (d, C[4a]), 145.6 (d, C[6a]), 148.7 (s, C[1b]), 156.0 (s, C[2a]).

TLC: 0.48 (LP/EtOAc 5:1)

GCMS: Retention time: 6.45 min. Main fragments: 294 (M^+, 20), 279 (15), 265 (100), 159 (16), 108 (57), 92 (84), 80 (15), 65 (57).

HRMS: calculated for $C_{21}H_{31}N_2$ $[M+H]^+$ 295.1417; found 295.1417; Δ = 0.4 ppm.

5.3.3.8. N-(1-(4-Methoxyphenyl)propyl)-3-methylpyridin-2-amine (15)

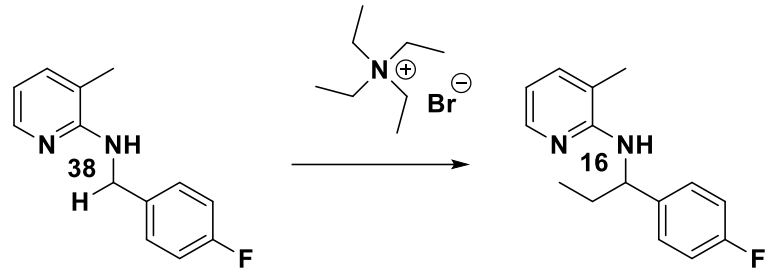


The reaction was carried out according to general procedure A with N-(4-methoxybenzyl)-3-methylpyridin-2-amine (**37**) (114 mg, 0.50 mmol, 1 eq.), tetraethylammonium bromide (105 mg, 0.50 mmol, 1 eq.), KOH (84 mg, 1.50 mmol, 3 eq.) and $[RhCl(cod)]_2$ (12 mg, 0.025 mmol, 0.05 eq.) in dry and degassed toluene (2 ml). The reaction mixture was heated for 16 h at 140 °C. The general work-up procedure B for C-H activation reactions was followed using gradient A. Product **15** was isolated in 71 % yield.

N-(1-(4-Methoxyphenyl)propyl)-3-methylpyridin-2-amine (15) Yellowish oil (92 mg, 71 %).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.93 (t, J = 7.4 Hz, 3H, C[4]-H_3), 1.78 – 1.91 (m, 1H, C[3]-H), 1.92 – 2.04 (m, 1H, C[3]-H), 2.10 (s, 3H, C[7a]-H_3), 3.78 (s, 3H, C[8b]-H_3), 4.34 (d, J = 7.6 Hz, 1H, N[1]-H), 5.13 (q, J = 7.2 Hz, 1H, C[2]-H), 6.47 (dd, J = 7.1, 5.1 Hz, 1H, C[5a]-H), 6.84 – 6.89 (m, 2H, C[3b; 5b]-H), 7.19 (ddq, J = 7.1, 1.7, 0.9 Hz, 1H, C[4a]-H), 7.27 – 7.32 (m, 2H, C[2b; 6b]-H), 7.97 (ddd, J = 5.1, 1.8, 0.7 Hz, 1H, C[6a]-H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 10.9 (q, C[4]), 17.2 (q, C[7a]), 30.2 (t, C[3]), 55.3 (q, C[8b]), 55.6 (d, C[2]), 112.6 (d, C[5a]), 113.9 (d, C[3b; 5b]), 116.4 (s, C[3a]), 127.8 (d, C[2b; 6b]), 136.3 (s, C[1b]), 136.9 (d, C[4a]), 145.6 (d, C[6a]), 156.3 (s, C[4b]), 158.5 (s, C[2a]).

TLC: 0.41 (LP/EtOAc 5:1)
GCMS: Retention time: 7.31 min. Main fragments: 256 (M^+, 21), 227 (96), 149 (41), 133 (14), 121 (68), 108 (21), 92 (100), 77 (13), 65 (24).
HRMS: calculated for $C_{21}H_{31}N_2$ $[M+H]^+$ 257.1648; found 257.1666; Δ = 6.95 ppm.

5.3.3.9. N-(1-(4-fluorophenyl)propyl)-3-methylpyridin-2-amine (16)



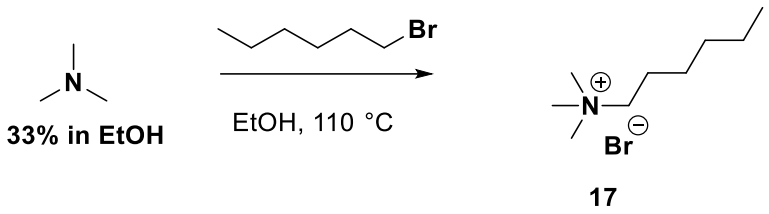
The reaction was carried out according to general procedure A for C-H activation reactions with N-(4-fluorobenzyl)-3-methylpyridin-2-amine (**38**) (108 mg, 0.50 mmol, 1 eq.), tetraethylammonium bromide (105 mg, 0.50 mmol, 1 eq.), KOH (84 mg, 1.50 mmol, 3 eq.) and $[RhCl(cod)]_2$ (12 mg, 0.025 mmol, 0.05 eq.) in dry and degassed toluene (2 ml). The reaction mixture was heated for 16 h at 140 °C. The general work-up procedure B for C-H activation reactions was followed using gradient A. Product **16** was isolated in 50 % yield.

N-(1-(4-fluorophenyl)propyl)-3-methylpyridin-2-amine (16) Yellow oil (61 mg, 50 %).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.94 (t, J = 7.4 Hz, 3H, C[4]-H_3), 1.80 – 2.00 (m, 2H, C[3]-H_2), 2.12 (s, 3H, C[7a]-H_3), 4.35 (d, J = 7.5 Hz, 1H, N[1]-H), 5.15 (q, J = 7.2 Hz, 1H, C[2]-H), 6.49 (dd, J = 7.1, 5.1 Hz, 1H, C[5a]-H), 6.93 – 7.04 (m, 2H, C[3b; 5b]-H), 7.16 – 7.23 (m, 1H, C[4a]-H), 7.29 – 7.39 (m, 2H, C[2b; 6b]-H), 7.95 (dd, J = 5.2, 1.7 Hz, 1H, C[6a]-H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 10.9 (q, C[4]), 17.2 (q, C[7a]), 30.4 (t, C[3]), 55.6 (d, C[2]), 112.9 (d, C[5a]), 115.2 (d, J_{CF} = 21.2 Hz, C[3b; 5b]), 116.4 (s, C[3a]), 128.2 (d, J_{CF} = 7.9 Hz, C[2b; 6b]), 137.0 (d, C[4a]), 140.1 (s, J_{CF} = 3.2 Hz, C[1b]), 145.6 (d, C[6a]), 156.1 (s, C[2a]), 161.8 (s, J_{CF} = 244.2 Hz, C[4b]).

TLC: 0.49 (LP/EtOAc 5:1)
GCMS: Retention time: 6.52 min. Main fragments: 244 (M^+, 16), 215 (100), 152 (9), 119 (11), 109 (59), 92 (59), 65 (28).
HRMS: calculated for $C_{21}H_{31}N_2$ $[M+H]^+$ 245.1449; found 245.1463; Δ = 6.21 ppm.

5.3.4. Synthesis of Quaternary Ammonium Salts

5.3.4.1. N,N,N-Trimethylhexylammonium bromide (17)



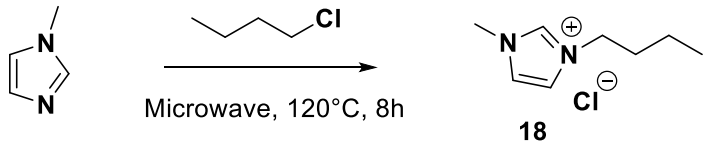
17

1-Bromohexane (1.40 ml, 10 mmol, 1 eq.) and ethanol (40 ml) were placed in an oven dried 100 ml flask and trimethylamine (4 ml, 33 % solution in EtOH) was added slowly while stirring at r.t. The reaction was refluxed at 110°C for 42 h (TLC).
The solvent was evaporated under reduced pressure leaving pure product with 92 % yield. The analytical data were in accordance with literature.[46]

N,N,N-Trimethylhexylammonium bromide (17) Beige solid (2.07 g, 92 %)
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.84 (t, J = 7.4 Hz, 3H, N-$(CH_2)_5$-*CH_3*), 1.21 – 1.39 (m, 6H, N-$(CH_2)_2$-(*CH_2*)*$_3$*-CH_3), 1.65 – 1.77 (m, 2H, N-CH_2-*CH_2*-$(CH_2)_3$-CH_3), 3.43 (s, 9H, N-*$(CH_3)_3$*), 3.53 – 3.62 (m, 2H, N-*CH_2*-$(CH_2)_4$-CH_3).
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 13.9 (q, N-$(CH_2)_5$-*CH_3*), 22.4 (t, N-$(CH_2)_4$-*CH_2*-CH_3), 23.2 (t, N-$(CH_2)_2$-*CH_2*-$(CH_2)_2$-CH_3), 25.8 (t, N-CH_2-*CH_2*-$(CH_2)_3$-CH_3), 31.3 (t, N-$(CH_2)_3$-*CH_2*-CH_2-CH_3), 53.4 (q, N-*$(CH_3)_3$*), 67.0 (t, N-*CH_2*-$(CH_2)_4$-CH_3).

MP: 176.9-178.1 °C

5.3.4.2. 1-Butyl-3-methylimidazolium chloride (18)



18

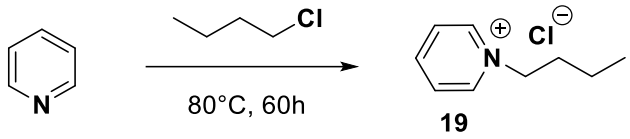
1-Methylimidazole (0.96 ml, 12 mmol, 1 eq.) and distilled 1-chlorobutane (1.75 ml, 16.8 mmol, 1.4 eq.) were placed in a 20ml microwave vial with a septum cap and flushed with argon. The reaction was carried out in microwave at 120 °C for 8 hours (^{1}H-NMR showed full conversion). The solution was washed with EtOAc and dried under reduced pressure at 80 °C for 18 h which

led to a colorless solid with 92 % yield.
The analytical data were in accordance to literature.[47]

1-Butyl-3-methylimidazolium chloride (18) Colorless solid (1.92 g, 92 %)
^{1}H-NMR (400 MHz, DMSO-d6): δ = 0.89 (t, J = 7.4 Hz, 3H, N-$(CH_2)_3$-*CH_3*), 1.18 – 1.33 (m, 2H, N-$(CH_2)_2$-*CH_2*-CH_3), 1.69 – 1.81 (m, 2H, N-CH_2-*CH_2*-CH_2-CH_3), 3.86 (s, 3H, N-*CH_3*), 4.18 (t, J = 7.2 Hz, 2H, N-*CH_2*-CH_2-CH_2-CH_3), 7.75 (t, J = 1.8 Hz, 1H, H5), 7.82 (t, J = 1.8 Hz, 1H, H4), 9.32 – 9.39 (m, 1H, H2).
^{13}C-NMR (101 MHz, DMSO-d6): δ = 13.3 (q, N-$(CH_2)_3$-*CH_3*), 18.7 (t, N-$(CH_2)_2$-*CH_2*-CH_3), 31.4 (t, N-CH_2-*CH_2*-CH_2-CH_3), 35.7 (q, N-*CH_3*), 48.4 (t, N-*CH_2*-CH_2-CH_2-CH_3), 122.2 (d, C[4]), 123.6 (d, C[5], 136.6 (d, C[2]).

MP: 69.4-70.3 °C

5.3.4.3. 1-Butylpyridinium chloride (19)



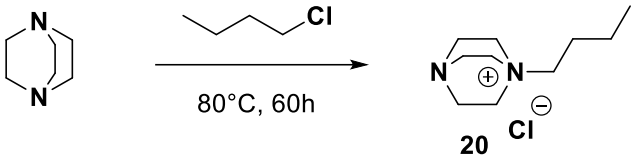
19

Anhydrous pyridine (0.97 ml, 12 mmol, 1 eq.) and distilled 1-chlorobutane (1.63 ml, 15.6 mmol, 1.3 eq.) were placed in an 8 ml glass vial with septum screw cap and flushed with argon. The reaction was carried out in a heating block at 80 °C for 60h. A solid precipitated and was filtered, washed with EtOAc and cold Et_2O and dried under reduced pressure. An off-white solid was obtained in 82% yield.
The analytical data were in accordance to literature.[48]

1-Butylpyridinium chloride (19) Offwhite solid (1.68 g, 82 %)
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.92 (t, J = 7.4 Hz, 3H, N-$(CH_2)_3$-*CH_3*), 1.30 – 1.48 (m, 2H, N-$(CH_2)_2$-*CH_2*-CH_3), 1.94 – 2.10 (m, 2H, N-CH_2-*CH_2*-CH_2-CH_3), 5.03 (t, J = 7.4 Hz, 2H, N-*CH_2*-CH_2-CH_2-CH_3), 8.13 (t, J = 7.1 Hz, 2H, H3; H5), 8.47 (t, J = 7.9 Hz, 1H, H4), 9.74 (d, J = 5.5 Hz, 2H, H2; H6).
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 13.6 (q, N-$(CH_2)_3$-*CH_3*), 19.4 (t, N-$(CH_2)_2$-*CH_2*-CH_3), 34.0 (t, N-CH_2-*CH_2*-CH_2-CH_3), 61.8 (t, N-*CH_2*-CH_2-CH_2-CH_3), 128.5 (d, C[3]; C[5]), 144.9 (d, C[4]), 145.6 (d, C[2]; C[6]).

MP: 130.1-131.0 °C

5.3.4.4. 1-Butyl-1,4-diazabicyclo[2.2.2]octane-1-ium chloride (20)

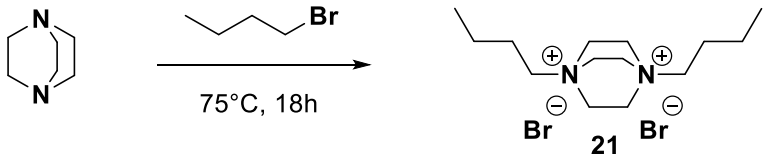


DABCO (1 ml, 9.09 mmol, 1 eq.), distilled 1-chlorobutane (1.04 ml, 10 mmol, 1.1 eq.) and EtOAc (2 ml) were placed in an 8 ml glass vial with septum screw cap and flushed with argon. The reaction was carried out in a heating block at 80 °C for 60 h. A solid precipitated and was filtered, washed with cold Et_2O and dried under reduced pressure. A colorless solid was obtained in 85% yield.
The analytical data were in accordance to literature.[49]

1-Butyl-1,4-diazabicyclo[2.2.2]octane-ium-chloride (20) Colorless solid (1.58 g, 85 %)
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.95 (t, J = 7.3 Hz, 3H, N[1]-$(CH_2)_3$-*CH_3*), 1.38 (q, J = 7.4 Hz, 2H, N[1]-$(CH_2)_2$-*CH_2*-CH_3), 1.72 (m, 2H, N[1]-CH_2-*CH_2*-CH_2-CH_3), 3.25 (t, J = 7.5 Hz, 6H, N[4]-*$(CH_2)_3$*), 3.46 – 3.57 (m, 2H, N[1]-*CH_2*-CH_2-CH_2-CH_3), 3.67 (t, J = 7.5 Hz, 6H, N[1]-*$(CH_2)_3$*).
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 13.8 (q, N[1]-$(CH_2)_3$-*CH_3*), 19.9 (t, N[1]-$(CH_2)_2$-*CH_2*-CH_3), 24.1 (t, N[1]-CH_2-*CH_2*-CH_2-CH_3), 45.5 (t, N[4]-*$(CH_2)_3$*), 52.5 (t, N[1]-*$(CH_2)_3$*), 64.4 (t, N[1]-*CH_2*-CH_2-CH_2-CH_3).

MP: 133.4-134.4 °C

5.3.4.5. 1,4-Dibutyl-1,4-diazabicyclo[2.2.2]octane-1,4-diium dibromide (21)



DABCO (0.49 ml, 4.46 mmol, 1 eq.), distilled 1-bromobutane (1.46 ml, 13.37 mmol, 3 eq.) and ethanol (2 ml) were placed in an 8 ml glass vial with septum screw cap and flushed with argon. The reaction was carried out in a heating block at 75 °C for 18 h. The solvent was evaporated under reduced pressure until the reaction mixture became a colorless oil. The crude product was washed with cold Et_2O until a colorless solid precipitated, which was dried under reduced pressure. A colorless solid was obtained in 87% yield.
The analytical data were in accordance to literature.[50]

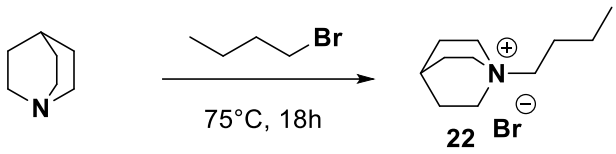
1,4-Dibutyl-1,4-diazabicyclo[2.2.2]octane-1,4-diium dibromide (21) Colorless solid (1.50 g, 87 %)

^{1}H-NMR (400 MHz, D_2O): δ = 0.98 (t, J = 7.4 Hz, 6H, 2 x N-$(CH_2)_3$-*CH_3*), 1.44 (h, J = 7.4 Hz, 4H, 2x N-$(CH_2)_2$-*CH_2*-CH_3), 1.76 – 1.91 (m, 4H, 2x N-CH_2-*CH_2*-CH_2-CH_3), 3.54 – 3.66 (m, 4H, N-*CH_2*-CH_2-CH_2-CH_3), 4.02 (s, 12H, 2x N-*$(CH_2)_3$*).

^{13}C-NMR (101 MHz, D_2O): δ = 12.7 (q, 2x N-$(CH_2)_3$-*CH_3*), 18.8 (t, 2x N-$(CH_2)_2$-*CH_2*-CH_3), 23.4 (t, 2x N-CH_2-*CH_2*-CH_2-CH_3), 51.1 (t, 2x N-*$(CH_2)_3$*), 65.1 (t, 2x N-*CH_2*-CH_2-CH_2-CH_3).

MP: 241.2-242.3 °C

5.3.4.6. 1-Butylchinuclidin-1-ium bromide (22)



22

Chinuclidin (500 mg, 4.50 mmol, 1 eq.), distilled 1-bromobutane (0.53 ml, 4.95 mmol, 1.1 eq.) and EtOAc (2 ml) were placed in an 8 ml glass vial with septum screw cap and flushed with argon. The reaction was carried out in a heating block at 75 °C for 18 h. The reaction mixture became a colorless solid already after 30 min. The crude solid was filtered and washed with a plenty amount of cold Et_2O and dried under reduced pressure. A colorless solid was obtained in 89% yield.

The analytical data were in accordance to literature.[51]

1-Butylchinuclidin-1-ium bromide (22) Colorless solid (1.11 g, 89 %)

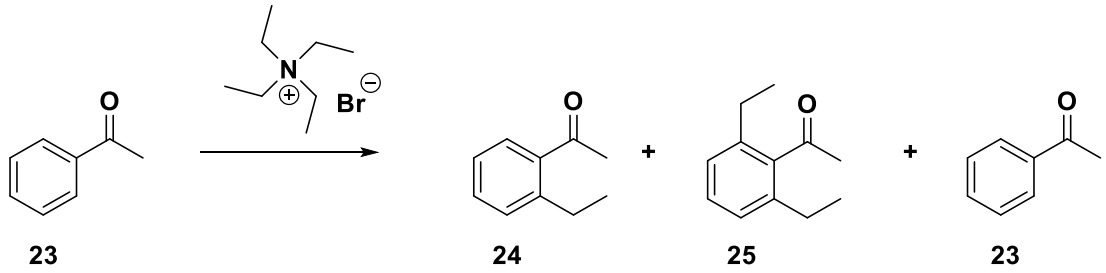
^{1}H-NMR (400 MHz, D_2O): δ = 0.95 (t, J = 7.4 Hz, 3H, N-$(CH_2)_3$-*CH_3*), 1.36 (h, J = 7.4 Hz, 2H, N-$(CH_2)_2$-*CH_2*-CH_3), 1.64 – 1.79 (m, 2H, N-CH_2-*CH_2*-CH_2-CH_3), 1.92 – 2.05 (m, 6H, C[3]-H_2; [C5]-H_2; C[8]-H_2), 2.15 – 2.23 (m, 1H, C[4]-H), 3.06 – 3.17 (m, 2H, N-*CH_2*-CH_2-CH_2-CH_3), 3.35 – 3.46 (m, 6H, C[2]-H_2; [C6]-H_2; C[7]-H_2).

^{13}C-NMR (101 MHz, D_2O): δ = 12.8 (q, N-$(CH_2)_3$-*CH_3*), 19.1 (d, C[4]), 19.3 (t, N-$(CH_2)_2$-*CH_2*-CH_3), 23.4 (t, N-CH_2-*CH_2*-CH_2-CH_3; C[3]; [C5]; C[8]), 54.5 C[2]; [C6]; C[7]), 64.1 (t, N-*CH_2*-CH_2-CH_2-CH_3).

MP: 240.8-241.7 °C

5.3.5. Alternative Substrates

5.3.5.1. 1-(2-Ethylphenyl)ethan-1-one (24)



The reaction was carried out according to general procedure A with **23** (60 mg, 0.50 mmol, 1 eq.), tetraethylammonium bromide (315 mg, 1.50 mmol, 3 eq.), KOH (84 mg, 1.50 mmol, 3 eq.) and $RuH_2(CO)(PPh_3)_3$ (18 mg, 0.02 mmol, 0.04 eq.) in dry and degassed toluene (2 ml). The reaction mixture was heated for 22 h at 150 °C. The solid material was removed by filtration using a Pasteur pipette with cotton and silica (Silica was conditioned with EtOAc with 1% triethylamine to neutralize the acidic groups). The residue was washed with EtOAc. The combined organic phases were concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (LP/EtOAc; 2% EtOAc - both solvents with 1% triethylamine). Product **24** could not be separated from starting material **23** and byproduct **25** by column chromatography. Therefore we isolated a mixture of product, byproduct and starting material, which was quantified with ^{1}H-NMR. 73 mg of a brown liquid was obtained. Ratio of this 73 mg mixture was determined by NMR: product **24** / byproduct **25** / starting material **23** = 1/0.38/0.11. Calculated yields with Ratio: 67.1% product, 25.5% byproduct, 7.3% starting material.

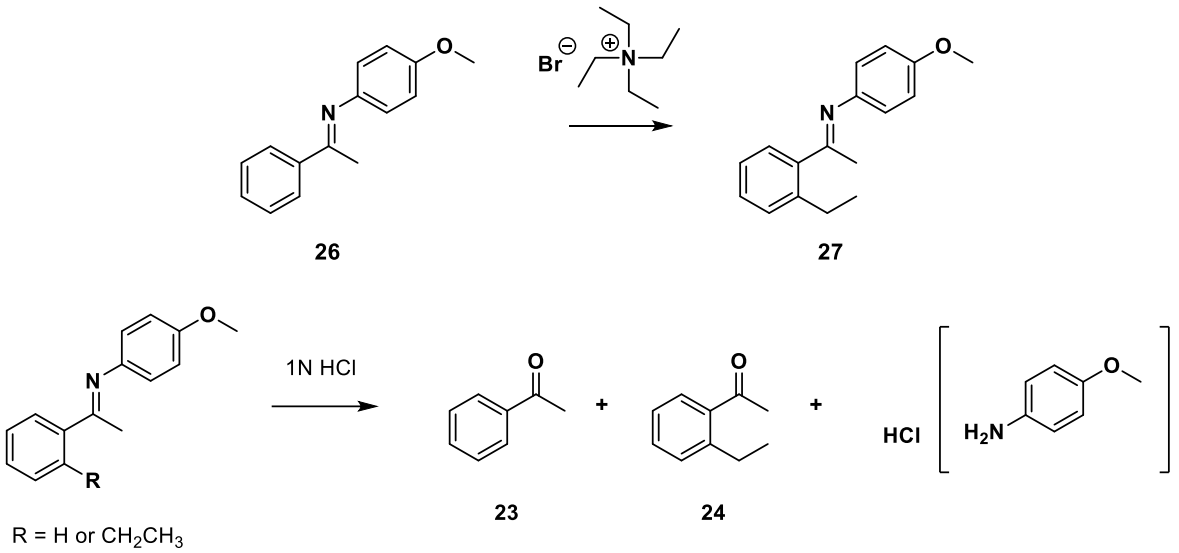
1-(2-Ethylphenyl)ethan-1-one (24)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.21 (td, J = 7.5, 1.7 Hz, 3H, CH_2-*CH_3*), 2.58 (s, 3H, CO-*CH_3*), 2.88 (q, J = 7.5 Hz, 2H, *CH_2*-CH_3), 7.25 – 7.29 (m, 2H, C[3]-H; C[5]-H), 7.40 (td, J = 7.5, 1.5 Hz, 1H, C[4]-H), 7.62 (dd, J = 7.7, 1.4 Hz, 1H, C[6]-H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 16.1 (q, CH_2-*CH_3*), 27.2 (t, *CH_2*-CH_3), 30.1 (q, CO-*CH_3*), 125.7 (d, C[3]), 129.1 (d, C[6]), 130.6 (d, C[5]), 131.6 (d, C[4]), 138.6 (s, C[1]), 144.3 (s, C[2]), 202.4 (s, C=O).

GCMS of Compound 24: Retention time: 3.90 min. Main fragments: 148 (M^+, 28), 133 (100), 115 (12), 105 (33), 91 (16), 79 (27).

5.3.5.2. 1-(2-ethylphenyl)-N-(4-methoxyphenyl)ethan-1-imine (27)



The reaction was carried out according to general procedure A with **26** (113 mg, 0.50 mmol, 1 eq.), tetraethylammonium bromide (315 mg, 1.50 mmol, 3 eq.), KOH (84 mg, 1.50 mmol, 3 eq.) and $RhCl(PPH_3)_3$ (23 mg, 0.025 mmol, 0.05 eq.) in dry and degassed toluene (2 ml). The reaction mixture was heated for 22 h at 150 °C. After cooling to r.t. 5 ml 1N HCl was added and stirred vigorously for 45 min. The hydrolyzed compounds were extracted with Et_2O and the combined organic layers were dried over Na_2SO_4. The solvents were evaporated under reduced pressure. The resulting crude material was purified with column chromatography (LP/EtOAc; 2% EtOAc - both solvents with 1% triethylamine). Product **24** could not be separated from compound **23** by column chromatography. Therefore a mixture was isolated which was quantified with ^{1}H-NMR. 62 mg of a brown liquid was obtained. Ratio of this 62 mg mixture was determined by NMR: product **24** / starting material **23** = 0.65/1. Calculated yields with Ratio: 39.4% product, 60.6% starting material.

1-(2-Ethylphenyl)ethan-1-one (24)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.22 (td, J = 7.5, 1.7 Hz, 3H, CH_2-*CH_3*), 2.58 (s, 3H, CO-*CH_3*), 2.88 (q, J = 7.5 Hz, 2H, *CH_2*-CH_3), 7.26 – 7.30 (m, 2H, C[3]-H; C[5]-H), 7.38 – 7.43 (m, 1H, C[4]-H), 7.62 (dd, J = 7.8, 1.4 Hz, 1H, C[6]-H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 16.1 (q, CH_2-*CH_3*), 27.2 (t, *CH_2*-CH_3), 30.1 (q, CO-*CH_3*), 125.7 (d, C[3]), 129.1 (d, C[6]), 130.6 (d, C[5]), 131.6 (d, C[4]), 138.1 (s, C[1]), 144.3 (s, C[2]), 202.4 (s, C=O).

GCMS of Compound 27: Retention time: 7.17 min. Main fragments: 253 (M^+, 31), 238 (16), 146 (21), 131 (75), 123 (100), 108 (48), 91 (31), 77 (49), 64 (23).

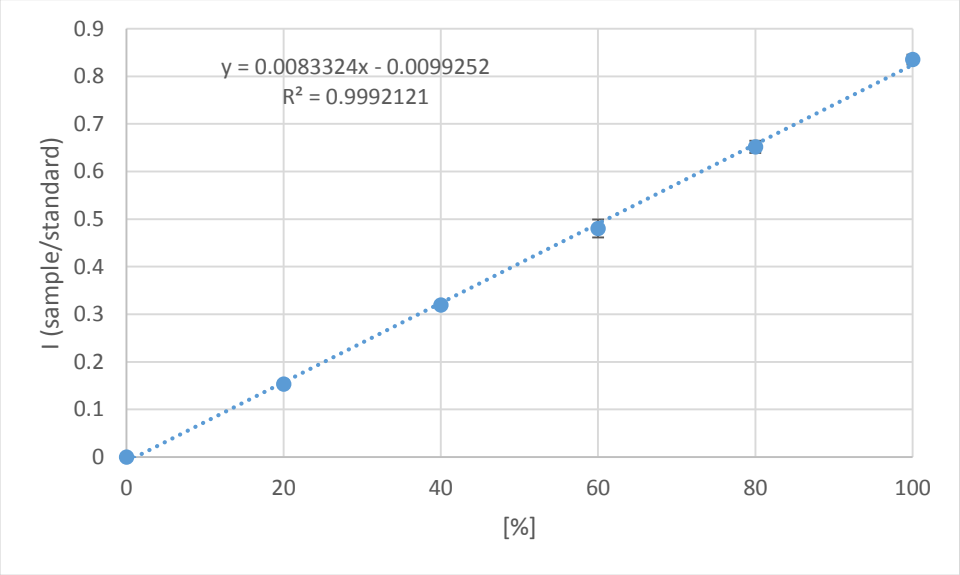
5.4. GC Calibration

5.4.1. General Procedure

The very pure compound was placed in a 10 ml volumetric flask and dissolved in 10 ml EtOAc. This stock solution was diluted 5 times by taking 0.8; 0.6; 0.4; 0.2 ml and backfilling the sample to 1 ml with EtOAc. Also a blank sample containing only 1 ml EtOAc without any compound was measured. At this stage, dodecane was added as internal standard to every 1 ml sample separately. The amount of compound (mol/ml) in the stock solution was calculated, and the same amount of dodecane was added to every sample. Each dilution series was performed twice, and each sample was measured twice by GC to exclude any operational failures in the procedure.

5.4.2. N-Benzyl-3-methylpiridin-2-amine (1)

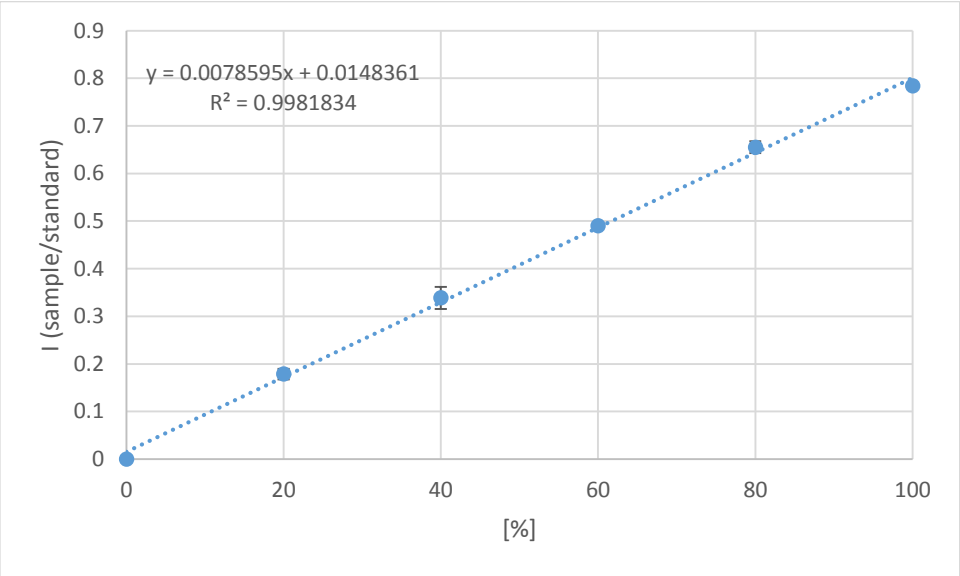
	WP [mg]	Stock sol. [mg/ml]	n [mmol]	[µl]
Compound 1	50.7	5.07	0.0256	
Dodecane			0.0256	5.8



Exp.	Compound	Standard	C/STD	Average	St.deva	Yield [%]
1A	4795378	5772722	0.8307	0.8351	0.0063	100
1B	4968112	5917073	0.8396			
2A	3591105	5629744	0.6379	0.6519	0.0199	80
2B	3954529	5936940	0.6661			
3A	2957209	6169331	0.4793	0.4802	0.0012	60
3B	2760808	5738035	0.4811			
4A	1942723	5979335	0.3249	0.3194	0.0076	40
4B	1781911	5673429	0.3140			
5A	908326	5693157	0.1595	0.1532	0.0088	20
5B	893569	6078104	0.1470			
6A	0	6015655	0	0	0	0
6B	0	6200815	0			

5.4.3. 3-Methyl-N-(1-phenylpropyl)pyridin-2-amine (2)

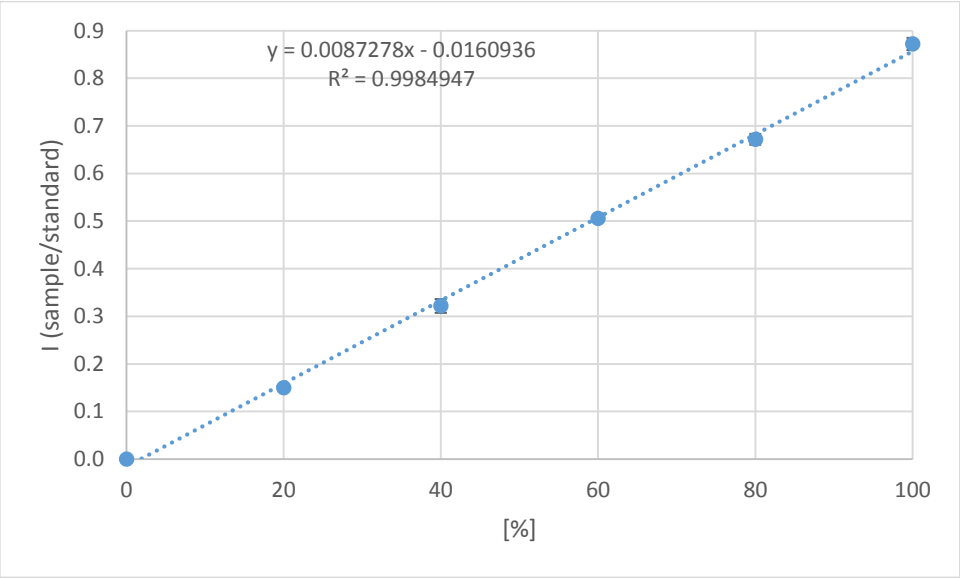
	WP [mg]	Stock sol. [mg/ml]	n [mmol]	[µl]
Compound 2	51.9	5.19	0.0229	
Dodecane			0.0229	5.2



Exp.	Compound	Standard	C/STD	Average	St.deva	Yield [%]
1A	5338061	6838969	0.7805	0.7839	0.0048	100
1B	5368112	6817073	0.7874			
2A	4542839	6838969	0.6642	0.6553	0.0126	80
2B	4354529	6736940	0.6463			
3A	3269098	6684184	0.4890	0.4902	0.0017	60
3B	3360808	6838035	0.4914			
4A	2427078	6833748	0.3551	0.3386	0.0233	40
4B	2181911	6773429	0.3221			
5A	1204454	7049999	0.1708	0.1786	0.0110	20
5B	1263569	6778104	0.1864			
6A	0	6515655	0	0	0	0
6B	0	6700815	0			

5.4.4. 3-Methyl-N-(1-phenylpentyl)pyridin-2-amine (4)

	WP [mg]	Stock sol. [mg/ml]	n [mmol]	[µl]
Compound 4	56.3	5.63	0.0221	
Dodecane			0.0221	5.0



Exp.	Compound	Standard	C/STD	Average	St.deva	Yield [%]
1A	7083177	8206139	0,8632	0.8722	0.0127	100
1B	7125337	8086306	0,8812			
2A	5460570	8226270	0,6638	0.6717	0.0112	80
2B	5452322	8022359	0,6796			
3A	4087478	8112093	0,5039	0.5059	0.0029	60
3B	4148791	8167410	0,5080			
4A	2850068	8587257	0,3319	0.3218	0.0143	40
4B	2647071	8492676	0,3117			
5A	1095848	7244834	0,1513	0.1502	0.0015	20
5B	1167961	7831471	0,1491			
6A	0	8112093	0	0	0	0
6B	0	8167410	0			

6. Literature

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