PALLADIUM-CATALYZED PMHS REDUCTIONS OF IMINES

By

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ABSTRACT

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We explored the Pd-catalyzed reductions of imines using polymethylhydrosiloxane (PMHS) in the presence of aqueous KF. This methodology developed by our group facilitates the reduction of nitrogen-containing functional groups under mild conditions and short reactions times. To the best of our knowledge, there are no prior reports of imine reductions using Pd/PMHS/KF. After optimization of the reaction conditions with respect to the PMHS and KF concentrations, a screening of palladium salts was conducted. This screening proved that $Pd(OAc)_2$ is the most efficient catalyst for these reductions.

Chemoselective reductions of aromatic imines were achieved in the presence of nitriles, nitro, fluoride, and chloride substituents. On the other hand ketones, double bonds and bromide did not survive under these conditions and gave a complex mixture of products.

The addition of PMHS to a $Pd(OAc)_2$ solution result in the formation of polysiloxane encapsulated Pd-nanoparticles, and we were able to confirm the existence of these nanoparticles using transmission electron microscopy (TEM). The crucial role of KF was confirmed on these studies; without addition of KF agglomeration of the Pd-nanoparticles was observed.

ACKNOWLEDGMENTS

The work described in this dissertation would not have been possible without the guidance, advice and scientific support of my research advisor, Professor. Robert E. Maleczka, Jr. His strong work ethic and passion for science helped me evolve both as person and as a scientist.

I would also like to thank the members of my thesis committee Dr. Gregory L. Baker, Dr. William D. Wulff and Dr. Merlin L. Bruening, for always taking time to assist me with my scientific endeavors. A note of appreciation goes to the Chemistry Department and staff at MSU, for providing me with this excellent educational opportunity. I particularly want to thank Dr. Dan Holmes, for his help and suggestions related to the NMR experiments.

I am especially indebted to the Dr. Maleczka Research Group, for the late nights working together and their support in the lab. Especially I want to thank Luis S., Luis M., and Monica for their friendship, as well as useful conversations.

Last but certainly not least, I would like to thank my family, for their unconditional love and prayers during the years. My parents Teresa and Marino have been exceptionally supportive, without their help I would have never made it throughout graduate school. I also thank my sister Magaly and my aunt Julia, for being great friends and always believing in me. Finally, I want to thank Mohanish, for all his tolerance, encouragement, patience and help even in this difficult time. I cannot express how deeply I appreciated everything that he has done for me.

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LIST OF ABBREVIATIONS

Acac	acetylacetonate
aq	aqueous
CH_2Cl_2	dichloromethane
$Cl_2Pd(PPh_3)_2$	dichlorobis(triphenylphosphine)palladium(II)
dba	dibenzylideneacetone
DMF	N,N-dimethylformamide
EDS	energy dispersive spectroscopy
equiv	equivalent
EtOAc	ethyl acetate
g	gram
h	hour
KF	potassium fluoride
Min	minutes
M	molar
mL	milliliter
Mmol	millimole
$Pd(OAc)_2$	palladium (II) acetate
Ph	phenyl
PMHS	polymethylhydrosiloxane
r.b.	round bottom

r.t.	room temperature
TEM	transmission electron microscopy
THF	tetrahydrofuran

CHAPTER 1: IMINE REDUCTIONS

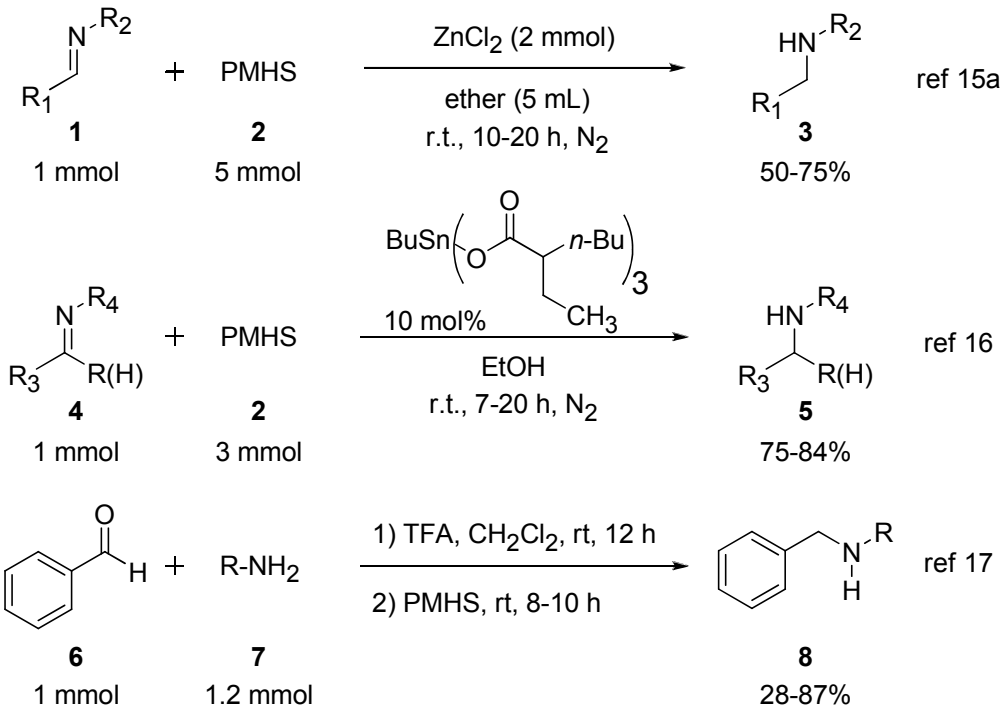
1.1 Introduction

The importance of the amino functionality in the pharmaceutical industry is considerable, for example secondary amines are vital building blocks for alkaloid and pharmaceutical drug syntheses.[1] Besides synthetic transformations can be fine-tuned to improve currents methods and obtain target amino compounds of any complexity from relatively simple structures.

One of the most noteworthy pathways for the synthesis of these nitrogen-containing building blocks is their preparation from readily available imine compounds. Conventional approaches to obtain secondary amines by reduction of imines usually involve the use of reagents that are difficult to handle like $NaBH_4$,[2] $LiAlH_4$,[3] $BH_3(CH_3)_2NH/CH_3COOH$ (glacial),[4] Ra-Ni/aluminum isopropoxide/iPr-OH,[5] NH_3/Ra-Ni,[6] $BH_3S(CH_3)_2$.[7] However, these protocols usually generate copious waste and involve a difficult work up to isolate the desired amine.

Several efforts have also been extended forward the development of asymmetric syntheses of secondary amine using chiral catalyst and ligands.[8,9a-c] Most recently the use of reductive amination reactions, a powerful transformation for fragment coupling of ketones or aldehydes with amines in the presence of a chiral catalyst and a reducing reagent have been increasing.[10] Applications of this reaction in both academic research and chemical industries[1,11] highlight once again the importance of imines as key intermediates that can provide direct access to chiral amines.

An alternative route applied towards imine reduction is the use of silanes and siloxanes as reducing reagents. Different methods have employed triethylsilane in combination with Zn,[12] Mo,[13] Ti[9a-b] catalysts or metal free conditions.[14] In the quest for environmentally friendly and inexpensive procedures, polymethylhydrosiloxane (PMHS) seems to be a safe and economic hydride source. Consequently several protocols have been reported using PMHS in combination with Zn,[15a] Sn,[16] Ti,[9a-c] In,[8] and Cd [8] catalysts, as well as a recent publication in where PMHS is activated only by trifluoroacetic acid.[17] However, long reactions times, harsh conditions, poor chemoselectivity or lower yields governs the outcome of the reductions (Scheme 1.1).

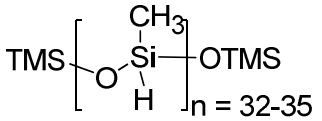


Scheme 1.1 Previous examples of reduction of imines with PMHS

In these methods PMHS is used as an environmentally friendly, non expensive and readily available reducing agent.

1.2 PMHS applications and background

PMHS is a powerful reagent that can perform a wide range of reactions, such as dehalogenation,[18] opening of aziridines,[19] reduction of ketones,[20] double bonds,[21] carboxylic esters,[22] carboxamides,[23] and organotin halides and oxides.[24] It is a byproduct of the silicon industry's synthesis of cyclicsiloxanes, so it is inexpensive (approximately $7.2 per mol of hydride).[25] Moreover, PMHS is air and moisture stable (can be stored on the bench for years); and is assumed to be non-toxic (Scheme 1.2).



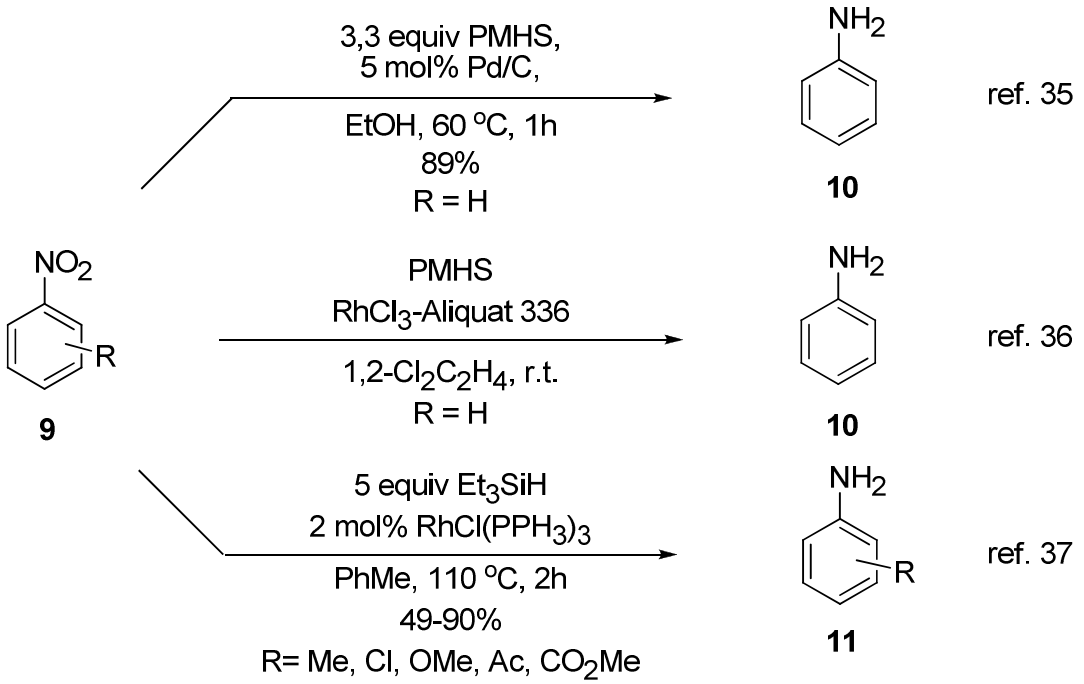
2
Polymethylhydrosiloxane

Scheme 1.2 PMHS structure

PMHS was first synthesized by Sauer[26] in 1946; but its applications have largely been developed in the last decades.[27] Several protocols using PMHS in combination with Ti,[9,22] Pd,[19,21,28] Zn,[20a-b,29] Cu, [20c-d] Sn, [20e,24a,30] Ti,[9,22] Zr,[22] Ru,[23] Fe,[31] and I_2[32] are highlighted in the literature. It is also known that PMHS can be activated to a hypercoordinate species with a fluoride source.[20f,24b,33] Maleczka and co-workers[34] showed that the combination of KF and PMHS, in ethereal solution, yielded tributyltin hydride from the corresponding tributyltin chloride.

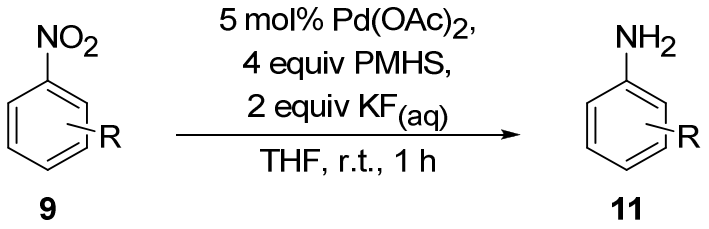
Another important application of PMHS is in nitro reductions. An attractive route for those reductions entailed the use of silanes and siloxanes as hydride source. Early examples by

Lipowitz and Bowman[35] recounted the used of PMHS with a Pd/C catalyst towards the reduction of nitrobenzene to aniline. Almost 20 years later, Bulm and Volhardt[36] highlighted again the use of PMHS to reduce nitrobenzene; using instead a rhodium catalyst for this transfer hydrogenation reaction (Scheme 1.3). Another successful methodology was reported years later by Brinkman and Miles,[37] who employed triethylsilane with a Wilkinson's catalyst for the reduction of several nitrobenzenes.



Scheme 1.3 Previous examples of nitroarenes reductions using silyl hydrides.

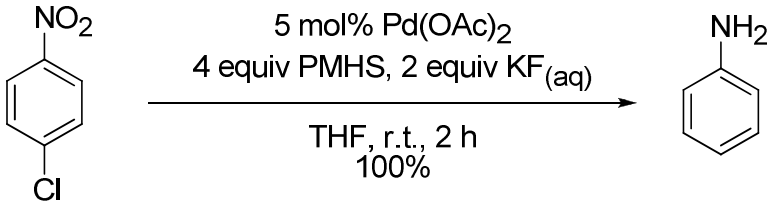
Encouraged by these results, the Maleczka group developed a methodology that facilitates the reductions of nitrogen-containing functional groups under milder conditions and shorter reaction times based on Pd-catalyzed reductions using PMHS in presence of aqueous KF (Scheme 1.4).



9 **11**

Scheme 1.4 Reduction of nitro compounds with Pd/PMHS/$KF_{(aq)}$ at room temperature.

The combination of these reagents was initially tested on the hydrodehalogenation of aryl chlorides.[18b] During those chlorodehalogenation studies, the reduction of the nitro group in 1-chloro-4-nitrobenzene was also observed (Scheme 1.5). Therefore, nitrobenzene was subjected to the optimized dehalogenation conditions to yield the desired amine.[38]



12 **10**

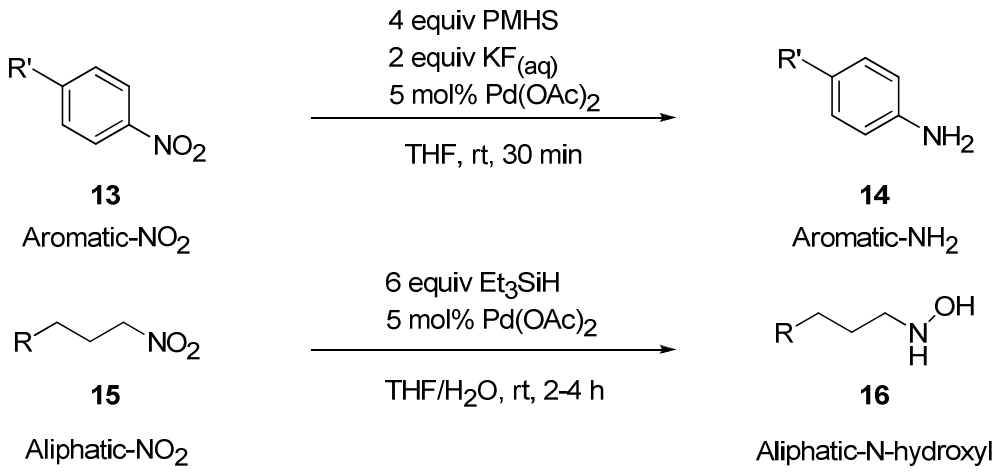
Scheme 1.5 Preliminary $Pd(OAc)_2$/PMHS/$KF_{(aq)}$ nitro reduction

In order to optimize this nitro reduction; different palladium catalysts, fluoride sources, and siloxanes/silanes were screened using 2-nitrotoluene as the control substrate.[38] It was found that the combination of $Pd(OAc)_2$/PMHS/$KF_{(aq)}$ gave the highest yields and shortest reaction times.

These results highlight the importance of the fluoride source to activate the PMHS.[18a,33,34] Moreover, the formation of highly activated palladium nanoparticles as reported

previously by Chauhan[39] when $Pd(OAc)_2$ and PMHS were combined seems to favor the outcome of these reductions. This methodology displayed a broad substituent group tolerance independent of their ring position. Electron-donating and withdrawing groups on the arene were tolerated affording the aniline products in quantitative yield. Chemoselective reductions of the nitro group were also observed, in which carboxylic acids, esters, amides, and fluoro substituents survive; however ketones, nitriles, bromo, chloro, olefins and triple bonds gave side products. Exceptions to this chemoselectivity are substrates containing sulfur, which is assumed to poison the catalyst.[38]

This methodology was extended to heteroaromatic[38] and aliphatic nitro compounds[40] giving the corresponding anilines and N-hydroxylamines (Scheme 1.6). In the second case the optimization conditions required exchange of PMHS for a non-polymeric silicon hydride as triethylsilane and removal of the fluoride source. One-pot reductive conversion of nitroarenes to amides, carbamates or sulfonamides was also reported by the Malezcka group[41] and in recent work, the formation of cyclic nitrones from the reduction of nitroketones.[42]



Scheme 1.6 Pd-catalyzed silicon hydride reductions of aromatic and aliphatic nitro groups.[40]

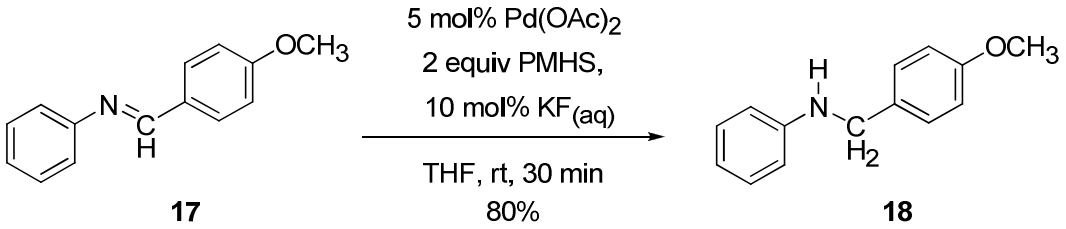
These successful studies on the reduction of nitro compounds using the Pd/PMHS/KF system sparked our interest to further investigate its application to the synthesis of secondary amines from the direct reduction of imines. Therefore, the aim of this thesis is to report our results on imine reductions as well as their advantages of short reaction times, low catalyst loadings and the formation of Pd nanoparticles that seems to guide the chemoselective outcome of these reductions.

CHAPTER 2: APPLICATION OF $Pd(OAc)_2$/PMHS/KF SYSTEM IN THE REDUCTION OF IMINES

The methodology developed by Malezcka's group seems to be hold a great potential for the reduction of imines. To the best of our knowledge there has been no report of using $Pd(OAc)_2$/PMHS/KF for this reductive amination. Therefore the reduction of aromatic and aliphatic imines using the Pd/PMHS/KF system was studied.

2.1 Optimization of the $Pd(OAc)_2$/PMHS/$KF_{(aq)}$ system

Initially *N*-phenyl-4-methoxybenzylideneamine was obtained in quantitative yield following standards procedures.[43] The freshly synthesized imine was subjected to our reduction methodology (Scheme 2.1) and afforded the desired secondary amine in only 30 min. In order to optimize conditions for this reductive amination, control experiments were run without $Pd(OAc)_2$ or aqueous KF; however no reaction was observed after 24 h. A similar result was obtained without PMHS, after 12 hours any reduction of the imine was observed (Table 2.1). This last result highlights that under our reduction conditions imine hydrolysis is not observed, so the reaction goes through a hydrogenolysis pathway. On the other hand, the order of addition was important: mixing the $Pd(OAc)_2$ with the imine solution in THF/KF(aq) followed by addition of PMHS assured shorter reaction times. Furthermore, the equivalents of PMHS needed were reduced to 2, and the concentration of $KF_{(aq)}$ to 10 mol%. Finally the addition of 5 mol% of the $Pd(OAc)_2$ catalyst gave us the best conditions for imine reduction.



Scheme 2.1 Reduction of *N*-phenyl-4-methoxybenzylideneamine with Pd/PMHS/KF system

Table 2.1 Control experiments with the $Pd(OAc)_2$/PMHS/$KF_{(aq)}$ system

Entry	Pd $(OAc)_2$	PMHS	KF	Time	Result
1	5 mol %	2 equiv	10 mol%	30 min	Complete conversion
2	---	2 equiv	10 mol%	24 h	No reaction
3	5 mol%	2 equiv	---	24 h	No reaction
4	5 mol%	---	10 mol%	12 h	No reaction

In order to confirm that $Pd(OAc)_2$ was the best catalyst for these reductions, we tested different Pd catalysts under the same reaction conditions of PMHS/$KF_{(aq)}$ previously established (Table 2.2).

Using 5 mol% of each catalyst and 1 mmol of *N*-phenyl-4-methoxybenzylideneamine, the control reactions were performed and monitored by ^{1}H-NMR between 30 min and 2 hours. In the first two attempts using $Pd(Cl)_2$ and $Pd(CN)_2$ (entries 1 and 2 on Table 2.2) the ^{1}H NMR spectrum of the crude reaction mixture displayed only the signals of the starting material. Therefore we continued both reactions for an additional 30 min; however no conversion was observed and the catalyst precipitated after 2 hours in both cases.

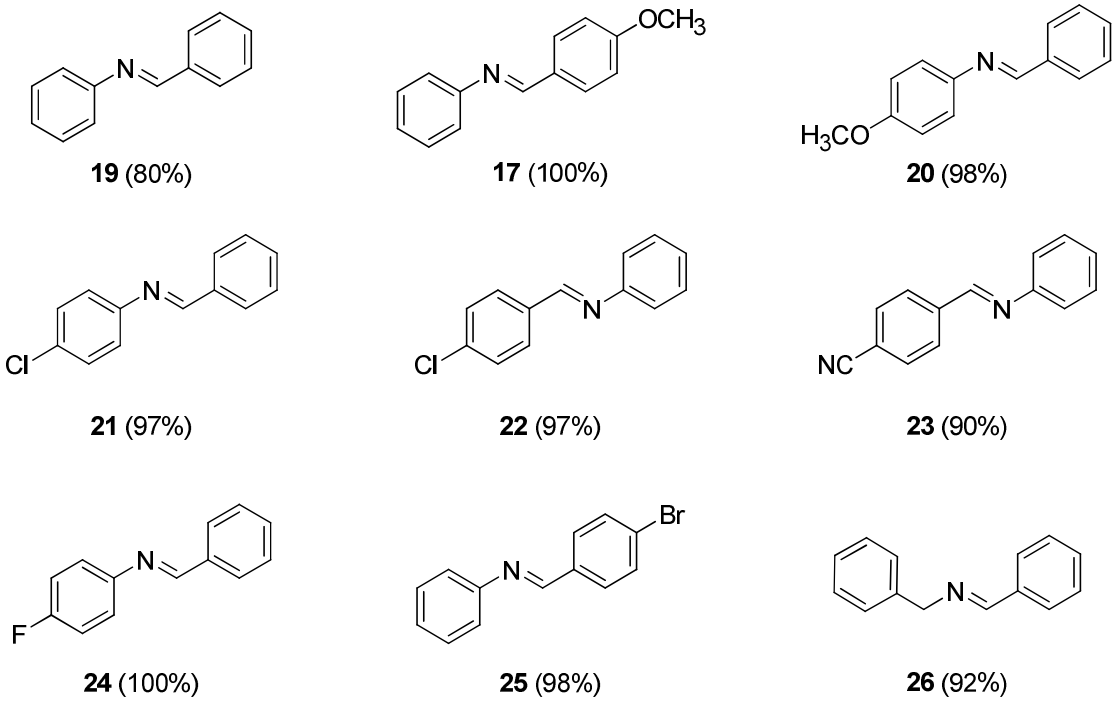
Table 2.2 Screening of different Pd catalysts for imine reduction

Entry	Catalyst	Time	% conversion
1	$Pd(Cl)_2$	30 min	0
2	$Pd(CN)_2$	30 min	0
3	$Pd(PPh_3)_2(C_6H_5)Cl$	30 min	0
4	$Pd(PPh_3)_2Cl_2$	30 min	0
5	$Pd(NH_3)_2Cl_2$	30 min	0
6	$Pd_2(dba)_3$	30 min	50
7	Pd black	30 min	50
8	Pd/C activated	30 min	50
9	$Pd(OH)_2/C$	30 min	50
10	$Pd(acac)_2$	30 min	80

When phosphine ligands were employed (entries 3 and 4) no conversion to the desired amine was observed after 30 min, instead hydrolysis of the imine generated a complicated mixture as judged by ^{1}H NMR. The same result was observed when $Pd(NH_3)_2Cl_2$ was used as a catalyst (entry 5). On the other hand, when $Pd_2(dba)_3$, Pd black, Pd/C activated and $Pd(OH)_2/C$ were employed, partial reduction of the imine was observed at 30 min. The secondary amine to imine ratio was 1:1; complete conversion was observed by ^{1}H NMR after 1 hour (entries 6 to 9). The last catalyst tested, $Pd(acac)_2$, gave the highest conversion in 30 min. The ratio of secondary

amine to imine was 4:1 and the reaction was complete after 45 min. In summary, these findings confirmed that $Pd(OAc)_2$ was the best catalyst, giving complete conversion in as little as 30 min.

With these results in hand, several imines where prepared,[43,44] not only to study reductive amination, but also to further investigate the chemoselectivity of this reduction in the presence of other functional groups such as alkenes, ketones, nitriles, halogens and nitro substituents (Scheme 2.2).

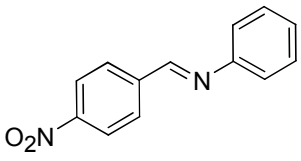


19 (80%) **17** (100%) **20** (98%)

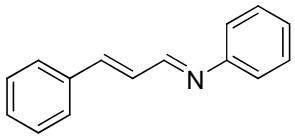
21 (97%) **22** (97%) **23** (90%)

24 (100%) **25** (98%) **26** (92%)

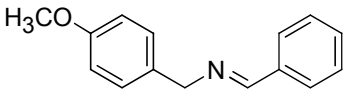
Scheme 2.2 Imines prepared for reductive amination (isolated yield)



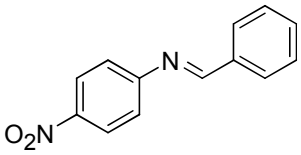
27 (87%)



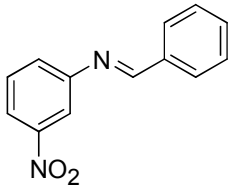
28 (100%)



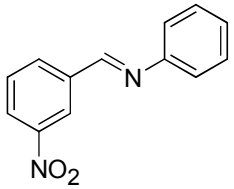
29 (75%)



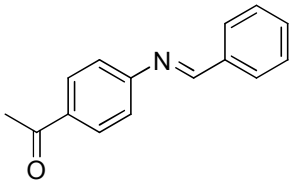
30 (100%)



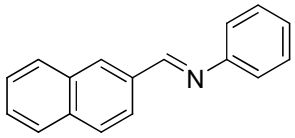
31 (97%)



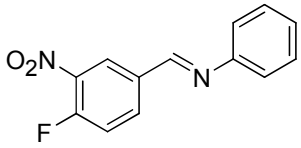
32 (91%)



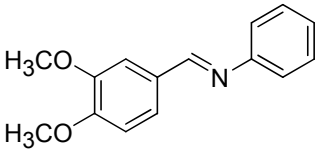
33 (98%)



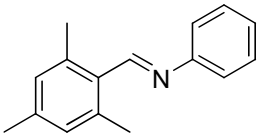
34 (97%)



35 (74%)



36 (78%)



37 (100%)

Scheme 2.2 (cont'd)

The secondary amines were identified by ^{1}H-NMR, the spectra usually display an imine proton (N=C**H**) around 8.4 ppm for the starting material. After reduction, this signal disappears and a new peak for the methylene protons (NH-C**H**$_2$) of the secondary amine is observed around 4.3 ppm (Figure 2.1).

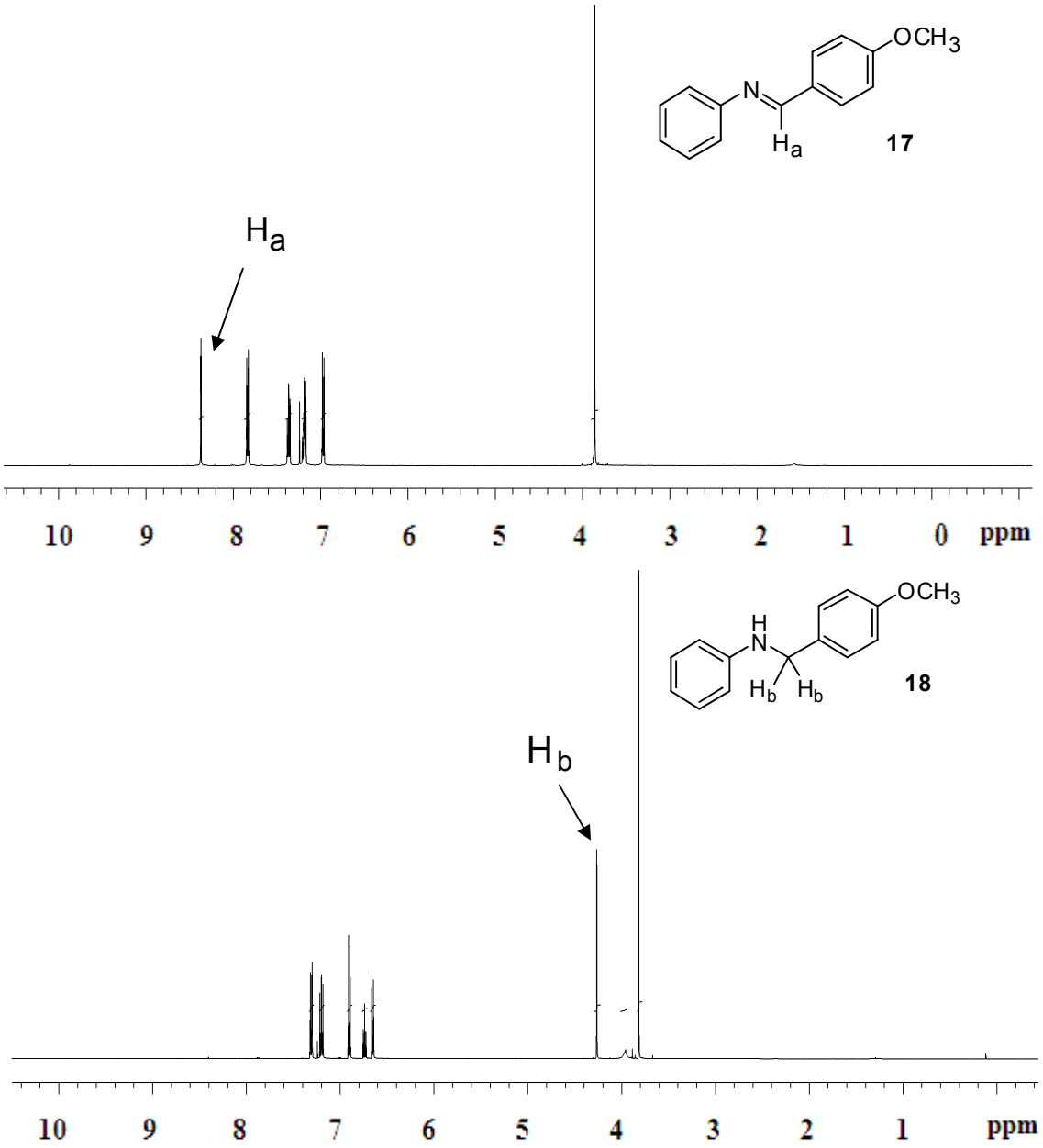
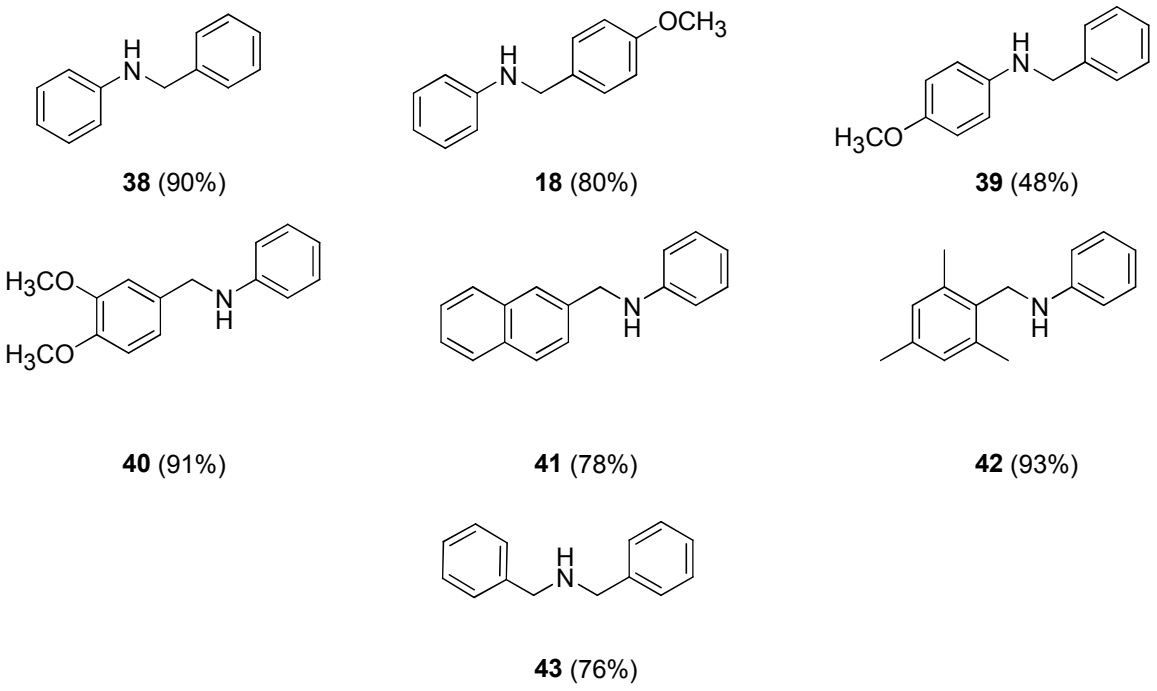


Figure 2.1 Comparison of the ^{1}H-NMR spectrum of imine **17** (top) and secondary amine **18** (bottom)

The initial work up for the *N*-phenyl-4-methoxybenzylideneamine reduction included addition of ether, which precipitated the catalyst after stirring. A quick filtration of the Pd through a plug of Celite (top layer) and neutral alumina (bottom layer) gave a high crude

recovery; however the yield of product recovered after column chromatography was <50% and some contamination with PMHS was observed by ^{1}H NMR. To circumvent this problem, a new work up was attempted in which a mixture of H_2O/Et_2O (1:1) was added to the crude. After stirring, the organic phase was separated, dried with $MgSO_4$, filtered and concentrated. The crude product was dissolved in EtOAc and treated with a 3M HCl solution. The white solids formed were filtered, washed with EtOAc and dried overnight to give the desired secondary amine as a hydrochloride salt. The latter was dissolved in a H_2O/methanol (1:1) mixture and $NaHCO_3$ (sat) solution was added. The solution was concentrated under reduced pressure to the minimum, and then extracted with EtOAc. The organic layers were dried and concentrated to give the secondary amine in 65%. Optimization of the work up with a shorter acid/base procedure increased the yield to 80% of *N*-(4-methoxybenzyl)phenylamine. In this work up, a mixture of Et_2O/1M HCl (1:1) was added and stirred for 10 min. The organic phase was separated and washed with 1M HCl. Then the aqueous layers were combined, made basic with addition of $KOH_{(s)}$, and extracted with EtOAc. Finally, the combined organic layers were dried, filtered and concentrated.

In summary, the secondary amines were successfully synthesized[16,45] and fully characterized (Scheme 2.3). Reaction times varied between 15 min to 1 hour and the yields ranged from 48 to 93%.



38 (90%) **18** (80%) **39** (48%)

40 (91%) **41** (78%) **42** (93%)

43 (76%)

Scheme 2.3 Secondary amines synthesized (isolated yield)

2.2 Chemoselectivity studies

The second part of this project is concerned with the reactivity of the imine in the presence of other functional groups. The first substrates selected contained NO_2 groups in the para and meta position of the aniline or benzaldehyde ring. When the electron withdrawing group was on the meta position, reduction of both functionalities was observed in 1 hour. For m-NO_2 anilines (imine **31**), only the over reduction product (**44**) was observed; but m-NO_2 benzaldehydes (imine **32**) gave a 1:1 mixture of the nitro secondary amine (**45**) and the over reduction product (**46**) was recovered after 1 hour (Figure 2.2). Leaving the reaction for longer times reduced the yield of the desired secondary amine and new signals of aniline become the major product in the crude mixture. A similar outcome was observed in the reduction of imine

35, which contains m-NO_2 and a fluoro group in the para position of the same ring. The ^{1}H NMR spectrum of the crude reaction mixture, showed the reducted imine; however two secondary amines could be identified. One where the NO_2 group survived, and another where over reduction took place. No dehalogenated product could be identified in the complicated mixture.

Better chemoselectivity was observed when the nitro substituent was at the para position. Regardless whether the p-NO_2 group was on an aniline or benzaldehyde ring, the nitro group survived the reduction conditions and no over reduced product (**47**) was observed after one hour (Figure 2.3). However, some starting imine remained in the reaction. Leaving the mixture for longer time reduces the yield of the target secondary amine and increase the formation of aniline derivative.

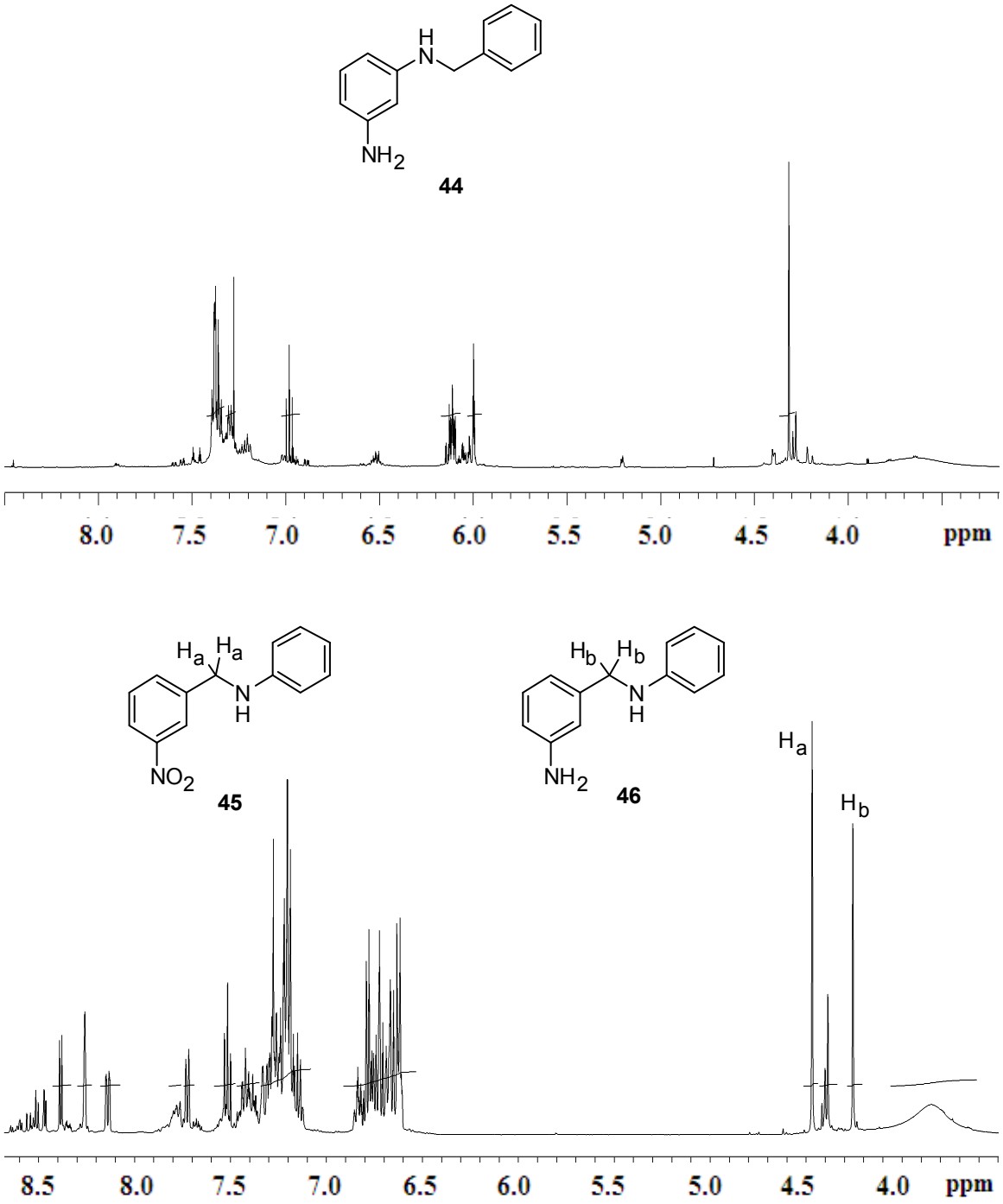


Figure 2.2 ^{1}H-NMR spectrum of over reduced m-NO_2 imine **44** (top) and ^{1}H-NMR spectrum of the crude mixture of secondary amines **45** and **46** (bottom)

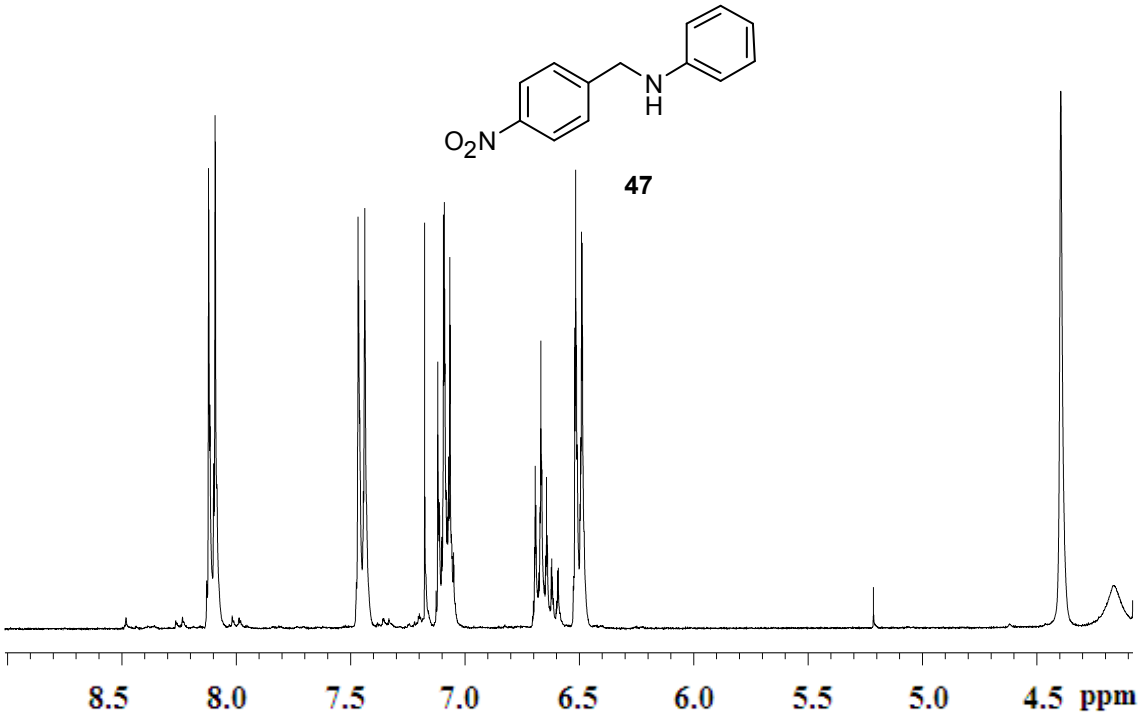


Figure 2.3 ^{1}H-NMR spectrum of chemoselective reduction of imine vs. NO_2 group

Chemoselective reduction of the imine was also observed in the presence of nitrile substituents (imine **23**). Impressively, the nitrile group survives the reaction conditions and no primary amine or aldehyde were detected by ^{1}H NMR.

Previous studies of this methodology in the presence of halogen substituents showed dehalogenation as a side reaction. However, under the optimized imine reduction conditions no dehalogenated products where observed in the case of F (imine **24**) and Cl (imine **22**) containing substrates. In the reduction of imine (**24**), the ^{1}H NMR spectrum displayed a complicated mixture of the starting material (**24**), the target secondary amine (**48**) and 4-fluoroaniline (**49**) (Figure 2.4). This reaction was also monitored by GC. Injecting known samples of 4-fluoroaniline (**49**) and the starting imine (**24**), we were able to observe the consumption of the

imine (**24**) and the formation of the target amine (**48**). However, the increasing formation of 4-fluoroaniline (**49**) with the time, reduced the yield of the secondary amine (**48**) (Table 2.3).

Table 2.3 Reduction of imine **24** monitored by NMR and GC analysis

Entry	Crude NMR	Imine **24**	Secondary Amine	4-fluoroaniline
1	at 30 min	5.3%	80.9%	13.7%
2	at 1 h	4%	79.7%	16.3%
3	at 3 h	1.4%	37.4%	61.1%
Entry	GC analysis			
4	at 1 h	1.6%	82.2%	12.2%
5	at 2 h	2.9%	52.8%	44.9%

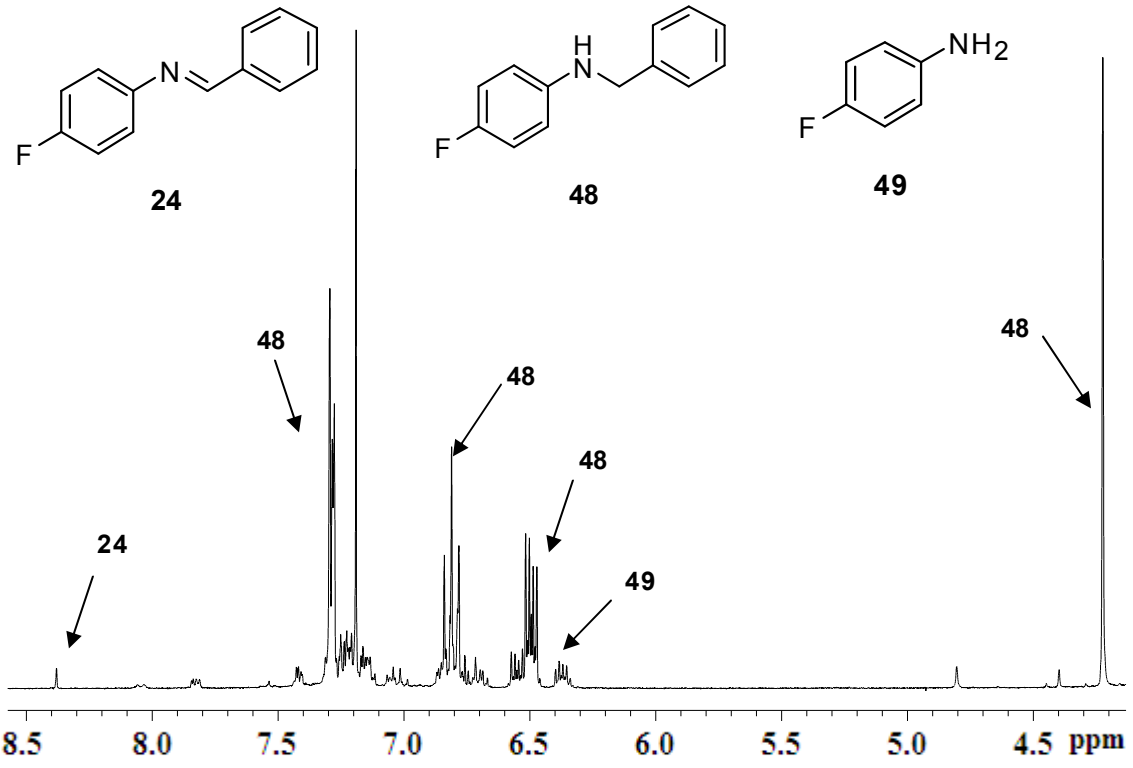


Figure 2.4 ^{1}H-NMR spectrum of imine **24** reduction crude at 1 hour

On the other hand, the imine reduction with Br containing substrate (imine **25**) displayed a complicated mixture in the ^{1}H NMR spectrum, where four different compounds could be identified: two secondary amines (**38**, **52**) and two imines (**19**, **25**) as a consequence of dehalogenation. Furthermore, hydrolysis of the two imines present in the mixture was also observed (compounds **50** and **51**). Attempts to separate this mixture, even by preparative TLC, were unsuccessful (Figure 2.5).

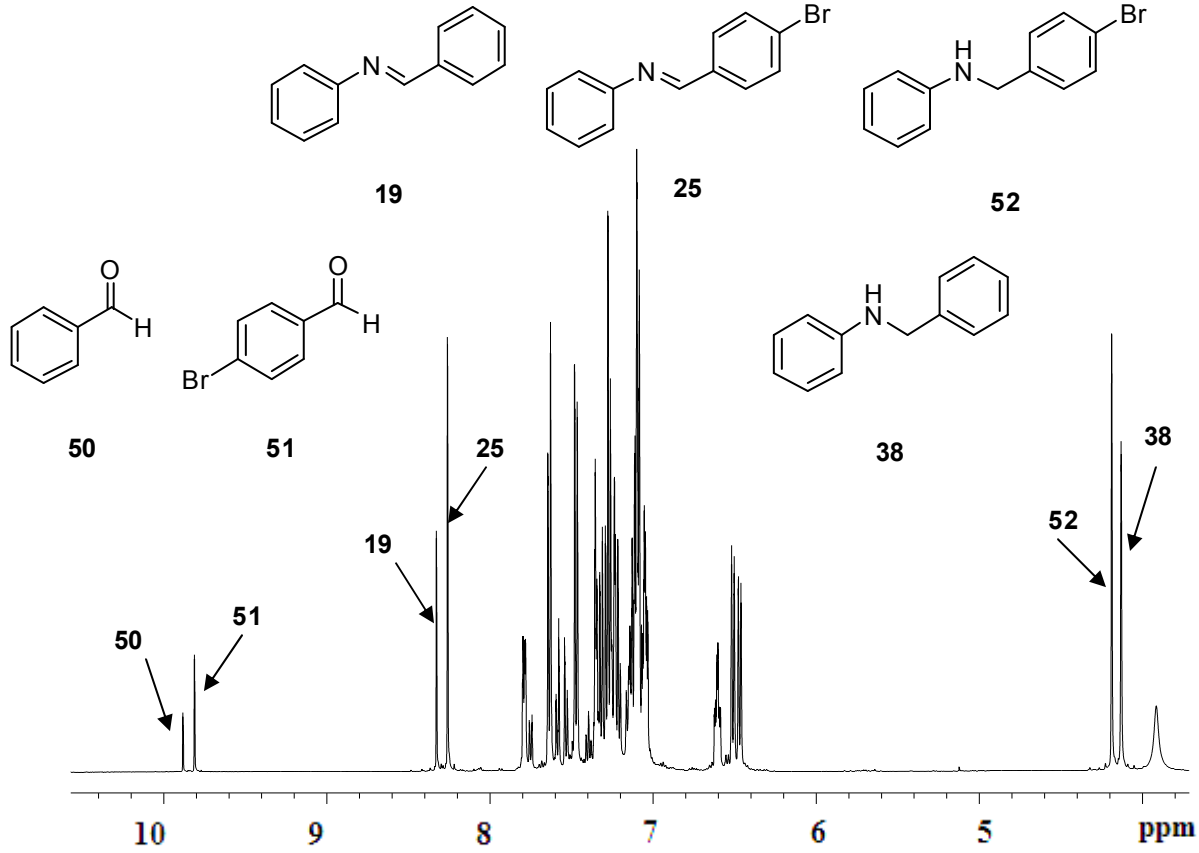
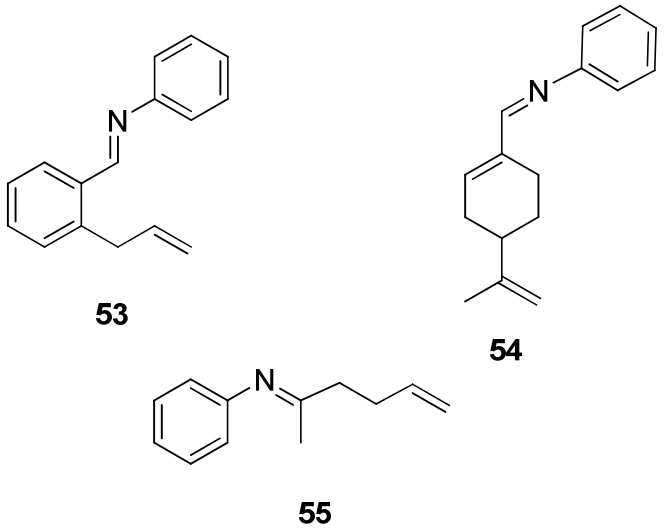


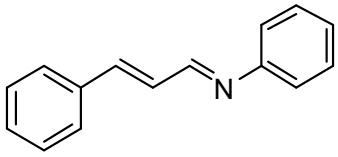
Figure 2.5 ^{1}H-NMR spectrum of complex mixture of imine **25** reduction

A limitation of this methodology was observed in the presence of conjugated and non-conjugated double bonds. In the former case, the presence of the conjugated double bond accelerates the reaction, yielding complete reduction in only 15 min (Figure 2.6). An important

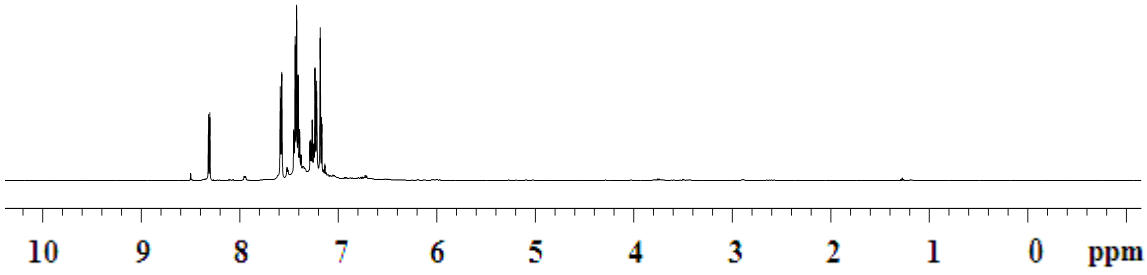
observation was that the complete formation of the secondary amine (**56**) was detected even before the typical bubbling and color change could be observed. Expecting a different result with non-conjugated double bonds, three different imines were envisioned as potential substrates (Scheme 2.4). However inability to purify the substrate and further contamination with aniline prevented us from employing our reduction methodology. Among these substrates, ketoimine (**55**) showed the lowest aniline contamination. To address this issue, fewer equivalents of aniline were added; however we were unable to obtain a pure product. Nonetheless, we decided to employ this crude mixture for the imine reduction step. Unfortunately, after only 30 min the ^{1}H NMR signals of the double bond between 5 and 6 ppm disappeared, and the over reduced secondary amine (**57**) was recovered after preparative TLC (Figure 2.7). At this point we cannot discount the possibility that the excess aniline present serves as an additive that promotes the reduction of the double bond. Therefore it might be interesting to ascertain whether a reduction of a non-conjugated double bond can be avoided in the absence of the aniline impurity.

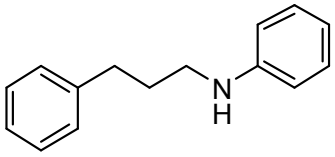


Scheme 2.4 Potential imine substrates



28





56

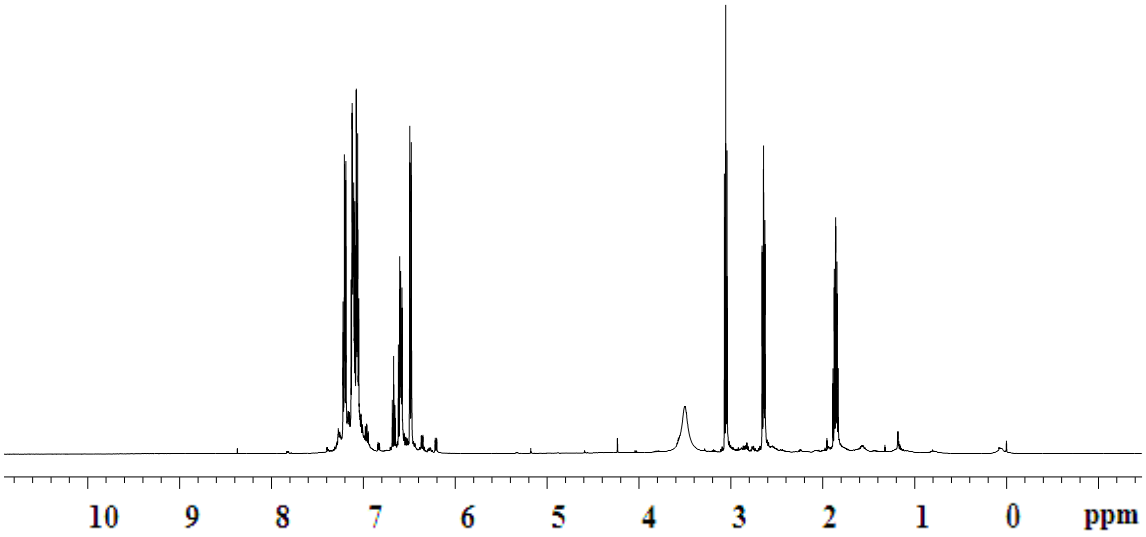


Figure 2.6 Comparison ^{1}H-NMR spectrum of imine **28** (top) and over reduced secondary amine **56** (bottom)

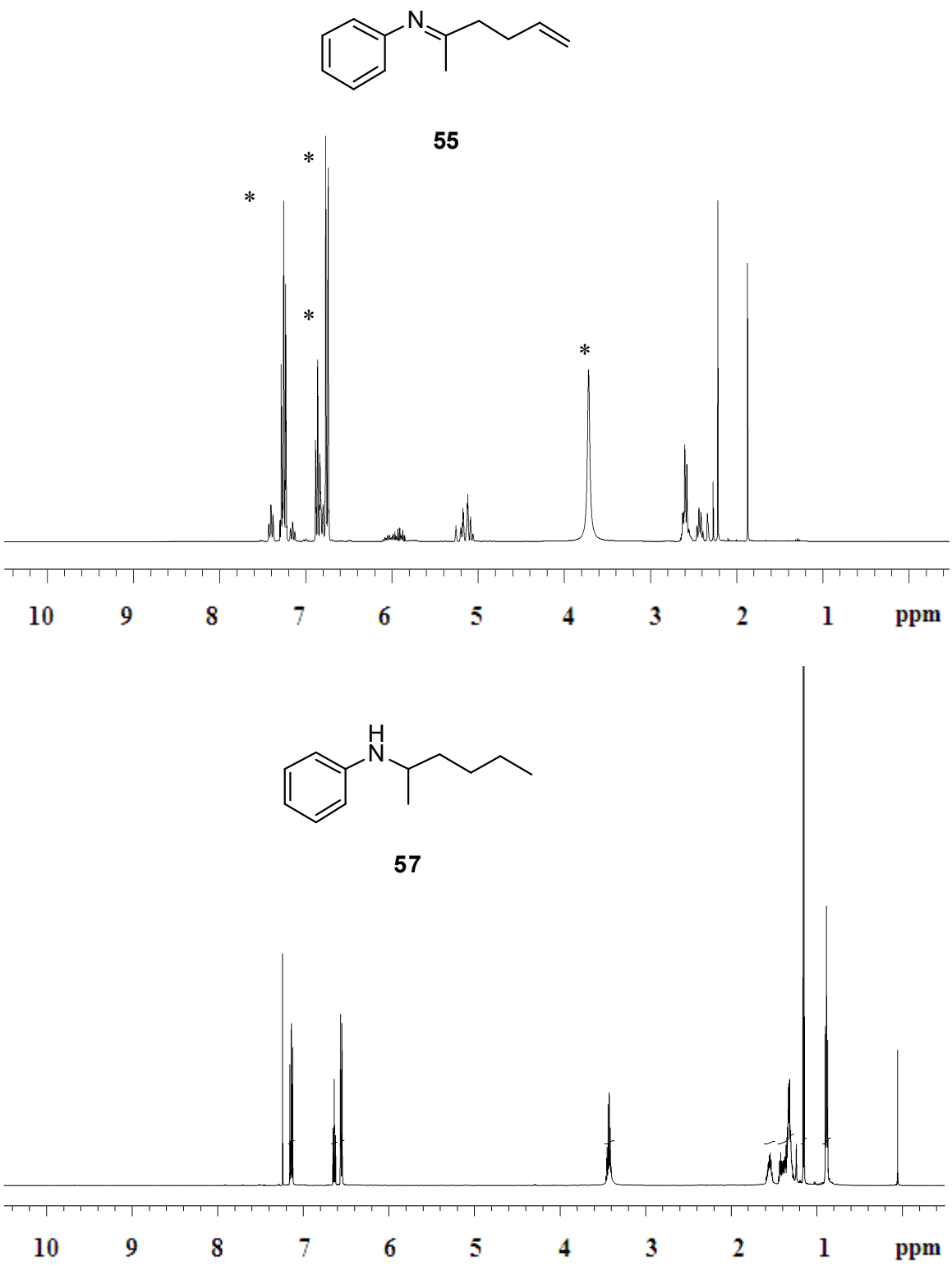


Figure 2.7 Comparison ^{1}H-NMR spectrum of imine **55** with aniline contamination (*) (top) and over reduced secondary amine **57** (bottom)

Continuing our studies on chemoselectivity, reductions of imines in the presence of ketones (imine **33**) were carried out. Unfortunately analysis of the crude ^{1}H NMR spectrum after 30 min displayed a mixture of selective imine reduction (secondary amine) and the over reduction product (conversion of ketone to alcohol and secondary amine) in a ratio 1:0.3. The usual work up developed for the isolation of the secondary amines did not allow us to isolate the alcohol product, therefore optimization of the isolation and purification of these products is still underway.

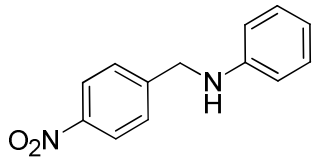
Finally, a different result was obtained when N-benzylidene-4-methoxyaniline (imine **20**) was subjected to the reduction conditions. At 30 min, the target secondary amine **39** was observed by ^{1}H NMR, along with 4-methoxyaniline as an impurity (Table 2.4). The presence of small quantities of starting imine **20** led us to leave the reaction for another 30 min. Surprisingly, another compound was detected in the crude mixture but after purification and concentration of the solvent, only the secondary amine **39**, imine **20** and 4-methoxyaniline were recovered. In a different batch, left for 5 hours, the desired secondary amine **39** was not detected. Instead, toluene and 4-methoxyaniline were the major components in the mixture, along with a small percent of starting material. Leaving the reaction overnight let to complete consumption of the imine, yielding only toluene and 4-methoxyaniline (Table 2.4). These findings suggest the possibility of hydrogenolysis of the secondary amine **39** with time.

Table 2.4 Possible hydrogenolysis of the secondary amine **39** with time

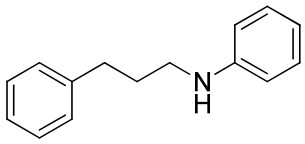
Entry	Crude NMR	N-benzylidene-4-methoxyaniline	Secondary amine **39**	Toluene	4-methoxyaniline
1	at 30 min	5.8%	44%	9.8%	39.6%
2	at 1 h	5.1%	37.8%	16%	41.2%
3	at 5 h	3.7%	---	43.6%	52.7%
4	at 21 h	---	---	46.8%	53.2%

2.3 Conclusions

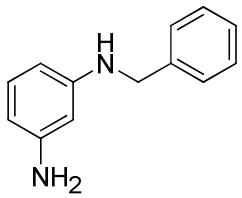
In this dissertation we focused on the reactivity of several imines in the presence of the $Pd(OAc)_2/PMHS/KF_{aq}$ system. This methodology was selective in the presence of nitriles, fluoride, chloride and p-nitro substituents, yielding the target secondary amine in short reaction times at room temperature.



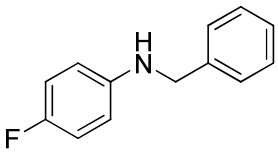
47 (33%)



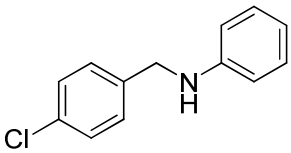
56 (67%)



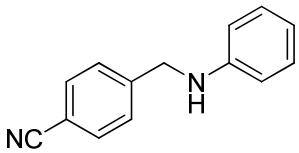
44 (52%)



49 (69%)



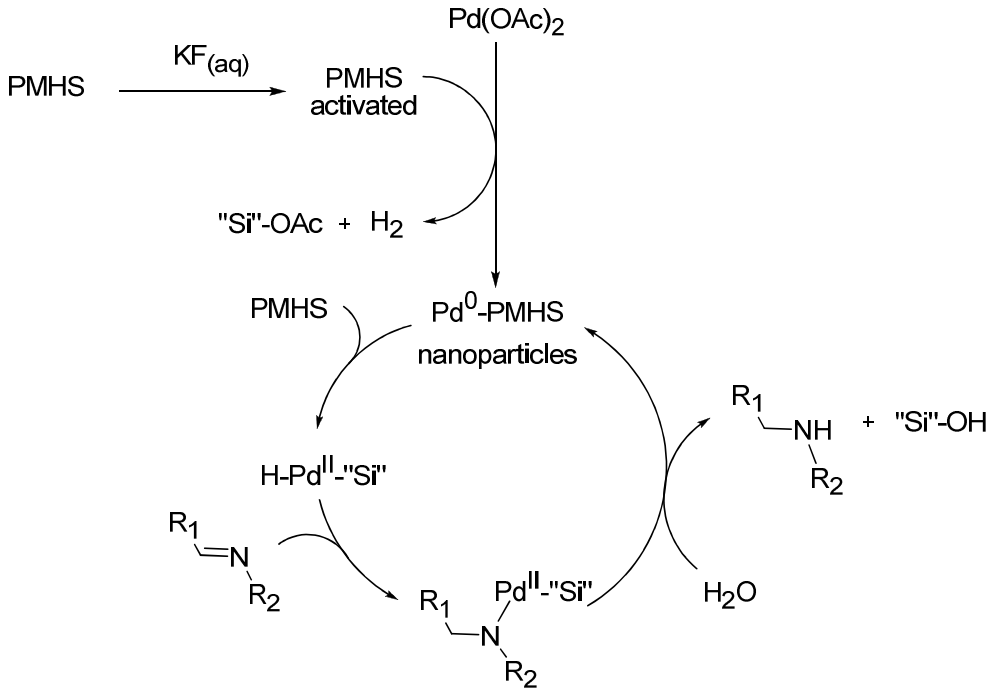
58 (55%)



59 (72%)

Scheme 2.5 Secondary amine synthesized for chemoselectivity studies (isolated yield)

Unfortunately ketones, double bonds and bromide did not survive under the optimized conditions establish for imine reduction. Continued efforts are still underway in order to increase the chemoselectivity of the reduction, as well as to uncover a better purification process to remove the excess of PMHS. Moreover, the identification of the gas (bubbles) generated after the addition of PMHS is another issue to address for future work. If $H_{2(g)}$ is forming during the reduction, a two-step mechanism can be proposed (Scheme 2.6). In the first step, it is known that the Si center of the PMHS can be activated by a fluoride source, in our case $KF_{(aq)}$. Then the active catalyst is generated when $Pd(OAc)_2$ reacts with PMHS/KF forming Pd-PMHS nanoparticles, evidence of the formation of this encapsulated Pd-polysiloxane nanoparticles was reported previously by Chauhan.[27] On the second step the imine is reduced to the secondary amine by palladium catalyzed hydrosilation.



Scheme 2.6 Proposed imine reduction catalytic cycle

CHAPTER 3: Pd NANOPARTICLE STUDIES

3.1 Introduction

We observed that the addition of PMHS to a $Pd(OAc)_2$ solution generates polysiloxane encapsulated Pd-nanoclusters as reported previously in the literature.[39] Conversely, the mechanism by which the catalytic action of $Pd(OAc)_2/PMHS/KF_{aq}$ system functions is unknown. Using Transmission Electron Microscopy (TEM) to explore the morphology of the catalyst medium, we were able to confirm the existence of the Pd-nanoparticles (Figure 3.1). The presence of these nanoparticles could explain the selectivity of this reaction system, however, the stability and exact composition of these Pd-nanoparticles remains unexplored.

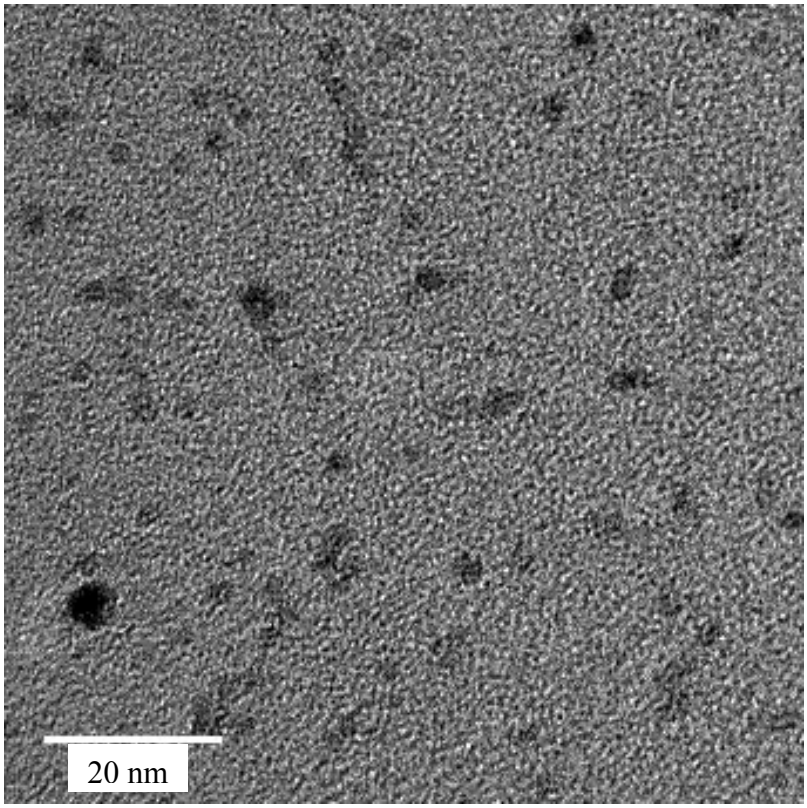


Figure 3.1 TEM image of Pd nanoparticles using Gatan Digital MSC camera at X200k magnification[46]

3.2 TEM and EDS studies

Samples were prepared under the same reaction conditions without the substrate. One hour after the addition of PMHS to a solution of $Pd(OAc)_2/KF_{aq}$ in THF, an aliquot was taken from the reaction mixture and added dropwise to a coated copper grid (carbon film support). The concentration of the sample is about 0.7 mM of the catalyst. Using tweezers, we dispersed the sample on the grid, but in some areas saturation was observed. TEM images of the catalyst at high resolution displayed Pd nanoparticles with an average size between 2 to 4 nm (Figure 3.1). One important finding in this project was the crucial role of the additive KF. When the samples were prepared without KF solution, agglomeration of the Pd-nanoparticles was observed (Figure 3.2).

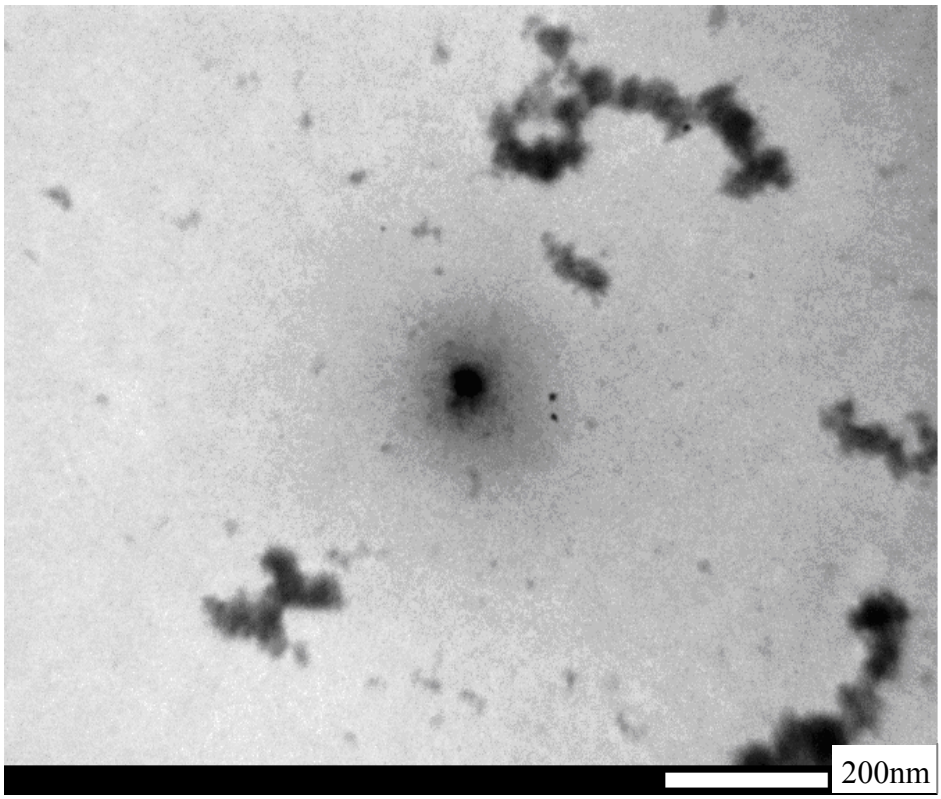


Figure 3.2 TEM image of reaction mixture of $Pd(OAc)_2$/PMHS in THF/H_2O without $KF_{(aq)}$ at X80k magnification

X-ray energy dispersive spectroscopy (EDS) gave the chemical composition highlighting the presence of K, Si, O and Pd. The spectrum collected at different locations confirmed that the darker particles were the Pd-nanoparticles (Figure 3.3).

In addition, it was possible to confirm the formation of Pd-nanoparticles under the reaction conditions, furthermore the crucial role of the additive KF was observed.

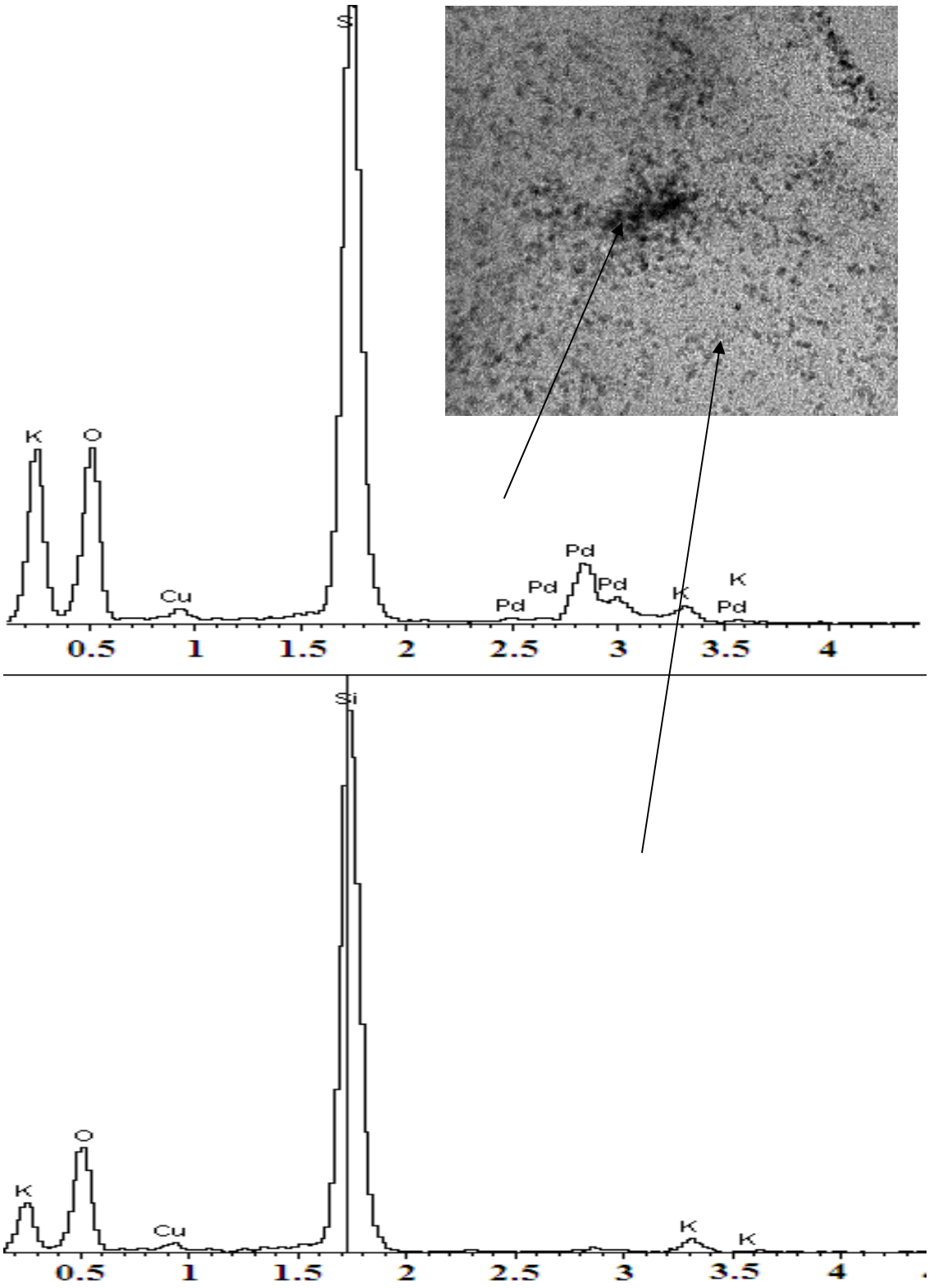


Figure 3.3 EDS of normal sample (spectrum top). EDS of coated film without selecting darker particles (spectrum bottom).

CHAPTER 4: EXPERIMENTAL

4.1 General Materials and Methods

All starting materials were used as received, unless otherwise stated. Diethyl ether and tetrahydrofuran were distilled from sodium and benzophenone under nitrogen. Toluene was distilled from calcium hydride. All reactions were carried out in oven-dried or flame dried glassware under nitrogen atmosphere, unless otherwise stated. All reactions were performed with magnetic stirring and monitored by 1H-NMR and GC-FID. Palladium (II) acetate purchased from Strem, anhydrous A.C.S. grade potassium fluoride and polymethylhydrosiloxane (PMHS) purchased from Sigma-Aldrich were used without purification. Flash chromatography was performed with silica gel 60 Å (230-400 mesh) purchased from Silicycle, monitored by thin-layer chromatography using 0.25-nm pre-coated silical gel aluminum plates and developed with uv and/or phosphomolybdeneic acid. Yields refer to chromatographically and spectroscopically pure compounds unless other wise stated. ^{1}H NMR and ^{13}C NMR spectra were recorded on either Varian Gemini-300 or Varian VXR-500 spectrometer (300, 500 MHz for ^{1}H, respectively, and 75, 125 MHz for ^{13}C, respectively). Chemical shifts are reported relative to the residue peaks of solvent $CDCl_3$ (δ 7.24 ppm for ^{1}H and 77.0 ppm for ^{13}C). TEM sample were acquired at the Michigan State University Center for Advanced Microscopy using a JEOL 2200FS TEM microscope.

4.2 Experimental

General procedure for imine formation:

Method A: a dried r.b. flask was charged with the corresponding aromatic aldehyde (1.0 mmol), the appropriate aniline (1.0 mmol) and 10 mL of Ethanol. The reaction mixture was stirred at room temperature and checked by ^{1}H-NMR until the reaction was finished (usually 24 h). Then the solvent was removed under reduced pressure and the pure imine was obtained without an additional purification. For some imines recrystallization was required and it was indicated in each case.

Method B: a dried r.b. flask was charged with the corresponding aromatic aldehyde (1.0 mmol), the appropriate aniline (1.0 mmol) and 50 mL of Toluene. The reaction mixture was refluxed at 120 °C for 24 hours using a Dean Strak apparatus. Then the solvent was evaporated in reduce pressure and the pure imine was obtained.

General procedure for the reduction of aromatic imines to amines:

A dry 25 mL round bottom flask was charged with $Pd(OAc)_2$ (0.05 mmol, 0.011g), an imine (1 mmol) and 5 mL of freshly distilled THF. The flask was sealed, and placed under nitrogen while stirring. Then a $KF_{(aq)}$ solution (0.1 mmol, 0.1 mL) was added via syringe. This aqueous solution was previously degassed using vacuum and liquid N_2. The nitrogen outlet was replaced by a balloon filled with N_2. After 5 min PMHS (2 mmol, 0.12 mL, 1 mmol is equal to 0.06 mL) was added dropwise via syringe. Bubble formation is observed and the mixture turns black. The reaction was stirred for 30 min or until completed conversion as judged by NMR or GC analysis. Three different work up procedure were employed.

Alternate work up procedure I

The reaction mixture was diluted with ether (5 mL). The organic phase was filtrated through a plug with celite (top layer) and neutral alumina (bottom layer) in a 1 cm diameter column by flushing with EtOAc. The mixture was then dried over $MgSO_4$ and concentrated. Finally the crude was purified by silica gel column chromatography.

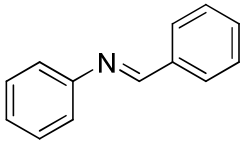
Alternate work up procedure II

A mixture of 10 mL H_2O/Et_2O (1:1) was added to the crude, the layers were separated, and the aqueous layer back extracted with Et_2O. After stirring the organic phase was separated, dried with $MgSO_4$, filter and concentrated. The crude was dissolved in EtOAc and treated with a 3M HCl solution. The white solids formed were filtered, washed with EtOAc and dried over night to give the desired secondary amine as hydrochloride salt. The latter was dissolved in a H_2O/methanol (1:1) mixture and $NaHCO_3$ (sat) solution was added. The volume was reduced to the minimum and extracted with EtOAc (4 x 10 mL), dried and concentrated.

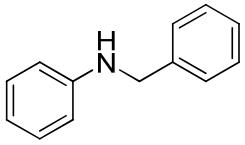
Alternate work up procedure III

Upon addition of 10 mL Et_2O/1M HCl (1:1) and stirring for 10 min, the organic phase was separated and extracted with 1M HCl (3 x 10 mL). Then the aqueous layers were combined, made basic with addition of $KOH_{(s)}$, and extracted with EtOAc (4x 15 mL). Finally, the organic layers were dried, filtered and concentrated.

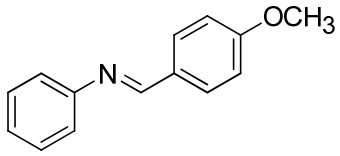
Experimental details and spectroscopic data:



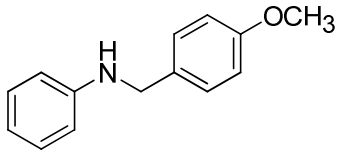
***N*-phenylbenzylideneamine:** Using the general procedure for imine formation (Method A) a colorless solid was obtained after recrystallization from hexanes. Yield: 80%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.42 (s, 1H, CH-imine), 7.94 (m, 2H, Ar-H), 7.51-7.50 (m, 3H, Ar-H), 7.45-7.41 (m, 2H, Ar-H), 7.28-7.24 (m, 3H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.4, 152.1, 136.3, 131.4, 129.2, 128.8, 128.7, 125.9, 120.8.



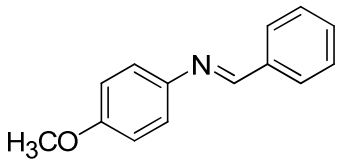
***N*-phenylbenzylamine:** N-phenylbenzylideneamine (181 mg, 1 mmol) was reduced in 2h, following the general procedure for imine reduction. The amine was obtained using the work up procedure I and purified by column chromatography. Yield: 90%; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.39-7.33 (m, 4H, Ar-H), 7.27 (t, *J* = 7.0 Hz, 1H, Ar-H), 7.18 (t, *J* = 7.0 Hz, 2H, Ar-H), 6.72 (t, *J* = 7.5 Hz, 1H, Ar-H), 6.68 (d, *J* = 8.5 Hz, 2H, Ar-H), 4.27 (s, 2H, Ar-CH_2), 4.07 (s br, 1H, -NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 148.1, 139.4, 129.2, 128.5, 127.4, 127.2, 117.5, 112.8, 48.3.



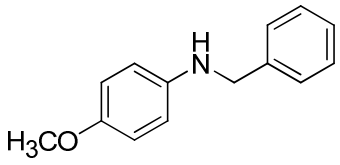
***N*-phenyl-4-methoxybenzylideneamine:** Using the general procedure for imine formation (Method A) a white solid was obtained after recrystallization from hexanes. Yield: 100%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.34 (s, 1H, CH-imine), 7.84 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.38-7.34 (m, 2H, Ar-H), 7.21-7.16 (m, 3H, Ar-H), 6.97 (d, *J* = 8.5 Hz, 2H, Ar-H), 3.86 (s, 3H, Ar-OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.3, 159.7, 152.4, 130.5, 129.3, 129.1, 125.5, 120.9, 114.1, 55.4.



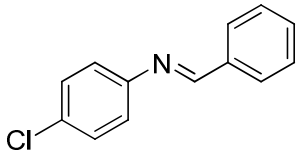
***N*-(4-methoxybenzyl)phenylamine:** *N*-phenyl-4-methoxybenzylideneamine (211 mg, 1 mmol) was reduced in 30 min, following the general procedure for imine reduction. The amine was obtained using the work up procedure III and purified by column chromatography. Yield: 80%; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.31 (d, *J* = 9 Hz, 2H, Ar-H), 7.19 (t, *J* = 7.5 Hz, 2H, Ar-H), 6.90 (d, *J* = 8.5 Hz, 2H, Ar-H), 6.74 (t, *J* = 7.5 Hz, 1H, Ar-H), 6.65 (d, *J* = 9 Hz, 2H, Ar-H), 4.26 (s, 2H, Ar-CH_2), 4.00 (s br, 1H, -NH), 3.81 (s, 3H, Ar-OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.7, 148.2, 131.3, 129.2, 128.7, 117.4, 113.9, 112.7, 55.2, 47.7.



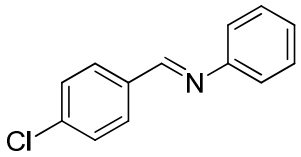
***N*-(4-methoxyphenyl)benzylideneamine:** Using the general procedure for imine formation (Method A) a yellow solid was obtained. Yield: 98%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.50 (s, 1H, CH-imine), 7.91-7.89 (m, 2H, Ar-H), 7.48-7.47 (m, 3H, Ar-H), 7.26 (d, *J* = 6.5 Hz, 2H, Ar-H), 6.96 (d, *J* = 7 Hz, 2H, Ar-H), 3.86 (s, 3H, Ar-OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.3, 158.2, 144.9, 136.4, 130.9, 128.7, 128.5, 122.1, 114.3, 55.4.



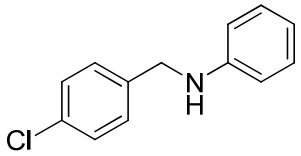
***N*-benzyl-(4-methoxyphenyl)amine:** *N*-(4-methoxyphenyl)benzylideneamine (211 mg, 1 mmol) was reduced in 30 min, following the general procedure for imine reduction. The amine was obtained using the work up procedure III and purified by column chromatography. Yield: 48%; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.41-7.35 (m, 4H, Ar-H), 7.30-7.27 (m, 1H, Ar-H), 6.81 (d, *J* = 7 Hz, 2H, Ar-H), 6.63 (d, *J* = 7 Hz, 2H, Ar-H), 4.31 (s, 2H, Ar-CH_2), 3.86 (s, 1H, -NH), 3.76 (s, 3H, Ar-OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.4, 139.6, 128.5, 127.5, 127.1, 122.1, 114.8, 114.1, 55.7, 49.2.



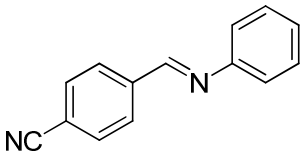
***N*-(4-chlorophenyl)-benzylideneamine:** Using the general procedure for imine formation (Method A) a white solid was obtained after recrystallization from hexane. Yield: 97%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.41 (s, 1H, CH-imine), 7.88-7.86 (m, 2H, Ar-H), 7.48-7.45 (m, 3H, Ar-H), 7.34 (d, *J* = 8 Hz, 2H, Ar-H), 7.14 (d, *J* = 7 Hz, 2H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.7, 150.5, 135.9, 131.6, 131.4, 129.2, 128.8, 128.8, 122.1.



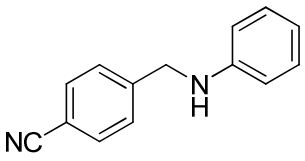
***N*-phenyl-4-chlorobenzylideneamine:** Using the general procedure for imine formation a yellow solid was obtained. Yield: 97%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.45 (s, 1H, CH-imine), 7.88 (d, *J* = 8 Hz, 2H, Ar-H), 7.48 (d, *J* = 8 Hz, 2H, Ar-H), 7.43 (t, *J* = 7.5 Hz, 2H, Ar-H), 7.29-7.27 (m, 1H, Ar-H), 7.24 (d, *J* = 8.5 Hz, 2H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.7, 151.6, 137.3, 134.7, 129.9, 129.1, 129.0, 126.1, 120.8.



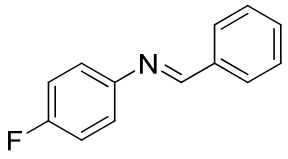
***N*-(4-chlorobenzyl)phenylamine:** *N*-phenyl-4-chlorobenzylideneamine (215 mg, 1 mmol) was reduced in 2 h, following the general procedure for imine reduction. The amine was obtained using the work up procedure I and purified by column chromatography. Yield: 55%; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.18-7.13 (m, 4H, Ar-H), 6.75-6.59 (m, 3H, Ar-H), 6.61 (d, *J* = 8 Hz, 2H, Ar-H), 4.29 (s, 2H, Ar-CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 129.2, 129.1, 129.0, 128.7, 128.6, 120.8, 117.7, 112.8, 47.5.



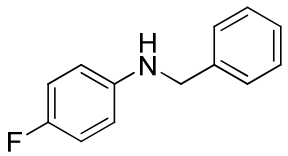
***N*-phenyl-4-nitrilebenzylideneamine:** Using the general procedure for imine formation (Method A) a yellow solid was obtained. Yield: 90%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.51 (s, 1H, CH-imine), 8.03 (d, *J* = 6.5 Hz, 2H, Ar-H), 7.78 (d, *J* = 7.5, 2H, Ar-H), 7.44 (t, *J* = 8 Hz, 2H, Ar-H), 7.32-7.25 (m, 3H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.8, 151.0, 139.9, 132.5, 129.2, 129.1, 126.8, 120.9, 118.4, 114.4.



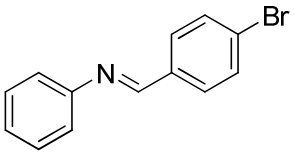
***N*-(4-nitrilebenzyl)phenylamine:** *N*-phenyl-4-nitrilebenzylideneamine (206 mg, 1 mmol) was reduced in 2 h, following the general procedure for imine reduction. The amine was obtained using the work up procedure I and purified by column chromatography. Yield: 72%; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 8 Hz, 2H, Ar-H), 7.51 (d, *J* = 8 Hz, 2H, Ar-H), 7.20 (t, *J* = 7.5 Hz, 2H, Ar-H), 6.77 (t, *J* = 7.5 Hz, 1H, Ar-H), 6.61 (d, *J* = 8 Hz, 2H, Ar-H), 4.41 (s, 2H, Ar-CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.3, 145.4, 132.4, 129.3 (2C), 127.6, 118.8, 118.0, 112.8, 47.9.



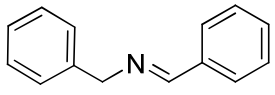
***N*-(4-fluorophenyl)-benzylideneamine:** Using the general procedure for imine formation (Method A) a brown solid was obtained. Yield: 100%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.42 (s, 1H, CH-imine), 7.88-7.86 (m, 2H, Ar-H), 7.47-7.44 (m, 3H, Ar-H), 7.19-7.17 (m, 2H, Ar-H), 7.08-7.04 (m, 2H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.1, 160.1, 131.4, 128.7, 128.7, 122.3, 122.2, 115.9, 115.7.



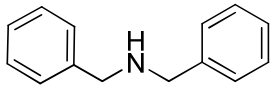
***N*-benzyl-(4-fluorophenyl)amine:** *N*-(4-fluorophenyl)-benzylideneamine (199 mg, 1 mmol) was reduced in 1 h, following the general procedure for imine reduction. The amine was obtained using the work up procedure II and purified by column chromatography. Yield: 69%; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.43-7.39 (m, 4H, Ar-H), 7.35-7.32 (m, 1H, Ar-H), 6.95-6.90 (m, 2H, Ar-H), 6.62-6.59 (m, 2H, Ar-H), 4.33 (s, 2H, Ar-CH_2), 3.96 (s, 1H, -NH).



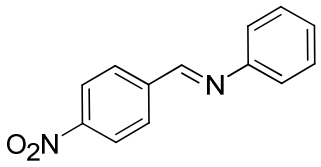
***N*-phenyl-4-bromobenzylideneamine:** Using the general procedure for imine formation (Method A) a white solid was obtained. Yield: 98%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.43 (s, 1H, CH-imine), 7.80 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.63 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.42 (t, *J* = 8.5 Hz, 2H, Ar-H), 7.28-7.22 (m, 3H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.9, 151.6, 135.1, 132.0, 130.1, 129.1, 126.2, 125.8, 120.8.



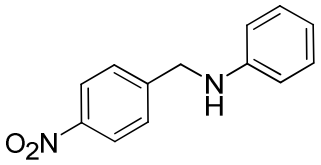
***N*-benzylbenzylideneamine:** Using the general procedure for imine formation (Method A) a yellow oil was obtained. Yield: 92%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.43 (s, 1H, CH-imine), 7.83-7.81 (m, 2H, Ar-H), 7.47-7.44 (m, 3H, Ar-H), 7.39-7.37 (m, 4H, Ar-H), 7.31-7.28 (m, 1H, Ar-H), 4.87 (s, 2H, Ar-CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.9, 139.2, 130.7, 128.6, 128.5, 128.4, 128.2, 127.9, 126.9, 64.9.



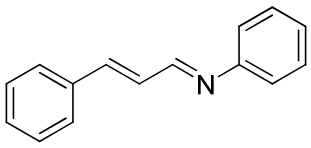
Dibenzylamine: *N*-benzylbenzylideneamine (195 mg, 1 mmol) was reduced in 2 h, following the general procedure for imine reduction. The amine was obtained using the work up procedure I and purified by column chromatography. Yield: 76%; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.40-7.35 (m, 8H, Ar-H), 7.31-7.28 (m, 2H, Ar-H), 3.90 (s, 1H, -NH), 3.85 (s, 4H, Ar-CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 140.2 (2C), 128.3 (2C), 128.1 (2C), 126.8 (2C), 53.1 (2C).



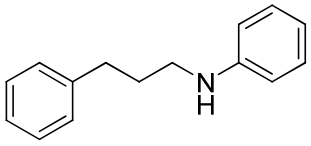
***N*-phenyl-4-nitrobenzylideneamine:** Using the general procedure for imine formation (Method A) a yellow solid was obtained. Yield: 87%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.59 (s, 1H, CH-imine), 8.36 (d, *J* = 8.5 Hz, 2H, Ar-H), 8.11 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.46 (t, *J* = 8 Hz, 2H, Ar-H), 7.34-7.27 (m, 3H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.3, 150.9, 141.5, 129.4, 129.3, 127.0, 124.0, 120.9, 104.9.



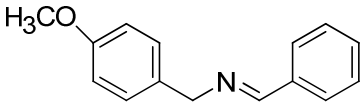
***N*-(4-nitrobenzyl)phenylamine:** *N*-phenyl-4-nitrobenzylideneamine (226 mg, 1 mmol) was reduced in 1 h, following the general procedure for imine reduction. The amine was obtained using the work up procedure III and purified by prep. TLC. Yield: 33%; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.21 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.55 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.19 (t, *J* = 7.5 Hz, 2H, Ar-H), 6.76 (t, *J* = 8.4 Hz, 1H, Ar-H), 6.60 (d, *J* = 8.5 Hz, 2H, Ar-H), 4.49 (s, 2H, Ar-CH_2), 4.25 (s, 1H, -NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.4, 129.4, 129.3, 127.6, 123.9, 123.8, 118.1, 112.8, 47.5.



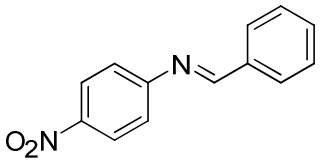
***N*-1, 3-diphenyl-(E)-2-propenimine:** Using the general procedure for imine formation (Method A) an orange solid was obtained. Yield: 100%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.32 (d, *J* = 6.5 Hz, 1H, CH-imine), 7.58 (d, *J* = 7.5 Hz, 2H, CH=CH), 7.43-7.40 (m, 5H, Ar-H), 7.30-7.18 (m, 5H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.6, 151.7, 143.9, 135.5, 129.5, 129.1, 128.8, 128.5, 127.4, 126.1, 120.8.



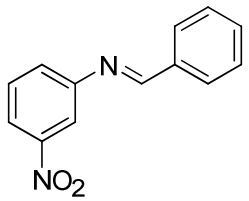
***N*-1-[(E)-3-phenyl-2-propenyl]phenylamine:** *N*-1, 3-diphenyl-(E)-2-propenimine (207 mg, 1 mmol) was reduced in 15 min, following the general procedure for imine reduction. The amine was obtained using the work up procedure III. Yield: 67%; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.32-7.29 (m, 2H, Ar-H), 7.27-7.16 (m, 5H, Ar-H), 6.72-6.69 (m, 1H, Ar-H), 6.59 (d, *J* = 8.5 Hz, 2H, Ar-H), 3.64 (s, 1H, -NH), 3.17 (t, *J* = 7.5 Hz, 2H, -N-CH_2), 2.75 (t, *J* = 7.5 Hz, 2H, Ar-CH_2), 2.01-1.94 (m, 2H, -CH_2) . ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.3, 141.6, 129.2, 129.1 (2C), 128.3 (2C), 125.9, 118.5, 117.1, 115.0, 112.7, 43.3, 33.3, 31.0.



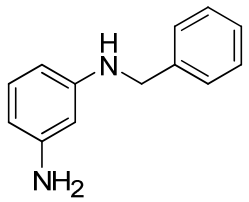
***N*-(4-methoxybenzyl)-benzylideneamine:** Using the general procedure for imine formation (Method A) a yellow solid was obtained. Yield: 75%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.41 (s, 1H, CH-imine), 7.85-7.84 (m, 2H, Ar-H), 7.47-7.46 (m, 3H, Ar-H), 7.33 (d, *J* = 8.25 Hz, 2H, Ar-H), 6.95 (d, *J* = 8.5 Hz, 2H, Ar-H), 4.83 (s, 2H, Ar-CH_2), 3.83 (s, 3H, -OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.4, 158.6, 136.1, 131.2, 130.5, 129.1, 128.4, 128.1, 113.7, 64.2, 55.1.



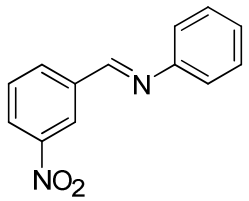
***N*-(4-nitrophenyl)-benzylideneamine:** Using the general procedure for imine formation (Method B) a yellow solid was obtained. Yield: 100%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.45 (s, 1H, CH-imine), 8.30 (d, *J* = 9.5 Hz, 2H, Ar-H), 7.96-7.94 (m, 2H, Ar-H), 7.58-7.54 (m, 3H, Ar-H), 7.27 (d, *J* = 9 Hz, 2H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.6, 157.9, 132.4, 129.7, 129.2, 128.9, 128.9, 125.0, 121.2.



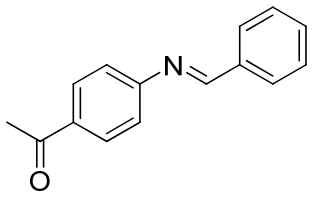
***N*-(3-nitrophenyl)-benzylideneamine:** Using the general procedure for imine formation (Method A) a white-yellow solid was obtained. Yield: 97%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.47 (s, 1H, CH-imine), 8.07 (td, *J* = 2 Hz, *J* = 7.5 Hz, 1H, Ar-H), 8.22 (t, *J* = 2 Hz, 1H, Ar-H), 7.91 (dd, *J* = 2 Hz, *J* = 6.5 Hz, 2H, Ar-H), 7.55-7.47 (m, 5H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.5, 153.1, 148.9, 135.4, 132.1, 129.8, 129.1, 128.9, 127.5, 120.4, 115.3.



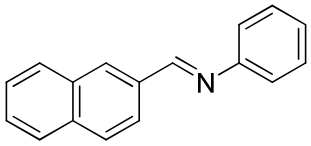
***N*-benzyl-(3-aminophenyl)amine:** *N*-(3-nitrophenyl)-benzylideneamine (226 mg, 1 mmol) was reduced in 1 h, following the general procedure for imine reduction. The amine was obtained using the work up procedure III and purified by prep. TLC. Yield: 52%; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.39-7.34 (m, 5H, Ar-H), 6.98 (t, *J* = 7.5 Hz, 1H, Ar-H), 6.15-6.09 (m, 2H, Ar-H), 6.00-5.99 (m, 1H, Ar-H), 4.31 (s, 2H, Ar-CH_2), 3.60 (s, 1H, -NH).



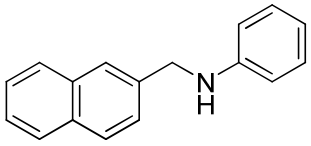
***N*-phenyl-3-nitrobenzylideneamine:** Using the general procedure for imine formation (Method A) a brown solid was obtained. Yield: 91%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.80 (s, 1H, CH-imine), 8.59 (s, 1H, Ar-H), 8.38 (d, *J* = 7.2 Hz, 1H, Ar-H), 8.30 (d, *J* = 7.8 Hz, 1H, Ar-H), 7.71 (t, *J* = 8.1 Hz, 1H, Ar-H), 7.48 (t, *J* = 7.8 Hz, 2H, Ar-H), 7.36-7.29 (m, 3H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.1, 150.8, 148.7, 137.8, 134.0, 129.7, 129.2, 126.8, 125.5, 123.4, 120.9.



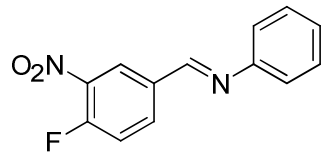
4-(N-benzylideneamino)acetophenone: Using the general procedure for imine formation (Method B) a white solid was obtained. Yield: 98%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.46 (s, 1H, CH-imine), 8.03 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.94 (dd, *J* = 1.5 Hz, *J* = 8 Hz, 2H, Ar-H), 7.54-7.52 (m, 3H, Ar-H), 7.25 (d, *J* = 9 Hz, 2H, Ar-H), 2.64 (s, 2H, CH_3).



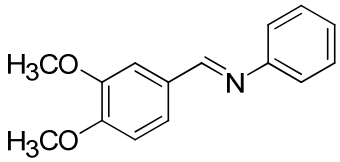
N-phenyl-1-napthylideneamine: Using the general procedure for imine formation (Method A) a white solid was obtained. Yield: 97%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.64 (s, 1H, CH-imine), 8.22 (s, 1H, Ar-H), 8.19 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.95 (t, *J* = 7.5 Hz, 2H, Ar-H), 7.90 (d, *J* = 7.5 Hz, 1H, Ar-H), 7.60-7.54 (m, 2H, Ar-H), 7.46-7.42 (m, 2H, Ar-H), 7.30-7.27 (m, 3H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.3, 152.0, 135.0, 133.9, 133.0, 131.2, 129.1, 128.7, 128.6, 127.9, 127.5, 126.6, 125.9, 123.9, 120.9.



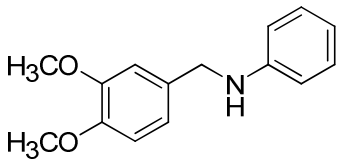
N-(1-napthylmethyl)-phenylamine: N-phenyl-1-napthylideneamine (231 mg, 1 mmol) was reduced in 1 h, following the general procedure for imine reduction. The amine was obtained using the work up procedure I and purified by column chromatography. Yield: 78%; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.85-7.83 (m, 4H, Ar-H), 7.52-7.46 (m, 3H, Ar-H), 7.19 (t, *J* = 7.5 Hz, 2H, Ar-H), 6.74 (t, *J* = 8 Hz, 1H, Ar-H), 6.70 (t, *J* = 8 Hz, 2H, Ar-H), 4.52 (s, 2H, Ar-CH_2), 4.15 (s, 1H, -NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.4, 137.2, 133.7, 133.0, 129.5, 128.6, 128.0, 127.9, 126,4, 126.1, 125.9, 125.9, 117.9, 113.2, 48.7.



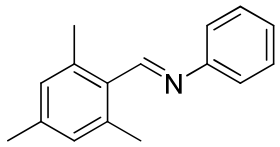
***N*-phenyl-3-nitro-4-fluorobenzylideneamine:** Using the general procedure for imine formation (Method A) an orange solid was obtained. Yield: 74%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.64 (d, J = 8 Hz, 1H, Ar-H), 8.53 (s, 1H, CH-imine), 8..30-8.25 (m, 1H, Ar-H), 7.52-7.43 (m, 3H, Ar-H), 7.38-7.34 (m, 1H, Ar-H), 7.32-7.27 (m, 2H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.7, 155.7, 134.8, 134.7, 129.3, 126.9, 126.3, 126.3, 120.8, 119.1, 118.9.



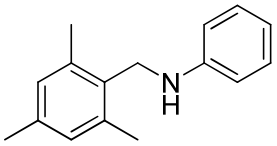
***N*-phenyl-3,4-dimethoxybenzylideneamine:** Using the general procedure for imine formation (Method A) a brown oil was obtained. Yield: 78%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.34 (s, 1H, CH-imine), 7.60 (d, *J* = 2 Hz, 1H, Ar-H), 7.36 (t, *J* = 8 Hz, 2H, Ar-H), 7.29 (dd, *J* = 2 Hz, *J* = 7 Hz, 1H, Ar-H), 7.19-7.17 (m, 3H, Ar-H), 6.92 (d, *J* = 8.5 Hz, 1H, Ar-H) 3.94 (s, 3H, -OCH_3), 3.93 (s, 3H, -OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.8, 152.3, 152.0, 149.5, 129.6, 129.1, 125.6, 124.4, 120.8, 110.5, 108.9, 56.1, 56.0.



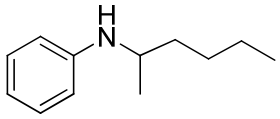
***N*-(3,4-dimethoxybenzyl)phenylamine:** *N*-phenyl-3,4-dimethoxybenzylideneamine (241 mg, 1 mmol) was reduced in 1 h, following the general procedure for imine reduction. The amine was obtained using the work up procedure III. Yield: 91%; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.21 (t, *J* = 7.5 Hz, 2H, Ar-H), 6.95-6.94 (m, 2H, Ar-H), 6.86 (d, *J* = 9 Hz, 1H, Ar-H), 6.76 (t, *J* = 7.5 Hz, 1H, Ar-H), 6.68 (d, *J* = 7.5 Hz, 2H), 4.28 (s, 2H, Ar-CH_2), 3.90 (s, 3H, -OCH_3), 3.89 (s, 3H, -OCH_3), 3.85 (s, 1H, -NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.9, 148.1, 148.0, 131.8, 129.1, 119.1, 117.4, 112.7, 111.0, 110.6, 55.8, 55.7, 48.1.



***N*-phenyl-2,4,6-trimethylbenzylideneamine:** Using the general procedure for imine formation (Method A) a white solid was obtained. Yield: 100%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.80 (s, 1H, CH-imine), 7.46-7.42 (m, 2H, Ar-H), 7.27-7.23 (m, 1H, Ar-H), 7.21-7.18 (m, 2H, Ar-H), 6.95 (s, 2H, Ar-H), 2.56 (s, 6H, Ar-CH_3), 2.34 (s, 3H, Ar-CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.8, 153.1, 139.7, 138.5, 130.5, 129.7, 129.0, 125.4, 120.6, 21.2, 21.0.



***N*-(2,4,6-trimethylbenzyl)phenylamine**: *N*-phenyl-2,4,6-trimethylbenzylideneamine (223 mg, 1 mmol) was reduced in 1 h, following the general procedure for imine reduction. The amine was obtained using the work up procedure III. Yield: 93%; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.37-7.33 (m, 2H, Ar-H), 7.03 (s, 2H, Ar-H), 6.86 (t, *J* = 7.5 Hz, 1H, Ar-H), 6.79 (d, *J* = 7.5 Hz, 2H, Ar-H), 4.32 (s, 2H, Ar-CH_2), 3.4 (s, 1H, -NH), 2.48 (s, 6H, Ar-CH_3), 2.42 (s, 3H, Ar-CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.5, 137.4, 137.2, 132.1, 129.2, 129.0, 117.1, 112.3, 42.2, 20.8, 19.3.



***N*-(hexan-2-yl)phenylamine**: (E)-*N*-(hex-5-en-2-ylidene)phenylamine (173 mg, 1 mmol) in a mixture with aniline (1:4) was reduced in 30 min, following the general procedure for imine reduction. The amine was obtained using the work up procedure I. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.13 (t, *J* = 8 Hz, 2H, Ar-H), 6.63 (t, J = 7 Hz, 1H, Ar-H), 6.55 (d, *J* = 8 Hz, 2H, Ar-H), 3.43 (q, *J* = 6 Hz, 1H, -N-CH), 3.4 (s br 1H, -N-H), 1.43-1.29 (m, 6H, CH_2), 1.15 (d, *J* = 6 Hz, 3H, CH_3), 0.88 (t, *J* = 7 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.6, 129.2, 116.6, 113.0, 48.3, 36.8, 28.3, 22.7, 20.7, 14.1.

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(46) Gatan Image software, version 3.4, was used for microscope operation. High resolution images were taken using Gatan Digital Multi-Scan Camera (MSC).