DIPLOMARBEIT

Alkyl halides as olefin surrogates in direct alkylation reactions via C-H activation

ausgeführt am

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Neque porro quisquam est, qui dolorem ipsum, quia dolor sit, amet, consectetur, adipisci velit.

—Marcus Tullius Cicero

For if we could be satisfied with anything, we should have been satisfied long ago.

—Seneca

Acknowledgements

First and foremost, I would like to thank my parents Heide and Wilhelm for the great support through all my life so far. Not only did they support me monetary throughout the whole studies so far but also they supported me in a very inter personal way. The same is true for my sister Clara and my brother Virgil, who always entertained me by enchanting messages. Together, you often helped me to bear bovine days.

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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 olefins, alkyl halides and even quaternary ammonium salts were already investigated in our group. However, the possibilities of the reaction using alkyl halides have not been elucidated so far. Preliminary results showed that alkyl halides undergo elimination to olefins prior to CH-activation reaction. 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 alkyl halides was the goal of this thesis. Alkyl halides are liquid at room temperature (until C16), not particular dangerous and cheap. Therefore, these compounds are easy to work with in the organic lab. In the progress of this thesis, we managed to find a working protocol exploiting alkyl halides as alkylating agents. Furthermore, the reaction conditions were optimized allowing us to perform this reaction with longer chained alkyl halides up to C22, generating in that case 1-docosene in the reaction mixture upon elimination. Moreover, two esters could be submitted to the respective reaction conditions with the ester moiety being retained in the final product. What is more, a scope of different substituted benzylic amines could be successfully alkylated.

Deutsche Kurzfassung

Diese Arbeit legt den Fokus hauptsächlich auf Rh(I)-katalysierte C-H Alkylierungsreaktionen. In dieser Gruppe wurden bereits Übergangsmetall-katalysierte direkte Alkylierungsreaktionen benzylischer Amine untersucht, wobei jeweils Olefine, Alkylhalogenide und sogar Quartäre Ammoniumsalze als Alkylierungsreagenzien zur Anwendung kamen. Jedoch wurden bisher die vollen Möglichkeiten der Reaktion mit Alkylhalogeniden noch nicht untersucht bzw. ausgeschöpft. Erste Resultate einer anderen Abschlussarbeit zeigten, dass Alkylhalogenide zuerst zu Olefinen eliminieren bevor sie im Rahmen einer C-H-Aktivierung reagieren. Das dabei gebildete Olefin kann in einer direkten C-H Alkylierung an benzylischen Aminen am benzylischen Kohlenstoffatom, wobei es von dem 3-substituierten pyridin-2-yl dirigiert wird, reagieren. Olefine werden oft als Alkylierungsreagenzien in der organischen Chemie verwendet, jedoch sind kurzkettige Olefine wie Ethen, Propen oder Buten bei Raumtemperatur gasförmig und hochentzündlich. Diese Nachteile zu überwinden, indem diese Olefine durch Alkylhalogenide ersetzt werden, war Ziel dieser Diplomarbeit. Alkyl Halogenide sind bei Raumtemperatur flüssig (bis C16), nicht besonders gefährlich und billig. Deshalb kann man mit dieser Substanzklasse gut im organischen Labor arbeiten.

Im Zuge dieser Arbeit wurde ein Protokoll entwickelt, das beschreibt, wie man Alkylhalogenide bestmöglich als Alkylierungsreagenzien benützt. Darüber hinaus wurden auch die Reaktionsbedingungen optimiert, sodass auch langkettige Alkylhalogenide bis C22 verwendet werden konnten, wobei dabei 1-Docosene nach vorangegangener Eliminierungsreaktion in der Reaktionsmischung entstand. Außerdem konnten zwei Alkylhalogenide, die auch Ester-Gruppen enthielten, zur Reaktion gebracht werden, wobei die Ester im fertigen Produkt wiedergefunden werden konnten.
Dann konnte noch ein Scope verschieden substituierter benzylischer Amine erfolgreich alkyliert werden.

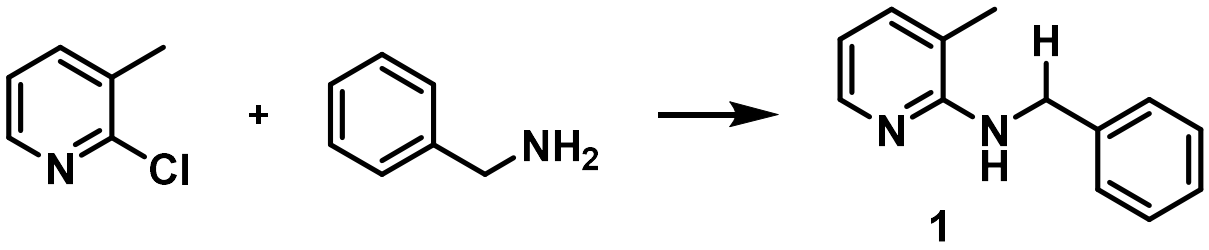
Key

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



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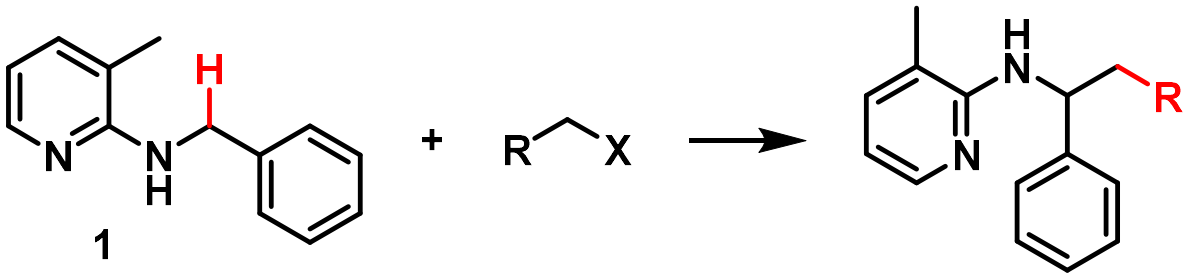

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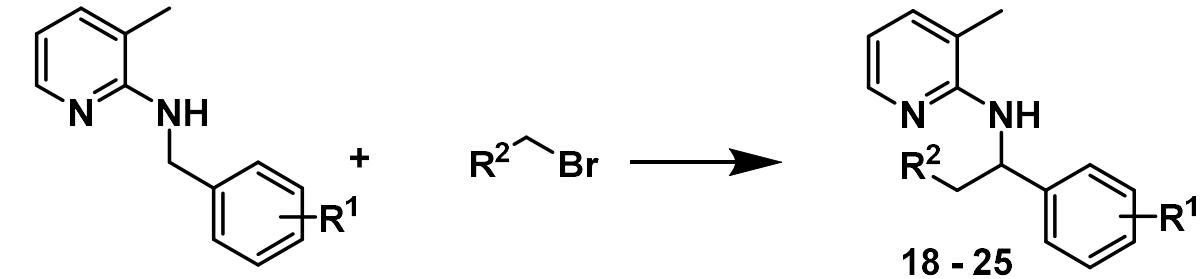
Table 1: Isolated yields of compounds using different chained alkyl halides up to C22

Compound Number	R	Isolated Yield [%]
2	methyl	25
3	ethyl	55
4	n-prop	56
5	n-but	54
6	n-pent	50
7	n-hex	38
8	n-hept	42
9	n-non	56
10	n-dec	60
11	n-undec	50
12	n-henicos	31
13	isobutyl	55
14	toluyl	43
18	ethyl propionate	57
19	ethyl butyrate	35



15: $R^1 = CH_3$
16: $R^1 = OCH_3$
17: $R^1 = CF_3$

Table 2: Isolated substrate scope on the target compound

Compound Nummer	R^1	R^2	Isolated Yield [%]
20	OCH_3	n-prop	56
21	OCH_3	n-non	56
22	CH_3	n-prop	47
23	CH_3	n-non	25
24	CF_3	n-prop	50
25	CF_3	n-non	62

2. Introduction

Direct C-H functionalization via metal catalysis is emerging as one of the most frequently investigated methods in recent years. This can be deduced from the large number of contributions published almost on a daily basis, and the number of review articles summarizing various aspects of the field. [1][2][3][4] The largest part of research is dedicated to functional group directed C-H functionalization reactions. By now literally all of the most frequently occurring functional groups have been used as a directing group, at least in a small set of examples. [5][6] Regarding the transformations which have been reported, the variety has increased in recent years as well. Besides arylation, alkylation, and alkenylation reactions, also more and more C-heteroatom bond forming reactions are disclosed. Regarding alkylation reactions, olefins are the most frequently applied alkyl source. [7] However, it has to be mentioned that literature examples often limit themselves to functional group-substituted or long-chain alkenes to avoid working with gaseous reagents.

If so, for introduction of short alkyl chains gaseous reagents could be replaced by liquid ones, which would still be more convenient than using their gaseous counterparts. We have previously investigated such a transformation briefly, and found that the reaction actually proceeds via initial elimination to the olefin, which is then the true alkylating agent. [8] However, we then focused on mechanistic investigations of the alkylation protocol using hex-1-ene and did not investigate the substrate scope of the alkyl bromide protocol. [9]

In literature, alkyl halides are known to be suitable alkyl sources for direct alkylation reactions. For most of them, such a mechanistic pathway can be excluded since alkyl halide substrates which cannot give elimination to an olefin are amongst the reported examples (e.g. benzyl halides or iodomethane). However, among the reported examples, there are some contributions in which there is a high probability that initial elimination might precede the actual alkylation.

In 2011 Ackermann and coworkers investigated sp^2-alkylation reactions of ketimines with alkyl halides catalyzed by ruthenium. With the optimized reaction conditions in hand the

substrate scope was explored. The scope was constituted mostly of linear alkyl halides but included also branched ones like neopentylbromide and even two esters. Based on these findings, the following catalytic cycle was proposed. [10]

The first step is an initial reversible cyclometalation, along with a subsequent activation of alkyl halide 2 and finally a reductive elimination.

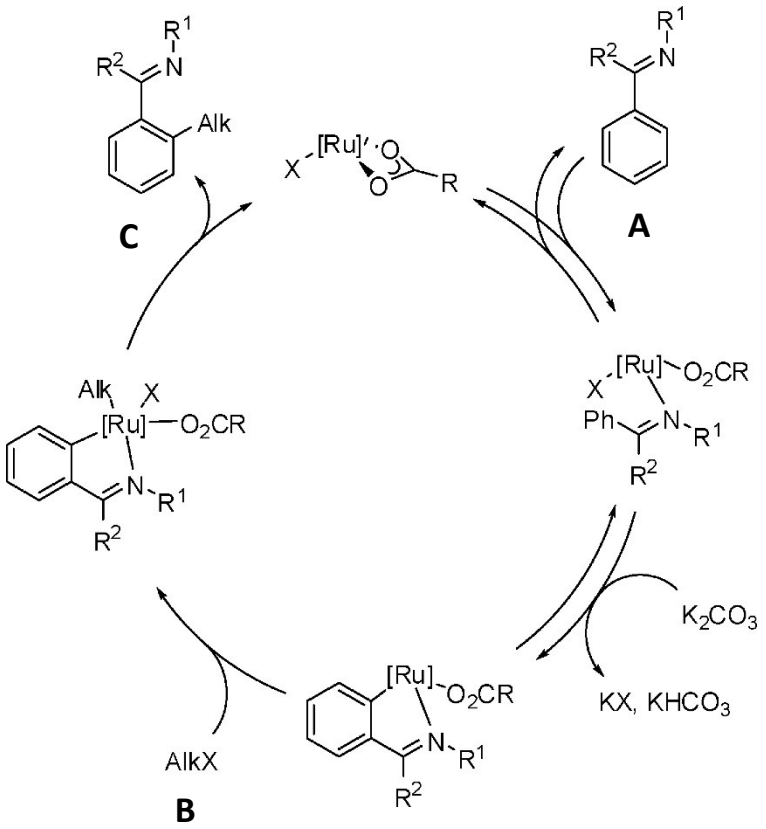
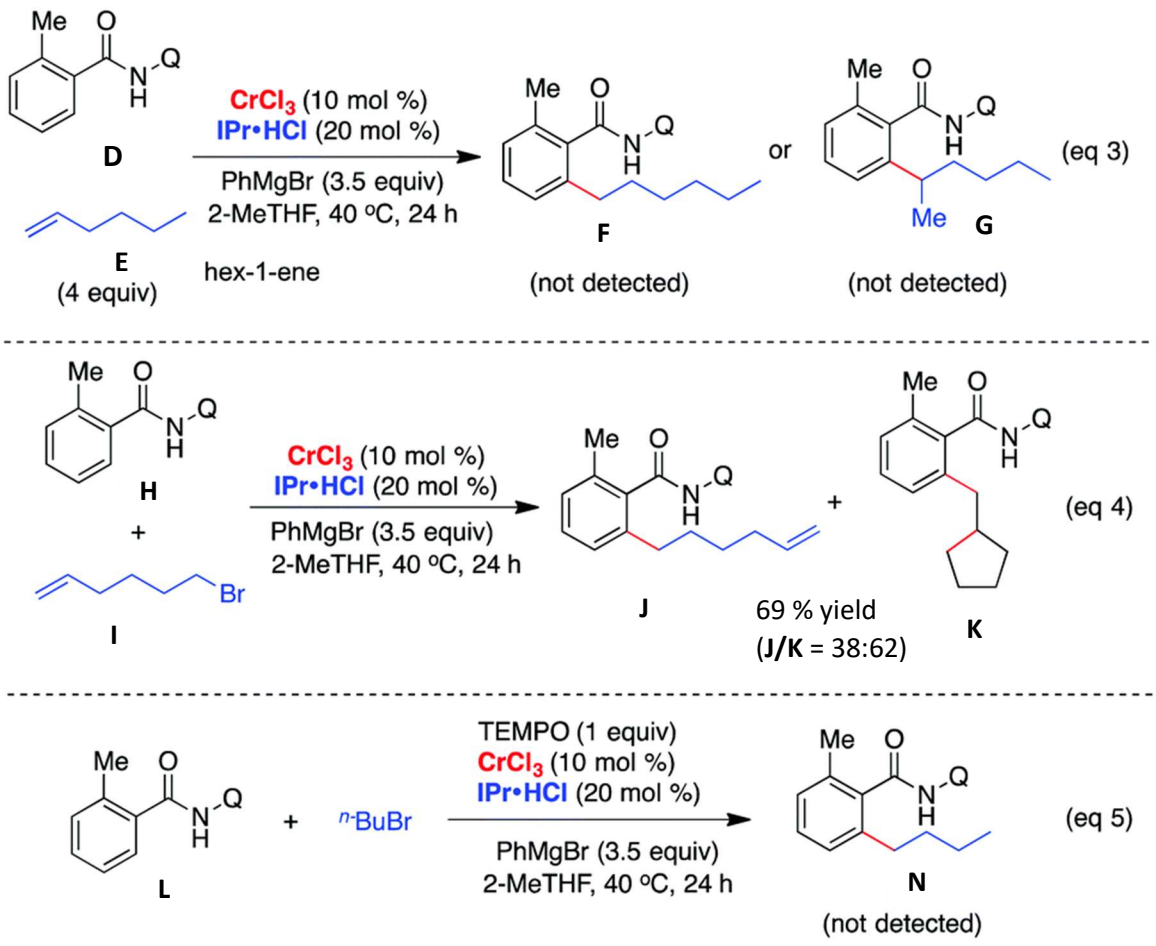


Figure 1: Proposed Mechanism of Ruthenium-Catalyzed Direct Alkylations (Ackermann, Hofmann, et al., 2011)

Gao and coworkers on the other hand used cobalt in combination with N-heterocyclic carbenes as preligands for their catalyst. But in parallel to the aforementioned reaction done by Ackermann they also alkylated ketimines. First, they investigated the substrate scope of primary alkyl halides, and then they investigated the substrate scope of secondary alkyl halides. In both substrate scopes the group delivers numerous examples delivering quite satisfying yields. Also the formation of olefins during the reaction that were formed by β-H-elimination was noticed. However, control experiments revealed, that terminal olefins are much less reactive then alkyl halides regarding the respective reaction in the case of primary halides or do not react at all in the case of secondary

halides. Thus, Gao concludes that olefins would not be involved in the major productive pathway of the present reaction. [11]

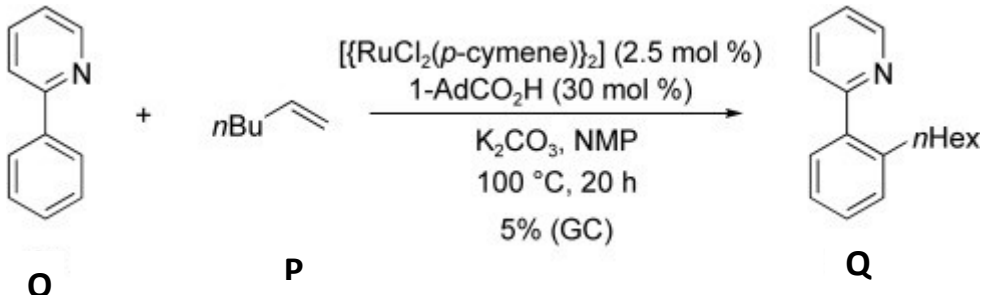
Tang also did investigations regarding CH-activation using alkyl halides. As substrate he used benzamides and as catalyst chromium and N-heterocyclic carbenes. When doing investigations regarding the mechanism, he encountered that no product was formed, when using an olefin. Thus, he concluded, that a process involving hydroarylation of olefins was not involved in the transformation. However, when submitting 6-bromo-1-hexene to the reaction two products were formed, see Scheme 1. Thus he concluded that the reaction works over a radical mechanism. This hypothesis is supported by the fact that no product was detected when TEMPO as radical scavenger was added. (Scheme 1) [12]



Scheme 1: Mechanistic Studies (Tang et al., 2018)

Another group from Japan used Nickel as central atom of the catalyst when alkylating aromatic amides containing an 8-aminoquinoline moiety as directing group. The group mostly used bromides but also tried iodides and chlorides. While the reaction worked fine with iodides, no reaction was observed, when using chlorides. Moreover, an experiment using an olefin instead of a halide was done but there was not observed any production of any product either. The group as well proposes a mechanism in which the alkyl halide enters the catalytic cycle as alkyl halide, i.e. without reacting before. [13]

Ackermann again says that a mechanism involving initial β-elimination of HX from the alkyl halide, along with a subsequent ruthenium-catalyzed hydroarylation, could be ruled out, as alkene 4 yielded only trace amounts of pyridine derivative 3 a under otherwise identical reaction conditions (Scheme 2). On the other hand, the respective reaction worked fine when subjecting alkyl halides to the reaction conditions. [14]



Scheme 2: Alkylation with an olefin

In another publication Ackermann investigates direct CH-activation with unactivated β-hydrogen-containing alkyl halides. Nevertheless he suggests a radical involving mechanism instead of β-hydrogen-elimination prior to CH-activation reaction. [15]

Again Chen investigated in a CH-activation reaction employing iodoalkans and received quite good yields. When he substituted the iodides by bromides, the yields dropped dramatically. Yet when optimizing the reaction conditions (higher cat-load, higher temperature, prolonged reaction time) the yield became quite satisfactory. Interestingly an alkyl bromide containing a terminal olefin delivered only a very low yield, however the terminal olefin was retained in the final product. Other functional groups were also

tolerated such as esters or acetals. Mechanistically the group proposes a six-membered palladacycle intermediate, however the paper does not go into detail whether the halide enters the catalytic cycle as halide or as an olefin. [16]

Wu used nickel as catalyst for his CH-activation reactions. To optimize the reaction, he used 1-iodopentane to couple with an amide, bearing also a quinoline as directing group. He investigated the substrate scope, using other linear alkyl halides. When using iododecane, he even could detect decene via GC-MS. This would be a hint, that β-H-elimination occurs on the target molecule. This elimination is also possible to occur at all substrates he uses for the substrate scope. Nevertheless, he proposes a mechanism that does not involve β-H-elimination. (see figure 2) Coordination of amide 1 to a Ni^{II} species followed by a ligand exchange process under basic conditions generates nickel complex A, which gives rise to the intermediate B via a reversible cyclometalation process. Oxidative addition of intermediate B with an alkyl halide followed by reductive elimination generates the intermediate D, which produces the desired product 2 upon protonation and regenerates the Ni^{II} species. Alternatively, the Ni^{III} complex E could be involved in this process by oxidation of intermediate B with an alkyl radical. Reductive elimination of the intermediate E followed by protonation generates the desired product 2 and a Ni^{I} species. Treatment of the Ni^{I} species with an alkyl halide produces the alkyl radical and Ni^{II} species. It is noteworthy that in the reaction of 1a with 1-iododecane, a small amount of decene, the β-H eliminated product of the alkyl metal intermediate, was detected by GC/mass, which indirectly supports the formation of the intermediate C or E. It should be mentioned that although this process could potentially begin with a Ni^{0} species, the extremely low yield of 2a with a catalytic amount of $Ni(COD)_2$ indicates that the catalytic cycle is unlikely initiated by a Ni^{0} species. [17]

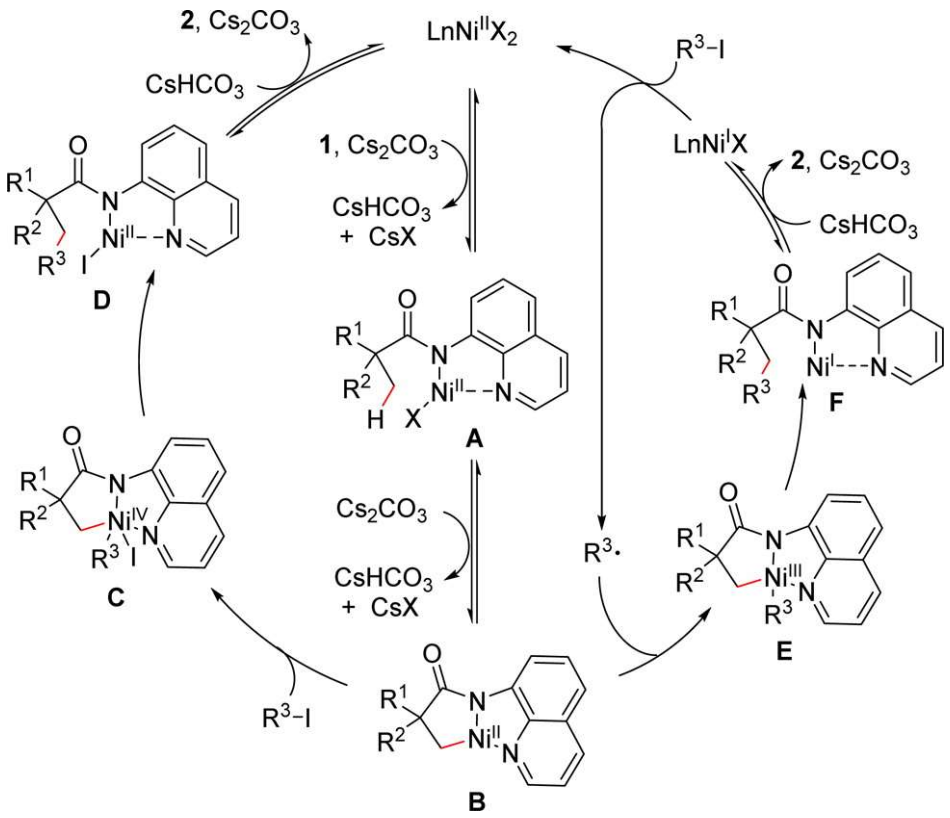
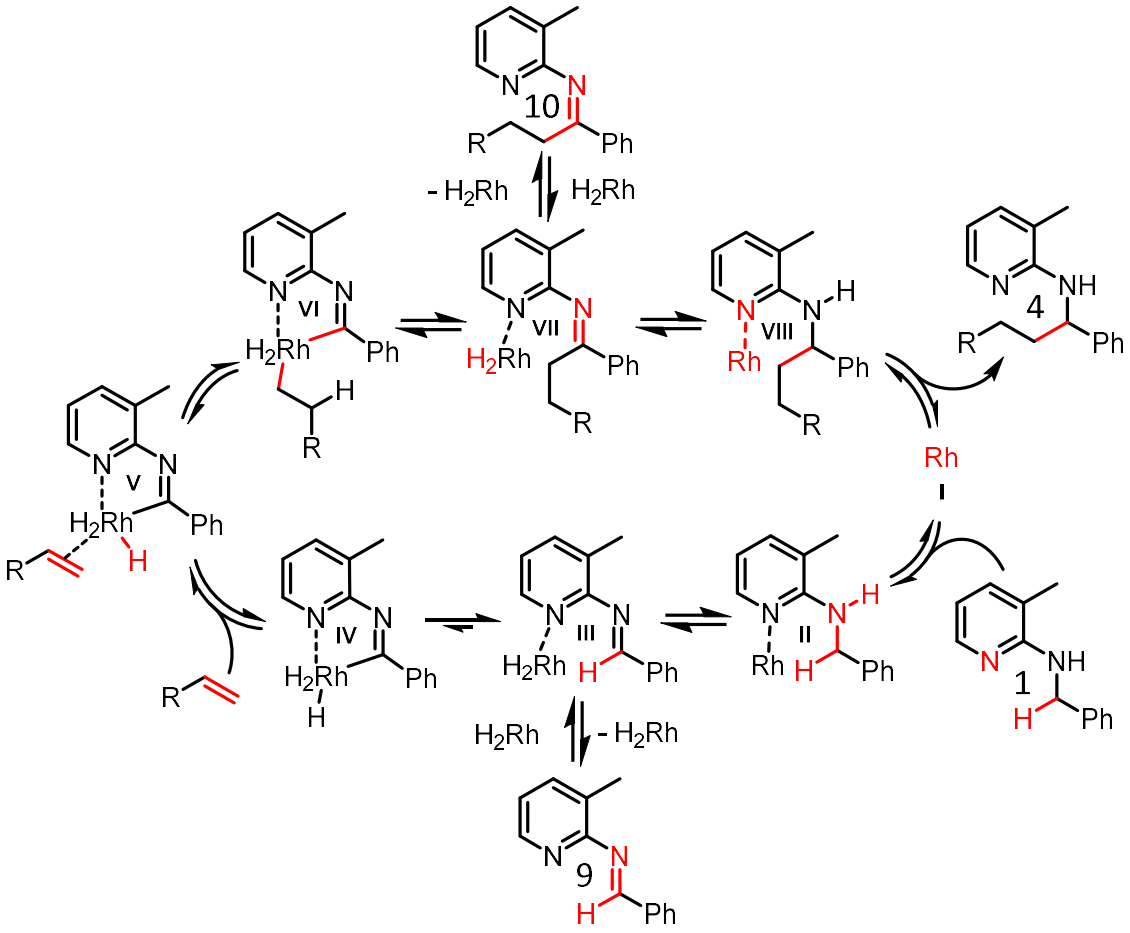


Figure 2: Proposed reaction mechanism by Wu (Wu et al., 2014)

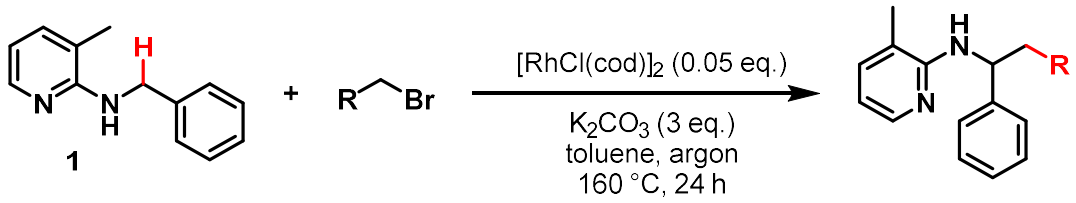
2.1. Direct Alkylation of Benzylic Amines in our Group

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, [8] using alkyl halides and later also olefins as alkyl source. Furthermore, ongoing kinetic and mechanistic investigations showed that the reaction did not proceed directly via the amines, but instead over the corresponding imines. This proved, that the formal C(sp^3)-H activation reactions did indeed proceed over a C(sp^2)-H activation pathway. This led directly to a new mechanistic proposal for the direct C-H alkylation reactions of benzylic amines (Scheme 3).



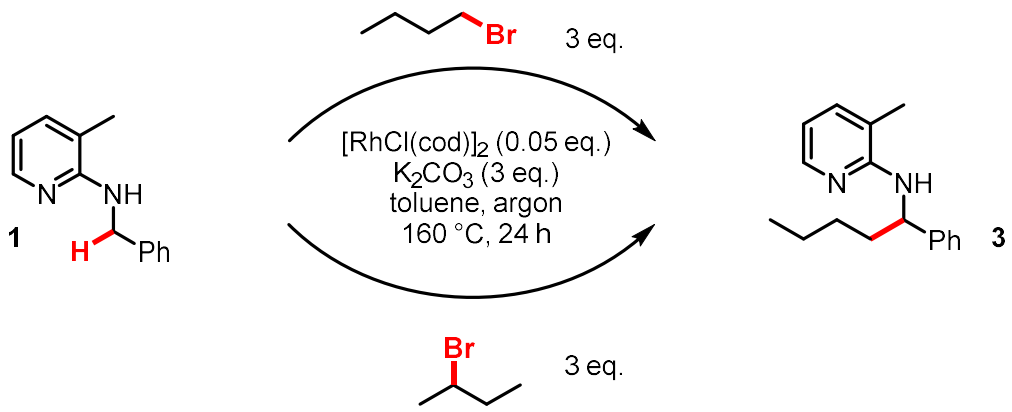
Scheme 3: Catalytic cycle

The catalytic cycle starts with pre-coordination of the benzylic amine to the rhodium species (Species II). After a reversible transformation to the corresponding imine complex (Species III), a cyclometalation step occurs (Species IV). Then, alkylation of this cyclometalated imine intermediate complex by an olefin (Species V) and reductive elimination (Species VII) leads to the product formation (Species VIII) and reactivation of the catalytic active species (Species I). 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. (Scheme 4)



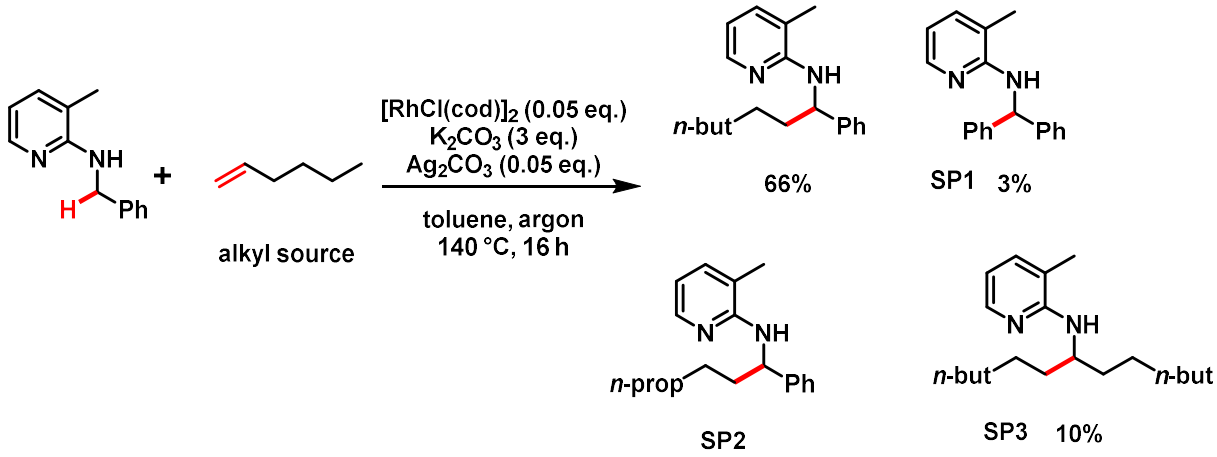
Scheme 4: Reaction with alkyl bromides

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 of the alkyl bromide, again the terminal position reacted (Scheme 5).



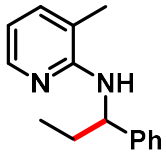
Scheme 5: Primary and secondary alkyl bromide lead to the same product.

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, as mentioned before. [18][19] In that case, using directly the olefin instead of generating it in-situ by elimination of an alkyl halide may be beneficial for the reaction. So further studies and optimization were focused on using olefins. Soon after, optimized conditions using olefins in this direct alkylation reactions were identified (Scheme 6). 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.



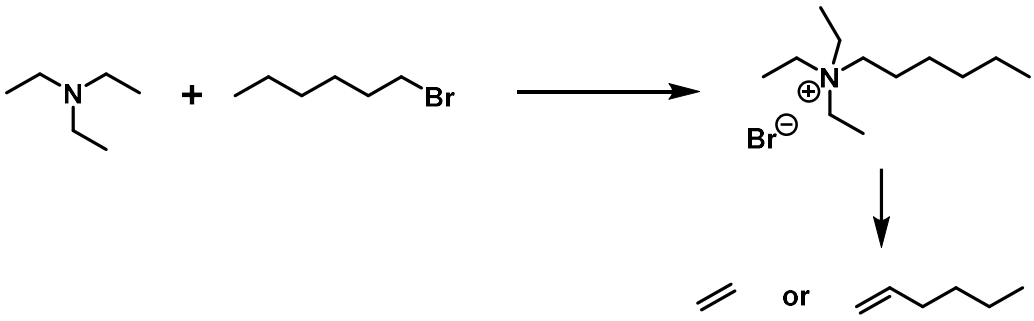
Scheme 6: Optimized reaction conditions for direct alkylation reaction using olefins. Also, showing the typical side products that are formed

The first major improvement in the reaction rate for this reaction was adding Ag_2CO_3 (0.05 equiv.). Further improvements focused on two main goals: Decreasing the reaction temperature and at the same time decreasing the amount of side products and with that increasing 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 SP2 could be significantly reduced. However, when Et_3N was available in the reaction mixture, a new byproduct was formed (Scheme 7)

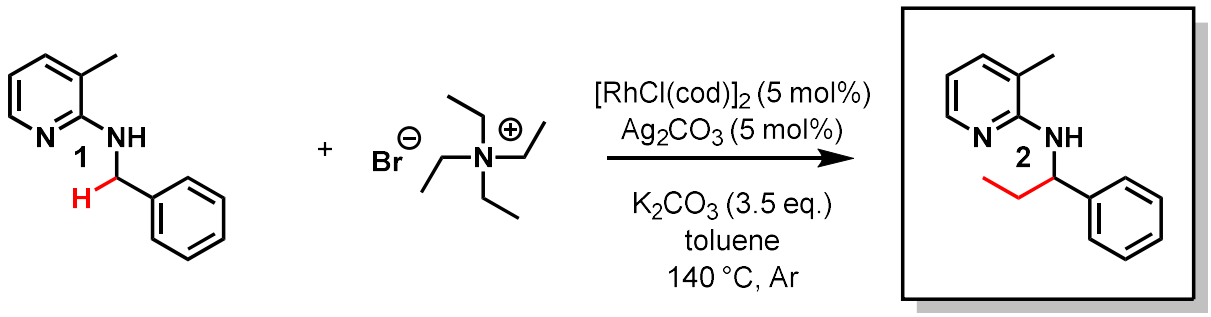


Scheme 7: The ethylated side product was formed as new side product once Et_3N was added to the reaction mixture.

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 8 and 9).



Scheme 8: Formation of ethylene and hexene respectively in situ via Hofmann elimination



Scheme 9: Formation of the ethylated side product

Due to the fact that quaternary ammonium salts are solid at room temperature, not particular dangerous and cheap. These compounds are easy to work with in the organic lab. Therefore, the reaction conditions were optimized resulting in a practical protocol to use solid materials instead of a gaseous or liquid olefin. This protocol allowed 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 with this method.

1. Motivation for this Thesis

The aforementioned knowledge built the basis for this thesis. Investigations into the unexpected product (Scheme 5) became the starting point for further experiments. The hypothesis of generating an olefin in-situ from the corresponding alkyl halide by E2-elimination became a very promising theory.

In comparison to the already mentioned quaternary ammonium salts, alkyl halides bear some advantages. First, they are used for the synthesis of quaternary ammonium salts, so using them directly for the CH-activation reaction circumvents one step in the synthesis. Moreover also complex and especially sterically demanding substrates are accessible by using alkyl halides as substrate for this reaction. Out of such substrates no quaternary ammonia salts can be made. Another benefit of the reaction with alkyl halides is that no potassium hydroxide is necessary for the reaction, making the reaction conditions milder. And last but not least, alkyl halides are cheap and they are available in every lab. Since they are liquid at room temperature, they are easy to handle in the lab. Hence, establishing alkyl halides as alternative alkylating agents was the ultimate goal of this thesis.

2. Results and Discussion

Before turning towards the substrate scope evaluation, we wanted to revisit the reaction optimization briefly. We started using the reaction conditions of a former member of this group.

1.2.1. Optimization

As mentioned before, previously in this group, experiments were made using 1-bromobutane as alkylating reagent, which yielded the desired product. When using 2-bromobutane for the same reaction, the result was kind of surprising, because the reaction delivered the same product as the aforementioned reaction. Thus, we concluded, that the respective bromobutane first eliminates to the respective (terminal) olefin before undergoing the reaction. So, the true alkylating reagent is not the alkylhalide but the in situ created olefin.

Then, in a first experiment, the reaction conditions of this original protocol were used on substrate **1** but the olefin was replaced with 1-bromohexane. The first result was not very satisfactory, delivering only 6 % yield of the desired product. So, we did some optimization efforts. First, we did two experiments once increasing and once decreasing the amount of base. Decreasing the amount of the base to 0.5 equivalents had a detrimental effect. The yield was decreased by half to 6 %. On the other side the threefold amount of base led to a slightly increased yield of 16 %. Next the temperature was increased up to 160 °C. This also led to an increase in yield by 22 %. Moreover we substituted the catalyst ($[RhCl(cod)]_2$ by $[RhOH\ (cod)]_2$. As we know from previous findings made in our group, the catalytically active species of the catalyst is the one in which the chlorine is replaced by the hydroxy group. This is created during the reaction by traces of water within the reaction mixture that react with the catalyst. Nevertheless, this did not lead to a higher yield in our case.

In a next step, we prolonged the reaction time first to 46 hours then to 70 ours. The resulting yield was 36 % and 41 % respectively.

The final step regarding the optimization was substituting KOH by K_2CO_3 and, at the same time, increasing the amount to 4.5 equivalents. The yield of this reaction was 50 % already within 22 hours.

Table 3 summarizes the results of the optimization efforts.

Table 3: Optimization results

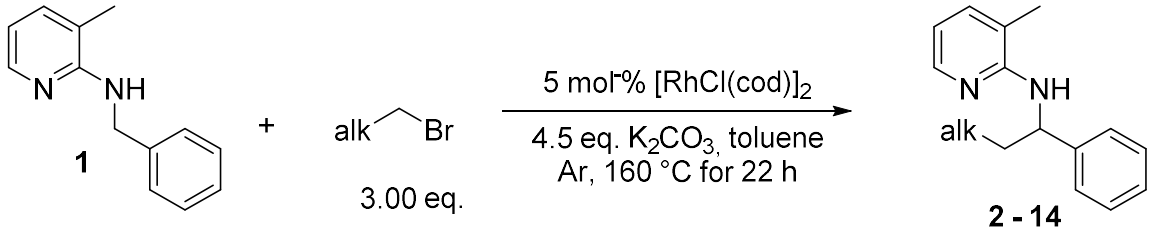
Entry	Base	Eq. Base	Catalyst (5 mol %)	Temperature [°C]	Time [h]	1-Bromohexane (Eq.)	Yield [%]
1	KOH	0.5	$[RhCl(cod)]_2$	140	22	3	6
2	KOH	1	$[RhCl(cod)]_2$	140	22	3	12
3	KOH	1.5	$[RhCl(cod)]_2$	140	22	3	21/19/19/15
4	KOH	1.5	$[RhOH(cod)]_2$	160	22	3	20
5	KOH	1.5	$[RhOH(cod)]_2$	160	36	3	22
6	KOH	1.5	$[RhOH(cod)]_2$	160	48	3	20
7	KOH	2	$[RhCl(cod)]_2$	140	22	3	26
8	KOH	2.5	$[RhCl(cod)]_2$	140	22	3	44
9	KOH	3	$[RhCl(cod)]_2$	140	22	3	16
10	KOH	3	$[RhCl(cod)]_2$	160	22	3	22
11	KOH	3	$[RhCl(cod)]_2$	160	46	3	36
12	KOH	3	$[RhCl(cod)]_2$	160	70	3	41
13	K_2CO_3	4.5	$[RhCl(cod)]_2$	160	22	3	50

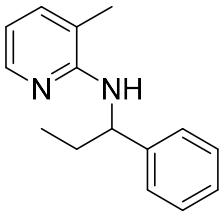
1.2.2. Substrate Scope

With the final conditions in hand, we started investigating the substrate scope with respect to alkyl bromides. First, we used different alkyl halides with a carbon chain length up to C22 (Scheme 10, products **2–14**).

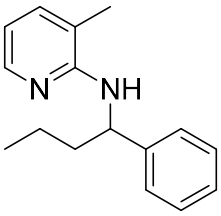
2-Bromoethane gave an isolated yield of only 25 % of **2**. However, for this example $N(Et)_4Br$ can be used giving 68% of the same product. [20] Using longer alkyl bromides gave much better results and yields typically around 50 %. Especially alkyl chains from C3 to C6 and C10 to C12 gave basically the same isolated yield, within experimental error (Scheme 10, compounds **3–6**; **9-11**, 50−60%). One reason, that longer chained alkyl halides work better might be, that the shorter chained substrate volatilizes before reacting. Interestingly, 1-bromoheptyl and 1-bromooctyl gave a slightly lower yield (**7**, 38% and **8**, 42%) the reason for that being currently unclear. To go to the extreme, we also tested 1-bromodocosane (C22, product **12**, 31%) and observed that such a long alkyl chain is still a potential substrate for this kind of reaction delivering the final product in 31 % yield.

In general, the yields obtained by the reactions with alkyl bromides instead of quaternary ammonium salts are slightly lower but alkyl halides are cheaper than quaternary ammonium salts, thus outweighing the disadvantages.

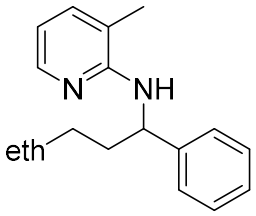




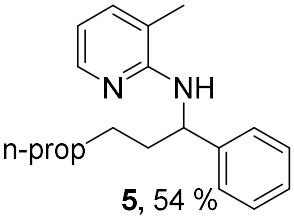
2, 25 %



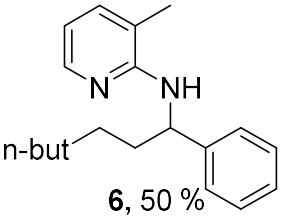
3, 55 %
32 % using 2-Br-propane



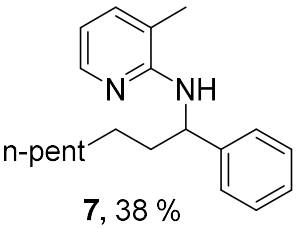
4, 56 %
19 % using 2-Br-butane



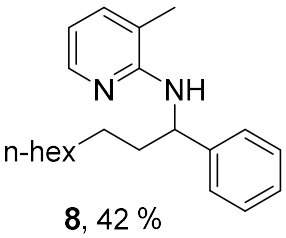
5, 54 %



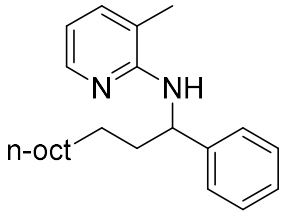
6, 50 %



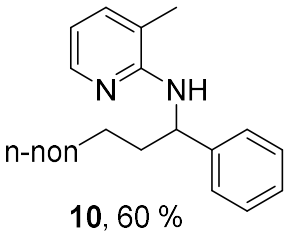
7, 38 %



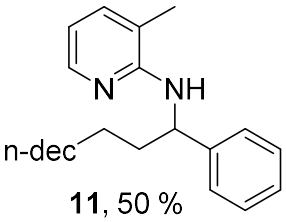
8, 42 %



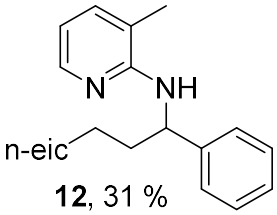
9, 56 %



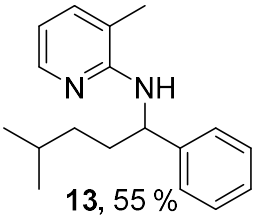
10, 60 %



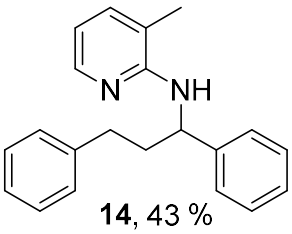
11, 50 %



12, 31 %



13, 55 %

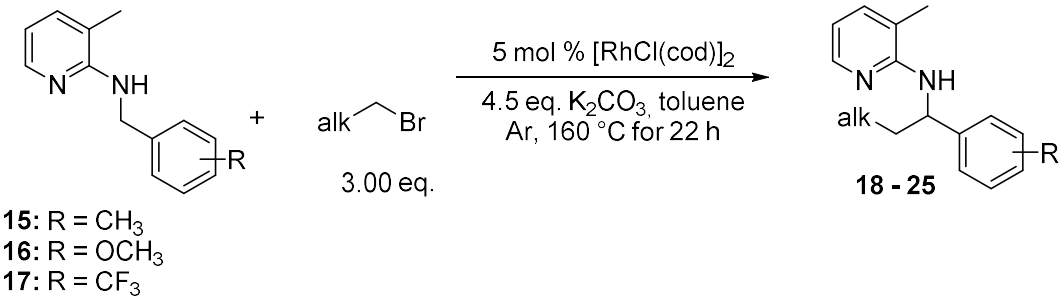


14, 43 %

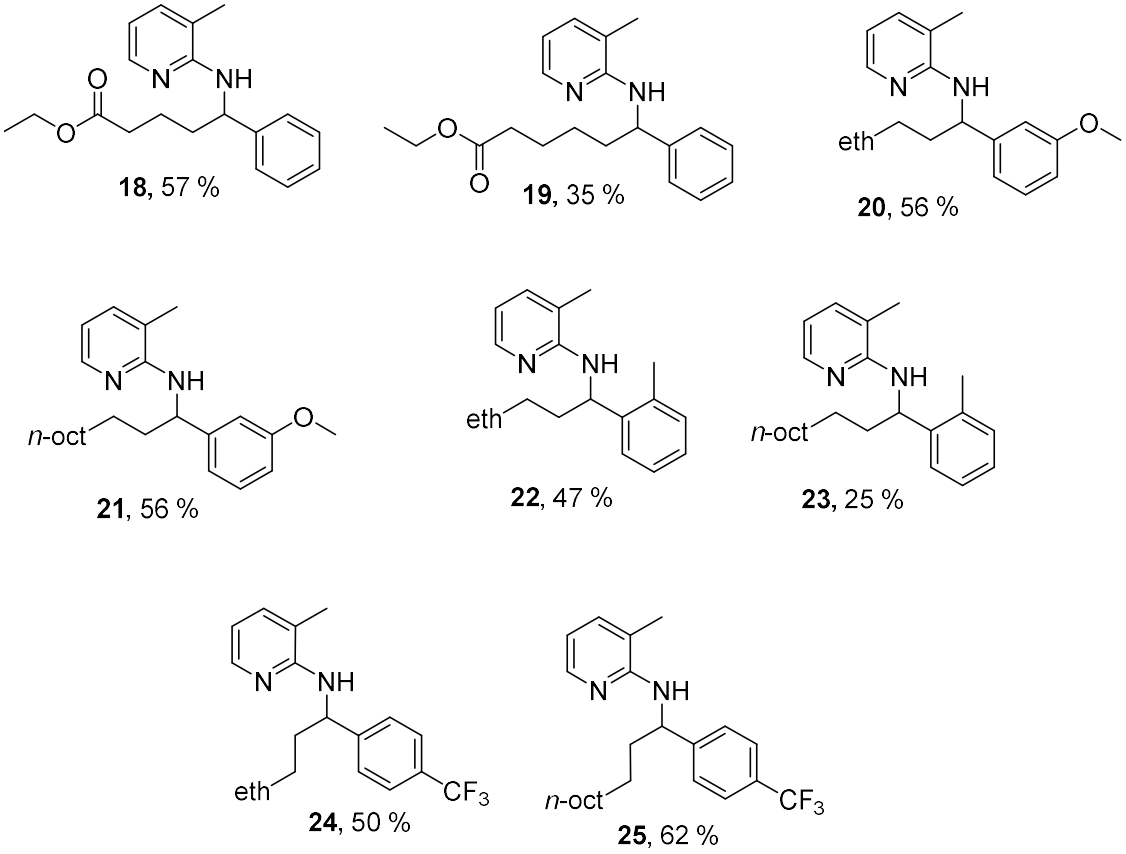
Scheme 10: Substrate Scope Alkyl Bromides

In addition to linear primary alkyl bromides, other alkyl bromides were tested as well. Secondary linear alkyl bromides such as 2-bromopropane and 2-bromobutane gave the same product as their primary isomers although in considerably lower yield. This goes along with the previous finding, that alkyl halides that are substituted at position 2 are bound to the substrate at position 1. The lower yield may be explained by the fact, that the initial elimination to the corresponding olefin in case of 2-bromopropane is slower compared to 1-bromopropane. Additionally, 2-bromobutane can deliver two different olefins upon elimination, of which only the terminal one can react, although the internal one is the more stable one. That internal olefins cannot react was also shown by using cyclohexyl bromide as substrate, which gave no conversion at all. This will be discussed later on.

Next, branched primary bromo alkanes were tested. The reaction with 1-bromo-3-methylbutane as branched alkyl bromide delivered the product **13** in quite a good yield of 55% (Scheme 10, **13**). Also, the alkylation with 1-bromo-2-phenylethane, which delivers styrene upon elimination, worked with an acceptable yield of 43 % (Scheme 10, **14**). These two substrates are examples for substrates, which are not accessible for this reaction via quaternary ammonium salts due to their steric demand.



15: R = CH_3
16: R = OCH_3
17: R = CF_3



Scheme 11: Extended Substrate Scope

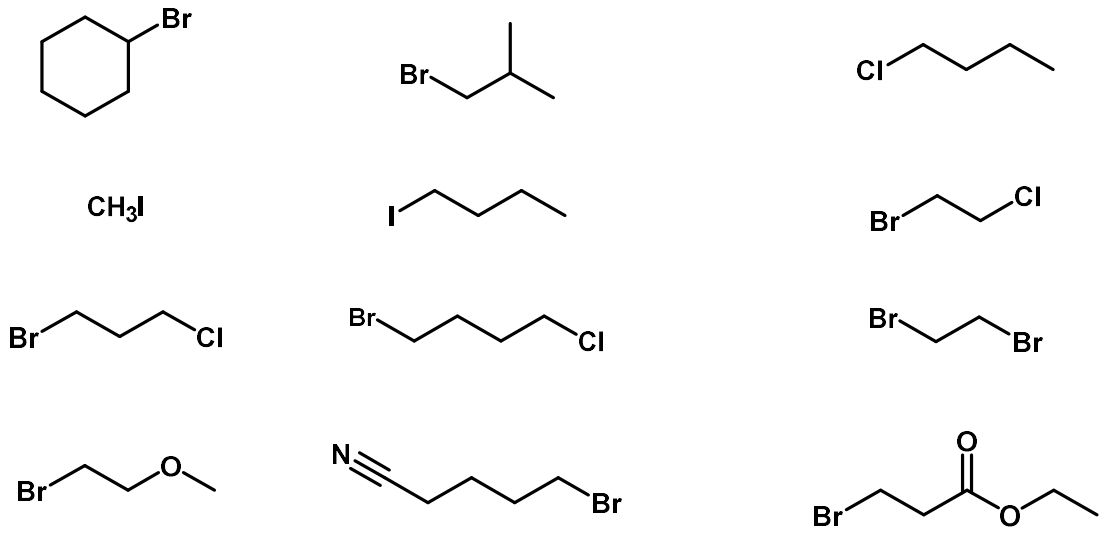
Furthermore, the substitution pattern at the ortho-, meta- and para-position of the benzyl group of the starting material was changed. Substrate **15** is bearing an o-methyl group, **16** is bearing an m-methoxy group and **17** is bearing a p-trifluoromethyl group. The rationale behind using these groups is to find out, whether the reaction is influenced by sterically demanding groups, as well as both electron donating and withdrawing groups.

These substrates were tested in n-butylation and n-decylation reactions respectively, in order to demonstrate the utility of our protocol to introduce both a short and a long alkyl chain. As can be seen in Scheme 11 (compounds **20 – 25**) again the same range of yields was obtained (47 – 62 %), apart from one reaction. It was observed that the methyl group at the benzylic ortho-position decreased the yield compared to the unsubstituted starting compound **1** (Scheme 11, compound **22** and **23**). This can be rationalized using steric arguments. The decrease in yield is much more dramatic in case of 1-bromodecane as coupling partner as compared to 1-bromobutane, which again hints towards a steric effect.

An m-methoxy group gave good yields of 56 % in both cases (Scheme 11, compounds **20** and **21**). Additionally, an electron withdrawing substituent such as a p-CF_3-group seems to have no impact on the isolated yield since 50 % of **24** and 62 % of **25** were obtained.

1.2.3. Limitations:

Although the reactions with some substrates worked quite well, some did not work so well, as can be seen in Scheme 12. This scheme lists all substrates that gave very low conversion or no conversion at all.

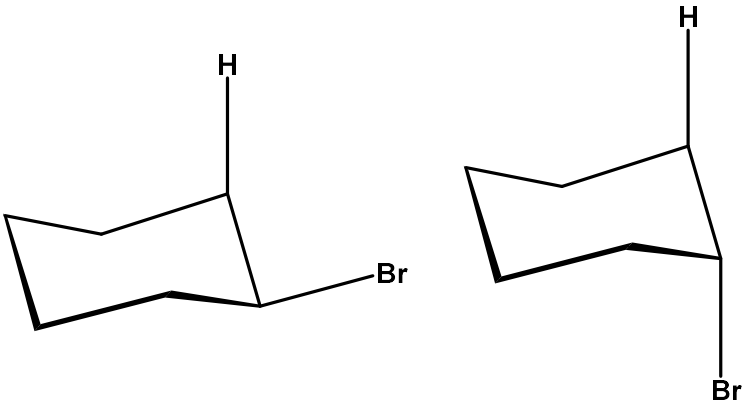


Scheme 12: Limitations

1.2.4. Cyclohexylbromide

As mentioned before, the alkyl bromide eliminates most likely via an E2-mechanism to the corresponding olefin. Therefore, the bromide has to be in axial position (Scheme 13 right hand side). However, the equilibrium between the two conformations lies on the side of the equatorial position (Scheme 13 left hand side). That is why the elimination to the corresponding olefin does not occur and thus the CH-activation via our protocol is not possible. Another detrimental effect that comes within this very molecule is, that the double bond of the olefin that undergoes CH-activation, has to be in in a terminal position. Since cyclohexylbromide is a cyclic molecule, it has no terminal position. That is

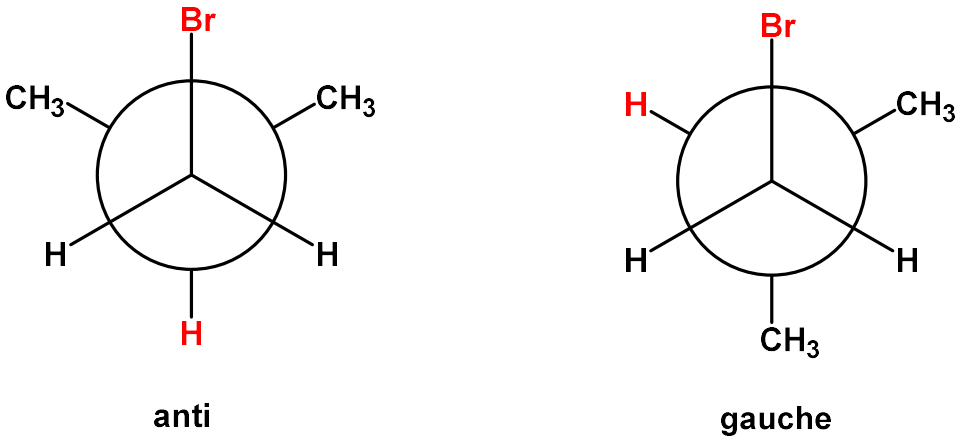
why an olefin that would form upon elimination would not even be able to undergo this kind of CH-activation.



Scheme 13: axial vs. equatorial position

1.2.5. Isobutyl bromide

The reaction with isobutyl bromide only gave a very low yield even though the reaction time was extended in relation to the usual reaction time of 22 h. There are two reasons for this observation. First, elimination to an olefin is rather unlikely on this molecule, the reason for that being following: In order to eliminate to an olefin the bromine and the hydrogen atom of isobutyl bromide have to be in anti-position. This is displayed by the Newman-projection of this molecule on the left hand side in picture 1. However, as bromine has a rather great steric demand, they are in gauche position, as can be seen in picture 1 on the right hand side. The second reason, why the reaction with isobutyl bromide worked so poorly is that even if the elimination to the olefin was possible easily, the obtained olefin would have a rather great steric demand due to the methyl groups. Thus the reaction with the substrate would be very unlikely as well.



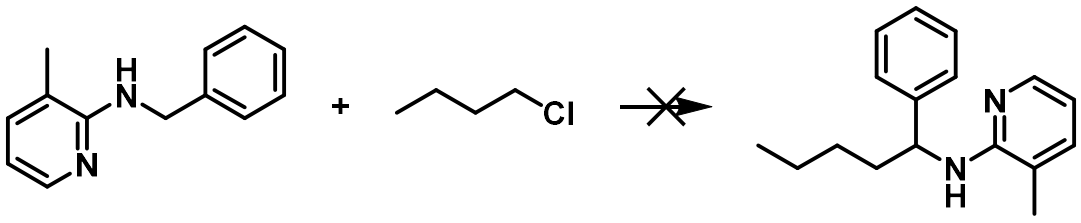
Picture 1: Newman projection of isobutyl bromide

1.2.6. Alternative alkyl-halides:

Next, we tested the reaction with other alkyl halides than alkyl bromides.

First: **1-Chlorobutane**

The reaction with 1-chlorobutane did not show any reaction at all. The reason for that is that chloride is too strong as base, hence being a very bad leaving group. So the elimination to 1-buten did not happen.

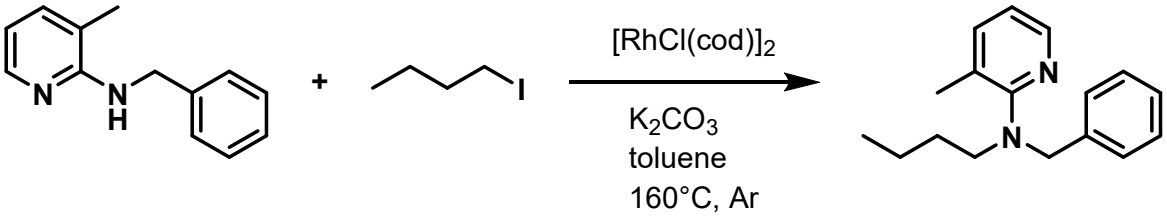


Scheme 14: Reaction with butyl chloride

1-Iodobutane

When doing the reaction with 1-iodobutane, the GC-MS showed nearly full conversion of the substrate. However, after working up the reaction and isolating the final product, we noticed that the final product was not the desired one, where the benzylic carbon gets

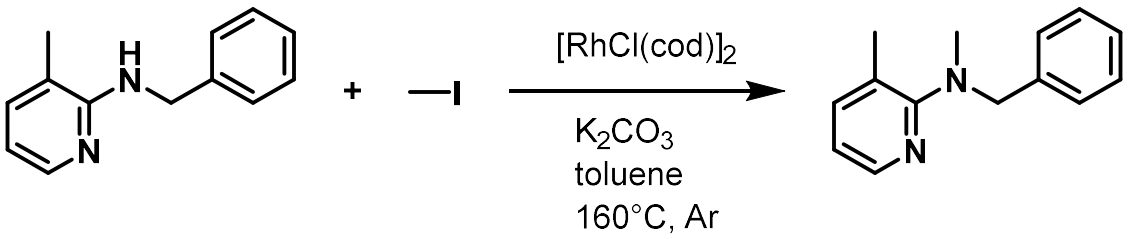
alkylated but instead the nitrogen got alkylated, see scheme 15. This reaction can be seen as competing reaction to the elimination of the iodide, since the nitrogen is a nucleophile and the iodide is a very good leaving group. So, in this case, just a nucleophilic substitution happened.



Scheme 15: Nucleophilic substitution with butyl iodide

Iodo methane

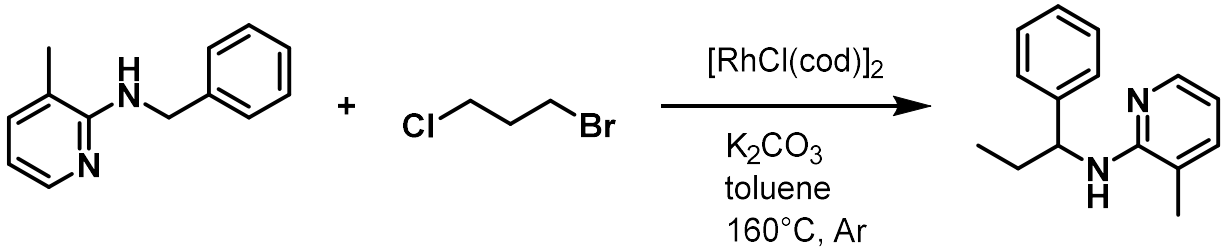
At first thought iodomethane does not seem as a suitable substrate for this kind of reaction since iodomethane cannot form an olefin upon elimination. Yet when doing this kind of reaction with tetramethylammonium bromide, a fraction of the desired product was formed. Our hypothesis to explain this finding is, that the methyl group forms a carbene when reacting with rhodium of the catalyst. This rhodium carbene then may enter the catalytic cycle undergoing CH-activation eventually.
However, when doing the reaction with iodomethane according to our established protocol, the nitrogen was methylated in analog to the reaction with butyl iodide, scheme 16. Also there was observed nearly full conversion of the starting material, which is not too surprising, as iodomethane is a very potent methylating agent.



Scheme 16: Methylation of the substrate

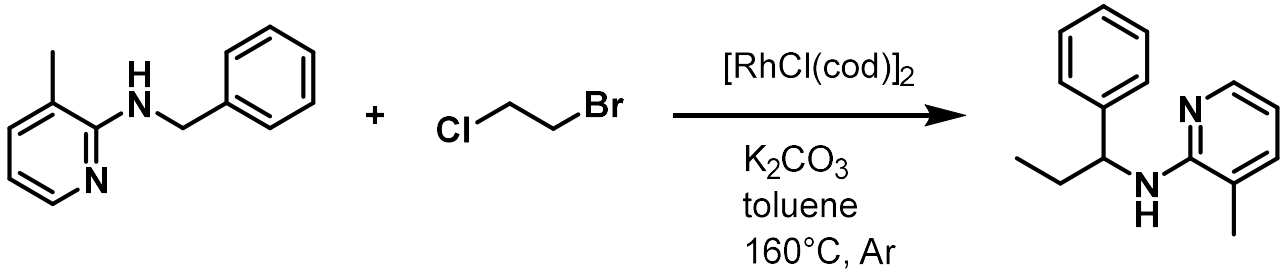
Then we subjected an alkyl halide bearing two halogen moieties to our protocol. The rationale behind this experiment was, to introduce a new reactive site into the final molecule for possible further reactions. When subjecting 1-bromo-3-chloropropane to the reaction, we expected that the bromine would eliminate to the corresponding olefin and the chlorine would remain in the final product.

However when analyzing the final product, we made a surprising discovery. The substrate got alkylated indeed, but not the way we expected it to, it got ethylated and the halogen moieties got lost completely (Scheme 17). At present the reaction pathway leading to this surprising result is not known, but additional experiments gave similar results.



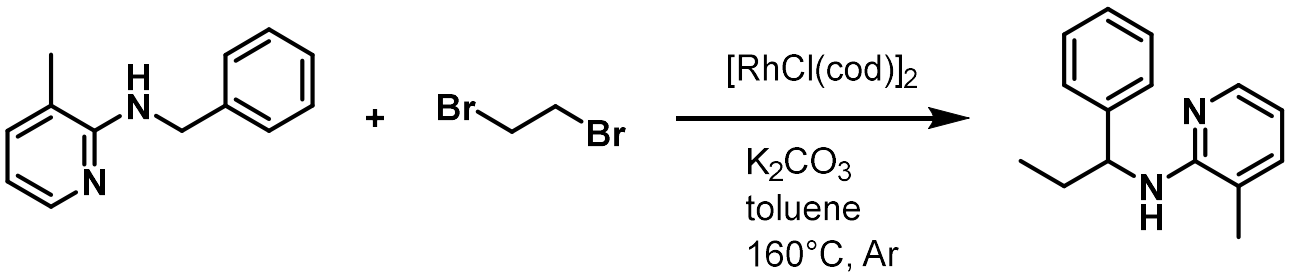
Scheme 17: Reaction with an alkyl bearing two halogen moieties

Next, we performed the same reaction with 1-bromo, 2-chloroethan to see what happens, when we put an ethyl-chain into the reaction right away from the beginning. Again the substrate got ethylated but the halogen moieties both were gone completely. (Scheme 18)



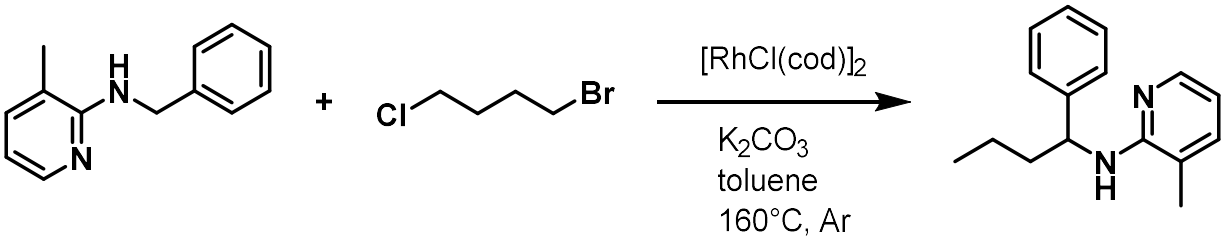
Scheme 18: Reaction with 1-bromo, 2-chloroethane

The very same happened, when doing the reaction with 1,2-dibromoethane. (Scheme 19)



Scheme 19: Reaction with 1,2-dibromoethane

As we could not come up with an explanation let alone a solution for this problem, we did another experiment with 1-bromo, 2-chlorobutane. The final product of this reaction again did not contain any halogen moiety, however the alkyl chain in the final product was a propyl chain. (Scheme 20)



Scheme 20: Reaction with an alkyl bearing two halogen moieties

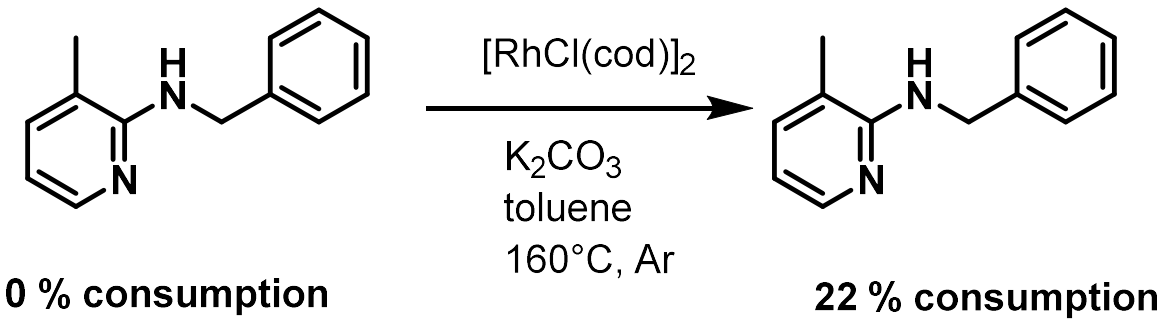
So we came up with the hypothesis that the catalyst chews off CH_2-groups from the substrate and/or the final product respectively. That is why the reaction product of the reaction with dihalogenated propane got ethylated and the reaction product of the reaction with dihalogenated butane got propylated. The loss of one carbon unit was already observed as side product in previous investigations (see Scheme 6), which

actually led to the discovery of the Hofmann elimination protocol. It seems that a terminal halide promotes this “one-carbon-loss” making the corresponding products the dominant ones. Elucidation of the mechanism of this reaction was beyond the scope of this work.

1.2.7. Stability Tests

As mentioned before, some experiments gave the hint, that the substrate and/or the product respectively may not be entirely stable under the respective reaction conditions. So, we did some stability tests to confirm this hypothesis. Therefore, we set up the reaction as usual however omitting the alkyl halide. Then we measured the substrate consumption with respect to the internal standard before heating up the reaction and again after heating the reaction for 22h for 160 °C. To get a better idea of the test see scheme 21.

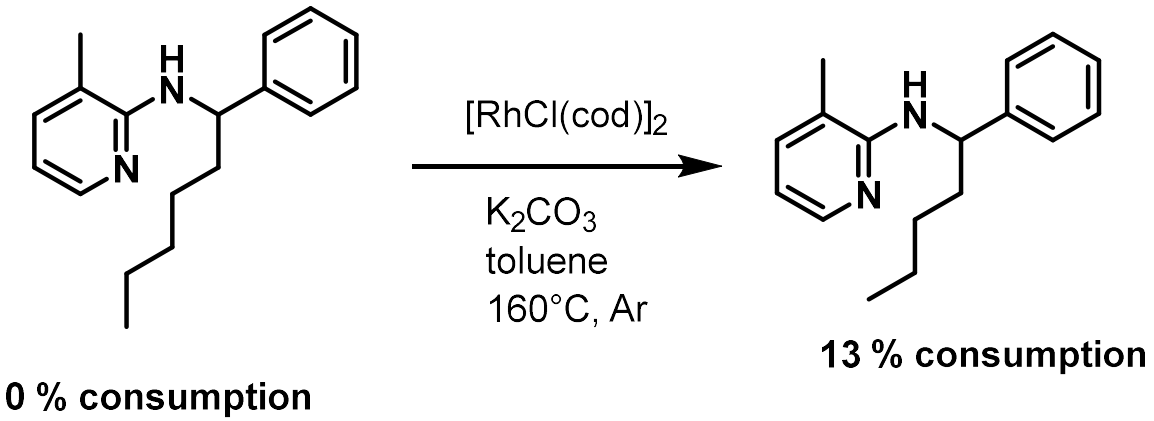
The result of this experiment was that the consumption at the end of the reaction was 22 percentage points compared to the beginning, meaning that the substrate was decomposed by the catalyst to some extent under the respective reaction conditions.



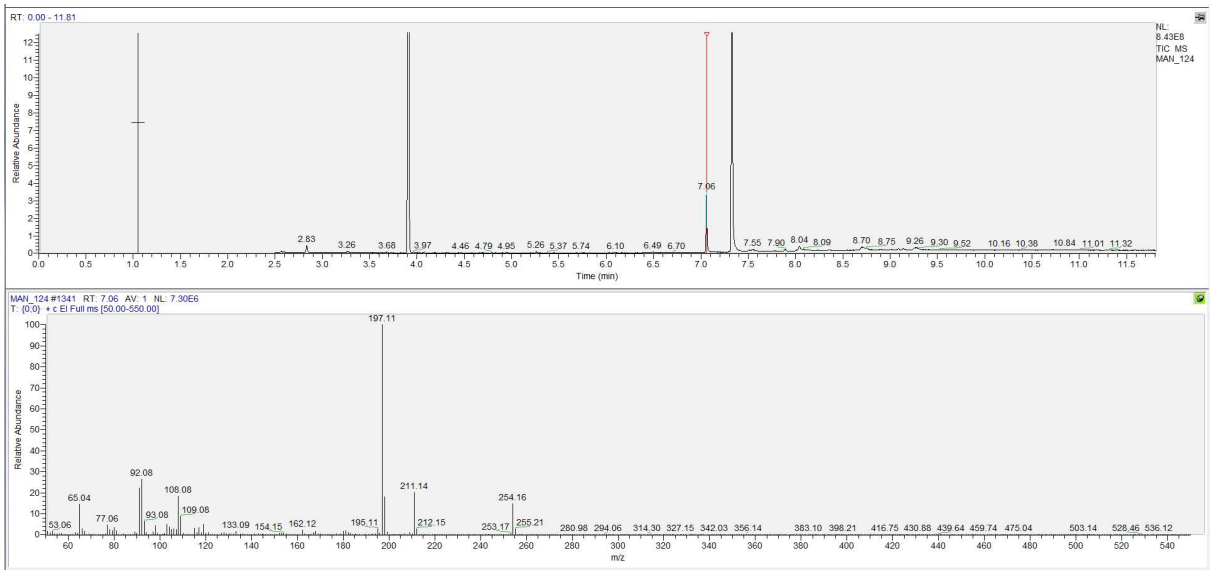
Scheme 21: Stability test with substrate

For another stability test 3-methyl-N-(1-phenylhexyl) pyridin-2-amine (“the pentylated product”) was subjected to the standard reaction conditions. Again, substrate

consumption with respect to the internal standard was measured before and after the reaction. Again, the consumption of the substrate after the reaction was 13%. What is of significant importance as well is that GC-MS shows that the alkyl chain is repeatedly shortened by one-carbon-units. (Scheme 22)



Scheme 22: Stability test of product



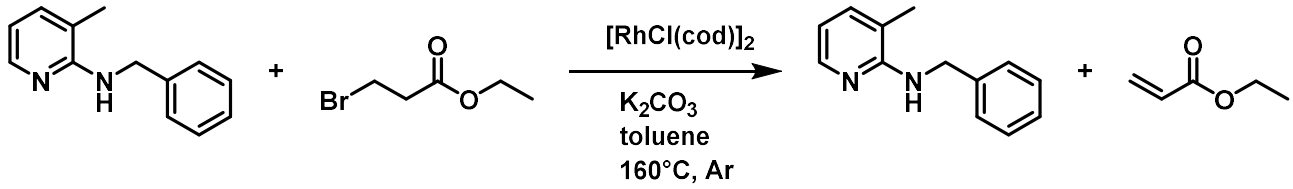
Scheme 23: Gas-Chromatogram (above) and mass-spectrum (below) of the partly decomposed product

Scheme 23 depicts the respective GC-MS of the discussed reaction. The peak at 7.33 min shows the substrate that did not react. However, the peak at 7.06 min shows the partly decomposed substrate, where the alkyl chain was shortened by one –CH2 chain. Finally the rather big peak at 3.91 min shows dodecane, the internal standard.

So we considered our hypothesis confirmed that the catalyst decomposes the substrate and the product respectively to some extent. The very same happened to the reaction products of the reactions with di-halogenated alkyl halides, although with this kind of reaction the decomposition of the product is much more pronounced than with other reaction products.

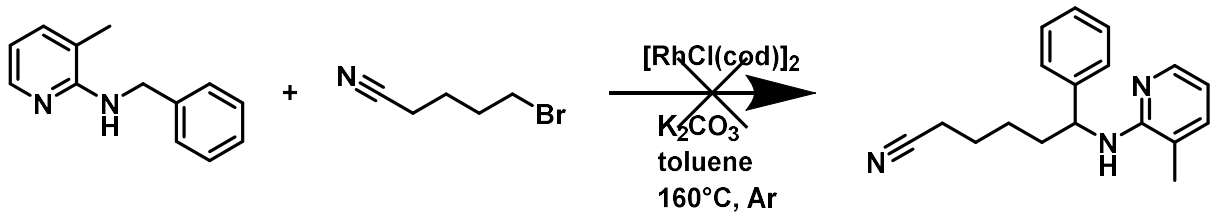
More Limitations…

Next, we wanted to extend the substrate scope to other functional groups in order to see the functional group tolerance of this kind of reaction. As mentioned before, the reaction with alkyl halides containing an ester moiety worked quite well. However, when the alkyl halide containing an ester moiety forms an acrylate upon elimination there is no consumption of the substrate at all. (Scheme 24)



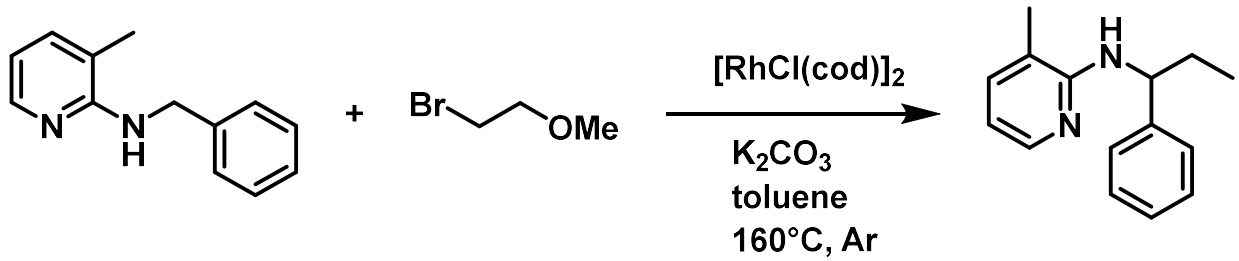
Scheme 24: Forming of an acrylate

When using a nitrile as substrate there was no consumption of the substrate as well. That may be due to the fact that the nitrogen of the nitrile coordinates to the catalyst and thus preventing it from undergoing the desired catalytic cycle during which the nitrogen of the substrate has to bond to the catalyst. (Scheme 25)



Scheme 25: No reaction with nitrile

Also the reaction with 1-bromo-2-methoxyethane, that was our example for an ether moiety, did not deliver the desired product, although substrate was consumed. Via GC-MS we just detected the ethylated product, analogous to what we saw when using alkyl halides containing two halogen moieties. (Scheme 26) The amount, detected via GC-MS was very little, i.e. just traces.



Scheme 26: Reaction with an ether

3. Conclusion

In conclusion alkyl bromides can be used as olefin precursors in the direct alkylation of C(sp^3)-H bonds of benzylic amines. The reaction works with slightly lower efficiency than the previously disclosed protocol using quaternary ammonium salts. [20]

Not only middle chained olefins such as hexene or pentene but also longer chained ones like decene, dodecene or even docosane could be successfully replaced by the corresponding alkyl bromides. Moreover also short chained olefins like ethylene or propylene could be replaced by alkyl bromides giving moderate yields.

The reaction was optimized and a practical protocol was found to use liquid materials instead of gaseous olefins or solid quaternary ammonium salts.

Generally linear and unsubstituted alkyl bromides gave the best results. Functional group tolerance on the amine substrate was good, but limitations were observed when substituted alkyl bromides were used. If elimination to an allylic or vinylic olefin would need to occur, the reaction is inefficient. Additionally, not many functional groups were tolerated. However, carboxylic acid esters work well.

What is more to say regarding limitations is, that only alkyl bromides work with this protocol as opposed to chlorides or iodides.

Moreover, a triad of different benzylic amines with a variety of functional groups could be alkylated with this method delivering the product in fairly good yields.

This gives a handle for further elaboration of the obtained products. Finally, cleavage of the directing group was demonstrated as well, an important feature in DG-assisted C-H functionalization.

4. Experimental

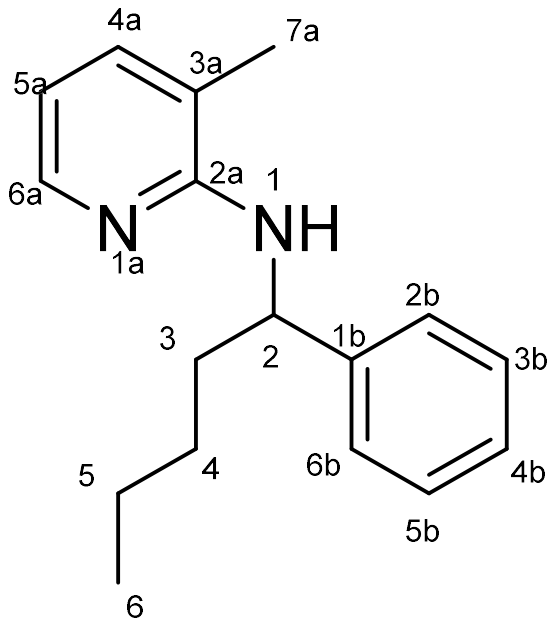
List of Abbreviations

BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
boc	tert-butoxycarbonyl
but	butyl
cod	1,5-cyclooctadiene
d	doublet
eth	ethyl
eq.	equivalent(s)
Et_2O	diethyl ether
EtOAc	ethyl acetate
hex	hexyl
LP	light petroleum
m	multiplet
MeOTf	methyl trifluoromethanesulfonate
mp	melting point
prop	propyl
q	quartet
rac	racemic
r.t.	room temperature
s	singlet
t	triplet
TEA	triethylamine

1.4.1. 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, ^{13}C-NMR and HSQC spectra were recorded on a Bruker Advance 400, chemical shifts are reported in ppm, using Me_4Si as internal standard. NMR signals were assigned according to Scheme 27.



Scheme 27: Scheme for assigning NMR Signals

For GC-MS, usually the method GC-MS 2 was used. In exceptional cases, GC-MS 1 was used.

GC-MS 2 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-MS 1 Temperature program: Start at 100 °C (hold 2 min), 18 °C/min, 280 °C (hold 3 min)

For TLC aluminum backed silica gel 60 with fluorescence indicator F 254 was used. Column chromatography was performed on Silica 60 from Merck (40 µm – 63 µm). Flash chromatography, was carried out on a Büchi SepacoreTM 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.

1.4.2. General Procedures

1.4.3. 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, liquid starting materials, 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.

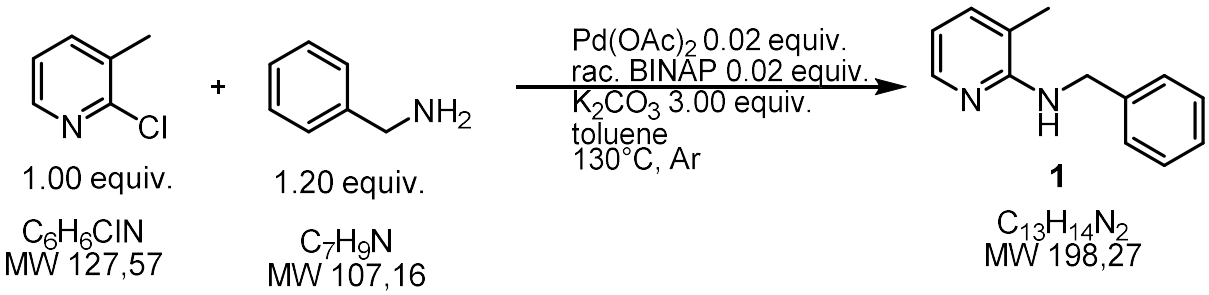
1.4.4. General work-up procedure B for C-H activation reactions

After cooling the reaction mixture to room temperature, the solid material was removed by filtration using a Pasteur pipette with cotton and Hyflo. 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.

1.4.5. Synthetic Procedures

1.4.5.1. Precursor Synthesis

1.4.5.1.1. *N*-Benzyl-3-methylpiridin-2-amine (1)



1.00 equiv.
C_6H_6ClN
MW 127,57

1.20 equiv.
C_7H_9N
MW 107,16

1
$C_{13}H_{14}N_2$
MW 198,27

$Pd(OAc)_2$ (67 mg, 0.3 mmol, 0.02 eq.), rac. BINAP (187 mg, 0.3 mmol, 0.02 eq.) and K_2CO_3 (7.214 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 (1.63 ml, 15 mmol, 1 eq.), freshly distilled benzyl amine (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 5 % EtOAc to 10 % EtOAc over the course of 20 minutes. Then flash column chromatography was continued with 10 % EtOAc. Drying under reduced pressure delivered 2.55 g (86 %) **1** as beige solid. Analytical data are in accordance to literature. [21]

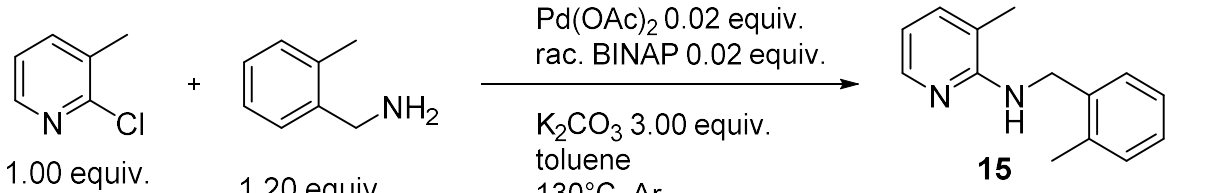
M.p.: 49.4-50.9 °C,

TLC: 0.31 (LP/EtOAc 10:1),

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.07 (s, 3H, C[7]-H_3), 4.39 (t, J = 5.7 Hz, 1H, N[8]-H), 4.71 (d, J = 5.4 Hz, 6.56 (dd, J = 7.1, 5.1 Hz, 1H, C[1]-H), 2H, C[9]-H_2), 7.45 – 7.18 (m, 6H, C[6]-H, C[11-15]-H), 8.07 (dd, J = 5.1, 1.8 Hz, 1H, C[2]-H).

^{13}C-NMR (101 MHz, CDCl3): δ 17.0 (q, C[7a]), 45.9 (t, C[2]), 112.9 (d, C[5a]), 116.6, 116.7 (s, C[3a]), 127.2 (d, C[4b]), 127.9 (d, C[2b]; C[6b]), 128.6 (d, C[3b]; C[5b]), 136.9 (d, C[4a]), 140,0 (s, C[1b]), 145.4 (d, C[6a]), 156.6 (s, C[2a]).

1.2.1. 3-Methyl-*N*-(2-methylbenzyl)pyridin-2-amine (15)



Chemical Formula: $C_{14}H_{16}N_2$
Molecular Weight: 212,30

The catalyst $Pd(OAc)_2$ (0.02 eq., 68 mg, 0.3 mmol), 1.878 g rac. BINAP (0.02 eq., 0.3 mmol), 7.25 g K_2CO_3 (3.5 eq., 52.5 mmol) were placed in a 3-necked-flask, evacuated and flushed with argon three times. Then 1.65 mL 2-chloro-3-methylpyridin (1 eq., 15 mmol), 2.23 mL 2-methylbenzylamine (1.2 eq., 18 mmol, 2.18 g) and 38 mL toluene were added through a septum with a syringe. The mixture was refluxed at 130 °C maintaining the argon atmosphere with a balloon. After 19 h consumption of substrate was completed (TLC). The reaction mixture was allowed to reach RT. The organic phase was filtered and washed with 60 mL dichloromethane and concentrating the solution (rotavap) resulted in a yellow/green-residue. The residue was suspended with silica and dichloromethane, after evaporation the solid was loaded onto a column of silica (20 cm) and eluated with LP:EtOAc 10:1. The fractions were collected in 15 mL test tubes. The fractions containing product were collected and concentrated, leading to a yellow oil crystallizing after a while.
Yield: 2.34 g (11,02 mmol, 73.46%)

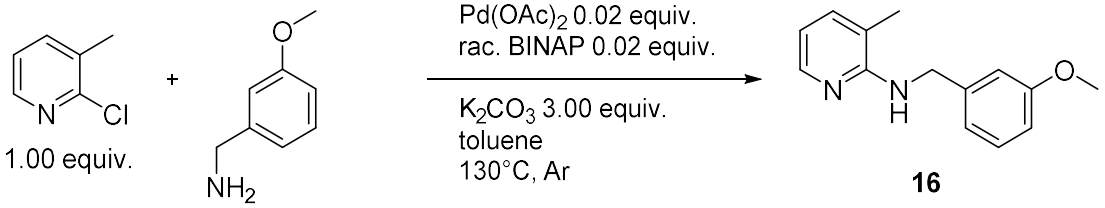
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.07 (s, 3H, C[7a]-H_3), 2.39 (s, 3H, C[7b]-H_3), 4.20 (s, 1H, N[1]-H), 4.66 (d, J = 4.9 Hz, 2H, C[2]-H_2), 6.57 (dd, J = 7.0, 5.2 Hz, 1H, C[5a]-H), 7.20 (m, 3H, C[4a; 2b; 4b]-H), 7.25 (d, J = 6.6 Hz, 1H, C[3b]-H), 7.34 (d, J = 6.6 Hz, 1H, C[5b]-H), 8.07 (d, J = 4.2 Hz, 1H, C[6a]-H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 17.1 (q, C[7a]), 19.2 (q, C[7b]), 44.3 (t, C[2]), 112.9 (d, C[5a]), 116.7 (s, C[3a]), 126.2 (d, C[2b]), 127.6 (d, C[4b]), 128.8 (d, C[5b]), 130.6 (d, C[4a]), 136.9 (s, C[2b]), 137.0 (d, C[3b]), 137.6 (s, C[1b]) 145.4 (d, C[6a]), 156.7 (s, C[2a]).

TLC: 0.2 (LP/EtOAc 10:1)

HRMS: calculated for $C_{14}H_{16}N_2$ $[M]^+$ 212,2389; found 212,2378; Δ = 5,25 ppm.

1.2.2. *N*-(3-Methoxybenzyl)-3-methylpyridin-2-amine (16)



16

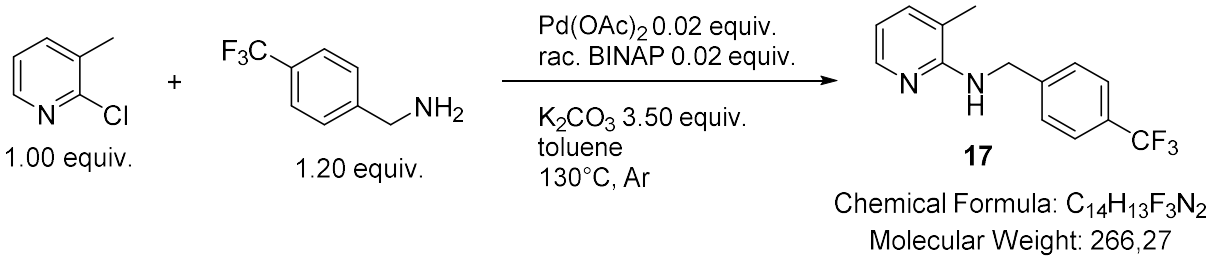
Chemical Formula: $C_{14}H_{16}N_2O$
Molecular Weight: 228,30

$Pd(OAc)_2$ (29 mg, 0.13 mmol, 0.02 equiv.), rac. BINAP (77 mg, 0.12 mmol, 0.02 equiv.) and K_2CO_3 (2.93 g, 21.2 mmol, 3.5 equiv.) were combined under inert atmosphere (Ar). 2-Chloro-3-methylpyridine (0.78 g, 6.1 mmol, 1 equiv.), 3-methoxybenzylamine (1 g, 7.3 mmol, 1.2 equiv.) and toluene (30 ml) were added through a rubber septum. The reaction mixture is stirred at 130 °C for 18 h. The conversion of the starting material is checked with TLC (PE:EE = 5:1). After cooling to room temperature, the brown mixture is filtered, and the solid residue is washed with dichloromethane. The combined organic layers are concentrated under reduced pressure. The crude product is purified by flash column chromatography (PE/EE, gradient starting with 3% and ending with 100 % EE). The fractions containing the product (TLC) were combined and the solvent removed, giving 0.41 g (63.5% of theory) white solid product.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.10 (s, 3H, C[7a]-H_3), 3.80 (s, 3H, C[8b]-H_3), 4.42 (s, 1H, N[1]-H), 4.68 (d, *J* = 5.2 Hz, 2H, C[2]-H_2), 6.56 (dd, *J* = 7.0, 5.2 Hz, 1H, C[2b]-H), 6.83 (dd, *J* = 8.2, 2.1 Hz, 1H, C[4b]-H), 7.03 – 6.92 (m, 2H, C[5a; 6b]-H), 7.33 – 7.19 (m, 2H, C[4a; 5b]-H), 8.05 (d, *J* = 6.0 Hz, 1H, C[6a]-H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 17.0 (q, C[7a]), 45.9 (q, C[8b]), 55.2 (d, C[2]), 112.6 (d, C[2b]), 113.0 (d, C[4b]), 113.5 (d, C[5a]), 116.7 (s, C[3a]), 120.1 (d, C[6b]), 129.6 (d, C[5b]), 137.0 (d, C[4a]), 141.6 (s, C[1b]), 145.25 (d, C[6a]), 156.6 (s, C[3b]), 159.86 (s, C[3a]).

1.2.3. 3-Methyl-*N*-(4-(trifluoromethyl)benzyl)pyridin-2-amine (17)



Chemical Formula: $C_{14}H_{13}F_3N_2$
Molecular Weight: 266,27

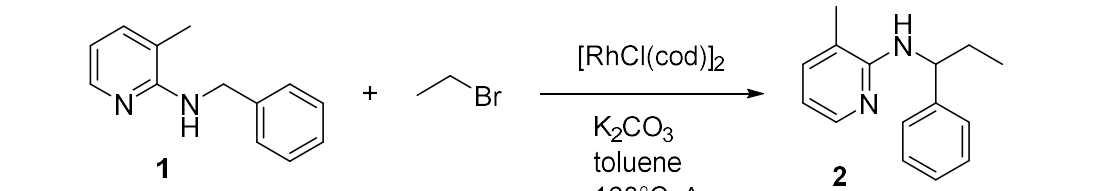
$Pd(OAc)_2$ (0.02 eq, 67 mg, 0.3 mmol), rac. BINAP (0.02 eq, 187 mg, 0.3 mmol) and K_2CO_3 (3.5 eq, 7.258 g, 52.5 mmol) were placed in a pre-dried 100 mL three-necked flask with reflux condenser, thermometer, septum and argon balloon. After being evacuated and flushed with argon three times, 2-chloro-3-methylpyridine (1 eq, 1,64 mL, 15 mmol), 4-(trifluoromethyl)benzyl amine (1,2 eq, 2,56 mL ,18 mmol) and 38 mL toluene were added through the septum with a syringe. The yellow slurry was heated to reflux (temperature in the solution: 110 °C) and stirred for 19 h. The orange solution was separated from the white solid and concentrated *in vacuo* to result in a brown oil. The product was purified *via* column chromatography (10:1 LP:EE) to give yellow crystals in 81% (3.24 g) yield. Analytical data are in accordance with the literature. [22]

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.12 (s, 3H, C[7a]-H_3), 4.55 (s, 1H, N[1]-H), 4.78 (d, *J* = 5.5 Hz, 2H, C[2]-H_2), 6.58 (dd, *J* = 7.1, 5.1 Hz, 1H, C[5a]-H), 7.26 (d, *J* = 6.5 Hz, 1H, C[4a]-H), 7.48 (d, *J* = 8.0 Hz, 2H, C[2b; 6b]-H), 7.58 (d, *J* = 8.1 Hz, 2H, C[3b; 5b]-H), 8.02 (dd, *J* = 5.0, 1.8 Hz, 1H, C[6a]-H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 16.9 (q, C[7a]), 45.1 (t, C[2]), 113.3 (d, C[5a]), 116.7 (s, C[3a]), 122.9 (s, C[7b]), 125.4 (d, C[3b; 5b], 127.8 (d, C[2b; 6b], 129.3 (s, C[4b]), 137.2 (d, C[4a]), 144.4 (s, C[1b]), 145.3 (C[6a]).

1.2.4. Substrate Scope – Alkyl Halides

1.2.5. 3-Methyl-*N*-(1-phenylpropyl)pyridin-2-amine (2)



1
Chemical Formula: $C_{13}H_{14}N_2$
Molecular Weight: 198,27

2
Chemical Formula: $C_{15}H_{18}N_2$
Molecular Weight: 226,32

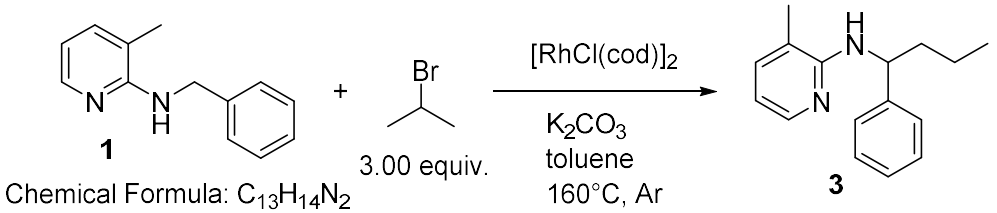
The reaction was carried out according to general procedure A with 1 (100 mg, 0.50 mmol, 1 eq.), 1-bromoethane (163 mg, 1.50 mmol, 3 eq.), K_2CO_3 (311 mg, 2.25 mmol, 4.5 eq.) and $[RhCl(cod)]_2$ (12 mg, 0.025 mmol, 0.05 eq.) in dry and degassed toluene (2 ml). The reaction mixture was heated for 22 h at 160 °C. The general work-up procedure B for C-H activation reactions was followed. The combined organic layers were evaporated and the resulting crude product was purified by flash column chromatography (LP/EtOAc, 45 g SiO_2 Flowrate 30 ml/min) starting with pure LP for 10 min and then continuing using a gradient which varies the solvents from 0% to 5 % EtOAc within 45 min. The product was dried under reduced pressure and **2** was isolated in 25 % (29 mg) yield as yellow oil. Analytical data are in accordance with the literature. [20]

^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.93 (t, *J* = 7.4 Hz, 3H, C[4]-H_3), 1.80-2.05 (m, 2H, C[3]-H_2), 2.10 (s, 3H, C[7a]-H_3), 4.35-4.42 (m, 1H, N-H), 5.18 (q, *J* = 7.2 Hz, 1H, C[2]-H), 6.46 (dd, *J* = 7.1, 5.1 Hz, 1H, C[5a]-H), 7.15-7.24 (m, 2H, C[4a; 4b]-H), 7.25-7.39 (m, 4H, C[2b; 3b; 5b; 6b]-H), 7.95 (dd, *J* = 5.1, 1.8 Hz, 1H, C[6a]-H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 10.8 (q, C[4]), 17.1 (q, C[7a]), 30.2 (t, C[3]), 56.1 (d, C[2]), 112.6 (d, C[5a]), 116.4 (s, C[3a]), 126.6 (d, C[2b; 6b]), 126.8 (d, C[4b]), 128.4 (d, C[3b; 5b]), 136.9 (d, C[4a]), 144.1 (s, C[1b]), 145.3 (d, C[6a]), 156.1 (s, C[2a]).

TLC: 0.69 (LP/EtOAc 10:1)
GCMS: Retention time: 6.58 min. Main fragments: 226 (M+, 17), 211 (8), 197 (100), 108 (21), 91 (28), 65 (19).

1.2.6. 3-Methyl-*N*-(1-phenylbutyl)pyridin-2-amine (3)



1
Chemical Formula: $C_{13}H_{14}N_2$
Molecular Weight: 198,27

3
Chemical Formula: $C_{16}H_{20}N_2$
Molecular Weight: 240,35

The reaction was carried out according to general procedure A with **1** (100 mg, 0.50 mmol, 1 eq.), 2-Bromopropane (184 mg, 1.50 mmol, 3 eq.), K_2CO_3 (311 mg, 2.25 mmol, 4.5 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 22 h at 160 °C. The general work-up procedure B for C-H activation reactions was followed. The combined organic layers were evaporated and the resulting crude product was purified by flash column chromatography (LP/EtOAc, 45 g SiO_2 Flowrate 30 ml/min) using a gradient which varies the solvents from 0 % to 5 % EtOAc within 45 min. The product was dried under reduced pressure and **3** was isolated in 32 % (39 mg) yield as orange oil. Analytical data are in accordance with the literature. [20]

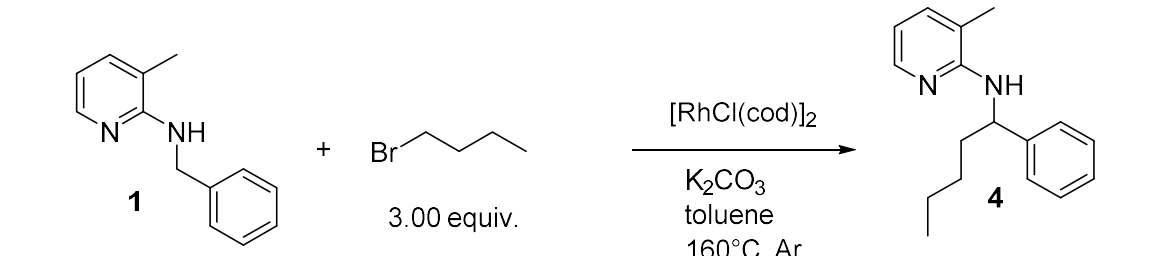
^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.97 (t, *J* = 7.4 Hz, 3H, C[5]-H_3), 1.23-1.58 (m, 2H, C[4]-H_2) 1.79-2.03 (m, 1H, C[3]-H_2), 2.14 (s, 3H, C[7a]-H_3), 4.43 (s, 1H, N-H), 5.31 (d, *J* = 6.5 Hz, 1H, C[2]-H), 6.50 (dd, J = 7.1, 5.1 Hz, 1H, C[5a]-H), 7.14-7.25 (m, 2H, C[4a; 4b]-H), 7.27-7.44 (m, 4H, C[2b; 3b; 5b; 6b]-H), 7.99 (d, *J* = 4.7 Hz, 1H, C[6a]-H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 14.1 (q, C[5]), 17.1 (q, C[7a]), 19.6 (t, C[4]), 39.8 (t, C[3]), 54.4 (d, C[2]), 112.5, (d, C[5a]), 116.2 (s, C[3a]), 126.5 (d, C[2b; 6b]), 126.7 (d, C[4b]), 128.4 (d, C[3b; 5b]), 136.8 (d, C[4a]), 144.6 (s, C[1b]), 145.5 (d, C[6a]), 156.2 (s, C[2a]).

TLC: 0.74 (LP/EtOAc 10:1)

GCMS: Retention time: 6.81 min. Main fragments: 240 (M+, 17), 211 (23), 197 (100), 108 (22), 91 (38), 65 (25).

1.2.7. 3-Methyl-*N*-(1-phenylpentyl)pyridin-2-amine (4)



Chemical Formula: $C_{13}H_{14}N_2$
Molecular Weight: 198,27

Chemical Formula: $C_{17}H_{22}N_2$
Molecular Weight: 254,38

The reaction was carried out according to general procedure A with **1** (100 mg, 0.50 mmol, 1 eq.), 1-bromobutane (206 mg, 1.50 mmol, 3 eq.), K_2CO_3 (311 mg, 2.25 mmol, 4.5 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 22 h at 160 °C. The general work-up procedure B for C-H activation reactions was followed. The combined organic layers were evaporated and the resulting crude product was purified by flash column chromatography (LP/EtOAc, 45 g SiO_2 Flowrate 30 ml/min) using a gradient which varies the solvents from 0% to 5% EtOAc within 45 min. The product was dried under reduced pressure and **4** was isolated in 56 % (71 mg) yield as pale yellowish oil. Analytical data are in accordance with the literature. [20]

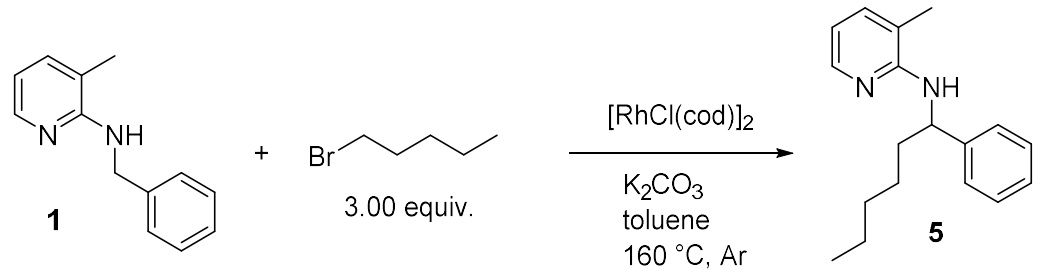
^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.79 (t, J = 7.0 Hz, 3H, C[6]-H_3), 1.13-1.40 (m, 4H; C[4-5]-H_2), 1.69-1.90 (m, 2H; C[3]-H_2), 2.02 (s, 3H; C[7a]-H_3), 4.29 (s, 1H; N-H), 5.16 (t, J = 7.4 Hz, 1H; C[2]-H), 6.37 (dd, J = 7.1, 5.1 Hz, 1H, C[5a]-H), 7.06-7.16 (m, 2H, C[4a; 4b]-H), 7.18-7.32 (m, 4H, C[2b; 3b; 5b;6b]-H), 7.87 (dd, J = 5.1, 1.8 Hz, 1H, C[6a]-H),

^{13}C NMR (101 MHz, $CDCl_3$): δ 14.1 (q, C[6]), 17.1 (q, C[7a]), 22.7 (t, C[4]), 28.6 (t, C[5]), 37.3 (t, C[3]), 54.6 (d, C[2]), 112.5 (d, C[5a]), 116.2 (s, C[3a]), 126.6 (d, C[3b; 5b]), 126.7 (d, C[4b]), 128.4 (d, C[2b; 5b]), 136.8 (d, C[4a]), 144.6 (s, C[1b]), 145.6 (d, C[6a]), 156.2 (s, C[2a]),

TLC: 0.60 (LP/EtOAc 10:1)

GCMS 1: Retention time: 9.72 min. Main fragments: 254 (M+, 6), 211 (18), 197 (100), 108 (39), 91 (49).

1.2.1. 3-Methyl-*N*-(1-phenylhexyl)pyridin-2-amine (5)



Chemical Formula: $C_{13}H_{14}N_2$
Molecular Weight: 198,27

3-methyl-*N*-(1-phenylhexyl)pyridin-2-amine
Chemical Formula: $C_{18}H_{24}N_2$
Molecular Weight: 268,40

The reaction was carried out according to general procedure A with **1** (100 mg, 0.50 mmol, 1 eq.), 1-bromopentane (225 mg, 1.50 mmol, 3 eq.), K_2CO_3 (311 mg, 2.25 mmol, 4.5 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 22 h at 160 °C. The general work-up procedure B for C-H activation reactions was followed. The combined organic layers were evaporated and the resulting crude product was purified by flash column chromatography (LP/EtOAc, 45 g SiO_2 Flowrate 30 ml/min) starting with pure LP for 10 min. Then the flash column chromatography was continued using a gradient which varies the solvents from 0% to 10% EtOAc within 45 min. The product was dried under reduced pressure and **5** was isolated in 35% (46 mg) yield as pale yellowish oil. Analytical data are in accordance with the literature. [20]

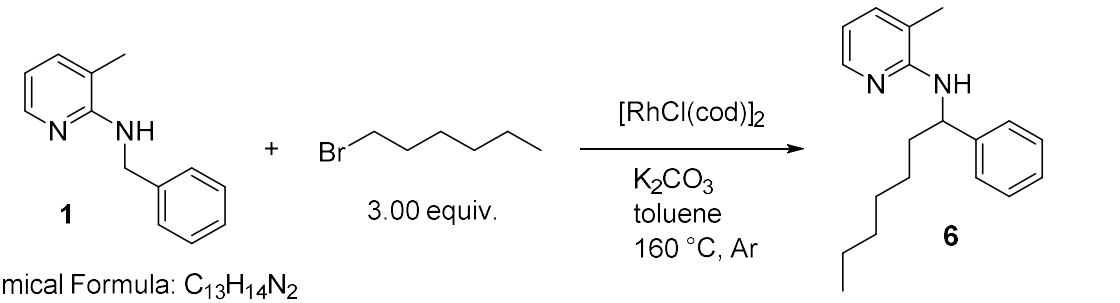
^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.77 (t, J = 6.7 Hz 3H, C[7]-H_3, 1.12 - 1.38 (m, 6H, C[4-6]-H_2), 1.68-1.90 (m, 2H, C[3]-H_2), 2.02 (s, 3H, C[7a]-H_3), 4.25-4.33 (m, 1H, N-H), 5.16 (q, J = 6.7 Hz, 1H, C[2]-H), 6.37 (dd, J = 7.1, 5.1 Hz, 1H, C[5]-H), 7.05-7.15 (m, 2H, C[4a; 4b]-H), 7.18-7.34 (m, 4H, C[2b; 3b; 5b; 6b]-H), 7.87 (dd, J = 5.1, 1.8 Hz, 1H, C[6a]-H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 14.1 (q, C[7]), 17.1 (q, C[7a]), 22.6 (t, C[6]), 26.1 (t, C[5]), 31.8 (t, C[4]), 37.5 (t, C[3]), 54.6 (d, C[2]), 112.5 (d, C[5a]), 116.2 (s, C[3a]), 126.6 (d, C[3b; 5b]), 126.7 (d, C[4b]), 128.4 (d, C[2b; 6b]), 136.8 (d, C[4a]), 144.6 (s, C[1b]), 145.6 (d, C[6a]), 156.2 (s, C[2a]).

TLC: 0.60 (LP/EtOAc 10:1)

GCMS 1: Retention time: 10.21 min. Main fragments: 268 (M+, 9), 211 (19), 197 (100), 108 (23), 91 (23).

1.2.2. 3-Methyl-*N*-(1-phenylheptyl)pyridin-2-amine (6)



Chemical Formula: $C_{13}H_{14}N_2$
Molecular Weight: 198,27

Chemical Formula: $C_{19}H_{26}N_2$
Molecular Weight: 282,43

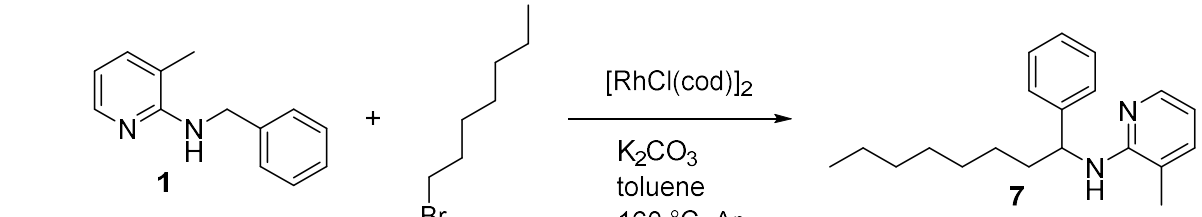
The reaction was carried out according to general procedure A with **1** (100 mg, 0.50 mmol, 1 eq.), 1-bromohexane (248 mg, 1.50 mmol, 3 eq.), K_2CO_3 (311 mg, 2.25 mmol, 4.5 eq.) and $[RhCl(cod)]_2$ (12 mg, 0.025 mmol, 0.05 eq.) in dry and degassed toluene (2 ml). The reaction mixture was heated for 22 h at 160 °C. The general work-up procedure B for C-H activation reactions was followed. The combined organic layers were evaporated and the resulting crude product was purified by flash column chromatography (LP/EtOAc, 45 g SiO_2, flowrate 30 ml/min) starting with pure LP for 10 min. Then the flash column chromatography was continued using a gradient which varies the solvents from 0% to 10% EtOAc within 45 min. The product was dried under reduced pressure and **6** was isolated in 40% (56 mg) yield as pale yellowish oil. Analytical data are in accordance with the literature. [20]

^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.88 (t, J = 6.7 Hz, 3H, C[8]-H_3), 1.08-1.54 (m, 8H, C[3; 4; 6; 7]-H_2), 1.69-2.03 (m, 2H, C[5]-H_2), 2.13 (s, 3H, C[7a]-H_3), 4.40 (d, J = 7.6 Hz, 1H, N-H), 5.27 (q, J = 7.2 Hz, 1H, C[2]-H), 6.48 (dd, J = 7.1, 5.1 Hz, 1H, C[5a]-H), 7.09-7.49 (m, 6H, C[4a]-H, C[2b-6b]-H), 7.97 (dd, J = 5.2, 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]), 26.4 (t, C[4]), 29.4 (t, C[5]), 31.9 (t, C[6]), 37.7 (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]), 145.6 (d, C[6a]), 156.2 (s, C[2a]),

TLC: 0.40 (LP/EtOAc 10:1)
GCMS: Retention time: 7.59 min. Main fragments: 282 (M+, 11), 211 (19), 197 (100), 108 (22), 92 (26), 65 (11).

1.2.1. 3-Methyl-*N*-(1-phenyloctyl)pyridin-2-amine (7)



Chemical Formula: $C_{13}H_{14}N_2$
Molecular Weight: 198,27

Chemical Formula: $C_{20}H_{28}N_2$
Molecular Weight: 296,46

The reaction was carried out according to general procedure A with **1** (100 mg, 0.50 mmol, 1 eq.), 1-bromoheptane (269 mg, 1.50 mmol, 3 eq.), K_2CO_3 (311 mg, 2.25 mmol, 4.5 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 22 h at 160 °C. The general work-up procedure B for C-H activation reactions was followed. The combined organic layers were evaporated and the resulting crude product was purified by flash column chromatography (LP/EtOAc, 45 g SiO_2 Flowrate 30 ml/min) starting with pure LP for 5 min. Then the flash column chromatography was continued using a gradient which varies the solvents from 0% to 5 % EtOAc within one hour. Drying under reduced pressure delivered **7**in 38 % (57 mg) yield as yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.86 (t, *J* = 14.6, 9.8 Hz, 3H, C[9]-H_3), 1.14-1.38 (m, 10H, C[4-8]-H_2), 1.87 (ddd, *J* = 22.3, 9.6, 6.8 Hz, 1H, C[3]-H), 2.12 (s, 3H, C[7a]-H_3), 4.37 (d, *J* = 7.6 Hz, 1H, N-H), 5.24 (d, *J* = 7.3 Hz, 1H, C[2]-H), 6.47 (dd, *J* = 7.1, 5.1 Hz, 1H, C[5a]-H), 7.15-7.25 – (m, 2H, C[4a; 4b]-H), 7.27-7.41 (m, 4H, C[2b; 3b; 5b; 6b]-H), 7.95 (dd, *J* = 5.0, 1.8 Hz, 1H, C[6a]-H).

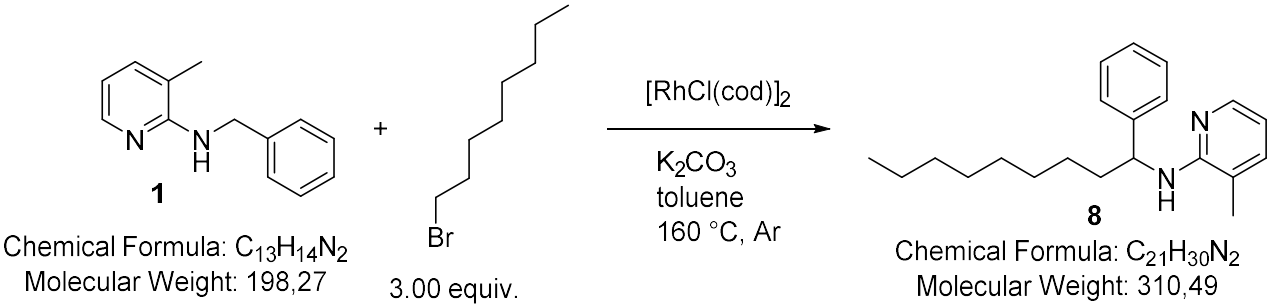
^{13}C NMR (101 MHz, $CDCl_3$): δ 14.1 (q, C[9]), 17.1 (q, C[7a]), 22.7 (t, C[8]), 26.4 (t, C[7]), 29.2 (t, C[6]), 29.6 (t, C[5]), 31.8 (t, C[4]), 37.6 (t, C[3]), 54.6 (d, C[2]), 112.5 (d, C[5a]), 116.2 (s, C[3a]), 126.5 (d, C[2b; 6b]), 126.7 (d, C[4b]), 128.4 (d, C[3b; 5b]), 136.7 (d, C[4a]), 144.6 (s, C[1b]), 145.6, (d, C[6a]), 156.2 (s, C[2a]).

TLC: 0.59 (LP/EtOAc 10:1),

GCMS: Retention time: 7.86 min. Main fragments: 296 (M+, 11), 211 (19), 197 (100), 108 (22), 91 (21), 65 (11).

HRMS: calculated for $C_{20}H_{28}N_2$ $[M+H]^+$ 297.2325; found 297.233; Δ = 1.53 ppm.

1.2.2. 3-Methyl-*N*-(1-phenylnonyl)pyridin-2-amine (8)



1
Chemical Formula: $C_{13}H_{14}N_2$
Molecular Weight: 198,27

8
Chemical Formula: $C_{21}H_{30}N_2$
Molecular Weight: 310,49

The reaction was carried out according to general procedure A with **1** (100 mg, 0.50 mmol, 1 eq.), 1-bromooctane (290 mg, 1.50 mmol, 3 eq.), K_2CO_3 (311 mg, 2.25 mmol, 4.5 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 22 h at 160 °C. The general work-up procedure B for C-H activation reactions was followed starting with pure LP for 10 min. Then the flash column chromatography was continued using a gradient which varies the solvents from 0% to 5 % EtOAc within 1 hour. Drying under reduced pressure delivered **8** in 42 % (65 mg) yield as yellow oil. Analytical data is in accordance with the literature. [20]

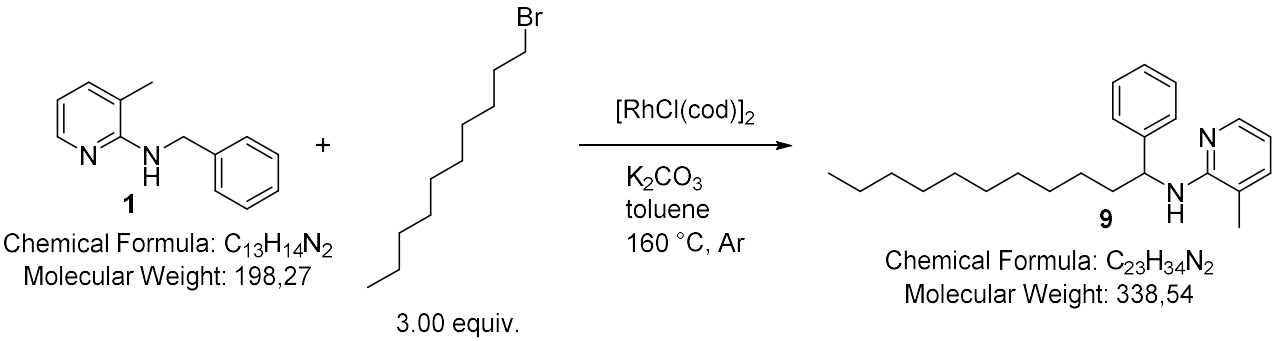
^{1}H-NMR (400 MHz, CDCl3): δ 0.87 (t, *J* = 6.8 Hz, 3H, C[10]-H3), 1.15-1.48 (m, 12H, C[4-9]-H2), 1.73-2.01 (m, 2H, C[3]-H2), 2.11 (s, 3H, C[7a]-H3), 4.38 (d, *J* = 7.6 Hz, 1H, N-H), 5.25 (q, *J* = 7.2 Hz, 1H, C[2]-H), 6.46 (dd, *J* = 7.1, 5.1 Hz, 1H, C[5a]-H), 7.14-7.25 (m, 2H, C[4a; 4b]-H), 7.27-7.40 (m, 4H, C[2b; 3b; 5b; 6b]-H)), 7.96 (dd, *J* = 5.1, 1.8 Hz, 1H, C[6a]-H).

^{13}C NMR (101 MHz, CDCl3): 14.1 (q, C[10), 17.1 (q, C[7a]), 22.7 (t, C[9]), 26.4 (t, C[8]), 29.3 (t, C[7]), 29.5 (t, C[6]), 29.6 (t, C[5]), 31. 9 (t, C[4]), 37.6 (t, C[3]), 54.7 (d, C[2]), 112.5 (d, C[5a]), 116.2 (s, C[3a]), 126.5 (d, C[2b; 6b]), 126.7 (d, C[4b]), 128.4 (d, C[3b; 5b]), 136.8 (d, C[4a]), 144.6 (s, C[1b]), 145.6 (d, C[6a]), 156.2 (s, C[2a]).

TLC: 0.51 (LP/EtOAc 10:1)

GCMS: Retention time: 8.12 min. Main fragments: 310 (M+, 10), 211 (20), 197 (100), 108 (24), 91 (20), 65 (10).

1.2.3. 3-Methyl-*N*-(1-phenylundecyl)pyridin-2-amine (9)



Chemical Formula: $C_{13}H_{14}N_2$
Molecular Weight: 198,27

Chemical Formula: $C_{23}H_{34}N_2$
Molecular Weight: 338,54

The reaction was carried out according to general procedure A with **1** (100 mg, 0.50 mmol, 1 eq.), 1-bromodecane (332 mg, 1.50 mmol, 3 eq.), K_2CO_3 (311 mg, 2.25 mmol, 4.5 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 22 h at 160 °C. The general work-up procedure B for C-H activation reactions was followed using a gradient which varies the solvents from 0% to 5 % EtOAc within one hour. Drying under reduced pressure delivered **9** in 56 % (65 mg) yield as yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.88 (t, J = 6.8 Hz, 3H, C[12]-H_3), 1.10-1.48 (m, 16H, C[4-11]-H_2), 1.77-1.98 (m, 2H, C[3]-H_2), 2.12 (s, 3H, C[7a]-H_3), 4.37 (d, *J* = 7.4 Hz, 1H, N-H), 5.24 (q, *J* = 7.1 Hz, 1H, C[2]-H), 6.47 (dd, *J* = 7.1, 5.0 Hz, 1H, C[5a]-H), 7.15-7.27 (m, 2H, C[4a; 4b]-H), 7.27-7.44 (m, 4H, C[2b; 3b; 5b; 6b]-H), 7.96 (dd, *J* = 5.1, 1.8 Hz, 1H, C[6a]-H).

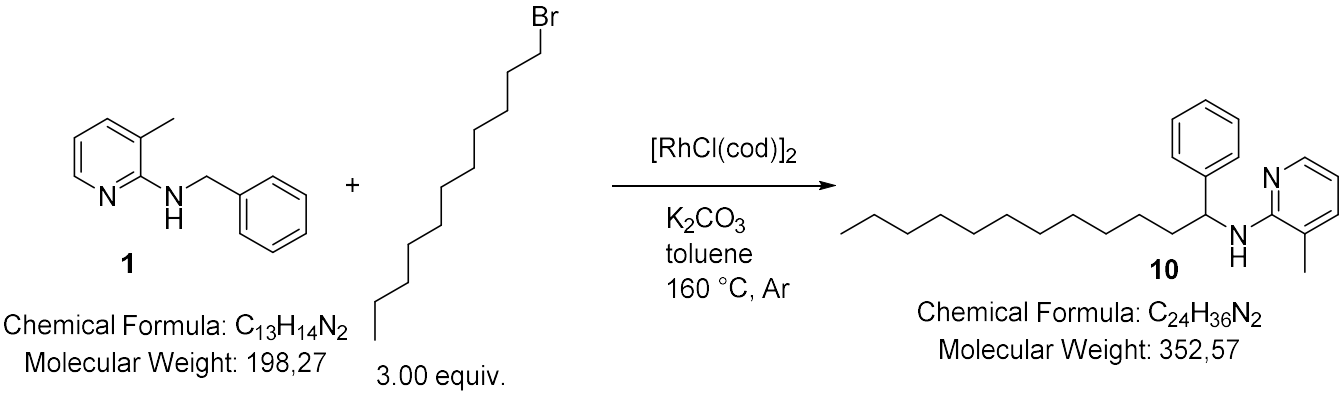
^{13}C NMR (101 MHz, $CDCl_3$): δ 14.1 (q, C[12]), 17.1 (q, C[7a]), 22.7 (t, C[6]), 26.4 (t, C[7]), 29.3 (t, C[5]), 29.5 (t, C[8; 9]), 29.6 (t, C[4a; 4b]), 31.9 (t, C[11]), 37.6 (t, C[3]), 54.6 (d, C[2]), 112.5 (d, C[5a]), 116.1 (s, C[3a]), 126.5 (d, C[2b; 6b]), 126.7 (d, C[4b]), 128.1 (d, C[3b; 5b]), 136.8 (d, C[4a]), 144.6 (s, C[1b]), 145.8 (d, C[6a]), 156.2 (s, C[2a]).

TLC: 0.57 (LP/EtOAc 10:1)

GCMS: Retention time: 8.73 min. Main fragments: 338 (M+, 8), 211 (20), 197 (100), 108 (23), 91 (18), 65 (7).

HRMS: calculated for $C_{23}H_{34}N_2$ $[M+H]^+$ 339,2931; found 339;2926 Δ = 1,46 ppm.

1.2.4. 3-Methyl-*N*-(1-phenyldodecyl)pyridin-2-amine (10)



The reaction was carried out according to general procedure A with 1 (100 mg, 0.50 mmol, 1 eq.), 1-bromoundecane (353 mg, 1.50 mmol, 3 eq.), K_2CO_3 (311 mg, 2.25 mmol, 4.5 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 22 h at 160 °C. The general work-up procedure B for C-H activation reactions was followed starting with pure LP for 10 min. Then the flash column chromatography was continued using a gradient which varies the solvents from 0% to 5 % EtOAc within 1 hour. Drying under reduced pressure delivered **14** in 60 % (106 mg) yield as orange oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.93 (s, 3H, C[13]-H_3), 1.28 (s, 18H, C[4-12]-H_2), 1.81-2.03 (m, 2H, C[3]-H_2), 2.15 (s, 3H, C[7a]-H_3), 4.43 (s, 1H, N - H), 5.30 (q, *J* = 7.1 Hz, 1H, C[2]-H), 6.50 (dd, *J* = 7.1, 5.1 Hz, 1H, C[5a]-H), 7.19-7.30 (m, 2H, C[4a; 4b]-H)), 7.30-7.45 (m, 4H, C[2b; 3b; 5b; 6b]-H), 8.00 (dd, *J* = 5.0, 1.9 Hz, 1H, C[6a]-H).

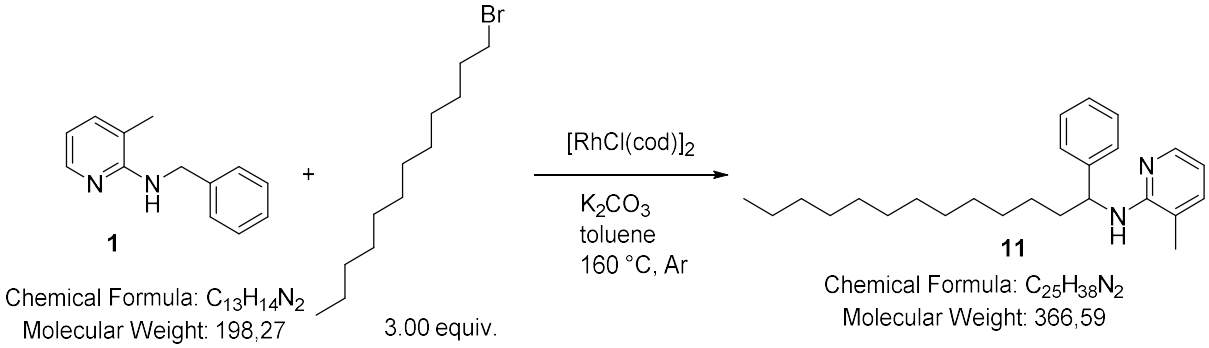
^{13}C NMR (101 MHz, CDCl3): δ 14.2 (q, C[13]), 17.1 (q, C[7a]), 29.6 (t, C[5 - 10]), 32.0 (t, C[11]), 37.6 (t, C[3]), 54.7 (d, C[2]), 112.5 (d, C[5a]), 116.2 (s, C[3a]), 126.5 (d, C[2b; 6b]), 126.7 (d, C[4b]), 128.4 (d, C[3b; 5b]), 136.8 (d, C[4a]), 144.6 (s, C[1b]), 145.5 (d, C[6a]), 156.2 (s, C[2a]).

TLC: 0.55 (LP/EtOAc 10:1)

GCMS: Retention time: 8.73 min. Main fragments: 352 (M+, 8), 211 (19), 197 (100), 108 (23), 91 (19), 65 (7).

HRMS: calculated for $C_{24}H_{34}N_2$ $[M-2H]^+$ 350,2729; found 350,2722; Δ = 2,06 ppm.

1.2.5. 3-Methyl-*N*-(1-phenyltridecyl)pyridin-2-amine (11)



The reaction was carried out according to general procedure A with 1 (100 mg, 0.50 mmol, 1 eq.), 1-bromododecane (374 mg, 1.50 mmol, 3 eq.), K2CO3 (311 mg, 2.25 mmol, 4.5 eq.) and [RhCl(cod)]2 (12 mg, 0.025 mmol, 0.05 eq.) in dry and degassed toluene (2 cm3). The reaction mixture was heated for 22 h at 160 °C. The general work-up procedure B for C-H activation reactions was followed using first 5 minutes pure LP and continuing using a gradient which varies the solvents from 0% to 5 % EtOAc within 1 hour. Drying delivered 24 in 56 % (96 mg) yield as pale yellowish oil.

^{1}H-NMR (400 MHz, CDCl3): δ 0.88 (t, J = 6.8 Hz, 3H, C[14]-H3), 1.21 – 1.36 (m, 20H, C[4-13]-H2), 1.78-1.97 (m, 2H, C[3]-H2), 2.12 (s, 3H, C[7a]-H3), 4.41 (s, 1H, N-H), 5.26 (q, J = 7.3 Hz, 1H, C[2]-H), 6.47 (dd, J = 7.1, 5.1 Hz, 1H, C-[5a]-H), 7.18-7.25 (m, 2H, C[4a; 4b]-H), 7.31 (t, J = 7.5 Hz, 2H, C[2b; 6b]-H, 7.37 (d, J = 7.5 Hz, 2H, C[3b; 5b]-H), 7.95 (dd, J = 5.1, 1.7 Hz, 1H, C[6a]-H);

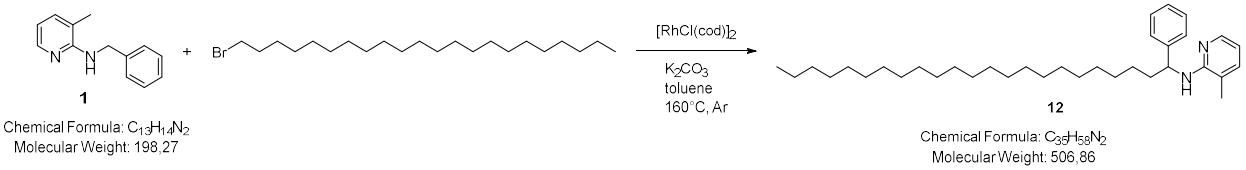
^{13}C NMR (101 MHz, $CDCl_3$): 14.14 (q, C[14]), 17.09 (q, C[7a]), 22.71 (t, C[13]), 26.35 (t, C[12]), 29.31 – 29.75 (m) (t, C[5-11]), 31.94 (t, C[4]), 37.55 (t, C[3]), 54.72 (d, C[2]), 112.50 (d C[5a]), 126.53 (d, C[3b; 5b]), 126.73 (d, C[4b]), 128.39 (d, C[2b; 6b]), 136.91 (d, C[4a]), 144.43 (s, C[1b]).

TLC: 0.9 (LP/EtOAc 10:1)

GC-MS: Retention time: 9.22 min. Main fragments: 366 (M^+ 8), 267 (1), 211 (19), 197 (100), 108 (26), 91 (18), 65 (6);

HRMS: calculated for $C_{25}H_{38}N_2$ $[M+H]^+$ 367,3114; found 367,3119; Δ = 3.14 ppm.

1.2.6. 3-methyl-*N*-(1-phenyltricosyl)pyridin-2-amine (12)



Chemical Formula: $C_{13}H_{14}N_2$
Molecular Weight: 198,27

Chemical Formula: $C_{35}H_{58}N_2$
Molecular Weight: 506,86

The reaction was carried out according to general procedure A with **1** (133mg, 0.50 mmol, 1 eq.), 1-Bromodocosane (584 mg, 1.50 mmol, 3 eq.), K_2CO_3 (311 mg, 2.25 mmol, 4.5 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 22 h at 160 °C. The general work-up procedure B for C-H activation reactions was followed using a gradient which varies the solvents from 0% to 20 % EtOAc within 45 min. Upon recrystallization the pure product was isolated in 31 % (80 mg) yield as white crystals.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.7 Hz, 3H, C[24]-H_3),), 1.19-1.33- (m, 40H, C[4-23]-H_2), 1.80-1.90 (m, 2H, C[3]-H_2), 2.13 (s, 3H, C[7a]-H_3), 4.52 (s, 1H, N-H), 5.32 (s, 1H, C[2]-H), 6.49 (dd, *J* = 7.1, 5.2 Hz, 1H, C[5a]-H), 7.18-7.25 (m, 2H, C[4a; 4b]-H), 7.31 (t, *J* = 7.5 Hz, 2H, C[2b; 6b]-H), 7.39 (d, *J* = 7.5 Hz, 2H, C[3b; 5b]-H), 7.95 (dd, *J* = 5.2, 1.7 Hz, 1H, C[6a]-H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 14.1 (q, C[24]), 17.1 (q, C[7a]), 22.7 (t, C[23]), 26.3 (t, C[4]), 29.8 – 29.3 (m) (t, C[5-21]), 31.9 (t, C[22]), 37. 6 (t, C[3]), 55,0 (d, C[2]), 112.5 (d, C[5a]), 126.5 (d, C[3b; 5b]), 126.9 (d, C[4b]), 128. 5 (d, C[2b; 6b]).

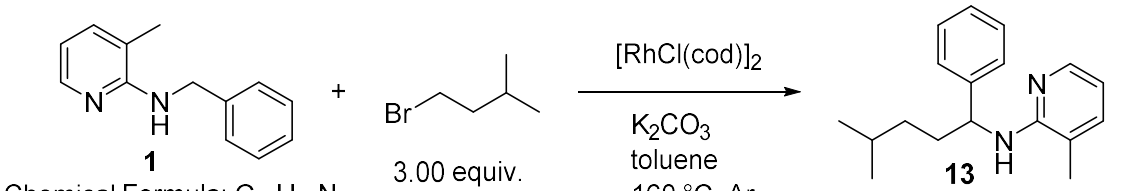
TLC: 0.8 (LP/EtOAc 5:1)

M.p.: 47.5-47.6 °C

LCMS: Retention time: 2.28 min. Main fragments: MS: m/z (relative Intensity): 507.40 (M+H+, 100), 508.4 (40), 509.4 (7), 493.4 (18), 322.2 (16), 314.2 (10), 282.2 (28).

HRMS: calculated for $C_{35}H_{59}N_2$ $[M+H]^+$ 507,4677; found 507,4678; Δ = 0,26 ppm.

1.2.7. 3-Methyl-*N*-(4-methyl-1-phenylpentyl)pyridin-2-amine (13)



Chemical Formula: $C_{13}H_{14}N_2$
Molecular Weight: 198,27

Chemical Formula: $C_{18}H_{24}N_2$
Molecular Weight: 268,40

The reaction was carried out according to general procedure A with **1** (100 mg, 0.50 mmol, 1 eq.), 1-Bromo-3-methyl-butane (227 mg, 1.50 mmol, 3 eq.), K_2CO_3 (311 mg, 2.25 mmol, 4.5 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 22 h at 160 °C. The general work-up procedure B for C-H activation reactions was followed. The combined organic layers were evaporated and the resulting crude product was purified by flash column chromatography (LP/EtOAc, 45 g SiO_2 Flowrate 30 ml/min) starting with pure LP for 10 min. Then the flash column chromatography was continued using a gradient which varies the solvents from 0% to 5 % EtOAc within 45 min. Drying under reduced pressure delivered **13** in 55 % (90 mg) yield as pale yellowish oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.87 (dd, J = 6.6, 3.5 Hz, 6H, C[6;7]-H_3), 1.09-1.39 (m, 2H, C[3]-H_2), 1.58 (dp, J = 13.3, 6.7 Hz, 1H, C[5]-H), 1.73-2.00 (m, 2H, C[4]-H_2), 2.12 (s, 3H, C[7a]-H_3), 4.39 (d, J = 7.5 Hz, 1H, N-H), 5.23 (q, J = 7.2 Hz, 1H, C[2]-H), 6.47 (dd, J = 7.1, 5.1 Hz, 1H, C[5a]-H), 7.14-7.25 (m, 2H, C[4a; 4b]-H), 7.27-7.42 (m, 4H, C[2b; 3b; 5b; 6b]-H), 7.95 (dd, J = 6.0, 1.8, Hz, 1H, C[6a]-H).

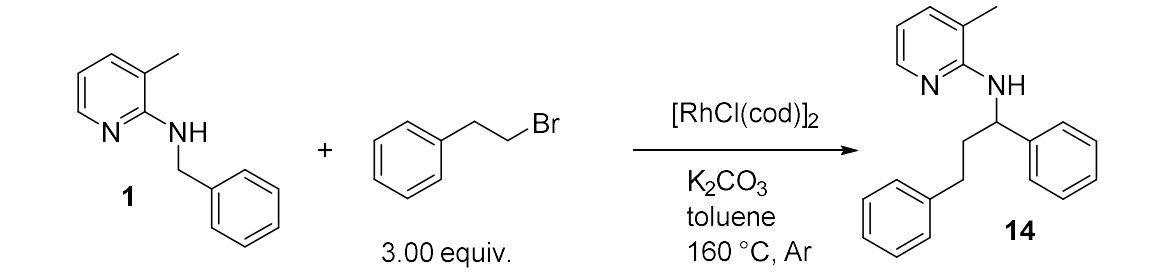
^{13}C NMR (101 MHz, $CDCl_3$): δ 17.2 (q, C[6; 7]), 22.7 (q, C[7a]), 28.2 (d, C[5]), 35.4 (t, C[4]), 35.6 (t, C[3]), 55.0 (d, C[2]), 112.6 (d, C[5a]), 116.4 (s, C[3a]), 126.7 (d, C[2b; 6b]), 126.9 (d, C[4b]), 128.5 (d, C[3b; 5b]), 137,0 (d, C[4a]), 144.6 (s, C[1b]), 145.5 (d, C[6a]), 156.2 (s, C[2a]).

TLC: 0.67 (LP/EtOAc 10:1),

GCMS 1: Retention time: 9.97 min. Main fragments: 268 (M+, 6), 211 (17), 197 (100), 108 (30), 91 (20).

HRMS: calculated for $C_{18}H_{25}N_2$ $[M+H]^+$ 269,2438; found 269,2454; Δ = 5,92 ppm.

1.2.8. *N*-(1,3-Diphenylpropyl)-3-methylpyridin-2-amine (14)



Chemical Formula: $C_{13}H_{14}N_2$
Molecular Weight: 198,27

Chemical Formula: $C_{21}H_{22}N_2$
Molecular Weight: 302,42

The reaction was carried out according to general procedure A with **1** (100 mg, 0.50 mmol, 1 eq.), (2-bromoethyl)benzene (278 mg, 1.50 mmol, 3 eq.), K_2CO_3 (311 mg, 2.25 mmol, 4.5 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 22 h at 160 °C. The general work-up procedure B for C-H activation reactions was followed. The combined organic layers were evaporated and the resulting crude product was purified by flash column chromatography (LP/EtOAc, 45 g SiO_2 Flowrate 30 ml/min) starting with pure LP for 10 min. Then the flash column chromatography was continued using a gradient which varies the solvents from 0% to 5 % EtOAc within 45 min. Drying under reduced pressure delivered **14** in 23 % (36 mg) yield as pale yellowish oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.95 (s, 3H, C[7a]-H_3), 1.96-2.28 (m, 2H, C[4]-H), 2.70 (dddd, *J* = 51.9, 14.0, 9.8, 6.0 Hz, 2H, C[3]-H_2), 4.27-4.34 (m, 1H, N-H), 5.30 (q, *J* = 7.1 Hz, 1H, C[2]-H), 6.40 (dd, *J* = 7.1, 5.1 Hz, 1H, C[5a]-H), 7.04-7.28 (m, 9H, C[2b; 3b; 5b; 6b; 2c-6c]-H), 7.28-7.36 (m, 2H, C[4a; 4b]-H), 7.88 (dd, *J* = 5.2, 1.8 Hz, 1H, C[6a]-H).

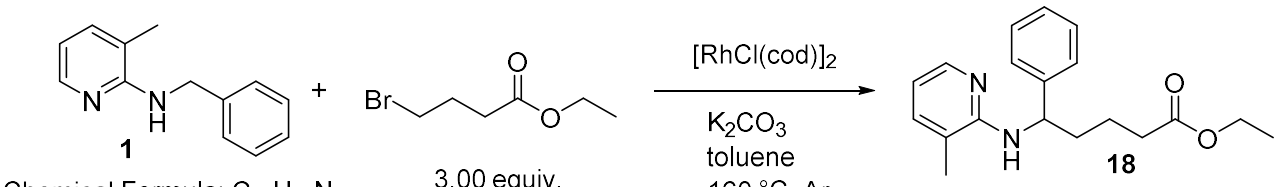
^{13}C NMR (101 MHz, $CDCl_3$): δ 17.0 (q, C[7]), 32.8 (t, C[4]), 38.9 (t, C[3]), 54.7 (d, C[2]), 112.7 (s, C[3a]), 116.4 (d, C[5a]), 125.9 (d, C[2b; 6b]), 126.6 (d, C[4b]), 127.0 (d, C[3b; 5b]), 127.7 (d, C[4c]), 128.5 (d, C[3c; 5c]), 128.6 (d, C[2c; 6c]), 136.9 (d, C[4a]), 142.1 (s, C[1c]), 144.1 (s, C[1b]), 145.4 (d, C[6a]), 156.0 (s, C[2a]).

TLC: 0.46 (LP/EtOAc 10:1)

GCMS: Retention time: 8.50 min. Main fragments: 302 (M+, 9), 211 (85), 197 (100), 108 (20), 91 (52), 65 (30).

HRMS: calculated for C21H22N2 [M]+ 302,1783; found 302,1785; Δ = 0,62 ppm.

1.2.9. Ethyl 5-((3-methylpyridin-2-yl)amino)-5-phenylpentanoate (18)



Chemical Formula: $C_{13}H_{14}N_2$
Molecular Weight: 198,27

Chemical Formula: $C_{19}H_{24}N_2O_2$
Molecular Weight: 312,41

The reaction was carried out according to general procedure A with **1** (100 mg, 0.50 mmol, 1 eq.), Ethyl-4-bromobutyrate (293 mg, 1.50 mmol, 3 eq.), K_2CO_3 (311 mg, 2.25 mmol, 4.5 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 22 h at 160 °C. The general work-up procedure B for C-H activation reactions was followed. The combined organic layers were evaporated and the resulting crude product was purified by flash column chromatography (LP/EtOAc, 9 g SiO_2 Flowrate 15 ml/min) using a gradient which varies the solvents from 0% to 5 % EtOAc within 45 min. Drying under reduced pressure delivered **18** in 26 % (41 mg) yield as dark yellowish oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.05-1.25 (m, 3H, C[9]-H_3), 1.46-1.95 (m, 4H, C[3; 4]-H_2), 2.02 (s, 3H, C[7a]-H_3), 2.11-2.35 (m, 2H, C[5]-H_2), 4.01 (q, J = 7.1 Hz, 2H, C[8]-H_2), 4.38 (d, J = 7.7 Hz, 1H, N-H), 5.19 (q, J = 7.1 Hz, 1H, C[2]-H), 6.38 (dd, J = 7.1, 5.1 Hz, 1H, C[5a]-H), 7.07-7.15 (m, 2H, C[4a; 4b]-H), 7.17-7.37 (m, 4H, C[2b; 3b; 5b; 6b]-H), 7.85 (dd, J = 5.2, 1.7 Hz, 1H, C[6a]-H).

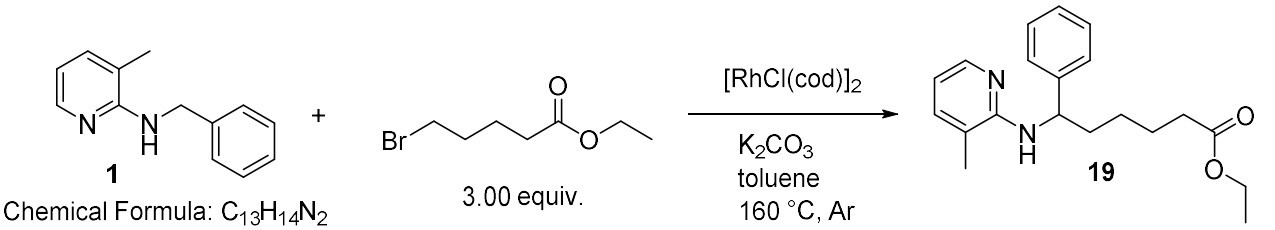
^{13}C NMR (101 MHz, $CDCl_3$): δ 14.3 (q, C[9]), 17.1 (q, C[7a]), 21.8 (t, C[3]), 34.0 (t, C[4]), 36.7 (t, C[5]), 54.3 (d, C[2]), 60.3 (d, C[8]), 112.7 (d, C[5a]), 116.4 (s, C[3a]), 126.5 (d, C[2b; 6b]), 126.9 (d, C[4b]), 128.5 (d, C[3b; 5b]), 136.9 (d, C[4a]), 144.0 (s, C[1b]), 145.4 (d, C[6a]), 156.1 (s, C[2a]), 173.5 (s, C[6]).

TLC: 0.47 (LP/EtOAc 10:1)

GCMS: Retention time: 8.10 min. Main fragments: 312 (M+, 16), 267 (10), 211 (42), 197 (100), 117 (10), 108 (25), 91 (15), 65 (16).

HRMS: calculated for $C_{19}H_{24}N_2O_2$ $[M+H]^+$ 313.1911; found 313.1925; Δ = 4.57 ppm.

1.2.10. Ethyl 6-((3-methylpyridin-2-yl)amino)-6-phenylhexanoate (19)



The reaction was carried out according to general procedure A with **1** (100 mg, 0.50 mmol, 1 eq.), Ethyl-5-bromopentanoate (314 mg, 1.50 mmol, 3 eq.), K_2CO_3 (311 mg, 2.25 mmol, 4.5 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 22 h at 160 °C. The general work-up procedure B for C-H activation reactions was followed using a gradient which varies the solvents from 0% to 10 % EtOAc within 45 min. Drying under reduced pressure delivered **19** in 35 % (56 mg) yield as orange oil.

TLC: 0.16 (LP/EtOAc 10:1)

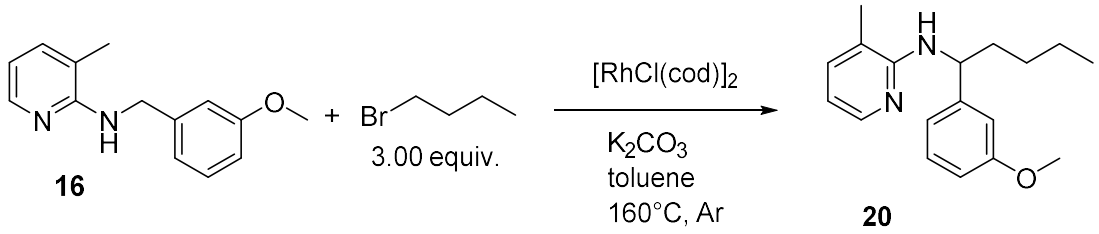
^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.13 (t, *J* = 7.1 Hz, 3H, C[10]-H_3), 1.17-1.47 (m, 2H, C[4]-H_2), 1.58 (p, *J* = 7.6 Hz, 2H, C[5]-H_2), 1.70-1.95 (m, 2H, C[3]-H_2), 2.02 (s, 3H, C[7a]-H_3), 2.19 (t, *J* = 7.5 Hz, 2H, C[6]-H_2), 4.09 (q, *J* = 7.1 Hz, 2H, C[9]-H_2), 4.39 (d, *J* = 7.8 Hz, 1H, N-H), 5.26 (q, *J* = 7.3 Hz, 1H, C[2]-H), 6.47 (dd, *J* = 7.1, 5.1 Hz, 1H, C[5a]-H), 7.15-7.24 (m, 2H, C[4a; 4b]-H), 7.27-7.44 (m, 4H, C[2b; 3b; 5b; 6b]-H), 7.95 (dd, *J* = 5.2, 1.8 Hz, 1H, C[6a]-H)

^{13}C NMR (101 MHz, $CDCl_3$): δ 14.2 (q, C[10]), 17.1 (q, C[7a]), 24.9 (t, C[5]), 25.9 (t, C[4]), 34.2 (t, C[3]), 37.0 (t, C[6]), 54.6 (d, C[2]), 60.2 (t, C[9]), 112.6 (d, C[5a]), 116.4 (s, C[3a]), 126.5 (d, C[2b; 6b]), 126.9 (d, C[4b]), 128.5 (d, C[3b; 5b]), 137.0 (d, C[4a]), 144.1 (d, C[6a]), 155.9 (s, C[2a]), 173.7 (s, C[7]).

GCMS: Retention time: 8.41 min. Main fragments: 326 (M+, 12), 281 (9), 197 (100), 108 (20), 91 (19), 65 (10).

HRMS: calculated for $C_{20}H_{26}N_2O_2$ $[M+H]^+$ 327.2067; found 313.2084; Δ = 5.09 ppm.

1.2.11. *N*-(1-(3-Methoxyphenyl)pentyl)-3-methylpyridin-2-amine (20)



Chemical Formula: $C_{14}H_{16}N_2O$
Molecular Weight: 228,30

Chemical Formula: $C_{18}H_{24}N_2O$
Molecular Weight: 284,40

The reaction was carried out according to general procedure A with **16** (114 mg, 0.50 mmol, 1 eq.), 1-bromobutane (206 mg, 1.50 mmol, 3 eq.), K_2CO_3 (311 mg, 2.25 mmol, 4.5 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 22 h at 160 °C. The general work-up procedure B for C-H activation reactions was followed using a gradient which varies the solvents from 0% to 10 % EtOAc within 45 min. Drying under reduced pressure delivered **20** in 56 % (80 mg) yield as orange oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.90 (t, *J* = 7.0 Hz, 3H, C[6]-H_3), 1.24-1.52 (m, 4H, C[3; 5]-H_2), 1.89 (tdt, *J* = 16.4, 9.6, 4.5 Hz, 2H, C[4]-H_2), 1.89 (tdt, *J* = 16.4, 9.6, 4.5 Hz, 2H, C[19]-H_2), 2.14 (s, 3H, C[7a]-H_3), 3.82 (s, 3H, C[8b]-H_3), 4.42 (s, 1H, N-H), 5.26 (q, *J* = 7.5 Hz, 1H, C[2]-H), 6.50 (dd, *J* = 7.1, 5.1 Hz, 1H, C[4b]-H), 6.78 (ddd, *J* = 8.1, 2.6, 1.1 Hz, 1H, C[5a]-H), 6.93-7.03 (m, 2H, C[2b; 6b]-H), 7.18-7.30 (m, 2H, C[4a; 4b]-H), 7.98 (dd, *J* = 5.1, 1.8 Hz, 1H, C[6a]-H).

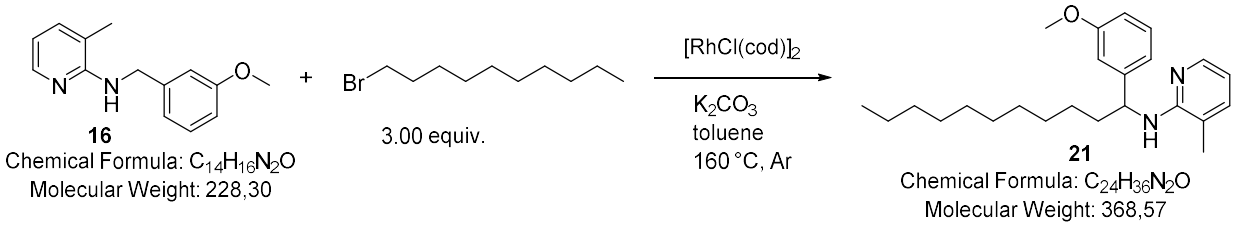
^{13}C NMR (101 MHz, $CDCl_3$): δ 14.0 (q, C[6]), 17.1 (q, C[7a]), 22.7 (t, C[4]), 28.5 (t, C[3]), 54.7 (d, C[2]), 55.2 (q, C[8b]), 111.8 (d, C[2b]), 112.6 (d, C[4b]), 112.7 (d, C[5b]), 116.5 (s, C[3a]), 118.9 (d, C[6b]), 129.4 (d, C[5a]), 137.1 (d, C[4a]), 145.0 (d, C[6a]), 146.2 (s, C[1b]), 155.9 (s, C[3b]), 159.7 (s, C[2a]).

TLC: 0.42 (LP/EtOAc 10:1)

GCMS: Retention time: 8.41 min. Main fragments: 326 (M+, 12), 281 (9), 197 (100), 108 (20), 91 (19), 65 (10).

HRMS: calculated for $C_{18}H_{25}N_2O$ $[M+H]^+$ 285,1980; found 285,1967; Δ = 4,56 ppm.

1.2.12. *N*-(1-(3-methoxyphenyl)undecyl)-3-methylpyridin-2-amine (21)



The reaction was carried out according to general procedure A with **16** (114 mg, 0.50 mmol, 1 eq.), 1-bromodecane (332 mg, 1.50 mmol, 3 eq.), K_2CO_3 (311 mg, 2.25 mmol, 4.5 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 22 h at 160 °C. The general work-up procedure B for C-H activation reactions was followed using a gradient which varies the solvents from 0% to 5 % EtOAc within 45 min. The product was dried under reduced pressure and **21** was isolated in 56 % (102 mg) yield as pale yellowish oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.91 (t, *J* = 6.9 Hz, 3H, C[12]-H_3), 1.19-1.51 (m, 16H, C[4-11]-H_2), 1.81-1.97 (m, 2H, C[3]-H_2), 2.15 (s, 3H, C[7a]-H_3), 3.82 (s, 3H, C[8b]-H_3), 4.41-4.48 (m, 1H, N-H), 5.27 (q, *J* = 7.3 Hz, 1H, C[2]-H), 6.51 (dd, *J* = 7.1, 5.1 Hz, 1H, C[5a]-H), 6.75-6.83 (m, 1H, C[4b]-H), 6.94-7.04 (m, 2H, C[5b; 6b]-H), 7.25 (q, *J* = 7.5 Hz, 2H, C[2b; 4a]-H), 7.99 (dd, *J* = 5.2, 1.8 Hz, 1H, C[6a]-H).

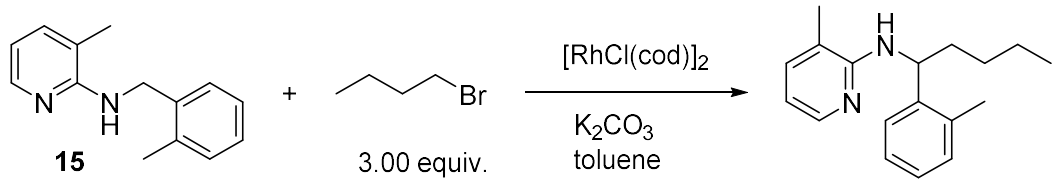
^{13}C NMR (101 MHz, $CDCl_3$): δ 14.1 (q, C[12]), 17.1 (q, C[7a]), 22.7 (t, C[11]), 26.4 (t, C[4]), 29.3 (t, C[5]), 29.6 (t, C[6-9]), 31.9 (t, C[10]), 37.5 (t, C[3]), 54.7 (d, C[2]), 55.2 (q, C[8b]), 111.8 (d, C[6b]), 112.5 (d, C[4b]), 112.6 (d, C[5a]), 116.4 (s, C[3a]), 118.8 (d, C[2b]), 129.4 (d, C[5a]), 137.6 (d, C[4a]), 145.3 (s, C[1b]), 146.2 (d, C[6a]), 156.6 (s, C[5b]), 159.7 (s, C[2a]).

TLC: 0.65 (LP/EtOAc 10:1)

GCMS: Retention time: 9.48 min. Main fragments: 368 (M+, 9), 241 (21), 227 (100), 207 (6), 108 (26), 91 (6) 65 (5).

HRMS: calculated for $C_{24}H_{34}N_2O$ $[M-2H]^+$ 366,2678; found 366,2671; Δ = 1,82 ppm.

1.2.13. 3-Methyl-*N*-(1-(o-tolyl)pentyl)pyridin-2-amine (22)



15
Chemical Formula: $C_{14}H_{16}N_2$
Molecular Weight: 212,30

22
Chemical Formula: $C_{18}H_{24}N_2$
Molecular Weight: 268,40

The reaction was carried out according to general procedure A with **15** (100 mg, 0.47 mmol, 1 eq.), 1-bromobutane (206 mg, 1.50 mmol, 3.2 eq.), K_2CO_3 (311 mg, 2.25 mmol, 4.8 eq.) and $[RhCl(cod)]_2$ (12 mg, 0.025 mmol, 0.05 eq.) in dry and degassed toluene (2 cm^3). The reaction mixture was heated for 22 h at 160 °C. The general work-up procedure B for C-H activation reactions was followed using a gradient which varies the solvents from 0% to 5 % EtOAc within 1 hour. Thereafter a gradient that varies the solvents from 5 % to 10 % EtOAc was applied. Drying delivered **22** in 47 % (60 mg) yield as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.87 (t, *J* = 7.0 Hz, 3H, C[6]-H_3), 1.19 – 1.46 (m, 4H, C[4-5]-H_2), 1.74 – 1.99 (m, 2H, C[3]-H_2), 2.11 (s, 3H, C[7a]-H_3), 2.32 (s, 3H, C[7b]-H_3), 4.39 (s, 1H, (m, 1H, N-H)), 5.22 (q, *J* = 7.5 Hz, 1H, C[2]-H), 6.47 (dd, *J* = 7.1, 5.1 Hz, 1H, C[5a]-H), 7.12 (d, *J* = 7.8 Hz, 2H, C[4a;4b]), 7.23 – 7.16 (m, 1H, C[2b]), 7.27 (d, *J* = 8.1 Hz, 2H, C[3b; 5b]), 7.96 (dd, *J* = 5.1, 1.8 Hz, 1H, C[6a]-H);

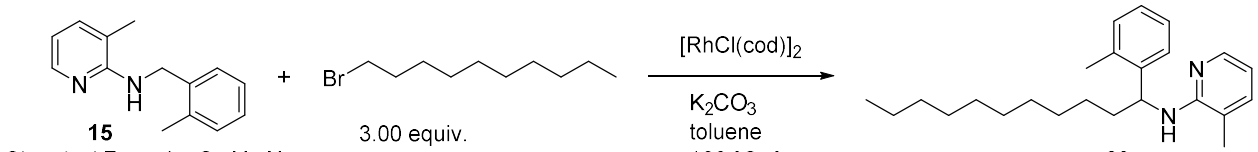
^{13}C NMR (101 MHz, $CDCl_3$): δ 14.1 (q, C[12]), 17.2 (q, C[7a]), 21.2 (t, C[7b], 22.8 (t, C[4]), 28.7 (t, C[5]), 37.3 (t, C[3]), 54.5 (d, C[2]), 112.5 (d, C[5a]), 116.4 (s, C[3a]), 126.6 (d, C[2b]), 129.2 (d, C[4b]), 136.6 (d, C[4a]), 137.0 (d, C[3b]), 141.6 (s, C[1b]), 156.2 (d, C[5b]).

TLC: 0.6 (LP/EtOAc 10:1);

GC-MS: Retention time: 8.88 min. Main fragments: 352 (M+, 5), 225 (8), 211 (100), 108 (19), 92 (22) 65 (4).

HRMS:

1.2.14. 3-Methyl-*N*-(1-(o-tolyl)undecyl)pyridin-2-amine (23)



15
Chemical Formula: $C_{14}H_{16}N_2$
Molecular Weight: 212,30

23
Chemical Formula: $C_{24}H_{36}N_2$
Molecular Weight: 352,57

The reaction was carried out according to general procedure A with **15** (106 mg, 0.50 mmol, 1 eq.), 1-bromodecane (332 mg, 1.50 mmol, 3 eq.), K_2CO_3 (311 mg, 2.25 mmol, 4.5 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 22 h at 160 °C. The general work-up procedure B for C-H activation reactions was followed using a gradient which varies the solvents from 0% to 5 % EtOAc within 45 min. Drying under reduced pressure delivered **23** in 25 % (44 mg) yield as pale yellowish oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.92 – 0.86 (m, 3H, C[12]-H_3), 1.39 – 1.20 (m, 16H, C[4-11]-H_2), 1.97 – 1.75 (m, 2H, C[3]-H_2), 2.10 (s, 3H, C[7a]-H_3), 2.50 (s, 3H, C[7b]-H_3), 4.53 – 4.30 (m, 1H, N-H), 5.49 (q, *J* = 6.4 Hz, 1H, C[2]-H), 6.47 (dd, *J* = 7.1, 5.1 Hz, 1H, C[5a]-H), 7.23 – 7.08 (m, 4H, C[2b-5b]-H), 7.36 – 7.30 (m, 1H, C[4a]-H), 7.97 (dd, *J* = 5.2, 1.8 Hz, 1H, C[6a]-H).

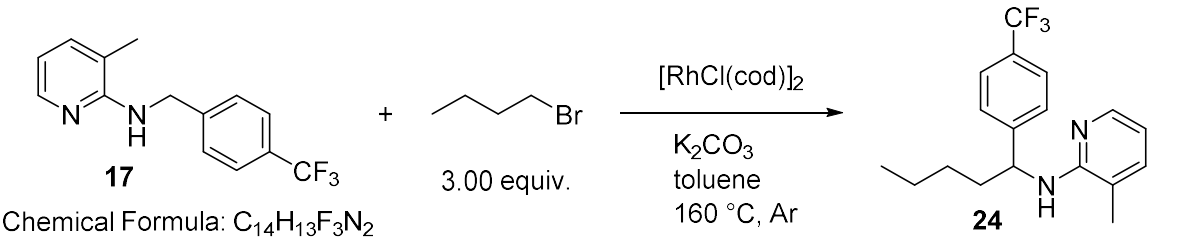
^{13}C NMR (101 MHz, $CDCl_3$): δ 14.2 (q, C[12]), 17.1 (q, C[7a]), 19.6 (q, C[7b]), 22.7 (t, C[11]), 26.5 (t, C[9]), 29.5 (t, C[8]), 29.6 (t, C[7]), 29.6 (t, C[5]), 29.7 (t, C[6]), 31.9 (t, C[4]), 34.5 (t, C[10]), 36.8 (t, C[3]), 51.0 (d, C[2]), 112.4 (s, C[6b]), 116.1 (s, C[3a]), 124. 8 (d, C[5a]), 126.1 (d, C[4b]), 126.5 (d, C[2b]), 130.5 (d, C[3b]), 136.2 (d, C[4a]), 142.8 (s, C[1b]), 145.4 (d, C[6a]), 156.0 (d, C[5b]), 174.0 (s, C[2a]).

TLC: 0.8 (LP/EtOAc 5:1)

GCMS: Retention time: 8.88 min. Main fragments: 352 (M+, 5), 225 (8), 211 (100), 108 (19), 92 (22) 65 (4).

HRMS: calculated for $C_{24}H_{34}N_2$ $[M-2H]^+$ 350,2730; found 350,2722; Δ = 2,34 ppm.

1.2.15. 3-Methyl-*N*-(1-(4-(trifluoromethyl)phenyl)pentyl)pyridin-2-amine (24)



Chemical Formula: $C_{14}H_{13}F_3N_2$
Molecular Weight: 266,27

Chemical Formula: $C_{18}H_{21}F_3N_2$
Molecular Weight: 322,38

The reaction was carried out according to general procedure A with **17** (133mg, 0.50 mmol, 1 eq.), 1-bromobutane (206 mg, 1.50 mmol, 3 eq.), K_2CO_3 (311 mg, 2.25 mmol, 4.5 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 22 h at 160 °C. The general work-up procedure B for C-H activation reactions was followed using a gradient which varies the solvents from 0% to 5 % EtOAc within 45 min. Drying under reduced pressure delivered **24** in 50 % (81 mg) yield as pale yellowish oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.89 (t, J = 6.9 Hz, 3H, C[6]-H_3), 1.18-1.49 (m, 4H, C[4-5]-H_2), 1.77-1.96 (m, 2H, C[3]-H_2), 2.16 (s, 3H, C[7a]-H_3), 4.48 (s, 1H, N-H), 5.31 (p, *J* = 7.4 Hz, 1H, C[2]-H), 6.50 (dd, *J* = 7.1, 5.1 Hz, 1H, C[5a]-H), 7.23 (d, *J* = 7.1 Hz, 1H, C[4a]-H), 7.49 (d, *J* = 8.2 Hz, 2H, C[2b; 6b]-H), 7.55 (d, *J* = 8.1 Hz, 2H, C[3b; 5b]-H), 7.91 (dd, *J* = 5.1, 1.8 Hz, 1H, C[6a]-H).

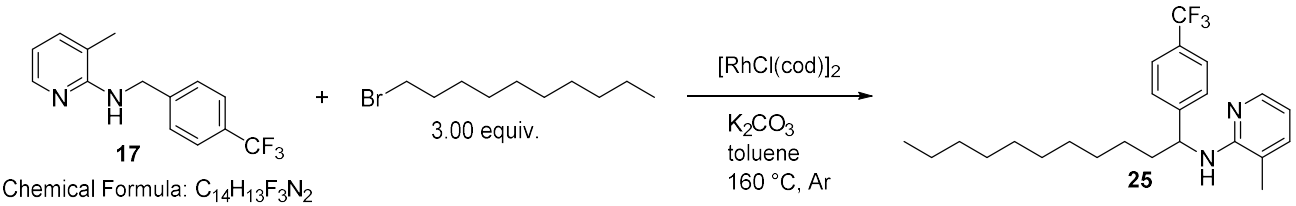
^{13}C NMR (101 MHz, $CDCl_3$): δ 14.1 (q, C[6]), 17.2 (q, C[7a]), 22.7 (t, C[5]), 28.6 (t, C[4]), 37. 5 (t, C[3]), 54.7 (d, C[2]), 113.1 (d, C[5a]), 116.6 (s, C[3a]), 123.1 (s, C[7b]), 125.5, (d, C[3b; 5b]), 126.9 (d, C[2b; 6b]), 129.3 (s, C[6b]), 137.4 (d, C[4a]), 147.3 (s, C[1b]), 148.8 (d, C[6a]), 155.5 (s, C[2a]).

TLC: 0.41 (LP/EtOAc 10:1)

GCMS: Retention time: 6.94 min. Main fragments: 322 (M+, 18), 265 (100), 159 (11), 108 (41), 92 (46) 65 (24).

HRMS: calculated for $C_{18}H_{21}F_3N_2$ $[M+H]^+$ 323.173; found 323.1744; Δ = 4.37 ppm.

1.2.16. 3-methyl-*N*-(1-(4-(trifluoromethyl)phenyl)undecyl)pyridin-2-amine (25)



Chemical Formula: $C_{14}H_{13}F_3N_2$
Molecular Weight: 266,27

Chemical Formula: $C_{24}H_{33}F_3N_2$
Molecular Weight: 406,54

The reaction was carried out according to general procedure A with **17** (133mg, 0.50 mmol, 1 eq.), 1-bromodecane (332 mg, 1.50 mmol, 3 eq.), K_2CO_3 (311 mg, 2.25 mmol, 4.5 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 22 h at 160 °C. The general work-up procedure B for C-H activation reactions was followed using a gradient which varies the solvents from 0% to 5 % EtOAc within 45 min. Drying under reduced pressure delivered **25** in 62 % (126 mg) yield as pale yellowish oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.87 (t, *J* = 6.8 Hz, 3H, C[12]-H_3), 1.19-1.39 (m, 16H, C[7-11]-H_2), 1.78-1.94 (m, 2H, C[3]-H_2), 2.16 (s, 3H, C[7a]-H_3), 4.47 (d, *J* = 7.0 Hz, 1H, N-H), 5.30 (q, *J* = 7.2 Hz, 1H, C[2]-H), 6.50 (dd, *J* = 7.1, 5.2 Hz, 1H, C[6a]-H), 7.23 (d, *J* = 7.1 Hz, 1H, C[4a]-H), 7.48 (d, *J* = 8.1 Hz, 2H, C[2b; 6b]-H), 7.55 (d, *J* = 8.1 Hz, 2H, C[3b; 5b]-H), 7.91 (dd, *J* = 5.1, 1.7 Hz, 1H, C[6a]-H),

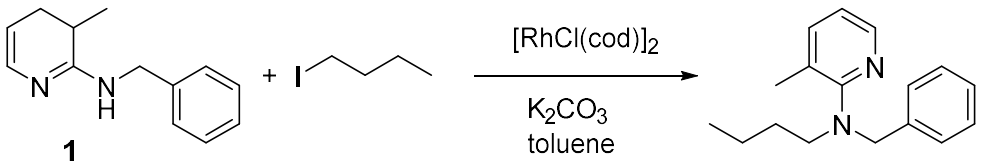
^{13}C NMR (101 MHz, $CDCl_3$): δ 14.1 (q, C[12]), 17.0 (q, C[7a]), 22.7 (t, C[11]), 26.3 (t, C[10]), 29.3 (t, C[8]), 29.5 (t, C[6; 7]), 29.6 (t, C[9; 5]), 31.9 (t, C[4]), 37.6 (t, C[3]), 54.6 (d, C[2]), 113.0 (d, C[5a]), 122.9 (s, C[7b]), 125.3 (d, C[3b; 5b]), 126.8 (d, C[2b; 6b]), 128.7 (s, C[3a]), 129.1 (s, C[4b]), 137.8 (d, C[4a]), 145.0, (s, C[1b]), 148.8 (d, C[6a]), 155.5 (s, C[2a]).

TLC: 0.79 (LP/EtOAc 10:1),

GCMS: Retention time: 8.52 min. Main fragments: 406 (M+, 11), 279 (34), 265 (100), 159 (8), 108 (64), 92 (30) 65 (11).

HRMS: calculated for $C_{24}H_{33}F_3N_2$ $[M+H]^+$ 407.2669; found 407.2684; Δ = 3.7 ppm.

1.2.17. *N*-Benzyl-*N*-butyl-3-methylpyridin-2-amine (26)



1

Chemical Formula: $C_{13}H_{16}N_2$
Molecular Weight: 200,29

26

Chemical Formula: $C_{17}H_{22}N_2$
Molecular Weight: 254,38

The reaction was carried out according to general procedure A with **1** (100 mg, 0.50 mmol, 1 eq.), 1-Iodobutane (276 mg, 1.50 mmol, 3 eq.), K_2CO_3 (311 mg, 2.25 mmol, 4.5 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 22 h at 160 °C. The general work-up procedure B for C-H activation reactions was followed. The combined organic layers were evaporated and the resulting crude product was purified by flash column chromatography (LP/EtOAc, 45 g SiO_2 Flowrate 30 ml/min) using a gradient which varies the solvents from 0% to 5 % EtOAc within 45 min. Drying under reduced pressure delivered **26** in 11 % (14 mg) yield as dark yellow oil.

^{1}H-NMR (400 MHz, CDCl3): δ 0.74 (t, *J* = 7.3 Hz, 3H, C[6]-H3), 1.15 (dq, *J* = 14.7, 7.2 Hz, 2H, C[5]-H2), 1.30-1.43 (m, 2H, C[4]-H2), 2.24 (s, 3H, C[7a]-H3), 2.98-3.07 (m, 2H, C[3] -H2), 4.29 (s, 2H, C[2]-H), 6.74 (dd, *J* = 7.3, 4.8 Hz, 1H, C[5a]-H), 7.09-7.19 (m, 2H, C[4a; 4b]-H), 7.20-7.39 (m, 4H, C[2b; 3b; 5b; 6b]-H), 8.08 (dd, *J* = 4.9, 1.9 Hz, 1H, C[6a]-H).

^{13}C NMR (101 MHz, CDCl3): δ 13.6 (q, C[19]), 20.2 (q, C[7a]), 20.4 (t, C[5]), 29.7 (t, C[4]), 51.6 (t, C[3]), 55.4 (t, C[2]), 117.6 (d, C[5a]), 125.9 (s, C[3a]), 126.7 (d, C[4b]), 128.1 (d, C[2b; 6b]), 128.2 (d, C[3b; 5b]), 139.4 (d, C[4a]), 139.8 (s, C[1b]), 145.1 (d, C[6a]), 161.7 (s, C[2a]).

TLC: 0.61 (LP/EtOAc 10:1),

GCMS: Retention time: 6.80 min. Main fragments: 254 (M+, 7), 211 (18), 197 (44), 163 (68), 91 (100).

HRMS: calculated for $C_{17}H_{20}N_2$ $[M-2H]^+$ 252,1631; found 252.1626; Δ = 1,68 ppm.

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